Studies on the Diastereoselective Preparation of Bis-cyclopropanes

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The identification of two natural products, FR-900848 and U-106305, has stimulated interest concerning the relationship between configurational isomerism, conformational isomerism, and biological activity of polycyclopropanes. Efforts to investigate the relationship between configurational and conformational isomerism through molecular modeling suggest that significantly different three-dimensional structures will result from unique primary structures. Any effort to address these issues demands that stereoselective methods for the preparation of polycyclopropanes be developed. We have investigated the application of zinc−carbenoid cyclopropanation in the presence of chiral dioxaboralanes to the preparation of eight stereochemically unique bicyclopropanes. The *trans*-vinylcyclopropane starting materials demonstrated very little substrate-induced stereoselectivity, while the *cis*-vinylcyclopropane demonstrates modest to excellent stereocontrol. A model for the substrate-based stereocontrol is proposed. We also used the spectroscopic data gathered in this investigation to probe the substrate-mediated stereocontrol in the rhodium(II)-catalyzed cyclopropanation of vinylcyclopropanes with ethyl diazoacetate.

The recent identification of two novel polycyclopropanated natural products, FR-900848 (**1**) and U-106305 (**2**), has aroused our interest in developing strategies for the stereoselective preparation of polycyclopropanated fatty amides. Reported by the Fujisawa Company in 1990, FR-900848 has attracted attention due to its combination of unusual biological activity and unprecedented structure.[1] FR-900848 (**1**) contains a 5,6-dihydrouridine moiety, a 5′-deoxy-5′-amino ribose, and a remarkable fatty amide side chain possessing five cyclopropane units, four of which are located consecutively. At the time of its isolation, no stereochemical assignment had been made for the multiple stereogenic centers on the fatty amide; however, recent efforts by Falck and by Barrett have demonstrated that the fatty amide chain possesses a repeating *trans*-*syn*-*trans*-polycyclopropane network.[2] This information was utilized in two successful total syntheses of FR-900848.[3]

The isolation of a second member of the polycyclopropanated fatty amide natural product family was reported in 1995.[4] This natural product, U-106305 (**2**), is an inhibitor of cholesteryl ester transfer protein (CEPT), an enzyme responsible for the redistribution of cholesteryl esters. The structural analogy of U-106305 to FR-900848 suggested a similar *trans*-*syn*-stereochemistry. This expectation was confirmed by a recent total synthesis.[5]

Even though the preparation of polycyclopropanes (chains of cyclopropane rings connected by a single σ bond) is not a recent phenomenon,[6] many studies on the asymmetric synthesis of polycyclopropanes have been stimulated by the identification of these two natural products.[2,3,5,7] Unlike most of the early synthetic approaches to polycyclopropanes, efforts directed toward the preparation of FR-900848 (**1**), U-106305 (**2**), or analogous polycyclopropanes require that the multiple *cis*-*trans*- and *syn*-*anti*-stereochemical relationships be controlled. It is this mandate of stereocontrol that makes the preparation of polycyclopropanes particularly challenging. We report here the details of our investigation into the diastereoselective preparation of bis-cyclopropanes. We also utilize the unique spectroscopic data of each individual bis-cyclopropane to investigate the stereoselectivity of bis-cyclopropane formation through the use of rhodium carbenoids.

Results and Discussion

Our interest in studying the relationships of polycyclopropane configuration and conformation to the chemistry and biochemistry of polycyclopropanated fatty acids demanded access to all possible stereochemical relation-

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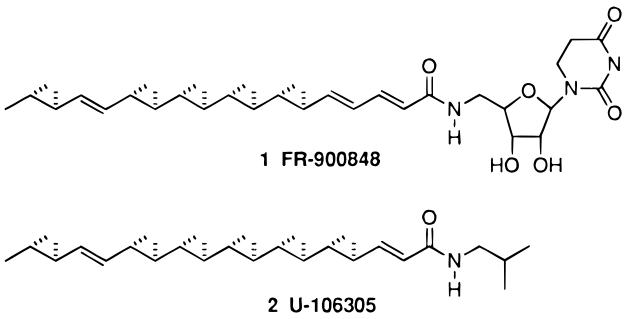
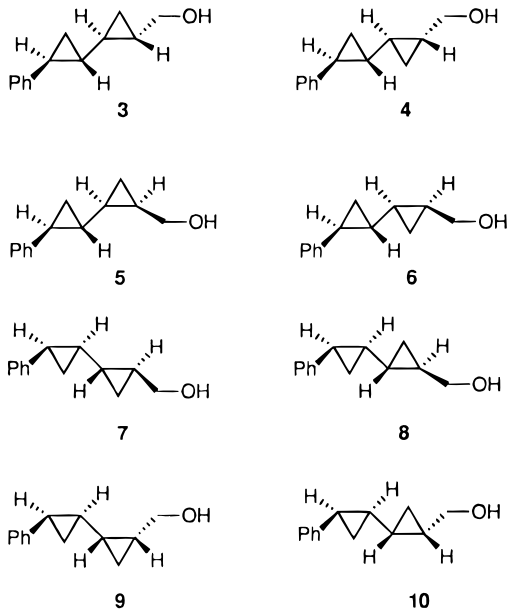


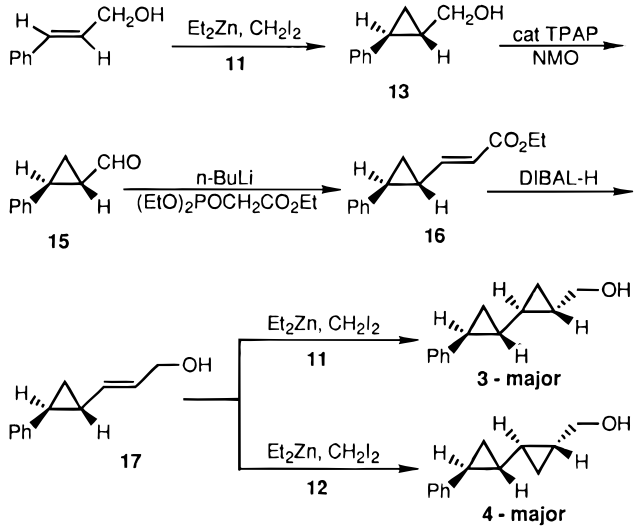
ships. We were interested in developing an iterative strategy by which we could prepare any isomeric combination of cyclopropanes while efficiently controlling their diastereomeric relationship. We set as our goal the preparation of the eight bis-cyclopropane stereoisomers **3**−**10** using a stereoselective, iterative process. The successful preparation of these eight stereoisomers would demonstrate the likely utility of this iterative approach in the preparation of diverse stereoisomeric polycyclopropanes.



