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Diastereoselectivity in the dihydroxylation of isopropenyl substituted three-membered rings

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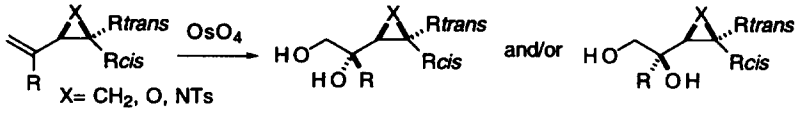
Abstract

The diastereoselectivity of the dihydroxylation of isopropenylcyclopropanes, oxiranes and aziridines has been investigated.

Keywords: cyclopropanes; oxiranes; aziridines; dihydroxylation.

The stereoselective preparation of organic compounds containing cyclopropanes, oxiranes or aziridines is of great interest due to the versatile reactivity of these strained three-membered rings.[1] The control of the relative configuration between these three-membered rings and their adjacent stereocenters usually involves one of two strategies consisting of either a substrate directed cyclopropanation, epoxidation or aziridination,[2] or the chemical transformation of a prochiral group directly attached to the ring, as illustrated by nucleophilic additions onto cyclopropyl, oxiranyl and aziridinylcarbonyl derivatives.[3] However, the diastereoselectivity of electrophilic reactions of the corresponding alkenyl derivatives has received much less attention.

Recently, we have reported that the hydroboration of *cis*-substituted isopropenylcyclopropanes proceeded with a high degree of stereocontrol. In continuation of our studies on developing diastereoselective synthetic transformations of alkenyl substituted three-membered rings, the dihydroxylation reaction was investigated (Scheme 1).



Scheme 1. Dihydroxylation of alkenyl substituted three-membered rings

Alkenylcyclopropanes,[4] oxiranes[5] and aziridines[6] were synthesized and subjected to an osmium tetroxide catalyzed dihydroxylation (Table 1).[7]

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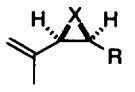
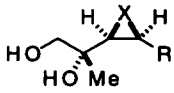
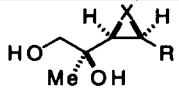
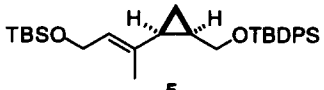
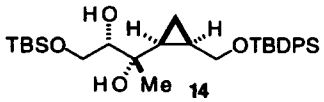
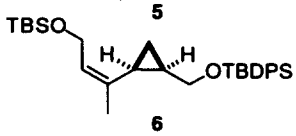
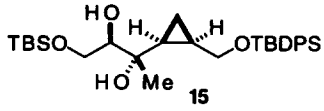
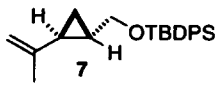
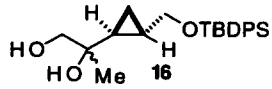
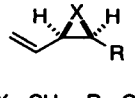
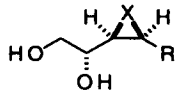
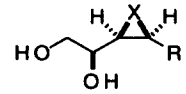
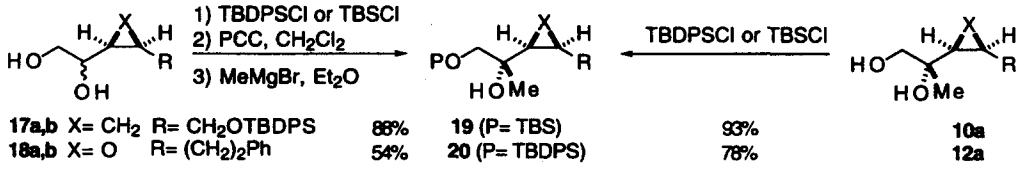
Table 1
Dihydroxylation of alkenyl substituted three-membered rings

Substrate	Product(s)		d.r.*	Yield
				
1 X= CH_2 R= $CH_2OTBDPS$	**10a**	**10b**	≥ 96/4	72%
2 X= CH_2 R= 	**11a**	**11b**	93/7	85%
3 X= O R= $(CH_2)_2Ph$	**12a**	**12b**	96/4	95%
4 X= NTs R= *i*-Pr	**13a**	**13b**	82/18	86%
 5	 14		≥ 96/4	90%
 6	 15		≥ 96/4	93%
 7	 16		50/50	91%
				
8 X= CH_2 R= $CH_2OTBDPS$	**17a**	**17b**	55/45	90%
9 X= O R= $(CH_2)_2Ph$	**18a**	**18b**	50/50	85%

* Diastereoisomeric ratio estimated from the ^1H NMR spectrum of the crude product

