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Stereospecific 1,2-Rearrangement of Cyclopropyl Group. Synthesis of Chiral α-Cyclopropyl Ketones and α-Cyclopropyl Aldols

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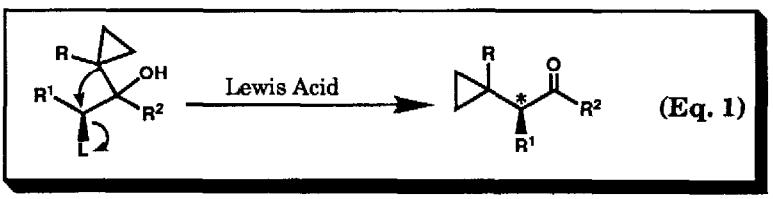
Summary: Stereospecific 1,2-rearrangement of cyclopropyl group is described as an efficient route to stereo-defined α-cyclopropyl ketones and α-cyclopropyl aldols. Acceleration of the reaction by the introduction of trimethylsilyl (TMS) group to the α-position of cyclopropyl group is also noted.

Cyclopropane-containing compounds are gaining growing interest in view of their specific and potentially useful biological functions such as enzyme inhibitory effects.[1] Thus, the synthetic methods which allow the selective preparation of this class of compounds are now needed.

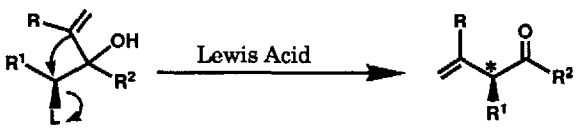
The chemistry of cyclopropyl group is characterized by the unusual bonding structure, *i.e.* bent bonds.[2] The significant π-character makes the chemical reactivities of this "sub-functional group" similar to those of C=C double bonds, which is the basis of many synthetically useful reactions of cyclopropyl groups including ring opening, ring enlargement and so on.[2]

Some time ago, we reported a method for acyclic stereocontrol based on the Lewis acid-promoted stereospecific 1,2-rearrangements, where vinyl group, or more generally, alkenyl groups are utilized as the versatile migrating group as shown in Eq. 2.[3,4] Based on the intrinsically donating nature stated above, we reasoned that cyclopropyl group may also act as a good migrating group in this type of cationic rearrangement reactions (Eq. 1).[5] The problem resides in the stereospecificity of the 1,2-migration as well as the possible competing reactions such as ring enlargement or ring fissions, the feature of which may be interesting from the theoretical standpoints.

In this communication, we wish to report the aspects of 1,2-rearrangement of cyclopropyl group which actually proceeds stereospecifically to offer a good route to a unique class of compounds, that is, chiral α-cyclopropyl carbonyl compounds. Also described is the remarkable rate acceleration of the 1,2-rearrangement by the introduction of TMS substituent to the α-position of the cyclopropyl group.

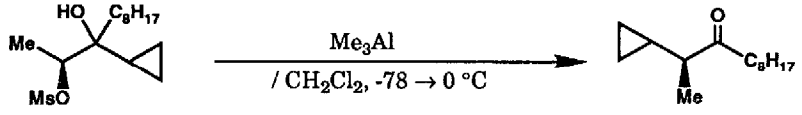


(Eq. 1)



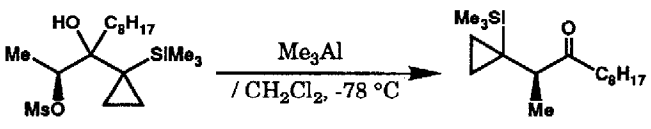
(Eq. 2)

First, the pinacol-type rearrangement was examined.[3] The starting β-mesyloxy alcohol **1** was prepared in optically active form from an *(S)*-lactic acid derivative.[6] Chiral mesylate **1** was treated with Me_3Al (2.5 equiv.) in CH_2Cl_2 at -78 °C and the temperature was gradually raised to 0 °C during 1 hr. Under these conditions, smooth 1,2-rearrangement of the cyclopropyl group occurred to give ketone **2** in 81% yield.[7] There were no products arising from the potential side reactions such as ring fission of the three membered ring. Moreover, the product resulting from the migration of the octyl group was also not detected, which indicates the difference of the migratory aptitudes between the cyclopropyl group and the alkyl (octyl) group is large enough to allow the selective migration.[5, 8]

