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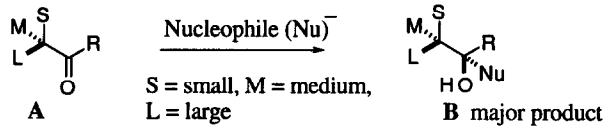
Effect of the Substituents on the Diastereoselectivity in the Reduction of Cyclopropyl Ketones

Patrick H. M. Delanghe and Mark Lautens*

Department of Chemistry, University of Toronto, Toronto, M5S 1A1, Canada

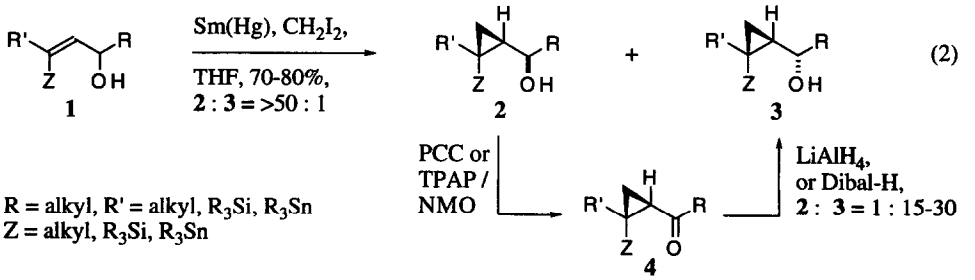
Abstract: The reduction of several cyclopropyl ketones with hydride reagents was studied. High diastereoselectivities (15 to 20 : 1) were obtained with *cis*-cyclopropyl ketones, while virtually no facial selectivity was observed for the *trans*-analogues.

One of the continuing areas of investigation in organic synthesis is the stereoselective construction of compounds via carbonyl addition strategies.[1] Stereocontrol in the reduction of acyclic ketones is governed by nearby stereocenters and the facial preference can often be predicted on the basis of an analysis of the reactive conformation in the transition state, eq. 1. We were interested in determining the diastereoselectivity of hydride addition in substrates bearing a cyclopropyl ring adjacent to the carbonyl group. We now report that the selectivity varies as a function of the stereochemistry of the substituent on the cyclopropyl ring.



(1)

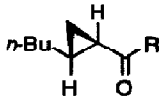
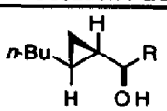
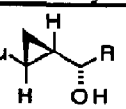
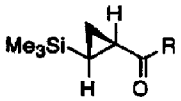
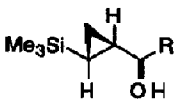
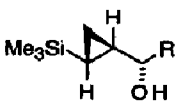
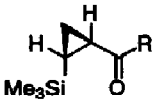
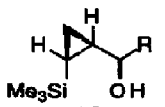
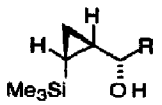
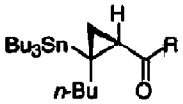
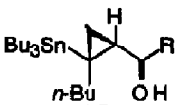
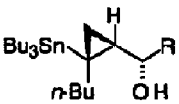
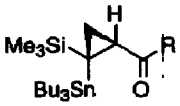
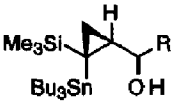
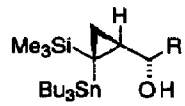
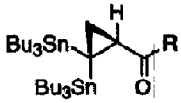
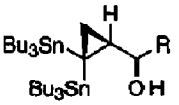
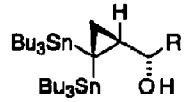
We recently described a highly diastereoselective cyclopropanation process of allylic alcohols **1**, using samarium metal and dihalomethane for the synthesis of bimetallic cyclopropyl carbinols, eq. 2.[2a] Cyclopropanes **2** are obtained as the major diastereomer whenever a (*Z*)-substituent is present (selectivities >50 : 1). Similar selectivities were noted by Molander for the analogous alkyl substituted derivatives.[2b,c] However, the diastereomeric products **3** are not directly accessible via the cyclopropanation of allylic alcohols.