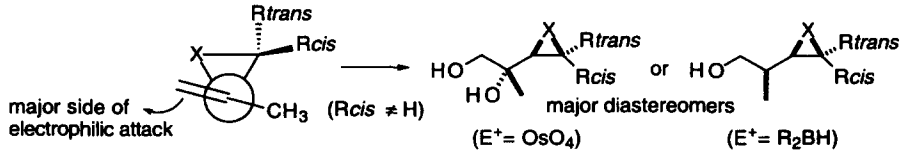
Under these conditions, high levels of diastereoselectivity were observed for *cis*-isopropenylcyclopropane **1** (d.r.≥96/4). Cyclopropane **2**, bearing an adjacent stereocenter, was also dihydroxylated with a synthetically useful level of diastereoselectivity. The dihydroxylation of the isopropenyloxirane **3** also proceeded with a high degree of stereocontrol, whereas the diastereomeric ratio was lower in the case of the *cis*-isopropenylaziridine **4**. Whatever the olefinic configuration, the trisubstituted alkenylcyclopropanes **5** and **6** underwent a highly diastereoselective reaction. In contrast, little or no diastereoselectivity was observed in the dihydroxylation of either *trans*-isopropenylcyclopropane **7** or *cis*-vinylcyclopropane **8** and oxirane **9**.

The relative configuration of **10a** and **12a** was established by a chemical correlation starting, respectively, from **17a,b** and **18a,b**. The primary alcohol function of the latter compounds was first protected as a silyl ether and the secondary hydroxyl was subsequently oxidized with PCC to give, respectively, the corresponding ketones. Condensation with MeMgBr proceeded in a highly diastereoselective fashion (d.r.≥96/4) to give the corresponding tertiary alcohols **19** and **20**, whose relative configuration was attributed on the basis of the known sense of nucleophilic additions onto oxiranyl and cyclopropylketones.[3] The establishment of the relative configuration of **10a** and **12a** was thus straightforward, since protection of their primary alcohol function as a silyl ether also gave the tertiary alcohols **19** and **20**, respectively (Scheme 2). The relative configuration of the other compounds was assumed to be similar by analogy with this result.



Scheme 2. Correlation of configuration for **10a** and **12a**

The results obtained during the course of this study clearly demonstrate that hydroboration and dihydroxylation of *cis*-isopropenyl substituted three-membered rings occur on the same face of the prochiral alkene moiety.[8] Although the ground state and the reactive conformer are not necessarily the same, the ground state conformation of various olefinic molecules bearing the propene moiety plays an important role in the stereochemical outcome of π-facial selectivity.[9] We initially suggested that electrophilic additions onto alkenylcyclopropanes could occur on the more reactive bissected conformer, in which overlap between the cyclopropane π-system and the alkene is supposed to be maximal.[4] However, in light of these new results indicating a closely related behaviour of all the *cis*-isopropenyl substituted three-membered rings, another plausible explanation of the uniform diastereoselectivity of these processes would be to consider that the electrophilic additions are occurring on the less-crowded face of the olefin in the *gauche* conformation (Scheme 3), which has been shown, in the case of isopropenyloxiranes[10] and aziridines,[6] to be the more stable in the ground state, by ab initio calculations, X-ray diffraction studies and ^{1}H NMR spectroscopic analyses. It is thus clear that the lack of steric interactions in the case of *cis*-vinyl or *trans*-isopropenyl substituted three-membered rings results in stereorandom reactions.



Scheme 3. *Gauche* conformation of isopropenyl substituted three-membered rings

We have thus shown that dihydroxylation of *cis*-isopropenyl substituted cyclopropanes, oxiranes and aziridines proceeds with good to excellent levels of diastereoselectivity. Since these compounds can undergo a variety of ring-opening reactions, the present methodology should find useful applications in the stereocontrolled synthesis of acyclic chiral building blocks.

Acknowledgements

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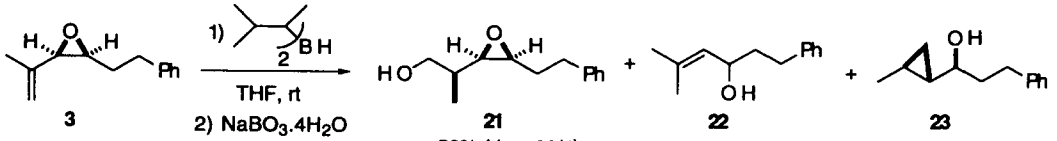
8. Hydroboration of *cis*-isopropenyloxirane **3** with diisoamylborane, followed by oxidation with sodium perborate also proceeded in a highly diastereoselective fashion (d.r.≥96/4) but in this case side products **22** and **23**, respectively, resulting from S_N2' reduction of the epoxide and 1,3-elimination of the intermediate γ-epoxy organoborane were also formed (unpublished results).



3 → **21** 58% (d.r.≥ 96/4) + **22** 12% + **23** 3%

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