Retrosynthetic analysis of bis-cyclopropanes **3**−**10** suggests that suitable precursors would be allylic alcohols obtained by reduction of an ester. The generation of diastereomerically enriched bis-cyclopropanes from these allylic alcohols requires that a methylene unit be incorporated in a diastereofacially selective fashion with the most likely source of the unsubstituted methylene unit arising from a metallocarbenoid. The crucial selection of either the *cis*- or *trans*-stereochemistry for the second cyclopropane ring can be controlled through formation of appropriate olefin stereochemistry utilizing Horner−Emmons reaction variations. Although this *E* or *Z* stereocontrol is not always trivial, once established, the stereospecific zinc−carbenoid reaction will generate the respective *trans*- or *cis*-cyclopropane. Therefore, the greatest challenge of preparing diastereomerically enriched polycyclopropanes lies not in the control of *cis*- or *trans*-stereochemistry, but in the efficient control of the relative *syn*- or *anti*-stereochemistry.

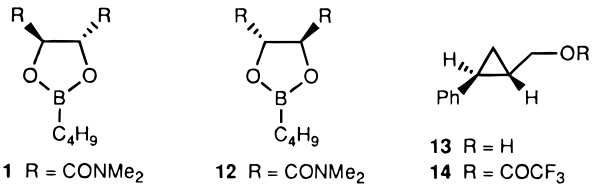
Our initial investigations on the formation of bis-cyclopropanes from allylic alcohols was performed on racemic allylic alcohols generated in a fashion similar to

Scheme 1



Scheme 1. Although we commenced our studies on the cyclopropanation of racemic allylic alcohols by utilizing the samarium-promoted methodology of Molander and Haring,[8] better yields of bis-cyclopropanes were obtained with the Furukawa modification of the Simmons−Smith reaction.[9,10] In both cases, it was demonstrated that the stereoselective incorporation of the second cyclopropane ring while relying on the initial cyclopropane's stereocenters was ineffective. Therefore, it was believed that the stereoselective preparation of bis-cyclopropanes **3**−**10** could only be accomplished through the use of a reagent-stereocontrolled process.

We began to explore cyclopropanation methods that utilize stereocontrolling elements other than the preexisting cyclopropane stereocenters. The use of a reagent-controlled process for bis-cyclopropane formation requires that the absolute stereochemistry be controlled in the first cyclopropanation event. Although many methods exist for the asymmetric incorporation of individual cyclopropanes,[11] we eventually turned to the recently reported methodology of Charette and co-workers in which a chiral noncovalently bound dioxaboralane derivative is utilized as a directing group in the Furukawa cyclopropanation.[12] Both high yields and high enantiomeric excesses have been reported when using an L-tartrate-derived dioxaboralane **11** as the chiral inducing agent. Dioxaboralane **11** is formed from *n*-butylboronic acid and (*R*,*R*)-(+)-*N*,*N*,*N*′,*N*′-tetramethyltartardiamide,



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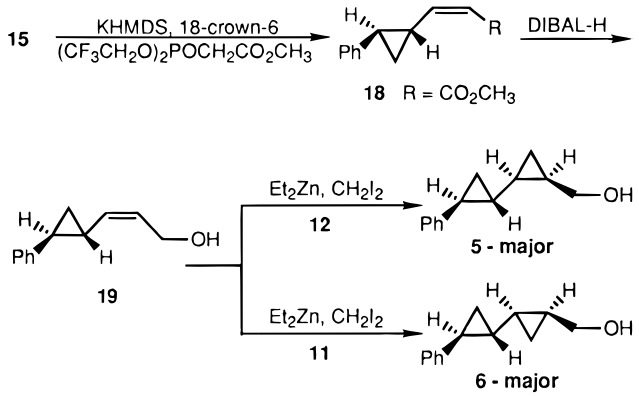
(12) (a) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651. (b) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081.

Scheme 2



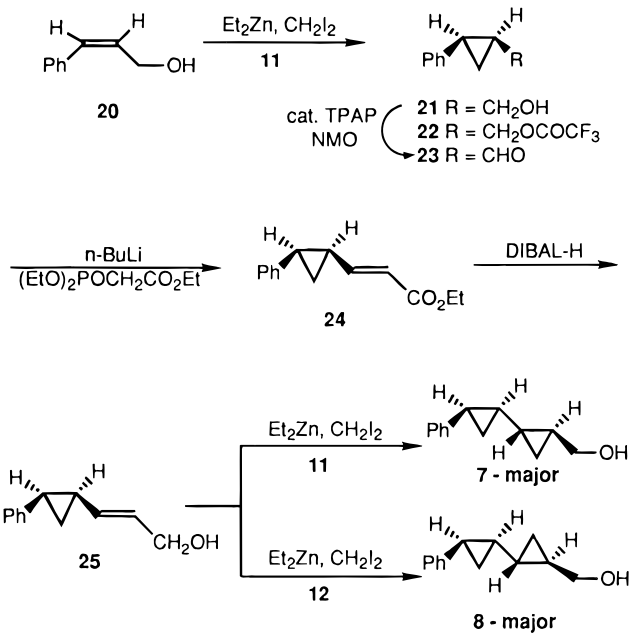
while the enantiomeric D-tartrate-derived dioxaboralane **12** is generated from the (*S*,*S*)-tartaramide. Cyclopropanation of cinnamyl alcohol via this strategy resulted in the efficient, enantioselective (89% ee) preparation of *trans*-2-phenylcyclopropylmethanol (**13**) (Scheme 1). Chiral GC analysis of the trifluoroacetate derivative **14** using a trifluoroacetyl-derivatized γ-cyclodextrin column was performed to determine the ratio of enantiomers. The data received from the chiral chromatography proved to be consistent with the enantiomeric excess estimated using published optical rotation values.[13]

Oxidation of the enantiomerically enriched (hydroxymethyl)cyclopropane (**13**) to aldehyde **15** with catalytic tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide[14] was followed by formation of the α,β-unsaturated ethyl ester **16** using a classical Horner−Emmons reaction. It was possible to separate the minor *cis*-product from the desired *trans*-isomer by careful chromatography on silica.[15] Following the DIBAL-H reduction of **16**, the enantiomerically enriched bis-cyclopropane precursor allylic alcohol **17** was in hand.