(2)

When a cyclopropyl ketone **4**, bearing a substituent *cis* to the acyl group, was treated with $LiAlH_4$ in THF at 0 °C, the diastereomeric alcohol **3** was obtained in good yield and selectivity, eq. 2. The generality of this result was explored and the results are presented in Table 1.[3]

Table 1. Diastereoselectivity in the Reduction of Cyclopropyl Ketones.

Entry	Substrate	Reagent[a], Temperature, Time	Products / Diastereoselectivity[b]	Yield(%)[c]
			 **6**  **7**	
1	**5a** R = *c*-hexyl	$LiAlH_4$, 0 °C, 5 min	1 : 1	92
2	**b** *i*-Pr	$LiAlH_4$, 0 °C, 5 min	1 : 1	62
			 **9**  **10**	
3	**8** R = *c*-hexyl	$LiAlH_4$, 0 °C, 5 min	1 : 2.5	60
			 **12**  **13**	
4	**11** R = *n*-Pr	$LiAlH_4$, 0 °C, 5 min	1 : 15	48
			 **15**  **16**	
5	**14** R = *c*-hexyl	$LiAlH_4$, 0 °C, 5 min	1 : 15	88
			 **18**  **19**	
6	**17** R = *c*-hexyl	$LiAlH_4$, 0 °C, 5 min	1 : 20	85
7	**17**	Dibal-H, 0 °C, 5 min	1 : 26	92
8	**17**	Dibal-H, -78 °C, 3 h	1 : 29	95
9	**17**	L-Selectride, 0 °C to rt, 17 h	1 : 18	87
			 **21**  **22**	
10	**20** R = *c*-hexyl	$LiAlH_4$, 0 °C, 5 min	1 : 17	88

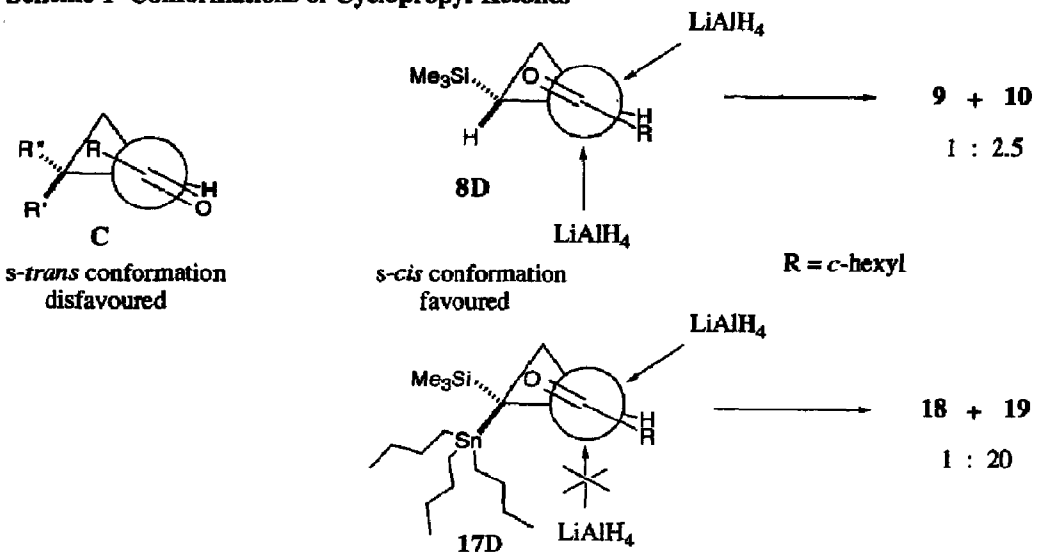
a) All reactions were performed as a 0.1 M solution of the ketone in THF, followed by addition of the reducing agent (1.1-1.5 eq) at the desired temperature. b) The diastereoselectivity was measured by ^1H NMR (400 MHz) on the crude mixture. c) Isolated yields of pure product are reported.

