CROATICA CHEMICA ACTA CCACAA **69** (4) 1421–1436 (1996)

ISSN-0011-1643
CCA-2385 *Original Scientific Paper*

Beta Secondary Deuterium Kinetic Isotope Effects on the Thermal Stereomutations of 1,2-Diphenylcyclopropanes†

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Received May 2, 1996; accepted July 2, 1996

(+)-(1*S*,2*S*)-*trans*-1,2-Diphenylcyclopropane and (–)-(1*R*,2*R*)-*trans*-1,2-diphenyl-3,3-d_2-cyclopropane at 234 °C interconvert reversibly with the corresponding enantiomers and *cis*-1,2-diphenylcyclopropanes. For the unlabeled *trans* isomer, the ratio of rate constants for one-center epimerization (k_1) and two-center turnover (k_{12}) was found to be 1.1. A small normal k_H/k_D effect, 3% per deuterium, was observed for the rate constant for one-center epimerization (k_1); a substantial normal k_H/k_D effect, 17% per deuterium, was observed for the rate constant for two-center turnover (k_{12}). Thus different transition structures, presumably EF and EE 1,3-diphenyltrimethylene diradicals, dominate the two sorts of stereomutations.

INTRODUCTION

The thermal stereomutations of cyclopropanes and substituted cyclopropanes may involve interconversions between diastereomers and enantiomers; the mechanistic aspects of such geometrical and optical isomerizations have received substantial experimental and theoretical attention over the past 30 years.[1] Yet there has been but one report of experimentally determined secondary deuterium kinetic isotope effects for such reactions: at 242 °C, the *trans*-to-*cis* geometrical isomerizations of 1-cyano-2-phenylcyclopropanes take place with normal k_H/k_D effects for the sum of the two one-

† *In memoriam:* Stanko Borčić (March 1, 1931 – December 21, 1994).

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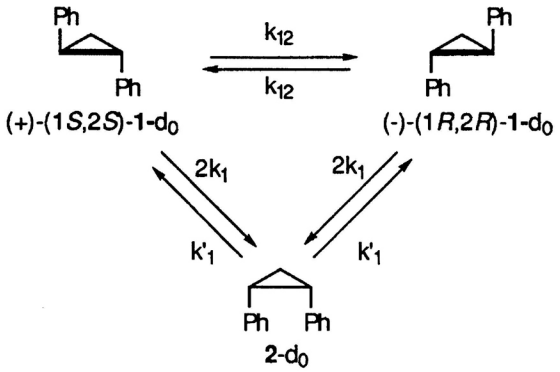
center epimerization rate constants ($k_1 + k_2$) of 1.07 ± 0.02 for deuterium substitution at C1 and 1.13 ± 0.02 for monodeuterium substitution at C3.[2] Attempts to extend this initial study to secure experimental k_H/k_D ratios for k_1, k_2, and k_{12} were not successful, for the experimental uncertainties and the apparent k_H/k_D ratios were found to be of comparable magnitudes.[3]

The present work was undertaken to determine β secondary deuterium kinetic isotope effects on the thermal interconversions among the 1,2-diphenylcyclopropanes. This system was selected for it is relatively simple kinetically, there is no doubt about which C-C bond of the cyclopropane cleaves, and the enantiomeric *trans* forms may be resolved through HPLC on a chiral triacetylcellulose column,[4] thus providing a sensitive and accurate method for following changes in enantiomeric excess values. Further, the required substrates were thought to be synthetically accessible in excellent optical purity and very high deuterium incorporation, and no complications attendant upon thermal structural isomerizations to 1,3-diphenylpropenes were anticipated.



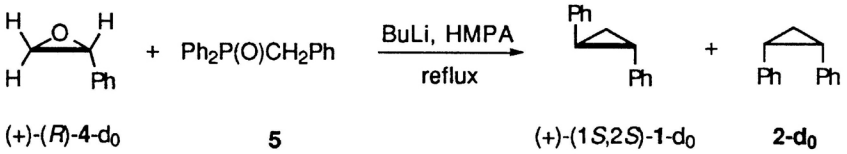
Scheme I

Earlier work on the *cis, trans* isomerization of 1,2-diphenylcyclopropanes[5,6] was capped by a kinetic study of the interconversions of Scheme I starting with (–)-(1*R*,2*R*)-**1**-d_0 reported by Crawford and Lynch in 1968;[7] the $k_1 : k_{12}$ rate constant ratio was found to be about 2 : 1, thus demonstrating for the first time the mechanistically most significant fact that one-center and two-center thermal epimerizations of substituted cyclopropanes take place at comparable rates. In subsequent years this result has turned out to be quite general for geometrically unconstrained cyclopropanes, whatever the substituents.[1]

RESULTS

Syntheses

Samples of *rac*-**1**-d_0 and **2**-d_0 were prepared from benzylideneacetophenone,[8] and optically active *trans*-1,2-diphenylcyclopropane, (+)-(1*S*,2*S*)-**1**-d_0, was synthesized[9–11] from commercially available styrene oxide, ((+)-(*R*)-**4**-d_0), of 100% ee as determined by chiral GC. On a Cyclodex B capillary GC column at 90 °C (+)-(*R*)- styrene oxide had a retention time of 27.2 min; its enantiomer elutes at 28.9 min (Figure 1). The *trans*-1,2-diphenylcyclopropane product (+)-(1*S*,2*S*)-**1**-d_0 obtained was determined to be of 100% ee



by chiral HPLC (Figure 2). Under the HPLC conditions employed, **2**-d_0 elutes some 14 min after the second enantiomer, and does not interfere with determinations of ee.

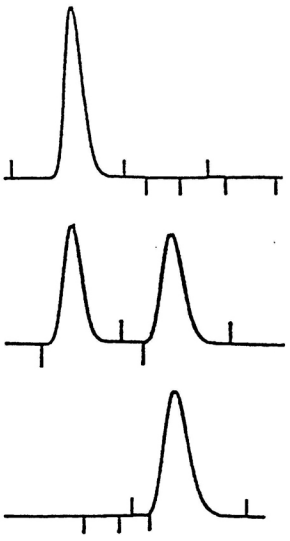


Figure 1. Chiral GC resolution of styrene oxides on a Cyclodex B column at 90 °C: top, (+)-(*R*)-**4**-d_0, retention time 27.2 min; middle, *rac*-**4**-d_0; bottom, (–)-(*S*)-**4**-d_2, retention time 28.9 min.

