Asymmetric Synthesis

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Highly Enantioselective Construction of Tricyclic Derivatives by the Desymmetrization of Cyclohexadienones**

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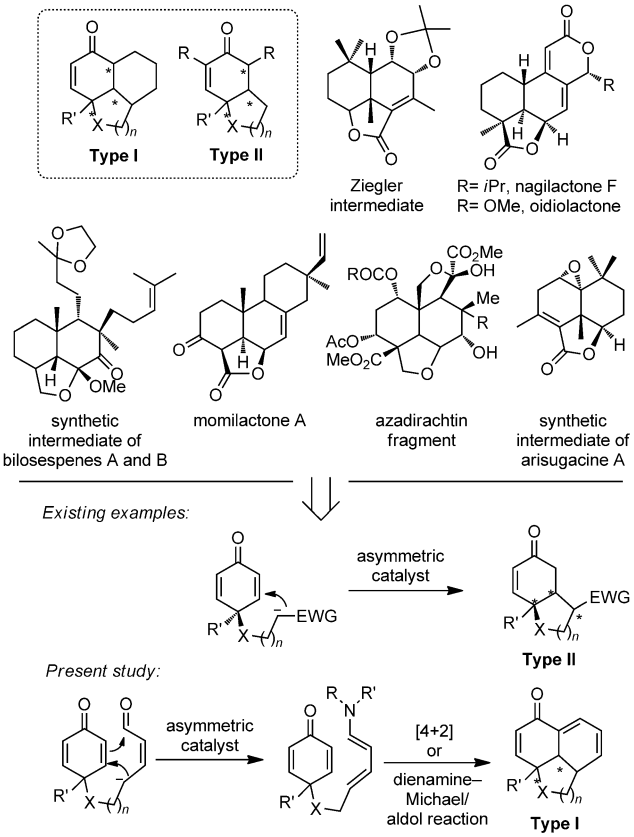
Abstract: *The asymmetric synthesis of tricyclic compounds by the desymmetrization of cyclohexadienones is presented. The reaction tolerated a large variety of substituents at different positions of the cyclohexadienone, and heterocyclic rings of different sizes were accessible. Density functional theory calculations showed that the reaction proceeds through an asynchronous [4+2] cycloaddition.*

Tricyclic structures of type I (Scheme 1) are included in a large group of important biologically active and natural products, such as the Ziegler intermediate,[1] momilactone A,[2] azadirachtin,[3] nagilactone F, and oidiolactone,[4] and they have also been used in the synthesis of bilosespenes A and B[5] and arisugacine A.[6,7] Because of the diverse biological activities presented by these compounds, rapid and direct methods for their enantioselective synthesis are required. In this context, desymmetrization processes are among the most important methods for the enantioselective synthesis of chiral molecules.[8] Thus, the oxidative dearomatization of arenes has attracted considerable attention as a rapid and elegant enantioselective method for the construction of complex bicyclic derivatives of type II (Scheme 1) from simple and accessible starting materials. This strategy has been applied to the asymmetric desymmetrization of cyclohexadienones by different reactions, such as the Heck,[9] Stetter,[10] Michael,[11,12] and Rauhut–Currier reactions,[13] all of which provided access to enantiomerically enriched bicyclic derivatives. The principal advantage of these methods for the synthesis of bicyclic products of type II is the ready accessibility of the starting materials. However, these methodologies give access only to skeletons of type II, since all are formally nucleophilic addition reactions of carbanions stabilized by α electron-withdrawing groups (EWGs; see Scheme 1). The use of other nucleophiles at a more remote position has not yet been explored.



Scheme 1. Synthesis of biologically active tricyclic derivatives and important synthetic intermediates.

As part of an effort to extend the utility of the oxidative dearomatization of arenes, we disclose herein a new direct process for the synthesis of tricyclic compounds of type I by using dienamine catalysis,[14] for which a plausible conjugate-addition/aldol or a Diels–Alder pathway can be postulated. We also performed density functional theory (DFT) calculations to explain the [4+2] cycloaddition pathway.

