A Highly Diastereoselective and Enantioselective $Ti(OTos)_2$−TADDOLate-Catalyzed 1,3-Dipolar Cycloaddition Reaction of Alkenes with Nitrones

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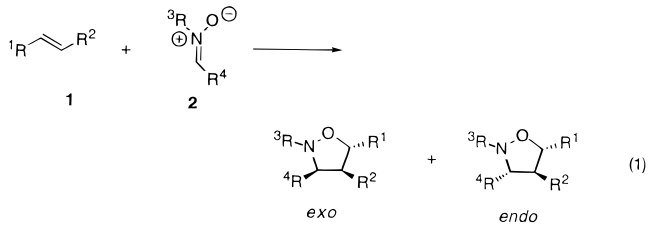
Abstract: A highly diastereo- and enantioselective metal-catalyzed 1,3-dipolar cycloaddition reaction of 3-((*E*)-2′-alkenoyl)-1,3-oxazolidin-2-ones with nitrones has been developed. A series of TiX_2−TADDOLate catalysts are investigated for their effects on the rate and diastereo- and enantioselectivities in the 1,3-dipolar cycloaddition reaction of alkenes with nitrones. The $TiCl_2$−TADDOLate catalysts are known to catalyze the 1,3-dipolar cycloaddition reaction of alkenes with nitrones, giving primarily the *exo*-isomer of the isoxazolidines with an optical purity of up to 60% ee. If the chloride atoms of the catalyst are substituted with more bulky ligands, such as the tosylato ligand, the *endo*-isomer is obtained with a diastereoselectivity of >90%. The synthetic aspects of this new method are presented by a series of reactions in which diastereoselectivities of >90% are generally obtained and, most remarkably, enantioselectivities of >90% are frequently obtained. The diastereo- and enantioselectivities of the reaction of the alkenes with nitrones can be accounted for by a transition state model directly derived from a $TiCl_2$−TADDOLate−3-cinnamoyloxazolidinone intermediate which has recently been isolated and characterized.

Introduction

Since the important contribution to the field of 1,3-dipolar cycloaddition reactions by Huisgen *et al.* in the 1960s,[1] the application of 1,3-dipoles has developed to be a cornerstone in organic synthesis.[2] One of today's challenges in this field is to control the regio-, diastereo- and enantioselectivities of these reactions. The 1,3-dipolar cycloaddition reaction of alkenes with nitrones is one of the fundamental reactions in this field, since the isoxazolidines formed are very usefull "building block" in organic synthesis.[2] The 1,3-dipolar cycloaddition reaction of alkenes **1** with nitrones **2** proceeds to give a pair of diastereomers of the isoxazolidine, *exo* and *endo*, respectively, each consisting of a pair of enantiomers which can contain up to three contiguous asymmetric centers (eq 1).



(1)

The diastereoselective synthesis of isoxazolidines by the application of optically active starting material is described in numerous reports.[3,4] Kanemasa *et al.*[5] and others[6] have described the application of metal complexes to control the diastereoselectivity of the reaction. However, only a few reports from outside this laboratory describe the use of a chiral metal catalyst to induce both diastereo- and enantioselectivities in the 1,3-dipolar cycloaddition reactions of alkenes with nitrones.[7]

In a previous paper we described the application of 10 mol% $TiCl_2$−TADDOLate catalyst, which strongly activates alkenes, such as **1a**, for a 1,3-dipolar cycloaddition reaction with a nitrone, such as **2a**, giving primarily the *exo*-isoxazolidine **3a** with an ee of 60% (eq 2).[8a] More recently it has been shown

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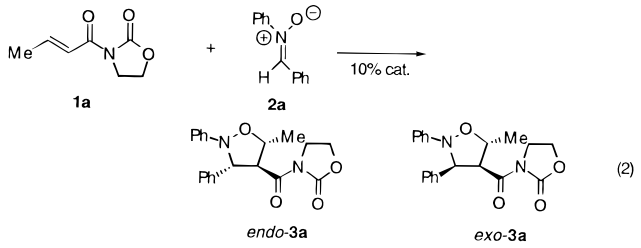
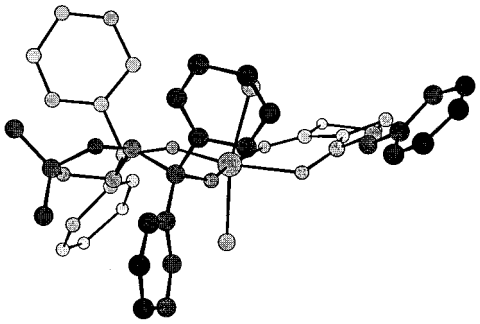
that Mg(II)−bisoxazoline complexes can selectively catalyze the formation of *endo*-**3a** with an optical purity of 79% ee for a similar type of substrate (eq 2).[8b]



1a **2a**

endo-**3a** *exo*-**3a** (2)

In a recent paper we described the isolation and characterization of complex **4** consisting of 3-cinnamoyloxazolidinone chelated to the asymmetric $TiCl_2$−TADDOLate catalyst.[9]



