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Diels–Alder Reactions of Chiral Isoimidium Salts: A Computational Study

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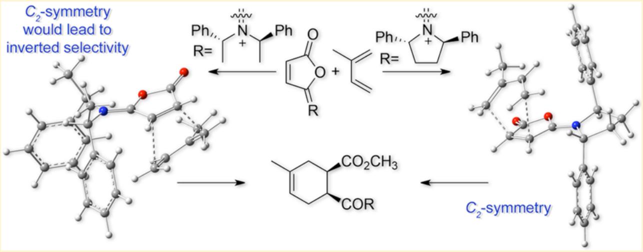
Ⓢ *Supporting Information*



ABSTRACT: Recently, important efforts have been devoted to asymmetric Diels–Alder (DA) cycloadditions. Several chiral auxiliaries and catalysts were tested, originating a multitude of selectivities. Here, we study the ability of the isoimidium group as a dienophile activator in DA reactions, as well as its behavior in the induction of selectivity, when incorporated in chiral auxiliary units. We study dienophiles attached to isoimidium auxiliaries derived from (2*R*,5*R*)-2,5-diphenylpyrrolidine and from (*R*)-bis((*R*)-1-phenylethyl)amine, and show that they lead to low activation energies in DA additions to different dienes. Reported experimental regio- and *endo*/*exo* selectitivites are also fully rationalized. While diastereoselectivities originated by (2*R*,5*R*)-2,5-diphenylpyrrolidine based dienophiles can easily be rationalized by a C_2 symmetric transition state, several transition states have to be simultaneously accounted for the rationalization of the selectivity obtained with dienophiles based on (*R*)-bis((*R*)-1-phenylethyl)amine. In this case, the C_2 symmetric structure leads to opposite selectivities to those experimentally observed. Thus, while the structures of the dienophiles derived from these two amines seem similar, their behavior in the induction of stereoselectivity in DA reactions is quite different. Our models, which substantially differ from those previously proposed in the literature, can also be adapted to other reactions in which this type of chiral auxiliaries is used.

■ INTRODUCTION

The Diels–Alder (DA) cycloaddition is a highly versatile atom-economic carbon–carbon bond-forming reaction that can originate high regio- and stereoselectivities.[1–13] The mechanism of the DA reaction has long been the subject of intense studies. Initially, these studies focused on the concertedness of the reaction[14] and on the stereocontrol effects of a multitude of substituents.[15–18] It is now generally accepted that symmetric dienes and dienophiles react by single-step synchronous DA pathways.[14] The former discussion on two-step diradical mechanisms is more or less superseded following experimental studies that showed high stereospecificity in key examples.[19] Theoretical studies also indicated that the two-step diradical process is of higher energy than the single-step alternative.[20] However, there are also reports indicating that, in special cases, the diradical pathway is also possible.[21,22] On the other hand, asymmetric polar dienes or dienophiles usually react by single-step asynchronous transition states (TSs) or, when the polarization becomes very strong, the mechanism can shift to a two-step process, via a zwitterionic intermediate.[14–18,23–26] DA reactions that follow a single-step mechanism are usually designated as synchronous or asynchronous concerted processes, meaning that the two bonds are formed simultaneously or at different rates. However, recently several reports by Berski,[27,28] Domingo,[24,29] and their co-workers have considerably changed these interpretation, by introducing the new concept of single-step two-stage reactions.

Independently of this interesting discussion, in recent years the main interest of experimentalists and theoreticians working in the field has shifted to enantio- and diastereoselective DA reactions, either inter- or intramolecular. The vast amount of experimental data,[5,7,30–38] together with the advent of modern computing capabilities, has motivated new theoretical work in the field.[39–44] In this context, we studied, by computational tools, the interesting experimental results reported by Boeckman and collaborators on asymmetric DA reactions of isoimidium salts, under stereocontrol by chiral auxiliairies (Scheme 1).[45]

The use of chiral auxiliaries in DA reactions is known for a long time,[46] but has gained a renewed interest after the work reported by Evans and collaborators.[47] These authors used chiral *α*,*β*-unsaturated *N*-acyloxazolidinones as dienophiles, activated by several types of Lewis acids (LAs). The LA activation was needed both for the improvement of the reaction chemical yield and stereoselectivity.[43,48] However, the work performed by Boeckman and collaborators[45] follows a different approach, as the chiral dienophile is an isoimidium salt, thus expected to be highly activated for DA additions (Scheme 1).[49]

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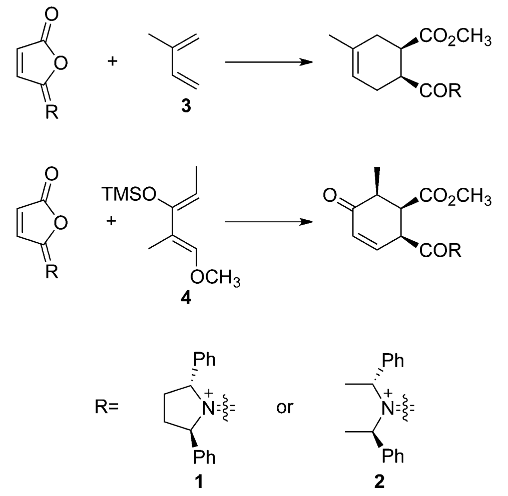
Scheme 1. Selected DA Reactions of Isoimidium Salts with Isoprene (3) and Danishefsky's Diene (4)[45]



At the same time, the isoimidium double bond renders the dienophile structure very rigid, which is important in the attainment of high regio- and stereoselectivities.[49,50] These properties proved to be quite effective, as the authors reached very high *endo*/*exo* ratios and regioselectivities in the addition of dienophiles **1** and **2** to isoprene (**3**) and the Danishefsky's diene (**4**), while medium to very high diastereoselectivites were obtained (Table 1). Other dienes were also used, but the results are similar to those obtained for **3** and **4**.[45] The dienophile activation by the isoimidium moiety was clearly demonstrated, as the reaction proceeded at temperatures as low as −60 °C. In order to explain the observed selectivities, the authors proposed a reaction mechanism via a TS with two different diastereofaces, in which the chiral auxiliary adopts a C_2 symmetric conformation. The asymmetry at the two stereofaces was proposed to be resulting from different electronic effects and different steric contacts between the attacking diene and the chiral auxiliary substituents.

Table 1. Main Results Obtained by Boeckman and Collaborators[45] for the Reaction of Dienophiles 1 and 2 with Dienes 3 and 4[a]

entry	dienophile	diene	yield (%)	dr
1	**2**	**3**	89	89:11
2	**1**	**3**	90	>99:1
3	**2**	**4**	49	75:25
4	**1**	**4**	56	>99:1

[a] All reactions were conducted at −45 °C, in dichloromethane. Only *endo* attack and a single regioisomer were observed in all cases.

