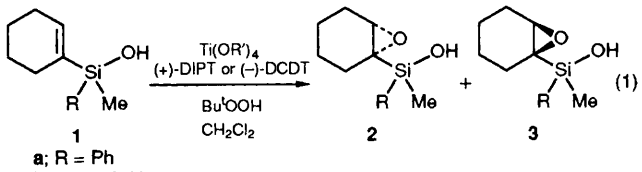
Kinetic Resolution of (±)-Cyclohex-1-enylsilanols by the Sharpless Asymmetric Epoxidation

Keiji Yamamoto,* Yukio Kawanami and Masahiro Miyazawa

Department of Chemical Engineering, Tokyo Institute of Technology, O-okayama, Meguro, Tokyo 152, Japan

Unprecedented kinetic resolution of (±)-cyclohex-1-enylsilanols **1** by the Sharpless asymmetric epoxidation has been accomplished, the rate difference between enantiomers, k_{rel}, being >11 to give enantiomerically pure cyclohex-1-enylcyclohexylmethylsilanol **1b** in a particular case.

We report here the first example of kinetic resolution *via* the Sharpless epoxidation[1] of racemic cyclohex-1-enylsilanols **1** [eqn. (1)]. Although it is known that one should be wary of attempting to asymmetrically epoxidize or kinetically resolve allylic alcohols of high steric demands,[2] there has been a report[3] which involves an efficient asymmetric epoxidation of dimethylstyrylsilanol, a sila-analogue of *tertiary* allylic alcohol, under the standard Sharpless conditions.[1b] However, our attempted epoxidation of racemic methylphenylstyrylsilanol was found to exhibit neither acceptable diastereoselection in the epoxides nor detectable kinetic resolution in the substrate, but rather resulted in forming siloxane predominantly.



1 **2** **3**

a; R = Ph
b; R = c-C_6H_{11}

The desired cyclohex-1-enylmethylphenylsilanol **1a**† was prepared by a sequential introduction of phenylmagnesium bromide and cyclohex-1-enyllithium to $MeSiCl_3$ to give c-$C_6H_9MePhSiCl$ which in turn was hydrolysed using a buffer solution (KH_2PO_4–NaOH, pH 7.0). Also, cyclohex-1-enylcyclohexylmethylsilanol **1b**† was obtained by way of the Pt-catalysed hydrosilylation of cyclohexene with $HSiMeCl_2$ to give an intermediate dichlorosilane, c-$C_6H_{11}MeSiCl_2$.

The stoichiometric Sharpless epoxidation of **1a** (1 mmol) using $Ti(OPr^i)_4$–(+)-diisopropyl tartrate (DIPT)–Bu^tO_2H (TBHP: 2.9 mol dm^{-3} isooctane solution) in a ratio 1.0:1.2:0.6 in dry CH_2Cl_2 (10 ml) at −20 °C for 2 days proceeded steadily to form a diastereoisomer mixture of 1,2-epoxycyclohexylmethylphenylsilanol (**2a** and **3a**)† in a ratio 75:25 in 43% combined yield (at 57% conversion) along with a recovery of **1a** in 32% isolated yield. The enantiomeric excess (e.e.) of each component was determined by ^1H NMR using a chiral shift reagent, Eu(hfc)$_3$‡ to be 8% e.e. (**1a**), 8% e.e. (**2a**) and 15% e.e. (**3a**), respectively. Thus, the calculated rate difference, k_{rel}, was 1.2. [By definition, $k_{rel} = k_{fast}/k_{slow} = \ln(1 - conv)(1 - e.e.)/\ln(1 - conv)(1 + e.e.)$]. In addition, it is noteworthy that, without any tartrate ligand, the epoxidation of **1a** proceeded very rapidly in the presence of 1 equiv. of $Ti(OPr^i)_4$ and TBHP, respectively, reaching almost completion in 3 h and that the diastereoselection for **2a** and **3a** was unchanged (75:25).

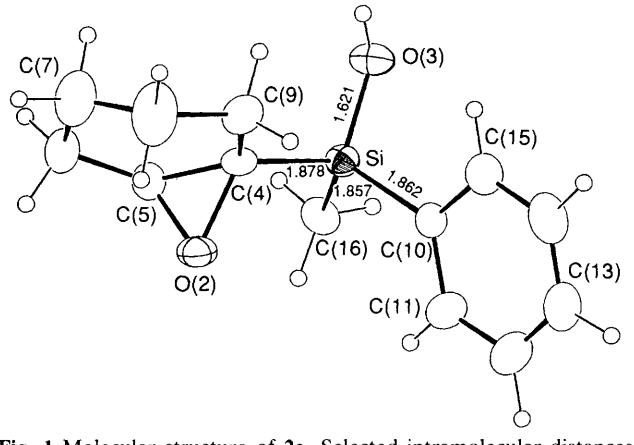


Fig. 1 Molecular structure of **2a**. Selected intramolecular distances (Å) are given.

