Control of Diastereo- and Enantioselectivity in Metal-Catalyzed 1,3-Dipolar Cycloaddition Reactions of Nitrones with Alkenes. Experimental and Theoretical Investigations

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Received July 5, 1995[⊗]

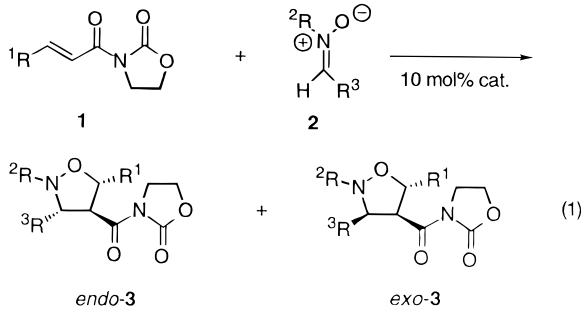
The scopes and limitations of the catalytic effects of achiral and chiral Mg(II) and Cu(II) complexes on the stereochemistry of the 1,3-dipolar cycloaddition reaction of nitrones with alkenes have been investigated. A remarkably high degree of *endo*-selectivity (*endo*/*exo* > 20) is induced in the 1,3-dipolar cycloaddition reaction by the presence of a catalytic amount of, especially, a Mg(II)−phenanthroline complex. The diastereochemical assignment of the product is confirmed by an X-ray crystallographic determination of the structure of the *exo*-isoxazolidine. By the reaction of an alkene bearing a chiral auxiliary, with different nitrones and a catalytic amount of the Mg(II)−phenanthroline complex, one of four possible diastereomers of the isoxazolidines is exclusively formed. The absolute stereochemistry of this product is also assigned by an X-ray crystallographic investigation. The presence of a catalytic amount of a chiral Mg(II)−bisoxazoline complex in the 1,3-dipolar cycloaddition reaction leads to high *endo*-selectivity and occasionally with an ee > 80%. The reaction mechanism of the Mg(II)-catalyzed reaction is discussed on the basis of the experimental results and semiempirical quantum chemical calculations. The calculations are used to account for the catalytic effect of the Mg(II)−ligand complexes and to determine transition state energies for both the uncatalyzed and Mg(II)−ligand-catalyzed reactions.

Introduction

The 1,3-dipolar cycloaddition reaction between an alkene and a nitrone is an effective procedure for the introduction of new chiral centers attached to heteroatoms.[1] Due to the concerted nature and the often high degree of regioselectivity of the 1,3-dipolar cycloaddition reaction, only a limited number of product isomers are formed,[1] and attempts to control the selectivity with respect to the four possible stereoisomers formed by this reaction have attracted still more attention during the last decade.[2] To some extent, the stereochemical course of the reaction can be controlled applying chiral starting material.[2] However, only a few reports describe the application of metal catalysts to control the stereochemical outcome of the 1,3-dipolar cycloaddition reaction of alkenes with nitrones,[3] and to our knowledge only one previous paper from another laboratory describes the application of a catalytic amount of a chiral catalyst for the introduction of enantioselectivity in the reaction.[4]

In a recent paper, we described the first example of a transition metal-catalyzed asymmetric 1,3-dipolar cycloaddition reaction between an alkene and a nitrone.[5] This reaction was developed employing a chiral titanium catalyst generated in situ from Ti(*i*-PrO)$_2$Cl$_2$ and chiral diols.[5] Diastereofacial discrimination in favor of the *exo* isomer was achieved, and isoxazolidines with an ee up to 62% were obtained from this reaction. We also succeeded in the isolation and characterization by X-ray crystallography of a chiral titanium-catalyst−substrate complex[6a] which has been proposed as the intermediate in the 1,3-dipolar cycloaddition reaction and the metal-catalyzed asymmetric Diels-Alder reaction.[6b]

In this paper, we present the metal−ligand-induced control of diastereo- and enantioselectivity in the 1,3-dipolar cycloaddition reaction of alkenes **1** with nitrones **2** (reaction 1). It will be shown that one can favor the



1 **2**

endo-**3** *exo*-**3** (1)

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1995.

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Table 1. Influence of Different Metal−Ligand Complexes on the Diastereoselectivity of the Reaction of 3-Crotonoyl-1,3-oxazolidin-2-one (1a) with Benzylidenephenylamine *N*-Oxide (2a)[a]

entry	catalyst[b]	conversion[c] (%)	*endo*-**3a**:*exo*-**3a**
1		<2	
2	Ti(*i*-OPr)$_2$Cl$_2$	68	13:87
3	**7**	91	5:95
4	**5a**	63	81:19
5	**5b**[d]	<2	
6	MgI$_2$−I$_2$	>90	15:85
7	**6a**	>90	>95:<5
8	**6b**[d]	>90	>95:<5

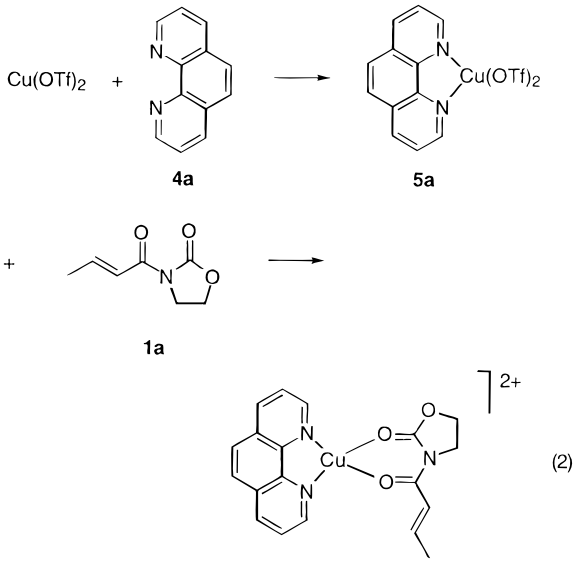
[a] Reaction conditions: **1a** (0.1 mmol) and **2a** (0.125 mmol) were mixed in CH_2Cl_2 (2 mL) with 50 mg of 4 Å powdered molecular sieves. After the mixture was stirred for 15 min, the catalyst was added. For further details see the Experimental Section. [b] The catalysts were applied in 10 mol %. [c] Reaction time 20 h. [d] 2,9-Dimethylphenanthroline is used as ligand instead of **4a**.

formation of the *endo*-isomer **3**. Furthermore, it will be presented that the reaction between alkenes having a chiral auxiliary and nitrones, in the presence of a catalytic amount of Mg(II)−phenanthroline, leads to a double diastereoselective 1,3-dipolar cycloaddition reaction giving exclusively one stereoisomer. The *endo*-selective reactions can also be performed enantioselectively with a high ee by exchanging the phenanthroline ligand with chiral bisoxazoline ligands. The absolute configuration of the products from the 1,3-dipolar cycloaddition reactions are assigned by X-ray structural determinations. The mechanism for the *endo*- and enantioselectivity in the 1,3-dipolar cycloaddition reaction of alkenes with nitrones is investigated using semiempirical calculations applying the MOPAC-PM3 method.[7]

Results and Discussion

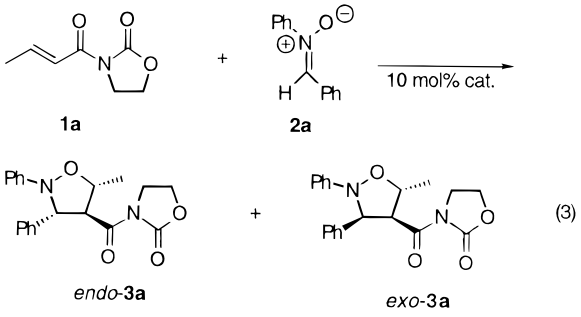
I. Synthetic Aspects. The present new catalytic approach for the 1,3-dipolar cycloaddition reaction between alkenes **1** and nitrones **2** is made possible by changing the coordination geometry at the metal center of the catalyst in the reaction. The activation of **1** at the metal in the titanium-catalyzed 1,3-dipolar cycloaddition reactions lead to an octahedral complex.[6] However, choosing metal complexes such as Mg(II) or Cu(II) complexes, which have been applied as catalysts in asymmetric reactions such as the Diels−Alder reaction,[8,9] could in combination with **1** and a ligand form a complex having another geometry at the metal center, leading to a different reaction course for the 1,3-dipolar cycloaddition reaction of alkenes with nitrones compared with the titanium-catalyzed reaction.