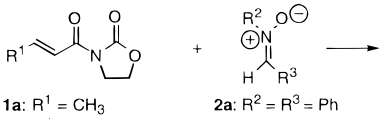
4

Complex **4** is proposed to be an intermediate, not only in the 1,3-dipolar cycloaddition reaction of alkenes with nitrones but probably also in the asymmetric $TiCl_2$−TADDOLate-catalyzed Diels−Alder reaction.[10] The structure of the reactive intermediate responsible for the stereochemical outcome of the $TiCl_2$−TADDOLate-catalyzed Diels−Alder reaction has recently been subject to some discussion.[10,11] DiMare *et al*. suggests, on the basis of NMR experiments, a structure with the four oxygen atoms attached to the titanium atom in the same plane, very similar to the isolated structure **4**, to be most abundant at −70 °C.[11] However, they and others propose a different structure, in which the two chloride atoms attached to the titanium atom are facing *cis* to each other, to be more reactive, and to be responsible for the reaction course.[10c−e,11] In a recent paper we suggested, on the basis of reactions of **4** with cyclopentadiene, and several other Diels−Alder reactions catalyzed by the $TiCl_2$−TADDOLate complex **4** and related complexes, that **4** can account for the diastereo- and enantioselectivities in the $TiCl_2$−TADDOLate-catalyzed Diels−Alder reaction.[12]

The structural assignment of the possible intermediate **4** in the $TiCl_2$−TADDOLate-catalyzed addition reactions is important, not only for an understanding of the mechanism of these reaction, but also for the development of new catalysts and for the improvement of the diastereo- and enantioselectivities. On the basis of the structural assignment of **4**, we have developed a new TiX_2−TADDOLate complex to be the first highly diastereo- and enantioselective catalyst for the 1,3-dipolar cycloaddition reaction of alkenes with nitrones.

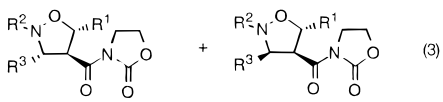
Results and Discussion

The reaction of alkene **1a** with nitrone **2a** (eq 3) in the presence of different TiX_2−TADDOLate catalysts **5a**−**g** has been performed in order to investigate the impact on the 1,3-dipolar cycloaddition reaction of changing the two chloride ligands of the $TiCl_2$−TADDOLate catalyst with other ligands.



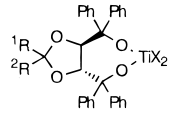
1a: $R^1 = CH_3$
1b: $R^1 = CH_2CH_2CH_3$

2a: $R^2 = R^3 = Ph$
2b: $R^2 = CH_2CH_2CH_3$, $R^3 = Ph$
2c: $R^2 = CH_2Ph$, $R^3 = Ph$
2d: $R^2 = Ph$, $R^3 = p$-tolyl



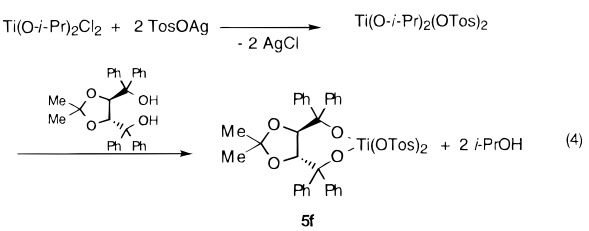
endo-**3** *exo*-**3** (3)

3a: $R^1 = CH_3$, $R^2 = Ph$, $R^3 = Ph$
3b: $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = Ph$
3c: $R^1 = CH_3$, $R^2 = CH_2Ph$, $R^3 = Ph$
3d: $R^1 = CH_3$, $R^2 = Ph$, $R^3 = p$-tolyl
3e: $R^1 = CH_2CH_2CH_3$, $R^2 = Ph$, $R^3 = Ph$
3f: $R^1 = CH_2CH_2CH_3$, $R^2 = CH_2CH_2CH_3$ $R^3 = Ph$
3g: $R^1 = CH_2CH_3CH_3$, $R^2 = CH_2Ph$, $R^3 = Ph$
3h: $R^1 = CH_2CH_3CH_3$, $R^2 = Ph$, $R^3 = p$-tolyl



5a: $R^1 = R^2 = Me$, X = Cl
5b: $R^1 = Me$, $R^2 = Ph$, X = Cl
5c: $R^1 = R^2 = Me$, X = O*i*-Pr
5d: $R^1 = R^2 = Me$, X = Br
5e: $R^1 = R^2 = Me$, X = OTf
5f: $R^1 = R^2 = Me$, X = OTos
5g: $R^1 = Me$, $R^2 = Ph$, X = OTos

Catalysts **5a**−**d** are synthesized according to the literature,[10a,d] whereas the new Ti(pseudo-halide)$_2$−TADDOLate catalysts **5e**−**g** have been synthesized as outlined for catalyst **5f** in eq 4. The most efficient method for the synthesis of **5e**−**g** is by treatment of $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ with silver tosylate (eq 4) or silver triflate, respectively, followed by filtration and addition of the TADDOL ligand.[13]



(4)