We initially examined the reactivity of different catalysts by using substrate **1a**. Selected conditions studied for the

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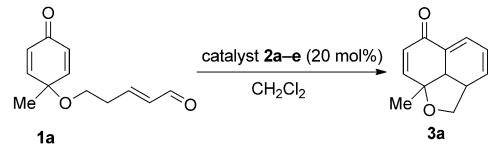
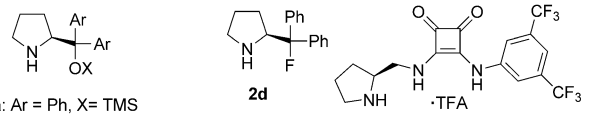
Table 1: Screening of reaction conditions for the synthesis of **3a**.[a]





2a: Ar = Ph, X= TMS
2b: Ar = 3,5-$(CF_3)_2C_6H_3$, X= TMS
2c: Ar = Ph, X= OH

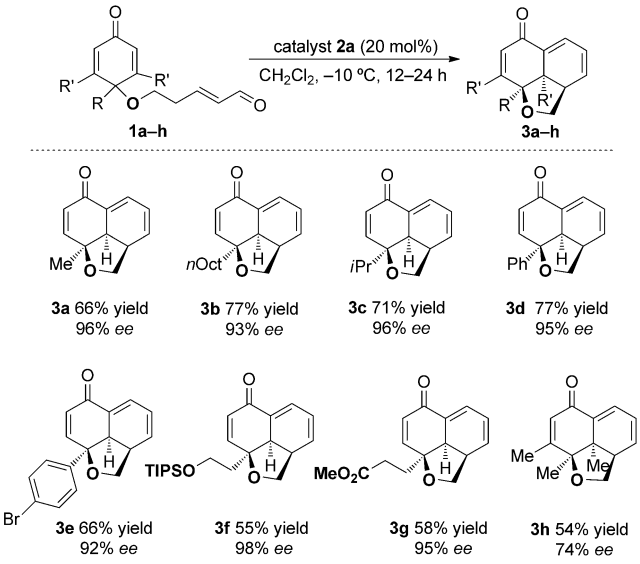
Entry	Catalyst	*T* [°C]	*t* [h]	Conversion[b]	*ee* [%][c]
1	(*S*)-**2a**	RT	1	>99	90
2	(*S*)-**2b**	RT	5	>99	94
3	(*S*)-**2c**	RT	5	–	nr[d]
4	(*S*)-**2d**	RT	1.5	>99	80
5	(*S*)-**2e**	RT	–	–	nr[d]
6	(*S*)-**2b**	−10	20	72	98
7[e]	(*S*)-**2a**	−10	20	99	91
8	(*S*)-**2a**	−10	20	99	96

[a] Reaction conditions: **1a** (0.2 mmol), catalyst **2** (20 mol%), CH_2Cl_2 (0.2 mL). [b] Conversion was determined by ^{1}H NMR spectroscopic analysis. [c] The *ee* value was determined by supercritical fluid chromatography. [d] No reaction. [e] The reaction was carried out in $CHCl_3$. TFA = trifluoroacetic acid.

reaction are shown in Table 1 (for full screening, see the Supporting Information). To our delight, a unique diastereomer was obtained after 1 h with full conversion and 90% *ee* with catalyst **2a** (Table 1, entry 1). Other catalysts, such as **2b** and **2d**, also gave good results (Table 1, entries 2 and 4), but the use of catalyst **2c** and squaramide catalyst **2e** gave no conversion (entries 3 and 5). With the two best catalysts **2a** and **2b**, we screened a range of reaction conditions to improve the results (see the Supporting Information for full details) and found that the best solvents were CH_2Cl_2 and $CHCl_3$. The selectivity was improved by decreasing the temperature to −10 °C, but the conversion was lower at this temperature with **2b** (Table 1, entry 6). However, when the reaction was carried out with the more active catalyst **2a** at −10 °C in CH_2Cl_2 or $CHCl_3$ (Table 1, entries 7 and 8), product **3a** was obtained with excellent conversion, and with slightly improved enantioselectivity in CH_2Cl_2 (entry 8).

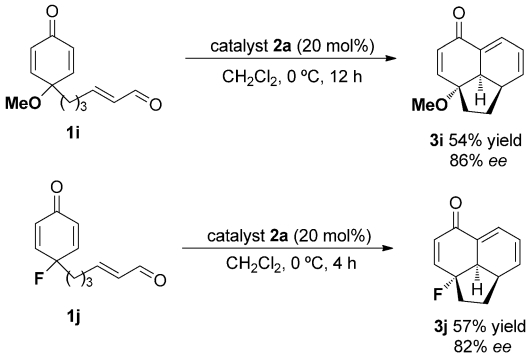
Next, we applied the optimized conditions to cyclohexadienones with different substituents R and R′ (Scheme 2). The reaction proceeded in good yield with excellent enantioselectivity for alkyl and aromatic R substituents (products **3a**–**e**). The incorporation of alkyl chains functionalized with an ester or a protected alcohol proceeded with even higher enantioselectivity to give access to the more highly functionalized tricyclic products **3f** and **3g**. The addition of an R′ substituent in cyclodienone **1** resulted in a longer reaction time, but enabled the synthesis of **3h**, which contains two adjacent quaternary centers, with slightly lower enantioselectivity.

