

TADDOL–TiCl₂ catalyzed Diels–Alder reactions: unexpected influence of the substituents in the 2-position of the dioxolane ring on the stereoselectivity

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Abstract: Several $\alpha,\alpha,\alpha',\alpha'$ -tetra(3,5-dimethylphenyl)-1,3-dioxolane-4,5-dimethanols have been synthesized, and their TiCl₂ derivatives used as catalysts in the reaction of cyclopentadiene with (*E*)-2-butenoyl-1,3-oxazolidin-2-one. The substituents in the 2-position of the dioxolane ring exert a decisive influence on the extent and direction of the asymmetric induction and, consequently any possible enantiomer of the cycloadducts can be preferentially obtained by changing these substituents. Molecular mechanics calculations of the structures and relative energies of the possible dienophile–catalyst complexes offer a tentative explanation for the results described. © 1997 Elsevier Science Ltd

Introduction

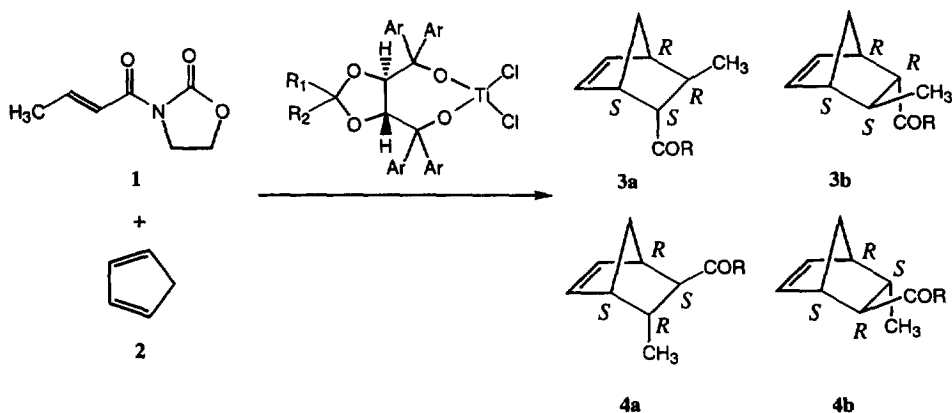
TADDOLs ($\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanols), first reported by Seebach,¹ have been frequently used as chiral auxiliaries in several Ti^{IV}-catalyzed reactions.² In particular, the TiCl₂–TADDOLates promote asymmetric Diels–Alder reactions^{3–6} with high enantioselectivity. Several mechanistic studies dealing with the structure and relative reactivity of the different dienophile–catalyst complexes have been carried out.^{4–8}

Seebach and co-workers have studied the influence of several factors, including the TADDOL structure, in the Diels–Alder reaction of cyclopentadiene with (*E*)-3-butenoyl-1,3-oxazolidin-2-one. In reactions promoted by catalysts derived from (*R,R*)-tartrate, the (*2S*)-cycloadducts are the major products. Surprisingly, a reversal of the absolute topicity was observed with TADDOLs bearing four 1-naphthyl groups as the aryl substituents. With these chiral auxiliaries the (*2R*)-cycloadducts are preferentially obtained (Scheme 1).⁶

Very recently, polymer-supported TADDOL–TiCl₂ complexes have been used as catalysts for the same Diels–Alder reaction.^{9,10} The catalyst obtained from (*4R,5R*)-2-(hydroxyphenyl)- $\alpha,\alpha,\alpha',\alpha'$ -tetra(3,5-dimethylphenyl)-1,3-dioxolane-4,5-dimethanol, grafted onto chloromethylated polystyrene–divinylbenzene, and TiCl₂(*O*^{*i*}Pr)₂ gives rise to the same reversal of topicity to give the (*2R*)-cycloadducts as the major products.¹⁰ Given that TADDOLs bearing four 3,5-dimethylphenyl groups as the aryl substituents had not previously shown this behaviour,^{4,6} we have studied the use of the TiCl₂ complexes of several TADDOLs of this kind as catalysts in the reaction of (*E*)-3-butenoyl-1,3-oxazolidin-2-one **1** with cyclopentadiene **2** (Scheme 1).

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Scheme 1.

R ₁	R ₂	Ar	Compound
3-BnO-C ₆ H ₄	H	C ₆ H ₅	5
3-BnO-C ₆ H ₄	H	3,5-diMe-C ₆ H ₃	6
C ₆ H ₅	H	3,5-diMe-C ₆ H ₃	7
C ₆ H ₅	CH ₃	3,5-diMe-C ₆ H ₃	8
C ₆ H ₅	C ₆ H ₅	3,5-diMe-C ₆ H ₃	9

Figure 1. Structures of the TADDOLs used in this work.

Results and discussion

In view of the results obtained with the above-mentioned polymer-grafted catalyst,¹⁰ we have prepared different TADDOLs (Figure 1).