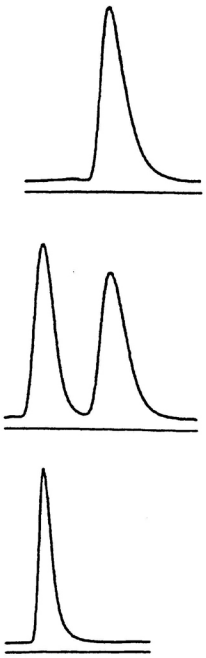
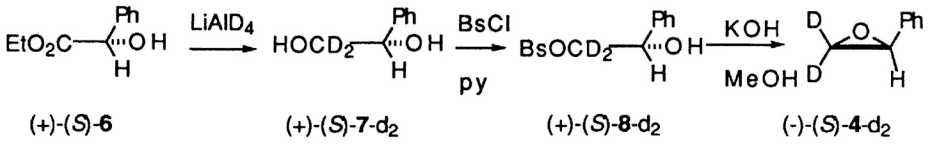
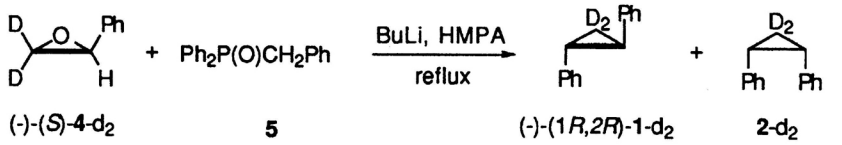


Figure 2. HPLC analyses of *trans*-1,2-diphenylcyclopropanes on a triacetylcellulose column; top, (+)-(1*S*,2*S*)-**1**-d_0), retention time 65.5 min; middle, *rac*-**1**-d_0; bottom, (–)-(1*R*,2*R*-)-**1**-d_2, retention time 49.5 min.

Syntheses of (–)-(1*R*,2*R*)-**1**-d_2 depended on the same chemistry and on the corresponding deuteriated styrene oxide, (–)-(*S*)-**4**-d_2, which was secured from ethyl (+)-(*S*)-mandelate following the precedent of Tömözközi.[10,11] The deuteriated styrene oxide (–)-(*S*)-**4**-d_2 was of 100% ee as determined by chiral GC (Figure 1) and of 100% deuterium incorporation as determined by ^{1}H-NMR criteria.

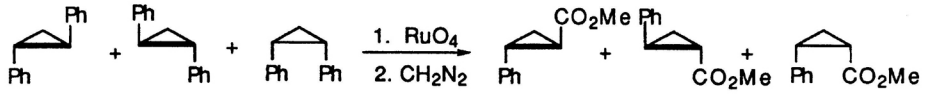
Reaction of (–)-(*S*)-**4**-d_2 with benzyldiphenylphosphine oxide gave *cis*-1,2-diphenyl-3,3-d_2-cyclopropane and (–)-(1*R*,2*R*)-*trans*-1,2-diphenyl-3,3-d_2-cyclopropane in good yield and with 100% deuterium incorporation, according to ^{1}H-NMR criteria. The sample of (–)-(1*R*,2*R*)-**1**-d_2 was enantiomerically pure (Figure 2).





(-)-(*S*)-**4**-d_2 **5** (-)-(1*R*,2*R*)-**1**-d_2 **2**-d_2

In order to check the enantiomeric excess character of *trans*-1,2-diphenylcyclopropanes from thermal reaction mixtures by an independent method, the hydrocarbons were converted to methyl 2-phenylcarboxylates. Oxidation with ruthenium tetroxide converted one of the two phenyl groups in each 1,2-diphenylcyclopropane to a carboxylic acid function; esterification of the mixture with diazomethane then gave (1*R*,2*R*)-**9**, (1*S*,2*S*)-**9**, and *rac*-**10**. Six of the ten kinetic product mixtures were subjected to RuO_4 oxidation, esterification, and chiral GC analysis; on the Lipodex E column used, the (1*R*,2*R*) enantiomer eluted first.[12]



(1*R*,2*R*)-**1**-d_0 (1*S*,2*S*)-**1**-d_0 **2**-d_0 (1*R*,2*R*)-**9** (1*S*,2*S*)-**9** rac-**10**

Kinetics

The reversible thermal interconversions of *cis* and *trans* isomers of 1,2-diphenylcyclopropanes at a given temperature depend on only two kinetic parameters when no distinctions are made between enantiomers; in terms of the rate constants defined in Scheme I they may be expressed as $k_i = 2(k_1 + k'_1)$ and the equilibrium constant $K = k'_1/k_1$. The time-dependent mol fractions of each isomer are given by Eqs. 1 and 2.

$$[\mathbf{1}(t)] = K/(K + 1) - ((K/(K + 1)) - [\mathbf{1}(t = 0)]) * \exp(-k_i t) \quad (1)$$

$$[\mathbf{2}(t)] = 1/(K + 1) - ((1/(K + 1)) - [\mathbf{2}(t = 0)]) * \exp(-k_i t) \quad (2)$$

When isomerizations of chiral *trans* isomers are studied the racemization of the system of *trans* and *cis* isomers follows simple first-order kinetics (Eq. 3); the relative optical activity at any time is dependent on the enantiomeric excess and the mol fraction of the *trans* diastereomer present (Eq. 4).

$$\alpha/\alpha_0 = \exp(-k_\alpha t) \quad (3)$$

$$\alpha/\alpha_0(t)(\%) = \text{ee of } \mathbf{1}(t)(\%) * [\mathbf{1}(t)] \quad (4)$$

The loss of optical activity of a chiral version of **1** results from direct formation of its enantiomer and from the formation of achiral **2**. Hence the rate constant equality $k_\alpha = (2k_{12} + 2k_1)$ applies.