5f

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Table 1. Catalytic Effects of TiX_2−TADDOLate Complexes on the 1,3-Dipolar Cycloaddition Reaction of Alkene **1a** with Nitrone **2a**

entry	catalyst	amount (%)	conv[a] (time (h))	*endo*:*exo*[a]	ee (%), *endo*[b] (*exo*)[c]
1	**5a**	10	98 (48)	10:90	62 (60)
2	**5b**	100	93 (20)	12:88	− (22)
3	**5c**	100	0	−	−
4	**5d**	10	98 (20)	64:36	76 (64)
5	**5e**	10	73 (20)	79:21	0
6	**5f**	10	<10 (20)	−	−
7	**5f**	25	55 (48)	82:18	90
8	**5f**	50	99 (48)	>95:<5	93
9	**5g**	50	86 (48)	85:15	85

[a] Conversions and *endo*:*exo* ratios were determined by ^{1}H NMR spectroscopy of the crude product. [b] The enantiomeric excess of *endo*-**3a** was determined by HPLC (Daicel Chiralcel OD using hexane/*i*-PrOH, 90:10). [c] The ee was determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as the chiral shift reagent.

The results obtained in the reaction of **1a** with **2a** in the presence of the catalysts **5a**−**g** are presented in Table 1. The $TiCl_2$−TADDOLate catalyst **5a** has proved to be the most effective chloride-containing catalyst for the asymmetric 1,3-dipolar cycloaddition reaction of alkenes with nitrones. In the reaction of **1a** with **2a** an *endo:exo* ratio of 10:90 with an ee of 60% *exo*-**3a** is obtained, while *endo*-**3a** is formed in 62% ee (Table 1, entry 1).[8a] The $TiCl_2$−TADDOLate complex **5b** which has been applied with success in Diels−Alder reactions[10a,e] gives poor results in the 1,3-dipolar cycloaddition reaction (entry 2).[8a] The complex **5c** does not accelerate the reaction rate sufficiently, since no conversion is observed after 24 h (entry 3). This lack of catalytic effects of **5c** is probably caused by the increased electron donation of the alkoxide ligands attached to the titanium atom compared with chloride ligands, but steric effects might also affect the reaction rate. When catalyst **5d**, the bromide analog to **5a**, is applied as the catalyst at 10 mol % in the reaction of **1a** with **2a**, a faster reaction rate is observed. The diastereoselectivity now changes to give a slight excess of the *endo*-isomer, and the enantioselectivity is improved to 76% ee of *endo*-**3a**, while *exo*-**3a** is formed in 64% ee (entry 4). In order to increase the steric bulk at the titanium atom and still obtain a fair conversion, we focused on the application of pseudo-halides as ligands at the titanium atom. By the application of catalyst **5e** in the reaction, a slightly lower conversion is observed compared with the respective chloride catalysts (entry 5). The reaction now proceeds in an *endo*-selective manner, but the product is unfortunately racemic. Using 10 mol % tosylato derivative **5f** as catalyst for the 1,3-dipolar cycloaddition reaction of **1a** with **2a** leads to a low conversion (<10%) after 20 h (entry 6). By the application of 25 mol% catalyst **5f**, the reaction rate is still low; however, a conversion of 55% is observed after 2 days with the *endo*-isomer as the predominant product (entry 7). Most remarkably, the isolated *endo*-isomer proved to have an optical purity of 90% ee (entry 7). Enhancing the catalyst amount to 50 mol % gives a satisfactory conversion after 48 h, and the reaction proceeds now with an excellent *endo*-selectivity as the *endo*-**3a**:*exo*-**3a** ratio is >95:<5 (entry 8). The optical purity of the *endo*-isoxazolidine obtained in this reaction is 93% ee, and this is the highest observed so far for catalytic 1,3-dipolar cycloaddition reactions of alkenes with nitrones. This level of asymmetric induction is comparable to the best results obtained in the asymmetric $TiCl_2$−TADDOLate-catalyzed Diels−Alder reactions.[10] The catalyst **5g** is also promising; however, slightly lower selectivities are observed in the reactions of this catalyst, compared with the use of **5f** (entry 9).

Table 2. $Ti(OTos)_2$−TADDOLate-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions of Alkenes **1a**,**b** with Nitrones **2a**−**d** in the Presence of 50 mol % Catalyst

entry[a]	alkene	nitrone	product	yield[b] (%)	*endo*:*exo*[c]	ee (%), *endo*[d]
1	**1a**	**2a**	**3a**	61	>95:<5	93
2	**1a**	**2b**	**3b**	56	>95:<5	40
3	**1a**	**2c**	**3c**	54	>95:<5	51
4	**1a**	**2d**	**3d**	71	>95:<5	91
5	**1b**	**2a**	**3e**	63	>95:<5	93
6	**1b**	**2b**	**3f**	66	>95:<5	53
7	**1b**	**2c**	**3g**	58	>95:<5	56
8	**1b**	**2d**	**3h**	55	>95:<5	92

[a] The reactions were performed on a 0.5 mmol scale in toluene at 0 °C, employing 50 mol% catalyst. For further details see the Experimental Section. [b] Isolated yields. [c] The *endo:exo* ratio was determined by ^{1}H NMR spectroscopy. [d] The ee of the *endo*-isomer was determined by HPLC using a Daicel Chiralcel OD column.