Reaction of benzaldehyde, acetophenone or benzophenone with a mixture of (*R,R*)-dimethyl tartrate and HC(OMe)₃ afforded the corresponding ketals,¹⁰ from which compounds 7–9 were prepared by treatment with excess 3,5-dimethylphenylmagnesium bromide. Yields of ca. 60% were obtained for the first step, and addition of the organomagnesium reagent gave yields in the 40–60% range. In both cases, yields refer to the pure product isolated after chromatographic purification on silica gel. TADDOLs 5 and 6 were prepared by *O*-benzylation of the corresponding 2-(3-hydroxyphenyl)- $\alpha,\alpha,\alpha',\alpha'$ -tetrakis(3,5-dimethylphenyl)-1,3-dioxolane-4,5-dimethanols using benzyl bromide as the alkylating agent and NaH in dry THF as the base, along with a small amount of NBu₄I and 18-crown-6.¹⁰

TADDOLs 6–9, containing four 3,5-dimethyl groups in the α - and α' -positions, show spectroscopic features which reveal the presence of several conformers having a slow interconversion on the NMR time scale. For example, compound 9 shows at least three different methyl signals at different temperatures (0–60°C) in its ¹H NMR spectra and, in addition, the use of spin saturation transfer experiments (at 0°C) showed the presence of three exchanging signals (appearing as broadened singlets) at 1.65, 4.38 and 4.55 ppm for the protons of the dioxolane ring. It is worth mentioning that, for compound 9, the presence of the two phenyl rings at the 2-position is reflected in an appreciable shielding of the protons of the dioxolane ring. The normal chemical shift for these signals in related systems is in the 5–6 ppm region and the shielding is very large for one of the conformers present.

Table 1. Results obtained in the reaction of (*E*)-3-butenyl-1,3-oxazolidin-2-one **1** with cyclopentadiene **2**, promoted by the TiCl₂-TADDOL catalysts in toluene at 25°C in 24 h

Entry	R ₁	R ₂	Ar	% Conv. ^a	3:4 ^b	3a:3b ^c
1 ^d	3-(P)-O-C ₆ H ₄	H	3,5-diMe-C ₆ H ₃	95	71:29	38:62
2	3-BnO-C ₆ H ₄	H	3,5-diMe-C ₆ H ₃	100	71:29	31:69
3	3-BnO-C ₆ H ₄	H	C ₆ H ₅	100	83:17	67:33
4 ^e	CH ₃	CH ₃	3,5-diMe-C ₆ H ₃	95	89:11	91:9
5 ^e	CH ₃	CH ₃	C ₆ H ₅	25	83:17	72:28
6	C ₆ H ₅	H	3,5-diMe-C ₆ H ₃	100	70:30	31:69
7	C ₆ H ₅	CH ₃	3,5-diMe-C ₆ H ₃	100	70:30	38:62
8	C ₆ H ₅	C ₆ H ₅	3,5-diMe-C ₆ H ₃	22	80:20	50:50
9 ^e	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	74	87:13	90:10

^a Determined by GC. ^b Determined by ¹H-NMR. ^c Determined by ¹H-NMR in the presence of Eu(hfc)₃. ^d Data from ref. 10. ^e Data from ref. 6.

The TiCl₂-TADDOL complexes were used as catalysts in the aforementioned Diels-Alder reaction (Scheme 1). Table 1 shows the results obtained in these reactions together with some results previously described using similar chiral catalysts.

Comparison of the results obtained with the polymer-supported catalyst (entry 1) and the analogous results obtained in the homogeneous phase (entry 2) shows that the polymer support is not responsible for the unexpected preference towards the (1*R*,2*R*)-cycloadduct **3b**. The replacement of the four 3,5-dimethylphenyl groups by four phenyl groups gives rise to a catalyst which leads to the normally observed preference for the (1*S*,2*S*)-cycloadduct **3a**, with about the same enantiomeric excess (entry 3), which clearly shows the influence of the 3,5-dimethylphenyl groups on the reversal of topicity. However, it has been described^{4,6} that in some cases the replacement of phenyl groups by 3,5-dimethylphenyl groups increases the preference for the (1*S*,2*S*)-cycloadduct (entries 4 and 5). Therefore, comparison of these results indicates that there is an unknown influence of the substituent at the 2-position of the dioxolane ring on the direction of the asymmetric induction. The reaction promoted by the catalyst derived from (4*R*,5*R*)-2-phenyl- $\alpha,\alpha,\alpha',\alpha'$ -tetrakis(3,5-dimethylphenyl)-1,3-dioxolane-4,5-dimethanol yields 38% ee of the (1*R*,2*R*)-norbornene derivative **3b**, showing that the substitution of the phenyl group in the dioxolane ring has no influence on either the catalytic activity or on the *endo/exo* and enantioselectivities (entries 2 and 6). The introduction of additional substituents in the 2-position of the dioxolane ring further modifies the asymmetric induction. Thus, the catalyst obtained from the 2-methyl-2-phenyl-substituted diol leads to a slightly lower enantiomeric excess of the (1*R*,2*R*)-cycloadduct **3b** (entry 7), whereas the 2,2-diphenyl derivative does not induce asymmetry at all (entry 8). This result is quite surprising given the excellent results obtained with other C₂-symmetric TADDOLs bearing either four 3,5-dimethylphenyl groups as the aryl substituents (entry 4), or possessing two phenyl groups in the dioxolane ring (entry 9).