Geometrical Isomerizations

The first-order approach to *cis-trans* equilibrium governed by k_i and K was followed starting from labeled and unlabeled *cis-* and *trans*-1,2-diphenylcyclopropanes, using capillary GC for analyses; the data are summarized in Tables I and II. The experimental points were fit by the two-parameter functions given by Eq. 1 and 2, using DeltaGraph software.[13] Equal values of k_i are required starting from either diastereomer, and they were found with $K = 6.4$ (at equilibrium, 86.5% *trans*, 13.5% *cis*); the equilibrium isotope effect was taken to be unity. Starting from the *cis* isomers **2**-d_0 and

TABLE I

Isomer distributions from thermal stereomutations of *cis*-1,2-diphenylcyclopropane (**2**-d_0) and *cis*-1,2-diphenyl-3,3-d_2-cyclopropane (**2**-d_2) at 234 °C

Time min	**2**-d_0	*rac*-**1**-d_0	*rac*-**1**-d_0 (calc)[a]	**2**-d_2	**1**-d_2	**1**-d_2 (calc)[b]
0	100	0	0	100	0	0
25	75.1	24.9	25.0	77.0	23.0	23.8
50	57.6	42.4	42.7	59.2	40.8	41.0
75	43.9	56.1	55.4	45.8	54.2	53.5
105	34.5	65.5	65.8	35.9	64.1	64.0

[a] *rac*-**1**-$d_0(t) = 86.5 * (1 - \exp(-2.27 \times 10^{-4}\ s^{-1} * t))$.

[b] **1**-$d_2(t) = 86.5 * (1 - \exp(-2.14 \times 10^{-4}\ s^{-1} * t))$.

TABLE II

Isomer distributions from stereomutations of *rac*-**1**-d_0 and (–)-**1**-d_2 at 234 °C

Time min	**2**-d_0	*rac*-**1**-d_0	*rac*-**1**-d_0 (calc)[a]	**2**-d_2	(–)-**1**-d_2	(–)-**1**-d_2 (calc)[b]
0	0	100	100	0	100	100
25	4.0	96.0	96.1	4.2	95.8	96.3
50	6.8	93.2	93.3	6.6	93.4	93.6
75	8.6	91.4	91.4	8.4	91.6	91.7
100	10.0	90.0	90.0	9.8	90.2	90.2

[a] *rac*-**1**-$d_0(t) = 86.5 + (13.5 * \exp(-2.27 \times 10^{-4}\ s^{-1} * t))$.

[b] (–)-**1**-$d_2(t) = 86.5 + (13.5 * \exp(-2.14 \times 10^{-4}\ s^{-1} * t))$.

2-d_2 the rate constants $k_i(d_0) = 2.27 \times 10^{-4}$ s^{-1} ($R^2 = 0.997$) and $k_i(d_2) = 2.14 \times 10^{-4}$ s^{-1} ($R^2 = 0.999$) were obtained. These rate constants provided excellent predictions for relative concentrations as functions of time for reactions starting with **1**-d_0 and **1**-d_2. For k_i values the k_H/k_D ratio is only 1.06, or 3% per deuterium. Since $k_i = 2(k_1 + k'_1)$, and at equilibrium 6.4 * $2k_1 = 2k'_1$, one may calculate $k_1(d_0) = 1.53 \times 10^{-5}$ s^{-1} and $k_1(d_2) = 1.45 \times 10^{-5}$ s^{-1}.

Enantiomerizations and Racemizations

Kinetic experiments with samples of both (+)-**1**-d_0 and (–)-**1**-d_2, 100% ee by chiral HPLC analyses (Figure 2), were run in parallel to obtain the data summarized in Tables III and IV.

TABLE III

Isomer distributions of **1**-d_0 and **2**-d_0 from stereomutations of (+)-**1**-d_0 at 234 °C as determined by capillary GC and chiral HPLC

Time/h	**1**-d_0 (obs)	**1**-d_0 (calc)[a]	**1**-d_0 (% ee)	α/α_0[b]	α/α_0[c]
0	100	100	100	1.00	1.00
1	92.6	92.5	82.8	0.766	0.812
3	88.7	87.7	59.6	0.523	0.535
6	88.6	86.6	32.6	0.282	0.286
9	88.8	86.5	17.8	0.154	0.153
12	89.1	86.5	9.4	0.081	0.082

[a] **1**-$d_0(t) = 86.5 + (13.5 * \exp(-2.27 \times 10^{-4}\ s^{-1} * t))$.

[b] (ee of **1**-d_0 (%)) * **1**-d_0 (calc)/100.

[c] $\alpha/\alpha_0(t) = \exp(-5.79 \times 10^{-5}\ s^{-1} * t)$.

Some reaction mixtures from chiral samples were subjected to an alternative mode of analytical assessment: the ee values for the *trans*-1,2-diphenylcyclopropanes were deteremined by chiral GC of the corresponding *trans*-2-phenylcyclopropanecarboxylates **9**-d_0 and **9**-d_2 obtained through oxidation of one phenyl group followed by esterification with diazomethane. The findings are presented in Table V. The chiral GC and chiral HPLC methods for measuring the enantiomer excesses of the 6-, 9- and 12-h kinetic points provided results showing quite a fair agreement. All the experimental data, 9 (time, α/α_0) points for labeled and for unlabeled systems, were used to find the best one-parameter matches with the theoretical exponential functions: the values found were $k_\alpha(d_0) = 5.79 \times 10^{-5}$ s^{-1} ($R^2 = 0.998$) and $k_\alpha(d_2) = 4.89 \times 10^{-5}$ s^{-1} ($R^2 = 0.998$).