In this manuscript we first analyze, by theoretical methods, the dienophile activation, the regioselectivity, and the *endo*/*exo* selectivity induction by the isoimidium moiety, and we compare the calculated values with others obtained for systems activated by a conventional LA ($AlCl_3$). In the second part of our discussion, we analyze the ability of the empirical model proposed by Boeckman and collaborators[45] in the induction of diastereoselectivity. Our main conclusions indeed indicate that the isoimidium cation is a very strong dienophile activator, albeit not as good as $AlCl_3$, and is able to induce very high *endo*/*exo* and regioselectivities. However, the empirical TS proposed by Boeckman and collaborators[45] does not apply to dienophile **2**, as this compound adopts several different conformations, in which the lowest energy conformer is considerably different from the one proposed in the experimental paper. Therefore, with dienophile **1**, the observed selectivity indeed results from different steric and electrostatic contacts between the attacking diene and the substituents at the C_2 symmetric chiral auxiliary, as proposed in the experimental paper.[45] On the other hand, with dienophile **2**, the final selectivity results from a C_1 symmetric conformation of the chiral auxiliary, while the C_2 symmetric structure, as proposed in the experimental paper,[45] leads to the opposite configuration. The following discussion will be based on optimized energies obtained with the M06−2X functional, using the 6−311G(d,p) basis set, with dichloromethane (DCM) as solvent. Single point values, calculated with the M06−2X/6−311+G(d,p) model (in DCM) are also given in the tables. Other theoretical models were used, and the obtained values are available in the Supporting Information.

■ RESULTS AND DISCUSSION

The main results obtained by Boeckman and collaborators[45] are summarized in Table 1, for dienophiles **1** and **2** and dienes **3** and **4**. Other dienes were used, but the results are similar and, therefore, are not analyzed in this manuscript.

Table 1 clearly shows that the best results were obtained when dienophile **1** was used, a compound that incorporates a C_2 symmetric pyrrolidine as chiral auxiliary unit. In all cases, only products from *endo* attack were observed, and only one regioisomer was obtained for each diastereomer. All reactions were conducted at −45 °C, in dichloromethane, indicating that the dienophiles are quite activated, as predicted by the authors. Since very high *endo*/*exo* and regioselectivities were achieved, we believe that before any attempt to rationalize the high diastereoselectivities also obtained, we shall analyze the isoimidium system, aiming at a better understanding of the origins of the high *endo*/*exo* and regioselectivities. At the same time, we shall compare the isoimidium-based dienophiles with more conventional systems, with or without LA complexation, in order to evaluate the relative activation induced by the isoimidium group. For this purpose, we calculated the DA addition of isoprene to two simplified versions of isoimidium salts (**5** and **6**) (Table 2 and Figure 1), as well as to maleic anhydride (**7**) uncomplexed or complexed with $AlCl_3$ as LA (Table 2 and Figure 2).

The results in Table 2 indicate that the isoimidium moiety is, in fact, a quite strong activating group in the dienophile,[49] but not as good as $AlCl_3$ complexed with a carbonyl group. Indeed, while the activation energy for the isoprene *endo* addition to uncomplexed maleic anhydride is 19.5 kcal mol^{-1}, it becomes only 9.6 kcal mol^{-1} when this compound is complexed with $AlCl_3$. On the other hand, when isoprene adds to isoimidium salts **5** and **6**, the activation energies are, respectively, 11.7 and 13.0 kcal mol^{-1}. If we compare the charge transfer from the diene to the dienophile in the most stable TS of each transformation, the conclusion is that the maximum value is obtained for the complex of maleic anhydride (0.42 e^-), while the isoimidium additions (0.40 (**5**) and 0.36 (**6**) e^-), lay between this value and the one found for the addition to free maleic anhydride (0.23 e^-). Finally, the asynchronicity (d_1/d_2) follows the same order (complexed maleic anhydride: 1.31; **5**: 1.26; **6**: 1.20; maleic anhydride: 1.03), which supports the conclusions above.

Table 2. DA Reaction of Isoprene with Dienophiles **5** and **6** and with Maleic Anhydride Uncomplexed (**7**) or Complexed with $AlCl_3$ as LA (**7-**$AlCl_3$)[a]

			optimization			single-point	
entry	dienophile	TS	$\Delta\Delta G$ (ΔG)	d_1/d_2	charge transfer	$\Delta\Delta G$ (ΔG)	charge transfer
1	**5**	**TS-1**$_{endo}$	0.00 (11.72)	1.256	0.400	0.00 (12.10)	0.411
2	**5**	**TS-2**$_{endo}$	1.18	1.100	0.351	1.26	0.361
3	**5**	**TS-3**$_{exo}$[b]	3.14	1.352	0.426	2.86	0.437
regioselectivity			86.2%			88.2%	
endo/*exo*			99.9:0.1			99.8:0.2	
4	**6**	**TS-4**$_{endo}$	0.00 (12.99)	1.199	0.355	0.00 (13.64)	0.366
5	**6**	**TS-5**$_{endo}$	2.74	1.053	0.320	2.66	0.330
6	**6**	**TS-6**$_{exo}$[b]	4.01	1.255	0.368	3.79	0.377
regioselectivity			99.6%			99.4%	
endo/*exo*			100.0:0.0			100.0:0.0	
7	**7**	**TS-7**$_{endo}$	0.00 (19.47)	1.027	0.232	0.00 (19.90)	0.248
8	**7**	**TS-8**$_{exo}$	3.21	1.029	0.228	2.90	0.244
endo/*exo*			99.9:0.1			99.8:0.2	
9	**7-**$AlCl_3$	**TS-9**	0.00 (9.56)	1.308	0.422	0.00 (10.10)	0.429
10	**7-**$AlCl_3$	**TS-10**	2.87	1.129	0.359	2.68	0.366
11	**7-**$AlCl_3$	**TS-11**	0.70	1.340	0.426	0.30	0.434
12	**7-**$AlCl_3$	**TS-12**	2.10	1.162	0.364	1.60	0.372
regioselectivity[c,d]			98.2%			95.8%	

[a] All Gibbs energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) and sp PCM M06−2X/6−311+G(d,p), in DCM as solvent and at −45 °C and were calculated relative to the reagents (isoprene in *s-trans* conformation). NBO charge transfers from the diene to the dienophile are in electron. In parenthesis are the activation energies of the most stable TSs in each series. [b] The regioisomeric TSs for the *exo* attacks were not calculated, as their relative energies would be at least 3.14 and 4.01 kcal mol^{-1}. [c] The regioselectivity applies only to the regioisomeric TSs, as the product has no regioisomers. [d] All *exo* TSs for the addition to **7-**$AlCl_3$ are at least 4 kcal mol^{-1} more energetic than **TS-9** and are not shown (*endo*/*exo* = 100.0:0.0; see the Supporting Information, Table S1).

The *endo*:*exo* relation in DA additions has been extensively studied before and is now accepted to be dependent on electronic, electrostatic, and steric effects.[15−17] Usually electronic effects dominate but the other factors can also play an important role.[17] In the addition of isoprene to any one of the four dienophiles, the predicted *endo*:*exo* relation is always 100/0. However, if we compare the energy difference between the most stable *endo* and *exo* TS structures of dienophiles **5** and **6**, we conclude that **5**, which is a stronger activated dinophile, induces lower *endo*:*exo* selectivity (Table 2 and Figure 1, 3.14 kcal mol^{-1} and 4.01 kcal mol^{-1}, respectively). This means that the steric interactions between the methyl groups in **6** are, indeed, quite important in the establishment of the TSs activation energy. However, they are irrelevant for the calculation of the final selectivity, as the electronic effects are very strong and, alone, originate predicted selectivities near 100%.