The catalytic properties of Mg(II) and Cu(II) coordinated to an achiral ligand such as phenanthroline **4a**, and Ti(IV)−ligand complexes have been studied for the reaction of 3-crotonoyl-1,3-oxazolidin-2-one (**1a**) with benzylidenephenylamine *N*-oxide (**2a**) in order to investigate the influence of the catalyst on the diastereoselectivity. The Cu(II) complex **5a** is synthesized by mixing **4a** with Cu(OTf)$_2$ in dry CH_2Cl_2 and stirring for 5 h before use. When **1a** chelates to **5a**, the two triflates dissociate from the metal to give a double cationic complex which activates the alkene part of **1a** for the 1,3-dipolar cycloaddition reaction (reaction 2).



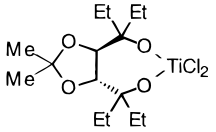
An analogous Mg(II)−phenanthroline complex **6a** is prepared by mixing an excess of Mg with I_2 in Et_2O under N_2 with the formation of MgI_2. After filtration and evaporation of the solvent, MgI_2 is dissolved in CH_2Cl_2 and **4a** dissolved in CH_2Cl_2 is added and the resulting suspension is stirred for 2 h. One equiv of I_2 is added, and after being stirred for 2 h the catalyst is ready for use.

These catalysts are applied in the reaction between 3-crotonoyl-1,3-oxazolidin-2-one (**1a**) and benzylidenephenylamine *N*-oxide (**2a**) (reaction 3).



The results for the catalytic properties and influence of the different metal complexes on the diastereoselectivity in reaction 3 are presented in Table 1.

Without the presence of a catalyst, practically no conversion takes place after 20 h (Table 1, entry 1). By using Ti(*i*-OPr)$_2$Cl$_2$ as the catalyst, *exo*-**3a** is primarily formed (Table 1, entry 2), and with the chiral dichlorotitanium alkoxide **7** an *endo*-**3a**:*exo*-**3a** ratio as high as 5:95 is obtained (Table 1, entry 3).[5] Both reactions proceed with a relatively high conversion.



Changing the catalyst from the Ti(IV) complexes to the Cu(II) and the Mg(II) complexes changes the diastereo-

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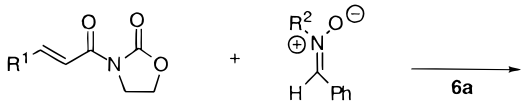
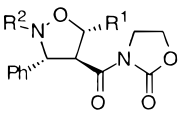
(10) The freshly prepared MgI_2 must be dissolved completely in CH_2Cl_2 to give satisfying selectivities.

selectivity dramatically. Now the reaction proceeds with a high *endo*-selectivity, as observed for the catalysts **5a** and **6a**,**b** (Table 1, entries 4, 7, and 8). The copper catalysts are not as effective as the titanium and magnesium catalysts for the 1,3-dipolar cycloaddition reaction of alkenes with nitrones as much lower conversions are observed (Table 1, entries 2−8). If traces of water are present in the copper-catalyzed reactions it destroys the nitrone, and therefore, the presence of 4 Å powdered molecular sieves is necessary to obtain a good conversion. If 2,9-dimethylphenanthroline is applied as ligand instead of **4a** in the Cu(II)-catalyzed reaction catalyst **5b** is formed, but it shows no catalytic activity in the present reaction (Table 1, entry 5). Contrary to $Cu(II)(OTf)_2$, which has no catalytic effects without the presence of **4a**, MgI_2-I_2 catalyzes the 1,3-dipolar cycloaddition reaction of **1a** with **2a** (Table 1, entry 6), and the diastereoselectivety is comparable with the results obtained with $Ti(i\text{-}OPr)_2Cl_2$ as the catalyst, as *exo*-**3a** is formed as the major isomer (Table 1, entry 6). However, if **6a** is applied as the catalyst an astonishingly high *endo*-selectivity is achieved as an *endo*-**3a**:*exo*-**3a** ratio of >95:<5 is obtained (Table 1, entry 7). The conversion is also high by the application of **6a** as the catalyst, but minor amounts of iodinated byproducts are formed. When the ligand is changed from **4a** to 2,9-dimethylphenanthroline, the Mg(II) complex **6b** gives, unlike the Cu(II) complex, the same conversion and high *endo*-selectivity in the reaction of **1a** with **2a** (Table 1, entry 8).

To illustrate a more general application of the diastereoselective Mg(II)−phenanthroline-catalyzed reaction, **6a** has been applied as a catalyst for a series of other substrates (reaction 4):



1a: $R^1 = CH_3$ **2a**: $R^2 = Ph$
1b: $R^1 = CH_2CH_2CH_3$ **2b**: $R^2 = CH_2Ph$



(4)

endo-**3**

3a: $R^1 = CH_3$, $R^2 = Ph$
3b: $R^1 = CH_3$, $R^2 = CH_2Ph$
3c: $R^1 = CH_2CH_2CH_3$, $R^2 = Ph$
3d: $R^1 = CH_2CH_2CH_3$, $R^2 = CH_2Ph$

The results for reaction 4 are presented in Table 2 where the diastereoselectivities are based on ^1H NMR spectroscopy of the crude products.

It appears from Table 2 that the *endo*-selectivities generally are very high, especially for entries 1−4 as *endo*:*exo* ratios >95:<5 are obtained. For entries 1−3, the starting material is consumed after 48 h, but small quantities of iodinated products are formed as byproducts. The sterically most crowded combination is the reaction of **1b** with **2b**, and this reaction proceeds more slowly than the other, leading to a conversion of 64% after 48 h at room temperature (rt), but with a very high *endo*:*exo* ratio (Table 2, entry 4). Unfortunately, the diastereoselectivity decreases as the molar scale for the reaction is increased (entries 1, 5, and 6). When the reaction isperformed at a 0.5 mmol scale the *endo*:*exo* ratio decreases to 93:7, and at a 1.0 mmol scale the ratio is 84:16, but still in favor of the *endo*-isomer. Upon the application of titanium alkoxides, no such changes in diastereoselectivity are observed on scaling up the reaction.[5] Although much effort has been given to this problem it remains unsolved.

Table 2. *Endo*-Selective Reactions of Alkenes 1a,b with Nitrones 2a,b in the Presence of 6a as the Catalyst

entry	alkene	nitrone	molar scale[a] (mmol)	product	conversion[b] (%)	*endo*:*exo*[c]
1	**1a**	**2a**	0.1	**3a**	>90	>95:<5
2	**1a**	**2b**	0.1	**3b**	>90	>95:<5
3	**1b**	**2a**	0.1	**3c**	>90	>95:<5
4	**1b**	**2b**	0.1	**3d**	64	>95:<5
5	**1a**	**2a**	0.5	**3a**	88[d]	93:7
6	**1a**	**2a**	1.0	**3a**	75[d]	84:16

[a] The molar scale is defined from **1** which is mixed with 1.25 mol equiv of **2** in CH_2Cl_2 after the addition of 50 mg of 4 Å powdered molecular sieves per 0.1 mmol of **1**. After the mixture was stirred for 15 min, 10 mol % **6a** was added. [b] Reaction time 48 h. [c] Determinated by ^1H NMR spectroscopy of the crude product. [d] Isolated yields of the *endo*-isomer.

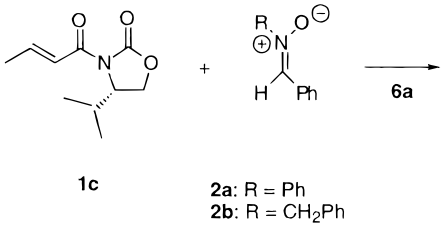
The next goal for our studies of exploring the utility of Mg(II)−phenanthroline (**6a**) as a catalyst for 1,3-dipolar cycloaddition reaction of alkenes with nitrones was to introduce a chiral auxiliary in the starting material with the purpose of making optically pure isoxazolidines. We chose the valine-derived 4(*S*)-isopropyl-1,3-oxazolidin-2-one as chiral auxiliary.[11] The reactions were performed by mixing **1c** and **2a**,**b** in CH_2Cl_2 in the presence of 4 Å powdered molecular sieves and by the application of 10 mol % of **6a** as the catalyst (reaction 5). The results obtained are listed in Table 3.