Application of Charette's cyclopropanation protocol to the allylic alcohol **17** made possible the preparation of the *trans-syn-trans*-bis-cyclopropane **3** in 67% yield (ratio **3**:**4**; 10:1) using the L-tartrate-derived dioxaboralane **11** and the *trans-anti-trans*-bis-cyclopropane **4** in 72% (ratio **3**:**4**; 1:10) yield using the D-tartrate-derived dioxaboralane **12**. A third cyclopropanation was conducted on chiral **17** in the absence of dioxaboralane. By comparison of the ^{13}C-NMR data generated from the reagent-controlled processes, the anti diastereomer **4** was identified as the major product (ratio **3**:**4**; 1:1.3) in the substrate-stereocontrolled cyclopropanation reaction.[16]

The formation of *trans-cis*-bis-cyclopropanes **5** and **6** required the incorporation of a *Z*-olefin into the allylic alcohol **19** (Scheme 2). The *Z*-selective Horner−Emmons reaction developed by Still and co-workers[17] proceeded with excellent selectivity to give optically active **18**. The *E* and *Z* isomers were separated, and a subsequent DIBAL-H reduction gave the desired allylic alcohol **19**. We again performed the two reagent-controlled and one substrate-controlled cyclopropanation reactions on compound **19**. The *syn*-diastereomer **5** was produced utilizing the D-tartrate-derived dioxaboralane **12** and the *anti*-diastereomer **6** using the L-tartrate-derived dioxaboralane **11**. Each substrate-mediated reaction gave a modest diastereomeric excess, while cyclopropanation in the absence of chiral dioxaboralane provided once again very little substrate-based stereocontrol.

Scheme 3

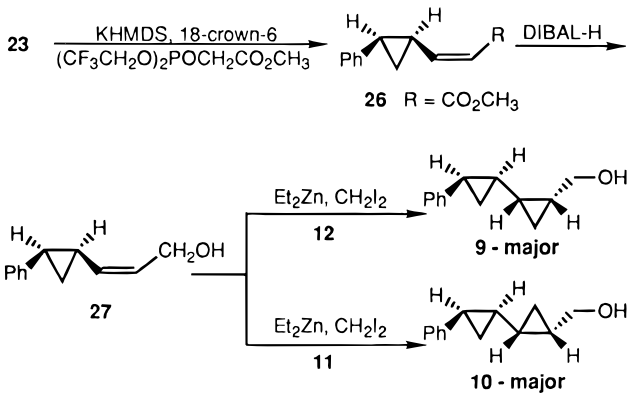


In order to prepare the *cis*-cyclopropane precursors **25** and **27** for the four remaining bis-cyclopropanes **7**−**10**, (*Z*)-3-phenyl-2-propenol **20** was synthesized by the method of Pelter.[18] This allylic alcohol was subjected to cyclopropanation in the presence of L-dioxaboralane **11** to give the (hydroxymethyl)cyclopropane (**21**) in 90% yield (Scheme 3). The optical purity (83% ee) of the trifluoroacetyl derivative **22** was determined by chiral GC analysis, since conflicting optical rotation values had been reported in the literature.[19,20] Oxidation of **21** with TPAP/NMO gave the enantiomerically enriched aldehyde **23**, which was subjected to *E*-selective Horner−Emmons reaction conditions to yield the α,β-unsaturated ester **24**. Purification of **24** by chromatography and reduction with DIBAL-H provided the allylic alcohol **25**.

The diastereomerically enriched bis-cyclopropanes **7** and **8** were produced by directed cyclopropanations on **25** utilizing the L- and D-tartrate-derived dioxaboralanes **11** and **12**, respectively. It was significant to note that the *cis-anti-trans*-bis-cyclopropane **8** was formed quite selectively (ratio of **7**:**8**; 1:>10), while the preparation of the *cis-syn-trans*-bis-cyclopropane **7** was poorly stereoselective (ratio of **7**:**8**; 2.5:1). Cyclopropanation of the allylic alcohol in the absence of dioxaboralane demonstrated that the existing cyclopropane stereocenters exert significant influence on the resulting stereochemistry favoring the formation of the *cis-anti-trans*-bis-cyclopropane **8** (ratio of **7**:**8**; 1:9). Therefore, the use of D-tartrate-derived dioxaboralane **12** in the cyclopropanation of **25**

(13) Yasui, S. C.; Keiderling, T. A. *J. Am. Chem. Soc.* **1987**, *109*, 2311.
(14) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(16) The ratio of isomers was determined by acquisition of a ^{13}C-NMR spectrum such that full relaxation of all carbons was assured and integration of the corresponding ^{13}C resonances between the two diastereomers. When it was impossible to determine the corresponding ^{13}C resonances between the two diastereomers, averages of multiple resonances were compared.
(17) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(18) Pelter, A.; Ward, R. S.; Little, G. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2775.
(19) Scholl, B.; Hansen, H.-J. *Helv. Chim. Acta* **1986**, *69*, 1936.
(20) Aratani, T.; Nakanisi, Y.; Nozaki, H. *Tetrahedron* **1970**, *26*, 1675.

Scheme 4



to form the *cis-anti-trans*-bis-cyclopropane **8** was essentially unnecessary since it merely duplicated the substrate-based selectivity. The application of the L-tartrate-derived dioxaboralane **11** to the cyclopropanation of **25** resulted in mismatched stereodirecting elements that made the preparation of bis-cyclopropane **7** the least selective in this series.[21]

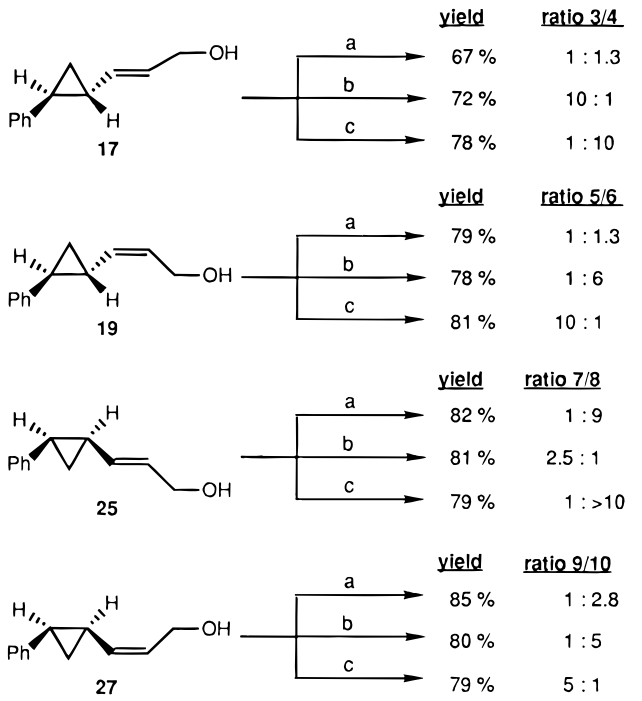
The allylic alcohol **27**, the precursor to the final two bis-cyclopropanes **9** and **10**, was prepared by application of a *Z*-selective HWE reaction to aldehyde **23**, followed by reduction with DIBAL-H (Scheme 4). The *syn*- and *anti*-bis-cyclopropanes **9** and **10** were obtained by application of Charette's cyclopropanation methodology utilizing the dioxaboralanes **12** and **11**, respectively. Some substrate-based stereocontrol was observed in the absence of dioxaboralane (ratio of **9**:**10**; 1:2.8), although it was less pronounced than in the formation of bis-cyclopropanes from compound **25**.

