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Stereoselective Reduction of α-Cyclopropyl Ketones and α-Cyclopropyl Aldols. Stereo-directing Effect by α-Trimethylsilyl Group

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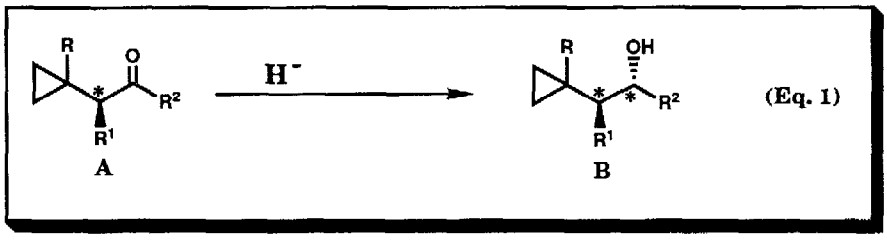
Summary: Stereoselective reduction of α-chiral α-cyclopropyl ketones and α-cyclopropyl aldols is described. Introduction of trimethylsilyl (TMS) group to the α-position of cyclopropyls leads to virtually complete stereoselection to give the stereo-defined β-cyclopropyl alcohols and 2-cyclopropyl-1,3-diols.

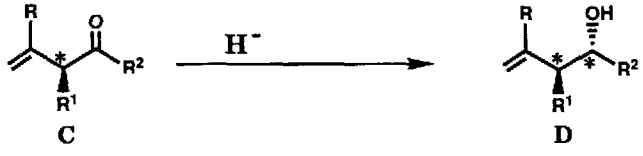
The stereochemical issue of the nucleophilic addition to α-chiral carbonyl compounds, known as the Cram problem, has long attracted interests from various standpoints.[1] Theoretically, several transition state models have been proposed to understand and predict the sense of π-facial selection including the original Cram model[2a] and the elaborated descendants by Felkin,[2b] Anh,[2c] and Houk.[2d] Synthetically, on the other hand, much efforts have been devoted to finding out the suitable substrates or reagents which enable the high stereoselectivity.

We wish to add here a novel example of the substrate structure which allow the highly Cram-selective reduction, that is, the α-chiral cyclopropyl carbonyl compounds **A** which are now readily obtainable by the stereospecific 1,2-rearrangements as described in the preceding paper.[3]

In our systematic study on the reduction of α-chiral α-vinyl carbonyl compounds **C** (Eq. 2)[4] there was documented the large stereo-directing effect of α-TMS group (R = TMS in **C**) which dictates the nucleophilic attack to **C** highly selective leading to **D**.[4] The effect is so large that the selectivity holds for a large variety of substrates possessing the substructure of **C**. Through the present study, the same tendency turned out to be true for the homologous cases, *i.e.* the cyclopropyl cases (Eq. 1), and the complete Cram-selectivity by introducing the TMS substituent in **A** (R = TMS) is also the subject of the present communication.

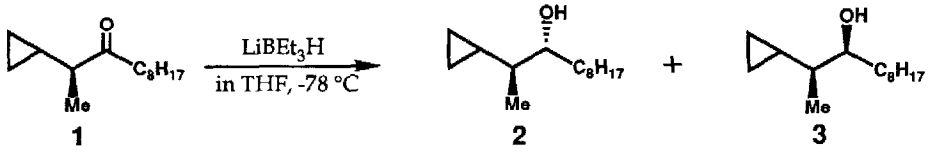


A **B** (Eq. 1)



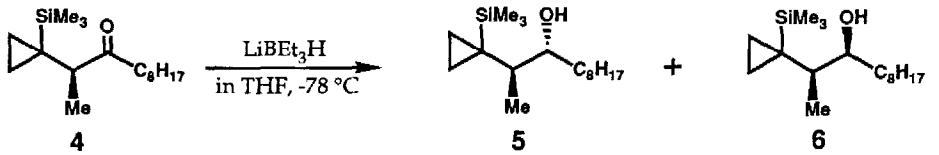
C **D** (Eq. 2)

First, we examined the reduction of α-cyclopropyl ketone, prepared by the pinacol-type rearrangement.[3] Ketone **1** was reduced with $LiBEt_3H$ in THF at -78 °C where the *anti*/*syn* ratio was 78 / 22.[5] Thus, the cyclopropyl group exerts the stereochemical bias in favor of the Cram-type reduction in 4/1 level of selectivity. The bias is further reinforced by the introduction of α-TMS substituent as can be clearly recognized in the reduction of **4**, which gave *anti*-alcohol **5** as the sole detectable product.[5-8]



1 **2** **3**

2 / 3 = 78 / 22



4 **5** **6**

5 / 6 = >99 / <1

These stereochemical features could be understood by the Felkin-Anh type model (Fig. 1) and the introduction of the TMS group (R = TMS) strongly encourages the reactions to occur *via* this transition state. Considering the pseudo-π character of the cyclopropyl bonds, the factor of orbital interaction between those of the cyclopropyl and carbonyl may be involved in stabilizing this transition state as pointed out by Anh,[2c] although the extent is not clear.

