Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1829–1835

TETRAHEDRON: *ASYMMETRY*

A test for the coexistence of reactive intermediates with different molecular composition in chiral Lewis acid-catalysed reactions: the case of Ti-TADDOLate-catalysed Diels–Alder reactions

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Received 11 May 2001; accepted 11 June 2001

Abstract—The Diels–Alder reactions between cyclopentadiene **2** and (*E*)-3-butenoyl-1,3-oxazolidin-2-one **1** catalysed by several TADDOL-$TiCl_2$ complexes have been studied with different [dienophile]/[catalyst] ratios and different concentrations of reagents and catalyst. The enantioselectivity of some of the reactions depends on these factors, which indicates the participation of intermediate complexes with different catalyst and dienophile compositions (1:1, 1:2 and 2:1). The best results are obtained under conditions that favour the formation of an equimolecular intermediate, whereas the conditions favouring the formation of intermediates containing two molecules of dienophile and one of catalyst give rise to lower enantiomeric excesses (e.e.s). In one case the asymmetric induction was not dependent on the above factors, meaning that the effect described strongly depends on the structure of the chiral ligand. The results described show that this kind of mechanistic study complements those carried out on the influence of the enantiomeric composition of the chiral ligand on the enantioselectivity.

1. Introduction

An understanding of the mechanisms of enantioselective reactions promoted by chiral catalysts is necessary in order to design new catalysts that are able to improve catalytic activity and selectivity. In this regard, the determination of the structure of the reactive intermediates involving the catalyst is a key issue. A clear example of the importance of these studies is the autoinduction phenomenon, in which the cooperative interaction of the product with the catalyst gives rise to a more selective reaction.[1]

The study of the influence of the enantiomeric composition of the catalyst on the asymmetric induction of the reaction has become a very useful mechanistic tool to gain information regarding the molecular composition of these intermediates.[2] It is important to note that the presence of these non-linear effects (NLEs) is evidence for the existence of dimers (reactive or not) in which the chiral ligands have opposite absolute configuration. In fact, this behaviour can be observed even in cases in which dimers with chiral ligands of the same absolute configuration are not formed. In view of this, the presence of NLEs does not guarantee the formation of dimers when enantiomerically pure chiral auxiliaries are used, contrary to the frequently assumed. The existence of NLEs can be interpreted as proof of the participation of reactive dimers in the reaction. The influence of these intermediates on asymmetric catalysis can be affected by several factors, particularly the concentration of the catalyst, reagent and substrate,[3] which is a consequence of the effect of these parameters on the equilibrium between intermediates of different composition. Therefore, it seems logical to expect that, in reactions in which these kinds of intermediates participate, the reaction conditions may have an important influence on the asymmetric induction. For these reasons, the study of such an effect may constitute a mechanistic tool to show the participation of intermedi-

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0957-4166/01/$ - see front matter
PII: S0957-4166(01)00267-1

ates with different composition, even in cases where enantiomerically pure compounds are used. In this regard these studies are complementary to those of non-linear effects.

One of the reactions in which non-linear effects on asymmetric induction have been described[4–6] is the Diels–Alder cycloaddition between (*E*)-3-butenoyl-1,3-oxazolidin-2-one **1** and cyclopentadiene **2** (Scheme 1), catalysed by Ti-TADDOLates. Using stoichiometric amounts of TADDOL, Narasaka et al. have observed NLE, and they have also isolated a precipitate that contained Ti-TADDOLate dimers of different absolute configuration in a 1:1 ratio.[4] In spite of these results, most of the mechanistic studies have been oriented towards the determination of the structure of the most reactive monomeric equimolecular dienophile–catalyst intermediates.[7–9] However, other results indicate that the stereochemical course of the Ti-TADDOLate-promoted Diels–Alder reactions is not easy to predict. For instance, when a TADDOL bearing 3,5-dimethylphenyl groups as the aromatic substituents is immobilised on organic polymers, the flexible or rigid structure of the polymer influences the direction of the enantioselection.[10] These results show that the mobility of the organic polymeric support, which may influence the local concentration of catalytic sites, determines the structure of the reactive intermediates.