Discussion

The stereoselectivity observed in bis-cyclopropane formation is summarized in Table 1. While most of the bis-cyclopropane isomers were formed in modest to good diastereoselectivities through the application of a reagent-controlled process, there are remarkable variations in the product distributions in the substrate-controlled reactions. An understanding of the stereoselectivity of the substrate-directed reactions requires an appreciation of the multiple conformers that exist in these vinyl cyclopropane systems.[22] However, it would be naive to assume that the selective formation of the *anti*-isomer in all of the substrate-stereocontrolled reactions could be explained by comparison of the low energy *trans*-conformation alone. In fact, formation of the favored *anti*-isomers appears to be at first analysis of the result of attack on the most sterically hindered face of the olefin.

The *anti*-preferences observed in the substrate-stereocontrolled reactions of the *trans*-cyclopropanes **17** and **19** were small, yet reproducible. A strong *anti*-preference observed in analogous vinylcyclopropane systems by Barrett was proposed to be the result of an interaction between the electron-rich cyclopropane σ-bond and alkene π-system.[7e] Similar analysis of compounds **17** and **19** predicts the observed *anti*-preference, although it is

Table 1. Yields and Diastereoselectivities in the Formation of Bis-cyclopropanes 3−10[a]



[a] Reagents and conditions: (a) Et_2Zn, CH_2I_2; (b) Et_2Zn, CH_2I_2, **11**; (c) Et_2Zn, CH_2I_2, **12**.

significantly reduced by the influence of the proximal hydroxyl group.

The significant *anti*-selectivity observed in the cyclopropanation of **25** and **27** is likely due to steric interactions between the zinc−alcohol complex and the pendent phenyl ring. Rotation about the cyclopropyl−olefin bond in order to alleviate this steric interaction results in carbenoid addition providing the *anti*-isomers. The *cis*-*Z*-isomer **27** experiences destabilizing sterics interactions in both of its gauche conformers, which results in an attenuation of this *anti*-selectivity.

Rhodium-Catalyzed Chemistry

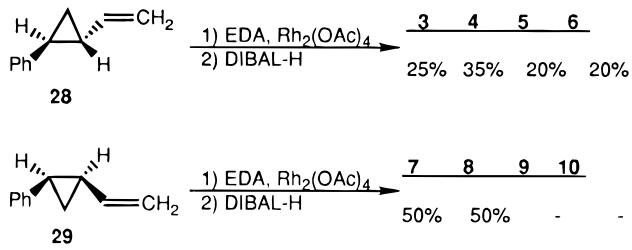
The bis-cyclopropane isomer prepared with the least selectivity through the reagent-mediated stereocontrolled process described above was the *cis-syn-trans*-isomer **7**. Although we have been able to attribute this difficulty in forming the *syn*-isomer to the overwhelming substrate-based *anti*-selective cyclopropanation reaction, we desired to prepare bis-cyclopropane **7** in a more selective fashion. Many synthetic methods exist which promote the formation of cyclopropanes from olefins. One potential synthetic route to bis-cyclopropane formation would involve transition metal-mediated addition of ethyl diazoacetate (EDA) to an appropriate vinylcyclopropane. Since the *cis*-cyclopropanes **25** and **27** showed a significant preference for *anti*-addition and since *trans*-cyclopropane formation is preferred in the rhodium-catalyzed reactions involving diazo esters,[23] we predicted that compound **7** might be formed selectively through the rhodium(II) diacetate mediated addition of ethyl diazoacetate to the *cis*-vinylcyclopropane (**29**).

(21) We have recently reported a substrate-mediated sulfur−ylide strategy in which enhanced stereoselectivity is observed in the preparation of **7**. Cebula, R. E. J.; Hanna, M. R.; Theberge, C. R.; Verbicky, C. A.; Zercher, C. K. *Tetrahedron Lett.* Accepted for publication.

(22) Runge, W. In *The Chemistry of the Cyclopropyl Group*; John Wiley and Sons: New York, 1987; Part 1, p 66.

(23) (a) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348. (b) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44. (c) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.

Scheme 5



The racemic aldehydes **15** and **23** were converted to vinylcyclopropanes (**28**) and (**29**), which were exposed to ethyl diazoacetate (EDA) and rhodium(II) acetate to provide a mixture of bis-cyclopropyl ethyl esters[24,25] (Scheme 5). The reaction products were reduced with DIBAL-H and purified by chromatography, and the ^{13}C-NMR spectrum of the rhodium-carbenoid derived bis-cyclopropanes was compared to the spectra of compounds **3**−**10** in order that the approximate product ratios could be elucidated (Scheme 5).

When the *trans*-vinylcyclopropane (**28**) was exposed to ethyl diazoacetate in the presence of rhodium(II) acetate and reduced, the *trans-trans*-bis-cyclopropanes **3** and **4** were formed as the major products (60%) in a 1:1.4 ratio. The *trans-cis*-bis-cyclopropane isomers **5** and **6** made up 40% of the product mixture in a ratio of nearly 1:1. Doyle has proposed that the preferred *trans*-selectivity in rhodium(II) catalyzed cyclopropanations is the result of electronic stabilization of the transition state, which leads to the *trans*-cyclopropane products through the interaction of the developing electrophilic carbon of the olefin with the nucleophilic carbonyl oxygen. Our results not only are in concert with Doyle's model, but they also reinforce our previous observation that little olefin facial selectivity is observed with the *trans*-substituted vinylcyclopropanes.

When the *cis*-vinylcyclopropane (**29**) was exposed to these same rhodium(II)-mediated reaction conditions, equal amounts of the *cis-trans*-bis-cyclopropanes **7** and **8** were observed. While it is true that increasing the steric bulk of monosubstituted olefins has been shown to lead to enhanced *trans*-selectivity,[23] we were intrigued that the newly formed cyclopropane rings in **7** and **8** were exclusively *trans*. Although this result appears to stand in contrast to the results of our study with the *trans*-vinylcyclopropane **28**, we feel the differences in product selectivity can be accurately ascribed to the intrinsic steric bulk differences of the *trans*- and *cis*-cyclopropane substituents of **28** and **29**. Nevertheless, we were surprised that no facial (*syn-anti*) selectivity was observed in the reaction of **29**. The reason for no facial selectivity is not perfectly clear; however, steric interaction of the carbenoid's carboxy ester functionality with the pendent cyclopropane would be expected to destabilize contribution of either gauche-conformer. The resulting *trans*-conformational preference would allow nearly equal access to the two faces and result in equal amounts of *syn*- and *anti*-isomers.

