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Diastereoselective Reduction of Cyclopropenylcarbinol: New Access to *anti*-Cyclopropylcarbinol Derivatives

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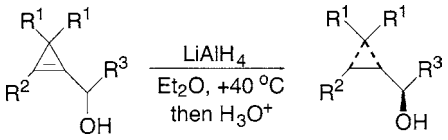
ABSTRACT

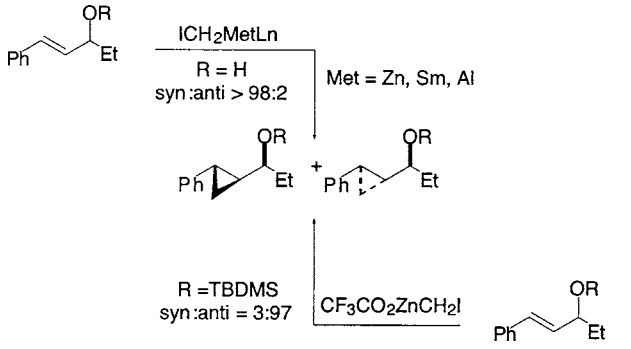


Cyclopropenylcarbinol derivatives are regio- and diastereoselectively reduced with $LiAlH_4$ in Et_2O into *trans*-cyclopropylcarbinols as a single isomer. The regioselectivity of the hydroalumination reaction on the cyclopropenyl ring has been mapped out by deuterium labeling experiments.

The directed cyclopropanation of acyclic allylic alcohols with halomethylmetal reagents such as zinc, samarium, or aluminum carbenoids is nowadays a well-known process, and many reagents and reaction conditions are known to lead to cyclopropylcarbinols with variable selectivities.[1] Interactions between the heteroatom functionality and the reagent usually precede the ensuing chemical transformations,[2] and in some cases, very high syn selectivities were observed either for (*E*)- or (*Z*)-disubstituted chiral allylic alcohols.[3] The nature of the carbenoid reagent used is extremely important for good diastereoselectivity (i.e., $EtZnCH_2I$, $Zn(CH_2I)_2$, and $IZn(CH_2I)$ gave different ratios for the same substrate).[1] However, the direct preparation of the *anti*-cyclopropylcarbinol derivative with good diastereoselection is a much more difficult task.

Some of these compounds are accessible by the reduction of the corresponding cyclopropyl ketone,[4] and more recently by a diastereoselective cyclopropanation of silyl-protected chiral allylic alcohols[5] with use of Shi's zinc carbenoid (Scheme 1).[6]

Scheme 1



Moreover, in the halomethylmetal reagents based strategy for the cyclopropanation reactions of allylic alcohols, primary

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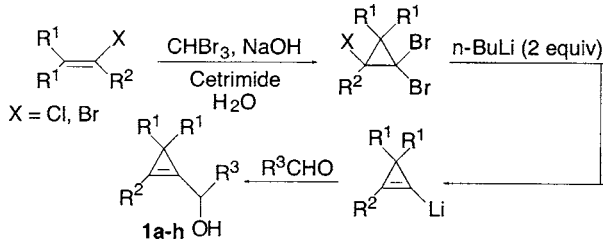
carbenoids are mainly used, and only a few examples are therefore described for the cyclopropanation reaction with unstable secondary and tertiary carbenoids.[7] On the other hand, diastereoselection in the hydrometalation of acyclic compounds is controlled by allylic,[2,8] homoallylic,[9] and even more remote stereogenic centers.[10] Moderate to high levels of anti selectivity are usually achieved.[8−10] Therefore, we thought that the diastereoselective reduction of cyclopropenylcarbinol[11] such as **1a**−**h** (Scheme 2) should be an

Scheme 2

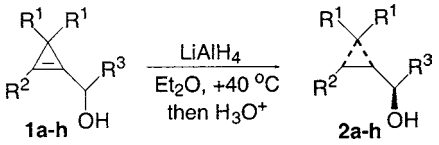


interesting and powerful solution to the preparation of *trans*-cyclopropylcarbinol derivatives.