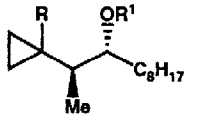


1 Yield 81 % **2**

In our previous study on the 1,2-rearrangement of alkenyl groups, we found that the introduction of an α-TMS substituent poses the rate enhancement effect.[3] By analogy, we prepared β-mesyloxy alcohol **3** in which the cyclopropyl group is armed with an α-TMS substituent. By the treatment of **3** with Me_3Al (2.5 equiv.), the reaction proceeded quite rapidly to be complete in 5 min at -78 °C (without warming) to afford α-chiral ketone **4** in essentially quantitative yield.[7] Therefore, also in the rearrangement of cyclopropyl group, the α-TMS substituent dramatically accelerates the rearrangement.[9]



3 Yield 95 % **4**



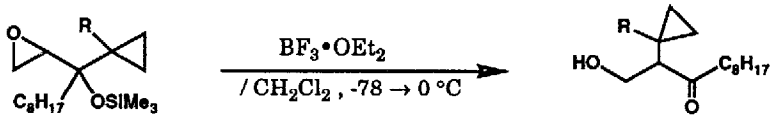
5: R^1 = H

6: R^1 = CF_3 Ph CO- OMe

(R = TMS, H)

The rearranged products, **2** and **4**, were proven to be optically pure within the limit of analysis, which verified the stereospecificity of the 1,2-rearrangement. The analyses were done for **6**, the MTPA derivatives of **5** (400 MHz ^1H NMR and HPLC). The hydride reductions of **2** and **4** by $LiBEt_3H$, performed for the preparation of **5**, were highly *anti*-selective as described in the following paper.[10]

Recently, we reported a new method for the stereoselective aldol synthesis *via* the 1,2-rearrangement of epoxy alcohols or epoxy silyl ethers.[4] We next examined the cyclopropyl group in this version of 1,2-rearrangement. Epoxy silyl ether **7a**[11] was treated with $BF_3 \cdot OEt_2$ (3 equiv.) in CH_2Cl_2 at -78 °C.



7 **8**

a: R = Me_3Si Yield 85 %

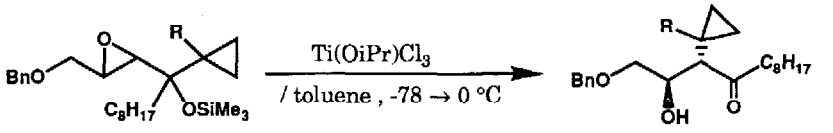
b: R = H Yield 59 %

During the gradual warming to 0 °C, silyl ether **7a** underwent clean 1,2-rearrangement of the cyclopropyl group to afford α-cyclopropyl aldol **8a** in 85% yield.[7] Silyl ether **7b** with simple cyclopropyl group also underwent 1,2-rearrangement to give aldol **8b**, however, in slightly decreased yield.

In order to confirm the stereospecificity, the reactions of isomeric epoxy silyl ethers *trans*-epoxide **9** and *cis*-epoxide **11** were examined. The reactions proceeded stereospecifically to give rise to *anti*-aldol **10** (from *trans*-epoxide **9**) and *syn*-aldol **12** (from *cis*-epoxide **11**) as expected.[7, 12] Thus, the cyclopropyl group undergoes stereospecific 1,2-migration with inversion in the rearrangement of epoxy silyl ethers.

Acceleration of the rearrangement by the TMS substituent was also obvious in this version of 1,2-rearrangements. In order that the rearrangement proceeds smoothly, the presence of this group is favorable (*Cf.* **7a** *vs.* **7b**, **9a** *vs.* **9b**) or indispensable (*Cf.* **11a** *vs.* **11b**).

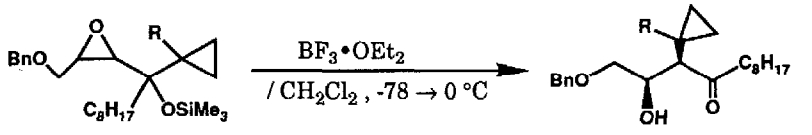
Although the reason is not clear, the rearrangements of *trans* isomers **9** with $BF_3 \bullet OEt_2$ failed leading to the formation of many undefinable products. Instead, the use of $Ti(OiPr)Cl_3$ in toluene gave satisfactory results.



9 **10**

a: R = Me_3Si Yield 79 %

b: R = H Yield 72 %



11 **12**

a: R = Me_3Si Yield 74 %

b: R = H Yield 25 %

These stereo-defined α-cyclopropyl aldols constitute an interesting class of compounds hardly accessible *via* conventional methods. Although the model reactions stated above were performed by using racemic epoxy silyl ethers, the easy accessibility of chiral starting materials (*e.g.* by Katsuki-Sharpless epoxidation)[13] renders this method an enantio- and diastereo-selective route to α-cyclopropyl aldols.

In summary, cyclopropyl group exhibits high migratory aptitude in the Lewis acid-promoted 1,2-rearrangement reactions, the pinacol-type rearrangement and the epoxy silyl ether rearrangement, which is reinforced by introducing an α-TMS substituent to the cyclopropyl group.