The reaction between **1c** and **2a** proceeds well at rt and with a high conversion after 48 h. Only one isomer, $endo_a$-**3e**, can be detected by ^1H NMR spectroscopy (Table 3, entry 1) when the reaction of **1c** with **2a** is run on a 0.1 mmol scale, and surprisingly, a similar result is achieved if the reaction is scaled up to 0.5 mmol (Table 3, entry 2). The *N*-benzyl nitrone **2b** reacts at a much lower rate and needs several days to give satisfactory yields, but this reaction also proceeds with a high degree of double diastereoselectivity, although minor amounts of other isomers could be detected in the crude ^1H NMR spectrum (Table 3, entry 3). Murahashi *et al*. have tried to employ cyclic nitrones and the phenylalanine-derived auxiliary for 1,3-dipolar cycloaddition reactions in an attempt to obtain high diastereoselectivity.[3c] ZnI_2 was applied in stoichiometric amounts for the introduction of higher selectivity than in the reaction in the absence of a metal; fair selectivities were introduced in some entries, but unfortunately, the metal lowered the reaction rate.[3c]

The reaction of **1c** with **2b** in the presence of Mg(II)−phenanthroline (**6a**) as the catalyst lead to the formation of $endo_a$-**3f** (reaction 5) which was isolated as a crystalline

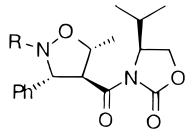
(11) See, *e.g.*: Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(12) The bisoxazolines have been applied as ligands in several asymmetric metal-catalyzed reactions. They are now purchased commercially from Aldrich. (a) Bolm, C. *Angew Chem.* **1991**, *103*, 556; *Angew Chem., Int. Ed. Engl.* **1991**, *30*, 542. (b) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (c) Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett* **1991**, 257. (d) Müller, D.; Umbricht, G., Weber, B.; Phaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (e) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 5328. See also ref 8a.



1c

2a: R = Ph
2b: R = CH_2Ph



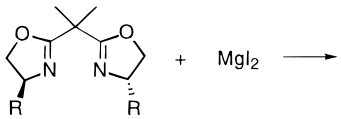
(5)

endo$_a$-**3**

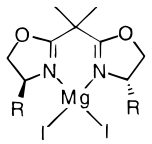
3e : R = Ph
3f : R = CH_2Ph

compound. In an attempt to elucidate the reaction mechanism for the addition step and the absolute stereochemistry of the isoxazolidine, the X-ray structure of *endo*$_a$-**3f** was determined (*vide infra*).

Finally, the aim of this work is also to induce enantioselectivity in the 1,3-dipolar cycloaddition reaction by the application of a chiral magnesium catalyst. The chiral magnesium catalysts (*R*)-**9a**, (*S*)-**9a**, and (*S*)-**9b** were prepared as outlined in reaction 6. As for the catalysts **6a**,**b**, the freshly prepared catalysts **9a**,**b** have the best catalytic activity, but comparable reaction rates and selectivities can be obtained with the catalysts after 14 days, if they are carefully stored under N_2 at rt by the exclusion of light.



8a: R = Ph
8b: R = *t*-Bu



9a,b (6)

The reaction of **1a**,**b** and **2a**,**b** in the presence of (*S*)-**9a**,**b** (only the reactions catalyzed by **9a** are presented) as the catalyst are presented in Table 4.

The reaction rate for the 1,3-dipolar cycloaddition reactions of alkenes **1a**,**b** with nitrones **2a**,**b** catalyzed by (*S*)-**9a** is low compared with the reactions catalyzed by **6a**. However, a conversion of 72% is observed after 24 h in the reaction of **1a** with **2a** (Table 4, entry 1). This reaction also proceeds in an *endo*-selective manner, giving an *endo:exo* ratio of 92:8. The ee of *endo*-**3a** was found to be 79% and is to our knowledge the highest ee so far induced by a catalytic amount of a catalyst in a 1,3-dipolar cycloaddition reaction. The addition of 4 Å activated powdered molecular sieves is of utmost importance to the reaction, and we have noticed that lack of, or too small amounts of, 4 Å activated powdered molecular sieves have a significant influence on the selectivity of the reaction. This influence caused by 4 Å activated powdered molecular sieves has also been observed for other metal-catalyzed reactions.[13] The reaction rate was not affected by the lack of 4 Å activated powdered molecular sieves, but the *endo*-selectivity was reduced

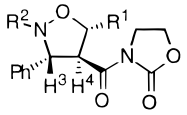
Table 3. Reaction of 3-Crotonoyl-4(*S*)-isopropyl-1,3-oxazolidin-2-one (1c) with the Nitrones 2a,b in the Presence of 6a (10 mol %) as the Catalyst

entry	nitrone	molar scale[a] (mmol)	product	yield[b] (%)	*endo*$_a$[c]	other diast
1	**2a**	0.1	**3e**	95	98	<2
2	**2a**	0.5	**3e**	99	98	<2
3	**2b**	0.5	**3f**	67	93	7[c,d]

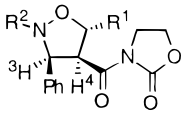
[a] The molar scale is defined from **1c**. [b] Isolated yields. [c] Ratios are based on ^1H NMR spectrocopy of the crude material. [d] Which one of the *endo*$_b$, *exo*$_a$, or *exo*$_b$ isomers was not identified.

to an *endo:exo* ratio of 65:35 (Table 4, entry 2). The most dramatic effect was a decrease in ee from 79% to below 2% (Table 4, entry 2). Scaling up the reaction five times causes only a slightly lower *endo:exo* ratio and only a slight decrease in enantioselectivity. In this manner, (+)-*endo*-**3a** (*vide infra*) is obtained with a good *endo*-selectivity and with an ee of 71% (Table 4, entry 3). By the application of (*R*)-**9a** as the catalyst, (−)-*endo*-**3a** is isolated in a yield of 81% having an ee of 75% (Table 4, entry 4). The reaction of the *N*-benzyl nitrone **2b** with **1a** proceeds slowly with a good *endo:exo* ratio, but unfortunately the product is racemic (Table 4, entry 5). The reaction of **2a** with the 3-hexenoyloxazolidinone (**1b**) is very slow at rt, but after 14 days a conversion of >95% could be detected (Table 4, entry 6). The *endo:exo* ratio is good, and after isolation of *endo*-**3c** the ee is measured to be 82%. Scaling up this reaction to 0.5 mmol destroys the diastereoselectivity; however, an ee of 82% can still be obtained (Table 4, entry 7).

II. X-ray Structural Determinations and Absolute Assignment of the Stereochemistry. The differentiation between, and the identification of, the *endo* and the *exo* isomers of **3** are based on the coupling constants between H^3 and H^4 in *endo*-**3** and *exo*-**3**.[14]



endo-**3**



exo-**3**

It has been found that racemic *exo*-**3a** precipitates from a methanolic solution of *exo*-**3a** with an ee of 62%, leaving the dissolved material with an optical purity >95%.[5] To be absolutely sure that the stereochemistry is correctly assigned, these crystals of *exo*-**3a** have been subjected to an X-ray crystallographic investigation, and the structure of *exo*-**3a** is presented in Figure 1.

The crystal structure of *exo*-**3a** shows that it has two molecules in the asymmetric unit. According to the X-ray structure in Figure 1, it is clear that H^3 and H^4 of *exo*-**3a** are arranged *cis* to each other in the isoxazolidine ring. This is in agreement with the NMR experiments that reveal that the *exo*-isomer gives rise to a larger H^3-H^4 coupling constant than observed for the *endo*-isomer. The isoxazolidine ring adopts an envelope conformation,[15] with the following dihedral angles O−C3−C2−C1 of the isoxazolidine ring for the two molecules 29.0(4)° and

(13) (a) Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, (b) Hanson, R. N.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*,1922. (c) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106.

(14) Identification of *exo*/*endo*-isomers: Huisgen, R.; Hauck, H.; Seidl, H.; Burger, M. *Chem. Ber.* **1969**, *102*, 1117.

(15) See, *e.g.*, refs 2d,h,i,o for other isoxazolidines characterized.

Table 4. Metal-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions of 1a,b with 2a,b in the Presence of (*S*)-9a (10 mol %) as the Catalyst

entry	alkene	nitrone	molar scale[a] (mmol)	product	conversion (%)	*endo*:*exo*	ee *endo*[c] (%)
1	**1a**	**2a**	0.1	**3a**	72/24 h	92:8	79
2	**1a**	**2a**	0.1[b]	**3a**	73/24 h	65:35	<2
3	**1a**	**2a**	0.5	(+)-**3a**	>95/48 h	84:16	71
4	**1a**	**2a**	0.5[d]	(−)-**3a**	>95[e]/48 h	84:16	75 (72)[f]
5	**1a**	**2b**	0.1	**3b**	82/14 d	89:11	0
6	**1b**	**2a**	0.1[d]	(−)-**3c**	>95/14 d	>95:<5	82
7	**1b**	**2a**	0.5[d]	(−)-**3c**	>95[g]/14 d	53:47	82 (52)[f]

[a] The molar scale is defined from **1**. [b] Without 4 Å activated powdered molecular sieves. [c] ee of the *endo*-isomer was determinated by HPLC using a Daicel Chiralcel OD column. [d] (*R*)-**9a** 10 mol % was applied as the catalyst. [e] Isolated yield: 81%. [f] ee of the *exo*-isomer. The ee was determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as chiral shift reagent. [g] Isolated yield 66%.