The scope of this catalytic desymmetrization reaction was quite broad and enabled the synthesis of a range of



Scheme 2. Tricyclic products **3** obtained from aldehydes **1**. TIPS = triisopropylsilyl.

enantiomerically enriched tricyclic derivatives. In all examples in Scheme 2, the oxygen atom is incorporated in an endocyclic position, but the exocyclic incorporation of oxygen and other atoms in the tricyclic derivatives was also possible. Thus, substrate **1i** reacted in a similar manner to give the methoxy-substituted compound **3i** as a single diastereoisomer in good yield and with good enantioselectivity (Scheme 3). Importantly, electron-withdrawing groups, such as fluorine, which is well-known for its importance in pharmaceutical chemistry,[15] were also well-tolerated: Product **3j** was synthesized with good enantioselectivity in a shorter reaction time under the same reaction conditions (Scheme 3).

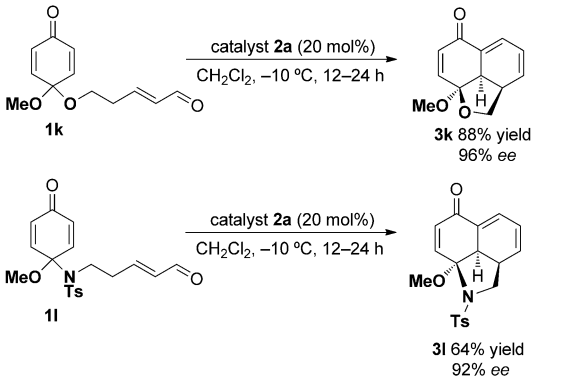


Scheme 3. Synthesis of oxygenated and fluorinated products.

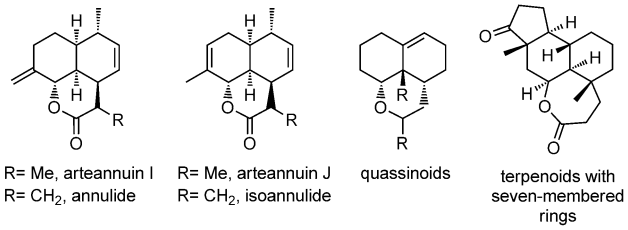
Acetals and hemiaminal ethers are ubiquitous scaffolds in natural products and numerous chiral pharmaceuticals, ranging from simple carbohydrates to complex spiroketals.[16] Methods for the enantioselective synthesis of chiral acetals are scarce and mostly rely on chiral starting materials; catalytic enantioselective methods remain limited.[17,18] Thus,

we studied the desymmetrization of the acetal and hemiaminal ether substrates **1k** and **1l** (Scheme 4). To our delight, the reaction yielded the products **3k** and **3l** in excellent yield with high enantioselectivity.

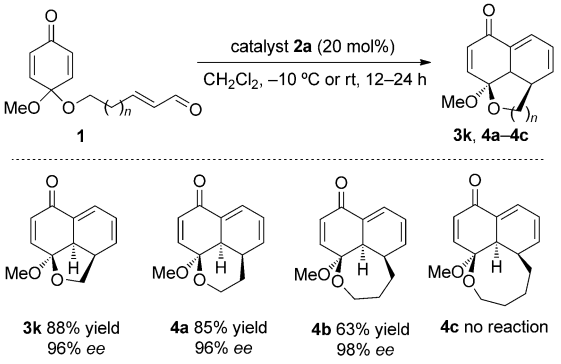
The tricyclic compounds discussed above are all 6,6,5-membered-ring systems. However, in nature and in some bioactive products, different heterocyclic-ring sizes are found (Scheme 5). For example, arteannuin I, arteannuin J, and quassinoids with antiparasitic activity are six-membered-ring tricyclic compounds containing oxygen.[19a,b] Some bioactive terpenoids also contain seven-membered rings.[19c] Thus, we decided to investigate the synthesis of rings of different sizes, from five- to eight-membered rings (Scheme 6).