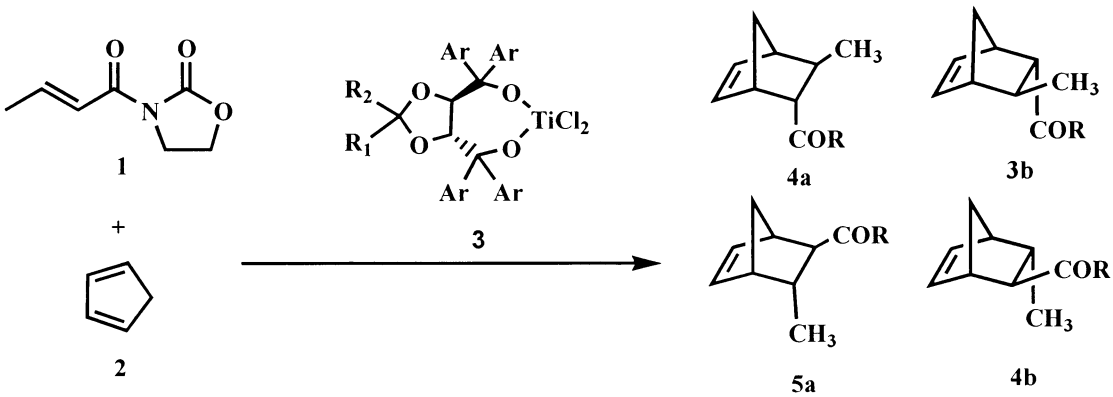
Herein, we present a study on the influence of several factors on the enantioselectivity of the Diels–Alder reaction of (*E*)-3-butenoyl-1,3-oxazolidin-2-one **1** and cyclopentadiene **2** catalysed by several Ti-TADDOLate complexes. The objective of this study is two-fold. Firstly, we aim to gain a deeper insight into the mechanism of this reaction. The second aim is to demonstrate that in reactions in which non-linear effects are observed the reaction conditions have a significant influence on the enantioselectivity, even when enantiomerically pure ligands are used, and that this influence gives complementary and useful information about the mechanism of the reaction.

2. Results and discussion

Initially, we studied the influence of several factors on the enantioselectivity of the aforementioned Diels–Alder reaction catalysed by the (4*R*,5*R*)-2-(3-benzyloxyphenyl)-α,α,α′,α′-tetra(3,5-dimethylphenyl)-1,3-dioxolane-4,5-dimethanol-$TiCl_2$ complex **3a** (Scheme 1), a combination of reaction and catalyst for which unexpected stereochemical behaviour has been described.[9,10]

This reaction was studied with different relative amounts of reagents and catalyst and with different concentrations of reactants. The results obtained are gathered in Table 1. It can be seen that the modifications considered do not have any great effect on either the chemical yield, which is very high in all cases, or on the *endo*/*exo* selectivity. With the exception of one particular reaction (entry 4), the *endo*/*exo* selectivity is within the narrow range 81:19–85:15. However, the asymmetric induction strongly depends on the factors described above. The results obtained clearly show that the main factor controlling the enantioselectivity is the [dienophile]/[catalyst] ratio. Indeed, for a very similar concentration of dienophile, the % e.e. changes from 3 to 50% as a function of this ratio (Table 1, entries 6, 13 and 18). The same is true for the reactions carried out with a similar concentration of catalyst but with different [dienophile]/[catalyst] ratios (Table 1, entries 1, 2, 6, 12 and 15) (Fig. 1). As can be seen, the best asymmetric inductions are obtained for a [dienophile]/[catalyst] ratio of about 10:1. The asymmetric induction decreases for the reactions carried out with a smaller excess of dienophile and is very low when the [dienophile]/[catalyst] ratio is 20:1.

These changes in the asymmetric induction clearly indicate that the mechanism changes as the [dienophile]/[catalyst] ratio changes, thus demonstrating the existence of different reactive intermediates with different dienophile/catalyst stoichiometries. In the reactions carried out with a large excess of dienophile, the formation of intermediates between two molecules of croto-



Scheme 1. **3a**: Ar = 3,5-dimethylphenyl, R_1 = H; R_2 = 3-benzyloxyphenyl; **3b**: Ar = 2-naphthyl, R_1 = H; R_2 = 3-benzyloxyphenyl; **3c**: Ar = phenyl, $R_1 = R_2 = CH_3$.