Conclusions

We have demonstrated that the preparation of diverse bis-cyclopropanes is possible through the application of a reagent-controlled process by the successful preparation of eight unique bis-cyclopropane isomers. The efficiency of this reagent-controlled approach suggests that the preparation of many polycyclopropane isomers should be possible. We have been able to use these diastereomerically enriched bis-cyclopropanes to analyze the efficiency of bis-cyclopropane formation through the rhodium-catalyzed diazoester addition to olefins. The various factors that control the diastereoselectivity of these various processes are not entirely clear, but the conformational preferences of the *cis*- and *trans*-vinylcyclopropanes have been proposed as important factors.

Experimental Section

General Experimental Procedures. Unless otherwise indicated, all reagents and solvents were commercially available and used without further purification. Tetrahydrofuran (THF), diethyl ether, and dimethoxyethane (DME) were distilled from sodium/benzophenone. Methylene chloride (CH_2Cl_2) was distilled from phosphorus pentaoxide, dimethylformamide (DMF) from calcium hydride, and dimethyl sulfoxide (DMSO) from calcium hydride and stored over 4 Å sieves. All reactions were performed under a nitrogen atmosphere using magnetic stirrers unless indicated otherwise. Proton spectra were obtained at 360 MHz, and ^{13}C spectra were obtained at 90 MHz. TLC plates supplied by EM (Merck) of silica gel 60 F_{254} at 250 mm thickness were used and were visualized with shortwave UV and anisaldehyde stain. Chromatography was conducted according to the procedure of Still[17] using Baker 40 mm silica gel. The term "concentrated under reduced pressure" refers to the use of a rotary evaporator equipped with a water aspirator. All optical rotations were conducted with samples in chloroform solution (unless indicated otherwise), and concentrations are given in g/mL. Mass spectral analyses were carried out by chemical ionization using NH_3 as the carrier gas. High-resolution mass spectrometry was performed by the University of California at Riverside Mass Spectrometry Facility.

Representative Procedure for *E*-Olefin Preparation. To a round-bottom flask was added 1.67 g (7.44 mmol) of triethyl phosphonoacetate and 150 mL of THF. The solution was stirred vigorously at 0 °C while 4.65 mL of a 1.6 M solution of *n*-BuLi in hexanes (7.44 mmol) was added. The reaction was stirred for 10 min before 0.903 g (6.20 mmol) of the appropriate aldehyde (**15** or **23**) in 30 mL of THF was added via cannula. The reaction was stirred at room temperature for 2.5 h and the reaction mixture quenched with saturated aqueous citric acid. The organic layer was removed, and the aqueous portion was washed with diethyl ether. The combined organic solutions were dried over anhydrous magnesium sulfate, filtered through Celite, and concentrated under reduced pressure to give a viscous yellow oil. The crude oil was taken up in diethyl ether, washed with water, dried with $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to give a yellow oil.

Ethyl (*E*)-3-(*trans*-(1*R*,2*S*)-2-Phenylcyclopropyl)propenoate (16). The crude oil was chromatographed on silica (200:1 hexanes:EtOAc) to yield pure **16** (72%) as a colorless oil (and a small portion of the slightly impure *Z*-isomer (3%) as a yellow oil) (22:1 ratio): $[\alpha]_D = +142.1°$ (*c* 0.0071); ^1H NMR δ ($CDCl_3$) 7.31−7.01 (m, 5H), 6.59 (dd, 1H, J = 9.8, 15.4 Hz), 5.89 (d, 1H, J = 15.4 Hz), 4.18 (q, 2H, J = 7.1 Hz), 2.17 (ddd, 1H, J = 4.1, 6.1, 9.0 Hz), 1.81 (dddd, 1H, J = 4.1, 5.3, 8.4, 9.8), 1.43 (ddd, 1H, J = 5.2, 6.1, 8.4 Hz), 1.29 (ddd, 1H, J = 5.2, 5.3, 9.0 Hz), 1.28 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ ($CDCl_3$) 166.6, 151.6, 140.7, 128.4, 126.1, 125.8, 118.8, 60.1, 26.8, 26.7, 17.7, 14.3; HRMS calcd for $C_{14}H_{20}NO_2$ ($M + NH_4^+$) 234.1494, found 234.1488.

Ethyl (*E*)-3-(*cis*-(1*R*,2*R*)-2-Phenylcyclopropyl)propenoate (24). The oil was subjected to flash chromatography (100:1 hexanes:EtOAc) to yield **24** (56%) as a colorless oil (and a small portion of the *Z*-isomer (9%) as an impure yellow oil) (6:1 ratio): $[\alpha]_D = -29.2°$ (*c* 0.0093); ^1H NMR δ ($CDCl_3$) 7.32−7.16 (m, 5H), 6.25 (dd, 1H, J = 10.5, 15.4 Hz), 5.91 (d, 1H, J

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= 15.4 Hz), 4.07 (q, 2H, *J* = 7.2 Hz), 2.57 (ddd, 1H, *J* = 6.8, 8.4, 8.5 Hz), 1.99 (dddd, 1H, *J* = 5.3, 8.4, 8.5, 10.5 Hz), 1.45 (ddd, 1H, *J* = 5.3, 8.4, 8.4 Hz), 1.27 (ddd, 1H, *J* = 5.3, 5.3, 6.8 Hz), 1.19 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ ($CDCl_3$) 166.2, 149.9, 137.4, 129.0, 128.3, 126.6, 120.2, 59.9, 25.5, 22.4, 14.2, 13.6; HRMS calcd for $C_{14}H_{20}NO_2$ (M + NH_4^+) 234.1494, found 234.1490.

Representative Procedure for *Z*-Olefin Preparation. To a flask were added 5.76 g (21.8 mmol) of 18-crown-6 and 1.52 g (4.8 mmol) of bis(2,2,2-trifluoroethyl) [(methoxycarbonyl)methyl]phosphonate. The flask was charged with 50 mL of THF, cooled to −78 °C, and stirred vigorously while 9.6 mL (4.8 mmol) of a 0.5 M solution of potassium bis(trimethylsilyl)-amide in toluene was added. The reaction was allowed to stir for 10 min before 638 mg (4.36 mmol) of the appropriate aldehyde (**15** or **23**) in 20 mL of THF was added via cannula. The reaction was allowed to stir at room temperature for 2 h and quenched with saturated aqueous ammonium chloride. The THF layer was removed and the aqueous portion extracted with diethyl ether. The combined organics were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to give a yellow oil.

