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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 stereocentre undergo cycloaddition with almost complete

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conservation of enantiomeric purity, a finding that argues against the involvement of oxyallyl cation intermediates that have been previously proposed for these types of reactions. We report theoretical and experimental investigations of the cycloaddition mechanism. The major enantiomer of cycloadduct is derived from an S_N2 -like reaction 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.

Keywords

(4+3) cycloaddition; density functional calculations; epoxides; reaction mechanisms; stereoselectivity

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: (i) concerted, (ii) two-step, and (iii) 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) cycloaddition. These reactions have previously been understood to involve 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), which could formally be attributed to facially selective reactions of **C** ($R^1 = H$) 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 *ee* is observed in the cycloaddition with furan. In the reaction with furan, the major (*endo*) diastereomer has a lower *ee*. 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 afford no clues as to the nature of the electrophile that is intercepted by the diene. We have therefore performed theoretical and experimental investigations to uncover the sequence of bond-forming and 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 electrophilic species **A–C** revealed only **A** and **C**, shown in Figure 1 as 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 silylated epoxide **4** do display significant distortion in the direction implied by **B**, with lengthening of the bond to the allyl carbon (C2). Silylated epoxide **4** undergoes ring opening to **5** via transition state **TS1** with an activation energy ($G^\ddagger$) of 23.3 kcal/mol in dichloromethane.

Transition states were computed for the (4+3) cycloadditions of **4** with cyclopentadiene and furan leading to 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 processes lag far behind the epoxide ring opening. In the TS the epoxide C–O bond has 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 a TS for 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 cycloadduct. 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 second C–C bond between the remote termini of the diene and allyl group. Alternative stepwise pathways, in which bond formation to the epoxide carbon precedes the closure of the seven-membered ring, are at least 2 kcal/mol higher in energy.

The activation energies ($G^\ddagger$) for **TS2a/b** and **TS3a/b** are 9–10 kcal/mol. These values are about 13 kcal/mol 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 in favor of *exo* for cyclopentadiene and 0.1 kcal/mol in favor of *endo* for furan.

Based on the 13 kcal/mol difference in energy between **TS1** and **TS2/TS3**, no ring-opening to the achiral oxyallyl 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* than the minor diastereomer (**3b**)^[7] (see also the Supporting Information). The losses of *ee* 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 cycloadduct are formed by reactions of the silylated epoxide with triflate ion. The ion pair **4** (Figure 1) represents the immediate product of reaction between the epoxide and TMSOTf. In **4**, the triflate anion remains associated with the TMS group, 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, **4_{alt}** (Figure 3), which is predicted to undergo triflate-induced ring opening (**TS1_{alt}**) with a very low barrier (2.4 kcal/mol). Displacement of OTf[−] from the ring-opened adduct **6** by the diene (**TS6**) gives cycloadduct *ent*-**2** or *ent*-**3** enantiospecifically.^[11]

The computed barrier for this double-S_N2 cycloaddition pathway (2.4 kcal/mol) is much smaller than the barrier for cycloaddition of the initial ion pair **4** (9–10 kcal/mol). 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** to **4_{alt}**. It is difficult to estimate the barrier for conversion of **4** to **4_{alt}**; however, separation of the ions by just 2 Å from their equilibrium geometry raises the energy by 5 kcal/mol. It is therefore reasonable that conversion of **4** to **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 (5 equiv), the reaction takes place predominantly through the pathway **4**→**TS2/TS3**→**2/3** rather than through **4**→**4_{alt}**→**TS1_{alt}**→**6**→**TS6**→*ent*-**2/3**.

Experimental support for the slow conversion of **4** to **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 conditions, a reversal of enantioselectivity occurs. The major products are now *ent*-**2** and *ent*-**3**, and the *ee* 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(C₆F₅)₄] in place of TESOTf. This catalyst, containing the non-nucleophilic tetra(pentafluorophenyl)borate anion, induces cycloaddition with no reversal nor loss of enantioselectivity.^[8]

In summary, experiment and theory together indicate that ion-pairing effects determine the mechanisms and enantioselectivities of (4+3) cycloadditions of 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; 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 Et₃N·3HF minimized the loss of ee, where the treatment of 2b or 3b with Et₃N·3HF over 24 h decreased the ee 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 oxyallyl cation C.^[8]
12. Additionally, the difference in $G^\ddagger$ for (bimolecular) cycloaddition versus (unimolecular) conversion of 4 to 4_{alt} is likely overestimated by a few kcal/mol, due to the tendency of continuum solvation to overestimate solute entropies.
13. Similar results are obtained with cyclopentadiene: see the Supporting Information.

Figure 1. Possible electrophilic species derived from epoxy enolsilane **1** ($R = \text{Me}$) 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, H and G in kcal/mol.

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

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

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

Scheme 2.

Asymmetric (4+3) cycloadditions of (a,b) disubstituted and (c) monosubstituted epoxy enolsilanes.^[6,7]

Table 1

Reversal of enantioselectivity of the (4+3) cycloaddition of **1** with furan following pre-mixing of **1** with TESOTf.

t [min]	Yield [%]	dr (endo/exo)	2b ee [%]	3b ee [%]
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