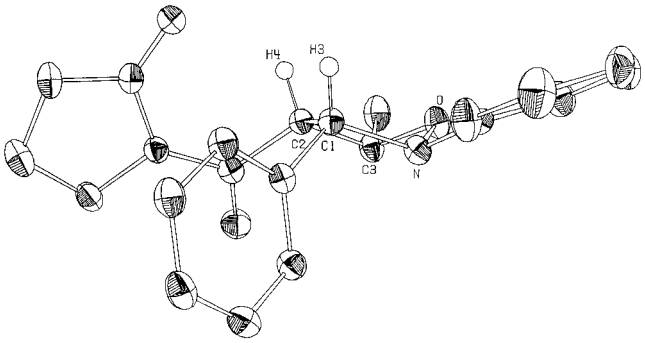


Figure 1. X-ray structure of *exo*-**3a** showing the structural *exo* arrangement of the isoxazolidine ring. Hydrogen atoms are only shown for the isoxazolidine ring.

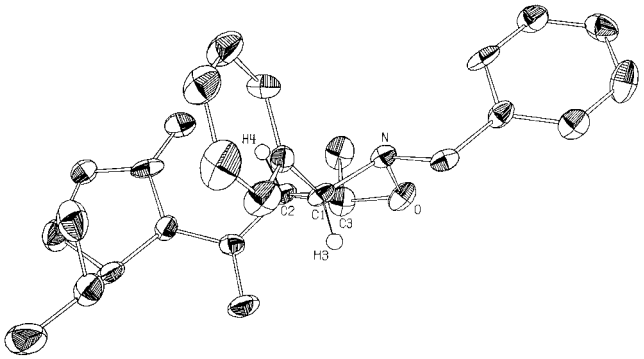


Figure 2. X-ray structure of *endo*$_a$-**3f** showing the absolute stereochemistry of the isoxazolidine ring.

Table 5. Selected Bond Lengths for the Isoxazolidine Ring of *exo*-3a (Two Molecules in Asymmetric Unit) and *endo*$_a$-3f[a]

	exo-**3a** (1)	*exo*-**3a** (2)	*endo*$_a$-**3f**
bond lengths (Å)			
O−N	1.453(4)	1.455(4)	1.476(7)
N−C1	1.494(5)	1.488(5)	1.478(10)
C1−C2	1.571(5)	1.565(5)	1.543(10)
C2−C3	1.539(5)	1.534(5)	1.553(10)
C3−O	1.428(5)	1.437(5)	1.425(10)
bond angles (deg)			
N−O−C3	101.7(3)	101.5(3)	104.6(5)
O−N−C1	105.6(3)	104.9(3)	99.3(5)
N−C1−C2	101.9(3)	102.1(3)	99.6(5)
C1−C2−C3	103.3(3)	103(7)	101.1(6)
O−C3−C2	103.1(3)	102.4(3)	105.8(6)
dihedral angles (deg)			
O−C3−C2−C1	29.0(4)	29.1(4)	7.7(8)

[a] For experimental details see the Experimental Section.

29.1(4)°. Some representative bond lengths, bond angles, and angles of the isoxazolidine ring of *exo*-**3a** are given in Table 5.

Inspection of the structural data in Table 5 for the isoxazolidine ring of the two molecules of *exo*-**3a** reveals that they are very similar to other isoxazolidines characterized[15] and will not be considered further in this section.

The reaction of alkene **1c** with the nitrone **2b** in the presence of Mg(II)−phenanthroline (**6a**) as the catalyst leads to a diastereoselective reaction with the formation of *endo*$_a$-**3f** which is isolated as a crystalline compound. The structural data for the isoxazolidine ring of *endo*$_a$-**3f** are also presented in Table 5. Comparing the structural data for *endo*$_a$-**3f** with those of *exo*-**3a** shows that the bond lengths for the isoxazolidine are very similar for the two compounds, while the bond angles are slightly different. The change in bond angles for the isoxazolidine ring in *endo*$_a$-**3f** compared with *exo*-**3a** is due to the change in dihedral angle for the former relative to the latter as the O−C3−C2−C1 dihedral angel in *endo*$_a$-**3f** is only 7.7(8)° compared with 29.0(4)° and 29.1(4)° for the former. A determination of the absolute configuration of the chiral centers in the isoxazolidine ring is now possible on the basis of the stereochemistry of the 4(*S*)-isopropyl-1,3-oxazolidin-2-one chiral auxiliary. The structure of *endo*$_a$-**3f** is shown in Figure 2.

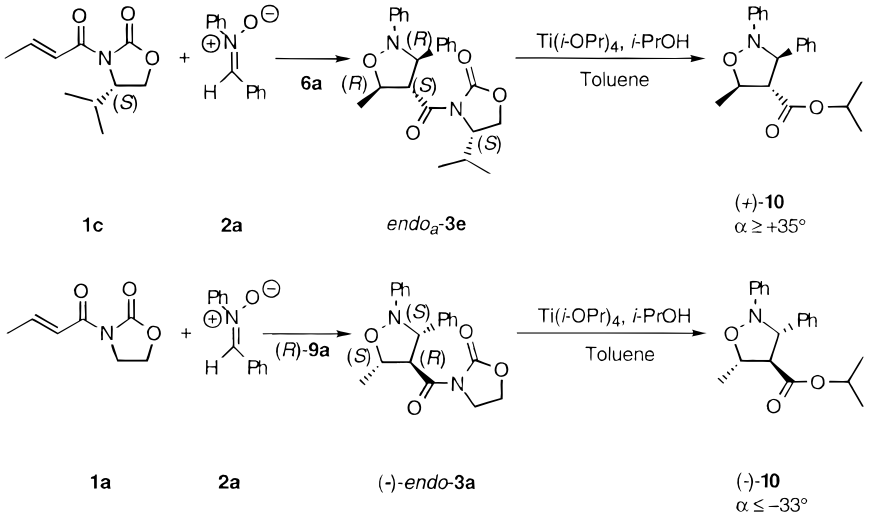
In order to compare the stereochemical assignment of *endo*$_a$-**3f** with the experimental results the reactions outlined in Scheme 1 have been performed.

The product *endo*$_a$-**3e** of the reaction of **1c** with **2a** using **6a** as a catalyst is transformed to the isopropyl ester (+)-**10** by refluxing in toluene with Ti(*i*-OPr)$_4$ and *i*-PrOH. The isopropyl ester (+)-**10** shows an optical rotation ≥+35°. In a similar manner is (−)-*endo*-**3a**, which is obtained by reaction of **1a** with **2a** in the presence of catalyst (*R*)-**9a**, converted to the isopropyl ester (−)-**10** which has an optical rotation of ≤−33°. The two isopropyl esters (+)-**10** and (−)-**10** are identical in all respects (NMR, MS, and TLC) except their optical rotation. The stereochemical centers of the isoxazolidine moiety of (−)-*endo*-**3a** are thus the mirror image compared with the corresponding centers of *endo*$_a$-**3e**. We assume that **2a** and **2b** approach the same face of the alkene in the reaction with **1c**. On the basis of the X-ray structure of *endo*$_a$-**3f**, we can now assign the three chiral centers in the isoxazolidine ring of *endo*$_a$-**3e** to be *3R,4S,5R* as outlined in Scheme 1.

With the knowledge of the absolute stereochemistry of the three chiral centers in the isoxazolidine ring of *endo*$_a$-**3e** and *endo*-**3a**, we can now propose the face of the alkene to which the nitrone approaches. The proposed reaction path of nitrone **2a** to alkene **1c** in the presence of Mg(II)−phenanthroline (**6a**) as the catalyst is outlined in Figure 3. The nitrone approaches *endo* to the α-*Si*-face of the alkene from above the plane of the oxazolidinone as the 4(*S*)-isopropyl substituent discriminates the α-*Re*-face of the alkene.

The reaction of alkene **1a** with nitrone **2a** in the presence of the Mg(II)−bisoxazoline complex (*R*)-**9a** leads

Scheme 1



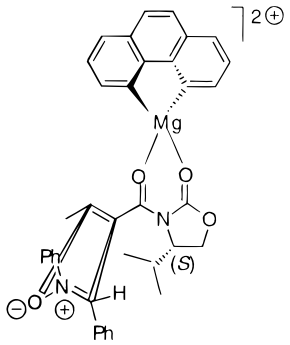


Figure 3. Approach of the nitrone **2a** to the α-*Si*-face of the alkene **1c** from above the plane of the oxazolidinone as the 4(*S*)-isopropyl substituent discriminates the α-*Re*-face of the alkene.