Table 1. Results obtained from the reaction of **1** and **2** catalysed by the TADDOL-Ti complex **3a** for different [dienophile]/[catalyst] ratios

Entry	[Catalyst][a]	[Dienophile]/[catalyst]	[Diene]/[dienophile]	Conv. (%)[b]	*endo* **3**/*exo* **4**[b]	% e.e. *endo*[c]
1	0.0100	1.1	21.4	99	81:19	7
2	0.0080	3.0	21.3	98	85:15	14
3	0.0430	5.0	24.4	99	84:16	14
4	0.0170	4.7	22.5	90	72:28	12
5	0.0104	5.7	22.3	99	81:19	27
6	0.0070	4.5	25.7	99	84:16	24
7	0.0032	5.0	24.3	99	81:19	28
8	0.0320	10.0	20.0	99	82:18	15
9	0.0120	10.0	21.4	100	84:16	15
10	0.0100	12.0	11.5	100	85:15	17
11	0.0080	10.0	9.6	100	82:18	41
12	0.0076	10.5	21.8	100	81:19	47
13	0.0040	10.0	22.0	99	82:18	50
14	0.0016	10.0	24.3	98	81:19	40
15	0.0076	19.7	21.8	98	83:17	3
16	0.0050	19.1	22.8	92	82:18	3
17	0.0043	19.8	22.0	93	82:18	3
18	0.0020	19.4	22.6	99	82:18	3

[a] Molar concentration.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$; **4a** is the major product.

nate and one molecule of catalyst can be envisaged. Given that the co-ordination of two molecules of dienophile prevents the formation of chelate complexes, the dienophile will have high conformational mobility, which justifies the low asymmetric induction. Intermediate **C** in Scheme 2 represents one of the possible structures for this reactive intermediate. In this general structure the carbonyl oxygen of the enoate moiety of one of the dienophile molecules is *trans* to one of the chlorine atoms. Given that O^2 is more basic than O^1, one intermediate in which both O^2 atoms co-ordinate

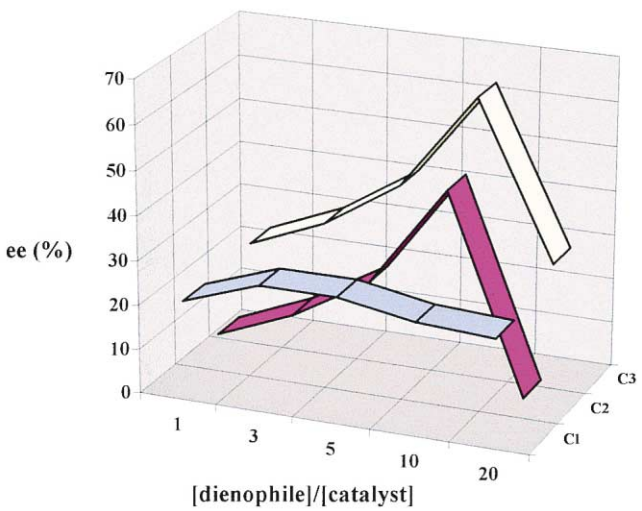
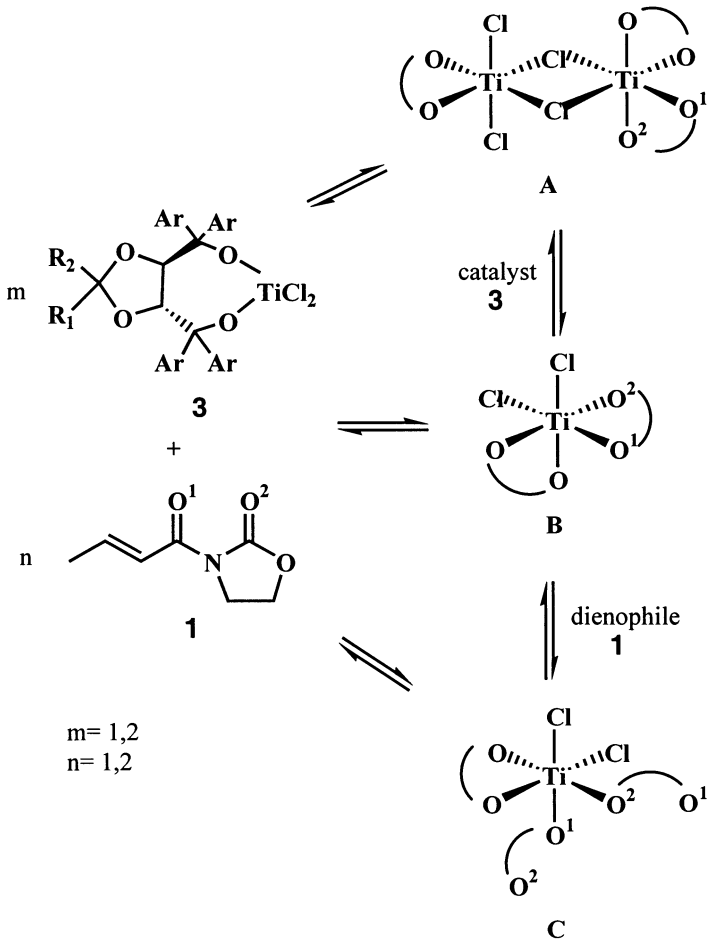