The regioselectivity in DA reactions is also dependent on electronic, electrostatic and steric effects.[18,51] The comparison of the calculated values for the maleic anhydride complex (98.2%) with those obtained for the isoimidium additons (86.2% for **5** and 99.6% for **6**), indicates that both steric contacts and electronic effects are major features in these reactions (Table 2, Figure 1 and Figure 2). Indeed, while the reactions of isoprene with compound **5** and with complexed maleic anhydride have similar steric effects (because in the maleic anhydride complexed TSs the LA lays away of the methyl group in the diene), they have, however, a large difference in regioselectivity, indicating that the most activated dienophile (maleic anhydride complex) induces better selectivity. On the other hand, dienophile **6** is less activated than dienophile **5**, but the regioselectivity calculated for **6** is considerably higher (even higher than the value predicted for the reaction of the most activated dienophile, 7-$AlCl_3$). This is a clear indication that the steric effects between the methyl group in the diene and the methyl groups in the isoimidium moiety are, indeed, very important in the establishment of the predicted regioselectivity.

If the results above are compared with those obtained for the reactions of dienophiles **1** and **2** with isoprene (Table 3), several conclusions can be obtained. The lowest activation energy for the reaction of **1** with isoprene is 12.0 kcal mol^{-1} (**TS-13**), while a value of 13.8 kcal mol^{-1} (**TS-19**) was obtained for the reaction of **2** with isoprene. Therefore, **1** is more activated than **2**, and similar to the model compound **5**. The regioselectivity for the reaction of dienophile **2** with isoprene was not calculated, due to the large number of possible conformational TSs that would need to be considered. However, the regioselectivity for the reaction of **1** with isoprene was calculated as 99.6% (compare Tables 2 and 3). Therefore, since the activation energy, charge transfer, and asynchronicity calculated for the reaction of **1** with isoprene are similar to the values calculated for the reaction of the simplified dienophile **5** with isoprene, but the regioselectivity is calculated to be substantially higher and similar to the one calculated for the reaction of **6** with isoprene, we are led to the conclusion that the electronic effects in **1** are similar to those in **5**, while the steric effects are similar to those existent in compound **6**. This means that the large phenyl groups in **1** and the small methyl groups in **6** induce similar steric effects.

The predicted *endo*:*exo* relation in the reactions of isoprene with dienophiles **1** and **2** is, in both cases, 100:0. This value is not unexpected, as the calculated *endo*:*exo* selectivities for the model compounds were also in this range. The activation energy differences between the *endo* and *exo* TSs in both reactions (isoprene with dienophiles **1** and **2**) are similar to the

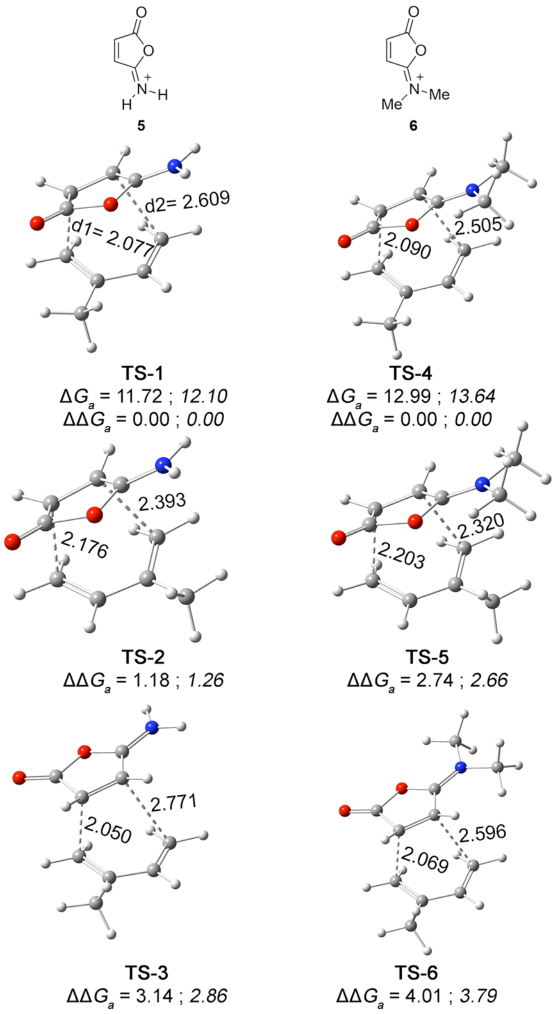


Figure 1. Calculated TSs for the addition of isoprene (**3**) to dienophiles **5** and **6**. Gibbs energy values are relative to **TS-1** and **TS-4**. All energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) in plain text, sp PCM M06−2X/6−311+G(d,p) in italic), in DCM as solvent and at −45 °C. Bond lengths are in Å.

value calculated for the reaction of isoprene with compound **6** (>4 kcal mol^{-1}, see the Supporting Information, Tables S1 and S2), indicating that steric contacts have also an important contribution to the predicted selectivity. This aspect becomes particularly important when diene **4** is used instead of isoprene, as the calculated activation energy differences increase substantially (between 1 and 2 kcal mol^{-1}, see the Supporting Information, Tables S4 and S6).

Resuming, our calculations properly predict both the regio- and *endo*:*exo* selectivities experimentally observed[45] and, by comparison with the model compounds, we can justify the large observed values as mainly due to electronic and steric effects.

While dienophiles **1** and **2** perform similarly in both regio- and *endo*:*exo* selectivities, they originate quite different experimental diastereoselectivities, as shown in Table 1 . Therefore, while dienophile **1** leads to diastereomeric ratios over 99:1 with both dienes **3** and **4**, dienophile **2** originates a diastereomeric ratio of only 89:11 with diene **3**, and only 75:25 with diene **4**. Our theoretical data is in quite good agreement with the experiment, as shown in Tables 3, and 4.

Since dienophile **1** performs quite better than dienophile **2**, and because **1** is a quite rigid structure that exists only as two possible conformers, we will analyze first its performance, followed by a full analysis of the performance of the flexible dienophile **2**.