The present results encouraged us to test catalyst **5f** in a series of reactions with other substrates on a 0.5 mmol scale. In the reaction of **1a** with **2a** identical diastereo- and enantioselectivities are observed as in the 0.1 mmol scale reaction (Table 2, entry 1), and it should also be noted that the enantioselectivity is not improved when the reaction is performed at −20 °C. In reactions of *N*-alkyl and *N*-benzyl nitrones **2b** and **2c** with **1a**, satisfying conversions and excellent diastereoselectivities are obtained (entries 2 and 3). However, for these substrates the enantioselectivities are only moderate (entries 2 and 3). In the reaction of **1a** with nitrone **2d** in which the α-*C*-substituent has been altered compared with **2a**, high diastereo- and enantioselectivities are observed in the presence of **5f** as the catalyst (entry 4). The same series of nitrones **2a**−**d** have also been employed in the reactions with 3-*N*-(2′-hexenoyl)-oxazolidinone (**1b**). In the four entries 5−8 a similar trend is observed as for the reactions with **1a**. In all entries fair yields and excellent diastereoselectivities (*endo:exo* = >95:<5) are obtained. The *N*-phenyl nitrones **2a** and **2d** react with the alkene **1b** in the presence of **5f** as the catalyst to give the isoxazolidines **3e** and **3h** with ee's of >90% (entries 5 and 8), whereas the less rigid nitrones **2b** and **2c** also give lower enantioselectivities in the reactions with **1b** (entries 6 and 7). The general features observed for these new $Ti(OTos)_2$−TADDOLate-catalyzed 1,3-dipolar cycloaddition reactions are thus (i) the reactions proceed generally with a diastereoelectivity of >90% to give the *endo*-isomer of the products **3a**−**h** and (ii) the enantioselectivity is not affected significantly by the substituent on the alkene, whereas it seems to be controlled by the substituent on the nitrone nitrogen atom, as the *N*-alkyl or *N*-benzyl nitrones give an ee of 40−56% and the more rigid *N*-phenyl nitrones give >90% ee.

The 1,3-dipolar cycloaddition reactions of **1a**,**b** with **2a**−**c** leading to the products **3a**−**c**,**e**−**g** have also been performed with **5a** as the catalyst, and the *endo*-isoxazolidines have the same absolute configurations as observed for the above reactions.[8a,14] In a recent work we have indirectly determined the absolute configuration of *endo*-**3a**.[8b] This was based on the structure of the (*S*)-valin-derived *endo*-isoxazolidine **6**, which has been determined by X-ray crystallography.[8b] In the present

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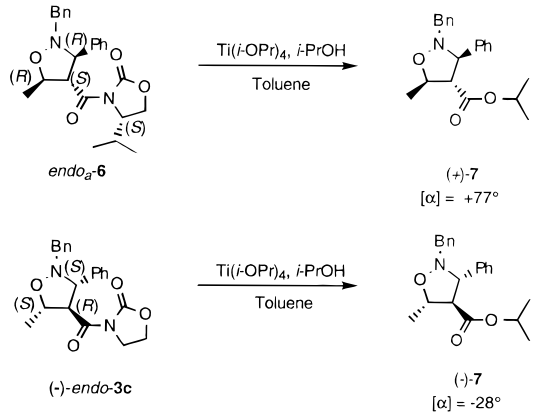
(14) The signs of the optical rotations in ref 8a in this work are the same; however, the relative optical rotations and ee's reported are in some entries not in full agreement. This is due to experimental error and the fact that the ee's reported in ref 8a are measured by ^{1}H NMR with Eu(hfc)$_3$ as the chiral shift reagent. We have observed deviations of up to 15% by this method.[21] The optical purities reported in this work are determined by HPLC with <2% deviations of the ee's.

Scheme 1



work we can directly determinate the absolute configuration of *endo*-**3c**. Upon treatment of isoxazolidine *endo*$_a$-**6** with Ti(O-*i*-Pr)$_4$ and *i*-PrOH, the isopropyl ester (+)-**7** is obtained with an optical rotation of +77°. The same procedure is performed with (−)-*endo*-**3c** (51% ee) to give (−)-**7** with an optical rotation of −28°. The reaction sequences are outlined in Scheme 1. The two isopropyl esters (+)-**7** and (−)-**7** are identical in all respects (NMR, MS, and TLC) except for their optical rotation. On the basis of the X-ray structure of **6**, we can now assign the three chiral centers in the isoxazolidine ring of *endo*-**3c** to be (3*S*,4*R*,5*S*).

On the basis of the experimental results presented in this paper and the X-ray structure of the intermediate **4**, a transtion state (TS) model for the reaction of alkenes with nitrones in the presence of the new Ti(OTos)$_2$−TADDOLate catalyst leading to the highly diastereo- and enantioselective reactions will now be proposed. For the reaction of **1a** with **2a** in the absence of a catalyst, the *exo*-TS energy is calculated to be 25 kcal·mol^{-1} lower in energy than the *endo*-TS, showing that the uncatalyzed reaction will lead to *exo*-**3a** in agreement with the experimental results.[8a,b] If one assumes that the intermediate in the Ti(OTos)$_2$−TADDOLate-catalyzed reaction, in which **1a** is coordinated to **5f**, has a geometry similar to **4**, we can now begin to understand the mechanism of the approach of the nitrone to the alkene coordinated to the catalyst.