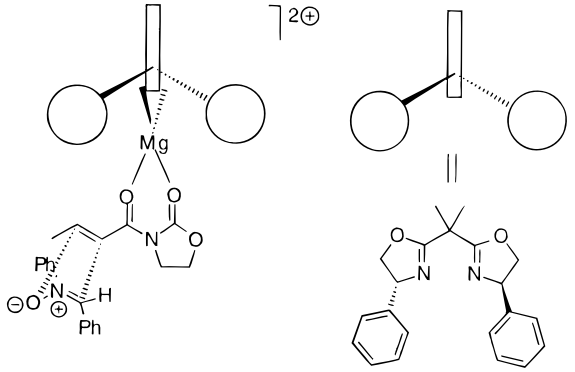


Figure 4. Proposed α-*Re* approach of nitrone **2a** to alkene **1a** coordinated to **9a**.

to an isoxazolidine, (−)-*endo*-**3a**, with the following stereochemical assignment at the three chiral centers: 3*S*,4*R*,5*S*. To obtain the this stereochemistry for (−)-*endo*-**3a**, the approach of **2a** to **1a** coordinated to (*R*)-**9a** must take place at the other face (α-*Re*) of **1a** compared with the approach outlined in Figure 3 (*vide infra*). The proposed *endo*-α-*Re* approach of **2a** to **1a** coordinated to **9a** is shown in Figure 4.

III. Theoretical Calculations. In the following we will try to account for the catalytic effects with respect to the rate and diastereo- and enantioselectivity of the achiral and chiral Mg(II) complexes applied as catalysts for the 1,3-dipolar cycloaddition reaction of alkenes with nitrones.[16] For these purposes we have used semiempirical quantum chemical calculations applying the MOPAC-PM3 method.[7] We will try to address the following questions: (i) what is the role of the Mg(II)−phenanthroline catalyst (**6a**) on the electronic structure of alkene **1a**, (ii) what is the effect of coordinating alkene **1a** to the Mg(II)−phenanthroline catalyst (**6a**) and to the Mg(II)−bisoxazoline catalyst (**9a**) on the relative energies for the *endo*- and *exo* transition states for the reaction of **1a** with nitrone **2a**, compared with the uncatalyzed reactions and (*iii*) can the experimental observations be accounted for by the theoretical calculations.

Let us start with the electronic structure of the alkene **1a**. In Figure 5, the frontier orbitals of the optimized structure of **1a**, which have the appropriate symmetry for an interaction with the frontier orbitals of a nitrone, are presented to the left.

The LUMO of **1a** is the $\pi^*_{C=C}$ orbital located perpendicular to the plane of the molecule. The energy of this orbital is calculated to be −0.35 eV and has the largest amplitude at the β-carbon atom with a coefficient of 0.64, compared with −0.47 at the α-carbon atom. The atomic charges at the α- and β-carbon atoms are −0.24 and −0.03, respectively. These results indicate that the β-carbon atom is most susceptible for nucleophilic attack. The HOMO of **1a** is found at −10.20 eV and is distributed at the two carbonyl oxygen atoms and at the nitrogen atom and is not of interest for the reaction of the alkene part of the molecule. The second HOMO is a $\pi_{C=C}$ orbital, and it is the bonding counterpart to the LUMO. The energy of this orbital is calculated to be −10.79 eV, and it has a slightly larger amplitude at the α-carbon atom compared with the β-carbon atom. The $C_\alpha-C_\beta$ bond length in **1a** is calculated to be 1.34 Å.

The frontier orbitals of the nitrone **2a**, set up for an interaction with the alkene of **1a**, are presented in the middle of Figure 5. The LUMO of **2a** is calculated to be −1.02 eV, while the HOMO is at −8.90 eV, and it appears that these are set up for an interaction with the HOMO and the LUMO, respectively, of **2a**. On the basis of the location of the frontier orbitals, it is obvious that the interaction of the LUMO of **1a** with the HOMO of **2a** is the most favorable interaction. This interaction is outlined as the dotted lines in Figure 5.

(16) For other theoretical calculations of 1,3-dipolar cycloaddition reactions of nitrones with alkenes, see *e.g.*: (a) Leroy, G.; Nguyen, M. T.; Sana, M. *Tetrahedron* **1978**, *34*, 2459. (b) Pascal, Y. L.; Chanet-Ray, J.; Vessiere, R.; Zeronal, A. *Tetrahedron* **1992**, *48*, 7197. (c) Rispens, M. T.; Keller, E., de Lange, B.; Zijlstra, R. W. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 607.

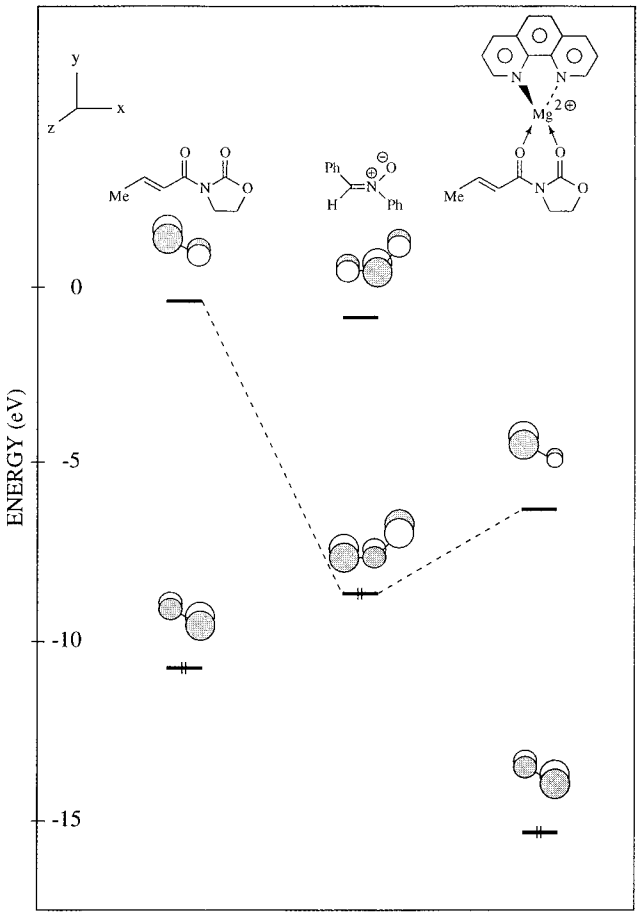
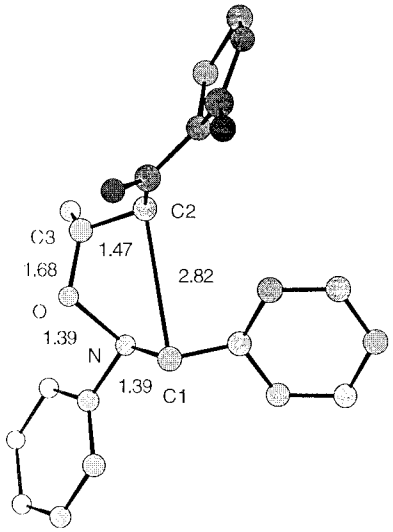


Figure 5. Frontier orbitals of the alkene **1a** (left) which are set up for an interaction with the frontier orbitals of the nitrone **2a** (middle). To the right are the frontier orbitals of **1a** coordinated to **6a**. The primary interactions are outlined as the dotted lines.

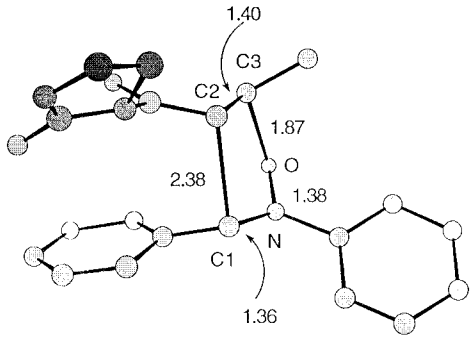
To the right in Figure 5 are outlined the frontier orbitals of alkene **1a** coordinated to the Mg(II)−phenanthroline catalyst (**6a**). The geometry of this complex has been optimized, and a tetrahedral arrangement of the ligands at the metal center is calculated to be 30 kcal/mol more stable than a planar geometry. We will not discuss the geometry of **1a** coordinated to **6a** but rather focus on the electronic structure of this intermediate. By coordination of **1a** to **6a** the $\pi^*_{C=C}$ orbital, which is the LUMO of the system, is lowered to −7.70 eV, while the $\pi_{C=C}$ orbital of **1a** coordinated to **6a** is found at −16.61 eV. The coordination of **1a** to **6a** also leads to other electronic changes of the alkene part of **1a** as the amplitude of the LUMO changes to be mainly located at the β-carbon atom, with only a very small coefficient at the α-carbon atom (0.06). The charges at the α- and β-carbon atoms of **1a** are also affected by the coordination to **6a**, as these have been calculated to be −0.35 and 0.17, respectively. Furthermore, the coordination of **1a** to **6a** has also a small influence on the $C_\alpha-C_\beta$ bond length as this is calculated to be 1.38 Å.

