Synthetic Methodology for the Construction of Structurally Diverse Cyclopropanes

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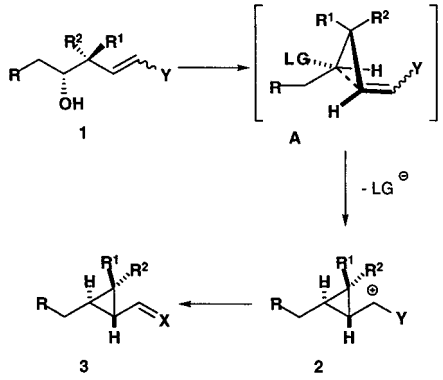
Received October 18, 2000

Abstract: Practical and efficient routes for the stereoselective conversion of homoallylic alchols to diastereomerically pure *cis*-, *trans*-1,2-disubstituted, and 1,2,3-trisubstituted cyclopropanes have been developed. The routes are highlighted by olefin metathesis strategies and the stabilization of an intermediate cyclopropylcarbinyl cation by the β-silicon effect. The stereospecificity of the key cyclization step has been rationalized by transition-state models in which the important determinants include (i) a minimization of the steric interactions about the forming cyclopropane bond and (ii) an inversion of stereochemistry at the activated homoallylic alcohol position. The cyclopropane product chirality is ultimately controlled by the choice of homoallylic alcohol starting material. Through this method nonracemic, diasteromerically pure homoallylic alcohols can be converted in two steps to nonracemic, diasteromerically pure cyclopropane structural units. The scope and limitations of this versatile methodology have also been investigated.

The cyclopropyl group has played a prominent role in organic chemistry for many reasons. Its strained structure, interesting bonding characteristics, and its use as an internal mechanistic probe continue to draw the attention of the physical organic community.[1] In addition, the prevalence of cyclopropane-containing compounds with biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, has inspired chemists to find novel and diverse approaches to their synthesis. Progress in the area of diastereo- and enantioselective methods for cyclopropane construction has been largely focused on the modification of allylic alcohols through intramolecular carbenoid intermediates[2] or intermolecular Simmons−Smith chemistry.[3] In contrast, we have been investigating the ready conversion of simple structures such as homoallylic alcohols to enantiomerically and diastereomerically pure cyclopropanes.[4] The key step in our route involves the generation, stabilization, and trapping of cyclopropylcarbinyl cations.[5] The stereochemistry of the resulting cyclopropane product, both absolute and relative, is controlled by the homoallylic alcohol **1** and the constraints of transition state **A**, Scheme 1. The presence of a carbocationic-stabilizing group Y allows for efficient, stereospecific cyclization through an inversion of the activated homoallylic alcohol, and the formation of unsaturation traps the cyclopropylcarbinyl cation before fragmentation, rearrangement, or potential loss of stereochemistry.

Scheme 1



For our first generation approach we chose Y = CH_2SiR_3 to exploit the cation stabilization of the β-silicon effect, **2**.[6,7] In this account, we introduce the application of olefin cross-metathesis for the preparation of our cyclization precursors. This process has now allowed the preparation of nonracemic, diasteromerically pure cyclopropanes in just two steps from readily available chiral precursors. We now present the synthetic and mechanistic details of this highly efficient route together with its scope and limitations.

Results

Ring-Closing Metathesis. There are numerous published methods for the preparation of homoallylic alcohols.[8] A representive series of homoallylic alcohol starting materials were

(1) (a) de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809. (b) Nonhebel, D. C. *Chem. Soc. Rev.* **1993**, *22*, 347.

(2) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763 and references therein.

(3) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *117*, 11943 and references therein.

(4) (a) Taylor, R. E.; Schmitt, M. J.; Yuan, H. *Org. Lett.* **2000**, *2*, 601. (b) Taylor, R. E.; Engelhardt, F. C.; Yuan, H. *Org. Lett.* **1999**, *1*, 1257. (c) Taylor, R. E.; Ameriks, M. K.; LaMarche, M. J. *Tetrahedron Lett.* **1997**, *38*, 2057.

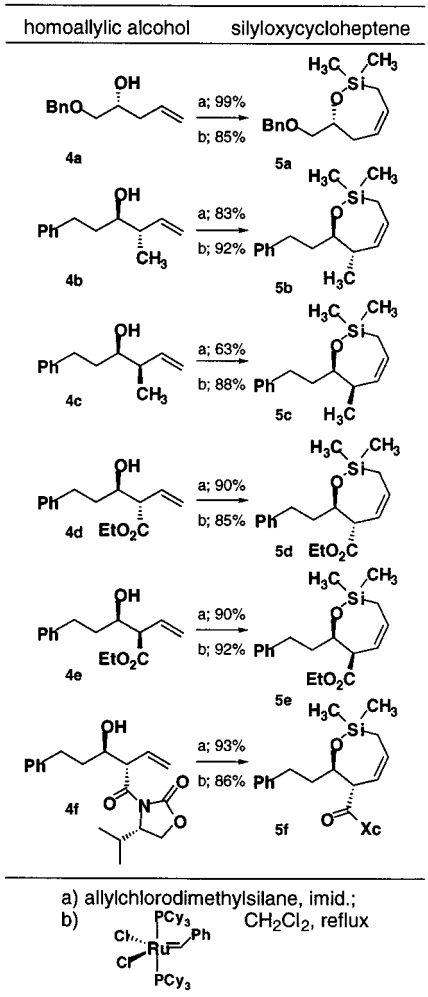
(5) For examples of chemical approaches to cyclopropanes via cyclopropylcarbinyl cationic intermediates, see: (a) Krief, A.; Provins, L. *Synlett* **1997**, 505. (b) Hanessian, S.; Reinhold: U.; Ninkovic, S. *Tetrahedron Lett.* **1996**, *37*, 8971. (c) White, J. D.; Jensen, M. S. *Synlett* **1996**, 31. (d) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6224. (e) Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, K. *Synlett* **1995**, 739. (f) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970.