Consideration of these results shows an unexpected influence of the substitution of the dioxolane ring on the direction of the asymmetric induction, together with a significant influence on the extent to which this asymmetric induction takes place. These facts are not easy to explain.

The mechanism of the Diels-Alder reactions catalyzed by TiCl₂-TADDOLs has been subject of controversy. Coordination of the catalyst to the dienophile leads to five isomeric complexes (Figure 2), and in each case the dienophile can be in the *s-cis* or the *s-trans* conformation. Theoretical and experimental studies have both shown that in chelate complexes the *s-cis* conformation is preferred in the *N*-acyl-1,3-oxazolidin-2-ones.^{7,8} The main subjects of debate have been the relative reactivity of these intermediate complexes and their ability to induce asymmetry on the basis of the differential shielding of both faces of the double bond. DiMare and co-workers have studied the NMR in solution of the complexes formed between (*E*)-3-hex-2-enoyl-1,3-oxazolidin-2-ones and several

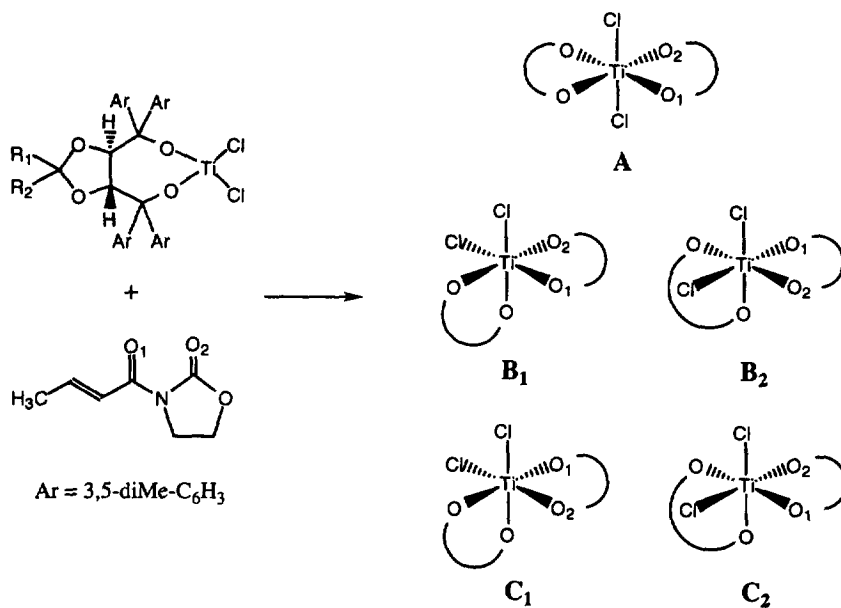


Figure 2. Structures of the possible diastereomeric complexes between the dienophile and the TADDOL–TiCl₂.

TiCl₂–TADDOLates, and they have observed three different adducts, the most abundant being the “symmetric” complex with both chlorine atoms in axial positions (A), whereas the second one is an “unsymmetric” intermediate (B).⁷ Jørgensen and co-workers have obtained crystals of the complex formed between (*E*)-3(3-cinnamoyl)-1,3-oxazolidin-2-one and the TiCl₂–TADDOLate prepared from (4*R*,5*R*)-2,2-dimethyl- $\alpha,\alpha',\alpha',\alpha'$ -tetraphenyl-1,3-dioxolane-4,5-dimethanol, and have shown that its structure corresponds to the “symmetric” intermediate (A).⁸

Both Seebach⁶ and DiMare⁷ propose that those intermediates in which the carbonyl oxygen atom of the enoate is in a *trans*-position with respect to a chlorine atom (B) experience a higher degree of Lewis acid activation, and therefore they must be more reactive. Very recently, Gothelf and Jørgensen have studied the use of TiCl(O^{*i*}Pr)₃ and TiCl(O^{*i*}Pr)–TADDOLate in the 1,3-dipolar cycloadditions between (*E*)-3-butenoyl-1,3-oxazolidin-2-one and benzylidenephénylamine-*N*-oxide,¹¹ and they have concluded that the intermediates having an axial chlorine are more reactive. They have extrapolated this conclusion to say that the intermediates (A) are not only the most abundant, but also the most reactive.¹¹