For the TiCl$_2$−TADDOLate-catalyzed reaction no significant steric repulsion between the nitrone α-*C*-substituent and the axial chloride ligand for the *exo*-approach of the nitrone to the alkene coordinated to the TiCl$_2$−TADDOLate catalyst is apparent and the *exo*-product is primarily obtained in agreement with the experimental results. We have used the *Z*-geometry of the nitrone **2a** as this is the most stable isomer at room temperature.[15] The approach of the nitrone **2a** to **1a** coordinated to the TiCl$_2$−TADDOLate catalyst **5a** leading to *exo*-**3a** is outlined in Figure 1.

When the chloride ligands are substituted with bromides, the Ti−X bond length increases, as well as the atomic radius of the ligand, and the increased sterical hindrance leads to an increased appearance of the *endo*-isomer (Table 1, entry 4). As

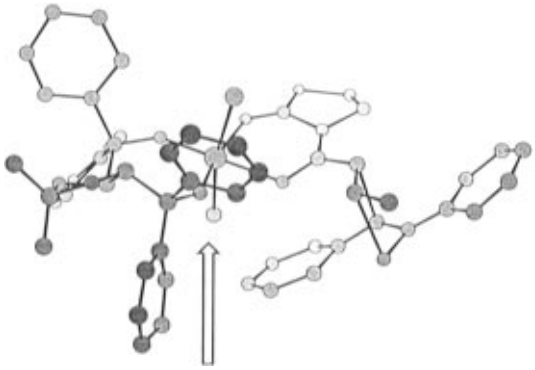


Figure 1. Proposed approach of nitrone **2a** to alkene **1a** coordinated to the TiCl$_2$−TADDOLate catalyst **5a**, leading to *exo*-**3a**. The arrow shows the axial chloride ligand which is exchanged with bulkier ligands.

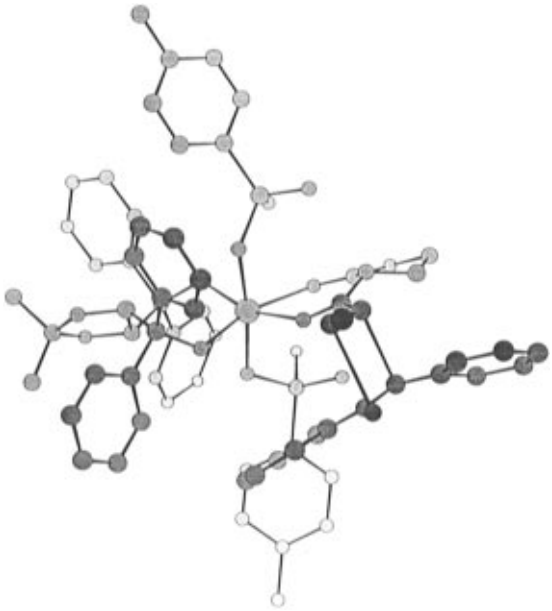


Figure 2. Proposed approach of nitrone **2a** to alkene **1a** coordinated to the Ti(OTos)$_2$−TADDOLate catalyst **5f**, leading to *endo*-**3a.**

the much more bulky ligands such as triflato and tosylato are introduced, the *exo*-approach (Figure 1; the arrow shows the axial chloride ligand which is exchanged with the bulky ligand) will indeed be unfavorable due to the repulsion between the axial ligand on the titanium atom and the nitrone α-*C*-substituent. However, no increased sterical hindrance is present for the *endo*-TS, which explains the high *endo*-selectivities observed for these catalysts. The proposed approach of nitrone **2a** to the alkene **1a** coordinated to the Ti(OTos)$_2$−TADDOLate catalyst **5f** leading to *endo*-**3a** is outlined in Figure 2.

On the basis of the approach of the nitrone to the alkene coordinated to Ti(OTos)$_2$−TADDOLate catalyst **5f**, it is thus obvious that the α-*C*-substituent of the nitrone is responsible for the *endo/exo*-selectivity obtained in reactions catalyzed by TiX$_2$−TADDOLate complexes. The absolute configurations of *endo*-**3a** and *endo*-**3c** are known, and both of the products arise from the *endo*-α-*Re*[16] approach of the nitrone to the alkene **2a** coordinated to the catalyst. We propose that this approach is similar for the reaction paths leading to the other *endo*-products **3b**,**d**−**h** obtained in these 1,3-dipolar cycloaddition reactions. It should be mentioned that for the TiCl$_2$−TADDOLate-

(15) It is generally accepted that acyclic nitrones obtain a stable *Z*-geometry at rt. (See, *e.g.*: DeShong, P.; Lander, S. W.; Leginus, J. M.; Dicken, M. C. In *Advances in Cycloaddition;* Curran, D. P., Ed.; Jai Press: London, 1988; Vol. 1, pp 87−128). In a recent publication (Bravo, P.; Bruché, L.; Farina, A.; Fronza, G.; Meille, S. V.; Merli, A. *Tetrahedron: Asymmetry* **1993**, *4*, 2131) it was claimed that the α-*C*,*N*-diphenyl nitrone **2a** exhibits a stable *E*-configuration at rt with reference to Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988 (ref 2b in this paper, pp 85); however, this postulate is not to be found there. Recently, Seerden *et al.*[7b] have described nitrone **2a** with an *E*-geometry referring to Bravo *et al. Tetrahedron: Asymmetry* **1993**, *4*, 2131. Thus, we assume that the proposed stable *E*-geometry of **2a** might be based on a misunderstanding.

