Reaction Mechanisms

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Concerted Ring Opening and Cycloaddition of Chiral Epoxy Enolsilanes with Dienes**

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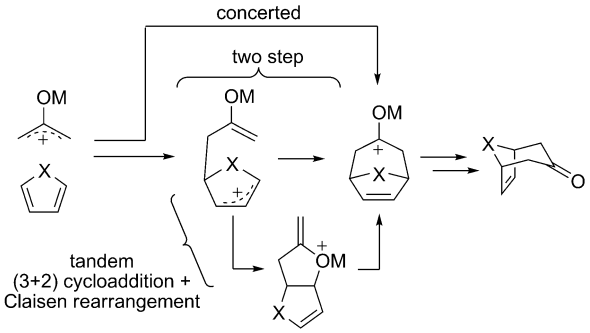
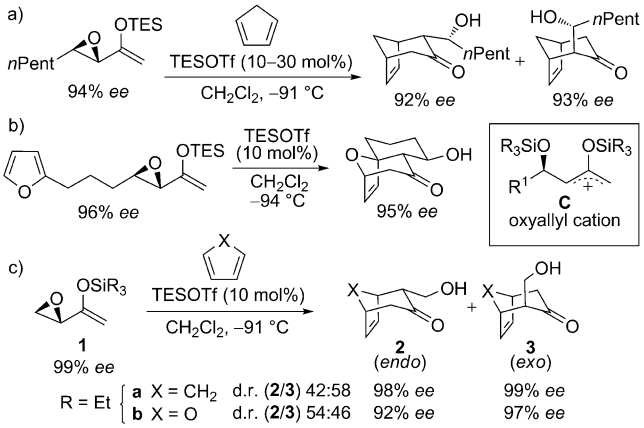
Abstract: *Silyl-triflate-catalyzed (4+3) cycloadditions of epoxy enolsilanes with dienes provide a mild and chemoselective synthetic route to seven-membered carbocycles. Epoxy enolsilanes containing a terminal enolsilane and a single stereocenter undergo cycloaddition with almost complete conservation of enantiomeric purity, a finding that argues against the involvement of oxyallyl cation intermediates which have been previously proposed for these types of reactions. Reported are theoretical and experimental investigations of the cycloaddition mechanism. The major enantiomers of the cycloadducts are derived from S_N2-like reactions of the silylated epoxide with the diene, in which stereospecific ring opening and formation of the two new C–C bonds occur in a single step. Calculations predict, and experiments confirm, that the observed small losses of enantiomeric purity are traced to a triflate-mediated double S_N2 cycloaddition pathway.*

The (4+3) cycloadditions of oxyallyl cations with dienes have found numerous applications in the asymmetric synthesis of seven-membered carbocycles.[1,2] Experimental and theoretical studies[1,3,4] have classified these reactions into three mechanistic categories: a) concerted, b) two-step, and c) tandem (3+2) cycloaddition–Claisen rearrangement (Scheme 1). The silyl-triflate-catalyzed reactions of epoxy enolsilanes with dienes (Scheme 2)[5,6] constitute a mild and chemoselective approach to (4+3) cycloadditions. These reactions have previously been understood to involve the intermediate oxyallyl cations **C** (Scheme 2), derived from ring opening of the silylated epoxide. High levels of diastereoselectivity are obtained in the inter- and intramolecular cycloadditions of disubstituted epoxy enolsilanes (Scheme 2a,b), and could formally be attributed to facially selective reactions of **C** ($R^1 \neq H$) with the diene. However, we recently discovered that monosubstituted epoxy enolsilanes (**1**; Scheme 2c) also undergo cycloaddition with excellent enantioselectivity.[7] Complete conservation of enantiomeric purity is obtained in the cycloaddition of **1** (R = Et) with cyclopentadiene, while a small (2–7%) erosion of the *ee* value is observed in the cycloaddition with furan. In the reaction with furan, the major (*endo*) diastereomer has a lower *ee* value. The high enantioselectivities obtained in the cycloadditions of **1** rule out any major role for oxyallyl cation **C**, which is achiral ($R^1 = H$), but



Scheme 1. Mechanisms of oxyallyl cation (4+3) cycloadditions.



