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The Chemo- and Enantioselective Cyclopropanation of Polyenes: Chiral Auxiliary vs Chiral Reagent-Based Approach.

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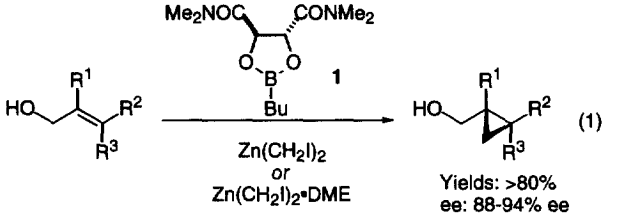
Abstract: The chemo- and enantioselective cyclopropanation of allylic alcohols containing additional olefins was investigated using the dioxaborolane-derived reagent. High chemo- and enantioselectivities were usually observed if a mixture of the chiral dioxaborolane ligand/allylic alcohol was treated with a solution of $Zn(CH_2I)_2$•DME complex.

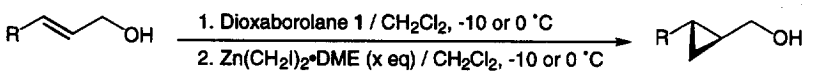
We recently reported that a chiral dioxaborolane derivative **1** was an efficient chiral ligand for the asymmetric cyclopropanation of allylic alcohols (eq 1).[1] One of the most attractive features of this enantioselective cyclopropanation is that high enantioselectivities are usually observed regardless of the substitution pattern of the olefin. The occurence of natural products containing both an olefin and a cyclopropane ring prompted us to investigate the chemo- and enantioselectivity of the cyclopropanation of substrates containing more than one olefin. It is fairly well-established that allylic alcohols can be chemoselectively cyclopropanated with mild success under the classical Simmons-Smith conditions.[2] Molander recently disclosed that iodomethylsamarium iodide was the reagent of choice for the achiral, chemoselective cyclopropanation of polyenes at the allylic alcohol position.[3,4] Quite surprisingly, there are only two reports of the use of the Furukawa's conditions[5] for the cyclopropanation of polyenes.[3,6,7] Furthermore, the efficiency of this type of cyclopropanation using a chiral ligand or auxiliary has not been demonstrated yet.[8] In this paper, we report that polyenes can be cyclopropanated at the allylic alcohol position with high chemo- and enantioselectivities using the dioxaborolane-derived ligand. When this method failed, the glucose-derived chiral auxiliary was a suitable alternative method to generate the corresponding monocyclopropyl derivatives in high diastereomeric excesses.

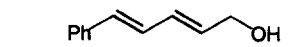
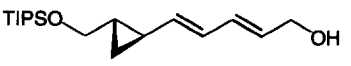
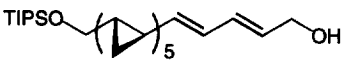
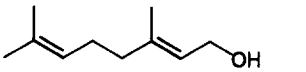
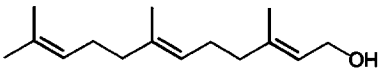
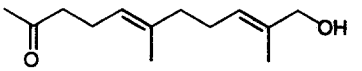
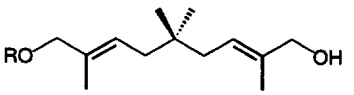


(1)

The enantioselective cyclopropanation of a variety of conjugated and unconjugated polyenes using chiral ligand **1** was optimized and the results are presented in Table 1. The reactions were best carried out by adding a solution of the $Zn(CH_2I)_2$•DME complex in CH_2Cl_2 to a mixture of the allylic alcohol and ligand **1**.[9] We found that the number of equivalents of the reagent necessary to get quantitative conversion to the monocyclopropane product was highly substrate-dependant. A larger excess of the reagent was necessary with the less reactive, conjugated 2,4-dien-1-ol derivatives (entry 1-3)[10] or when additional basic groups were present on the substrate (entry 6-9).[11] In all the cases, uniformingly high yields and monocyclopropane:biscyclopropane ratios were observed.