Methyl (*Z*)-3-(*trans*-(1*R*,2*S*)-2-Phenylcyclopropyl)propenoate (18). The crude oil was subjected to flash chromatography (100:1 hexanes:EtOAc), which yielded ester **18** (71%) as a yellow oil (and a small portion of the impure *E*-isomer (7%)) (10:1 ratio): $[\alpha]_D$ = +16.8° (*c* 0.0071); ^{1}H NMR δ ($CDCl_3$) 7.3−7.1 (m, 5H), 5.75 (d, 1H, *J* = 11.4 Hz), 5.64 (dd, 1H, *J* = 11.4, 11.4 Hz), 3.70 (s, 3H), 3.25 (dddd, 1H, *J* = 4.2, 5.0, 11.0, 11.4 Hz), 2.10 (ddd, 1H, *J* = 4.2, 6.1, 9.0 Hz), 1.44 (ddd, 1H, *J* = 5.0, 6.1, 11.0 Hz), 1.20 (ddd, 1H, *J* = 5.0, 5.1, 9.0 Hz); ^{13}C NMR δ ($CDCl_3$) 167.3, 153.1, 140.8, 128.4, 126.1, 126.0, 117.1, 51.0, 27.2, 23.9, 18.6; HRMS calcd for $C_{13}H_{18}NO_2$ (M + NH_4^+) 220.1338, found 220.1347.

Methyl (*Z*)-3-(*cis*-(1*R*,2*R*)-2-Phenylcyclopropyl)propenoate (26). The crude oil was subjected to chromatography (100:1 hexanes:EtOAc), which provided ester **26** (64%) as a yellow oil (and a small portion of the *E*-isomer (4%) as an impure oil) (15:1 ratio): $[\alpha]_D$ = −335.4° (*c* 0.0061); ^{1}H NMR δ ($CDCl_3$) 7.32−7.17 (m, 5H), 5.63 (dd, 1H, *J* = 0.6, 11.3 Hz), 5.38 (dd, 1H, *J* = 11.3, 11.3 Hz), 3.72 (s, 3H), 3.29 (ddddd, 1H, *J* = 0.6, 5.3, 8.3, 8.3, 11.3 Hz), 2.65 (ddd, 1H, *J* = 6.7, 8.3, 8.3 Hz), 1.51 (ddd, 1H, *J* = 5.2, 8.3, 8.3 Hz), 1.22 (ddd, 1H, *J* = 5.2, 5.3, 6.7 Hz); ^{13}C NMR δ ($CDCl_3$) 167.5, 151.5, 137.8, 129.3, 128.3, 126.5, 117.9, 51.0, 25.8, 19.5, 14.2; HRMS calcd for $C_{13}H_{15}O$ (M + H^+) 203.1072, found 203.1066.

Representative Procedure for DIBAL-H Reductions. A flask that contained 406 mg (1.87 mmol) of the appropriate ester (**16**, **18**, **24**, or **26**) was charged with 25 mL of THF, cooled to −78 °C, and stirred vigorously during slow addition of 2.61 mL (3.92 mmol) of a 1.5 M solution of DIBAL-H in toluene. The reaction was allowed to warm to room temperature, cooled in an ice−water bath, and quenched by the slow sequential addition of 0.2 mL of H_2O, 0.2 mL of 2 N NaOH, 0.2 mL of H_2O, and 0.2 mL of 2 N NaOH. The quenched reaction was allowed to stir overnight, dried with $MgSO_4$, filtered through Celite, and concentrated under reduced pressure.

(*E*)-3-(*trans*-(1*R*,2*S*)-2-Phenylcyclopropyl)-2-propenol (17). The crude oil was purified by chromatography (10:1 hexanes:EtOAc) to yield compound **17** (72%) as a colorless oil: $[\alpha]_D$ = +224° (*c* 0.0086); ^{1}H NMR δ ($CDCl_3$) 7.23−6.96 (m, 5H), 5.67 (dt, 1H, *J* = 6.1, 15.3 Hz), 5.33 (ddt, 1H, *J* = 1.2, 8.6, 15.3 Hz), 4.03 (dd, 2H, *J* = 1.2, 6.1 Hz), 1.85 (ddd, 1H, J= 4.4, 5.5, 8.8 Hz), 1.62 (dddd, 1H, *J* = 4.4, 5.5, 8.5, 8.6 Hz), 1.35 (s, 1H), 1.14 (ddd, 1H, *J* = 5.1, 5.5, 8.5 Hz), 1.02 (ddd, 1H, *J* = 5.1, 5.5, 8.8 Hz); ^{13}C NMR δ ($CDCl_3$) 142.1, 135.2, 128.3, 127.3, 125.61, 125.59, 63.4, 26.1, 25.1, 16.7.

(*Z*)-3-(*trans*-(1*R*,2*S*)-2-Phenylcyclopropyl)-2-propenol (19). The crude oil was purified by flash chromatography (10:1 hexanes:EtOAc) to yield compound **19** (80%) as a colorless oil: $[\alpha]_D$ = +115° (*c* 0.0196); ^{1}H NMR δ ($CDCl_3$) 7.30−7.04 (m, 5H), 5.59 (dt, 1H *J* = 6.8, 10.8 Hz), 5.07 (dd, 1H, *J* = 9.8, 10.8 Hz), 4.28 (d, 2H, *J* = 6.8 Hz), 1.92 (ddd, 1H, *J* = 4.3, 5.7, 8.6 Hz), 1.84 (dddd, 1H, *J* = 4.3, 5.3, 8.5, 9.8 Hz), 1.39 (s, 1H), 1.27 (ddd, 1H, *J* = 5.0, 5.7, 8.5 Hz), 1.05 (ddd, 1H, *J* = 5.0, 5.3, 8.6); ^{13}C NMR δ ($CDCl_3$) 141.9, 135.4, 128.3, 127.3, 125.8, 125.7, 59.0, 25.3, 22.7, 17.3.

(*E*)-3-(*cis*-(1*R*,2*R*)-2-Phenylcyclopropyl)-2-propenol (25). The crude oil was purified by flash chromatography (10:1 hexanes:EtOAc) to yield compound **25** (90%) as a colorless oil: $[\alpha]_D$ = −37.9° (*c* 0.0079); ^{1}H NMR δ ($CDCl_3$) 7.29−7.13 (m, 5H), 5.72 (dt, 1H, *J* = 6.1, 15.3 Hz), 4.98 (dd, 1H, *J* = 9.3, 15.3 Hz), 3.88 (d, 2H, *J* = 6.1 Hz), 2.34 (ddd, 1H, *J* = 5.5, 8.6, 8.6 Hz), 1.84 (dddd, 1H, *J* = 5.5, 8.6, 8.6, 9.3 Hz), 1.35 (s, 1H), 1.25 (ddd, 1H, *J* = 5.5, 8.6, 8.6 Hz), 1.02 (ddd, 1H, *J* = 5.5, 5.5, 5.5 Hz); ^{13}C NMR δ ($CDCl_3$) 141.9, 135.4, 128.4, 127.3, 125.7, 125.6, 63.4, 23.2, 21.6, 11.6.

