"Syn Effect" in the 1,4-Eliminative Ring Opening of [3-Substituted (*E*)-1-Propenyl]oxiranes to the Corresponding 2,4-Dienyl Alcohols

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Stereochemistry of the 1,4-eliminative ring opening of [3-substituted (*E*)-1-propenyl]oxiranes to the corresponding 2,4-dienyl alcohols by LDA was investigated. The *Z*/*E* ratios of the resulting 2,4-dienyl alcohols varied with the substituents at 3-position of the propenyl group. This phenomenon was discussed based on the concept of a "*syn*-effect," which is most primarily rationalized by a $\sigma \rightarrow \pi^*$ interaction. Furthermore, in the case of δ-benzyloxy-substituted vinyloxirane, [1,2]-Wittig rearrangement proceeded following the initial 1,4-eliminative ring opening to give a (*E*,*Z*)-2,4-dienyl 1,6-diol in a completely stereoselective manner.

The elimination reaction of allylic compounds is a useful method for the preparation of 1,3-dienes as versatile synthetic intermediates. Previously we investigated the stereochemistry of the desulfonylation reaction of α,α-dialkylated (*E*)-allylic sulfones with a base and found that the sterically unfavorable (*Z*)-dienes were predominantly formed.[1] The result was rationalized by "*conformational acidity*" that essentially implies a "*syn*-effect."[2,3] We proposed that the "*syn*-effect" is primarily caused by a $\sigma \rightarrow \pi^*$ interaction.[1,3b–3e] Recently, we revealed that the "*syn*-effect" works dominantly also in the elimination reaction of acyclic (*E*)-allylic acetates catalyzed by palladium under the specific conditions utilizing a base.[4]

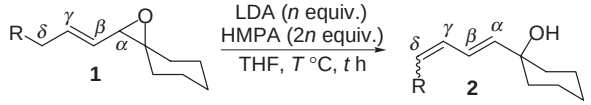
Vinyloxirane is also one of the allylic compounds and 1,4-eliminative ring opening by treatment with lithium or sodium amides proceeds to give dienols.[5] Herein, we investigated the stereochemistry of the 1,4-eliminative ring opening of (*E*)-vinyloxiranes, i.e., [3-substituted (*E*)-1-propenyl]oxiranes, by treatment with LDA, and the observed stereochemistry was rationalized by the concept of the "*syn*-effect."

First the 1,4-eliminative ring opening of an [(*E*)-1-pentenyl]oxirane (R = Et) **1a** was examined.[6] Among alkyllithiums and lithium amides examined, LDA was found to be a suitable base for the 1,4-eliminative ring opening in the presence of HMPA in THF at 25 °C. When 1 equiv. of LDA was used, the 1,4-eliminative ring opening scarcely proceeded. The use of 3 equiv. of LDA gave δ-ethyl-substituted 2,4-dienyl alcohol **2a** in 89% yield in the preference of (*Z*)-isomer[7] (Table 1, Entries 1–3). From the time course of the reaction, *Z*/*E* ratio of **2a** was confirmed to be little changed under these conditions. The 1,4-eliminative ring opening did not occur at −78 °C (Entry 4).

Next, the 1,4-eliminative ring opening of various (*E*)-vinyloxiranes was examined by using 3 equiv. of LDA in the presence of HMPA in THF. Contrary to δ-ethyl-substituted product **2a**, a δ-methyl-substituted product **2b** isomerized during the reaction (Entries 5–8). At the initial stage of the reaction, *Z*/*E* ratio of **2b** was higher than that of δ-ethyl-substituted product **2a** (Entry 5). *Z*-Selectivity was lowered along with the bulkiness of the substrates (Entries 9 and 10). In the case of the δ-phenyl substrate **2e**, *Z*-selectivity was as low as the case of δ-*t*-butyl substrate **2d** (Entry 11). When the reaction was carried out at −78 °C, *Z*-selectivity was slightly increased (Entry 12). δ-Fluoro and δ-benzyloxy groups were found to show complete *Z*-selectivity (Entries 13 and 14), while δ-benzylthio-substituted vinyloxirane **1h** afforded a 29/71 mixture of (*Z*)- and (*E*)-dienols **2h** (Entry 15). In the conversion of (*E*)-vinyloxiranes **1** to the corresponding 2,4-dienyl alcohols **2**, the relative degree of the "*syn*-effect" with respect to the δ-substituents R was found as follows:

$$\text{F-} \cong \text{PhCH}_2\text{O-} > \text{CH}_3\text{-} > \text{CH}_3\text{CH}_2\text{-} > (\text{CH}_3)_2\text{CH-} > \text{PhCH}_2\text{S-} > (\text{CH}_3)_3\text{C-} \cong \text{Ph-}$$