(6) Schaumann has previously reported the preparation of vinylcyclopropanes from similar starting materials through an allylic anion-mediated process. For a lead reference, see: Schaumann, E.; Kirschning, A.; Narjes, F. *J. Org. Chem.* **1991**, *56*, 717.

(7) (a) For an excellent review of the chemistry of allylsilanes, see: Fleming, I. *Org. React.* **1989**, *37*, 57. (b) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.

10.1021/ja0037163 CCC: $20.00
Published on Web 03/09/2001

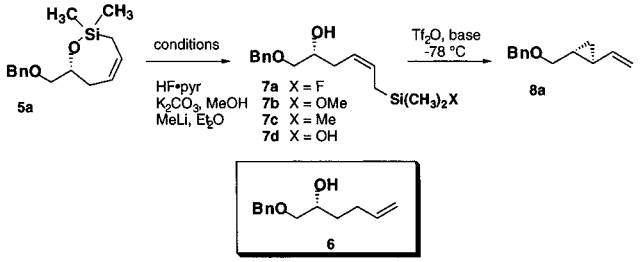
Table 1. Silylation and Ring Closing Metathesis



prepared, Table 1. Enantiomerically enriched benzyl ether **4a** was prepared in a single step (vinylMgBr, CuI) from commercially available, (*R*)-(−)-benzylglycidyl ether. Crotylation of hydrocinnamaldehyde provided *anti*-**4b** and *syn*-**4c** from crotylbromide/$CrCl_2$[9] and crotylstannane/BF_3·OEt_2,[10] respectively. A chromatographically separable mixture of *anti*-**4d** and *syn*-**4e** (3:1) was obtained from ethyl bromocrotonate/In(0),[11] and enantiomerically pure alcohol **4f** was prepared from the corresponding crotyl imide through the boron enolate methodology developed in the Evans' laboratory.[8b] For each homoallylic alcohol, incorporation of the necessary cation-stabilizing group (Y = CH_2SiMe_3) was accomplished by a two-step protocol. Protection of the secondary hydroxyl group of **4a**−**f** was accomplished with allylchlorodimethylsilane in the presence of imidazole. The resulting bis-olefin was then subjected to Grubbs' bis-(tricyclohexylphospine) ruthenium alkylidene catalyst[12] which provided silyloxycycloheptenes **5a**−**f** in excellent yield.[13]

Our next goal was to cleave the silyloxycycloheptene ring to expose the cyclization precursor **1**. Initially, we explored the use of tetrabutylammonium fluoride (TBAF). TBAF did indeed

Scheme 2



cleave the silyloxepene ring **5a** but, in addition, induced protodesilylation leading to isolation of the terminal olefin **6**, Scheme 2. In response, numerous methods were systematically explored to provide the desired allylsilane homoallylic alcohol. It was discovered that HF·pyr worked beautifully and provided the fluorosilane **7a** in quantitative yield. Alternatively, subjecting the cyclic silyl ether **5a** to milder conditions, basic methanol (K_2CO_3) provided methyl ether **7b** through a trans-etherification reaction. It is important to note that silanes **7a** and **7b** are not chromatographically stable with silica gel. Attempted purification of fluorosilane **7a** led to quantitiative protodesilylation and isolation of **6**. In contrast, silica gel chromatography of methyl ether **7b** provided a mixture of silanol **7d** and silyloxycycloheptene **5a** through acid-induced cyclization. Ultimately, it was discovered that treatment of **5a** with excess methyllithium in diethyl ether at room temperature provided the chromatographically stable trimethylsilane **7c** in high yields. The complementary nature of these silicon−oxygen cleavage conditions (HF·pyr or MeLi) provides the opportunity to prepare a variety of functionalized cyclopropane precursors.

At this point we envisioned that activation of the homoallylic alcohol by any of numerous methods would lead to vinylcyclopropane formation through a silicon-stabilized cyclopropylcarbinyl cationic intermediate **2**. In fact, activation of alcohol **7a**, with trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine provided exclusively the *trans*-vinylcyclopropane **8a** in 71% yield from **5a**. Additionally, trimethylsilane **7c** provided **8a** in 77% yield for the two-step sequence. In each case only the *trans*-vinylcyclopropane was observed, presumably controlled by a minimization of steric interactions as in transition state **A**, Scheme 1.[5e] Most importantly, a synthetic derivative of vinylcyclopropane **8a** was compared by chiral gc analysis (Cyclodex-B, J&W Scientific) to racemic material and shown to have retained the enantiomeric purity of the glycidol starting material. As shown in Scheme 3, vinylcyclopropane **8a** was converted to the previously prepared (−)-(1*R*,3*R*)-1,3-bis-(hydroxymethyl)cyclopropane[14] through a three-step sequence. The terminal olefin was cleaved by OsO_4/$NaIO_4$ and the resulting aldehyde reduced by $NaBH_4$. Hydrogenolysis of the benzyl ether provided the desired material, $[\alpha]^{23}_D = -16.3$, lit. enantiomer $[\alpha]^{25}_D = +16.1$.[14a] This sequence was carried out for both the allyldimethylfluorosilane **7a** as well as the allyltrimethylsilane **7c** (prepared via cross-metathesis as an inseparable *E:Z* mixture (2.3:1), vide infra **15a**). Despite the expected electronic and reactivity differences between allylsilanes **7a** and

(8) (a) For a recent review of the reaction of aldehydes with allylic metals, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) For an alternative preparation of homoallylic alcohols using chiral crotonate enolates, see: Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.