Scheme 4. Synthesis of acetal and hemiaminal ether derivatives.



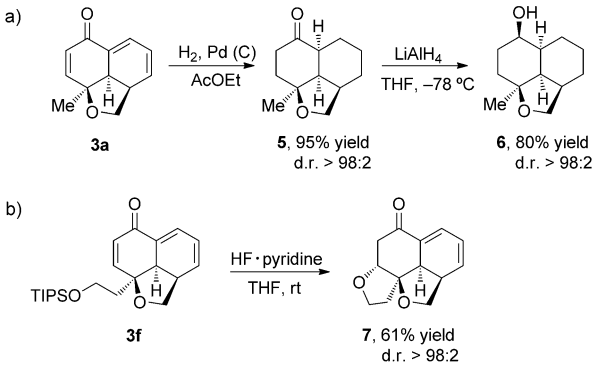
Scheme 5. Examples of natural products and bioactive compounds with different heterocyclic-ring sizes.



Scheme 6. Synthesis of acetals with different sizes of the heterocyclic ring.

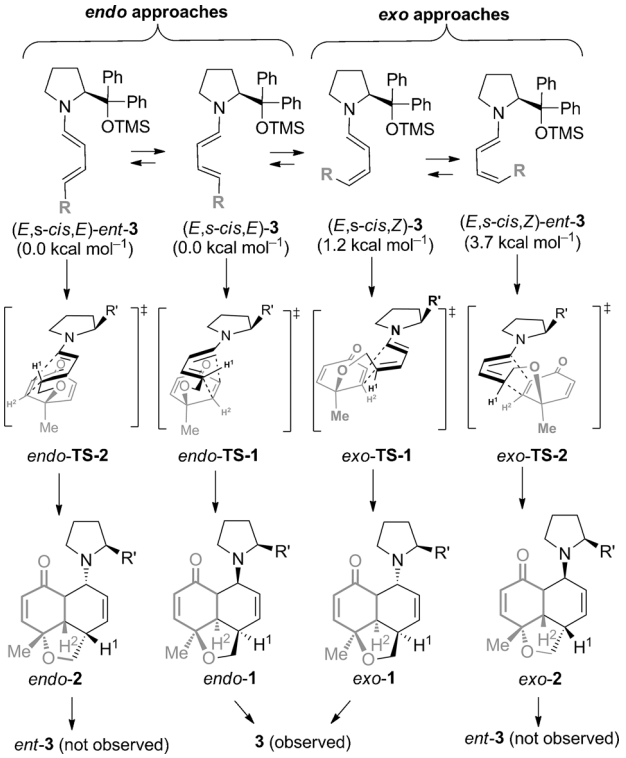
Initial attempts at the synthesis of the six-membered-ring compound were unsuccessful, and only polymerization of the corresponding starting material was detected by NMR spectroscopy. Sevenfold dilution of the reaction mixture was necessary for the formation of **4a** in good yield with excellent enantioselectivity (Scheme 6). The seven-membered-ring compound **4b** was synthesized at room temperature with excellent enantioselectivity in slightly lower yield. Unfortunately, all attempts to synthesize the corresponding eight-membered-ring compound **4c** were unfruitful.

We also synthesized a tricyclic analogue that belongs to the maalioxide family.[20] Thus, the hydrogenation of **3a** gave the saturated tricyclic derivative **5** as a single diastereoisomer in 95% yield (Scheme 7a).[21] The reduction of the ketone moiety then afforded the sesquiterpenoid derivative **6** as a single diastereoisomer[21] in good yield. Furthermore, the deprotection of alcohol **3f** yielded the tetracylic derivative **7** through an oxa-Michael reaction with complete diastereomeric control (Scheme 7b).[21]



Scheme 7. Different transformations of compounds **3**: a) reduction of the α,β-unsaturated ketone in **3a**; b) deprotection and cyclization of the alcohol in **3f**.