That the major epoxidation product is *erythro* was confirmed by an X-ray crystallography§ (see Fig. 1) of pure **2a** which was obtained by rapid epoxidation of **1a**. We have also prepared, from natural cholesterol and racemic c-$C_6H_9MePhSiCl$, 3-silyl-protected cholesterol **4** which forms colourless crystals. The diastereoisomeric mixture of **4** was resolved by recrystallization (from hexane–acetonitrile) to form single crystals **4a**,† an X-ray structure¶ of which is shown in Fig. 2, indicating an absolute configuration at the silicon atom *S*. Cleavage of **4a** with powdered KOH in hot xylene followed by hydrolysis (retention of configuration at Si)[4] gave $(S)_{Si}$-cyclohex-1-enylmethylphenylsilanol [$(S)_{Si}$-**1a**], which was fortuitously identical to that recovered from the present kinetic

† All new compounds prepared here gave satisfactory spectral and analytical data.

‡ *Abbreviations used*: Eu(hfc)$_3$ = tris[3-heptafluoropropylhydroxymethylene-(+)-camphorato]europium(III). Eu(fod)$_3$ = tris-(6, 6, 7, 7, 8, 8, 8-heptafluoro-2, 2-dimethyl-3, 5-octanedionato)europium(III). Eu(dppm)$_3$ = (+)-tris[di(perfluoro-2-propoxypropionyl)-methanato]europium(III).

§ *Crystal data* for **2a**: $C_{13}H_{18}O_2Si$, M = 234.36, monoclinic, space group $C2/c$ (No. 15), a = 29.459(11), b = 5.7431(8), c = 16.993(4) Å, β = 117.61(2)°, V = 2548(1) Å^3, Z = 8, D_c = 1.194 g cm^{-3}, λ(Mo-Kα) = 0.71059 Å, μ(Mo-Kα) = 1.62 cm^{-1}. Final R value 0.086, R_w = 0.088 for 2458 reflections with $F_o > 3\sigma(F_o)$. Intensity data were collected at 25 °C on a Rigaku AFC-5 automated four-circle diffractometer with graphite-monochromated Mo-Kα radiation in the $2° < 2\theta < 55°$ range. Data processing was performed on a FACOM A-70 computer by using the R-CRYSTAN structure solving system obtained from the Rigaku Corp., Tokyo, Japan. The position of the Si atom was located by the direct method (SAPI 85). Subsequent difference Fourier synthesis revealed the positions of all the non-hydrogen atoms. All the non-hydrogen atoms were refined anisotropically, and the positions of the hydrogen atoms were confirmed with B(H) = 0.9 B (C or O).

¶ *Crystal data* for **4a**: $C_{40}H_{62}OSi$, M = 587.025, monoclinic, space group $C2$, a = 44.870(2), b = 6.065(2), c = 13.920(2) Å, β = 102.269(7)°, V = 3701(1) Å^3, Z = 4, D_c = 1.053 g cm^{-3}, λ(Cu-Kα) = 1.54184 Å, μ(Cu-Kα) = 6.77 cm^{-1}, Final R value 0.071, R_w = 0.087 for 2058 relfection with $F_o > 3.0\sigma(F_o)$. Diffraction measurement was made on a Rigaku AFC-5R four-circle diffractometer by using graphite-monochromated Cu-Kα radiation in the $3° < 2\theta < 125°$. Data processing was performed on a Micro VAX II computer by using the TEXSAN crystallographic software package (Molecular Structure Corp., 1985). The structure was solved by direct methods and refined by full-matrix least-squares. Hydrogen atoms were calculated geometrically except those attached to C(1) to C(12), C(39) and C(40) which have large thermal parameters. Non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms were refined with fixed isotropic thermal parameters.