(9) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179.

(10) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889 and references therein.

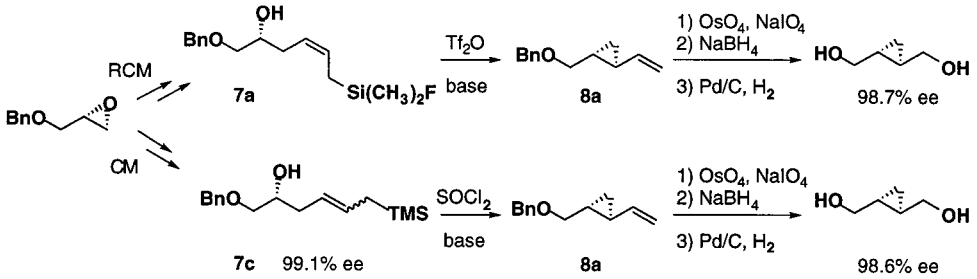
(11) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017.

(12) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (b) Schwab, P. E.; Grubbs, R. H.; Ziller. J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(13) For the preparation of olefinic diols via similar silyloxycycloalkenes, see: Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757. For the preparation of tetrahydrofurans and pyrans via similar silyloxycycloalkenes, see: Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861.

(14) (a) McDonald, W. S.; Verbicky, C. A.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 1215. (b) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575.

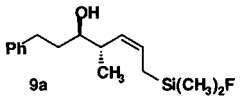
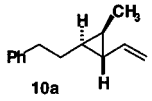
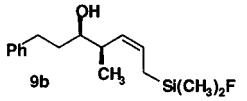
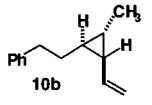
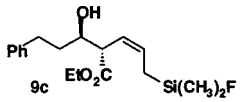
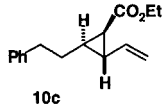
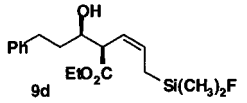
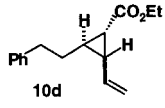
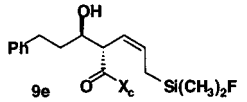
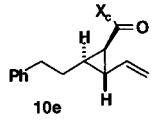
Scheme 3



7c, the successful preparation of (−)-(1*R*,3*R*)-1,3-bis(hydroxymethyl)cyclopropane, in high enantiomeric purity with both substrates, is supportive of an efficient inversion process (transition state **A**, Scheme 1).

Despite the expected deactivating effect, fluorosilanes **9a**−**e** provided 1,2,3-trisubsituted cyclopropanes **10a**−**e** under the identical activation conditions. The yields provided in Table 2 are for both steps (HF·pyr of **5b**−**f**; Tf_2O.) The diastereomeric *anti* and *syn* "propionates" **9a** and **9b** cyclized efficiently, to provide the 1,2,3-trisubstituted cyclopropanes **10a** and **10b**, respectively. In addition, the carboalkoxy-substituted systems **9c**, **9d**, and **9e** provided access to their corresponding functionalized trisubstituted cyclopropanes. Each of these reactions was completely diastereospecific, providing a single trisubsituted vinylcyclopropane. The successful preparation of an enantiomerically pure 1,2,3-trisubstituted cyclopropane was demonstrated by the conversion of hydrocinnamaldehyde to diastereomerically pure **10e** through the Evans' aldol intermediate **4f**.

Table 2. Cyclopropane Formation

homoallylic alcohol		cyclopropane
 **9a**	a, 74%	 **10a**
 **9b**	a, 62%	 **10b**
 **9c**	a, 40%	 **10c**
 **9d**	a, 70%	 **10d**
 **9e**	a, 39%	 **10e**

[a] Tf_2O, 2,6-lutidine, −78 °C.

Confirmation of the stereochemical assignments of each 1,2,3-trisubstituted cyclopropane came from an examination of the vicinal $^1H-^1H$ coupling constants for the ring protons. In general, cyclopropyl protons with a *cis* relationship have larger coupling constants (7−10 Hz) than those in a *trans* relationship (3−7 Hz). Vinylcyclopropanes **10b** and **10d** have revised stereochemical assignments from our original communication.[4a] Since each substrate, regardless of relative stereochemistry, provided a single, diastereomerically pure vinylcyclopropane, we originally believed that the C2 substituent played no role in the product stereochemistry. We have now unequivocally established that this is not the case.

