Communications

Diastereoselective Hydroboration of Isopropenylcyclopropanes

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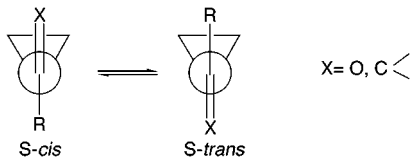
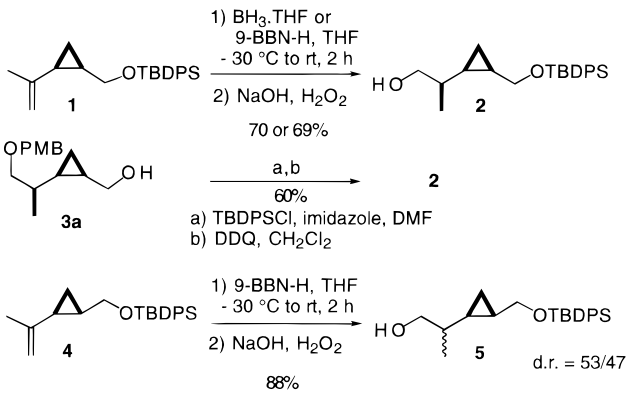
The stereoselective preparation of organic compounds containing cyclopropanes is of great interest because of their biological properties[1] and their versatile synthetic utility.[2] Due to the characteristic stereoelectronic effects of the cyclopropane ring, it has been recognized that interactions can exist with adjacent double bonds, leading to the preferential population of bissected conformers (Scheme 1), as evidenced by spectroscopic analysis, electron diffraction studies, and theoretical calculations.[3] Furthermore, experimental evidence has emerged from the results of the stereochemical outcome of nucleophilic additions onto cyclopropylcarbonyl derivatives.[4]

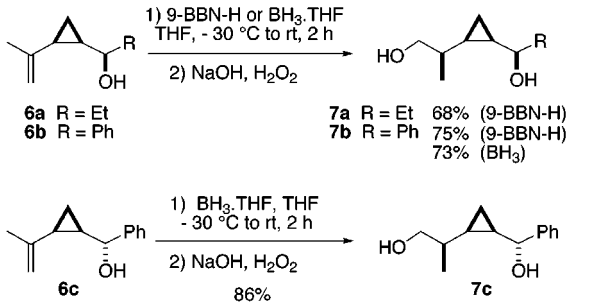
Scheme 1



Scheme 2



Scheme 3



Electrophilic additions onto alkenylcyclopropanes should also occur via these bissected conformations since the cyclopropane ring can act as a strong π-donor and interact in the transition state with the antibonding orbital of the double bond, thus enhancing its nucleophilicity and thereby facilitating the reaction. Herein, we disclose our preliminary results concerning the stereochemical outcome of the addition of organoboranes to substituted isopropenylcyclopropanes.

When cyclopropane **1**[5] was hydroborated using either BH_3·THF or 9-BBN-H in THF followed by a standard alkaline oxidative workup, the alcohol **2** was obtained as a single diastereoisomer in good isolated yields.[6] Its relative stereochemistry was readily assigned by comparison with

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(5) The preparation of the starting materials is described in the Supporting Information.

(6) No signals assignable to another diastereoisomeric product could be detected by GC−MS or NMR analyses of the crude material.

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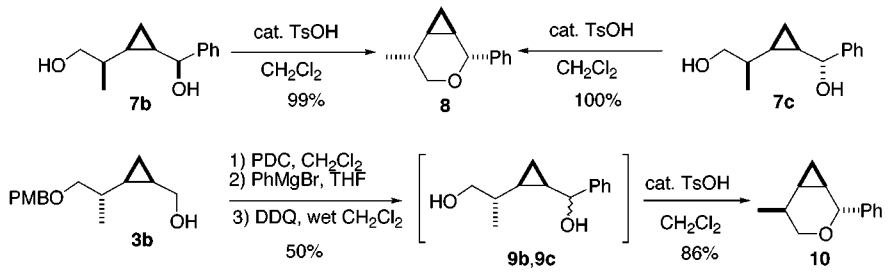
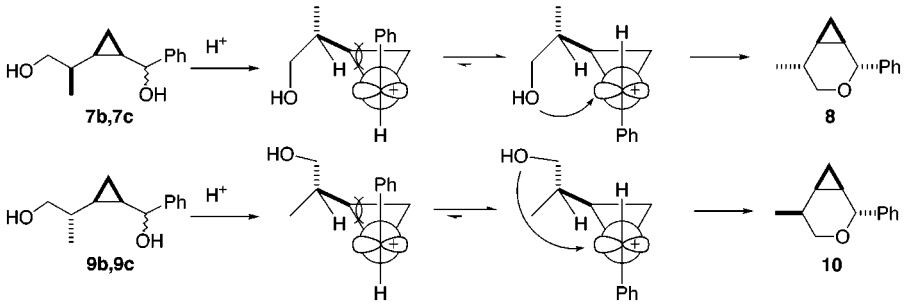
Scheme 4



