Cycloaddition

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Enantioselective Oxazaborolidinium-Catalyzed Diels–Alder Reactions without CH···O Hydrogen Bonding**

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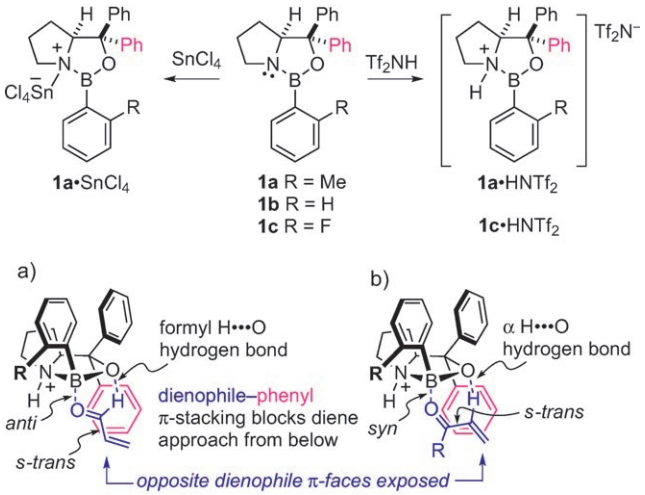
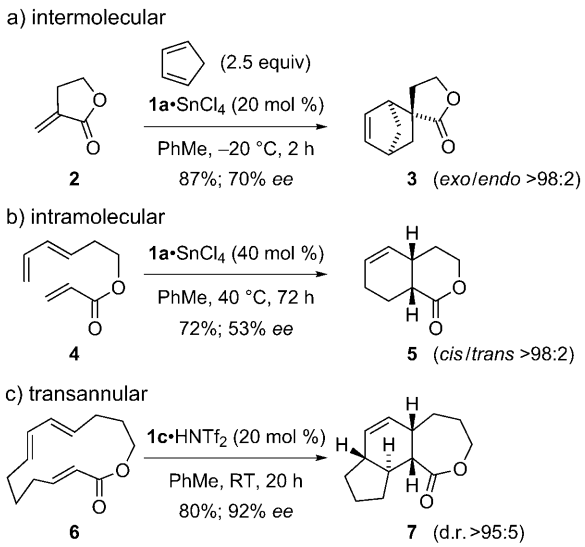
The oxazaborolidine Diels–Alder (DA) precatalysts first introduced by Corey et al. in 2002[1] are remarkable for several reasons. The derived oxazaborolidinium cations, for example **1a**·$HNTf_2$ or **1a**·MX_n (formed by exposure to either Brønsted[1–3] or Lewis[4] acids, Scheme 1), are active catalysts for enantioselective cycloadditions involving a broad range of dienes and dienophiles.[1–12] Perhaps the most significant quality of this family of Lewis acid (LA) catalysts, however, lies in their singular ability to promote cycloadditions of dienophiles carrying simple, common functional groups. Interestingly, aldehyde-activated dienophiles give the opposite π-enantiofacial selectivity relative to that of the corresponding esters, carboxylic acids, and ketones in reactions promoted by **1a**. This observation was explained by Corey and co-workers[2] in terms of the pre-transition-state assemblies shown in Scheme 1. A pivotal feature of these pre-transition-state models is the presence of an O···HC hydrogen bond, which is believed to facilitate π-enantiofacial selectivity by constraining the orientation of the dienophile–LA complex. Herein we present computational and experimental evidence that certain enantioselective DA reactions may take place in the absence of O···HC hydrogen bonding and that they might even prefer this pathway over the normal Corey pathway.



Scheme 1. Corey's oxazaborolidinium catalyst and pre-transition-state models (i.e. diene absent). a) Proposed mode of complexation for aldehydes. b) Proposed mode of complexation for ketones, esters, and acids.