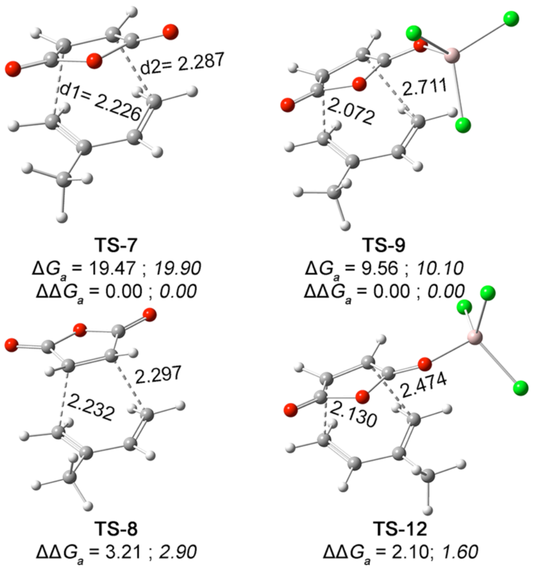


Figure 2. Calculated TSs for the addition of isoprene (**3**) to maleic anhydride (**7**) and to maleic anhydride complexed with $AlCl_3$ (**7+AlCl$_3$**). Gibbs energy values are relative to **TS-7** and **TS-9**. All energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) in plain text, sp PCM M06−2X/6−311+G(d,p) in italic), in DCM as solvent and at −45 °C. Bond lengths are in Å. All *exo* TSs for the addition to **7-AlCl$_3$** are at least 4 kcal mol^{-1} more energetic than **TS-9** and are not shown (*endo*/*exo* = 100.0:0.0). (see the Supporting Information, Table S1).

Dienophile **1** contains a chiral auxiliary known to adopt rigid conformations when the nitrogen atom is part of an amide group.[50] In dienophile **1** the system rigidity is even larger, as the nitrogen atom is connected to the alkene moiety via an imidium double bond (Scheme 1 and Figure 3). The two five membered rings become coplanar, with the substituent aromatic rings orientated either in axial or equatorial conformation (Figure 3). While the equatorial conformation of dienophile **1** is more stable than its axial counterpart, it leads to higher energetic TSs (compare entries 1 and 2 and entries 3 and 4 in Table 3). This behavior results from the shorter distances between the aromatic rings and the dienophile double bond, in the equatorial conformer, which originates larger steric repulsions with the attacking dienes. Since the contribution of TSs resulting from the equatorial conformation of dienophile **1** is very small, the following discussion will be based only on TSs bearing the aromatic rings in axial orientation (Figure 3). However, the selectivities in Tables 3 and 4 also include the contributions of the equatorial TSs.

The axial conformation of dienophile **1** is a rigid structure in which the *αβ*-double bond has two diastereofaces, being one of them more hindered by the aromatic rings.[49,50] Considering the absolute configuration of the two chiral centers in the pyrrolidine ring, it is expected a faster reaction at the C_α−*Si* face (Figure 3), as it was indeed experimentally observed.[45]

When dienophile **1** reacts with isoprene, it follows a single-step mechanism, via several possible asynchronous TSs. Considering the high regio- and *endo*:*exo* selectivities, as discussed before, we will only analyze the two *endo* possible TSs that lead to a single regioisomer (Figure 3). The energy difference between the two isomeric TSs (**TS-13** and **TS-15**) is

Table 3. Gibbs Energies Calculated for the Addition of Dienophiles 1 and 2 to Isoprene (3) Relative to the Most Stable TSs (TS-13 and TS-19)[a]

			optimization			single-point	
entry	dienophile	TS[b]	$\Delta\Delta G$ (ΔG)	d_1/d_2	charge transfer	$\Delta\Delta G$ (ΔG)	charge transfer
1	**1**	**TS-13**	0.00 (12.02)	1.300	0.404	0.00 (13.23)	0.413
2	**1**	**TS-14**$_{\mathbf{eq}}$	1.44	1.224	0.369	1.37	0.378
3	**1**	**TS-15**	2.01	1.310	0.406	1.82	0.416
4	**1**	**TS-16**$_{\mathbf{eq}}$	4.21	1.291	0.391	3.94	0.402
5	**1**	**TS-17**$_{\mathbf{regio}}$	2.79	1.111	0.326	2.74	0.337
6	**1**	**TS-18**$_{\mathbf{regio}}$	3.35	1.165	0.345	3.05	0.355
regioselectivity			99.6%			99.6%	
diastereomeric ratio			98.9:1.1			98.3:1.7	
7	**2**	**TS-19**	0.00 (13.76)	1.316	0.397	0.00 (14.72)	0.409
8	**2**	**TS-20**	0.58	1.168	0.344	0.52	0.356
9	**2**	**TS-21**	4.74	1.327	0.407	4.78	0.424
10	**2**	**TS-22**	1.90	1.310	0.399	1.66	0.411
11	**2**	**TS-23**	1.28	1.125	0.338	1.41	0.346
12	**2**	**TS-24**	1.87	1.341	0.408	1.87	0.424
diastereomeric ratio			93.4:6.6			93.9:6.1	

[a] The energies of the reference TSs were calculated relative to the *s-trans* form of isoprene and to dienophiles **1** and **2** respectively (in their most stable conformations). All energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) in plain text and sp PCM M06−2X/6−311+G(d,p) in italic), in DCM as solvent and at −45 °C. Charge transfers are in e$^-$. [b] All calculated *exo* TSs are at least 3.5 kcal mol^{-1} more energetic than **TS-13** or **TS-19**, respectively, and are not shown (*endo*/*exo* = 100.0:0.0; see the Supporting Information, Table S2).

Table 4. Gibbs Energies Calculated for the Addition of Dienophiles 1 and 2 to Diene 4 Relative to the Most Stable TSs (TS-25 and TS-30)[a]

			optimization			single-point	
entry	dienophile	TS[b]	$\Delta\Delta G$ (ΔG)	d_1/d_2	charge transfer	$\Delta\Delta G$ (ΔG)	charge transfer
1	**1**	**TS-25**	0.00 (3.21)	1.264	0.446	0.00 (4.84)	0.447
2	**1**	**TS-26**$_{\mathbf{eq}}$	2.56	1.248	0.435	2.35	0.439
3	**1**	**TS-27**	1.87	1.330	0.454	1.63	0.454
4	**1**	**TS-28**$_{\mathbf{eq}}$	7.68	1.365	0.461	7.36	0.439
diastereomeric ratio			98.4:1.6			97.4:2.6	
5	**2**	**TS-29**	3.97	1.366	0.445	3.88	0.448
6	**2**	**TS-30**	0.00 (4.42)	1.270	0.449	0.00 (5.80)	0.454
7	**2**	**TS-31**	1.01	1.413	0.497	0.79	0.501
8	**2**	**TS-32**	0.27	1.349	0.486	0.48	0.488
diastereomeric ratio			60.1:39.9			65.8:34.2	

[a] The energies of the reference TSs were calculated relative to the two isoenergetic conformations of diene **4** (see the Supporting Information) and to dienophiles **1** and **2**, respectively (in their most stable conformations). All energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) in plain text and sp PCM M06−2X/6−311+G(d,p) in italic), in DCM as solvent and at −45 °C. Charge transfers are in e$^-$. [b] All calculated *exo* and regioisomeric TSs are at least 4 kcal mol^{-1} more energetic than **TS-25** or **TS-30**, respectively, and are not shown (*endo*/*exo* = 100.0:0.0; see the Supporting Information, Tables S4 and S6).