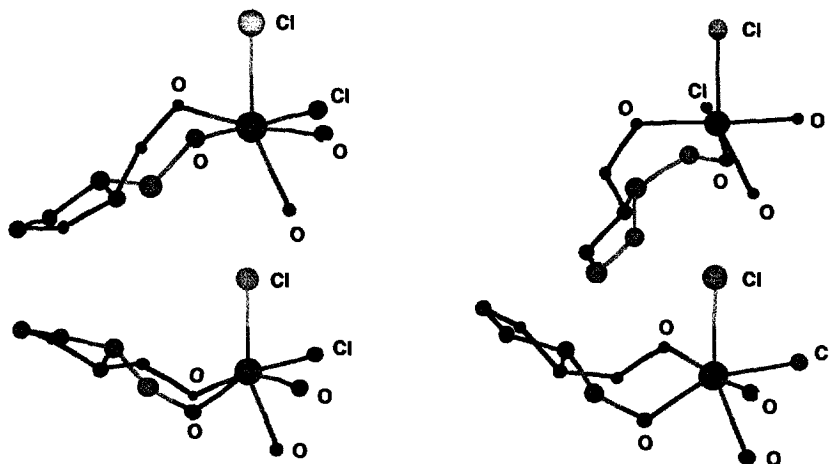
Whereas DiMare⁷ and Seebach⁶ assumed that in the “symmetric” intermediate (A) neither of the alkene faces is sufficiently hindered to account for the high enantioselectivity observed in some cases, Jørgensen and co-workers have explained these results on the basis of the X-ray structure of the isolated intermediate A.⁸

The results described in the present work make it even more difficult to find a clear explanation for the mechanism of these asymmetric reactions. In fact, the problem is very complex because the reaction of the diene with these intermediate complexes is the step that determines both the rate and the stereochemical course of the reaction. Therefore, following the Curtin–Hammett principle,¹² the selectivities of the reaction will be determined only by the relative energies of the different transition states. The five different intermediates can react with the diene by both faces of the double bond, which, apart from the conformational flexibility of the TADDOL moiety, means that the reaction can take place through ten *endo* and ten *exo* transition states. This fact, together with the size of the complexes, makes the calculation at a suitable theoretical level of the corresponding transition structures an impossible task. In view of these limitations, speculation based on calculated structures

Table 2. Calculated (MM2) relative energies (in kcal mol⁻¹) and indication of the less shielded face^a for the different TiCl₂-TADDOL-dienophile intermediates

R ₁	R ₂	A	B ₁	B ₂	C ₁	C ₂
CH ₃	CH ₃	11.1 (Re≈Si)	3.3 (Re)	0.0 (Si)	6.2 (Si)	1.8 (Re)
CH ₃	C ₆ H ₅	12.3 (Re≈Si)	0.5 (Re)	0.0 (Si)	5.8 (Si)	1.4 (Re)
C ₆ H ₅	C ₆ H ₅	12.9 (Re≈Si)	0.8 (Re)	0.0 (Si)	5.8 (Si)	1.1 (Re)

^a Re stands for C α -Re, C β -Si attack, and Si stands for C α -Si, C β -Re attack.

**Figure 3.** The two "twist-chair" (left) and two "boat" (right) possible conformations found for the titanium chelate seven-membered ring of the TADDOLate complexes.

of the intermediates represents a possible way to offer qualitative explanations for the experimental results obtained.

We have carried out molecular mechanics and molecular dynamics calculations, using the MM2 force field,¹³ on the five dienophile-catalyst complexes for three of the TADDOLs bearing the 3,5-dimethylphenyl substituents that lead to different results in the direction and extension of the asymmetric induction. Table 2 shows the relative energies of the different TiCl₂-TADDOLates, together with an indication of the less-shielded face of the double bond. The presence of several conformers in the TADDOLs, as discussed previously, indicates that several conformations are possible, at least in principle, in these intermediates. In view of this, we have carried out a molecular dynamics calculation for each intermediate in order to find the global energy minimum in each case, and the following discussion is based on these energy minima. As expected, in the case of complexes B and C, there are several conformers, whose differences lie in the conformation of the seven-membered ring formed by the TADDOL coordinated to the titanium atom. There are four main dispositions for the atoms in this ring, two of them in a "twist-chair" arrangement, and two others in a "boat" arrangement (Figure 3). These arrangements have a dramatic effect on the position of the 3,5-dimethylphenyl groups of the TADDOL with regard to the dienophile. In all cases, the most stable conformation is that in which a 3,5-dimethylphenyl group is just above and parallel to the dienophile, probably due to a stabilization through π -stacking interactions (see below). In the three other conformations, not only is the energy higher, but there are two aryl groups situated above and below the dienophile, so that it would be expected that these species, if present in solution, would not be very reactive due to the steric hindrance on both faces of the double bond.