Figure 1. Variation of the % e.e. as a function of the [dienophile]/[catalyst] ratio, for a constant dienophile concentration, in the reactions catalysed by **3a**, **3b** and **3c**. **C1**: Ar = C_6H_5, R = R′ = Me; **C2**: Ar = 3,5-*di*Me-C_6H_4, R = H,R′ = BnO-C_6H_4; **C3**: Ar = 2-naphthyl, R = H; R′ = BnO-C_6H_4.

with the titanium atom will be more stable but, for the same reason, will also be less reactive. The modification of the asymmetric induction for the other [dienophile]/[catalyst] ratios indicates the participation of equimolecular intermediates, such as those normally proposed[5–7] (Scheme 2, intermediate **B**), and also of intermediates formed by two (or several) molecules of catalyst and one molecule of dienophile. Intermediate **A** in Scheme 2 represents one of the possible structures for these intermediates. In this general structure, which was proposed by Seebach et al.,[4] the carbonyl oxygen of the enoate moiety is *trans* with regard to one of the chlorine atoms. In intermediates **B** and **A**, the dienophile forms a chelate complex with the catalyst, a situation that is in agreement with the higher asymmetric induction.

In spite of its relative complexity, the above description is far too simplistic to represent the real picture. Indeed, the e.e. can be significantly changed on altering the concentration of the reagents or catalyst. Thus, for the reactions carried out with [dienophile]/[catalyst] ratios of 5:1 (Table 1, entries 3–7), 10:1 (Table 1, entries 8–14), and 20:1 (Table 1, entries 15–18), the enantioselectivity decreased with increasing concentration of dienophile and/or catalyst (Fig. 2). This is not the case for the reactions carried out with a high dienophile/catalyst ratio.

It can be demonstrated, for a given [dienophile]/[catalyst] ratio, that if the reaction were to take place through intermediates of the same molecularity, the enantioselectivity would not depend on the dienophile and catalyst concentrations regardless of the number of these intermediates.



Scheme 2.

Scheme 3 represents the reaction through two diastereomeric intermediates, each of which leads to the two enantiomeric products (P_R and P_S). The application of the steady-state approach clearly shows that the asymmetric induction does not depend on the concentrations of the dienophile and catalyst for given values of **m** and **n**.

$$\frac{d[I_1]}{dt} = k_1[T]^m[F]^n - k_{-1}[I_1] - (k_{2R}+k_{2S})[I_1][D] = 0$$

$$[I_1] = \frac{k_1[T]^m[F]^n}{k_{-1}+(k_{2R}+k_{2S})[D]} \quad \text{(steady state)}$$

and analogously for I_2:

$$[I_2] = \frac{k'_1[T]^m[F]^n}{k'_{-1}+(k'_{2R}+k'_{2S})[D]}$$

from which it can be deduced that (Eq. (1)):