2.0 kcal mol^{-1}, being the most energetic structure (**TS-15**) slightly more asynchronous (1.31 vs 1.30) and with a slightly stronger charge transfer (0.406 e$^-$ vs 0.404 e$^-$; Table 3). These values clearly show the electronic similarity between the two structures, which means that the large energy difference has to arise from steric effects between the attacking diene and the pyrrolidine aromatic substituents, as shown in Figure 3. However, the steric repulsion is reduced by C−H···π interactions (nonconventional hydrogen bonds) between the olefinic hydrogen atoms and the aromatic rings. In the most stable TS (**TS-13**) the aromatic ring at the same face of the attacking diene suffers a strong rotation (46.8°), in order to orientate perpendicularly to the diene C^3−H bond, thus allowing for an optimal C−H···π contact. A similar interaction exists in the diastereomeric TS (**TS-15**) between the other aromatic ring and the C^4−H hydrogen atom, but with a smaller aromatic ring rotation (16.3°).

When dienophile **1** reacts with diene **4** (Table 4), the reaction mechanism changes from single-step to a two-step process (compare Figures 3 and 4).[52−54] Interestingly, the asynchronicity ratios are similar to those calculated for the reaction of dienophile **1** with isoprene (compare the data in Tables 3 and 4), but while the IRC analysis of **TS-13** and **TS-15** leads to the DA products, the same analysis of **TS-25** and **TS-27** leads to the respective zwitterionic intermediates (Figure 4). Considering the high regio- and *endo*:*exo* selectivities, we will discuss only the diastereoselectivity of the *endo* possible TSs that lead to a single regioisomer.

The two-step mechanism calculated for the reaction with diene **4** results from the extreme electron donor character of this molecule, as the activation energy clearly shows (ΔG_{act} = 12.0 kcal mol^{-1} and 3.2 kcal mol^{-1} for, respectively, the reaction of **1** with isoprene (**TS-13**) and with diene **4** (**TS-25**). The first reaction step originates a low energy intermediate (**Int-1**,

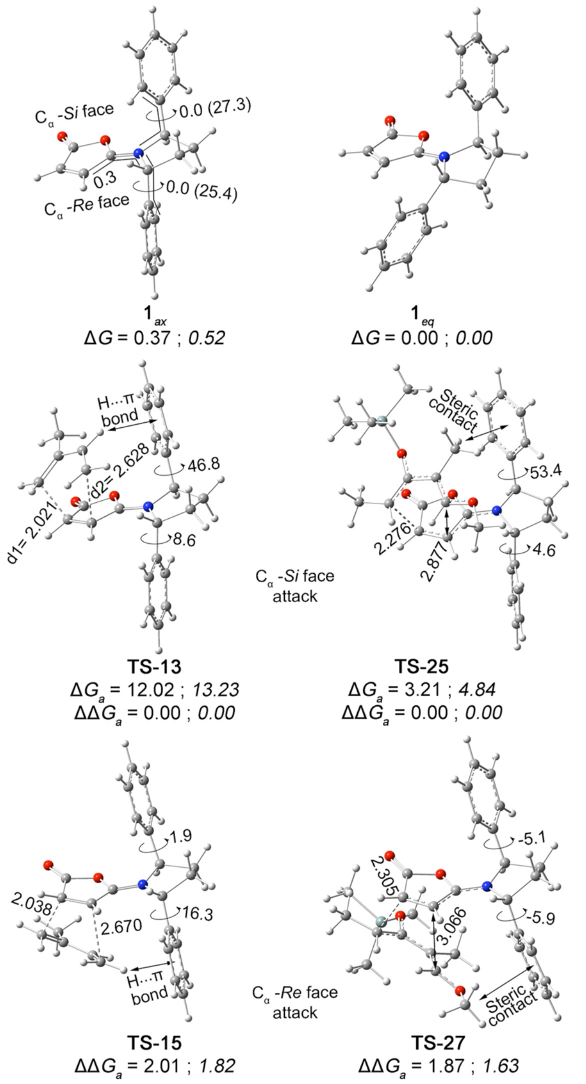


Figure 3. Conformations calculated for dienophile **1** and most stable TSs for its addition to isoprene (**3**) and to diene **4**. Gibbs energy values are relative to **TS-13** and **TS-25**. All energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) in plain text, sp PCM M06−2X/6−311+G(d,p) in italic), in DCM as solvent and at −45 °C. Bond lengths are in Å and angles in degrees.

Figure 4), in which the diene moiety can adopt several possible conformers. The most stable structure is more stable than the reagents by ca. 10.7 kcal mol^{-1}. **Int-1** reacts by a low energy TS (**TS-33** ≈ −10.1 kcal mol^{-1}, relative to the reagents) to form the DA addition product. Since the rate- and stereodetermining steps are associated with the first TS, we will not discuss in more detail the intermediates and second TSs, as they are irrelevant to the final predicted selectivities.

As the reaction is a two-step process, one could ask if the attack of the diene in its *s-trans* conformation would not lead to a lower energy TS. However, it has been recently shown that such an attack does not allow for diene rotation in the intermediate and, therefore, prevents the second reaction step that leads to the DA product.[25,53,54] In other words, independently of the mechanism, the diene has always to attack in *s-cis* conformation, to allow the DA product formation.

Dienophile **1** can also react with diene **4**, via a two-step mechanism, at the other possible diastereoface (**TS-27**, Figure 3). The activation energy of this TS is 1.9 kcal mol^{-1} higher than the value calculated for **TS-25**, which originates a diastereoselectivity of 98.4:1.6, in good agreement with the experimental value (exp. > 99:1). This means that in spite of the larger bulkiness of diene **4** relatively to isoprene, the second compound induces better selectivity. From the analysis of Figure 3, it is easy to understand the reason for this result. In fact, the large bulky syliloxy group in the diene does not affect the diastereoselectivity, as it lays, in both TSs, away of the aromatic substituents at the auxiliary moiety. Therefore, this group is important to increase the electro-donor ability of the diene, but is irrelevant in the achievement of high diastereoselectivity. In diene **4** there are no hydrogen atoms able to establish hydrogen bonds with the aromatic rings, as discussed above for isoprene. In fact, the two hydrogen atoms in isoprene that were able to interact with the aromatic rings are substituted, in the case of diene **4**, by a methoxy and a methyl group, and these substituents affect the selectivity by establishing steric repulsions with the aromatic rings. The methoxy group interacts with one aromatic ring when the diene attack occurs at the C_α−*Re* face, while the adjacent methyl group establishes a steric contact with the other aromatic ring when the attack occurs at the C_α−*Si* face (Figure 3). The steric interaction between the methyl group and the aromatic ring at the C_α−*Si* face is more important than the repulsion between the methoxy group and the aromatic ring at the C_α−*Re* face,