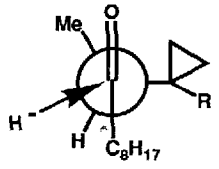
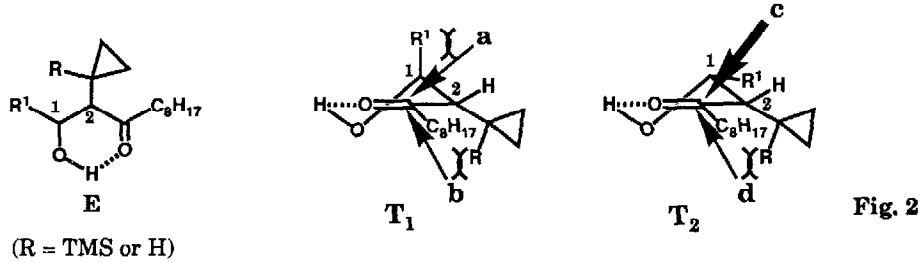


Fig. 1

Next, we turned our attention to the reduction of α-cyclopropyl aldols of general formula **E** (also obtainable *via* 1,2-rearrangement).[3] The effect of 1,3-chelate must be considered as an additional factor in these cases. Relevant to the reduction of α-substituted β-hydroxy carbonyl compounds, we proposed the hydrogen-bond chelate model, where the aldol itself **E** is the entity which undergoes the hydride attack rather than the metal aldolate. The model served well for explaining the stereochemical features of the reduction of α-vinyl aldols with $LiBEt_3H$.[4e]



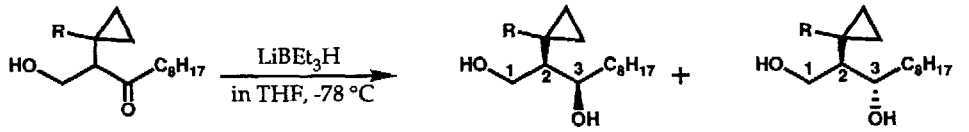
E **T_1** **T_2** **Fig. 2**

(R = TMS or H)

When the model is applied to the reduction of α-cyclopropyl aldols, following stereochemical predictions are available: The model for the reduction of *anti* aldols can be depicted as T_1 which predicts that the preferred stereochemical course depends on the relative size of the C(1)- and C(2)-substituents. On the other hand, in the case of *syn* aldols, the top face in T_2 is uniformly open for the hydride attack where the effects of two substituents (C(1), C(2)) work cooperatively. With these predictions in mind, we attempted the reduction of six substrates **7**, **10**, **13** (series **a** and **b**) and the isomeric compositions of the products were examined.

In the event, the reduction of α-cyclopropyl aldols with $LiBEt_3H$ proceeded in good accordance with these expectations.

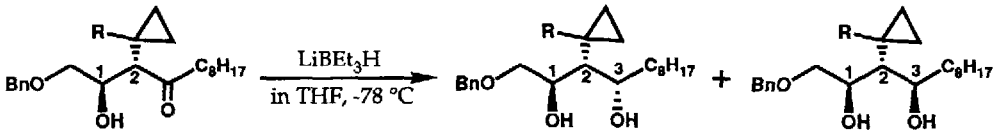
Aldol **7a** was reduced to *syn*-diol **8a** exclusively without the formation of *anti*-isomer **9a**.[5] In contrast, the reduction of **7b** without the TMS substituent proceeded in virtually non-stereoselective manner to give a mixture of **8b** and **9b**.[5]



7 **8** **9**

a: R = Me_3Si	>99	<1
b: R = H	60	40

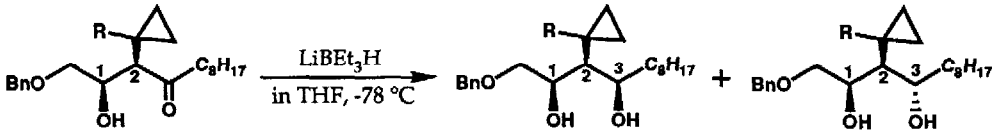
In the case of 1,2-*anti*-aldols **10**, an impressive reversal of the π-facial selection was observed *with/without* the TMS substituent. In the case of **10a** *with* the α-TMS substituent, the reduction led to the 2,3-*syn*-isomer **11a** exclusively. In sharp contrast, reduction of **10b** showed the reversed facial selectivity to afford 2,3-*anti* **12b** in high, if not exclusive, selectivity.[5] From these results, the stereochemistry of the products depends on the balance of steric biases of the cyclopropyl group and the benzyloxymethyl group. The trajectory **a** in T_1 is favored for **10a** (R = TMS), while the attack from **b** in T_1 is favored in the case of **10b** (R = H).



