Oxy-Cope Reaction Mechanism

On the Mechanism of the Anionic Oxy-Cope Rearrangement of *trans*-1,2-Dialkenylcyclobutanols**

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Sigmatropic rearrangements have frequently been utilized in the stereoselective construction of multiple stereocenters of easily predictable relative and absolute configurations. Among them, the anionic oxy-Cope rearrangement has evolved as a powerful tool for stereoselective syntheses because of dramatic rate acceleration.[1–3] Of particular note is the variant for ring expansion leading to medium-sized rings

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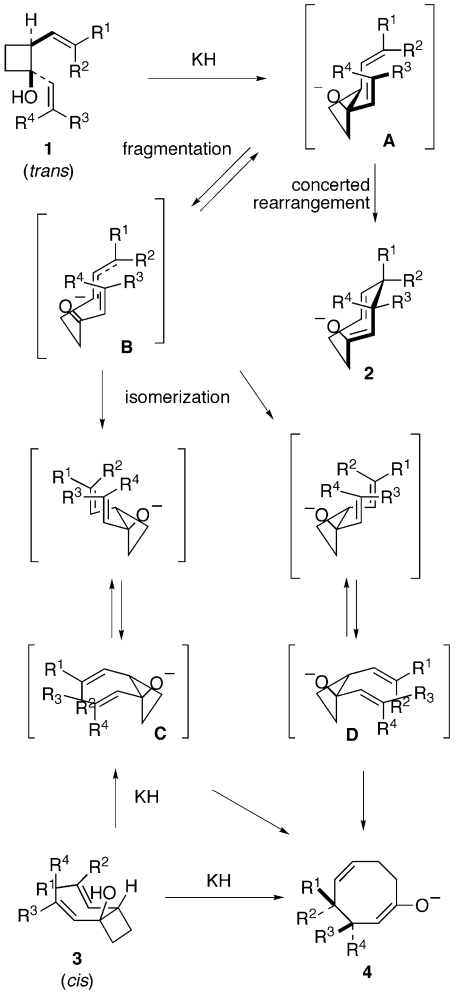
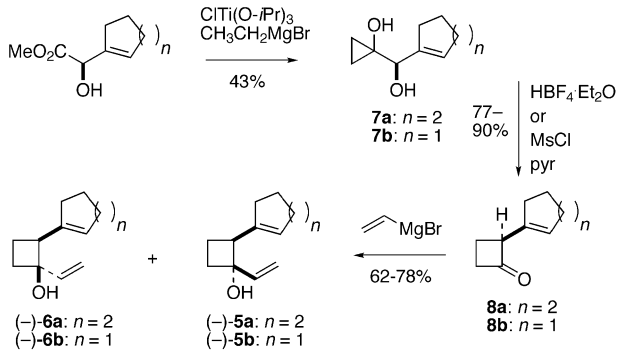
by employing 1,2-dialkenylcycloalkanols.[4] Adaptation of this variant to smaller rings (e.g., cyclopropanols and cyclobutanols) has provided unique avenues for the stereocontrolled construction of seven- and eight-membered rings.[5,6] A majority of ingenious and notable applications have relied on *cis*-1,2-dialkenylcyclopropanols and -cyclobutanols (**3**→**C**→**4**; Scheme 1).[1] In sharp contrast, only a handful of



Scheme 1. Concerted and stepwise pathways of the anionic oxy-Cope rearrangement of *trans*-1,2-dialkenylcyclobutanols.

examples are known for anionic oxy-Cope rearrangements of *trans*-cyclobutanols;[6] the feasibility of a concerted rearrangement (**1**→**A**→**2**) was considered by Gadwood et al., but discounted on the basis of the apparent difficulty of bringing the reacting termini within bonding distance.[6a,7] It has since become generally accepted that rearrangement of *trans*-1,2-dialkenylcyclobutanols to 4-cyclooctenones proceeds by a stepwise mechanism involving initial isomerization to the *cis* isomers (**A**→**B**→**C** and/or **A**→**B**→**D**) and subsequent anionic oxy-Cope rearrangement (**C** and/or **D**→**4**). However, there is no conclusive stereochemical information available. Here we report a stereochemical study which employs nonracemic *trans*-1,2-dialkenylcyclobutanols and supports a concerted anionic oxy-Cope rearrangement.