Scheme 5



an authentic sample prepared from the known alcohol **3a**.[7] Conversely, hydroboration of the *trans* diastereoisomer **4**[5] under the same conditions is nearly stereorandom (Scheme 2).

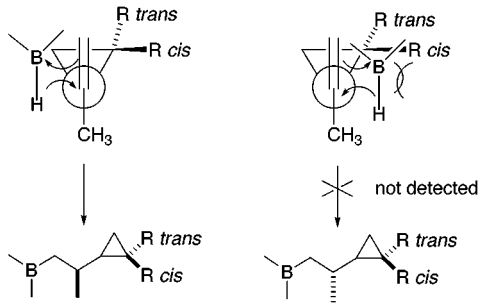
To expand the scope of this hydroboration reaction, other substituted isopropenylcyclopropylcarbinols were examined. When **6a**−**c**[5] were hydroborated with 9-BBN-H or BH_3·THF in THF, the diols **7a**−**c** were respectively obtained in good isolated yields and in a highly diastereoselective fashion (dr ≥ 96/4) (Scheme 3).[6]

It turned out that diols **7b** and **7c** were extremely acid-sensitive and readily cyclized to the same tetrahydropyran **8** in a highly diastereoselective fashion (dr ≥ 96/4).[6] On the other hand, the known alcohol **3b**[7] was oxidized with PDC, and the resultant aldehyde was treated with PhMgBr to give a mixture of diastereoisomeric alcohols. After deprotection of the *p*-methoxybenzyl ether with DDQ, the diastereoisomeric sensitive diols **9b** and **9c** were separated and, upon exposure to a catalytic amount of *p*-toluenesulfonic acid, both cyclized to the same tetrahydropyran **10** in a highly diastereoselective fashion (dr ≥ 96/4) (Scheme 4).[6]

Apparently, the cyclizations of **7b** or **7c** and **9b** or **9c** to **8** and **10**, respectively, occur through the formation of a benzylcyclopropylcarbonium ion, existing in the most stable bissected conformation,[8] in which steric interactions analogous to A[1,3] strain[9] are minimized (Scheme 5). Indeed the benzylic protons in **8** and **10** appear as broad singlets, respectively, at 4.68 and 4.41 ppm, indicating a *trans* relationship between the phenyl group and the cyclopropane.[10] The fact that **8** and **10** are diastereoisomers allows the establishment of the relative stereochemistry of **7b** and **7c**, the one of **7a** being attributed accordingly.

In the examples that we have considered, hydroboration of *cis*-isopropenylcyclopropanes proceeds with a high level of stereocontrol to give the *syn* diasteroisomers. At this stage of our investigations, we have tentatively rationalized these

Scheme 6



results by considering that hydroborations are occurring via the more reactive bissected S-*cis* conformers, in which the steric bulk of the R *cis* substituent will force the organoborane to approach on the opposite side of the double bond. It is thus clear that, in the absence of a bulky R-*cis* substituent, hydroboration is stereorandom as is the case for compound **4** (Scheme 6).

We have shown that hydroboration of *cis*-isopropenylcyclopropanes proceed with a high degree of stereocontrol, and further work is in progress to clearly elucidate the factors responsible for such a high diastereoselectivity. Furthermore, the cyclopropanes bearing two adjacent stereocenters should be useful synthons in the synthesis of natural products or conformationally restricted analogues of some biologically active substances.

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Supporting Information Available: Full experimental procedures and spectroscopic data are available for new compounds as well as for the intermediates involved in their preparation.

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