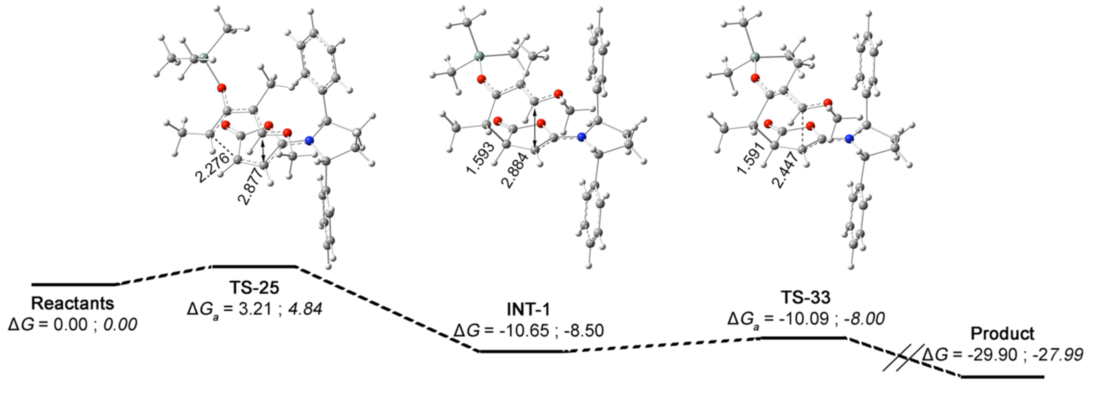


Figure 4. Two-step reaction pathway calculated for the addition of diene **4** to dienophile **1**, at the C_α−*Si* face. Gibbs energy values are relative to the reagents. The DA product undergoes an elimination process to form the final product, which has energy of −34.76; *−34.67* kcal mol^{-1} (Supporting Information, Table S10). All energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) in plain text, sp PCM M06−2X/6−311+G(d,p) in italic), in DCM as solvent and at −45 °C. Bond lengths are in Å.

and the result is a slight reduction of the selectivity, by comparison with the reaction with isoprene. This statement can be easily demonstrated, as when the methyl group is removed, the calculated diastereoselectivity considerably increases ($\Delta\Delta G$ = 3.2 kcal mol^{-1}, while with diene **4** $\Delta\Delta G$ = 1.9 kcal mol^{-1}; see the Supporting Information, Table S9).

While the selectivities obtained in the reactions of dienes **3** and **4** with dienophile **1** mainly result from TSs in which the two aromatic rings are in axial orientation, it is interesting to note that the equatorial conformation of the aromatic rings leads to higher selectivity (Table 3, entries 1 and 3 vs entries 2 and 4). As stated before, this happens because in this conformation the two aromatic rings become closer to the attacking diene, thus increasing the steric repulsion. The energy difference is particularly large when the bulkier diene 4 is used, as seen in Table 4 (entries 1 and 3 vs entries 2 and 4).

Dienophile **2** is less activated than diehophile **1**, as previously stated (ΔG_{act} = 13.8 kcal mol^{-1} and 12.0 kcal mol^{-1} for, respectively, the addition of isoprene to **2** and to **1**). However, the reaction asynchronicity and charge transfer are similar for both dienophiles (Table 3).

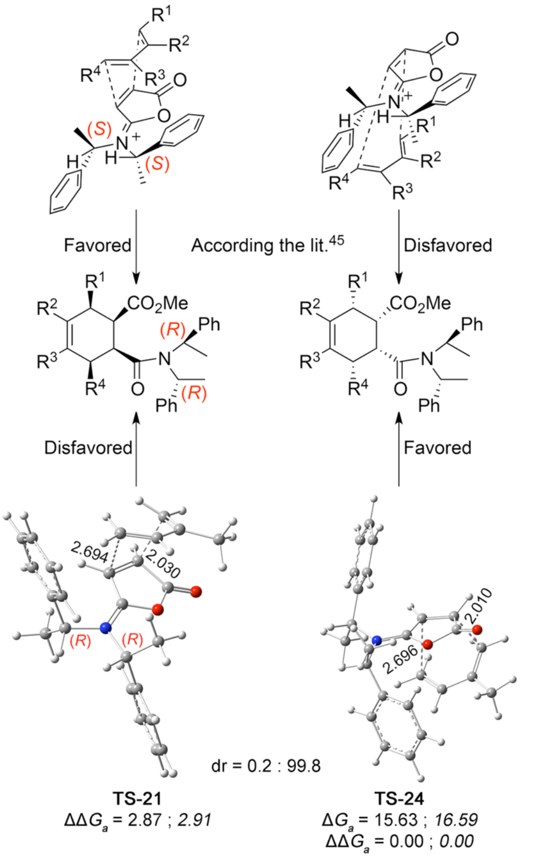


Figure 5. Selectivity rationalization proposed by Boeckman and collaborators,[45] for the addition of isoprene to dienophile **2**, showing the absolute configuration inconsistency between the TSs and the products (top). Calculated TSs for the reaction with isoprene, with the proper configuration at the auxiliary, that lead to the opposite selectivity (bottom). Activation energies are relative to the reagents. All energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) in plain text, sp PCM M06−2X/6−311+G(d,p) in italic), in DCM as solvent and at −45 °C. Bond lengths are in Å.

In a first look it seems acceptable to rationalize the selectivity obtained with dienophile **2** in a similar way to that followed for dienophile **1**. Indeed, Boeckman and collaborators[45] proposed two TSs for the reaction of isoprene with **2**, in which the two benzyl groups lay at two opposite diastereofaces, originating a C_2 symmetric system (Figure 5, top). If this structure indeed exists, all that was said relatively to dienophile **1** would then be directly applied to dienophile **2**. However, there are two main flaws within this approach. The first one results from a small lapse that Boeckman and collaborators[45] had when drawing their proposed TSs, as they used the *S,S* configuration of the bis(1-phenylethyl)amine (Figure 5) while they should use its enantiomer. Therefore, with the proper configuration (**TS-21** and **TS-24**, Table 3 and Figure 5, bottom) of the chiral auxiliary, they would arrive at the opposite selectivity, which would be in contradiction with the experimental result. The second flaw results from the full analysis of the conformational space of compound **2**. Indeed, our study indicates that the most stable conformer has the two aromatic rings at the same diastereoface (**2-Conf A**, Figure 6), while the C_2 symmetric conformer (**2-Conf C**) is ca. 2.8 kcal mol^{-1} more energetic. This data is in full agreement with the ORTEP structures shown in the Supporting Information of the experimental paper.[45] Indeed, the conformation of the chiral auxiliary moiety of the calculated lowest energy conformer (**2-Conf A**) and the chiral auxiliary moiety of the published crystal structures of two reaction products are very similar. Since **2-Conf A** is not a C_2 symmetric structure, it can exist in a second conformation (**2-Conf B**). These two conformational structures are near isoenergetic, and are stabilized by π hydrogen bonds between the two aromatic rings, which, in structure **2-Conf A**, are almost orthogonal. If the two aromatic rings adopt a coplanar orientation, by establishing π-π interactions between them, the energy rises by ca. 1.1 kcal mol^{-1} (**2-Conf D**, Figure 6) or 2.3 kcal mol^{-1}, in conformation **2-Conf E**. Other conformers have been obtained from the conformational search of structure **2**, but they are at least 3.2 kcal mol^{-1} more energetic than **2-Conf A**. Thus, since conformations **A** and **B** of compound **2** are the main reactive structures, and since they are not C_2 symmetric, the rationalization of the experimental selectivity has to be quite different from that previously discussed for dienophile **1**. In other words, while apparently similar, dienophiles **1** and **2** are, indeed, very different reactive species.

