

Review Article

Metal-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions[†]

Kurt V. Gothelf and Karl Anker Jørgensen*

Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Gothelf, K. V. and Jørgensen, K. A., 1996. Metal-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions. – Acta Chem. Scand. 50: 652–660. © Acta Chemica Scandinavica 1996.

The 1,3-dipolar cycloaddition reaction is an important reaction in organic chemistry since synthetically versatile isoxazolidines with up to three contiguous chiral centers can be formed. The most recent highlights in metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions of alkenes with nitrones are described. A new catalytic approach for the 1,3-dipolar cycloaddition reaction between *N*-acryloyloxazolidinones and nitrones has been developed. By the application of a chiral TiCl₂-TADDOLate catalyst this 1,3-dipolar cycloaddition reaction proceeds with both *exo*- and enantio-selectivity. When the coordination mode of the ligands at the catalyst is changed to, e.g., a Mg^{II}-phenanthroline catalyst, the 1,3-dipolar cycloaddition reaction proceeds with a high degree of *endo*-selectivity. Employing a chiral alkene in the Mg^{II}-phenanthroline-catalyzed reaction leads to high, or complete, double diastereoselectivity. By the use of a chiral Mg^{II}-bisoxazoline catalyst high *endo*-selectivity, and up to 82% enantioselectivity in the 1,3-dipolar cycloaddition reaction of alkenes with nitrones can be achieved. On the basis of a series of semiempirical quantum chemical calculations of the transition states for the magnesium(II) complex catalyzed reactions the catalytic and the diastereo- and enantio-selective course of the reactions can be accounted for. The *endo*- and enantio-selectivity in the 1,3-dipolar cycloaddition reaction of alkenes with nitrones can be further improved by replacement of the chloride ligands in the *exo*-selective TiCl₂-TADDOLate catalyst with tosylato ligands to give diastereo- and enantio-selectivities of >90%. The development of these aspects of the 1,3-dipolar cycloaddition reaction of alkenes with nitrones is based on the isolation and characterisation of a TiCl₂-TADDOLate-alkene intermediate which has led to an understanding of the mechanism of the approach of the nitron to the alkene.

One of the challenges in chemistry in the nineties is to perform selective reactions, i.e. to control both the electronic and steric factors that govern the outcome of a chemical reaction. Control of the electronic factors of a chemical reaction can be achieved by activation of the substrate, e.g. leading to a lowering of the transition state energy of the reaction, while the steric factors can discriminate between parts of the molecule, or even between the faces of a functionality such as an alkene. The greatest challenge with respect to control of the selectivity of a chemical reaction is to achieve regioselectivity, diastereoselectivity, and, probably most important in contemporary chemistry, enantioselectivity.

The use of metals and metal complexes as catalysts

[†] Contribution presented at the Nobel Symposium on *Catalytic Asymmetric Synthesis*, September 3–7, 1995 at Tammsvik, Bro, Sweden.

* To whom correspondence should be addressed.

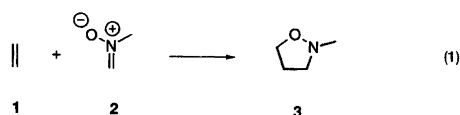
for organic reactions has been known since ‘the birth of chemistry’. The enormous interest in metal-catalyzed reactions observed since then is probably based on several factors. (i) we are beginning to understand the properties of enzymatic systems and are also able to obtain important information about the structure of the active site. These principles are now being used for the development of enzyme-like catalysts for organic reactions. (ii) The development of organometallic chemistry over the last few decades has brought a new class of reagents into the field of metal-catalyzed reactions. These organometallic compounds have contributed, and will in the future contribute, significantly to the library of methods available to the organic chemist. The use of metal complexes in organic reactions has led to the preparation of compounds which a few years ago could only be dreamed about.

Metal-catalyzed asymmetric reduction, functionalis-

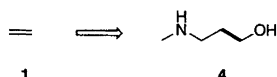
ation and carbon–carbon coupling reactions of alkenes have been extensively developed over the past decade and impressive results have been obtained.¹ One of the other cornerstones in organic chemistry is the concerted cycloaddition reactions of alkenes with various enophiles, as these reactions can lead to highly valuable compounds. One of the more important reactions in this field, besides the Diels–Alder reaction, is the 1,3-dipolar cycloaddition reaction.² In the present review we present our contribution to the development of the metal-catalyzed diastereo- and enantio-selective 1,3-dipolar cycloaddition reaction of alkenes with nitrones and the mechanistic aspects of this reaction.

Metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions of alkenes with nitrones

The 1,3-dipolar cycloaddition reaction of alkenes **1** with nitrones **2** leading to isoxazolidines **3** [reaction (1)] is a fundamental reaction in organic chemistry.