On the basis of the fact that these reactions proceed with inversion of stereochemistry two transition states are possible: (1) **B-1** which has a *trans* relationship between C1 and C3 and (2) **B-2** which has a *cis* relationship between C1 and C3, Figure 1. Substrates **7a** and **7c** ($R^1 = R^2 = H$) appear to proceed through **B-1** providing exclusively *trans*-vinylcyclopropanes. Homoallylic alcohols **9a**, **9c**, and **9e** (R^1 = alkyl, $R^2 = H$) also proceed through transition state **B-1**. However, this transition state is disfavored for substrates **10b** and **10d**. In contrast, these substrates prefer to adopt a conformation which minimizes the steric interactions between the C2 and C3 position such as seen in **B-2** ($R^1 = H$, R^2 = alkyl). Presumably, the longer C1−C3 bond length at the transition state can better accommodate a *cis* relationship.

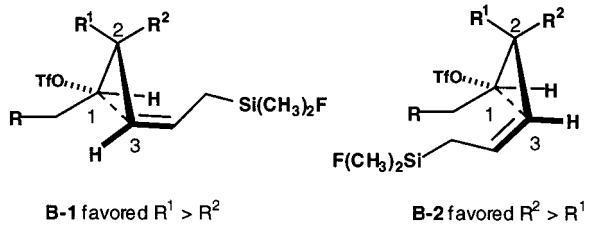
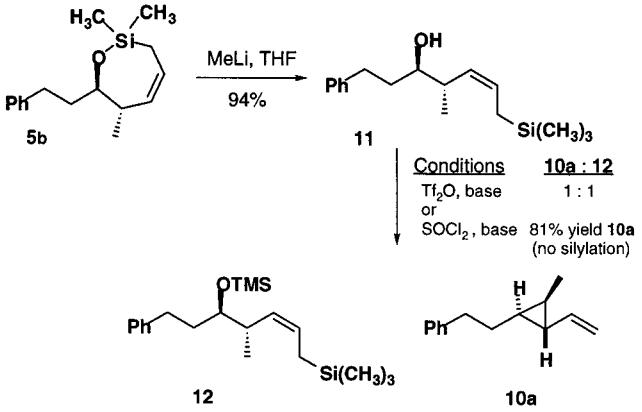


Figure 1. Transition state leading to 1,2,3-trisubstituted cyclopropanes.

Attempts to generate trisubstituted cyclopropanes from the trimethylsilane derivatives proved problematic, Scheme 4. Silyloxycycloheptene **5b** was efficiently cleaved by exposure to methyllithium in tetrahydrofuran, providing trimethylsilane **11** in 94% yield. However, in contrast to the successful cyclization of fluorosilane **9a**, exposure of **11** to our standard conditions cleanly provided an equal mixture of desired cyclopropane **10a** and silylated material **12**. While trimethylsilyl triflate is produced as a product of the cyclization, <5% silylation was observed in the conversion of allylsilane **7c** to 1,2-disubstituted vinylcyclopropane **8**. It appears that in more hindered homoallylic alcohols such as **11** activation with triflic anhydride is slow, relative to cyclization, allowing for competitive silylation to occur. However, this silylation problem could be circumvented with the use of an alternative, activating agent. In fact, no silylation was observed when thionyl chloride was used in the presence of pyridine or 2,6-lutidine at room temperature. Thionyl chloride activation of homoallylic alcohol **11** provided the *trans*-vinylcyclopropane **10a** in 81% yield. There are several potential reasons for the lack of silylation with thionyl chloride: (1) a decrease in the rate of cyclization relative to rate of hydroxyl activation, (2) the presence of chloride ion which assists in the desilylation step, or (3) silyl ether **12** may not be stable to the reaction conditions. The first suggestion is

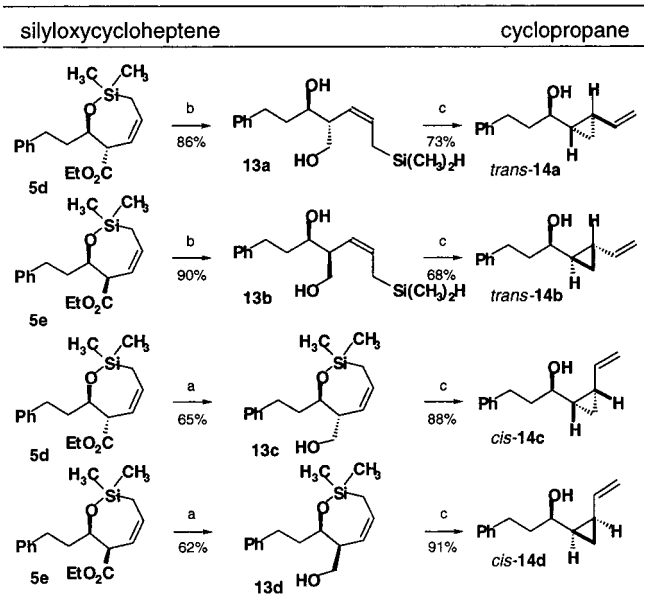
supported by the fact that the deactivated fluorosilane intermediates **9** do not cyclize efficiently with thionyl chloride. Whatever the rationale, these conditions substantially improve the practicality of our process efficiently, providing the cyclopropane products via an inexpensive activating agent under noncryogenic conditions.

Scheme 4



In addition to providing access to the 1,2,3-trisubstituted compounds (**10c**, **10d**) the ester-substituted silyloxepenes **5d** and **5e** have also provided access to both *cis*- and *trans*-1,2-disubstituted cyclopropanes, Table 3. In each case, reduction of the ethyl ester by exposure to excess DIBAL (5 equiv) yielded the isolable silanes **13a** and **13b**. Presumably, formation of the diol occurs through reductive cleavage of the silyloxepene ring after reduction of the ester functionality. Selective activation of the primary alcohol of **13a** and **13b**, easily accomplished with triflic anhydride at −78 °C, provided the *trans*-vinylcyclopropanes **14a** and **14b**, respectively, in good yield. The selective formation of exclusively *trans*-stereochemistry can again be rationalized by a minimization of steric interactions during ring closure.