The electronic structure of alkene **1a** is changed significantly by the coordination to **6a** as the alkene becomes a much better electron acceptor. The increased reactivity of **1a** coordinated to **6a**, relative to the reactivity of **1a**, comes from a decrease in the HOMO−LUMO difference, as the LUMO of **1a** coordinated to **6a** is much lower in energy (−7.35 eV) than the LUMO of **1a** and, thus, will interact much more favorably with the HOMO of the nitrone.

The geometry of the alkene **1a** and nitrone **2a** has been optimized and shows the expected bond lengths and angles; these will not be discussed further here. In a similar manner, the geometry of *endo*-**3a** and *exo*-**3a** is optimized. When the optimized geometry of the relevant part of *exo*-**3a** is compared with the X-ray structure of *exo*-**3a**, very similar structural data are obtained. The geometries of *endo*-**3a** and *exo*-**3a** are necessary for the calculation of the *endo* and *exo* transition states for the reaction of **1a** with **2a** as the transition states are located by the calculation of a reaction path profile for the reaction of **1a** with **2a** leading to either *endo*-**3a** or *exo*-**3a**, followed by a further optimization and characterization of the transition state (TS). The TS leading to *endo*-**3a** is shown in **11** (hydrogen atoms omitted in all the TS-drawings), while the TS giving *exo*-**3a** is presented in **12**. The calculated bond lengths for the TS's of interest for the present investigation are also given in **11** and **12**.



11

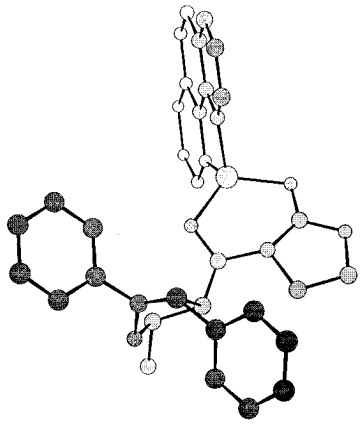


12

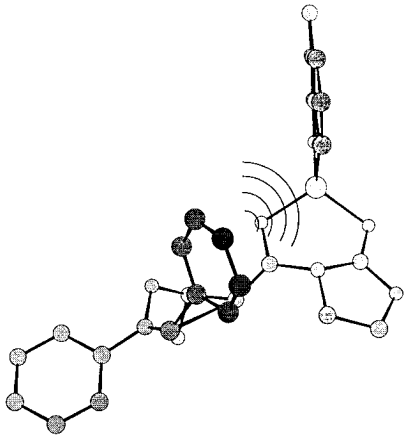
The TS energy for **12** is calculated to be 40 kcal/mol, while the one for **11** is 65 kcal/mol. The calculated TS energy for the formation of *exo*-**3a** is in agreement with the TS energy calculated for the 1,3-dipolar cycloaddition reaction of simple alkenes with nitrones.[16b] The calculated bond lengths in the TS for the formation of the isoxazolidine ring are also in the same range as those obtained by *ab initio* calculations, using a relatively simple basis set, as well as the AM1 method.[16a,b] The calculated TS energies for **11** and **12** indicate that the uncatalyzed reaction of **1a** with **2a** should primarily lead to the formation of *exo*-**3a** as the TS energy for the formation of *exo*-**3a** is 25 kcal/mol lower in energy than the one calculated for the formation of *endo*-**3a**. These re-

sults are in agreement with the experimental results for the reaction of **1a** with **2a** in the absence of a catalyst, where an *endo:exo* ratio of 91:9 is obtained.[5] If one compares the two TS's **11** and **12** it appears that they differ slightly for the bond lengths in the isoxazolidine ring; in the former, the C−O bond length is 1.68 Å, while it is 1.87 Å in the latter. The most significant change in bond lengths is found for the C−C bond length in the isoxazolidine ring: in **11** it is 2.82 Å while it is 2.38 Å in **12**.

The *endo*- and *exo* TS's for the reaction of alkene **1a** coordinated to the Mg(II)-phenanthroline catalyst **6a** with the nitrone **2a** have been calculated in a similar way. The *endo*-TS structure is presented in **13**, while the *exo*-TS is outlined in **14**.



13

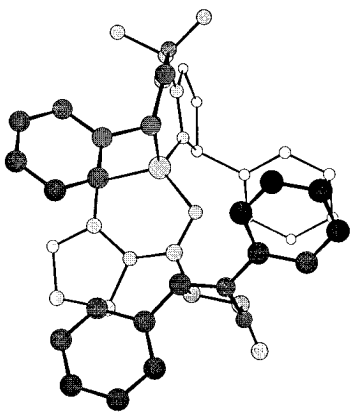


14

From an inspection of the two TS's **13** and **14** it appears that the *exo*-approach (**14**) of the **2a** to **1a** coordinated to **6a** leads to a significant repulsion between the *C*-phenyl substituent of the nitrone and the phenanthroline ligand compared with the *endo*-approach **13**. We propose that this steric repulsion accounts for the change in the diastereoselectivity when tetrahedral metal complexes are used as catalyst. The geometrical changes in the *endo*- and *exo*-TS's are also readable from the calculated energies of the two systems. The energy for the *exo*-TS is calculated to be 35 kcal/mol, and the energy for the *endo*-TS is calculated to be 20 kcal/mol. It thus appears that the coordination of Mg(II)−phenanthroline (**6a**) to **1a**, and performing the reaction of this complex with the nitrone **2a**, leads to a significant lowering of the TS energy for the formation of the *endo*-product. The TS energy for the formation of *endo*-**3a** is lowered by 45 kcal/mol by the coordination of **1a** to **6a**, whereas only a 5 kcal/mol lowering for the formation of *endo*-**3a** is calculated. These results are also in agreement with the catalytic role of **6a** and the experimentally observed *endo:exo* ratios presented in Tables 1 and 2. The TS for the *endo*-approach **13** can also be used to account for the double diastereoselective reaction in reaction 5 and Scheme 1 as the introduction of the 4(*S*)-isopropyl-1,3-oxazolin-2-one chiral auxiliary will discriminate the α-*Re*-face of the alkene in accordance with the experimental results.

In the following text we will compare the Mg(II)−phenanthroline (**6a**) TS **13** (the *endo*-approach) with the TS for the uncatalyzed *endo*-approach **11**. The following bond lengths for the isoxazolidine ring have been calculated for **13**: O−N, 1.43 Å; N−C1, 1.32 Å; C1−C2, 3.02 Å; C2−C3, 1.49 Å; C3−O, 1.47 Å. The most significant change in the TS geometry for the **6a**-catalyzed *endo*-approach **13** compared with the uncatalyzed TS **11** is the shorter C3−O and longer C1−C2 bond length in **13**. These changes are probably related to the change in the electronic structure of the alkene **1a** when coordinated to **6a** compared to **1a**: the alkene becomes a better electron acceptor when coordinated to **6a** (*vide supra*), and the shorter C3−O bond length in **13** can accounted for the LUMO of **1a** coordinated to **6a** being lower in energy and having a larger amplitude at the β-carbon atom compared with the LUMO of **1a**. Furthermore, the coordination of **1a** to **6a** also leads to an increased positive charge (0.17) at the β-carbon atom relative to −0.03 in **1a**. The electronic changes of the alkene when coordinated to **6a** will lead to a better interaction of the "nucleophilic part" of the nitrone **2a** compared with the interaction of the **2a** with **1a** and, therefore, the shorter C3−O bond length in the former case. The increased C1−C2 bond length in **13** relative to **11** might thus be related to the small amplitude and the more negative α-carbon atom on **1a** coordinated to **6a**. The electronic change at the α-carbon atom means that this atom cannot interact to the same extent with the nitrone carbon atom compared to the same interaction in the uncatalyzed reaction.

The TS for the four different approaches of the nitrone **2a** to **1a** coordinated to (*R*)-**9a** have been found. The four different approaches of the nitrone to the alkene part of the **1a** coordinated to (*R*)-**9a** are as follows: *endo*-α-*Re*, *endo*-α-*Si*, *exo*-α-*Re*, and *exo*-α-*Si*. The lowest calculated TS energy is for the *endo*-approach of the nitrone to the α-*Re* face of the alkene **15**. The energy of the TS is calculated to be 32 kcal·mol^{-1}, while the calculated TS energies for the three other approaches of the nitrone are more than 10 kcal·mol^{-1} higher in energy, and these TS's will not be considered further here.