Nonracemic **5a,b** and **6a,b** were chosen to probe the key issue of the concertedness of the rearrangement. If a stepwise pathway were operative in the anionic oxy-Cope rearrangement of *trans*-1,2-dialkenylcyclobutanols, the products could become racemic, as the *trans*→*cis* isomerization step might proceed (via **B**) with racemization.[8] Additionally, the stereochemistry of the products (e.g., **2** versus **4**) should provide decisive insight into the reaction mechanism. The cyclohexene and cyclopentene rings were chosen as one of the alkenyl groups in the stereochemical studies, since eight-membered carbocyclic rings that are found in bioactive natural products are typically embedded in fused polycyclic systems.[9] 2-Cycloalkenylcyclobutanones **8a,b** were prepared by titanium-mediated cyclopropanation of enantiomerically enriched α-hydroxy esters with ethylmagnesium bromide, followed by a pinacol-type rearrangement of the resulting cyclopropanols **7a,b** (Scheme 2).[10] Treatment of ketone **8a**



Scheme 2. Preparation of *cis*- and *trans*-1,2-dialkenylcyclobutanols.

with vinylmagnesium bromide in THF at −40 °C afforded an easily separable 1:25 mixture of (−)-**5a** and (−)-**6a** in 78% yield and 92% *ee* (Chiralcel). Similarly, a 1:20 mixture of (−)-**5b** and (−)-**6b** was obtained in 62% yield from **8b**.[11] As a control experiment, anionic oxy-Cope rearrangement of (−)-*cis*-**5a** was first carried out (5.0 equiv KH, 2.5 equiv [18]crown-6, THF, 5 min) at −35 °C to furnish (+)-**9a** ($[\alpha]_D = +83.4$, $c = 0.3$ in CH_2Cl_2) in 75–79% yield and 92% *ee* (Scheme 3).[12,13a] Sigmatropy of *cis*-1,2-dialkenylcyclobutanes and cyclobutanols has been well established to favor boatlike transition states in a concerted reaction. Under similar conditions, the rearrangement of (−)-**6a** gave (+)-**10a** ($[\alpha]_D = +103.0$, $c = 1.1$ in CH_2Cl_2) in 84–90% yield and 88% *ee* (i.e., 96% chirality transfer from (−)-**6a** of 92% *ee*). The absolute configuration of (+)-**10a** was determined by its facile isomerization (91%) by treatment with I_2 (ambient light) to (−)-**9a** ($[\alpha]_D = -80.9$, $c = 1.0$ in CH_2Cl_2). The latter product was thus enantiomeric to the rearrangement product of (−)-**5a**.[14]

The cognate rearrangement of (−)-**5b** and (−)-**6b** was next examined. Analogous to the anionic oxy-Cope rearrangement of (−)-**5a**, that of (−)-**5b** afforded (−)-**9b**,[13b] in 70% yield and 92% *ee*. Under the same conditions, rearrangement of (−)-**6b** yielded a 4.7:1:0.2 mixture (GC-MS) of (+)-**10b** ($[\alpha]_D = +43.4$, $c = 0.5$ in CH_2Cl_2; 89% *ee*, 97% chirality transfer), racemic **9b**, and an unidentified by-product