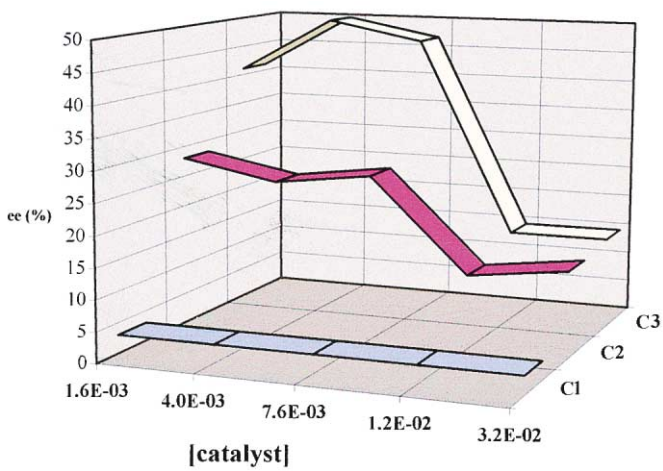
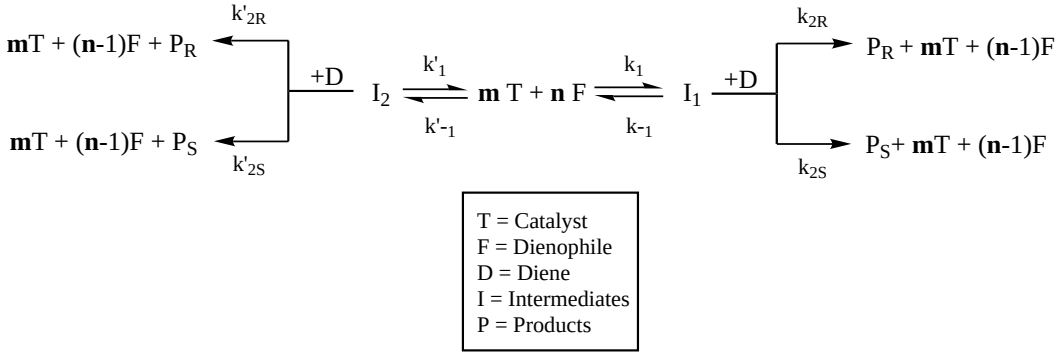


Figure 2. Influence of the dienophile and/or catalyst concentrations on the asymmetric induction, in the reaction catalysed by **3a**. **C1**: Ar = C_6H_5, R = R′ = Me; [dienophile]/[catalyst] = 20; **C2**: Ar = 3,5-*di*Me-C_6H_4, R = H; R′ = BnO-C_6H_4; [dienophile]/[catalyst] = 5; **C3**: Ar = 2-naphthyl, R = H; R′ = BnO-C_6H_4; [dienophile]/[catalyst] = 10.

$$\frac{[P_R]}{[P_S]} = \frac{k_{2R}[I_1]+k'_{2R}[I_2]}{k_{2S}[I_1]+k'_{2S}[I_2]} = \frac{k_{2R}k_1\{k'_{-1}+(k'_{2R}+k'_{2S})[D]\}+k'_{2R}k'_1\{k_{-1}+(k_{2R}+k_{2S})[D]\}}{k_{2S}k_1\{k'_{-1}+(k'_{2R}+k'_{2S})[D]\}+k'_{2S}k'_1\{k_{-1}+(k_{2R}+k_{2S})[D]\}} \quad (1)$$



Scheme 3.

This seems to be the case for the reaction carried out with a large excess of dienophile (Table 1, entries 15–17) but not for the other two [dienophile]/[catalyst] ratios investigated. In these cases the influence of the concentration of the dienophile and/or catalyst can only be explained by the coexistence of mechanisms involving intermediates with different dienophile/catalyst stoichiometries, i.e. with different values of **m** and **n**.

The equations obtained for the selectivity indicate that the only reagent whose concentration may have an influence on the enantioselectivity is the diene. However, a marked influence is not to be expected given Eq. (1) and the fact that the Diels–Alder reaction is normally the slower step. Thus, in this case a pre-equilibrium kinetic situation applies (Eq. (2)):

$$\frac{[P_R]}{[P_S]}=\frac{k_{2R}k_1k'_{-1}+k'_{2R}k'_1k_{-1}}{k_{2S}k_1k'_{-1}+k'_{2S}k'_1k_{-1}} \qquad (2)$$

We have studied the effect of the diene concentration in several reactions and the results obtained (Table 1, entries 9 and 10 and entries 11 and 12) show that neither the proportion nor the concentration of diene have a noticeable effect on the enantioselectivity. The small changes observed may be due to minor changes in the concentration of the catalyst.