First of all, it is important to note that the relative energies do not reflect the results obtained in solution and in the solid state, because the complexes bearing the two chlorine atoms in axial

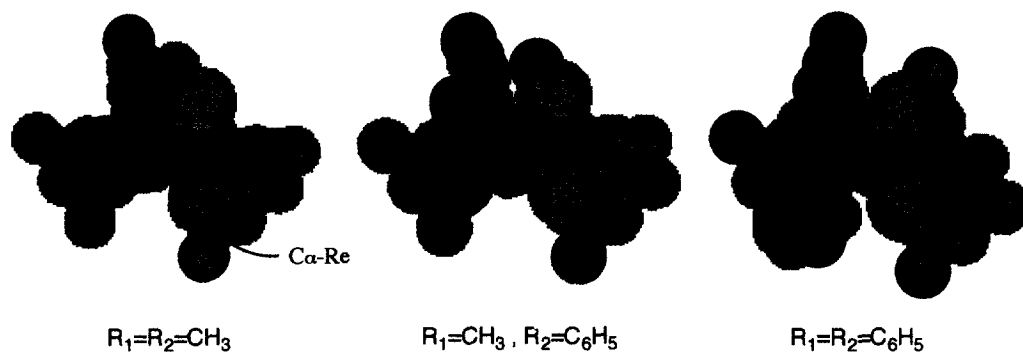


Figure 4. Calculated (MM2) geometries of the intermediates **A**. Hydrogen atoms have been omitted for clarity. The atoms in the carbon-carbon double bond of the dienophile and the aryl groups responsible for the shielding are coloured in black.

positions are calculated to be the most unstable. Also, the comparison between the X-ray and the MM2 geometries reveals some differences, which are particularly important for the O_1 -Ti- O_2 bond angle (Figure 2) formed by the carbonyl oxygen atoms of the dienophile and the metal (experimental=79°, calculated=65°). These discrepancies can be interpreted in terms of the adequacy of the MM2 parameters used to describe this kind of complex and so the results obtained should be interpreted with caution. In any case, comparisons between complexes with more similar structures should be more accurate. Therefore, comparisons between complexes with two chlorine atoms in vicinal positions will be more reliable than those involving one complex with two chlorine atoms in vicinal positions and another complex with two chlorine atoms in axial positions. Within the vicinal dichloro-complexes, the comparisons between complexes **B**₁ vs. **B**₂, and **C**₁ vs. **C**₂ will, in turn, be the most significant.

With regard to the asymmetric induction, complex **A** does not show a sufficiently high differential shielding to account for the high asymmetric induction obtained with the 2,2-dimethyl TADDOL, although the slight preference of the attack on the $C\alpha$ -Re face is in agreement with the direction of the enantioselectivity observed with this TADDOL (Figure 4). Modification of the substituent at the 2-position of the dioxolane ring does not noticeably change the geometry of this intermediate. This means that, although the lack of an important differential shielding between both faces of the double bond may account for the lack of enantioselectivity with the 2,2-diphenyl derivative, this structure does not explain the direction of the asymmetric induction observed in the case of the 2-methyl-2-phenyl TADDOL, given that in this case the attack of the diene takes place preferentially on the $C\alpha$ -Si face of the double bond (Figure 4).

Substitution of the 2-position of the dioxolane ring does not modify either the geometries or the relative energies of the complexes **C**₁ and **C**₂ (Table 2). Given that previous studies have shown that these intermediates are the less reactive,^{7,8} this fact does not seem to be relevant with regard to the influence of the substitution pattern in the dioxolane ring on the asymmetric induction.

With regard to **B**₁ and **B**₂, Seebach and co-workers have postulated that, apart from the aforementioned greater degree of Lewis acid activation, the less stable of these diastereomeric complexes is also the most reactive.⁶ Molecular mechanics calculations show that the relative energies of complexes **B**₁ and **B**₂ are indeed influenced by the substitution pattern in the dioxolane ring (Table 2 and Figure 5). The results obtained with the 2,2-dimethyl derivative are in agreement with the Seebach hypothesis. With this TADDOL the *endo* cycloadduct resulting from the attack of the diene on the less hindered face of **B**₁, namely the $C\alpha$ -Re face (Figure 5), is obtained with 82% ee.