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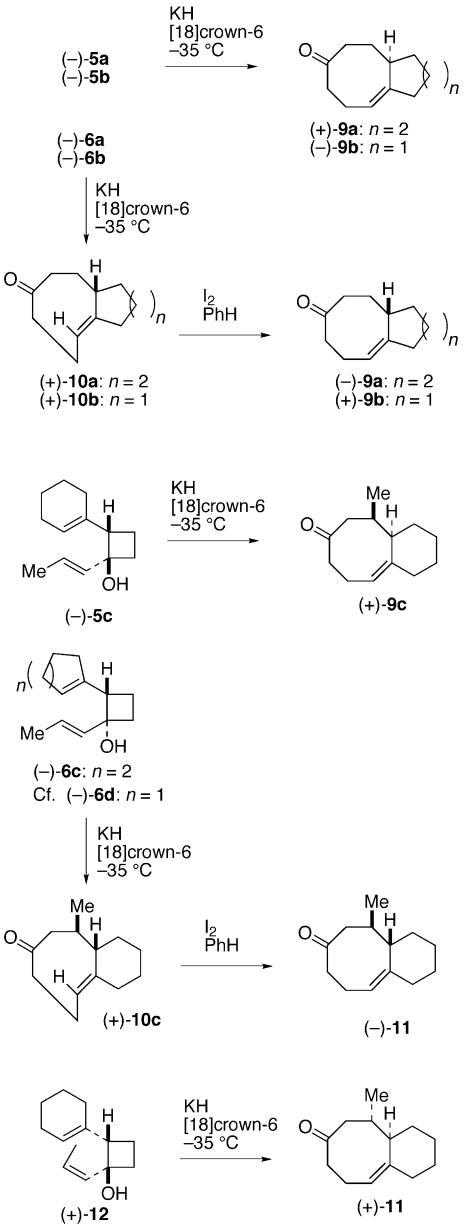
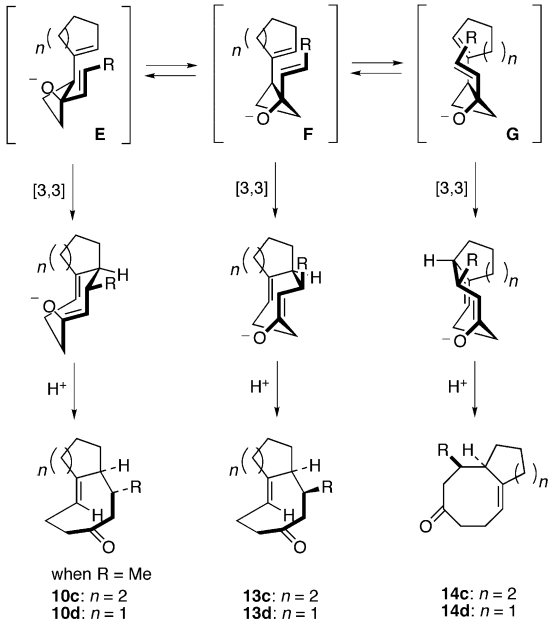


Scheme 3. Anionic oxy-Cope rearrangements of *cis*- and *trans*-dialkenylcyclobutanols.

in a total yield of 63–68 %.[15a,b] The product ratios of (+)-**10b** to (±)-**9b** appeared to be kinetic in origin, since the reaction time (e.g., 30 s and 2 min at −35 °C) had only a small influence on these ratios. Additionally, (+)-**10b** remained unchanged when resubjected to the rearrangement conditions. Finally, treatment of (+)-**10b** with I_2 resulted in facile isomerization to (+)-**9b**. Formation of (±)-**9b** indicates that initial isomerization to the *cis*-dialkenylcyclobutanol isomer is accompanied by racemization (**A**→**B**→**C** and **D**). The observations that the oxyanionic Cope rearrangement of (−)-**6b** gave (+)-**10b** with no loss of enantiopurity, yet racemic **9b** was formed, raises an interesting question about the epimerization step: Does fragmentation/recombination lead to exclusive formation of the *cis* isomer with racemization, or to the cogeneration of both *cis* and *trans* isomers, but with different degrees of racemization?[16] As reversion of **B** to the starting alkoxide would require very little motion or rotation of bonds, **B** may well revert to **A** with no loss of enantiopurity.[8]

High degrees of chirality transfer in the above-mentioned formation of (+)-**10a** and (+)-**10b** from (−)-**6a** and (−)-**6b**, respectively, provides strong evidence for a concerted mechanism. Among three possible transition states **E, F**, and **G** (Scheme 4), the observed *E* double-bond geometry of (+)-



Scheme 4. Analysis of three possible transition states **E**–**G**.

10a and (+)-**10b** ruled out the involvement of **G** (Scheme 4). To distinguish between the two remaining transition states **E** and **F**, diastereoselectivity was next examined by employing an (*E*)-propenyl substituent. Thus, (−)-**5c**, (−)-**6c**, (−)-**6d**, and (+)-**12** were prepared from **8a,b** in a manner analogous to Scheme 2. The anionic oxy-Cope rearrangement of (−)-**5c** afforded (+)-**9c** ($[\alpha]_D = +56.7$, $c = 0.7$ in CH_2Cl_2) in 78 % yield and with 92 % *ee* (≈100 % chirality transfer) under the above-mentioned conditions, whereas that of (−)-**6c** gave an approximately 2:1 mixture of (+)-**10c** (38 %; $[\alpha]_D = +29.1$, $c = 0.6$ in CH_2Cl_2; 91 % *ee* ≡ 99 % chirality transfer) and **9c** (20 %; ≈10 % *ee* by comparison of $[\alpha]_D$ values). The relative configuration of (+)-**10c** was unequivocally determined by X-ray analysis,[17] and its absolute configuration was established by its facile isomerization (91 %) to (−)-**11** ($[\alpha]_D = -28.1$, $c = 0.3$ in CH_2Cl_2) on exposure to I_2 (ambient light). This product was diastereomeric to (+)-**9c**, but enantiomeric to the rearrangement product (+)-**11** ($[\alpha]_D = +30.2$, $c = 0.6$ in CH_2Cl_2; 83 % yield) of the (*Z*)-propenyl substrate (+)-**12**. The diastereoselective formation of (+)-**10c** provides compelling evidence for the involvement of a chairlike transition state **E** (cf. **A**).[18]