Table 1. Enantioselective cyclopropanation of allylic alcohols with chiral ligand 1



Entry	Allylic alcohol	x eq (°C)	Yield[a]	Ratio[b] mono : bis	Selectivities
1		3.0 eq (-10)	84%	>20 : 1	21 : 1[c]
2		2.5 eq (-10)	85%[d]	8 : 1	>20 : 1[e]
3		3.0 eq (-10)	81%	9 : 1	>20 : 1[e]
4		1.6 eq (0)	87%	>20 : 1	28 : 1[f]
5		1.6 eq (0)	84%	>20 : 1	29 : 1[f]
6		4.2 eq (0)	>95%	>20 : 1	15 : 1[f]
					
7	R = TBDPS	4.2 eq (0)	88%	>20 : 1	14 : 1[f]
8	R = Ac	4.2 eq (0)	>95%	>20 : 1	12 : 1[f]
9	R = Bn	4.2 eq (0)	>95%	>20 : 1	13 : 1[f]

[a]Isolated yield. [b]Determined by ^1H NMR analysis. [c]Enantioselectivities was determined HPLC analysis on chiral stationary phase. [d]This yield includes *ca.* 10% of inseparable starting material and tricyclopropane. [e]The diastereoselectivities were evalued by ^{13}C NMR. [f]The enantioselectivities were determined by ^1H and ^{19}F NMR analysis of the corresponding Mosher esters.

The cyclopropanation of 5-cyclopropyl-2,4-dien-1-ol derivatives to produce *trans*-1,2-dicyclopropylolefins proceeded relatively well, but larger amounts of the dicyclopropanation derived products

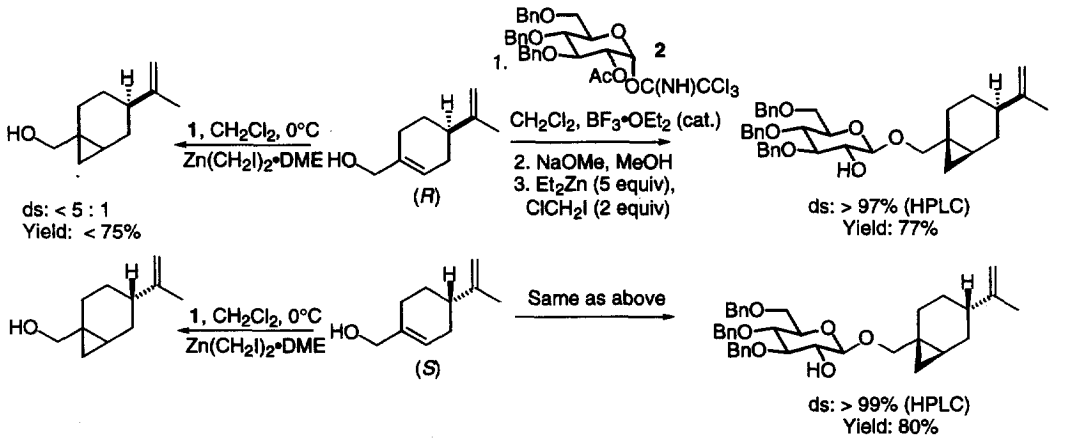
were obtained. These products are useful precursors to polycyclopropane containing natural products such as FR-900848[12] and U-106305.[13]

Geraniol (entry 4), farnesol (entry 5), and the SeO_2 oxidation product of geranylacetone[14] (entry 6) were all tested and provided the desired monocyclopropanation product with excellent selectivities.

Several monoprotected bis(allylic alcohols) could also be cyclopropanated exclusively at the allylic alcohol position (entry 7-9) with excellent stereocontrol. The nature of the protected group has little influence on the level of induction and on the chemoselectivity of the reaction.