Certain intermolecular, intramolecular, and transannular DA reactions of ester-activated dienophiles catalyzed by oxazaborolidinium species furnish products which do not correlate with the Corey pre-transition-state model shown in Scheme 1. Thus, under oxazaborolidinium catalysis,[13] α-methylene-γ-butyrolactone (**2**) undergoes a highly *exo*-selective intermolecular DA reaction with cyclopentadiene to give adduct **3** (Scheme 2a) as the major stereoisomer, and triene **4** undergoes a highly *cis*-selective intramolecular DA reaction to give **5** (Scheme 2b). In a series of elegant



Scheme 2. DA reactions proceeding with enantioselectivities that vary relative to those predicted by the Corey O···HC hydrogen-bonding model. a) and b) are results from this work, and c) is a result from the work of Balskus and Jacobsen.[14]

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experiments, Balskus and Jacobsen recently demonstrated[14] that macrocyclic lactones such as *E,E,E*-triene **6** undergo stereoselective transannular DA reactions to furnish tricycles such as **7** (Scheme 2c). The reason for the unexpected enantioselectivities obtained for these reactions has now been identified by DFT calculations.

The Corey catalyst used in the calculations is **1b**·H$^+$, protonated **1b**, which was used in an early experimental study.[1] In general, we limit our investigation to enantioselectivities in DA reactions leading to the observed major diastereomer (i.e. *cis*- or *trans*-fused bicycle, *exo*- or *endo*-intermolecular DA adduct). Comprehensive sets of reactant–**1b** complexes and plausible transition states (TSs) leading to the two enantiomeric cycloadducts were located for each reaction. Geometry optimizations and thermal corrections were calculated by using B3LYP/6-31G(d) theory[15] and more reliable single-point energies were calculated at the MPW1 K/6-31+G(d,p) level of theory.[16,17] The polarizable continuum model (PCM)[18] approximation was used to model the dichloromethane solvent ($\varepsilon = 8.93$).[19]

The Gibbs free energies (ΔG_{comp}) for formation of the most stable reactant–LA complex for several dienophiles are given in Table 1 together with the free energies of activation (ΔG_a^{+}), which are relative to the precursor complex (or include the diene for **2** and **13**), for the most favorable DA transition state.

Table 1: Gibbs free energies of formation (ΔG_{comp}) of the most stable **1b**·H$^+$ complexes of reactants and DA Gibbs free energies of activation (ΔG_a^{+}) relative to these complexes.[a]

	Gas phase		Dichloromethane solvent[b]	
Substrate	ΔG_{comp}	ΔG_a^{+}	ΔG_{comp}	ΔG_a^{+}
2	−34.7	90.0	−28.0	93.1
4	−23.2	91.2	−13.7	86.3
9	−41.7	66.8	−33.9	69.7
12	−16.1	85.3	−4.4	85.2
13	−38.9	99.4	−30.2	101.4

[a] MPW1 K/6-31+G(d,p)//B3LYP/6-31G(d) + B3LYP/6-31G(d) thermal corrections. Values reported in kJ mol^{-1}, calculated at 298.15 K. [b] Nonspecific solvent effect by using the polarizable continuum model. See Figure 1 for schematic transition structures.

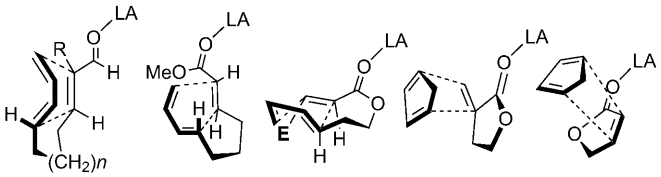
These data clearly show that, for each system, the numerical value of the free energy of complexation is considerably smaller than the corresponding free energy activation for the DA reaction. Assuming that the complex formation is essentially barrierless, we conclude that the complex formation is rapidly reversible on the DA reaction timescale.[20] Consequently, DA enantioselectivities in these LA-catalyzed DA reactions is determined solely by the relative free energies of competing TSs, upon which we now focus attention.

Table 2 presents the relative enthalpies (H_{rel}^{+}) and free energies (G_{rel}^{+}) between the most favorable TSs leading to each enantiomer for each system, and the *ee* values as calculated from the G_{rel}^{+} values. Figure 1 presents schematic representations of the predicted favored TSs. The predicted π-enantiofacial selectivities are in complete qualitative agreement with those observed experimentally (Table 2, entries 1 and 2, and 4–8). With one exception (Table 2, entry 5), the predicted *ee* values are in good agreement with the experimental values.[21]

Table 2: Relative enthalpies (H_{rel}^{+}) and relative Gibbs free energies (G_{rel}^{+}) between the two most stable **1b**·H$^+$-catalyzed DA TSs leading to opposite enantiomeric cycloadducts and predicted *ee* values based on the ΔG_{rel}^{+} values.[a]