Surprisingly, the anionic oxy-Cope rearrangement of (−)-**6d** failed to provide the (*E*)-cyclooctenone product, but the (Z)-cyclooctenone isomer (43 %; ≈32 % *ee*) was instead isolated, along with a product of [1,3]-sigmatropic rearrange-

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ment (10%). The above-mentioned angle strain and the methyl substituent might conspire to alter the mechanism in favor of a stepwise rearrangement pathway. With an increasing number of substituents at the double bonds, the difference in activation barrier between a concerted rearrangement and a stepwise pathway appears to become smaller; a delicate balance between the two mechanisms seems to depend on substitution patterns of the double bonds and could be easily tipped toward the latter mechanism for sterically hindered substrates. Further corroboration of the substituent effects is being sought by employing acylic alkenyl substituents.

In summary, we have shown that the anionic oxy-Cope rearrangement of sterically unencumbered *trans*-1,2-dialkenylcyclobutanols proceeds by a concerted mechanism with an excellent degree of chirality transfer, attributable to a chair-like transition state. On the other hand, the presence of substituents in the reacting termini results in partitioning between the concerted and stepwise pathways.

Experimental Section

Preparation of (+)-**10a**: A solution of (−)-**6a** (69 mg, 0.39 mmol) and [18]crown-6 (255 mg, 0.97 mmol) in THF (10 mL) was added to a suspension of potassium hydride (washed in hexane; 68 mg, 1.94 mmol) in THF (10 mL) at −35 °C. The reaction mixture was stirred for 10–15 min at the same temperature and then quenched with saturated aqueous NH_4Cl at −60 °C. The resulting mixture was allowed to warm to 0 °C and extracted with diethyl ether. The combined extracts were washed with H_2O, dried with $MgSO_4$, filtered, and concentrated. Purification of the concentrate by column chromatography (4% diethyl ether in hexane) afforded 59 mg (86%) of (+)-**10a**: $[\alpha]_D = +103.0$ ($c = 1.1$ in CH_2Cl_2); IR (neat): $\tilde{\nu} = 1699, 1449, 1432, 1098\ cm^{-1}$; ^1H NMR (360 MHz, $CDCl_3$, TMS): $\delta = 5.81$ (br d, $J(H,H) = 11.8$ Hz; 1H), 2.93–2.80 (m, 2H), 2.52 (td, $J(H,H) = 12.9$, 1.7 Hz; 1H), 2.40–2.14 (m, 5H), 2.07 (dd, $J(H,H) = 12.9$, 5.6 Hz; 1H), 1.78–1.41 (m, 7H), 1.15 ppm (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 214.3, 141.5, 125.6, 48.6, 44.8, 44.3, 31.9, 28.9$ (two peaks), 26.2, 25.2, 21.5 ppm; HRMS [M^+] calcd for $C_{12}H_{18}O$: 178.1358; found: 178.1341.

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Keywords: diastereoselectivity · reaction mechanisms · sigmatropic rearrangement · substituent effects · transition states

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[15] a) Because of the UV absorption of (+)-**10a**, (+)-**10b**, and (+)-**10c**, their enantiomeric purity was readily determined by HPLC analysis (Chiralcel OB column). b) The surprisingly unfavorable product ratio in the rearrangement of (−)-**6b** might be in part attributable to the higher activation energy leading to **10b** compared to **10a**, which is a consequence of the greater angle strain of the double bond exocyclic to the cyclopentane ring, compared to that for a cyclohexane ring.
[16] We thank Prof. Edwin Vedejs (University of Michigan) for insightful comments.
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