Table 1. 1,4-Eliminative ring opening of (*E*)-vinyloxiranes **1**

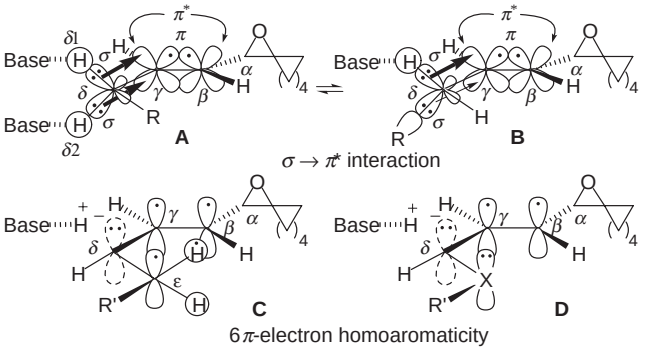


Entry	R		*n*	*T*/°C	*t*/h	Yield/%	*Z*/*E*[a]
1	CH_3CH_2	**a**	1.1	25	16.0	6	75/25
2			2.0	25	16.0	44	74/26
3			3.0	25	16.0	89	73/27
4			3.0	−78	6.0	nr[b]	
5	CH_3	**b**	3.0	25	0.5	49[c]	88/12
6			3.0	25	1.0	88[c]	70/30
7			3.0	25	2.0	>99[c]	33/67
8			3.0	25	3.0	>99[c]	23/77
9	$(CH_3)_2CH$	**c**	3.0	25	20.0	79	56/44
10	$(CH_3)_3C$	**d**	3.0	25	24.0	67	5/95
11	Ph	**e**	3.0	25	0.5	83	4/96
12			3.0	−78	1.0	70	8/92
13	F	**f**	3.0	−78	1.5	82	>99/1
14	$PhCH_2O$	**g**	3.0	−78	1.5	83	>99/1
15	$PhCH_2S$	**h**	3.0	−78	1.5	70	29/71

[a]The ratios were determined by 400 MHz ^{1}H NMR spectra. Only the stereochemistry of C_γ=C_δ bond is shown.[7] [b]No reaction. [c]Conversion yield determined by 400 MHz ^{1}H NMR spectrum of the crude product.

It seems to be possible to rationalize the relative degree of the *Z*/*E* ratios by the "*syn*-effect" in the transition state of deprotonation. In the transition state of deprotonation, the hyperconjugation of a developing anion generated by the interaction of H_δ with a base is recognized more effective in the eclipsed conformations **A** and **B**, in both of which the developing anion is aligned with the $\pi^*_{C=C}$ orbital, and the other conformations can be neglected,[8] according to our recent proposal that the $\sigma \rightarrow \pi^*$ interaction is the most probable explanation for the "*syn*-effect."[1,3b–3e,4] At the deprotonation of vinyloxiranes **1a**–**1c** (R = Me, Et, ^{i}Pr), the CC eclipsed *syn*-conformation **A** might

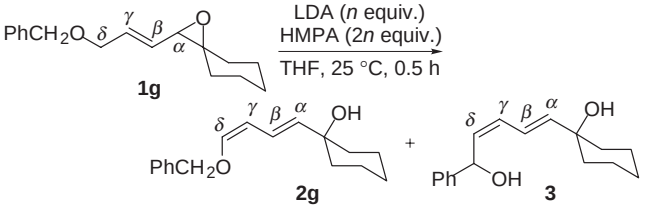
be rather preferred to CH eclipsed form **B**, because a hyperconjugative electron donation by the C–$H_{\delta 2}$ bond is more effective than that by the C–C bond,[9] since $H_{\delta 2}$ can also interact with a base to afford the developing anion. In the cases of δ-fluoro and δ-benzyloxy-substituted vinyloxiranes **1f** and **1g**, the CH eclipsed form **B** is unfavorable due to the low donor ability of the C–F and C–O bonds,[9c,10] resulting in an exclusive formation of (*Z*)-**2f** and **2g** via conformation **A**. In the cases of **1a**, **1b**, and **1f**–**1h**, it is also possible to stabilize the *syn*-conformation at the transition state of deprotonation by 6π-electron homoaromaticity involving the developing charge at the δ-position and a pseudo *p*-orbital of the neighboring CH_2 ($R = CH_2R'$), or a lone pair of electrons in a *p*-orbital of the neighboring hetero atom X ($XR' = F$, OCH_2Ph, or SCH_2Ph), as depicted in **C** and **D**, respectively (Scheme 1).[11]