With the 2-methyl-2-phenyl and the 2,2-diphenyl TADDOLates, neither the **B**₁ and **B**₂ geometries are noticeably modified, which again shows a significant degree of shielding of the $C\alpha$ -Si and $C\alpha$ -Re face of the double bond, respectively (Figure 5). However, there is a difference in the relative stabilities of both diastereomeric complexes. Thus the 3.3 kcal mol⁻¹ calculated for the 2,2-dimethyl

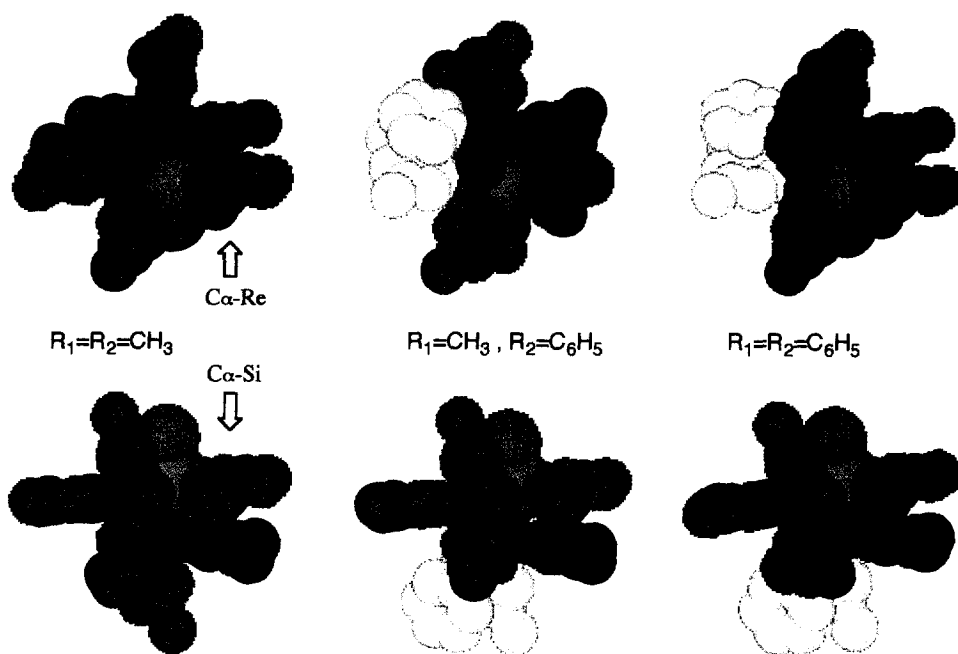


Figure 5. Calculated (MM2) geometries of the intermediates **B**₁ (top) and **B**₂ (bottom). Hydrogen atoms have been omitted for clarity. The atoms in the carbon-carbon double bond of the dienophile and the aryl group responsible for the shielding are coloured in black, whereas the aryl groups involved in a π -stacking interaction are coloured in white.

TADDOLate is reduced to 0.5 and 0.8 kcal mol⁻¹, respectively, for the 2-methyl-2-phenyl and 2,2-diphenyl derivatives. Given that the participation of **B**₂ in the reaction will be increasingly important as its energy difference relative to **B**₁ is reduced, this result can, at least qualitatively, explain the zero asymmetric induction observed in the case of the 2,2-diphenyl derivative, and the reversal of the asymmetric induction observed in the case of the 2-methyl-2-phenyl TADDOLate. For these complexes, the energy difference between **B**₁ and **B**₂ is the lowest.

What is the origin for these energy differences? In the case of those TADDOLs bearing at least one phenyl group in the 2-position of the dioxolane ring, there is a π -stacking interaction with one of the 3,5-diphenyl groups (Figure 5). We propose that this interaction (present in both complexes **B**₁ and **B**₂) is responsible for the energy approach observed. It is important to note that in the case of the 2,2-diphenyl derivative, only one such interaction is possible (due to geometrical constraints), so that the energy gap is much more important in passing from none (2,2-dimethyl TADDOLate) to one (2-methyl-2-phenyl-TADDOLate) phenyl group in the 2-position, than in introducing a second (2,2-diphenyl TADDOLate) phenyl group.

To summarize, the results obtained show how apparently minor changes in the structure of the TADDOL produce small conformational changes in the dienophile-catalyst intermediates. These changes would modify the relative energies of the different transition states. However, these minor changes have a decisive influence on the direction and extension of the asymmetric induction, which is logical, given that changes smaller than 2 kcal mol⁻¹ in the relative stabilities of the different transition states would account for the changes in enantioselectivity experimentally observed.