Scheme 2. Asymmetric (4+3) cycloadditions of disubstituted (a,b) and monosubstituted (c) epoxy enolsilanes.[6,7] TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

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afford no clues as to the nature of the electrophile which is intercepted by the diene. We have therefore performed theoretical and experimental investigations to uncover the sequence of bond-forming and bond-breaking processes in the (4+3) cycloadditions of **1**.

Our theoretical studies employed enolsilane **1** in which $OSiR_3$ is modeled by OTMS. Computations comprised geometry optimizations at the B3LYP/6-31G(d) level of theory in implicit dichloromethane (CPCM), followed by single-point energy calculations at the M06-2X/6-311+G-(d,p) level. Optimization in solvent and incorporation of the triflate counterion were essential for reproducing the conservation of enantiomeric purity observed experimentally. Calculations employing isolated cations (optimized either in the gas phase or in solution) predict complete enantioselectivity and are unable to account for the small losses of enantiomeric purity observed experimentally.[8]

Electrophilic intermediates that retain the stereochemical information of the reactant include the silylated epoxide **A** and the partially ring-opened, coordinated oxyallyl cation **B** (Figure 1). The fully ring-opened cation **C** is achiral. A search for the electrophilic species **A**–**C** revealed only **A** and **C**, shown in Figure 1, as the triflate salts **4** and **5**. The partially ring-opened cation (**B**) does not correspond to an energy minimum on the potential energy surface. However, the C–O bond lengths of **4** do display significant distortion as implied in **B**, with lengthening of the bond from oxygen to the allyl carbon C2. The silylated epoxide **4** undergoes ring opening to **5** via transition state **TS1** with an activation energy ($\Delta G^{\neq}$) of 23.3 kcal mol^{-1} in dichloromethane.

Transition states were computed for the (4+3) cycloadditions of **4** with cyclopentadiene and furan, thus leading to the cycloadducts **2a**/**3a** and **2b**/**3b**, respectively (Figure 2). The diene approaches the epoxide from the back side, thereby defining the absolute stereochemistry (with respect to the epoxide) of the cycloadduct. The C–C bond-forming process lags far behind the epoxide ring opening. In the TS the epoxide C–O bond is elongated by 0.2–0.3 Å while the diene still lies 3.1–3.8 Å away from the allyl moiety. For comparison, the corresponding C–C distance in the TS for an S_N2 reaction of cyclopentadiene with silylated oxirane is 2.5 Å.[8] The long C–C distances in **TS2** and **TS3** resemble van der Waals contacts (sum of van der Waals radii = 3.4 Å)[9] rather than typical TS bond lengths. Nonetheless, **TS2** and **TS3** lead directly to the cycloadducts. The reaction mechanism is therefore best described as a highly asynchronous, S_N2-like ring opening of the activated epoxide by the diene which leads without further barrier to the formation of the C–C bond between the remote termini of the diene and allyl group. Alternative stepwise pathways, in which bond formation to the epoxide carbon atom precedes the closure of the seven-membered ring, are at least 2 kcal mol^{-1} higher in energy.

The activation energies ($\Delta G^{\neq}$) for **TS2a/b** and **TS3a/b** are within the 9–10 kcal mol^{-1} range. These values are about 13 kcal mol^{-1} lower than the barrier for epoxide ring opening in the absence of any diene (**TS1**). The predicted diastereoselectivity [**TS2** (*endo*) vs **TS3** (*exo*)] is small, and consistent with experiment: 0.1 kcal mol^{-1} in favor of *exo* for cyclopentadiene and 0.1 kcal mol^{-1} in favor of *endo* for furan.