Scheme 1.

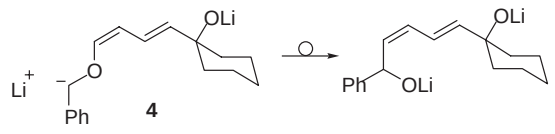
During the course of the investigation of the influence of the reaction temperature, the 1,4-eliminative ring opening of δ-benzyloxy-substituted vinyloxirane **1g** was carried out at 25 °C to afford (*Z*)-dienol **2g** still stereoselectively ($Z/E = >99/1$) by the use of 1.1 equiv. of LDA (Table 2, Entry 1). When 2.0 equiv. of LDA was used, a 2,4-dienyl 1,6-diol **3** was found to be produced stereoselectively (Entry 2). Finally the dienyl diol **3** was obtained in 85% yield with complete stereoselectivity ($Z/E = >99/1$) utilizing 3.0 equiv. of LDA (Entry 3). The diol **3** was assumed to be formed via [1,2]-Wittig rearrangement of an anion **4** generated from the initial 1,4-eliminative ring opening product with excess amounts of LDA.[12] The rearrangement occurred with complete retention of the geometry in the C_γ=C_δ bond (Scheme 2).[13] This result shows that the highest *Z*-selectivity based on the "*syn*-effect" observed for the oxygen-substituted substrate could be utilized for the successive stereoselective C–C bond formation.

Table 2. 1,4-Eliminative ring opening of δ-benzyloxy-substituted (*E*)-vinyloxirane **1g**



Entry	*n*	Recovery of **1g**/%	Yield of **2g**/%	Yield of **3**/%
1	1.1	50	38[a]	—
2	2.0	—	38[a]	46[a]
3	3.0	—	—	85[a]

[a]The Z/E ratio of C_γ=C_δ bond was found to be >99/1 by 400 MHz ^{1}H NMR spectrum.



Scheme 2.

In conclusion, the stereochemical outcome in the 1,4-eliminative ring opening of (*E*)-vinyloxiranes to the corresponding 2,4-dienyl alcohols could be well rationalized by the "*syn*-effect" in the transition state of deprotonation, which mainly arose from a $\sigma \rightarrow \pi^*$ interaction. It is noteworthy that [1,2]-Wittig rearrangement following the 1,4-eliminative ring opening in the case of δ-benzyloxy-substituted vinyloxirane could demonstrate a new entry of "*syn*-effect" applied to the further stereoselective transformation.

References and Notes

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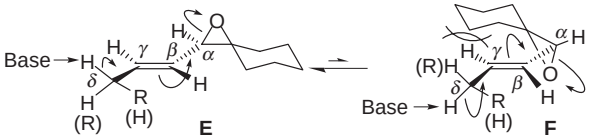
6 When [3-alkyl-substituted (*E*)-1-propenyl]oxiranes without spiro cyclohexane ring were subjected to the 1,4-eliminative ring opening instead of vinyloxiranes **1**, the desired rearranged products were not obtained, but a mixture of by-products were formed presumably via ring-opening alkylation of oxiranes: D. M. Hodgson, M. J. Fleming, and S. J. Stanway, *J. Am. Chem. Soc.*, **126**, 12250 (2004).

7 In this reaction, stereochemistry of C_α=C_β bond in **2** was *E* in all cases.[8] Herein, only the stereochemistry of C_γ=C_δ bond was discussed.

8 Due to the steric congestion between cyclohexane ring and H_γ, the conformation **F** might be excluded at the deprotonation, and only the isomer whose stereochemistry at C_α=C_β bond was *E* might be formed via conformation **E**.



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