(16) The approach of the (*Z*)-nitrone **2a** to the 3-(2′-(*E*)-alkenoyl)-1,3-oxazolidin-2-one **1a** is described by *endo*-α-*Re*, which means that the nitrone approaches the α,*β*-unsaturated carbonyl moiety of **1a** in the *endo*-fashion.[2a] The face of **1a** to which the nitrone approaches is the *Re*-face of the α-C atom in the α,*β*-unsaturated carbonyl moiety.

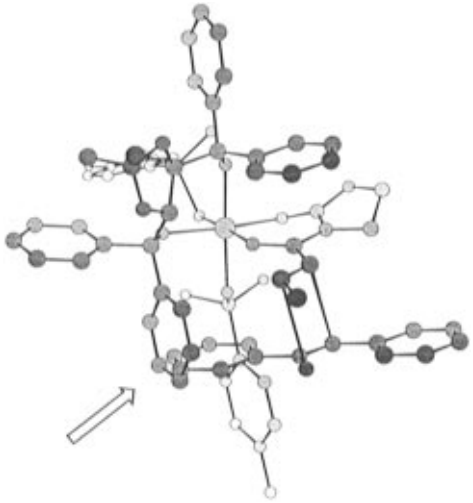


Figure 3. Approach of the nitrone **2a** to the alkene **1a** coordinated to the $Ti(OTos)_2$−TADDOLate catalyst having the two tosylato ligands placed in a *cis*-orientation at the titanium center. The steric repulsion between the *N*-phenyl substituent and the phenyl substituent of the TADDOL ligand is indicated by the arrow.

catalyzed Diels−Alder reaction the *endo*-α-*Re*-attack on **2a** chelated to the catalyst is also favored.[9,10,12] The *endo*-α-*Re*-attack outlined in Figure 2 can be accounted for by the following three points: (i) the axial phenyl group of the TADDOL ligand is shielding the upper side (α-*Si*) of the alkene. (ii) The alkene part is probably slightly tilted out of the plane, consisting of the four oxygen atoms attached to the titanium atom, leading to increased shielding of the α-*Si*-face of the alkene. (iii) The two tosylato ligands on the titanium atom facing *trans* to each other might be tilted toward the alkene, the upper ligand group more than the lower. Arguments i and ii are based on the X-ray structure of **4**.[9] For the large tosyl ligand the upper might be pushed further toward the alkene caused by steric repulsion with the axial phenyl substituent of the TADDOL ligand, giving rise to the excellent ee's observed with the present catalyst.

The *N*-substituent of the nitrone proved to be of major importance for the enantioselectivity of the reaction. Inspection of the model in Figure 2 reveals that an α-*Si*-approach of the rigid *N*-phenyl nitrone gives rise to major steric repulsion with the TADDOL-phenyl substituent, whereas reduced steric repulsion is present for the less rigid *N*-alkyl and *N*-benzyl nitrones in the α-*Si*-attack. This explains why much higher enantioselectivities are obtained with nitrones **2a** and **2d**, compared with **2b** and **2c**. By the present model for the TS of this new metal-catalyzed asymmetric 1,3-dipolar cycloaddition reaction, one can account both for the *endo*-α-*Re*-approach of the nitrone to the alkene and for the deviations in enantioselectivity.

DiMare *et al.* has proposed another structure with the two halides facing *cis* to each other to be the most reactive intermediate in the $TiCl_2$−TADDOLate-catalyzed Diels−Alder reaction.[11] Application of their alternative model for the present 1,3-dipolar cycloaddition reaction reveals that for this structure the α-*Re*-attack of the nitrone on the alkene will also be favored. In their model the phenyl group shielding the upper α-*Si*-side of the alkene is centered just above the double bond.

The approach of the nitrone **2a** to the alkene **1a** coordinated to the $Ti(OTos)_2$−TADDOLate catalyst having the tosylato ligands in a *cis*-orientation at the titanium atom is presented in Figure 3. By this approach of the nitrone, a significant steric repulsion of the *N*-phenyl substituent of the nitrone and the phenyl substituent at the TADDOL ligand is observed as indicated by the arrow in Figure 3. It should be noted that the bond lengths between the reacting atoms (2.5 Å) are similar to those used in Figures 2 and 3. If the less rigid *N*-alkyl and *N*-benzyl nitrones were going to approach the alkene coordinated to the $Ti(OTos)_2$−TADDOLate catalyst having the tosylato ligands in a *cis*-orientation at the titanium atom, the same high ee as for the *N*-phenyl nitrones should be observed, since the phenyl group shields the upper α-*Si*-side of the alkene and the approach of the nitrone should exclusively be expected to take place at the α-*Re*-face of the alkene. But the present results show a relatively large decrease in ee when the less rigid *N*-alkyl and *N*-benzyl nitrones are applied, which also seems to disfavor an intermediate with the two halogen/pseudo-halolgen ligands attached to the titanium atom in a *cis*-fashion.

We thus propose that the reaction path for the 1,3-dipolar cycloaddition reaction of nitrones with alkenes catalyzed by these new $Ti(OTos)_2$−TADDOLate complexes takes place via an intermediate where the two tosylato ligands at the titanium atom of $Ti(OTos)_2$−TADDOLate catalyst are placed *trans* at the titanium atom as proposed in Figure 2.