10 **11** **12**

a: R = Me_3Si	>99	<1
b: R = H	16	84

On the contrary, the reduction of 1,2-*syn*-aldols **13** proceeded in 2,3-*syn*-selective manner either in the presence of the TMS group (**13a**) or in its absence (**13b**) leading to **14a** and **14b**, respectively. The trend can be well understood by considering the model T_2.



13 **14** **15**

a: R = Me_3Si	>99	<1
b: R = H	86	14

These stereochemical features of the reduction of α-chiral α-cyclopropyl aldols are, as a whole, quite similar to those of the reduction of α-vinyl aldols.[4c-e]

The stereochemistries of 1,3-diols are based on the ^1H NMR (400 MHz) of their carbonate derivatives and the extensive correlation to the authentic samples[7] by ^1H NMR (400 MHz), GLC, and HPLC. The stereochemically pure samples of 2,3-*syn*-1,3-diols (**8b, 11b, 14b**) were obtained by desilylation of their TMS-homologs (**8a, 11a, 14a**) in high yields, respectively.[8]

In summary, the reduction of chiral α-cyclopropyl ketones and α-cyclopropyl aldols described herein, provides a useful synthetic method of stereo-defined alcohols and 1,3-diols possessing cyclopropyl group with rigorous selectivity. The stereo-directing effect of α-TMS group is quite versatile in this context, which, if necessary, may be removable in high yield.

The synthetic methods for the cyclopropane-containing compounds are now increasing the importance in relation to the synthesis of biologically active compounds.[9] Further work along these lines is in progress.

References and Notes

1) E. L. Eliel, *Asymmetric Synthesis*, Ed. by J. D. Morrison, Academic Press, New York, 1983, **2**, *pp* 125-156.

2) a) D. J. Cram & F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); b) M. Chérest, H. Felkin, & N. Prudent, *Tetrahedron Lett.*, **1968**, 2199; c) N. T. Anh & O. Eisenstein, *Nouv. J. Chim.*, **1**, 61 (1977); d) M. N. Paddon-Row, N. G. Rondan, & K. N. Houk, *J. Am. Chem. Soc.*, **104**, 7162 (1982).

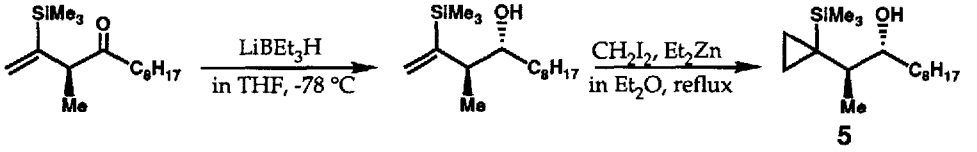
3) M.Shimazaki, H. Hara, & K. Suzuki, the preceding paper in this issue.

4) Stereo-directing effect of α-TMS group in the reduction of α-vinyl carbonyls: a) Review: K. Suzuki, *J. Synth. Org. Chem., Jpn.*, **46**, 365 (1988); b) K. Suzuki, E. Katayama, & G. Tsuchihashi, *Tetrahedron Lett.*, **25**, 2479 (1984); On the reduction of α-vinyl aldols: c) K. Suzuki, M. Shimazaki, & G. Tsuchihashi, *ibid.*, **27**, 6233 (1986); d) K. Suzuki, M. Miyazawa, M. Shimazaki, & G. Tsuchihashi, *ibid.*, **27**, 6237 (1986); e) K. Suzuki, M. Miyazawa, M. Shimazaki, & G. Tsuchihashi, *Tetrahedron*, **44**, 4061 (1988).

5) All new compounds were fully characterized by ^1H and ^{13}C NMR, IR, and high-resolution MS spectra.

6) The Mosher analysis (400MHz ^1H NMR and HPLC) of the alcohols **2** and **5** showed their homo-chiralities, which indicates that neither the 1,2-rearrangement step nor the reduction step involves racemization.

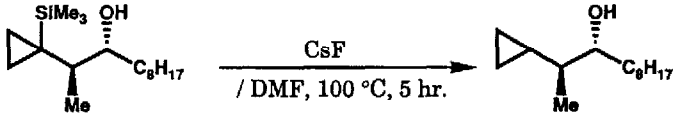
7) Authentic samples were prepared by Simmons-Smith methylenation of the stereochemically pure vinyl (nor-methylene) derivatives.[4] For example, a sample of **5** was prepared as follows.



5

For Simmons-Smith methylenation by Et_2Zn reagent: H. E. Simmons, T. L. Cairns, S. A. Vladuchick, & C. M. Hoiness, *Org. React.*, **20**, 1 (1973). For Zn-Cu reagent: R. J. Rawson & I. T. Harrison, *J. Org. Chem.*, **35**, 2057 (1970).

8) The TMS substituent can be easily removed from the cyclopropyl group. For example, the TMS group of **5** was removed as shown below to give **2** in 70% yield without any loss of optical purity.



5 **2**

9) C. J. Suckling, *Angew. Chem., Int. Ed. Engl.*, **27**, 537 (1988).

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