Data obtained from NMR experiments indicate that aggregate formation, in benzene-d_6, starts to be important for catalyst concentrations above 10^{-2} M. The ^{1}H NMR spectrum of TADDOL **3a** is very complex because of the presence of at least three different conformers exchanging slowly in the NMR time scale.[5,9b] For example, a 0.006 M solution of **3a** in benzene-d_6 shows several signals for the methyl groups of the 3,5-dimethylphenyl subunits, including one that appears at ca. $\delta=0.6$, most likely because of the close proximity of one of the aryl groups located at C(2) or at the α positions. The formation of the Ti complex is accompanied by changes in the NMR spectra of the TADDOL, revealing that conformational changes occur upon complexation. In particular, changes in the shape and intensity of the signals for the methyl groups are observed, including an increase in the relative intensity of the shielded signal at $\delta=0.6$. Similar trends are also observed after addition of the (*E*)-3-butenoyl-1,3-oxazolidin-2-one **1** at a 10:1 [dienophile]/[catalyst] ratio. The situation was, however, different when similar experiments were carried out starting from a 0.012 M solution of **3a** in benzene-d_6. In this case, upon formation of the Ti complex the signals broaden and a clear decrease in intensity is observed for the TADDOL signals when compared to those of the ^{i}PrOH formed. Significantly, the signal at $\delta=0.6$ cannot be observed. A similar situation is obtained after the addition of dienophile **1** (10:1, **3a**:**1** ratio). The normal intensities of the TADDOL signals are recovered when the NMR experiments are carried out using long delay times ($d1\geq10$). The same trends are observed for higher concentrations. Thus, the formation of aggregates, giving low enantioselectivities, at concentrations above 10^{-2} M is consistent with the clear decrease in ee that can be observed in Table 1 when the concentration is increased (compare entries 3–4 and 8–10 with entries 6–7 and 11–13, respectively).

It must be noted that the intermediates described are only tentative structures and the participation of other intermediates of the same molecularity, including the cationic species proposed by Seebach et al.,[4] cannot be ruled out. However, intermediate **B** can be accepted as the most reactive of the possible intermediates that participate in the equimolecular route.[5,9]

In summary, the results obtained in the reactions promoted by **3a** clearly show that the Ti-TADDOLate-catalysed Diels–Alder reaction of (*E*)-3-butenoyl-1,3-oxazolidin-2-one **1** with cyclopentadiene **2** can take place through three different kinds of reactive intermediates: With a large excess of dienophile the formation of intermediates involving two molecules of dienophile and one of catalyst is favoured independently of the concentration and, under these conditions, the enantioselectivity obtained is very low. The results obtained indicate that the more selective reaction takes place through equimolecular dienophile/catalyst complexes. In fact, when a low [dienophile]/[catalyst] ratio is used, the formation of complexes between two molecules of catalyst and one of dienophile is favoured and, under those conditions, the enantioselectivity decreases. In these cases an increase in the concentration, which must favour aggregation phenomena, reduces the enantioselectivity.

In order to obtain further information we studied the same reaction catalysed by two different Ti-TADDOLates **3b** and **3c**. The results obtained in the reaction catalysed by **3b** (Scheme 1) are gathered in Table 2. It can be seen that the [dienophile]/[catalyst] relationship is again a factor determining the enantioselectivity (Fig. 1), which does not depend on the proportion of diene.

Table 3 gathers the results obtained in the same reaction catalysed by **3c** (Scheme 1). In this case, the enantioselectivity does not seem to be greatly affected by the [dienophile]/[catalyst] ratio (Fig. 1). As a consequence, another important point is that the behaviour described is not general and it is related to the structure of the TADDOL used as a chiral ligand. In particular, the important role played by π–π interactions between substituents at C(2) of the dioxolane ring and aryl groups at the α positions must be considered in order to understand the different behaviour of TADDOL **3c**, which does not contain aryl groups at the dioxolane moiety.[9b–c]

It is important to note that the study carried out is able to discriminate between different mechanistic behaviours.

The results obtained demonstrate that this kind of study is a useful mechanistic tool. Such studies complement those of correlation between the asymmetric induction and the enantiomeric composition of the catalyst. On the one hand, the absence of a linear correlation between the enantioselectivity of the reaction and the enantiomeric composition of the chiral ligand indicates the participation of intermediates in which molecules of catalyst with different molecularities are involved. On the other hand, the influence of both the [reagent]/[catalyst] molar relationship and the concentration indicates the presence of intermediates with different molar compositions, even in the case of using enantiomerically pure catalysts, showing not only the presence of catalyst dimers, but also their roles as catalytic active species.