Experimental

1. Synthesis of the TADDOLs

(4*R*,5*R*)-2-Phenyl-4,5-bis(methoxycarbonyl)-1,3-dioxolane

HC(OMe)₃ (3.6 ml, 35 mmol) was added at 0°C to a solution of benzaldehyde (2.9 ml, 28 mmol) in dry benzene (caution)(50 ml) containing a small amount of PTSA. The mixture was stirred for 2 h and then (*R,R*)-dimethyl tartrate (5 g, 28 mmol) was added. Distillation of the benzene/methanol azeotrope was then carried out at 60°C, and, after cooling, Et₃N was added to neutralize the acid. The solvent was evaporated under vacuum to give *ca.* 8 g of a reddish oil. The crude product was purified by column chromatography (SiO₂) using hexanes/EtOAc mixtures (1:0, 20:1, 15:1, 10:1) as the eluent to give a white solid (4.87 g, 65%). Mp 72–73°C. [α]_D²⁰ = –34 (*c* 0.035, CHCl₃). IR (KBr, cm⁻¹): 3010, 2958, 1756, 1598, 1441, 1237, 1181. ¹H NMR (CDCl₃, *d*): 3.82 (s, 3 H), 3.87 (s, 3 H), 4.85–5.0 (two doublets, 2 H, *J*=3.7 Hz), 6.14 (s, 1 H), 7.26–7.57 (m, 5 H). ¹³C NMR (CDCl₃, *d*): 52.7, 77.0, 77.3, 106.5, 127.1, 127.5, 128.2, 129.8, 135.2, 169.3, 169.9. Anal. Calcd. for C₁₃H₁₄O₆: C, 58.65; H, 5.26. Found: C, 59.3; H, 5.4.

(4*R*,5*R*)-2-Phenyl-2-methyl-4,5-bis(methoxycarbonyl)-1,3-dioxolane

This compound was obtained as described above starting from acetophenone (3.4 g, 28 mmol). Yellowish solid. Yield: 4.6 g, 58%. Mp 76–77°C (lit. Bp 140°C (0.15 mm Hg)).^{3d} [α]_D²⁰ = +40.06 (*c* 0.03, THF)(lit. [α]_D²⁰ = +11, *c* 2.6, CH₂Cl₂).^{3d} IR (KBr, cm⁻¹): 3057, 2914, 1757, 1443, 1379, 1243. ¹H NMR (CDCl₃, *d*): 1.77 (s, 3 H), 3.49 (s, 3 H), 3.82 (s, 3 H), 4.82 (d, 1 H, *J*=5.3 Hz), 4.86 (d, 1 H, *J*=5.3 Hz), 7.28–7.53 (m, 5 H). ¹³C NMR (CDCl₃, *d*): 28.2, 52.4, 52.9, 76.4, 77.3, 113.2, 125.5, 128.0, 128.4, 141.5, 169.3, 169.6. Anal. Calcd. for C₁₄H₁₆O₆: C, 60.4; H, 5.8. Found: C, 59.8; H, 5.9.

(4*R*,5*R*)-2,2-Diphenyl-4,5-bis(methoxycarbonyl)-1,3-dioxolane

Obtained using the procedure described by Iurre *et al.*¹⁴ Mp 80–81°C. [α]_D²⁰ = +54.2 (*c* 0.964, CHCl₃).

General procedure for the preparation of (4*R*,5*R*)- α, α', α' -tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs). Synthesis of 7

A solution of (3,5-dimethylphenyl)magnesium bromide, obtained from 3,5-dimethylbromobenzene (6.1 ml, 0.05 mol) and Mg (1.2 g, 0.05 mol) in dry THF (40 ml), was carefully added to the ketal prepared from benzaldehyde (1 g, 0.004 mol) in dry THF (20 ml). When addition was complete, the mixture was refluxed for 20 h. After cooling, a saturated solution of NH₄Cl was added to obtain a uniform solution of the salts formed. The resulting solution was extracted with EtOAc, and the organic phase was dried (MgSO₄) and the solvent was evaporated under vacuum. The oil obtained was purified by column chromatography (SiO₂) using hexanes/CH₂Cl₂ mixtures as the eluent to give a yellowish solid (1.36 g, 57%). Mp 74–76°C. [α]_D²⁰ = +90.25 (*c* 0.013, THF). IR (KBr, cm⁻¹): 3566, 2921, 1612, 1456, 1380, 872, 813, 756. ¹H NMR (CDCl₃, T=50°C, *d*): 1.85 (s, 9 H), 2.35 (m, 15 H), 4.66 (s, 1 H), 5.49 (s, 1 H), 5.72 (s, 1 H), 6.82–7.81 (m, 17H). ¹³C NMR (CDCl₃, T=50°C, *d*): 20.8, 21.2, 22.1, 26.9, 29.7, 79.7, 80.5, 81.8, 105.14, 126.1, 126.4, 127.3, 127.9, 128.2, 129.0, 132.7, 133.0, 133.2, 133.3, 136.6, 137.1, 138.8. Anal. Calcd. for C₄₃H₄₆O₄: C, 82.4; H, 7.4. Found: C, 81.9; H, 7.6.