Based on the 13 kcal mol^{-1} difference in energy between **TS1** and **TS2**/**TS3**, no ring opening to the achiral oxyallyl

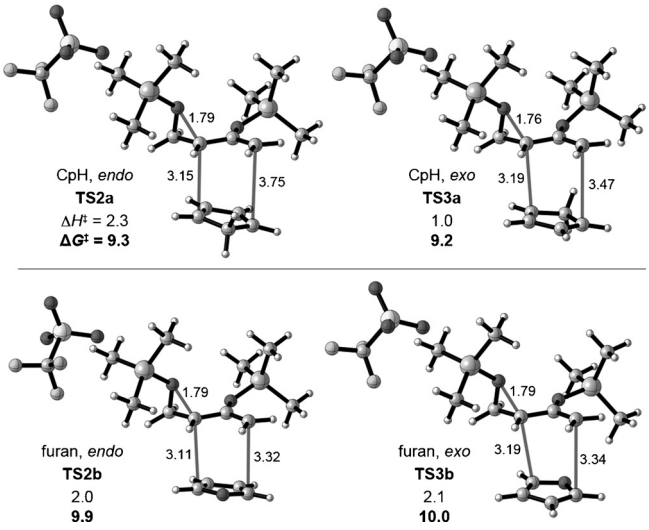


Figure 2. Transition states for S_N2-like (4+3) cycloadditions of **4** with cyclopentadiene and furan leading to **2a**/**3a** and **2b**/**3b**, respectively.

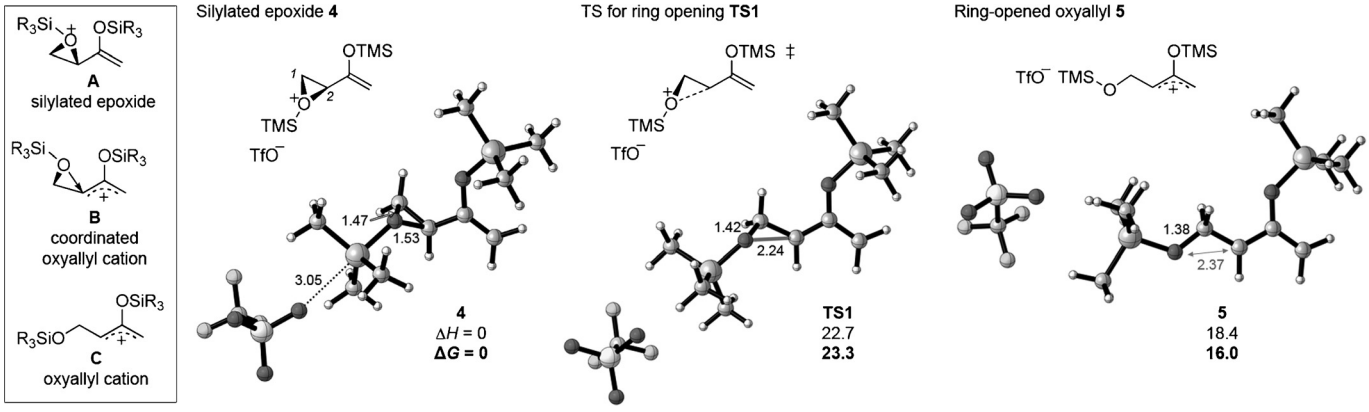


Figure 1. Possible electrophilic species derived from the epoxy enolsilane **1** (R = Me) and TMSOTf. Triflate salts of the silylated epoxide **4** and the oxyallyl cation **5**, and the transition state for ring opening of **4** to **5**, were computed at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) (CPCM) level of theory in dichloromethane. Distances in Å, ΔH and ΔG in kcal mol^{-1}. TMS = trimethylsilyl.