TABLE IV

Isomer distributions of **1**-d_2 and **2**-d_2 from (–)-**1**-d_2 at 234 °C as determined by capillary GC and chiral HPLC

Time/h	**1**-d_2 (obs)	**1**-d_2 (calc)[a]	**1**-d_2 (% ee)	α/α_0[b]	α/α_0[c]
0	100	100	100	1.00	1.00
1	93.0	92.7	88.8	0.823	0.839
3	90.7	87.8	66.2	0.581	0.590
6	89.0	86.6	39.4	0.341	0.348
9	89.2	86.6	23.0	0.199	0.205
12	88.6	86.5	15.2	0.131	0.121

[a] **1**-$d_2(t)$ = 86.5 + (13.5 * exp (–2.14 × 10^{-4} s^{-1} * t)).

[b] (ee of **1**-d_2 (%)) * **1**-d_2 (calc)/100.

[c] $\alpha/\alpha_0(t)$ = exp(–4.89 × 10^{-5} s^{-1} * t).

The data summarized in Tables III, IV, and V show relatively good agreement between experimental and best-fit calculated α/α_0 values; only one of the sixteen experimental data points, the 1-h d_0 α/α_0 ratio, seems to be a possible outlier. The ratio of racemization rate constants $k_\alpha(d_0)/k_\alpha(d_2)$ is appreciable, 1.18. Since k_α is dependent on k_1 and k_{12}, and the k_H/k_D effect on k_1 is relatively small, the large kinetic isotope effect observed must be caused by a relatively large $k_{12}(d_0)/k_{12}(d_2)$ ratio. From $k_\alpha = (2k_{12} + 2k_1)$ and the measured values of $k_\alpha(d_0)$, $k_\alpha(d_2)$, $k_1(d_0)$ and $k_1(d_2)$ one may calculate $k_{12}(d_0) = 1.37 \times 10^{-5}$ s^{-1} and $k_{12}(d_2) = 1.00 \times 10^{-5}$ s^{-1}, and thus $k_{12}(d_0)/k_{12}(d_2)$ is equal to 1.37. The β secondary deuterium kinetic isotope effect is 17% per deuterium.

TABLE V

Enantiomer excess values for methyl *trans*-2-phenylcyclopropanecarboxylates **9**-d_0 and **9**-d_2 and α/α_0 values for reaction mixtures from (+)-**1**-d_0 and (–)-**1**-d_2

Time/h	**9**-d_0	α/α_0[a]	α/α_0[b]	**9**-d_2 (% ee)	α/α_0[c]	α/α_0[d]
6	34.2	0.296	0.289	38.4	0.333	0.348
9	20.0	0.173	0.155	25.6	0.222	0.205
12	11.6	0.100	0.083	16.8	0.145	0.121

[a] (ee of **1**-d_0 (%)) * **1**-d_0 (calc)/100.

[b] $\alpha/\alpha_0(t)$ = exp(–5.79 × 10^{-5} s^{-1} * t).

[c] (ee of **1**-d_2 (%)) * **1**-d_2 (calc)/100.

[d] $\alpha/\alpha_0(t)$ = exp(–4.89 × 10^{-5} s^{-1} * t).

DISCUSSION

Determinations of rate constants through chromatographic methods may be subject to various sources of systematic error;[14] here this general consideration was elevated to a particular concern since $k_\alpha(d_0)$ and $k_\alpha(d_2)$ were estimated from ee values as functions of time starting from (+)-**1**-d_0 and (–)-**1**-d_2, and thus some hidden bias favoring one enantiomer would have led to an unreliable $k_\alpha(d_0)/k_\alpha(d_2)$ ratio. Hence the ee values for **1**-d_0 and **1**-d_2 samples from 6-, 9-, and 12-h product mixtures were determined a second time, through an independent method, one which incidently reversed the correlation between elution order and absolute stereochemistry (Figures 1 and 2). For the 6 ee values measured both ways, the largest discrepancy was 2.3%, the average difference was 1.6% (Tables III, IV, and V); agreement at this level is entirely satisfactory for such chromatographic analyses, and the $k_\alpha(d_0)/k_\alpha(d_2)$ ratio derived is thus more secure than it would have been in the absence of the data of Table V.

The present kinetic results for unlabeled reactants secured at 234 °C in the gas phase may be compared to the rate constants measured by Crawford and Lynch[7] for the same reactions in 1-butanol solutions at 229 °C: $k_\alpha = (4.91 \pm 0.26) \times 10^{-5}$ s^{-1}, $k_i = (3.65 \pm 0.21) \times 10^{-4}$ s^{-1}, and $K = 10.3$, from which one may calculate $k_1 = 1.62 \times 10^{-5}$ s^{-1} and $k_{12} = 0.84 \times 10^{-5}$ s^{-1}. Although different reaction conditions and analytical methods were employed, both investigations support the same key conclusion: the relative magnitudes of one-center versus two-center epimerization rate constants, $k_1 : k_{12} \approx 1.1$ in the present gas-phase study and $k_1 : k_{12} \approx 1.9$ in the 1968 investigation employing 1-butanol as the reaction solvent, demonstrate that both one-center and two-center epimerizations contribute to the stereomutations to comparable extents.

The β secondary deuterium kinetic isotope effects on rate constants k_1 and k_{12} are strikingly different. The normal k_H/k_D effect of 3% per deuterium observed for k_1 does not seem surprising, but the 17% per deuterium effect found for k_{12} is much larger than had been expected. The difference in k_H/k_D effects implies that quite diffferent transition structures must be involved in the two types of stereomutations, a proposition supported by theoretical work on the stereomutations of cyclopropane itself[15–17] but not previously demonstrated for any substituted cyclopropane through experimentally deteremined isotope effect differences. Presumably the k_1 epimerization of **1** passes through an »edge-to-face« or EF 1,3-diphenyltrimethylene diradical, and the k_{12} optical isomerization goes by way of an »edge-to-edge« or EE diradical structure. The substantial C-H bond weakening at the β position in the transition structure for the k_{12} process, one may speculate, could be associated with extended conjugation of the two benzyl radical moieties through the pi-symmetry CH_2 group orbitals, as in the $^1B_1$ molecular orbital of the »edge-to-edge« trimethylene.[18] Better matching of energy levels for pi-

symmetry CH_2 group orbitals and some benzyl radical molecular orbitals could lead to extensive interactions, and consequent weakening of the CH_2 bonds. Theoretical calculations to probe the plausibility of such speculation seem in order.