Cyclopropenylcarbinols **1a**−**h** are themselves obtained in one chemical step in good to excellent isolated yields from 1,1,2-trihalogenocyclopropanes (prepared by reaction of substituted vinyl halide derivatives with bromoform in the presence of a phase transfer catalyst such as cetrimide)[12] by a successive 1,2-dehalogenation reaction followed by a halogen−lithium exchange and reaction with various aldehydes as described in Scheme 2.[13]

For correlation purposes, we have first reduced unsubstituted cyclopropenylcarbinols **1a**,**b** (R^1 = H, R^2 = alkyl, see Scheme 3 and Table 1, entries 1 and 2) with 1 equiv of $LiAlH_4$ in Et_2O at +40 °C.[14] Under these conditions, we were pleased to obtain in good chemical yields the expected

Scheme 3



cyclopropylcarbinol products **2a**,**b** but with only a moderate anti selectivity (anti/syn 80/20; deduced from comparison with an authentic sample).[15]

Table 1. Diastereoselective Reduction of Cyclopropenylcarbinol into *trans*-Cyclopropylcarbinol

entry	pdt	R^1	R^2	R^3	dr[a]	yields (%)[b]
1	**1a**	H	CH_2CH_2Ph	Et	80:20	85
2	**1b**	H	CH_3	Et	80:20	50
3	**1c**	CH_3	CH_3	Et	>98:2	86
4	**1d**	CH_3	CH_3	CH_3	>98:2	74
5	**1e**	CH_3	H	Et	>98:2	80
6	**1f**	CH_3	H	*c*-C_6H_{11}	>98:2	75
7	**1g**	CH_3	CH_3	$CH_2CH{=}CHEt$	>98:2	80
8	**1h**	CH_3	$Si(CH_3)_3$	Et	>98:2[c]	64

[a] Diastereomeric ratio was determined by ^1H and ^{13}C NMR of the crude reaction mixture. [b] Yields of isolated pure products after column chromatography. [c] Diastereomeric ratio of the *trans*-cyclopropylcarbinol versus the secondary alcohol; ratio of the cis/trans cyclopropane itself is 40/60, see text.

On the other hand, when the three-membered ring of the cyclopropenylcarbinol has a geminal dialkyl group such as in **1c**−**h**, excellent diastereoselectivities are obtained as described in Table 1, entries 3 to 8.[16]

Indeed, the reduction of the fully substituted cyclopropenylcarbinol **1c** occurs readily with 1 equiv of $LiAlH_4$ in Et_2O to give *anti*-cyclopropylcarbinol **2c** as a single diastereoisomer. On the other hand, if only 0.5 equiv of $LiAlH_4$ is used, reduced products are obtained in low yields. Similarly, if THF is used as solvent instead of Et_2O, the anti/syn ratio of the reaction drops to only 6:1 in low yield. The presence of a free hydroxyl group is absolutely necessary for the reduction of cyclopropenylcarbinol derivatives (obviously the alcohol moiety is first deprotonated with $LiAlH_4$), and as illustration, when alcohol **1c** was protected as its *tert*-butyldimethylsilyl ether, no reduced product was observed under our experimental conditions. Similarly, neither the Schwartz reagent $Cp_2Zr(H)Cl$ or DIBAL-H led to the reduced product. An even smaller R^3 substituent can be used in this diastereoselective reduction, such as the methyl group (Table 1, entry 4). The reduced product **2d** is obtained as a single diastereoisomer in good overall yield. On the other hand, when R^3 is an aromatic group, the reduction also occurs but

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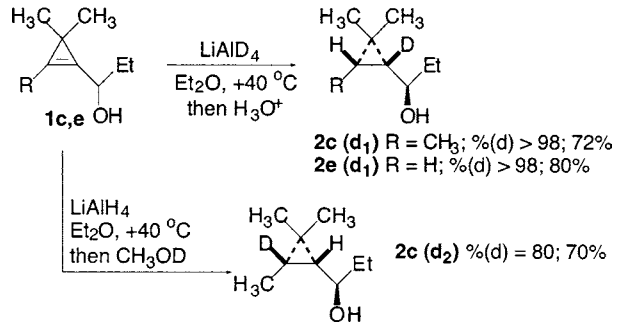
(16) Diastereoselectivity is measured by ^1H and ^{13}C NMR on the crude reaction mixture.