		Dichloromethane solvent[b]			
Entry	Substrate	H_{rel}^{+}[c]	G_{rel}^{+}[c]	*ee* [%][d]	Exp. *ee* [%][d]
1	**2**	5.3	6.3	85	70[e]
2	**4**	7.5	7.1	82	53[e]
3	**8**	6.6	10.6	97	–
4	**9**	5.0	6.9	94	90[f]
5	**10**	2.8	1.9	36	80[f]
6	**11**	6.2	6.9	87	93[f,g]
7	**12**	7.1	9.4	96	86[f]
8	**13**	8.13	5.09	77	88[h]

[a] MPW1 K/6-31+G(d,p)//B3LYP/6-31G(d) + B3LYP/6-31G(d) thermal corrections. The reported values are in kJ mol^{-1}, calculated at 298.15 K. [b] Nonspecific solvent effect using the polarizable continuum model. [c] $H_{rel}^{+} = H^{+}$(minor enantiomer) − H^{+}(major enantiomer); $G_{rel}^{+} = G^{+}$(minor enantiomer) − G^{+}(major enantiomer); [d] In all cases, computational and experimental results give the same major enantiomer (see Figure 1 for depictions of TSs leading to the major enantiomer.) [e] This work. [f] Reference [5]. [g] The -$CO_2CH_2CF_3$ group was used experimentally. [h] Reference [2].



8 TS *n* = 1, R = H **11 TS** **4 TS** **E** = H **2 TS** **13 TS**
9 TS *n* = 1, R = CH_3 **12 TS** **E** = CO_2Me
10 TS *n* = 2, R = CH_3

Figure 1. Schematic representation of the favored TS for each **1b**·H$^+$-catalyzed DA reaction studied. The depicted diastereoselectivities (*cis* or *trans* for triene precursors and *endo* or *exo* for dienophiles) and π-enantiofacial selectivities are those favored experimentally (LA = **1b**·H$^+$).

The essential features of Corey's pre-transition-state assembly models are clearly evident in the TS geometries (Figure 2). Thus, the lowest energy TSs[22] for the α,β-enals **8**, **9**, and **10** have the *s-trans* C=C–C=O conformation[23] and the boron center complexed to the oxygen atom through the lone pair *anti* to the C=C bond. This coordination mode, typified by **9-TS** (Figure 2a), is consistent with in the presence of a formyl CH···OB hydrogen bond having an H···O distance of 2.47 Å, which lies within the range from 2.41 to 2.59 Å as determined from X-ray crystal structures of aldehyde–boron complexes.[24] The 3.38 Å separation between the formyl carbon atom and C1′ of the *exo*-phenyl group at C5 might signal a stabilizing π–π interaction postulated in the Corey model.

The final feature of the Corey model—having the *exo*-phenyl group at C5 hinder approach of the diene from the C5