Table 3. Formation of *cis*- and *trans*-1,2-Disubstituted Cyclopropanes



[a] DIBAL (2 equiv). [b] DIBAL (5 equiv). [c] Tf_2O, 2,6-lutidine, −78 °C.

Alternatively, reduction of silyloxepenes **5d** and **5e** with DIBAL (2 equiv) provided the primary alcohols **13c** and **13d** with only a small amount of reductive cleavage observed. Activation of the homoallylic alcohol gave *cis*-cyclopropanes **14c** and **14d** in excellent yield. Here, the presence of the silyloxycycloheptene ring constrains the substituents in a *cis* orientation about the forming ring, Figure 2 (transition state **C**.) The closure is remarkably efficient despite the less than optimal orbital alignment between the ring carbon−silicon σ-bond and the developing cyclopropylcarbinyl cation.[7b]

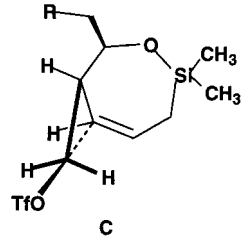


Figure 2. Transition state leading to *cis*-vinylcyclopropanes.

Cross Metathesis. A more efficient approach to the cyclopropane precursors was envisioned by considering an intermolecular metathesis reaction (cross-metathesis) between homoallylic alcohols **4a**−**f** and allyltrimethylsilane, Table 4. In fact, Crowe recently reported that cross-metathesis is an excellent method for the preparation of functionalized allylsilanes.[15] As the results in Table 4 clearly indicate, cross-metathesis between allyltrimethylsilane (4 equiv) and homoallylic alcohols **4a**−**f**, catalyzed by the Grubbs' 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium catalyst[16] efficiently provided the cyclopropane precursors in good yield with varying selectivity, but always favoring the *E*-isomer. The use of only 2 equiv of allyltrimethylsilane was still effective, but the reaction rate was markedly slower. Interestingly, the *E*/*Z* ratio of the cross-metathesis products was affected by the relative stereochemistry of the chiral precursors. The *anti* diastereomers, **4b**, **4d**, and **4f** provided the product allylsilanes in a >11:1 ratio in favor of the presumed thermodynamically more stable *E* isomer.[17] In contrast, both *syn* diastereomers, **4c** and **4e**, were less selective, <4:1. Most importantly, activation of the homoallylic alcohols with thionyl chloride led to isolation of diastereomerically pure vinylcyclopropanes without competitive silylation of starting material and verified the generality of the milder activating conditions. Finally, it is important to note that based on the successful results outlined in Table 4, olefin geometry (of the intermediate allylsilane) appears to have no effect on the efficiency of the cyclization.

Summary

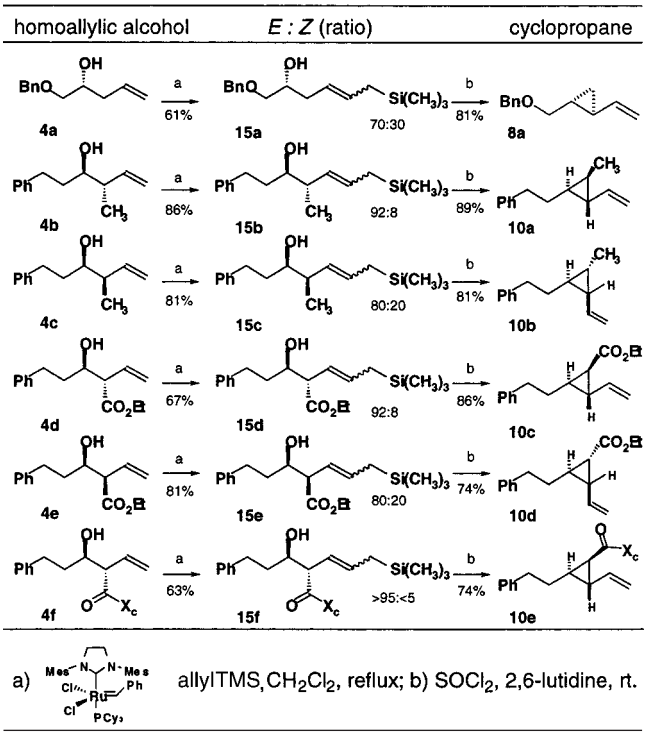
The synthetic utility of this new methodology for the preparation of enantio- and diastereomerically pure vinylcyclo-

(15) (a) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117. In this paper Crowe uses the Schrock molybdenum-based metathesis catalysts. While we originally explored the use of Grubbs' *bis*-Cy_3P-ruthenium catalyst, we have more recently found the dihydroimidazolylidene-ruthenium complex[16] remarkably efficient (vide infra). (b) While we have successfully prepared the dihydroimidazolylidene-Ru catalyst in our laboratories on a gram-scale, it is now commercially available from Strem Chemicals, Newburyport, MA.

(16) (a) Scholl, M.; Ding, S.; Lee C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751−1753. (c) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784. (d) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153.