EXPERIMENTAL

Commercial reagents from Aldrich Chemical company or other suppliers were used without further purification. Ether was freshly distilled from sodium benzophenone ketyl. Pyridine was heated to reflux and distilled from solid KOH and stored over Linde type 4A molecular sieves. Toluene was dried over sodium benzophenone ketyl and stored with Linde type 4A molecular sieves. Analytical TLC separations were done using pre-coated silica gel 60 F-254 plates (0.25 mm), developed using 1 : 1 hexanes-ethyl acetate, visualized with UV light, and stained with a solution of anisaldehyde. Column chromatographic separations were accomplished using large pore (70 micron) silica gel from Alfa. Gas chromatographic analyses were done using a Hewlett Packard 5890 A instrument equipped with HP Ultra 1 (cross-linked methyl silicone gum) and HP Ultra 2 (cross-linked 5% phenyl methyl silicone) capillary columns. Both columns (25 m × 0.2 mm × 0.3 μm film thickness) were attached to a single injection port maintained at 160 °C. The two FID detectors maintained at 300 °C were connected to a HP 3396 Series II dual channel integrator. Preparative GC purifications were accomplished utilizing a Varian Aerograph A90-P3 gas chromatograph with a 20% Carbowax 20 M on 60-80 Chromosorb P-NAW (1 m × 0.64 cm o.d.) preparative column. The oven temperature was kept at 175 °C and the helium pressure was 100 kPa (flow rate 38.5 mL/min) unless otherwise stated.

Melting points, determined using a Reichert melting point apparatus, are uncorrected. Mass spectral data were obtained with a Hewlett Packard 5970 series mass selective detector interfaced to a 5890 A gas chromatograph with an ultra performance cross-linked methyl silicone capillary column (25 m × 2 mm × 0.3 μm film thickness) and a 9336 computer. The ^{1}H- and ^{13}C-NMR spectra were taken on a GE QE-300 NMR spectrometer for samples in $CDCl_3$ containing 0.03% Me_4Si unless otherwise stated. Chemical shifts are reported in δ ppm downfield from Me_4Si. Optical rotations were measured with a Perkin Elmer Model 241 polarimeter at 589 nm; concentrations c are given in g/100 mL. Chloroform was used as the solvent for all $[\alpha]_D$ measurements. Enantiomer excesses of the styrene oxides were determined using a Hewlett Packard 5890 A gas chromatograph equipped with a fused silica Cyclodex B GC column (J & W Scientific, 30 m × 0.26 mm i.d.). The oven, injection port, and detector temperatures were maintained at 90 °C, 150 °C, and 300 °C, respectively. Enantiomer excesses of the *trans*-1,2-diphenylcyclopropanes were determined using a Rainin HPLC equipped with a Hewlett Packard Conbrio Triacetylcellulose HPLC column (Conbrio TAC, 15–25 μm, 250 × 5 mm) using a Gilson 112 UV detector monitoring at 254 nm. The eluting solvent used was HPLC grade absolute ethanol (0.125 mL/min) filtered through a 0.2 μm nylon membrane filter and sparged with helium prior to use. Samples were filtered using a 0.2 μm Acrodisc LC 13 or Acrodisc LC PVDF filter.

trans-1,2-Diphenylcyclopropane and *cis*-1,2-diphenylcyclopropane (*rac*-**1**-d_0 and **2**-d_0) were prepared[8] and purified by preparative GC; *rac*-**1**-d_0 was obtained as a

clear colorless liquid and **2**-d_0 as a white solid. The spectroscopic and analytical GC characteristics of both compounds were identical with those recorded for the (+)-(1*S*,2*S*)-**1**-d_0 and **2**-d_0 samples prepared from (+)-(*R*)-styrene oxide. Chiral HPLC analyses showed complete resolution of the enantiomers of *rac*-**1**-d_0: retention times ~ 49.4 and ~ 65.6 min (Figure 2).

*Benzyldiphenylphosphine Oxide (**5**)*[19]

To a flame-dried three-necked round-bottomed flask under nitrogen and equipped with a magnetic stirring bar and reflux condenser were added dry ether (200 mL), dry pyridine (8.8 g, 110 mmol, 9.0 mL) and anhydrous benzyl alcohol (11.9 g, 110 mmol, 11.4 mL). The solution was cooled to –78 °C and chlorodiphenylphosphine (Johnson Matthey Electronics, 24.6 g, 111 mmol, 20 mL) in 70 mL of dry ether was added dropwise over a 40-min period. The reaction mixture was stirred for 1.5 h at –78 °C and then allowed to warm to rt. Stirring was continued for an additional 45 min. The white precipitate, pyridinium hydrochloride, was filtered off while keeping the set-up under nitrogen. The slightly cloudy filtrate was concentrated by simple distillation to give a light yellow oil. The last traces of ether were removed by placing the flask under vacuum overnight. Dry toluene (334 mL) and a crystal of iodine were then added to the oil and the resulting bright yellow solution was heated to reflux for 24 h and then cooled to rt. The white needles that precipitated were collected, washed with a little dry toluene and ample amounts of dry ether, and then placed in a desiccator to dry (13.2 g, 42.9 mmol, 41% yield): m.p. 191–193 °C (lit.[19] m.p. 192–193 °C); ^{1}H-NMR δ: 7.70 (m, 5 H), 7.45 (m, 5 H), 7.15 (m, 5 H), 3.65 (d, J = 13.7 Hz, 2 H); ^{13}C-NMR δ: 132.91, 131.74, 131.71, 131.60, 131.17, 131.05, 130.12, 130.05, 128.50, 128.34, 128.30, 126.73, 126.69, 104.88, 104.85, 38.51, 37.63.