(*Z*)-3-(*cis*-(1*R*,2*R*)-2-Phenylcyclopropyl)-2-propenol (27). The crude oil was purified by chromatography (10:1 hexanes:EtOAc) to yield alcohol **27** (90%) as a colorless oil: $[\alpha]_D$ = −154.0° (*c* 0.0224 CCl_4); ^{1}H NMR δ ($CDCl_3$) 7.30−7.15 (m, 5H), 5.50 (dt, 1H, *J* = 6.8, 10.9 Hz), 4.83 (dd, 1H, *J* = 9.8, 10.9 Hz), 4.28 (d, 2H, *J* = 6.8 Hz), 2.39 (ddd, 1H, *J* = 5.4, 8.4, 8.4 Hz), 2.01 (dddd, 1H, *J* = 5.4, 8.4, 8.4, 9.8 Hz), 1.33 (ddd, 1H, *J* = 5.2, 8.4, 8.4 Hz), 1.28 (s, 1H), 1.02 (ddd, 1H, *J* = 5.2, 5.4, 5.4 Hz); ^{13}C NMR δ ($CDCl_3$) 138.5, 132.4, 129.0, 128.9, 128.0, 125.9, 58.8, 23.4, 17.3, 12.5.

Representative Procedure for Furukawa-Modified Simmons−Smith Cyclopropanation Utilizing a Tartrate-Derived Dioxaboralane. A round-bottom flask that contained 25 mL of methylene chloride was cooled to 0 °C, and 1.1 mL (0.0011 mol) of a 1.0 M solution of diethyl zinc in hexanes was added. This solution was treated with 0.182 mL (0.0022 mol) of methylene iodide, and the reaction was stirred for 5 min. To this solution was added 10 mL of a methylene chloride solution that contained 0.088 g (0.0005 mol) of allylic alcohol (**17**, **19**, **25**, or **27**) and, if desired, 0.148 g (0.000 55 mol) of the appropriate chiral dioxaboralane **11** or **12**. The reaction mixture was allowed to stir for 2 h, the reaction was quenched with 50 mL saturated NH_4Cl solution, and the aqueous portion was extracted with EtOAc. The combined organic solutions were dried over $MgSO_4$, filtered through Celite, and concentrated to give a yellow oil. If a dioxaboralane was used, the crude oil was dissolved in 10 mL of diethyl ether and stirred vigorously overnight with 10 mL of 5 N KOH. The ether layer was washed with 1 N HCl, 5% $NaHCO_3$, water, and brine. The organic portion was dried over magnesium sulfate, filtered through Celite, and concentrated under reduced pressure. The crude concentrate was subjected to flash chromatography (10:1 hexanes:EtOAc) to yield a colorless oil.

2-((1*R*,2*S*)-2-Phenylcyclopropyl)-(1*S*,2*R*)-1-(hydroxymethyl)cyclopropane (3). Application of dioxaboralane **11** to allylic alcohol **17** (**3**(syn):**4**(anti) 10:1) (67%): $[\alpha]_D$ = +140° (*c* 0.0016); ^{1}H NMR δ ($CDCl_3$) 7.20−6.92 (m, 5H), 3.45−3.32 (m, 2H), 1.62−1.56 (m, 1H), 1.42 (s, 1H), 1.15−1.08 (m, 1H), 0.97−0.65 (m, 4H), 0.37−0.26 (m, 2H); ^{13}C NMR δ ($CDCl_3$) 143.2, 128.1, 125.5, 125.2, 66.5, 24.3, 22.1, 20.0, 18.5, 13.9, 7.9; HRMS calcd for $C_{13}H_{20}NO$ (M + NH_4^+) 206.1545, found 206.1548.

2-((1*R*,2*S*)-2-Phenylcyclopropyl)-(1*R*,2*S*)-1-(hydroxymethyl)cyclopropane (4). Application of dioxaboralane **12** to allylic alcohol **17** (**3**(syn):**4**(anti) 1:10) (72%): $[\alpha]_D$ = +85° (*c* 0.0023); ^{1}H NMR δ ($CDCl_3$) 7.25−6.98 (m, 5H), 3.47−3.37 (m, 2H), 1.80 (s, 1H), 1.68−1.61 (m, 1H), 1.17−1.10 (m, 1H), 0.98−0.73 (m, 4H), 0.47−0.36 (m, 2H); ^{13}C NMR δ ($CDCl_3$) 143.2, 128.1, 125.5, 125.2, 66.5, 24.4, 21.8, 19.3, 18.6, 14.4, 8.6.

2-((1*R*,2*S*)-2-Phenylcyclopropyl)-(1*R*,2*R*)-1-(hydroxymethyl)cyclopropane (5). Application of dioxaboralane **12** to allylic alcohol **19** (**5**(syn):**6**(anti) 10:1) (81%): $[\alpha]_D$ = +116° (*c* 0.0015); ^{1}H NMR δ ($CDCl_3$) 7.25−7.00 (m, 5H), 3.73−3.57 (m, 2H), 1.80−1.72 (m, 1H), 1.45 (s, 1H), 1.22−1.11 (m, 1H), 1.03−0.80 (m, 4H), 0.70−0.64 (m, 1H), 0.18−0.12 (m, 1H); ^{13}C NMR δ ($CDCl_3$) 143.0, 128.3, 125.5, 125.4, 63.7, 22.9, 21.8, 18.9, 18.6, 16.0, 8.3; HRMS calcd for $C_{13}H_{20}NO$ (M + NH_4^+) 206.1545, found 206.1531.

2-((1*R*,2*S*)-2-Phenylcyclopropyl)-(1*S*,2*S*)-1-(hydroxymethyl)cyclopropane (6). Application of dioxaboralane **11** to allylic alcohol **19** (**5**(syn):**6**(anti) 1:6) (78%): $[\alpha]_D$ = +25° (*c* 0.0016); ^{1}H NMR δ ($CDCl_3$) 7.25−7.00 (m, 5H), 3.76−3.53 (m, 2H), 1.80−1.72 (m, 1H), 1.42 (s, 1H), 1.22−1.11 (m, 1H), 1.03−

0.80 (m, 4H), 0.72−0.66 (m, 1H), 0.21−0.16 (m, 1H); ^{13}C NMR δ ($CDCl_3$) 142.9, 128.3, 125.5, 125.4, 63.8, 23.3, 21.6, 18.9, 18.7, 15.8, 8.9.