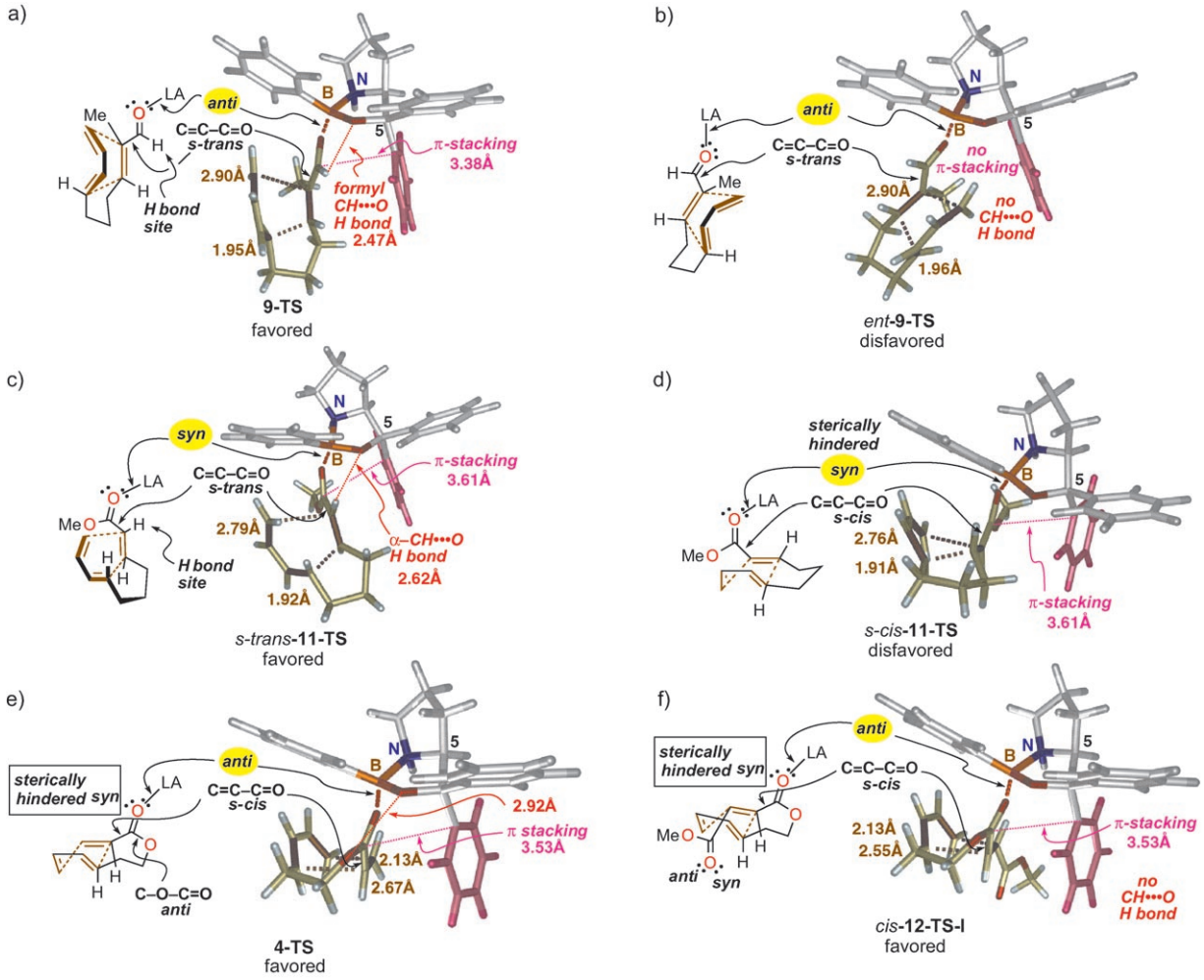


Figure 2. PCM B3LYP/6-31G(d) calculated transition-state structures for intramolecular Diels–Alder reactions catalyzed by oxazaborolidinium **1b**·H^+. a) and b) TSs for **9**; c) and d) TSs for **11**; e) TSs for **4**; f) TSs for **12**.

direction—is apparent in **9-TS**; the diene component, therefore approaches from the more open side which has the phenyl group attached to B. The lowest energy TS leading to the minor enantiomer (*ent*-**9-TS**, Figure 2b) does indeed involve diene approach from the hindered side (C5–Ph), but the developing steric congestion is eased by a substantial 56° twisting of the dienophile about the formyl O–B bond away from the *exo* phenyl group at C5, resulting in a closest diene–*exo*-phenyl group distance of 3.5 Å. However, this twisting comes at the cost of destroying the formyl CH···O hydrogen bond, making the H···O distance 3.46 Å.

The favored TS for 9*E*-ester **11**, *s-trans*-**11-TS** (Figure 2c), resembles the Corey model for α,β-unsaturated esters, that is, the C=C–C=O conformation is *s-trans* and the LA is coordinated *syn* with respect to the C=C; the diene approaches from the more open side having the B–Ph fragment. This TS displays an α-CH···O hydrogen bond of 2.62 Å.

The lowest free energy TS having an *s-cis* C=C–C=O conformation, *s-cis*-**11-TS** (Figure 2d), is 24 kJ mol^{-1} less stable than *s-trans*-**11-TS**, which reflects the highly unfavorable steric interaction between the *syn*-coordinated LA and the C=C bond of the dienophile in *s-trans*-**11-TS**;[25] thus the B···O=C angle widens from 126° in the *s-trans* TS to 133° in the *s-cis* TS. The β-CH···O distance in *s-cis*-**11-TS** is 2.55 Å, which is indicative of a β-CH···O hydrogen bond, but this energetic advantage is overwhelmed by the aforementioned steric interaction.