While the reduction of the disubstituted (*E*)-alkyl- and (*E*)-silyl cyclopropyl ketones **5a,b** and **8** was virtually non-selective, entries 1-3, treatment of the (*Z*)-silyl cyclopropyl ketone **11**, gave a 15 : 1 mixture of **13** and **12**, entry 4. Hydride delivery to the trisubstituted cyclopropyl ketones **14**, **17** and **20**, was also highly selective, entries 5-10.[4] A comparison of the hydride reagents showed that slightly higher diastereoselectivities can be obtained using Dibal-H (26-29 : 1), compare entries 6 with 7 and 8. L-Selectride^{R} offers no advantage over the aluminum based hydride reagents as the reaction is very sluggish and no improvement in the diastereoselectivity was observed, entry 9. For all cases examined, the diastereomeric alcohols were easily separated by flash chromatography on silica gel.

A survey of the literature revealed that little information on the selective reduction of *cis*-cyclopropyl ketones was available.[5,6] In an isolated example, a French group reported that treatment of a trisubstituted cyclopropyl ketone gave a 9 : 1 diastereomeric mixture of two cyclopropyl carbinols.[5] Later, Kitazume reported that trifluoromethyl cyclopropyl ketones could be diastereoselectively reduced using L-Selectride®. However, no specific selectivities were mentioned and the major cyclopropyl carbinols were obtained in low yield (37-46%).[6]

In order to explain the observed selectivity in the reduction, an understanding of the conformational analysis of cyclopropyl ketones is essential. The ability of the cyclopropyl group to conjugate with the adjacent carbonyl-π-electrons has been well established.[7] Both the s-*cis*-conformation **C** and s-*trans*-conformations **8D** and **17D**, are able to provide maximum stabilization, Scheme 1. In addition, it was found from both computational and spectroscopic studies, that the *s-cis-conformation* is favoured by 1.6-3.0 kcal mol^{-1} over the s-*trans*-conformation, depending on the substitution pattern on the cyclopropane.[7]

Scheme 1 Conformations of Cyclopropyl Ketones



The s-*cis*-conformer can be used as a model for the reduction of the cyclopropyl ketones, Scheme 1. It can be seen that in the case of the (*E*)-cyclopropyl ketone **8**, no facial preference for reduction of the ketone is expected. That is, the nucleophilic hydride experiences similar steric hindrance on both faces of the cyclopropyl ketone and a 1 : 2.5 mixture of alcohols **9** and **10** is obtained. This is in contrast to the (*Z*)-substituted

cyclopropyl ketone **17**, where a steric interaction between the (Z)-tributylstannyl substituent and the incoming hydride disfavours attack from one face of the ketone. Consequently, hydride attack will preferentially come from the less hindered side to form the diastereoisomer **19**. It is very interesting to realize that, just as in the cyclopropanation of the bimetallic allylic alcohols,[2a] it is again the (Z)-substituent which controls the diastereoselectivity in the reduction of these cyclopropyl ketones. The ability to remove the tin group following the cyclopropanation or reduction further highlights its use as a stereocontrol element.

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3. All cyclopropyl ketones were obtained in quantitative yield from oxidation of the cyclopropyl carbinols. While **5**, **8** and **11** were obtained via NaOAc buffered PCC oxidation of the alcohols **6**, **9** and **12**, milder conditions (TPAP, NMO) were required for conversion of the stannyl substituted cyclopropyl alcohols **15**, **18** and **21** to the corresponding ketones **14**, **17** and **20**. a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P. White, A. D. *J. Chem. Soc. Chem. Commun.* **1987**, 1625-1627. b) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13-19.
4. All new compounds were fully characterized using ^{1}H, ^{13}C and ^{119}Sn NMR, IR and high resolution mass spectral analysis or elemental analysis.
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