*(+)-(1*S*,2*S*)-*trans*-1,2-Diphenylcyclopropane and* cis*-1,2-Diphenylcyclopropane ((+)-(1*S*,2*S*)-**1**-*d*$_0$ and **2**-*d*$_0$)*

To a flame-dried three-necked flask equipped with a stirring bar and kept under nitrogen were added 500–600 mL of dry toluene by way of a cannula and benzyldiphenylphosphine oxide **5** (4.08 g, 14.0 mmol). Toluene and possibly some toluene-H_2O azeotrope were then removed by distillation until approximately 400–500 mL of solution was left. The flask was cooled to rt and hexamethylphosphoramide (HMPA, 2.6 mL, 14.9 mmol) and butyllithium (BuLi, 2.0 M in pentane, 7.5 mL, 14.9 mmol) were added dropwise to the flask. Once the addition was complete, the clear blood-red solution was quickly heated to 70 °C (internal temperature) and (+)-(*R*)-styrene oxide (0.5 mL, 0.53 g, 4.4 mmol; 100% ee, retention time 27.2 min by chiral GC;) in about 3 mL of dry toluene was added. The reaction mixture was then heated to reflux for 12–13 h. The flask was cooled to rt and the reaction mixture was washed with water until the pH of the aqueous layer was neutral. The organic material was then washed with brine, dried, and filtered; the filtrate was concentrated by rotary evaporation, and filtered through a plug of silica gel using 5 : 1 hexanes-ether to give a mixture of three compounds. Capillary GC analysis of the product mixture indicated the presence of three products (**2**-d_0, (+)-(1*S*,2*S*)-**1**-d_0, stilbene) in a 1 : 4 : 1 ratio.

The yield of (+)-(1*S*,2*S*)-**1**-d_0 based on analytical GC peak areas was 63% (539 mg). Preparative GC purification gave pure (+)-(1*S*,2*S*)-**1**-d_0 as a white solid: GC-MS 194 (M^+, 86.4%), 193 (M-1, 59.6), 179 (50.3), 178 (42.4), 116 (65.0), 115 (100), 91 (36.6),

77 (26.0), 51 (32.2), 39 (30.9); ^{1}H-NMR δ: 7.30 (m, 5H), 7.15 (m, 5H), 2.15 (t, J = 7.07 and 7.60 Hz, 2H), 1.45 (t, J = 7.14 and 7.53 Hz, 2H) (compare Ref. 20); ^{13}C-NMR δ: 142.48, 128.36, 125.73, 27.99, 18.18 (compare Ref. 21). Three determinations of $[\alpha]_D$ based on very small preparative GC purified samples were made: $[\alpha]_D$ = +490° (c = 0.82), +540° (c = 0.30), and +450° (c = 0.26); lit.[22] $[\alpha]_D^{20}$ +418° (c = 0.956, $CHCl_3$), lit.[23] $[\alpha]_D^{20}$ +421.7° ($CHCl_3$). Chiral HPLC analysis gave only one peak with retention time of ~ 65.5 min corresponding to the (1*S*,2*S*) enantiomer (Figure 2).

The yield of **2**-d_0 based on analytical GC peak areas was 15% (128 mg). Preparative GC purification gave **2**-d_0 material as a white solid: GC-MS m/z 194 (M^+, 85.9%), 179 (49.3), 178 (45.2), 117 (22.2), 116 (66.6), 115 (100), 103 (23.4), 91 (35.3), 77 (23.6), 51 (25.9), 40 (33.1), 39 (22.8); ^{1}H-NMR δ: 7.05 (m, 5 H), 6.95 (m, 5H), 2.50 (t, J = 6.40 Hz, 2H), 1.40 (m, 2H) (compare Ref. 20); ^{13}C-NMR δ: 138.36, 128.95, 127.62, 125.55, 24.29, 11.36 (compare Ref. 21, 24).

Preparative GC purification and recrystallization from 95% EtOH gave white plates of stilbene, m.p. 120–125 °C; GC-MS m/z 181 (13.16%), 180 (100), 179 (100), 178 (62.43), 176 (10.0), 165 (51.65), 152 (13.70), 102 (10.39), 89 (24.80), 77 (11.46), 76 (20.41), 63 (12.67), 51 (18.41), 50 (9.59), 39 (10.71) (compare Ref. 25); ^{1}H- and ^{13}C-NMR spectra were identical with those of authentic stilbene.

(+)-(S)-1-Phenyl-2,2-d_2*-ethane-1,2-diol ((+)-(S)-***7**-d_2*)*

Lithium aluminum deuteride (Cambridge Isotope Laboratories, 98%, 0.96 g, 23 mmol) and 26 mL of dry ether were placed in a flame-dried three-necked round-bottomed flask equipped with a magnetic stirring bar and reflux condenser and kept under nitrogen. Ethyl (+)-(*S*)-mandelate (4.0 g, 22 mmol) in 13 mL of dry ether was added dropwise using a dropping funnel over an 80-min period while the reaction mixture was kept in an ice-water bath. The reaction mixture was warmed to rt and stirred for 6 h; then it was heated to reflux for 1 h. The slurry was cooled to rt and then to 0 °C, and was quenched with 6.5 mL of moist ether followed by 17 mL of 10% aqueous H_2SO_4. The cloudy ether layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness by rotary evaporation to give a cloudy oil which solidified on standing in the refrigerator overnight (2.71 g of a white solid). Recrystallization from 3 : 2 benzene-petroleum ether gave 2.14 g of a white solid (15.3 mmol, 69% yield): m.p. 62–65 °C (lit.[10] m.p. 58–62 °C); GC-MS m/z 142 (M+2, 0.06%), 141 (M+1, 0.74), 140 (M^+, 8.5), 107 (100), 79 (85.5), 78 (53.4), 51 (16.3); ^{1}H-NMR δ: 7.35 (m, 5H), 4.80 (s, OH), 2.75 (s, 1H) (compare Ref. 26); ^{13}C-NMR δ: 140.44, 128.53, 128.00, 126.02, 74.55.