Synthesis of 8

This compound was obtained as described above starting from the ketal prepared from acetophenone (1.4 g, 0.005 mol). White solid (0.9 g, 39%). Mp 113.8–114.2°C. [α]_D²⁰ = +54.03 (*c* 0.020, THF). IR (KBr, cm⁻¹): 3555, 2921, 1607, 1449, 1380, 1170, 1032, 814, 766. ¹H NMR (CDCl₃, T=50°C, *d*): 1.48 (s, 3 H), 1.74 (s, 6 H), 2.16 (s, 6 H), 2.27 (s, 6 H), 2.32 (s, 6 H), 5.43 (s, 1 H), 5.62 (d, 1 H, *J*=4.7 Hz), 6.66–7.81 (m, 17 H). ¹³C NMR (CDCl₃, T=50°C, *d*): 20.7, 20.8, 20.9, 21.3, 21.4, 22.5, 26.9, 29.6, 80.3, 82.4, 82.7, 112.8, 120.2, 124.6, 125.0, 125.7, 125.9, 126.1, 127.3, 127.7, 128.1, 128.7, 130.7,

132.3, 132.9, 133.0, 133.2, 136.4, 136.8, 138.7, 139.8, 141.2, 146.2. Anal. Calcd. for C₄₄H₄₈O₄: C, 82.4; H, 7.5. Found: C, 82.5; H, 7.9.

Synthesis of 9

This compound was obtained as described above starting from the ketal prepared from benzophenone (2.7 g, 0.08 mol). The crude product was crystallized from hexane/CH₂Cl₂ to give the pure product as a white solid (0.9 g, 39%). Mp 243–244°C. [α]_D²⁰ = +285.34 (c 0.006, THF). IR (KBr, cm⁻¹): 3474, 3081, 3027, 2958, 1615, 1493, 1459, 1379, 1108, 759. ¹H NMR (CDCl₃, T=50°C, d): 1.35 (s, 6 H), 1.93 (s, 6 H), 2.23 (s, 6 H), 2.28 (s, 6 H), 4.14 (s, 1 H), 4.30 (s, 1 H), 4.37 (s, 1 H), 6.75–7.85 (m, 22 H). ¹³C NMR (CDCl₃, T=50°C, d): 20.6, 20.7, 21.2, 70.6, 83.0, 125.2, 126.3, 126.9, 128.8, 133.0, 133.4, 134.2, 136.8, 137.6, 137.7, 138.4. Anal. Calcd. for C₄₉H₅₀O₄: C, 83.8; H, 7.1. Found: C, 83.4; H, 7.2.

2. General procedure for the Diels-Alder reactions

Under argon, a solution of TiCl₄ (1 ml of a 1 M solution in toluene) and 1 mmol of Ti(OⁱPr)₄ in 6 ml of dry toluene was stirred at -30°C for 30 min and then at room temperature for 20 min. After this time, a solution of 1 mmol of the corresponding TADDOL (5–9) in 20 ml of dry toluene and 3.56 g of molecular sieves (4 Å) were added, and the stirring maintained at 0°C for an additional 60 min. A solution of (*E*)-3-butenoyl-1,3-oxazolidin-2-one (1.395 g, 9 mmol) in 30 ml of dry toluene and 7.29 g (120 mmol) of freshly distilled cyclopentadiene were then added. The mixture was stirred at room temperature for 24 h. 200 ml of 1 N HCl was added and the mixture stirred for 15 min. The organic phase was separated, filtered through celite, and the celite washed with 200 ml of 1 N HCl and 200 ml of diethyl ether. The organic phase was again separated and dried over anhydrous sodium sulphate. The degree of conversion was determined by gas chromatography (FID, cross-linked methyl silicone column 25 m × 0.2 mm × 0.33 μm, helium as carrier gas, 18 p.s.i., oven temperature program: 190°C (1 min)—5°C/min—200°C (10 min), retention times: 1 3.6 min, 3+4 7.7 min). The solvent was removed under reduced pressure and the conversion and *endo/exo* selectivity determined by means of ¹H-NMR spectroscopy by integration of the signals of the methyl group (4 0.81 ppm, 3 1.10 ppm, 1 1.94 ppm). The *endo* cycloadducts were purified by column chromatography on silica gel using *n*-hexane:ethyl acetate (2:1) as the eluent, and the enantiomeric excess in the *endo* cycloadducts was determined by ¹H-NMR spectroscopy in the presence of Eu(hfc)₃ (L/S molar ratio=0.3) and confirmed by polarimetry. The absolute configuration was assigned by taking into account the specific rotation of the pure enantiomers^{4d} and the form of the split signals of the vinyl protons of the cycloadducts.¹⁰

3. Theoretical calculations

All the molecular mechanics and molecular dynamics studies were carried out with the MM2 force field,¹³ as implemented in the Chem3D Pro program.¹⁵ In the first step, molecular dynamics simulations were carried out on each structure, using a step interval of 2 fs, a target temperature of 373 K, and a heating rate of 1.595 kcal/atom/ps. These simulations were run for a total time of at least 100 ps, long enough for the purposes of heating and equilibration. Intermediate structures and energies were sampled at intervals of 100 fs, and those of lower energy were used as starting points for the molecular mechanics minimization. These minimizations were carried out up to a rms (root mean square) gradient of 0.1. For each complex, only the lowest energy structure was retained for discussion.

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