(17) The *E*:*Z* ratios shown in Table 4 appear to be a result of a kinetically controlled process. Prolonged exposure of pure-*Z*-**15b** to the identical reaction conditions provided a 1:1 ratio of olefin isomers. A more detailed discussion of the factors controlling the cross-metathesis olefin geometry will be published elsewhere: Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. Manuscript in preparation.

Table 4. Cross Metathesis Route to Vinylcyclopropanes



propanes has been demonstrated. Each simple and efficient sequence allows the preparation of structurally complex cyclopropanes from readily available homoallylic alcohols. The ring-closing metathesis route is highlighted by the preparation of *trans*- and *cis*-1,2-disubstituted and 1,2,3-trisubstituted cyclopropanes in just two steps from a common intermediate. Additionally, the cross-metathesis route provides *trans*-1,2-disubstituted and 1,2,3-trisubstituted systems in just two steps from starting homoallylic alcohols. In comparison to our previous reported conditions, activation with inexpensive thionyl chloride at room temperature represents a significant improvement in the development of the process. The versatility of methodology demonstrated herein makes this chemistry a useful, practical alternative to other methods for cyclopropane construction. Most importantly, this investigation sets the stage for the application of the methodology to solid-phase synthesis and, ultimately, the generation of combinatorial libraries based on cyclopropane scaffolds.

Experimental Section

Representative Allylsilane Protection of a Homoallylic Alcohol Followed by a Ring-Closing Metathesis (RCM) Reaction. Preparation of *syn*-2,2,6-Trimethyl-7-phenethyl-2,3,6,7-tetrahydro-[1,2]oxasilepine (5c). To a solution of *syn*-4-methyl-1-phenyl-hex-5-ene-3-ol **4c** (133 mg, 0.70 mmol) in anhydrous DMF (2 mL) was added imidazole (238 mg, 3.5 mmol) and allylchlorodimethylsilane (200 μL, 1.3 mmol). The mixture was stirred at room temperature for overnight. The reaction mixture was diluted with Et_2O, washed with H_2O. The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes → 5% EtOAc in hexanes) to give *syn*-silyl ether (127 mg, 63%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38−7.22 (m, 5H), 5.96−5.82 (m, 2H), 5.15−4.93 (m, 4H), 3.68 (m, 1H), 2.81 (m, 1H), 2.62 (m, 1H), 2.41 (m, 1H), 2.12 (m, 1H), 1.80 (m, 1H), 1.73 (d, J = 8.1, 2H), 1.08 (d, J = 6.9, 3H), 0.22 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.8, 141.2, 134.5, 128.6, 128.5, 125.9, 114.7, 113.9, 76.3, 43.6, 35.8, 32.1, 25.5, 15.7, −1.3. FTIR (cm^{-1}) 3064, 3027, 2959, 1631, 1604, 1496, 1454, 1254, 1069. HRMS calculated for $C_{18}H_{28}OSi$ $(M + H)^+$ m/z 289.1988, found 289.2018. The *syn*-silyl ether (125 mg, 0.43 mmol) was then diluted in anhydrous CH_2Cl_2 (50 mL) and refluxed to which was added bis-tricyclohexylphosphinebenzylidene ruthenium chloride (Grubbs' catalyst, 70 mg, 0.085 mmol) via cannula in CH_2Cl_2 (1 mL). The solution was stirred at reflux overnight. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (silica gel, hexanes → 5% Et_2O in hexanes) to give the *syn*-silyloxycycloheptene **5c** (99 mg, 88%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.33−7.20 (m, 5H), 5.77 (m, 1H), 5.29 (m, 1H), 3.94 (m, 1H), 2.87 (m, 2H), 2.58 (m, 1H), 1.86 (m, 2H), 1.65 (m, 1H), 1.30 (dd, J = 15, 8.7, 1H), 1.00 (d, J = 7.2, 3H), 0.23 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.9, 133.5, 128.7, 128.5, 126.2, 125.8, 77.3, 39.9, 34.8, 33.3, 18.4, 16.3, −0.24, −0.20. FTIR (cm^{-1}) 3026, 2958, 2875, 1636, 1604, 1496, 1454, 1250, 1095. HRMS calculated for $C_{16}H_{24}OSi$ $(M + H)^+$ m/z 261.1675, found 261.1663.