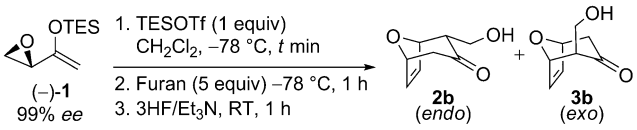
cation should occur under the typical reaction conditions. Experimentally, however, cycloadditions of **1** with furan display small losses of enantioselectivity (Scheme 2c). Moreover, the major diastereomer (**2b**) is isolated with a 4–16% lower *ee* value than the minor diastereomer (**3b**[7]; see the Supporting Information). The loss in *ee* value cannot be attributed to epimerization of the products.[10] In principle, one possible pathway leading to the minor enantiomers *ent*-**2b**/**3b** could be the addition of furan to the front side of **4** in an S_N2'-like process. However, the computed barriers for S_N2' reactions (see the Supporting Information) are too high to be significant under the experimental conditions.

We propose that the minor enantiomers of the cycloadducts are formed by reactions of the silylated epoxide with triflate ion. The ion-pair **4** (Figure 1) represents the immediate product of the reaction between the epoxide and TMSOTf. In **4**, the triflate anion remains associated with the TMS group, thus forming an O–Si interaction of 3.1 Å at the back side of the Si–O(epoxide) bond. As described above, this ion pair displays a strong preference to undergo cycloaddition rather than ring opening. However, moving the triflate ion to the lower face of the epoxide gives an alternative ion pair, $\mathbf{4}_{alt}$ (Figure 3), which is predicted to undergo triflate-induced ring opening ($\mathbf{TS1}_{alt}$) with a very low barrier (2.4 kcal mol^{-1}). Displacement of OTf^- from the ring-opened adduct **6** by the diene (**TS6**) gives the cycloadduct *ent*-**2** or *ent*-**3** enantiospecifically.[11]

The computed barrier for this double S_N2 cycloaddition pathway (2.4 kcal mol^{-1}) is much smaller than the barrier for cycloaddition of the initial ion-pair **4** (9–10 kcal mol^{-1}). One might therefore predict that *ent*-**2** and *ent*-**3** should be the major products. Experimentally, however, *ent*-**2** and *ent*-**3** are the minor products and we propose that this reflects rate-limiting conversion of **4** into $\mathbf{4}_{alt}$. It is difficult to estimate the barrier for conversion of **4** into $\mathbf{4}_{alt}$. However, separation of the ions by just 2 Å from their equilibrium geometry raises the energy by 5 kcal mol^{-1}. It is therefore reasonable that conversion of **4** into $\mathbf{4}_{alt}$ would be slow compared to cycloaddition via **TS2** or **TS3**.[12] Thus, under standard reaction conditions, where a catalytic amount of TESOTf is added to a solution of **1** and excess diene ($\geq$5 equiv), the reaction takes place predominantly through the pathway **4**→**TS2**/**TS3**→**2**/**3** rather than through **4**→$\mathbf{4}_{alt}$→$\mathbf{TS1}_{alt}$→**6**→**TS6**→*ent*-**2**/**3**.

Experimental support for the slow conversion of **4** into $\mathbf{4}_{alt}$ is obtained from applying a modified reaction protocol in which **1** is allowed to react with TESOTf before adding the diene (Table 1). Under such reaction conditions, a reversal of enantioselectivity occurs. The major products are now *ent*-**2** and *ent*-**3**, and the *ee* value of *ent*-**2**/**3** increases when a longer time is allowed for **1** to react with TESOTf before adding the diene.[13] Further evidence for the role of the anion is obtained from experiments using $TES[B(C_6F_5)_4]$ in place of TESOTf. This catalyst, which contains the non-nucleophilic tetra(pentafluorophenyl)borate anion, induces cycloaddition with no reversal nor loss of enantioselectivity.[8]

Table 1: Reversal of enantioselectivity of the (4+3) cycloaddition of **1** with furan following premixing of **1** with TESOTf.



t [min]	Yield [%][a]	d.r.[b] (*endo*/*exo*)	**2b** *ee* [%][c]	**3b** *ee* [%][c]
0	64	1.2:1	+88	+95
30	15	1.2:1	−7	−8
60	11	1.4:1	−22	−38
90	14	1.25:1	−37	−55

[a] Isolated yield. [b] Determined by chiral HPLC of the TBDPS-**2b**. [c] Determined by chiral HPLC of the TBDPS-**3b**.