Atomic coordinates, bond lengths and angles, and thermal parameters for compounds **2a** and **4a** have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

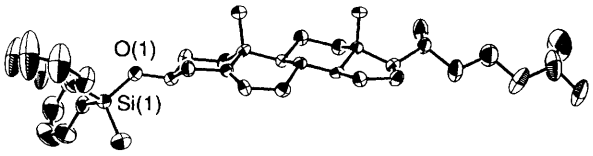


Fig. 2 ORTEP drawing of $(S)_{Si}$-[(cholest-5-en-3β-yl)oxy]cyclohex-1-enylmethylphenylsilane **4a**

resolution of (±)-**1a** (a sample with 20% e.e. obtained in another run). Thus, in consonance with the proposed transition state models for the asymmetric epoxidation of secondary allylic alcohols,[1c] we have identified both the moderate diastereoselectivity for **2a** over **3a** in the smooth epoxidation of a sila-analogue of tertiary allylic alcohol, **1a**, to be *erythro* and the fast reacting enantiomer in the epoxidation using the natural tartrate–Ti(OPr^i)$_4$–TBHP to be $(R)_{Si}$-**1a**, the efficiency of kinetic resolution being poor.

When **1b** was used, we have observed a definite rate difference in epoxidation, k_{rel} = 3.6, which results in giving enantiomerically enriched **1b**: To a mixture of (+)-DIPT (0.37 g, 1.6 mmol), **1b** (0.15 g, 0.66 mmol) and powdered molecular sieve 4A (300 mg) in dry CH_2Cl_2 (7 ml), cooled to −20 °C under an argon atmosphere, was added Ti(OEt)$_4$ (0.27 ml, 1.3 mmol) and the mixture was stirred for 0.5 h. Then, TBHP (3.4 mol dm^{-3} in CH_2Cl_2, 0.15 ml) was added and the whole mixture was stored at −20 °C for 39 h. After the usual workup, a mixture (0.46 g) of **1b**, **2b** and **3b** along with (+)-DIPT was obtained. An aliquot (5 mg) was analysed by ^{1}H NMR using Eu(fod)$_3$‡ (4.9 mg) to determine the conversion (64%) and the diastereoisomer ratio (**2b** : **3b** = 94 : 6). The remaining product mixture was separated by silica-gel column chromatography (eluent hexane–diethyl ether, 7 : 1) to give **1b** (58 mg, 39% recovery) and a mixture of **2b** and **3b**† (95 mg, 60% yield) as white crystals. The e.e.s of **1b**, **2b** and **3b** were determined using either Eu(dppm)$_3$‡ (20 mol%) or Eu(hfc)$_3$ (10 mol%), respectively, to be 62% **1b**, 30% **2b** and 52% **3b**; **1b**, $[\alpha]_D^{25}$ + 4.9 (*c* 0.49, cyclohexane). Furthermore, it is noted that among two sets of enantiomeric methyl singlets of ^{1}H NMR signals for **2b** and **3b** in the presence of Eu(hfc)$_3$, both the most-shifted signal **2b** and the least-shifted one **3b** exhibit the respective major enantiomer, most probably corresponding to the same configuration *R* at the silicon atom, and that this is the case for **2a** and **3a** described above. By substituting (−)-dicyclododecyl tartrate (DCDT: an unnatural tartrate) for (+)-DIPT and with added molecular sieve 4A under otherwise equal conditions, we have observed even higher rate difference k_{rel} > 11 at 71% conversion in the epoxidation, which gives rise to $(R)_{Si}$-**1b** with >99% e.e., diastereoisomer ratio being practically unchanged (**2b** : **3b** = 95 : 5).

In conclusion, although it is still unclear whether the reaction system for the epoxidation of the sila-analogue of *tertiary* allylic alcohols **1** is too congested around the chirally modified Ti atom(s) to exhibit effective rate discrimination between the enantiomers of **1**, we have achieved k_{rel} > 11 using **1b** under proper Sharpless conditions.

We thank Professor Y. Ohashi and Dr M. Akita (T.I.T.) for X-ray structure analyses of **4a** and **2a**, respectively. Support by the Ministry of Education, Science, and Culture, Japan (Grant No. 04403018) is gratefully acknowledged.

Received, 7th December 1992; Com. 2/06514B

References

1 (*a*) Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765; (*b*) B. E. Rossiter, *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1985, vol. 5, ch. 7, pp. 205–208; (*c*) M. G. Finn and K. B. Sharpless, *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1985, vol. 5, ch. 8, pp. 272–287; (*d*) R. A. Johnson and K. B. Sharpless, *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, New York, 1992, vol. 7, ch. 3.2.

2 M. J. Schweiter and K. B. Sharpless, *Tetrahedron Lett.*, 1985, **26**, 2543; B. H. McKee, T. H. Kalanter and K. B. Sharpless, *J. Org. Chem.*, 1991, **56**, 6966.

3 T. H. Chan, L. M. Chan and D. Wang, *J. Chem. Soc., Chem. Commun.*, 1988, 1280.

4 L. H. Sommer, *Stereochemistry, Mechanism, and Silicon*, McGraw-Hill, New York, 1965, p. 54.