Representative Methyl Lithium-Induced Silicon−Oxygen Bond Cleavage Followed by Cyclopropanane Formation. Preparation of (2-Vinyl-cyclopropylmethoxymethyl)-benzene (8a). In a 50 mL round-bottom flask, the seven-membered silyloxycycloheptene **5a** (310 mg, 1.18 mmol) was diluted in THF (10 mL). The flask was then flushed of all air and kept under an atmosphere of nitrogen. Then a 1.6 M solution of methyllithium (2.22 mL, 3.55 mmol) was added via syringe. Over the next 15 min the flask contents darkened to a transparent brown-orange. The reaction appeared complete at this point by TLC and was quenched with ammonium chloride. It was stirred for 15 min at room temperature after which the bulk of the THF was rotovapped off. Then the product was extracted with EtOAc (2 × 30 mL) and washed with brine. This methylated intermediate **7c** is stable to silica gel and can be purified before generating the cyclopropane; however, it was shown in subsequent reactions that purification was not necessary for the success of the cyclopropanation reaction. Thus, taking the crude mixture (336 mg, 1.2 mmol) in a 50 mL round-bottom flask, it was diluted in CH_2Cl_2 (10 mL). 2,6-lutidine (198 μL, 1.70 mmol) was added, and the reaction mixture was cooled to −78 °C. Quickly, the triflic anhydride was added to the reaction mixture followed immediately (within five minutes) by a quench Hunig's base (large excess). Again, the color change from yellow to red/purple was observed. Slowly the reaction mixture was allowed to warm to room temperature during which the reaction contents darkened. The product was isolated as a crude residue by removing the solvent under reduced pressure and was purified using a flash chromatography (silica gel, 6% EtOAc in hexanes) to give the enantiopure benzyl vinylcyclopropane **8a** (175 mg, 77%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.35−7.34 (m, 5H), 5.48−5.36 (m, 1H), 5.07 (dd, J = 1.7, 17, 1H), 4.88 (dd, J = 1.7, 10.3, 1H), 4.54 (d, J = 12.0, 1H), 4.53 (d, J = 12.0, 1H), 3.41 (dd, J = 6.6, 10.4, 1H), 3.35 (dd, J = 6.6, 10.4, 1H), 1.38−1.29 (m, 1H), 1.22−1.13 (m, 1H), 0.68 (t, J = 6.9, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 140.7, 138.4, 128.3, 127.7, 127.5, 112.2, 73.2, 72.4, 20.8, 20.2, 11.9. FTIR (cm^{-1}) 3067, 3004, 1720, 1637, 1497, 1454. HRMS (CI) calcd for $C_{13}H_{16}O$ $(M + H)^+$ m/z 189.1279, found 189.1281.

Representative Fluoride Silicon−Oxygen Bond Cleavage Followed by Cyclopropanane Formation. Preparation of *syn*-[2-(2-Methyl-3-vinyl-cyclopropyl)-ethyl]-benzene (10b). To a solution of the *syn*-[1,2]oxasilepine **5c** (23 mg, 0.088 mmol) in anhydrous THF (1 mL) was added HF/Pyridine (50 μL, ~1.9 mmol). The reaction mixture was stirred at room temperature for 10 min and was diluted with Et_2O and washed with H_2O. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product (23 mg, 100%) was directly subjected to the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.32−7.19 (m, 5H), 5.48 (m, 1H), 5.22 (m, 1H), 3.43 (m, 1H), 2.87 (m, 1H), 2.65 (m, 1H), 2.56 (m, 1H), 1.88 (m, 1H), 1.79−1.57 (m, 4H), 0.99 (d, J = 6.9, 3H), 0.24 (d, J = 7.5, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.5, 131.7, 128.64, 128.58, 126.0, 123.8, 75.5, 37.9, 36.0, 32.7, 18.8 (d, J = 13.6), 16.5, −1.3 (d, J = 15.1), −1.4 (d, J = 14.6). FTIR (cm^{-1}) 3586, 3392, 2961, 2930, 2872, 1497, 1455, 1257. HRMS calculated for $C_{16}H_{25}FOSi$ $(M + H)^+$ m/z 281.1737, found 281.1710. To a solution of the crude fluorosilane **9b** (22 mg, 0.079 mmol) in

anhydrous CH_2Cl_2 (1 mL) at −78 °C was added 2,6-lutidine (18 μL, 0.16 mmol) followed by trifluoromethanesulfonic anhydride (20 μL, 0.12 mmol). The reaction was stirred at −78 °C for 25 min and was quenched by H_2O (200 μL) and warmed to room temperature. Et_2O and H_2O were added, and layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes) to give *syn*-3-methyl-2-(2-phenylethyl)-vinylcyclopropane **10b** (9 mg, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.30−7.18 (m, 5H), 5.57 (ddd, J = 17.1, 10.2, 9.3, 1H), 5.09 (ddd, J = 17.1, 2.1, 0.9, 1H), 4.95 (dd, J = 10.2, 1.8, 1H), 2.68 (m, 2H), 1.65 (m, 2H), 1.2 (ddd, J = 4.4, 8.8, 8.8, 1H), 1.05 (d, J = 5.8, 3H), 0.71 (m, 1H), 0.57 (ddq, J = 5.3, 5.3, 5.8, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.7, 138.4, 128.7, 128.4, 125.8, 113.7, 36.1, 31.2, 28.7, 27.3, 21.5, 18.7. FTIR (cm^{-1}) 3083, 2999, 2927, 2860, 1633, 1496, 1454, 1076, 988. HRMS calculated for $C_{14}H_{18}$ $(M + H)^+$ m/z 187.1487, found 187.1463.

Representative Ethyl Ester Reduction and Silyloxy Ring Cleavage with DIBAL. Preparation of *anti*-2-[3-(Dimethyl-silanyl)-propenyl]-5-phenyl-pentane-1,3-diol (13a). A nitrogen-flushed solution of ethyl ester **13c** (100 mg, 0.31 mmol) in methylene chloride (2.5 mL) was cooled to −78 °C, to which was added dropwise a 1 M solution of DIBAL (1.55 mL) via syringe. The reaction was allowed to come to room temperature over 5 h. The reaction was quenched with a saturated solution of Rochelle salt. The resultant salts were filtered and washed with ethyl acetate. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 25% ether in hexanes) to afford **13a** (77 mg, 88%) as a clear oil; crystallization to a white solid occurred upon long periods of standing. Spectra for **13a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.32−7.15 (m, 5H), 5.73 (td, J = 8.7, 11.1, 1H), 5.32 (dd, J = 11.1, 11.0, 1H), 3.90−3.63 (m, 4H), 2.89−2.78 (m, 1H), 2.71−2.61 (m, 1H), 1.89−1.52 (m, 5H), 0.102 (d, J = 3.6, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.0, 130.4, 128.4, 128.4, 125.8, 123.1, 72.8, 65.0, 44.3, 36.4, 32.3, −4.5. FTIR (cm^{-1}) 3305, 3013, 2114, 1604, 1497, 1454. HRMS calculated for $C_{16}H_{26}O_2Si$ $(M + H)^+$ m/z 279.1780, found 279.1770.