In summary, experiment and theory together indicate that ion-pairing effects determine the mechanisms and enantioselectivities of (4+3) cycloadditions of the epoxy enolsilanes **1**. The silyl-triflate-catalyzed cycloadditions of **1** with dienes do not generally involve oxyallyl cation intermediates. Instead, the silylated epoxide triflate undergoes ring opening by the diene in an S_N2-like process, in concert with formation of a C–C bond between the remote termini of the allyl group and diene. Small losses of enantiomeric purity are traced to pathways involving triflate, and these pathways may become dominant and give reversals of enantioselectivity (albeit in low yield) through postponing the addition of the diene. These results lead us to surmise that previously reported low-temperature cycloadditions of other oxyallyl cation precursors based on enolsilanes may also be more accurately

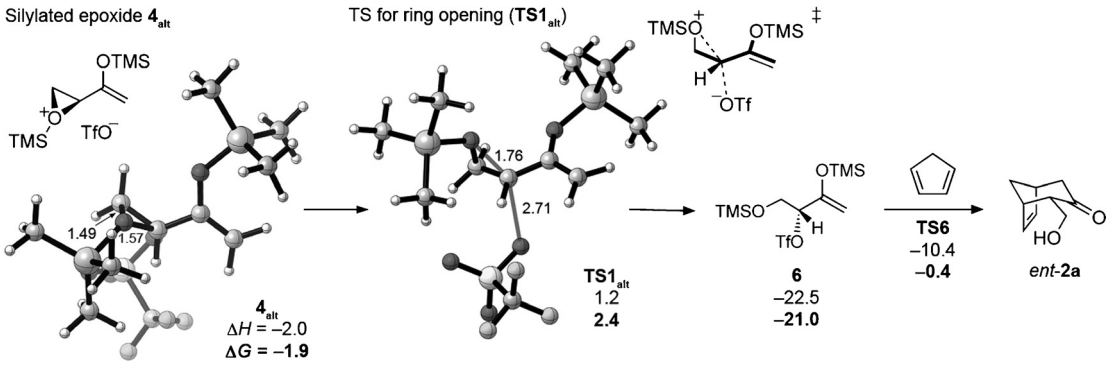


Figure 3. Alternative ion-pair geometries of **4** and the transition states for ring opening of **4** and cycloaddition of **4** with cyclopentadiene.

described by this mechanistic picture. These results also have more general implications for cation reactivity, for instance Friedel–Crafts alkylations. Enolsilanes that are more highly substituted than **1** are more prone to epoxide ring opening and our current investigations are focused on controlling the enantioselectivity of cycloadditions in such systems, as well as their applications to the asymmetric synthesis of bioactive compounds.

Keywords: cycloaddition · density functional calculations · epoxides · reaction mechanisms · stereoselectivity

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[10] Our previous work[7] showed that in the presence of TBAF, **3b** undergoes epimerization to *ent*-**2b**, while **2b** epimerized to *ent*-**3b**. Desilylation with $Et_3N{\cdot}3HF$ minimized the loss in *ee* value, where the treatment of either **2b** or **3b** with $Et_3N{\cdot}3HF$ over 24 h decreased the *ee* value by $<1\%$ only.

[11] Exploration of alternative ion-pair geometries for **TS1**–**TS3** indicates that a small fraction of the minor cycloadducts *ent*-**2** and *ent*-**3** may arise non-enantiospecifically via the oxyallyl intermediate **5**.[8]

[12] Additionally, the difference between the calculated $\Delta G^{\ddagger}$ values for (bimolecular) cycloaddition versus (unimolecular) conversion of **4** into $\mathbf{4}_{alt}$ is likely overestimated by a few kcal mol^{-1} because of the tendency of continuum solvation to overestimate solute entropies.

[13] Similar results are obtained with cyclopentadiene: see the Supporting Information.

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