the resulting vinyl aluminum species obtained before acidic hydrolysis undergoes a ring fragmentation into polysubstituted diene.[17] The cyclopropenylcarbinol can also bear three alkyl substituents as in **1e** (R^2 = H, Table 1, entry 5) or be substituted by a secondary alkyl group (**1f**, R^3 = cyclohexyl, Table 1, entry 6) without altering the diastereoselectivity of the reduction.

As the heat of hydrogenation for the conversion of cyclopropene to cyclopropane is ca. 54 kcal/mol and is considerably larger than that for the conversion of ethylene to ethane,[18] the chemoselective reduction of the cyclopropenylcarbinol containing a (*E*) double bond such as in **1g** (Table 1, entry 7) has been investigated. The expected *anti*-cyclopropylcarbinol **2g** was obtained in good yield as a unique isomer without any reduction of the external (*E*) double bond. Finally, the silyl cyclopropenylcarbinol **1h**, treated under our experimental conditions, leads to the expected adduct with an anti relationship between the cyclopropyl and the secondary alcohol moieties but as a mixture of trans and cis isomers on the silyl-cyclopropane ring itself (trans/cis 60/40). The presence of these two isomers came from the remarkably facile configurational isomerization of 1-silyl-1-aluminocyclopropyl derivatives.[19]

The regioselectivity of the hydroalumination reaction on the cyclopropenyl ring has been mapped out by deuterium labeling experiments. When $LiAlD_4$ was used as reducing agent followed by acid hydrolysis, **1c** and **1e** led to the deuteriocyclopropanes **2c(*d*$_1$)** and **2e(*d*$_1$)**, respectively, as unique isomers in good chemical yields as shown in Scheme 4. On the other hand, when **1c** was treated with $LiAlH_4$

Scheme 4

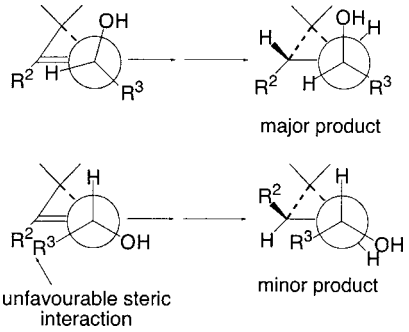


followed by deuterio methanolysis, **2c(*d*$_2$)** is obtained as the unique isomer. Therefore, both deuteriocyclopropylcarbinols can be selectively prepared.

Considering that the deprotonation of the alcohol precedes the reduction and assuming that the reaction occurs intramolecularly inducing the hydroalumination reaction on the same face as the oxygen atom, the anti-diastereofacial selectivity in the hydroalumination reaction of cyclopropenylcarbinol derivatives involved a transition state with the smallest substituent at the preexisting stereogenic center (hydrogen) oriented "inside" over the face of the transition state ring.

Minimization of the A-1,3 strain[20] is therefore the main controlling element for the good diastereocontrol and then the oxygen atom is oriented "outside" slightly (Houk's transition state model)[21] as described in Scheme 5.

Scheme 5



Moreover, the presence of the geminal dimethyl group on the upper carbon of the cyclopropenyl moiety also has an effect on the diastereoselectivity of the reduction (compare entries 2 and 3, Table 1). Due to the short bond lengths of the carbon−carbon bonds in the cyclopropene ring,[22] *syn*-pentane interactions (between the R substituent at the preexisting stereogenic center and the methyl groups) have an important effect on the diastereoselectivity. In conclusion, the diastereoselective reduction of polysubstituted cyclopropenylcarbinol with $LiAlH_4$ in Et_2O allows an easy and straightforward preparation of *trans*-cyclopropylcarbinol as a single isomer.

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Supporting Information Available: Experimental procedures with a description of ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The stereospecific formation of diene will be reported in due course.

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