Representative Ethyl Ester Reduction with DIBAL. Preparation of *anti*-(2,2-Dimethyl-7-phenethyl-2,3,6,7-tetrahydro-[1,2]oxasilepin-6-yl)-methanol (13c). A nitrogen flushed solution of ethyl ester **13c** (75 mg, 0.24 mmol) in methylene chloride (5 mL) was cooled to −78 °C, to which was added dropwise a 1 M solution of DIBAL (0.53 mL) via syringe. The reaction was closely monitored for disappearance of starting ester. After 2 h at −78 °C the reaction was quenched with a saturated solution of Rochelle salt, and the resultant salts were filtered and washed with ethyl acetate. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 25% ether in hexanes) to afford **13c** as a clear oil. Spectra for **13c**: ^{1}H NMR (300 MHz, CD Cl_3) δ (ppm) 7.31−7.14 (m, 5H), 5.99−5.90 (m, 1H), 5.41 (ddd, J = 11.2, 6.3, 1.2, 1H), 4.03 (td, J = 9.6, 2.4, 1H), 3.66 (d, J = 3.9, 2H), 2.97−2.86 (m, 1H), 2.64−2.46 (m, 2H), 1.99−1.87 (m, 1H), 1.80−1.65 (m, 2H), 1.54−1.44 (m, 2H), 0.20 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.5, 128.6, 128.5, 128.3, 128.2, 125.7, 71.9, 63.2, 50.3, 38.1, 32.4, 17.7, −0.8, −1.1. FTIR (cm^{-1}) 3392, 3025, 1639, 1604, 1496, 1454. HRMS calculated for $C_{16}H_{24}O_2Si$ $(M + H)^+$ m/z 276.1546, found 276.1526.

Representative Cross-Metathesis Reaction of a Homoallylic Alcohol with Allyltrimethylsilane. Preparation of (*E*)- and (*Z*)-*anti*-4-Methyl-1-phenyl-7-(trimethyl-silanyl)-hept-5-en-3-ol (15b). A solution of *anti*-4-methyl-1-phenyl-hex-5-ene-3-ol **4b** (40.2 mg, 0.212 mmol) was diluted in CH_2Cl_2 (5 mL) in a 25 mL flask and warmed to reflux under an atmosphere of nitrogen. The solution was allowed to reflux for 30 min, and then allyltrimethylsilane (134 μL, 0.846 mmol) was added via syringe to the reaction vessel, followed by the solid addition of Grubbs' 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium carbene (9 mg, 5 mol %). The solution immediately took on a transparent rose color and was stirred under reflux. The reaction was complete after 3 h (TLC), and the solution had taken on a clear gold color. The reaction vessel was removed from heat and stirred open to the air for several hours. During this time the solution darkened to an opaque brown color. The reaction volume was reduced to 1 mL by evaporation, and the residue was flushed through a plug of silica gel using CH_2Cl_2 (5 mL) followed by 16% EtOAc in hexanes (10 mL). The resulting light brown solution was concentrated in vacuo and purified by flash column chromatography through a pipet column (silica gel, 6% EtOAc in hexanes) to give an inseparable mixture of *E* and *Z* isomers (∼92:8) **15b** (50.1 mg, 86%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) −CH(OH)CH(C**H$_3$**)CH−: ***E*-isomer** 0.99 (d, J = 7.0, 3H), ***Z*-isomer** 0.95 (d, J = 6.7, 3H); −Si(C**H$_3$**)$_3$: **(*E*)** 0.01 (s, 9H), **(*Z*)** 0.02 (s, 9H). All Peaks: ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.5, 130.1, 129.2, 128.4, 128.3, 125.7, 74.7, 74.3, 43.8, 37.8, 36.1, 35.8, 32.5, 32.2, 32.1, 23.0, 18.9, 17.1, 16.9, −1.8, −2.0. HRMS calculated for $C_{17}H_{28}OSi$ $(M + H)^+$ m/z 277.1988, found 277.1997.

Acknowledgment. This paper is dedicated to the memory of Arthur G. Schultz. We gratefully acknowledge support from the National Science Foundation through an Early Career Award (CHE97-33253). This work has also been supported by the Petroleum Research Fund as administered by the American Chemical Society (31817-G1). F.C.E. acknowledges a Rohm & Haas Graduate Fellowship (2000-2001; UND). M.J.S. acknowledges an Amoco Graduate Fellowship (2000−2001; UND). R.E.T. is an Eli Lilly Grantee award recipient.

Supporting Information Available: Full characterization data for compounds **4a−f, 5a**, **5b**, **5d−f**, **9a**, **10a**, **10c−e**, **13b, 13d, 14a**, **14b**, **14c**, **14d**, **15a**, **15c−f** and ^{1}H- and ^{13}C NMR spectra for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0037163