Conclusion

A highly diastereo- and enantioselective $Ti(OTos)_2$−TADDOLate-catalyzed 1,3-dipolar cycloaddition reaction of alkenes with nitrones is developed. It is shown that the tosylato ligand at the titanium atom is of utmost importance for both the diastereo- and enantioselectivities. The $Ti(OTos)_2$−TADDOLate-catalyzed reaction of *N*-phenyl nitrones with alkenes proceeds to give the *endo*-isoxazolidines with a diastereoselectivity of >90% and very high enantioselectivities in the range of 91−93%. Reactions of *N*-alkyl and *N*-benzyl nitrones with different alkenes give the *endo*-isoxazolidines with the same high diastereoselectivity (>90%), but the ee is in the range of 40−56%. On the basis of the absolute configuration of the product an *endo*-α-*Re*-attack of the nitrone on the alkene coordinated to the $Ti(OTos)_2$−TADDOLate catalyst, in which the tosylato ligands are placed *trans* at the titanium atom, is proposed.

Experimental Section

General Methods. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 50 MHz, respectively. Chemical shifts for ^{1}H NMR and ^{13}C NMR are reported in parts per million downfield from tetramethylsilane (TMS). HPLC analysis was performed using a 4.6 mm × 25 cm Daicel Chiralcel OD column. Mass spectra were recorded at 70 eV with a direct inlet. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Preparative thin layer chromatography (TLC) was performed on 200 × 200 × 0.8 mm silica gel ($PF_{254+366}$ Art. 7748, Merck) on glass plates. Solvents were dried using standard procedures. The 4 Å powdered molecular sieves were activated by heating to 250 °C for 3 h in high vacuum. All glass equipment and syringes were dried in an oven at 130 °C prior to use.

Materials. The starting materials 3-((*E*)-2′-butenoyl)-1,3-oxazolidin-2-one (**1a**),[17] 3-((*E*)-2′-hexenoyl)-1,3-oxazolidin-2-one (**1b**),[17] benzylidenephenylamine *N*-oxide (**2a**),[18] benzylidenepropylamine *N*-oxide (**2b**),[19] benzylbenzylideneamine *N*-oxide (**2c**),[20] (4-methylbenzylidene)-phenylamine *N*-oxide (**2d**),[18] and (2*R*,3*R*)-2,3-*O*-(2-propylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrols[10d] were synthesized according to the literature. Silver *p*-toluenesulfonate was received from Fluka. Pow-

(17) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
(18) Wheeler, O. H.; Gore, P. H. *J. Am. Chem. Soc.* **1956**, *78*, 3363.
(19) Christensen, D.; Jørgensen, K. A.; Hazell, R. G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2391.
(20) Beckett, A. H.; Coutts, R. T.; Ogunbona, F. A. *Tetrahedron* **1973**, *29*, 4189.
(21) Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595.

dered molecular sieves (4 Å) were received from Aldrich. Millex filter units, 45 μm pore size, were received from Millipore.

Preparation of the Ti(OTos)$_2$−(*R,R*)-TADDOLate catalyst 5f. Silver *p*-toluene sulfonate (0.837 g, 3 mmol) is placed in a 25 mL flask with a magnetic stirring bar under N_2. A solution of Ti(O-*i*-Pr)$_2$Cl$_2$ (0.1 M, 1mmol) in toluene (10 mL) is added, and the suspension is stirred for 24 h at room temperature (rt). The suspension is transferred to a syringe and filtered through a Millex filter unit into a 25 mL flask containing the appropriate TADDOL ligand (0.513 g, 1.1 mmol), a magnetic stirring bar, and N_2. The 0.1 M catalyst solution is stirred 0.5 h prior to use.

General procedure for the Asymmetric Ti(OTos)$_2$-TADDOLate-Catalyzed 1,3-Dipolar Cycloaddition Reaction. To a 10 mL reaction flask containing a magnetic stirring bar, toluene (5 mL), and 4 Å powdered molecular sieves (250 mg) are added the alkene **1a** (0.5 mmol) and the nitrone **2a** (0.6 mmol). The flask is closed with a septum and cooled to 0 °C on an ice bath (occasionally to −20 °C on an ice/NaCl bath). After stirring for 15 min the above described catalyst solution of **5f** (2.5 mL, 0.25 mmol) is added through the septum via syringe. The reaction mixture is allowed to warm to rt over 24 h, and after a total reaction time of 48 h, 10 mL of 5% MeOH in CH_2Cl_2 is added to the reaction mixture. After stirring for 10 min, the mixture is filtered through a 20 mm layer of silica gel. The silica gel layer is washed with another 10 mL of 5% MeOH in CH_2Cl_2 and the solvent evaporated *in vacuo*. The crude product is purified by preparative TLC (silica gel, Et_2O/petroleum ether, 2:1, or MeOH/CH_2Cl_2, 1:99).