15

The calculated TS for the *endo*-approach of the nitrone to the α-*Re*-face of the alkene coordinated to (*R*)-**9a** outlined in **15** demonstrates nicely the combination of the tetrahedral complex accounting for the *endo*-selectivity (also outlined in **13** for the *endo*-approach of the nitrone of **1a** coordinated to **6a**) and the selective discrimination of the α-*Si*-face of the alkene by the phenyl substituent of the bisoxazoline ligand. The calculated geometry of the TS for the formation of the isoxazolidine ring in **15** is not significantly different from the one found in **13** and will therefore not be discussed further here. The stereochemical outcome of the reaction based on the theoretical calculations is also in agreement with the experimental results and accounts for both the catalytic effect of the catalyst and the diastereo- and enantioselectivity of the reaction.

Summary

A new catalytic approach has been developed for the 1,3-dipolar cycloaddition reaction of nitrones with alkenes. The Mg(II)-catalysts strongly accelerate the reaction. The "ligand-less" Mg(II)I_2−I_2 catalyst gave primarily the *exo*-diastereomer, and a similar diastereoselectivity was observed for the uncatalyzed reaction, which proceeds very slowly. These findings are in agreement with MOPAC-PM3 calculations of the uncatalyzed reaction of **1a** and **2a** which gave a transition state energy which was 25 kcal·mol^{-1} lower in energy for the *exo*-transition state compared with the *endo*-transition state. The *endo*:*exo* ratio is dramatically changed when Mg(II)−phenanthroline complex (**6a**) is used as the catalyst, and it is shown that for small scale reactions the *endo*:*exo* ratio is generally >95:<5 for the reaction of a series of nitrones with alkenes. The *endo*-selectivity for these reactions can be accounted for assuming a tetrahedral Mg(II)−phenanthroline−alkene intermediate where steric repulsion between the nitrone C-aryl substituent and the phenanthroline ligand disfavors the *exo*-transition state. The semiempirical calculations support these experimental findings as the *endo*-transition state is calculated to be 15 kcal·mol^{-1} lower in energy than the *exo*-transition. The calculations also account for the catalytic role of the Mg(II)−phenanthroline complex as the *endo*-transition state is calculated to be 45 kcal·mol^{-1} lower in energy compared with the uncatalyzed reaction. By the application of the chiral alkene **1c** in the reaction with two different nitrones catalyzed by the Mg(II)−phenanthroline complex, a double diastereoselective reaction is observed. In two of the cases only one of the four possible products are observed while in one case only minor amounts (7%) of other isomers are formed. On recrystallization, pure (+)-*endo*$_a$-**3f** is obtained. The crystals have been subjected to a X-ray crystallographic investigation, and on the basis of the amino acid derived chiral auxiliary in (+)-*endo*$_a$-**3f** the absolute stereochemistries of the three chiral centers in the isoxazolidine ring have been assigned. On the basis of the absolute structure, an *endo*-approach of the nitrone to the α-*Si*-face of the alkene in an *s-cis* conformation when coordinated to the Mg(II)−phenanthroline ligand has been proposed. The *endo*-diastereoselective Mg(II) catalysts have also been extended to chiral Mg(II)−bis(oxazoline) complexes which act as catalysts for both the diastereo- and enantioselective 1,3-dipolar cycloaddition reaction of nitrones with alkenes. The conversion ranges from fair to excellent with very high *endo*:*exo* ratios. The highest ee's are in the range 71−82%, with the best ee's obtained in metal-catalyzed 1,3-dipolar cycloaddition reaction of nitrones with alkenes. The absolute stereochemistry of the three chiral centers in the isoxazolidine ring has been assigned, and based on this assignment it is determined that the nitrone approaches *endo* to the α-*Re*-face of the alkene in an *s*-cis conformation when coordinated to the Mg(II)−bis(oxazoline) ligand. The theoretical calculations of the four possible transition states for the reaction are in nice agreement with the experimental results.

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 ppm downfield from tetramethylsilane (TMS). HPLC was performed using a 4.6 mm × 25 cm Daicel Chiracel OD column. Mass spectra were recorded at 70 eV with a direct inlet. Preparative thin layer chromatography (TLC) was performed on 200 × 200 × 1.8 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 was dried in an oven before use.

Materials. The starting materials 3-((*E*)-2′-butenoyl)-1,3-oxazolidin-2-one (**1a**),[11,17] 3-((*E*)-2′-hexenoyl)-1,3-oxazolidin-2-one (**1b**),[11,17] benzylidenephenylamine *N*-oxide (**2a**)[18] and benzylbenzylideneamine *N*-oxide[19] (**2b**) were synthesized according to the literature. (*S*)-(+)-3-Crotonoyl-4-isopropyl-2-oxazolidinone (**1c**), (*R*)-(+)- and (*S*)-(−)-2,2′-isopropylidenebis-(4-phenyl-2-oxazoline) (**9a**), magnesium (99%), Eu(hfc)$_3$, and 4 Å powdered molecular sieves were used as received from Aldrich. Cupric trifluoromethane sulfonate was used as received from Fluka. The Millex Filter Units 45 μm pore size was received from Millipore.

Preparation of the Cu−Phenanthroline Catalyst 5a, 0.05 M in CH_2Cl_2. To a CH_2Cl_2 (1 mL) suspension of Cu(OTf)$_2$ (36 mg, 0.1 mmol) was added phenanthroline (18 mg, 0.1 mmol) dissolved in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 5 h. The resulting catalyst was a blue suspension. Only the freshly prepared catalyst was used in the reactions.

Preparation of the Mg−Phenanthroline Catalyst 6a, 0.1 M in CH_2Cl_2. Magnesium (48 mg, 2.0 mmol) and I_2 (253 mg, 1.0 mmol) were placed in a 10 mL flask with a magnetic stirring bar under N_2. Diethyl ether (5 mL) was added, and the mixture was stirred at rt until the iodine color disappeared (2−3 h). The unreacted Mg was filtered off in a Millix Filter Unit 45 μm via syringe and into a flask containing a N_2 atmosphere and a magnetic stirring bar. The solvent was removed under reduced pressure at rt. The white MgI_2 was dissolved in CH_2Cl_2,[10] and to the resulting solution was added phenanthroline (225 mg, 1.25 mmol) dissolved in CH_2Cl_2 (5 mL). After the milky suspension was stirred for 2 h, I_2 (253 mg, 1 mmol) was added to the solution. The deep red suspension was stirred for 2 h before use.

Preparation of the Mg−Bisoxazoline Catalyst 9a, 0.1 M in CH_2Cl_2. The catalyst was prepared in the same manner as described above for the Mg−phenanthroline catalyst. Instead of phenanthroline, (*S*)- or (*R*)-2,2′-isopropylidenebis-(4-phenyl-2-oxazoline) (**8a**) (1.25 mmol, 410 mg) was used. The resulting catalyst was a deep red homogeneous solution.

General Procedure for the Stereoselective 1,3-Dipolar Cycloadditions. To a suspension of 50−100 mg of 4 Å powdered molecular sieves in CH_2Cl_2 (2 mL) in a 5 mL flask was added the alkene **1** (0.1 mmol) and the nitrone **2** (0.125 mmol), and the reaction mixture was stirred for 15 min. The catalyst (0.01 mmol) was added with a glass pipette. After

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the appropriate reaction time, the reaction mixture was stirred with 1 mL of 5% MeOH in CH_2Cl_2 and filtered through a 20 mm layer of silica gel. After the silica gel layer was washed with another 2 mL of 5% MeOH in CH_2Cl_2, the solvent was evaporated. The crude material was purified by preparative TLC (silica gel, Et_2O:petroleum ether, 3:1) to give the single diastereomers of **3**. Generally, the *endo*-isomers appeared with lower R_f values than the *exo* isomers.

The reaction on a 0.5 mmol scale was performed in the same manner by scaling everything up five times.

For mass and ^1H and ^{13}C NMR spectra of the compounds listed in Table 2, see ref 5.