The regioselectivities and the *endo*:*exo* ratios will not be discussed for dienophile **2**, as the reasons for the high values experimentally obtained are similar to those discussed for dienophile **1** and the simplified model compounds. The diastereoselectivities will be discussed mainly based on conformers **2-Conf A** and **2-Conf B**, because these two structures are responsible for almost 94% of the final products. However, the reported selectivities were calculated by Boltzmann averaging of all TSs originated from conformers **2-Conf A**, **2-Conf B** and **2-Conf C**. The TS structures originated from **2-Conf D** and **2-Conf E** converged to the TS structures obtained from **2-Conf A** and **2-Conf B** and were not accounted.

The energies of the two conformers (**A** and **B**) of dienophile **2** differ by only 0.3 kcal mol^{-1}, and are both important in the establishment of the final selectivities (Table 3 and Figure 7). Indeed, when the reagent is isoprene, while structure **2-Conf A** leads to ca. 74% of the final products (via **TS-19** and **TS-22**), structure **2-Conf B** contributes with ca. 25% (via **TS-20** and **TS-23**). However, it is interesting to observe that the two conformers do not contribute with similar diastereofaces to the final selectivity. The analysis of the two reactive conformations

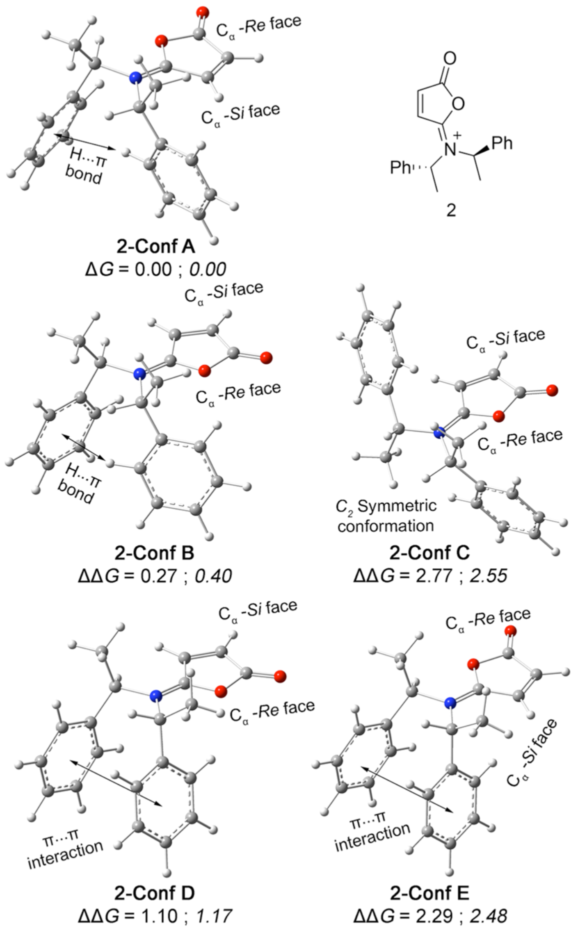


Figure 6. Most stable conformations calculated for dienophile **2**. Gibbs energy values are relative to **2-Conf A**. All energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) in plain text, sp PCM M06−2X/6−311+G(d,p) in italic), in DCM as solvent and at −45 °C.

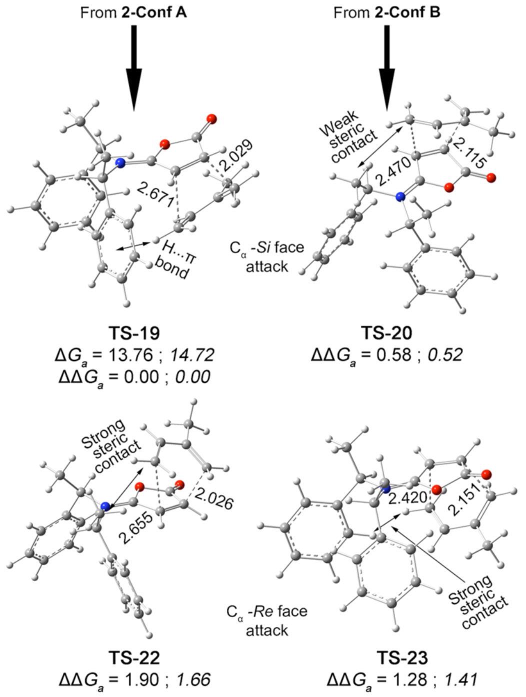


Figure 7. TS structures calculated for addition of isoprene (**3**) to dienophile **2** in conformations **2-Conf A** and **2-Conf B**. Gibbs energy values are relative to **TS-19**. All energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) in plain text, sp PCM M06−2X/6−311+G-(d,p) in italic), in DCM as solvent and at −45 °C. Bond lengths are in Å.

(**A** and **B**) suggests that the faces at where the aromatic rings are located are sterically more hindered, thus directing the attack at the opposite faces. For conformer **B** this is indeed the case, with isoprene preferentially attacking the C_α−*Si* face (**TS-20**, Figure 7). On the other hand, with conformer **A** the opposite is true, with isoprene preferentially attacking also at the C_α−*Si* face, which, in this conformer, contains the bulkier aromatic rings (**TS-19**). One reason for this difference is the π hydrogen bond established between isoprene and one of the aromatic rings in **TS-19**, which stabilizes this structure. The other reason is the steric interaction between isoprene and one of the methyl groups in **TS-22**, which makes this TS structure less stable. In the case of **TS-20** (originated from **2-Conf B**) the configuration of the benzylic carbon atom keeps the methyl group more distant of the attacking isoprene, thus reducing the steric energy. However, the attack at the second stereoface (**TS-23**) does not allow for π hydrogen bond interactions between isoprene and any of the aromatic rings, but originates a strong steric contact with the second aromatic ring. The overall result is a preferential attack at the C_α−*Si* faces in both reacting conformers, which is in agreement with the experimental selectivity. The Boltzmann averaging of the contribution of 6 TSs (Figures 5 and 6, and Table 3) originates a diastereomeric ratio of 93.4:6.6, which agrees quite well with the experimental value (89:11). Therefore, while our models indicate that part of the poor performance of dienophile **2** results from its conformational space that leads to a few possible TSs, in agreement with the proposal made by the authors of the experimental paper,[45] they also indicate that the same proposal is not correct when suggesting that the main selectivity results from a C_2 symmetric conformation of dienophile **2**, as this conformation contributes in only ca. 1% to the final products (Figure 5 and Table 3, entries 8 and 12), and the predicted selectivity (0.2:99.8, Figure 5) is opposite to that experimentally observed (89:11, Table 1).