*(+)-(S)-2-(*p*-Bromobenzenesulfonyloxy)-1-phenyl-2,2-*d_2*-ethanol ((+)-(S)-**8**-*d_2*)*

To a dry one-necked round-bottomed flask kept under nitrogen were added 17 mL of dry pyridine and 4-bromobenzenesulfonyl chloride (BsCl, 5.53 g, 21.6 mmol). The yellow solution was cooled to –3 °C and (+)-(*S*)-**7**-d_2 (3.00 g, 21.4 mmol) in 17 mL of dry pyridine was added to the cooled solution with stirring. The solution was then placed in the refrigerator for 2 d. By TLC, some starting diol was still present and the mixture was retreated with additional amounts of BsCl (1.05 g, 4.1 mmol) under the same conditions. After stirring for an additional 3 h, the reaction flask was placed in the refrigerator overnight. The contents were poured into a beaker containing 205 g of ice and 34 mL of concentrated HCl and the resulting gummy residue was dissolved in ether, washed with 10% aqueous HCl and then with water,

dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation. A yellow solid (5.29 g) was obtained upon refrigeration overnight. Recrystallization from 5 : 2 benzene-petroleum ether gave 3.81 g (10.6 mmol, 50% yield) of white needles: m.p. 83–87 °C (lit.[10] m.p. 76.2–88.8 °C for chiral unlabeled (+)-material); ^{1}H-NMR (DMSO-d_6) δ: 7.85 (d, J = 8.66 Hz, 2H), 7.75 (d, J = 8.62 Hz, 2H), 7.55 (s, 2H), 7.35 (s, 3H), 5.55 (broad s, OH), 4.75 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ: 147.55, 140.44, 134.43, 132.78, 130.68, 129.53, 128.33, 128.14, 127.77, 127.61, 126.31, 121.70, 69.69.

(–)-(S)-1-Phenyl-2,2-d_2*-oxirane ((–)-(S)-4-*d_2*)*

To a flame-dried one-necked round-bottomed flask was added (+)-(*S*)-**8**-d_2 (3.70 g, 10.3 mmol) dissolved in 20 mL of HPLC grade MeOH. The solution was cooled to 5 °C and a solution of KOH (Fisher Scientific, 86.9%, 0.78 g, 13.9 mmol) in 8 mL of HPLC grade MeOH was added dropwise. Upon the addition of the KOH solution, a white precipitate formed. The mixture was stirred for another 10 min at 5 °C and water (62 mL) was then added while the flask was kept at 5 °C. After stirring for another 5 min, the cloudy white mixture was extracted twice with 35-mL portions of ether; the combined ether extracts were washed three times with water, dried over anhydrous K_2CO_3, filtered, and concentrated by distillation under aspirator pressure. To the concentrate was added approximately 25 mL of dry benzene and both MeOH and benzene were removed by distillation. Kugelrohr distillation under vacuum (3.5 mm Hg) at a maximum pot temperature of 70 °C afforded 1.02 g of distillate (96.8% styrene oxide, 79% yield by GC, 0.99 g, 8.11 mmol). Preparative GC purification (110 °C, 100 kPa) gave pure material as a clear colorless liquid: GC-MS m/z 124 (M+2, 0.29%), 123 (M+1, 2.77), 122 (M^+, 15.9), 121 (M-1, 27.4), 94 (13.0), 93 (38.2), 92 (81.4), 91 (100), 66 (15.3), 65 (31.1), 63 (13.4), 51 (11.0), 39 (20.8); ^{1}H-NMR δ: 7.35–7.25 (m, 5H), 3.65 (s, 1H) ; ^{13}C-NMR δ: 131.81, 129.56, 128.96, 127.38, 50.44, 50.34 (compare Ref. 27). Chiral GC analysis gave only one peak with retention time of 28.9 min (Figure 1).

*(–)-(1*R*,2*R*)-*trans*-1,2-Diphenyl-3,3-*d_2*-cyclopropane and* cis*-1,2-Diphenyl-3,3-*d_2*-cyclopropane ((–)-(1*R*,2*R*)-1-*d_2 *and* 2*-d_2*)*

Following the procedure outlined for the synthesis of (+)-(1*S*,2*S*)-**1**-d_0 and **2**-d_0, (–)-(*S*)-**4**-d_2 (97% pure by GC, 100% ee, 0.5 mL) was converted to diphenylcyclopropanes. On the basis of analytical GC peak areas, about 540 mg of (–)-(1*R*,2*R*)-**1**-d_2 was obtained. Preparative GC afforded pure (1*R*,2*R*)-**1**-d_2 as a white solid: GC-MS m/z 199 (M+3, 0.06%), 198 (M+2, 1.1), 197 (M+1, 14.9), 196 (M^+, 100), 195 (M-1, 64.3), 181 (25.0), 180 (44.9), 179 (30.7), 178 (11.6), 119 (15.4), 118 (37.2), 117 (64.7), 116 (50.0), 115 (10.4), 104 (12.5), 93 (11.4), 92 (19.3), 91 (7.8), 90 (8.3), 89 (11.7), 78 (15.9), 77 (13.4), 63 (16.1), 51 (22.4), 39 (18.0); ^{1}H-NMR δ: 7.30 (m, 5H), 7.15 (m, 5H), 2.15 (s, 2H); ^{13}C-NMR δ: 142.47, 128.35, 125.73, 125.70, 27.83. Three determinations of $[\alpha]_D$ based on very small preparative GC purified samples were made: $[\alpha]_D^{22}$ –390° (c = 1.64), –360° (c = 1.26), and –320° (c = 0.985); lit.[28] $[\alpha]_D^{22}$= –423° (EtOH) for optically pure unlabeled material. Chiral HPLC analysis gave only one peak with retention time of ~ 49.5 min (Figure 2).

About 167 mg of **2**-d_2 was also obtained; preparative GC purification gave pure **2**-d_2 as a white solid: GC-MS m/z 198 (M+2, 1.0%), 197 (M+1, 15.0), 196 (M^+, 100), 195 (65.0), 181 (25.4), 180 (46.2), 179 (31.5), 178 (12.0), 167 (9.8), 166 (10.7), 165 (7.8), 119 (16.2), 118 (38.1), 117 (66.4), 116 (47.0), 115 (10.4), 104 (13.0), 93 (11.7), 92 (19.0), 91 (7.5), 90 (9.1), 89 (12.1), 78 (13.6), 77 (11.6), 63 (14.1), 51 (18.4), 39

(15.1); ^{1}H-NMR δ: 7.10 (m, 5H), 6.95 (m, 5H), 2.45 (s, 2H); ^{13}C-NMR δ: 138.32, 128.94, 127.60, 125.53, 24.11.