3. Conclusions

The main conclusion that can be drawn from this study is that there is a clear influence of the [reagent]/[catalyst] molar relationship on the enantioselectivity and that this shows the existence of competitive mechanisms involving reactive intermediates with different compositions, which lead to different enantioselectivities. As an example, the results presented show that some Ti-TADDOLate-promoted Diels–Alder reactions can take place through intermediates with different dienophile/catalyst molar compositions, the best results being obtained through the participation of a 1:1 isolated dienophile/catalyst complex.

4. Experimental

The TADDOL (4*R*,5*R*)-2-(3-benzyloxyphenyl)-α,α,α',α'-tetra(3,5-dimethylphenyl)-1,3-dioxolane-4,5-dimethanol was prepared according to literature methods.[10a]

4.1. General procedure for the Diels–Alder reaction

A solution of TADDOL (0.125 mmol) and $TiCl_2(O^iPr)_2$ (0.4 mL, 0.25 M in dry toluene) in dry toluene contain-

Table 2. Results obtained from the reaction of **1** and **2** catalysed by the Ti-TADDOLate **3b**

Entry	[Catalyst][a]	[Dienophile]/[catalyst]	[Diene]/[dienophile]	Conv. (%)[b]	*endo* **3**/*exo* **4**[b]	% e.e. *endo*[c]
1	0.0160	1.2	21.6	92	76:24	22
2	0.0135	3.3	21.4	97	81:19	29
3	0.0130	5.7	20.0	94	81:19	40
4	0.0080	10.9	30.3	97	76:24	62
5	0.0040	23.0	38.3	98	81:19	27

[a] Molar concentration.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by ^{1}H NMR spectroscopy in the presence of $Eu(hfc)_3$; **4b** is the major product.

Table 3. Results obtained from the reaction of **1** and **2** catalysed by the Ti-TADDOLate **3c**

Entry	[Catalysyt][a]	[Dienophile]/[catalyst]	[Diene]/[dienophile]	Conv. (%)[b]	*endo* **3**/*exo* **4**[b]	% e.e. *endo*[c]
1	0.0122	1.1	20.0	100	85:15	21
2	0.0125	3.0	20.0	100	84:16	27
3	0.0125	5.8	20.0	100	84:16	27
4	0.0125	10.2	20.0	97	85:15	24
5	0.0125	20.6	20.0	98	84:16	23
6	0.0100	5	20.0	98	82:18	29
7	0.0050	10	20.0	98	84:16	27

[a] Molar concentration.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by ^{1}H NMR spectroscopy in the presence of $Eu(hfc)_3$; **4b** is the major product.

ing molecular sieves (0.5 g) was stirred at 0°C for 30 min. After this period, a solution of (*E*)-3-butenoyl-1,3-oxazolidin-2-one and cyclopentadiene in dry toluene was added and the reaction mixture was stirred for 24 h at 0°C. 1N HCl was added and the resulting mixture was extracted three times with Et_2O. The organic solution was dried and the solvent removed under reduced pressure. The conversion and the *endo*/*exo* selectivity were determined by ^{1}H NMR spectroscopy by integrating the signals corresponding to the methyl group (*exo* cycloadducts $\delta = 0.83$, *endo* cycloadducts $\delta = 1.10$, 3-crotonoyl-1,3-oxazolidin-2-one $\delta = 1.94$). The *endo* cycloadducts were purified by column chromatography on silica gel using hexanes/EtOAc (2:1) as the eluent. In each case the e.e. of the *endo* cycloadducts was determined by ^{1}H NMR spectroscopy in the presence of $Eu(hfc)_3$ (l/s molar ratio 0.3). The e.e. was confirmed by HPLC [Daicel OD, Pr^{i}OH/hexanes (3:97), flow rate 1 mL min^{-1}, 254 nm, $t_{r,exo}$: 26.94 min, $t_{r,endo(2S,3R)}$: 30.09 min, $t_{r,endo(2R,3S)}$: 32.69 min) and by polarimetry.

Acknowledgements

This work was made possible by the generous financial support of the Comisión Interministerial de Ciencia y Tecnología (Project MAT99-1176).

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