The absolute configuration of products **3** was determined by X-ray crystallographic analysis of **3e**[22] (see the Supporting Information). To explain the stereochemical outcome and establish a plausible mechanism, we carried out DFT calculations.[23] Initially, we evaluated the thermodynamics of the four isomers of our starting material that can form tricyclic products: the two *E*,*s-cis*,*E* and two *E*,*s-cis*,*Z* conformers (Scheme 8).[24] Interestingly, although they are close in energy, significant thermodynamic discrimination was found for the different conformers.[25] We found a transition state that relates each isomer with *Z* geometry at the 3,4-position of the diene ((*E*,*s-cis*,*Z*)-*ent*-**3** versus (*E*,*s-cis*,*Z*)-**3**) with a different enantiomer of the final product (right-hand side of Scheme 8), whereby only the *exo* approaches enabled the formation of the correct diastereoisomer (H^1 and H^2 in the *syn* relative configuration). Furthermore, two other transition states that relate each isomer with *E* geometry ((*E*,*s-cis*,*E*)-*ent*-**3** versus (*E*,*s-cis*,*E*)-**3**) with a different enantiomer of the final product were found (left-hand side of Scheme 8), whereby the correct diastereoisomer was formed by the *endo* approach (H^1 and H^2 in the *syn* relative configuration).[26] Only one transition state relating each reagent with



Scheme 8. Intermediates and different reaction pathways (R′ = C(Ph)$_2$OTMS). TMS = trimethylsilyl.[23]

the corresponding product was isolated, thus suggesting a concerted mechanism instead of a stepwise pathway.

The transition states of these four conformers, two for *endo* approaches and two for *exo* approaches, mainly describe the formation of the first C–C bond between the C–H^2 and C–H^1 carbon atoms (see TSs in Scheme 8). However, the formation of the bicyclic structure prearranges the molecular geometry in such a way that the second C–C bond-forming step occurs without a kinetic barrier, thus indicating an asynchronous concerted [4+2] mechanism.[27] The origin of the enantioselectivity was considered by comparing the energy barriers that would lead our system to **3** (*exo*-**TS-1** and *endo*-**TS-1**) or to *ent*-**3** (*exo*-**TS-2** and *endo*-**TS-2**; Figure 1). The two *exo* approaches showed a higher energy barrier than the corresponding *endo* approaches (a difference of 6.5 kcal mol^{-1} for **TS-1** and 7.4 kcal mol^{-1} for **TS-2**). These results are in agreement with those of other [4+2] calculations.[28] For the more stable *endo* approaches, the pathway *endo*-**TS-1** (see Figure 2), which corresponds to the experimentally observed major enantiomer, evolves to a transition state that is 2.5 kcal mol^{-1} lower in energy than *endo*-**TS-2**. This scenario is consistent with a case of kinetic control of an irreversible reaction, which is generally the source of enantioselectivity phenomena. Such kinetic discrimination is probably due to the lower steric crowding in its corresponding transition state, *endo*-**TS-1**, as a result of repulsive interactions between the diene fragment and the $-OSi(CH_3)_3$ group (see the Supporting Information).

Calculations were carried out on an intermediate that contains catalyst **2a** still attached to the tricyclic structure as the product. To prove the formation of this plausible intermediate, *endo*-**1**, we carried out the reaction of the methyl-substituted cyclohexadienone **1o**. This reaction enabled the isolation of intermediate **8**, which cannot evolve to the final product because the elimination of the catalyst is blocked by a methyl group (Scheme 9).[20] The isolation of **8** confirms the validity of the computed reaction pathway leading to intermediate *endo*-**1**.

In summary, we have developed an asymmetric synthesis of tricyclic derivatives through the desymmetrization of cyclohexadienones by a [4+2] cycloaddition. The reaction tolerated a large variety of substituents at different positions of the cyclohexadienone, and heterocyclic rings of different sizes could be constructed. Mechanistic studies by DFT calculations showed that this transformation proceeds by an asynchronous [4+2] cycloaddition and not a stepwise reaction.