(+)-(3′*R*,4*S*,4′*S*,5′*R*)-4-Isopropyl-3-((5′-methyl-2′-*N*,3′-diphenylisoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (*endo*$_a$-3e). Synthesized according to the general procedure on a 0.5 mmol scale with catalyst **6a** (10 mol %): yield 99% (197 mg, 0.494 mmol); recrystallized from *i*-PrOH; mp = 102−4 °C; $[\alpha]_D = +59.7°$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.73 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 1.51 (d, J = 6.1 Hz, 3H), 2.32 (m, 1H), 4.20 (m, 2H), 4.48 (m, 2H), 4.93 (dd, J = 8.2, 7.2, 1H), 5.13 (d, J = 7.2, 1H), 6.95 (m, 3H), 7.22−7.40 (m, 5H), 7.49 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.8, 18.0, 18.4, 28.5, 59.2, 63.0, 63.4, 76.2, 79.9, 115.1, 122.2, 127.0, 128.5, 129.3, 129.5, 141.1, 152.3, 153.7, 171.1; MS m/z = 394 (M^+).

(+)-(3′*R*,4*S*,4′*S*,5′*R*)-4-Isopropyl-3-((2′-*N*-benzyl-5′-methyl-3′-phenylisoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (*endo*$_a$-3f). Synthesized and purified according to the general procedure on a 0.5 mmol scale with the catalyst **6a** (10 mol %): yield 67%; recrystallized from *i*-PrOH; mp = 115−6 °C; $[\alpha]_D = +35.1°$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.59 (d, J = 7.2 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 1.51 (d, J = 6.0 Hz, 3H), 2.28 (m, 1H), 3.92 (d, J = 14.2 Hz, 1H), 4.7 (m, 2H), 4.22 (dd, J = 9.3, 8.3 Hz, 1H), 4.39 (d, J = 8.2, 1H), 4.48 (m, 2H), 4.78 (dd, J = 8.2, 8.1 Hz, 1H), 7.22−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.8, 18.5, 21.1, 28.7, 59.2, 60.3, 61.9, 63.5, 76.3, 78.7, 127.6, 128.3, 128.7, 129.0, 129.3, 138.4, 138.4, 153.91, 172.6; MS m/z = 408 (M^+).

(−)-(3′*S*,4′*R*,5′*S*)-3-((5′-Methyl-2′-*N*,3′-diphenylisoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (*endo*-3a). Synthesized according to the general procedure on a 0.5 mmol scale with catalyst (*R*)-**9a** (10 mol %); yield 81%; ee = 75%; $[\alpha]_D = -13.1°$ (*c* 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 18.4, 43.6, 62.5, 63,1, 75.0, 80.2, 115.2, 122.3, 127.2, 128.5, 129.4, 129.6, 141.5, 152.1, 153.5, 171.3; HPLC (Daicel Chiralcel OD, hexane /*i*-PrOH = 9/1, flow rate = 1.0 mL/min.) t_R = 42 min (minor), t_R = 58 min (major). Minor amounts of *exo*-**3a** were isolated. Ee = 72%.[20]

A similiar procedure was performed with (*S*)-**9a** as the catalyst to give (+)-*endo*-**3a**: yield 57%; ee = 71%.

(−)-(3′*S*,4′*R*,5′*S*)-3-((2′-*N*,3′-Diphenyl-5′-propylisoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (*endo*-3c). Synthesized according to the general procedure on a 0.5 mmol scale with catalyst (*R*)-**9a** (10 mol %): yield 66%.

***endo*-3c**: yield 32% (61 mg, 0.16 mmol); ee = 82%; $[\alpha]_D$ = −28.6° (*c* =1.0, $CHCl_3$); HPLC (Daicel Chiralcel OD, hexane /*i*-PrOH = 9/1, flow rate = 1.0 mL min) t_R= 20 min (minor), t_R = 28 min (major).

***exo*-3c**: yield 34% (235 mg, 0.62 mmol); ee = 52%;[20] $[\alpha]_D$ = +12.5° (*c* = 1.0, $CHCl_3$).

Procedure for the Conversion of Isoxazolidines 3a and 3e into the Corresponding Isopropyl Esters 10. To the isoxazolidine **3** (0.1 mmol) dissolved in toluene (2 mL) were added Ti(*i*-OPr)$_4$ (295 μL, 1.0 mmol) and *i*-PrOH (2 mmol), and the mixture was refluxed for 5 h. The crude cooled solution was filtered through a 20 mm layer of silica gel. After the silica gel layer was washed with 2 mL of 5% MeOH in CH_2Cl_2, the solvent was evaporated *in vacuo*. The crude material was purified by preparative TLC (silica gel, Et_2O: petroleum ether, 1:2, R_f = 0.8).

(+)-(3*R*,4*S*,5*R*)-5-Methyl-2-*N*,3-diphenyl-4-(isopropoxycarbonyl)isoxazolidine ((+)-10). Synthesized from *endo*$_a$-**3e** according to the above-described procedure: ^1H NMR ($CDCl_3$) δ 1.19 (d, J = 6.0 Hz, 6H), 1.50 (d, J = 5.5 Hz, 3H), 3.13 (dd, J = 8.8, 7.1 Hz, 1H), 4.41 (dq, J = 8.8, 5.9, 1H), 5.02 (h, J = 6.3 Hz, 1H), 5.15 (d, J = 7.2 Hz, 1H), 6.92 (t, J = 7.1 Hz, 1H), 6.98 (d, J = 7.7 Hz, 2H), 7.27 (m, 4H), 7.38 (t, 7.1 Hz, 1H), 7.53 (d, 7.7 Hz, 2H); $[\alpha]_{589} > +35°$; MS m/z = 325 (M^+).

(−)-(3*S*,4*R*,5*S*)-5-Methyl-2-*N*,3-diphenyl-4-(isopropoxycarbonyl)isoxazolidine ((−)-10). Synthesized from (−)-*endo*-**3a** (75% ee) according to the above-described procedure. The ^1H NMR spectra were identical to the spectra obtained for (+)-**10**: $[\alpha]_{589} < -33°$; MS m/z = 325 (M^+).

X-ray Analysis of *exo*-3a and *endo*$_a$-3f.[20] X-ray diffraction analysis on *exo*-**3a** and on *endo*$_a$-**3f** were carried out on a HUBER 4-circle diffractometer at 120 K. The structure of *exo*-**3a** $C_{20}H_{20}N_2O_4$ (M_w 352.40 amu) was determined from a monoclinic crystal of dimensions 0.5 × 0.5 × 0.5 mm^3 (space group $P2_1/c$), with unit cell a = 34.080(11) Å, b = 9.517(5) Å, c = 10.619 (4) Å, β = 98.81(2)°, V = 3404.5 (2.5) Å^3. It has eight molecules per cell, D_x = 1.37353 g·cm^{-3}, μ = 0.0904 mm^{-1}, $F(000)$ = 1488. The cell dimensions were determined from the setting angles of 46 reflections with 14.4° < 2θ < 25.5° using Mo Kα radiation (λ = 0.710 73 Å). A total of 6008 reflections were measured (2θ < 50°) using the ω − 2θ step scan technique. Other similar looking crystals from the same preparation were found to be orthorhombic or to be a mixture of monoclinic and orthorhombic (O−D structure). A dataset from an orthorhombic crystal was collected at rt and showed the same structure but less well defined because of poorer crystal quality. This structure will not be discussed further.

endo$_a$-**3f**: $C_{24}H_{28}N_2O_4$ (M_w = 408.50 amu) was found to be triclinic, $P1$, with a = 9.091(3) Å, b = 6.473(3) Å, c = 9.542(4)) Å, α = 91.67(2)°, β = 95.82(2)°, γ = 100.89(2)°, V = 547.8 (0.4) Å^3, with one molecule per unit cell, μ = 0.0789 mm^{-1}, D_x = 1.2382 g·cm^{-3}, $F(000)$ = 218. The cell dimensions were determined from the setting angles of 46 reflections with 15.8° < 2θ < 23.3° using Mo Kα radiation (λ = 0.710 73 Å). A total of 2235 reflections were measured (2θ < 46°) using the ω − 2θ step scan technique. Data reductions for both datasets included corrections for background, deadtime, Lorentz, and polarization effects, whereas absorption was considered insignificant. Crystal deterioration was found to be negligible. The structures were solved using SIR92[22] and refined by full-matrix least-squares methods including positional and anisotropic thermal parameters for non-hydrogen atoms. Hydrogen atoms were introduced at calculated positions confirmed by difference maps. The final R values were 0.064 for 4532 reflections ($I > 2\sigma > (I)$) and 631 variables for *exo*-**3a**, 0.056 for 1154 reflections ($I > 2\sigma > (I)$) and 269 variables for *endo*$_a$-**3f**.

Supporting Information Available: Copies of NMR spectra (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951204E

(20) The ee's of the *exo*-isomers were determined by ^1H NMR spectroscopy using Eu(hfc)$_3$ as chiral shift reagent.

(21) The authors have deposited atomic coordinates and thermal parameters for *exo*-**3a** and *endo*$_a$-**3f** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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