In TSs with ester-linked tethers, for example, **4** and **12**, the carbonyl group of the tether is forced to adopt the *s-cis* C=C–C=O conformation with the C–O bond approximately *anti* to the carbonyl group (the dihedral angle O=C–O–C is about 160°). Coordination of the LA to the carbonyl group in **4-TS** (Figure 2e) takes place at the less hindered *anti* lone pair, rather than at the more congested *syn* lone pair. *Syn*-complexed TSs for **4** are predicted to be 15–22 kJ mol^{-1} less stable than the *anti*-complexed TSs, notwithstanding the presence of an CO···OB distance of only 2.92 Å in the *anti*-complexed TS. The recently reported examples of enantioselective oxazaborolidinium-catalyzed transannular DA reactions of macrocyclic unsaturated esters (Scheme 2c) may be explained in terms of *anti*-complexed TSs akin to that for **4**.[14]

The most favored TSs for the intermolecular DA reactions of **2** and **13** are readily explained in terms of the above discussion, namely *anti*-complexed **2** avoids steric interactions with the exocyclic methylene group, and *syn*-complexed **13** produces a stabilizing α-CH···O hydrogen bond in the TS.

For fumarate **12**, coordination to the LA in the TS may occur either at the *syn* position of the terminal -CO_2Me group (*s-trans* C=C–C=O conformation) or at the *anti* position of the ester tether (**12-TS**, Scheme 2), with the Corey model predicting the former, owing to the formation of an α-CH···O hydrogen bond in this coordination mode. Because both coordination modes give the same enantiomeric product, product analysis cannot distinguish between these mechanistic alternatives. Our calculations resolved this mechanistic ambiguity. Of the 24 DA TSs located for the experimentally observed *cis* addition (i.e. the terminal -CO_2Me group *exo* to the diene), the most stable *cis*-**12-TS-I** (Figures 2 f and 3) involves an *anti*-complexed species at the

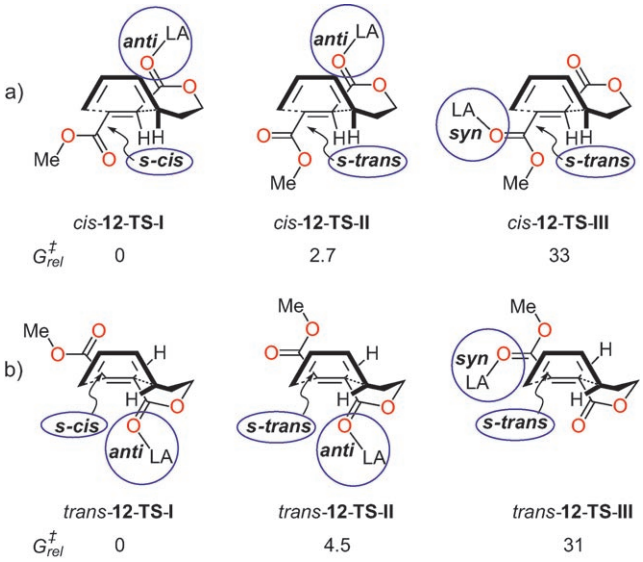


Figure 3. Relative free energies (kJ mol^{-1}) for selected a) *cis*-TSs and b) *trans*-TSs for fumarate **12** (LA = **1b**·H$^+$).

carbonyl group of the tether and an uncomplexed -CO_2Me group which adopts the *s-cis* C=C–C=O conformation (*cis*-**12-TS-II**, Figure 3). The -CO_2Me-complexed TS, *cis*-**12-TS-III**, is 33 kJ mol^{-1} higher in free energy than *cis*-**12-TS-I** and therefore plays no role in product formation. Why does the TS prefer the *anti*-complexation at the carbonyl group of the tether, which lacks a CH···O interaction, rather than the Corey-type complexation seen in *cis*-**12-TS-III**, having a stabilizing α-CH···O hydrogen bond?

There are two plausible explanations: 1) The uncatalyzed intramolecular Diels–Alder (IMDA) reaction of **12** is strongly *cis*-selective[26] and LA coordination at the *endo* carbonyl group of the tether will additionally stabilize the *cis* TS through strengthened secondary orbital interactions;[27] 2) the *anti* lone pair of the carbonyl group of the tether is more basic than the *syn* lone pair of the terminal -CO_2Me group (*s-trans* C=C–C=O conformation), because the former suffers from a combination of destabilizing electrostatic dipole–dipole and overlap repulsion interactions with the in-plane lone pair of the alkoxy oxygen center.[28] This destabilizing interaction is essentially removed upon formation of the *anti*-complexed species at the tether, but remains if cooordination occurs *syn* to the -CO_2Me group.