The cyclopropanation of (*R*)- and (*S*)-perillyl alcohol using the reagent-based approach was then investigated (Scheme 1). Although the chemoselectivities favoring the cyclopropanation reaction at the allylic alcohol position were relatively good even with 5 equivalents of the reagents the diastereselectivities were surprisingly low.[15] In both cases, low, but opposite diastereoselectivities were obtained. These results prompted us to evaluate the efficiency of the glucose-derived auxiliary to effect these two transformations. Glycosylation reactions between trichloroacetimidate **2** and (*R*)- and (*S*)-perillyl alcohol under standard conditions[16] produced the desired precursors. The best diastereomeric ratios and yields were obtained when a mixture of Et_2Zn (5 equiv) and $ClCH_2I$ (2 equiv) were sequentially added to the starting glycoside. In both cases, the chirality of the auxiliary clearly prevailed over that of the alcohol and produced the expected diastereomer in ≥95%. The glucose-derived auxiliary was also very effective for the monocyclopropanation of the glycoside derived from geraniol and farnesol (Yield: >80%, ds: >94%).

Scheme 1



In conclusion, we have shown that the dioxaborolane ligand **1** and the glucose-derived auxiliary are very effective chiral controllers for the stereo- and chemoselective cyclopropanation of polyenes.

General Procedure for Chemoselective Cyclopropanation of Diene. To a solution of alcohol (1.00 mmol) and dioxaborolane **1** (1.20 mmol) in CH_2Cl_2 (10 mL) at -10 °C was added dropwise a 0.49 M solution of $Zn(CH_2I)_2$•DME in CH_2Cl_2. The clear solution was stirred for 2 h at that temperature. Sat. aq. NH_4Cl was slowly added followed by 10% aq. HCl. The mixture was extracted with ether and the organic layer was successively washed with sat. aq. Na_2SO_3, 2M aq. NaOH containing 30% aq. H_2O_2, sat. aq. NH_4Cl , and sat. aq.

NaCl. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to produce the desired monocyclopropylmethanol.

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References and Notes

1. (a) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651-2652. (b) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081-1083.
2. Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1-131.
3. Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525-3532.
4. Regioselective cyclopropanation of allenic alcohols, see: Lautens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8526-8535.
5. (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53-58. (b) Furukawa, J.; Kawabata, N.; Fujita, T. *Tetrahedron* **1970**, *26*, 243-250.
6. Treatment of geraniol with 2 equiv of CH_2I_2 followed by 1.1 equiv of Et_2Zn in toluene at 0 °C resulted in the formation of the monocyclopropane with excellent chemoselectivity (≥95%) and yield (>95%).
7. For the effect of high pressure of the chemoselectivity see: Guerreiro, M. C.; Schuchardt, U. *Synth. Commun.* **1996**, *26*, 1793-1800.
8. During the course of our study, a first example of a selective cyclopropanation of a polyene was reported using the dioxaborolane **1**: Barrett, A. G. M.; Kasdorf, K. *J. C. S., Chem. Comm.* **1996**, 325-326.
9. The use of $Zn(CH_2I)_2$ without DME led to irreproducible results.
10. The 2,4-dienols in entry 1-3 were prepared from the corresponding aldehyde by a standard Horner-Emmons/reduction sequence. For the synthesis of the starting aldehyde in entry 2 and 3, see: Charette, A. B.; Lebel, H. *J. Am. Chem. Soc.* submitted for publication.
11. The monoprotected diols in entry 7-9 were prepared from the known dialdehyde (Fraenkel, G.; Steel, F.; Rizvi, S. Q. A. *J. Org. Chem.* **1979**, *44*, 2522-2529) by a Wittig olefination using $Ph_3P{=}C(CH_3)CHO$ (82%) followed by $NaBH_4/CeCl_3$ reduction (85%).
12. Yoshida, M.; Ezaki, M.; Hashimoto, M. Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiotics* **1990**, *43*, 748-754.
13. Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P. ; Kloosterman, D. A.; Spilman, C. H.; Marshall, V. P. *J. Am. Chem. Soc.* **1995**, *117*, 10629-10634.
14. McMurray, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942-6949.
15. The cyclopropanation of (*R*)- or (*S*)-perillyl alcohol using Et_2Zn, CH_2I_2 or $Sm/HgCl_2$, $ClCH_2I$ led to a 1:1 mixture of diastereomers indicating that the remote chiral center has little effect on the stereochemical outcome of the reaction. The dioxaborolane-mediated cyclopropanation of allylic alcohols having a β-substituent have produced the corresponding cyclopropanes with slightly lower enantiomeric excesses and lower reaction rates.
16. Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721-12732.

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