Dienophile **2** reacts with diene **4**, by **TS-30** (Table 4 and Figure 8), with the activation energy of 4.4 kcal mol^{-1}. This value confirms that, relatively to dienophile **1** (3.2 kcal mol^{-1}), compound **2** is, indeed, a lower activated dienophile. On the other hand, the diastereomeric ratio obtained with diene **4** is just 75:25, confirming the poorer performance of diene **4**, as previously discussed for its reaction with dienophile **1**.

In the reaction of isoprene with dienophile **2**, we considered the participation of 3 conformers of this structure, as we wished to clearly show that the experimental selectivity is indeed dependent on several possible TSs. However, a similar study with diene **4** would be extremely time-consuming, due to the size of the molecule. On the other hand, such a study would be of little relevance in the general discussion, as isoprene, with its rigid structure, allows for better evaluation of the dienophile behavior. Therefore, we shall discuss the calculated selectivity based only on the TSs resulting from conformers **2-Conf A** and **2-Conf B** (Figure 6).

As calculated for the reaction with dienophile **1**, the reaction of diene **4** with dienophile **2** occurs by a two-step mechanism, in which the first TS is the rate- and the selectivity-determining step. The relative energies of intermediates and second TSs are given in the Supporting Information (Table S7), but they will

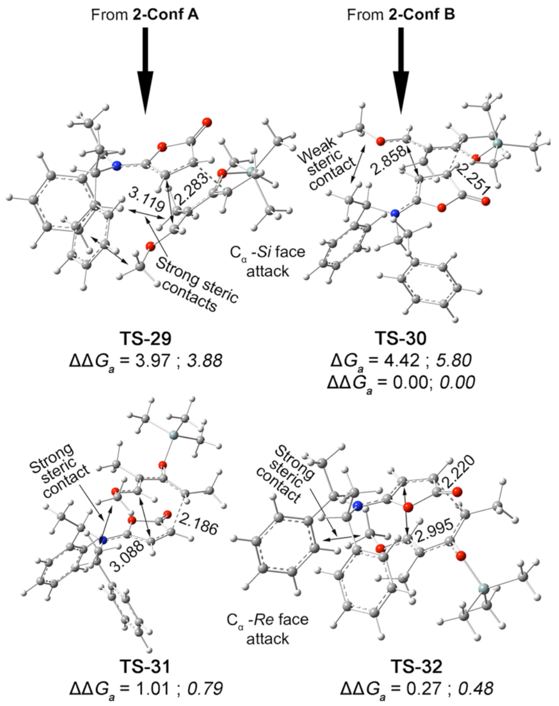


Figure 8. TS structures calculated for addition of diene **4** to dienophile **2** in conformations **2-Conf A** and **2-Conf B**. Gibbs energy values are relative to **TS-30**. All energy values are in kcal mol^{-1} (PCM M06−2X/6−311G(d,p) in plain text, sp PCM M06−2X/6−311+G(d,p) in italic), in DCM as solvent and at −45 °C. Bond lengths are in Å.

not be further discussed, as the behavior is similar to that described for the reaction with diehophile **1**, and is irrelevant in the rationalization of the final diastereoselectivity.

The four TSs originated from conformers **2-Conf A** and **2-Conf B** are shown in Figure 8. If we compare these structures with those in Figure 7 (reaction of dienophile **2** with isoprene), the most important conclusion is that the most stable TS in the reaction with isoprene (**TS-19**) is the highest energy TS in the reaction with diene **4** (**TS-29**). This happens due to the strong steric repulsion between the methoxy group in the diene and one of the aromatic rings in the auxiliary, together with the lack of π hydrogen bond between the same aromatic ring and the diene proton, which has been substituted by the methoxy group. On the other hand, the methyl group in the diene establishes also a strong steric repulsion with the second aromatic ring in the auxiliary. Together, these interactions rend **TS-29** as the most energetic TS. Interestingly, the most abundant stereoisomer keeps the same absolute configuration, because **TS-30** becomes the lowest energy TS, and **TS-29** and **TS-30** originate the same stereoisomer. With exception of **TS-29**, the remaining TSs in Figure 8 keep relative energies similar to those observed in Figure 7. Therefore, the main reason for the reduction of selectivity when diene **4** is used instead of isoprene, is the energy increase of **TS-29** (Figure 8) relative to **TS-19** (Figure 7).

CONCLUSIONS

The theoretical results discussed in this paper clearly show that the isoimidium group is, indeed, a very good dienophile activator in Diels−Alder reactions. The high regio- and *endo*/*exo* selectivities experimentally obtained can be rationalized mainly based on electronic effects, albeit the important role also played by steric contacts. With dienophiles attached to isoimidium chiral auxiliaries derived from (2*R*,5*R*)-2,5-diphenylpyrrolidine and from (*R*)-bis((*R*)-1-phenylethyl)amine, we show that, while the structures are apparently similar, the diastereoselectivities have quite different origins. Therefore, while the selectivity originated by (2*R*,5*R*)-2,5-diphenylpyrrolidine based dienophiles can easily be rationalized by a C_2 symmetric transition state, several transition states, conformationally related, have to be simultaneously accounted for the rationalization of the selectivity obtained with dienophiles based on (*R*)-bis((*R*)-1-phenylethyl)amine. In this case, the C_2 symmetric structure leads to opposite selectivities to those experimentally observed. Our models, which substantially differ from those previously proposed in the literature, can also be adapted to other reactions in which this type of chiral auxiliaries are used.

COMPUTATIONAL METHODS

Full geometry optimizations have been performed with the Gaussian 09, Revision B.01, software package[55] employing density functional theory (DFT)[56,57] with the functional M06−2X[58] and the 6−311G(d,p) basis set. Solvent effects in dichloromethane were included in the optimizations by using the polarizable continuum model (PCM).[59] Harmonic vibrational frequencies have been calculated for all located stationary structures to verify whether they are minima or transition states. Zero-point energies and thermal corrections have been taken from unscaled vibrational frequencies. Free energies of activation are given at −45 °C, relative to the reactants. Single-point PCM energy calculations, in dichloromethane, were performed at the M06−2X/6−311+G(d,p) level of theory, over the optimized PCM M06−2X/6−311G(d,p) geometries, and are given in all tables and figures. Single-point PCM calculations, in dichloromethane, over the optimized structures, have been also performed at M062X/6−311G(2d,p), M06−2X/6−311+G(2d,p), M06−2X/6−311G(2df,p), M06−2X/6−311+G(2df,p), B2PLYP/6−311+G(d,p),[60] and mPW2PLYP/6−311+G(d,p)[61] levels of theory, and the results are given in the Supporting Information. All bond lengths are in angstroms (Å), angles in degrees, energies in kcal mol^{-1}, and NBO charge transfers in e$^-$.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Cartesian coordinates, energies and imaginary frequencies at M06−2X/6−311G(d,p) as well as sp energies at M06−2X/6−311+G(d,p), M06−2X/6−311G(2d,p), M06−2X/6−311+G(2d,p), M06−2X/6−311G(2df,p), M06−2X/6−311+G(2df,p), B2PLYP/6−311+G(d,p) and mPW2PLYP/6−311+G(d,p). This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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