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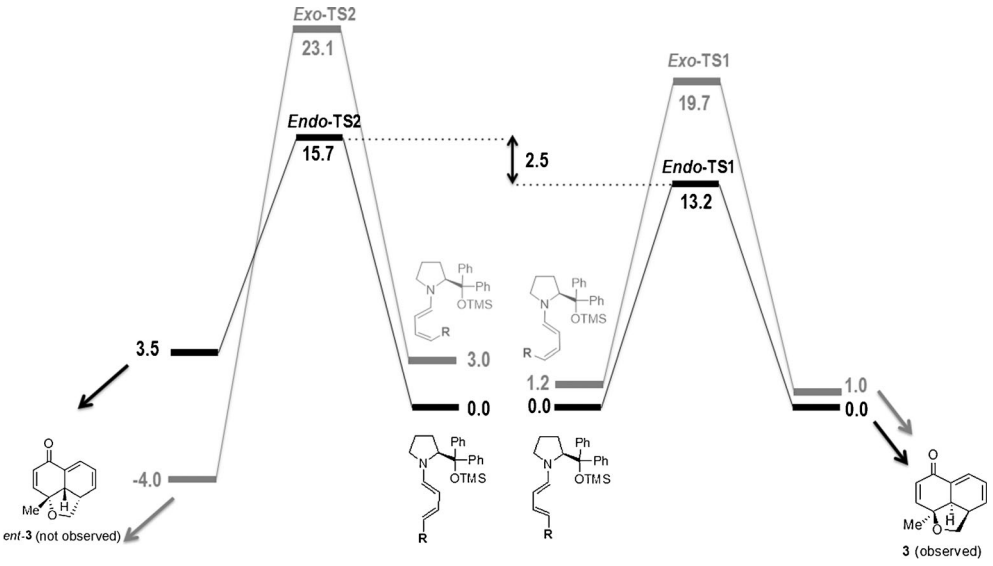


Figure 1. Energy profile for the cycloaddition process. Relative Gibbs free energies in kcal mol^{-1} for the intermediates and transition states are shown.[23]

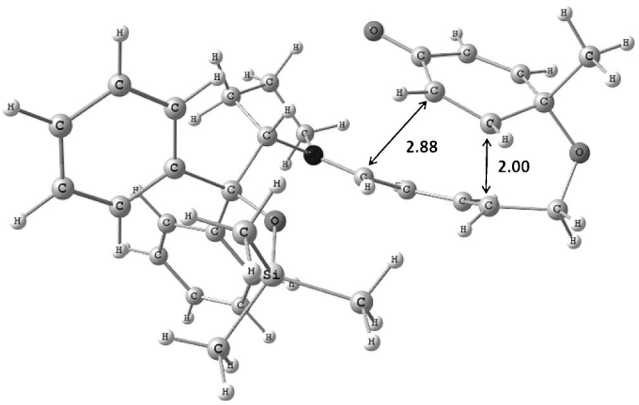
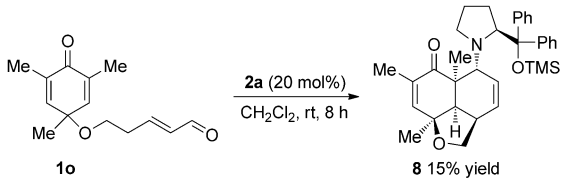


Figure 2. Geometry of the transition state of *endo*-**TS-1** (for other transition states, see the Supporting Information).[23]



1o **8** 15% yield

Scheme 9. Trapping of intermediate **8** by the use of aldehyde **1o**.

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[21] The relative configuration of the newly created stereocenters was assigned by 2D NMR spectroscopic experiments.

[22] CCDC 971440 (**3e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[23] Relative Gibbs free energies of the conformers were computed on the basis of DFT at the B3LYP/6-311+G(d,p)//B3LYP/6–31G(d) level, including solvent effects (CH_2Cl_2) with the SMD model in the single-point energy calculations, by using the Gaussian09 program: Gaussian 09 Revision B.01 2010, M. J. Frisch, et al., Gaussian Inc., Wallingford CT, **2009**.

[24] The four isomers with *s-trans* geometry were also evaluated. However, as shown in the Supporting Information, such isomers are not relevant to the reactivity expected for a Diels–Alder mechanism, which usually involves an *s-cis* rearrangement.

[25] Under the experimental conditions, all isomers are kinetically accessible through acid-assisted isomerization; see: S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973.

[26] We also considered the *endo* approaches for *E*,*s-cis*,*Z* conformers and the *exo* approaches for *E*,*s-cis*,*E* conformers. These approaches would yield the nonobserved *anti* relative configuration of H^1 and H^2 hydrogen atoms in products **3**; the formation of the corresponding products showed a higher energy barrier (26.1 and 26.3 kcal mol^{-1}).

[27] Analysis of the calculated intrinsic reaction coordinates (IRCs), including solvent effects, supports this statement (see the Supporting Information for IRCs). Interestingly, the IRC calculations show a very planar region of the potential surface that could correspond to the zwitterionic intermediate. However, a real minimum was not found, even when the closest structure in the IRC profile to the zwitterionic product was taken as a starting point for the minimization.

[28] H. V. Pham, R. S. Paton, A. G. Ross, S. J. Danishefsky, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 2397, and references therein.