*Thermal Isomerizations of 1,2-Diphenylcyclopropanes (+)-(1S,2S)-**1**-d$_0$, **2**-d$_0$, (–)-(1R,2R)-**1**-d$_2$, and **2**-d$_2$*

Pyrex tubing (7- and 16-mm o.d., medium wall), cut to the desired lengths (15.2 cm and 20.3 cm, respectively), were soaked in concentrated aqueous HCl for at least 12–15 h, rinsed with water, soaked in NH_4OH/EDTA solution for 24–72 h, washed with copious amounts of water, and placed in a 140 °C oven a minimum of 16 h. The kinetic bulbs made were approximately 85 cm in length (~ 10 mL) with the 7-mm tubing attached. Bulbs for unlabeled material were 10 cm longer. A constriction was placed in the 7-mm tubing to facilitate sealing. Kinetic samples, which consisted of approximately 5–10 mg of preparative GC purified material in about 10–15 μL of HPLC grade cyclohexane, were introduced into the bulbs using a gas tight syringe. The bulbs were cooled in liquid nitrogen, subjected to three pump-thaw-freeze cycles, and sealed under vacuum (0.1 mm Hg). Unlabeled and labeled samples were run in parallel for each kinetic point; kinetic runs were carried out in a mechanically stirred, well-insulated oil bath, with temperature maintained by a Bayley Model 253 precision temperature controller and monitored with a HP 2802 A thermometer equipped with a platinum resistance probe. Care was taken to ensure that each bulb was completely immersed in the oil bath. For the determinations of the rates of racemization, thermolyses of chiral samples of trans isomers were done at 234.2 ± 0.5 °C. For the determinations of the rates of geometrical isomerizations, thermolyses of both *trans* and *cis* isomers were done at 234.5 ± 0.5 °C.

After a given time interval, the kinetic bulbs were cooled to rt and then to –78 °C, and were opened. Each sample was diluted with HPLC grade absolute ethanol (0.5 mL) and then analyzed by capillary GC to determine the cis:trans ratio. Prior to HPLC analyses, additional amounts of absolute ethanol were added to obtain a concentration of ~ 0.5–0.8%, to ensure that the UV-vis detector was not overloaded. The GC and HPLC analyses of each kinetic sample were done in triplicate. The reported values are the averages of the three analyses. The sum of the peak areas, obtained by analytical GC, for the *cis* and *trans* products was taken to be 100% (Tables I and II). The sum of the peak areas, obtained by HPLC, for (–) and (+) enantiomers of trans compounds was also taken to be 100% (Tables III and IV).

Methyl trans*-2-Phenylcyclopropanecarboxylates from Kinetic Product Mixtures*

To a single-necked flask under nitrogen containing a kinetic sample (6.3 mg, 0.032 mmol) dissolved in 250 μL of CCl_4 were added 2 mL of CCl_4, 2 mL of CH_3CN, and 3.5 mL of H_2O. The biphasic solution was stirred for a few minutes and sodium metaperiodate (Mallinckrodt, $NaIO_4$, 180 mg, 0.84 mmol) and $RuCl_3 \cdot 3H_2O$ (Alfa, 0.5 mg, 0.002 mmol) were added. The biphasic solution immediately changed color to reddish-brown. After 24 h of stirring at rt, the upper aqueous layer was cloudy and the lower organic layer was lemon yellow. Some black precipitate was also present. Methylene chloride (20 mL) was added to the flask and the contents were filtered through a sintered glass funnel. After filtration, the upper aqueous layer was light yellow and the lower organic layer was a dark olive green. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic material was washed with 10 mL of H_2O, dried, filtered, and concentrated by rotary evaporation until about 1 mL of solution was left. Ether (3 mL) was then added and

the solution was filtered through a plug of Celite to give a yellow-green solution. After concentrating to almost dryness by rotary evaporation, the solution was filtered through a plug of Celite; the ethereal filtrate was treated with ethereal CH_2N_2 until the solution had a persistent yellow color. After about 30 min at rt, $MgSO_4$ was added to quench excess CH_2N_2, and the solution of methyl esters was filtered through a cotton plug and analyzed both by analytical and chiral GC using a Lipodex E fused-silica capillary column (Macherey-Nagel, 50 m × 0.25 mm i.d.).[12] The enantiomeric excess values found for samples of methyl *trans*-2-phenylcyclopropanecarboxylate (**9**) are summarized in Table V.

Acknowledgments. – We thank the National Science Foundation for support of this work through CHE 91-00246, and Professor Robert J. Crawford of the University of Alberta for helpful correspondence.

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SAŽETAK

Beta-sekundarni deuterijski kinetički izotopni efekti pri termalnoj stereomutaciji 1,2-difenilciklopropana

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(+)-(1*S*,2*S*)-*trans*-1,2-Difenilciklopropan i (–)-(1*R*,2*R*)-*trans*-1,2-difenil-3,3-d_2-ciklopropan pri 234 °C reverzibilno se pregrađuju u odgovarajuće enantiomere i *cis*-1,2-difenilciklopropane. Za nedeuterirani *trans*-izomer, omjer konstanti brzina za epimerizaciju jednog centra (k_1) i epimerizaciju dvaju centara (k_{12}) iznosi 1.1. Mali normalni k_H/k_D efekt, 3% po atomu deuterija, izmjeren je za konstantu brzine epimerizacije jednog centra (k_1); normalni k_H/k_D efekt, 17% po atomu deuterija, izmjeren je za konstantu brzine epimerizacije dva centra (k_{12}). Prema tome, različite prijelazne strukture, vjerojatno EF i EE 1,3-difeniltrimetilenski diradikali, prevladavaju u dvije vrste stereomutacija.