The first possibility is discounted because the most stable TS for the minor *trans*-IMDA pathway, *trans*-**12-TS-I** (Figure 3), has an LA coordinated to the carbonyl group of the tether, even though this carbonyl group is *exo* to the diene. The large energy differences between **12-TS-III** and **12-TS-II**—each having the terminal -CO_2Me group in an *s-trans* C=C–C=O conformation—for both the *cis*- and *trans*-IMDA reactions are consistent with the second explanation.

In all mechanistic discussions on the oxazaborolidinium-catalyzed DA reactions published to date, it has been implicitly assumed that reactant complexes and the TSs occurs at the less congested *exo* (convex) face of the catalyst, and our calculations confirm this preferred coordination mode in all reactant complexes and in the dominant TSs giving rise to the major enantiomers for all systems studied (e.g. Figure 2). However, this assumption fails when considering the formation of the minor enantiomer. Although the dominant TSs leading to the minor enantiomers in the DA reactions of **2**, **8**–**10**, and **13** involve *exo* (convex) face complexation, those for **4**, **11**, and **12** involve complexation to the *endo* (concave) face of the catalyst, as depicted for the case of **4** in Figure 4.[29] It appears that the steric congestion associated with *endo* (concave) face complexation in the TSs

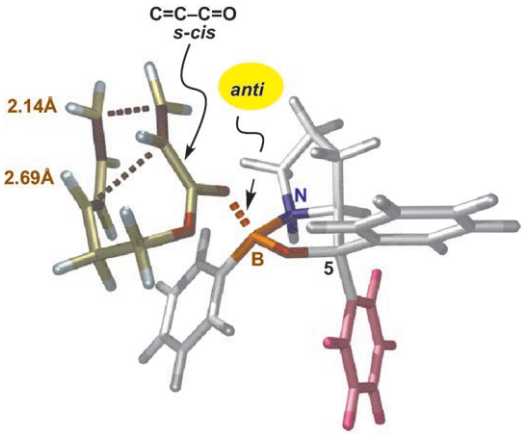


Figure 4. The lowest free energy TS for the DA reaction of **4** leading to formation of the minor enantiomer.

for these systems is more than compensated by the diene being able to approach from the more open side having the B–Ph fragment.[30] This finding suggests that increasing steric congestion on the *endo* (concave) face, by judicial placement of ring substituents, might improve enantioselectivity.

In summary, we report herein the first computational investigations into oxazaborolidinium-catalyzed Diels–Alder reactions, which validate Corey's pre-transition-state models with aldehyde- and ester-activated dienophiles and, furthermore, indicate an alternative coordination mode for esters

which does not involve a CH···O hydrogen bond. The new pre-transition-state model (Figure 5) operates with substrates undergoing DA reactions through *s-cis* C=C–C=O conformations and involves LA coordination at the *anti* lone pair of the ester carbonyl group. Our studies show that this new pathway may actually be preferred over the Corey pathway when the two are in competition. Importantly, this model explains the unexpected enantioselectivities seen in certain intermolecular, intramolecular, and transannular DA reactions.

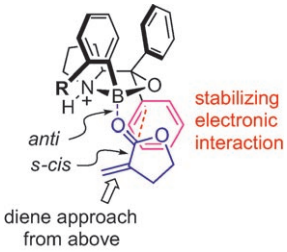


Figure 5. The new pre-transition-state model explaining the unexpected enantioselectivity with *s-cis* C=C–C=O, ester-activated dienophiles.

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[21] The agreement might even improve if the experimentally used precatalyst **1a** were employed in the calculations because it gives higher *ee* values than **1b**.[1]
[22] It turns out that for all systems investigated the most stable TS has both the smallest enthalpy and Gibbs free energy.
[23] In contrast, for the corresponding uncatalyzed DA reactions, the formyl group in the TS prefers the *s-cis* C=C–C=O conformation over the *s-trans* C=C–C=O conformation by approximately 2.5 kJ mol^{-1}.
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[29] The free energy preferences for *endo*-face over *exo*-face complexation are (kJ mol^{-1}): **4** (6.4); **11** (0.3); **12** (8.7).
[30] The corresponding *endo*-face-complexed TS for **12** still involves preferential complexation at the carbonyl group of the tether rather than at the CO_2Me group.