2-((1*R*,2*R*)-2-Phenylcyclopropyl)-(1*S*,2*R*)-1-(hydroxymethyl)cyclopropane (7). Application of dioxaboralane **11** to allylic alcohol **25** (**7**(syn):**8**(anti) 2.5:1) (81%): $[\alpha]_D = +6°$ (*c* 0.0096); ^{1}H NMR δ ($CDCl_3$) 7.34−7.16 (m, 5H), 3.39−3.30 (m, 1H), 2.81−2.74 (m, 1H), 2.17−2.10 (m, 1H), 1.25 (s, 1H), 1.07−1.00 (m, 1H), 0.93−0.85 (m, 2H), 0.81−0.71 (m, 1H), 0.51−0.45 (m, 1H), 0.36−0.27 (m, 2H); ^{13}C NMR δ ($CDCl_3$) 139.5, 128.8, 128.1, 125.9, 66.9, 21.7, 21.2, 21.1, 16.5, 10.2, 9.7; HRMS calcd for $C_{13}H_{20}NO$ ($M + NH_4^+$) 206.1545, found 206.1547.

2-((1*R*,2*R*)-2-Phenylcyclopropyl)-(1*R*,2*S*)-1-(hydroxymethyl)cyclopropane (8). Application of dioxaboralane **12** to allylic alcohol **25** (**7**(syn):**8**(anti) 1:>10) (79%): $[\alpha]_D = +83°$ (*c* 0.0054); ^{1}H NMR δ ($CDCl_3$) 7.34−7.16 (m, 5H), 3.28−3.17 (m, 1H), 2.89−2.81 (m, 1H), 2.20−2.12 (m, 1H), 1.25 (s, 1H), 1.20−1.10 (m, 1H), 0.93−0.85 (m, 1H), 0.81−0.71 (m, 1H), 0.70−0.64 (m, 1H), 0.43−0.37 (m, 1H), 0.36−0.27 (m, 2H); ^{13}C NMR δ ($CDCl_3$) 139.5, 129.6, 128.0, 125.9, 66.7, 21.4, 20.0, 19.8, 15.9, 9.4, 8.3.

2-((1*R*,2*R*)-2-Phenylcyclopropyl)-(1*R*,2*R*)-1-(hydroxymethyl)cyclopropane (9). Application of dioxaboralane **12** to allylic alcohol **27** (**9**(syn):**10**(anti) 5:1) (79%): $[\alpha]_D = +17°$ (*c* 0.0066); ^{1}H NMR δ ($CDCl_3$) 7.32−7.15 (m, 5H), 3.74−3.67 (m, 1H), 3.60−3.53 (m, 1H), 2.18−2.10 (m, 1H), 1.30 (s, 1H), 1.11−0.79 (m, 4H), 0.65−0.48 (m, 2H), 0.17−0.10 (m, 1H); ^{13}C NMR δ ($CDCl_3$) 139.5, 128.4, 128.0, 125.7, 63.6, 21.5, 18.3, 18.1, 14.7, 11.1, 9.7.

2-((1*R*,2*R*)-2-Phenylcyclopropyl)-(1*S*,2*S*)-1-(hydroxymethyl)cyclopropane (10). Application of dioxaboralane **11** to allylic alcohol **27** (**9**(syn):**10**(anti) 1:5) (80%): $[\alpha]_D = +8°$ (*c* 0.0052); ^{1}H NMR δ ($CDCl_3$) 7.32−7.15 (m, 5H), 3.88−3.79 (m, 1H), 3.66−3.58 (m, 1H), 2.27−2.19 (m, 1H), 1.45 (s, 1H), 1.11−0.79 (m, 4H), 0.65−0.57 (m, 1H), 0.22−0.10 (m, 2H); ^{13}C NMR δ ($CDCl_3$) 139.2, 129.3, 127.9, 125.8, 64.2, 21.4, 18.1, 17.4, 14.9, 10.4, 10.3; HRMS calcd for $C_{13}H_{20}NO$ ($M + NH_4$): 206.1545, found 206.1555; HRMS calcd for $C_{13}H_{20}NO$ ($M + NH_4^+$) 206.1545, found 206.1548.

Cyclopropanation of 17 in the absence of chiral dioxaboralane: (**3**(syn):**4**(anti) 1:1.3) (78%).

Cyclopropanation of 19 in the absence of chiral dioxaboralane: (**5**(syn):**6**(anti) 1:1.3) (79%).

Cyclopropanation of 25 in the absence of chiral dioxaboralane: (**7**(syn):**8**(anti) 1:9) (82%).

Cyclopropanation of 27 in the absence of chiral dioxaboralane: (**9**(syn):**10**(anti) 1:2.8) (85%).

General Procedure for the Rhodium Carbenoid-Mediated Cyclopropanation and Subsequent DIBAL-H Reduction of 28 and 29. Into a round-bottom flask was added 1.0 equiv of the vinylcyclopropane **28** or **29**, benzene (0.1 M),[26] and a catalytic amount of $Rh_2(OAc)_4$. The solution was stirred while 1 equiv of ethyl diazoacetate dissolved in benzene (0.2 M) was added over a 8.5 h period. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was chromatographed on silica (40:1 hexanes:EtOAc) to separate the mixture of bis-cyclopropyl ethyl esters, starting material, and ethyl cycloheptatrienoate. The bis-cyclopropyl esters were transferred into a round-bottom flask, and 25 mL of THF was added. The flask was cooled to −78 °C, excess DIBAL-H in toluene was added, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was cooled to 0 °C, quenched by the sequential addition of 2 N NaOH and H_2O, and stirred overnight during which time a white granular precipitate formed. The quenched reaction mixture was dried with $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. The crude concentrate was chromatographed on silica (10:1 hexanes:EtOAc) to yield a mixture of bis-cyclopropanes **3**−**10** that were identified by ^{13}C NMR.

Reaction of 28. Yield of bis-cyclopropyl esters: 38%. Yield of ethyl cycloheptatrienoate: 25%. Recovered starting material **28**: 10%. Yield of DIBAL-H reduction: 85%.

Reaction of 29. Yield of bis-cyclopropyl esters: 14%. Yield of ethyl cycloheptatrienoate: 32%. Recovered starting material **29**: 25%. Yield of DIBAL-H reduction: 96%.

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Supporting Information Available: Experimental procedures for the preparation of **13**−**15**, **21**−**23**, **28**, and **29** and ^{1}H and ^{13}C NMR spectra of **3**−**10**, **13**, **15**−**19**, **21**, and **23**−**27** (41 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(26) Methylene chloride was also used as a solvent in this reaction sequence. The yield of bis-cyclopropyl ester formation was slightly higher since none of the competing cycloheptatrienoate was formed. The stereoselectivity of the process was indistinguishable when moving between methylene chloride and benzene.