The ^{1}H NMR, ^{13}C NMR, and mass spectra of compounds **3a**−**c** and **3e**−**g** have been reported previously.[8a,b]

(−)-(3′*S*,4′*R*,5′*S*)-3-[(5′-Methyl-2′-*N*,3′-diphenylisoxazolidin-4′-yl)-carbonyl]-1,3-oxazolidin-2-one (*endo*-3a). Yield: 61%. $[\alpha]_D$: −15.5° (*c* =1.0, $CHCl_3$). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 9:1, flow rate 1.0 mL/min.): t_R = 42 min (minor), t_R = 60 min (major). Ee: 93%.

(−)-(3′*S*,4′*R*,5′*S*)-3-[(5′-Methyl-3′-phenyl-2′-*N*-propylisoxazolidin-4′-yl)carbonyl]-1,3-oxazolidin-2-one (*endo*-3b). Yield: 56%. $[\alpha]_D$: −0.8° (*c* =1.0, $CHCl_3$). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 9:1, flow rate 1.0 mL/min): t_R = 15 min (major), t_R = 22 min (minor). Ee: 40%.

(+)-(3′*S*,4′*R*,5′*S*)-3-[(2′-*N*-Benzyl-5′-methyl-3′-phenylisoxazolidin-4′-yl)carbonyl]-1,3-oxazolidin-2-one (*endo*-3c). Yield: 54%. $[\alpha]_D$: +5.5° (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 9:1, flow rate 1.0 mL/min): t_R = 28 min (major), t_R = 47 min (minor). Ee: 51%.

(−)-(3′*S*,4′*R*,5′*S*)-3-[(5′-Methyl-3′-(4″-methylphenyl)-2′-*N*-phenyl-isoxazolidin-4′-yl]carbonyl]-1,3-oxazolidin-2-one (*endo*-3d). Yield: 71%. $[\alpha]_D$: = −21.7° (*c* =1.0, $CHCl_3$). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 9:1, flow rate 1.0 mL/min): t_R= 33 min (minor), t_R = 55 min (major). Ee: 91%. ^{1}H NMR ($CDCl_3$): δ 1.56 (d, J = 6.0 Hz, 3H), 2.35 (s, 3H), 3.94 (m, 2H), 4.28 (m, 2H), 4.46 (m, 1H), 4.81 (dd, J = 6.7, 7.7 Hz, 1H), 5.16 (d, J = 7.2 Hz, 1H), 6.96 (m, 3H), 7.22 (m, 4H), 7.37 (d, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 17.6, 21.0, 42.8, 61.7, 62.3, 74.2, 79.3, 114.5, 121.5, 126.4, 128.6, 129.4, 137.4, 137.6, 151.3, 152.7, 170.6. MS: *m/z* = 366 (M^+).

(−)-(3′*S*,4′*R*,5′*S*)-3-[(2′-*N*,3′-Diphenyl-5′-propylisoxazolidin-4′-yl)-carbonyl]-1,3-oxazolidin-2-one (*endo*-3e). Yield: 63%. $[\alpha]_D$ = −31° (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 9:1, flow rate = 1.0 mL min): t_R= 21 min. (minor), t_R = 27 min. (major). Ee = 93%.

(−)-(3′*S*,4′*R*,5′*S*)-3-[(2′-*N*,5′-Dipropyl-3′-phenylisoxazolidin-4′-yl)-carbonyl]-1,3-oxazolidin-2-one (*endo*-3f). Yield: 66%. $[\alpha]_D$: −22.3° (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 9:1, flow rate 1.0 mL/min): t_R = 10 min (major), t_R = 15 min (minor). Ee: 53%.

(−)-(3′*S*,4′*R*,5′*S*)-3-[(2′-*N*-Benzyl-3′-phenyl-5′-propylisoxazolidin-4′-yl)carbonyl]-1,3-oxazolidin-2-one (*endo*-3g). Yield: 58%. $[\alpha]_D$: −7.8° (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 9:1, flow rate 1.0 mL/min): t_R = 18 min (major), t_R = 36 min (minor). Ee: 56%.

(−)-(3′*S*,4′*R*,5′*S*)-3-[(3′-(4″-Methylphenyl)-2′-*N*-phenyl-5′-propyl-isoxazolidin-4′-yl]carbonyl]-1,3-oxazolidin-2-one (*endo*-3h). Yield: 55%. $[\alpha]_D$: = −34.1° (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 9:1, flow rate 1.0 mL/min): t_R = 19 min (minor), t_R = 27 min (major). Ee: 92%. ^{1}H NMR ($CDCl_3$): δ 1.01 (t, J = 7.1 Hz, 3H), 1.50 (m, 1H), 1.72 (m, 2H), 1.99 (m, 1H), 2.35 (s, 3H), 3.93 (m, 2H), 4.25−4.39 (m, 3H), 4.87 (t, J = 7.1 Hz, 1H), 5.11 (d, J = 7.2 Hz, 1H), 6.96 (m, 3H), 7.22 (m, 4H), 7.37 (d, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 13.8, 19.6, 20.9, 34.1, 42.8, 61.1, 61.6, 74.3, 83.2, 114.4, 121.4, 126.3, 128.6, 129.4, 137.4, 137.5, 151.4, 152.6, 170.9. MS: *m/z* = 394 (M^+).

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of (−)-*endo*-**3d**, (−)-*endo*-**3h**, (+)-**7**, and (−)-**7** (4 pages). Spectra not found in the present supporting information are found in ref 8. This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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