These features may be attractive from the theoretical standpoints. Further work is in progress to study the theoretical as well as the practical aspects of the present process.

References and Notes

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

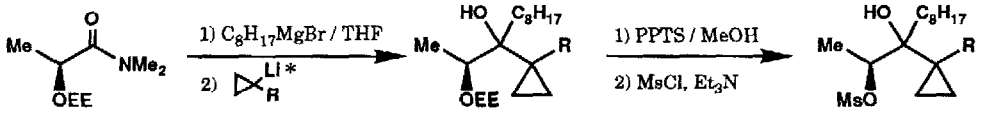
2) a) B. M. Trost, *Topics in Current Chemistry*, **133**, Springer, Berlin, 1986, *pp* 3-82; b) A. Greenberg & J. F. Liebman, *Strained Organic Molecules*, Academic, New York, 1978, *pp* 29-64.

3) a) Review: K. Suzuki, *J. Synth. Org. Chem., Jpn.*, **46**, 365 (1988) and references cited therein; b) K. Suzuki, E. Katayama, & G. Tsuchihashi, *Tetrahedron Lett.*, **25**, 1817 (1984); c) K. Suzuki, K. Tomooka, E. Katayama, T. Matsumoto, & G. Tsuchihashi, *J. Am. Chem. Soc.*, **108**, 5221 (1986).

4) a) K. Maruoka, M. Hasegawa, H. Yamamoto, K. Suzuki, M. Shimazaki, & G. Tsuchihashi, *J. Am. Chem. Soc.*, **108**, 3827 (1986); b) K. Suzuki, M. Miyazawa, & G. Tsuchihashi, *Tetrahedron Lett.*, **28**, 3515 (1987); c) M. Shimazaki, H. Hara, K. Suzuki, & G. Tsuchihashi, *ibid.*, **28**, 5891 (1987); d) K. Suzuki, M. Miyazawa, M. Shimazaki, & G. Tsuchihashi, *Tetrahedron*, **44**, 4061 (1988).

5) Former examples of the 1,2-migration of cyclopropyl group in cationic rearrangements follow: a) pinacol-type rearrangement: T. Shono, K. Fujita, S. Kumai, T. Watanabe, & I. Nishiguchi, *Tetrahedron Lett.*, **1972**, 3249; S. C. Bunce, S. D. Clemans, & B. A. Bennett, *J. Org. Chem.*, **40**, 961 (1975); b) Baeyer-Villiger oxidation: W. D. Emmons & G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

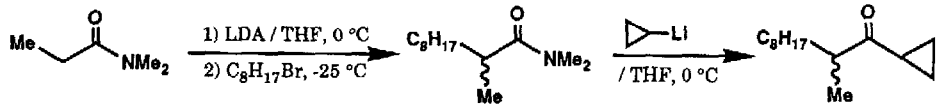
6) The starting material was prepared from (*S*)-lactamide derivative as follows. See ref. 3.



*) L. A. Paquette, G. J. Wells, K. A. Horn, & T.-H. Yan, *Tetrahedron*, **39**, 913 (1983).

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

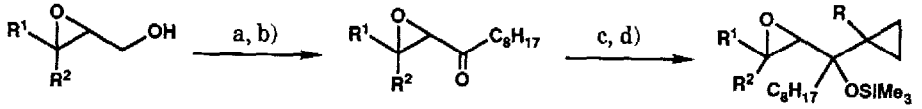
8) Authentic sample for the "wrong migration product" (by octyl migration) was prepared as follows.



9) The origin of this rate-acceleration by TMS may be ascribable to following two possible effects; 1) the effect of orbital interaction and 2) the steric compression to raise the energy level of the reactant. Work is in progress to clarify the relative significance of these factors.

10) M. Shimazaki, H. Hara, & K. Suzuki, the following paper in this issue.

11) Starting epoxy silyl ethers were prepared by the following scheme. See ref. 4.



a) Swern oxidation followed by $C_8H_{17}MgBr$ *in situ*, b) $(n\text{-}Pr)_4N^+RuO_4^-$, NMO*),
c) cyclo-(C_3H_4)(R)Li, d) TMSCl, imidazole.
*) W. P. Griffith, S. V. Ley, G. P. Whitcombe, & A. D. White, *J. Chem. Soc., Chem. Commun.*, **1987**, 1625.

12) For the stereochemistry of aldols **10** and **12**, see ref. 10.

13) T. Katsuki & K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980). For catalytic version: Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, & K. B. Sharpless, *ibid.*, **109**, 5765 (1987).

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