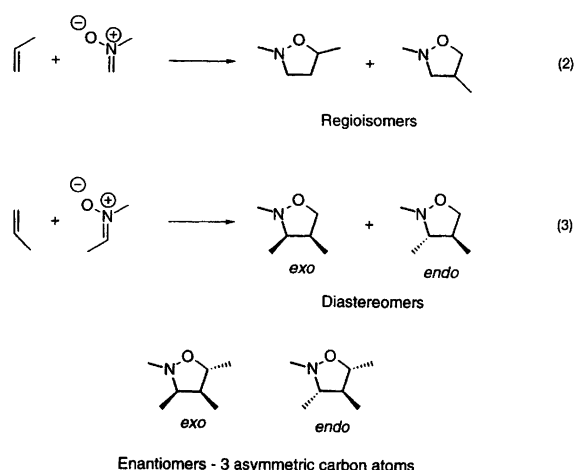


The isoxazolidines **3** formed are useful building blocks in synthesis as they are easily transformed into a range of compounds such as 3-amino alcohols **4** (the original alkene part is presented in bold), as well as other compounds which are important in organic chemistry.² The isoxazolidine route is therefore often used for the preparation of compounds of general interest such as β -amino acids, alkaloids, amino sugars and β -lactams, beside the 3-amino alcohols.^{2,3}



The reaction of an alkene with a nitrone is associated with three major selectivity problems as outlined in Scheme 1.

In reaction (2) in Scheme 1 the regioselectivity problem is presented. If the alkene has a substituent, the carbon atom to which this substituent is bound can add either to the nitrone oxygen atom giving the 5-substituted isoxazolidine, or to the α -carbon atom of the nitrone leading to the 4-substituted isoxazolidine. The regioselectivity of 1,3-dipolar cycloaddition reactions is controlled by both electronic and steric factors.⁴ Each regioisomer consists of a pair of diastereomers, the *endo* and *exo* isomers [Scheme 1, reaction (3)]. The diastereoselectivity of the 1,3-dipolar cycloaddition reaction of an alkene with a nitrone originates from the transition state of the reaction. The nomenclature *endo* and *exo* is well known from the Diels–Alder reaction.⁵ The *endo/exo*-selectivity in the 1,3-dipolar cycloaddition reaction is primarily controlled by the structure of the substrates.



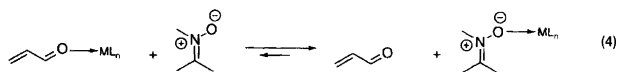
Scheme 1

Furthermore, each of the diastereomers is formed as a pair of enantiomers as outlined in Scheme 1. The selective formation of one of the enantiomers of isoxazolidine **3** is one of the crucial points of the 1,3-dipolar cycloaddition reaction of alkenes with nitrones. In this reaction three new chiral centers may be formed. One chiral carbon atom bound to a carbon atom, one chiral carbon atom bound to a nitrogen atom and finally a chiral carbon atom bound to an oxygen atom may be obtained depending on the substitution patterns of the substrates.

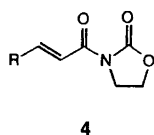
Numerous attempts to produce optically active isoxazolidines from chiral alkenes⁶ or chiral nitrones,⁷ occasionally assisted by metal complexes,⁸ have been attempted, but it is not until recently that a breakthrough in applying metal complexes for the control of the electronic and stereochemical factors governing the 1,3-dipolar cycloaddition reaction of alkenes with nitrones has been achieved. In the following we present the development of chiral metal catalysts, which in the presence of a specific class of alkenes allows one to control the regio-, diastereo- and enantio-selectivity of the 1,3-dipolar cycloaddition reaction of alkenes with nitrones.

The regioselectivity can be controlled by the introduction of a carbonyl functionality in the α -position to the alkene, as it has been observed that the reaction of α,β -disubstituted enones with nitrones leads mainly to one of the regioisomers of the isoxazolidine.² In an attempt to activate α,β -unsaturated carbonyl compounds towards 1,3-dipolar cycloaddition with nitrones a series of experiments and theoretical calculations were performed in which different Lewis acid complexes, such as boron, aluminium and titanium complexes, were tested as catalysts.⁹ These investigations showed that no significant acceleration of the reaction was induced by the metal complexes. We assume that the lack of activation of the α,β -unsaturated carbonyl compound is due to favourable coordination of the metal complexes to the nitrone oxygen atom rather than to the oxygen atom of the α,β -

unsaturated carbonyl compound. The equilibrium in reaction (4) is thus proposed to be almost completely shifted towards the right-hand side.



In order to activate an enone towards 1,3-dipolar cycloaddition to a nitron the equilibrium in reaction (4) needs to be shifted to the left-hand side. This can be accomplished by the use of an alkene possessing a bidentate coordination site and by the use of a metal catalyst that favours this type of chelation. It has been found that oxazolidinones, **4**, are excellent substrates for coordination to a variety of different metal complexes and that the alkene part of **4** thereby is activated towards a 1,3-dipolar cycloaddition to a nitron.⁹



Before proceeding to the reaction of **4** with nitrones it might be appropriate to rationalize the activation of **4** by Lewis acid complexes. The reaction of **4** with a nitron leading to the isoxazolidine is considered to be a concerted $[4\pi_s + 2\pi_s]$ cycloaddition reaction in which the alkene acts as the two-electron component, while the nitron is the four-electron component. The major interaction of an electron-deficient alkene, such as **4**, with a nitron is considered to be between the LUMO of the alkene and the HOMO of the nitron. The HOMO and LUMO of **4** ($R = \text{Me}$) are presented on the left in Fig. 1, while the HOMO and LUMO of the nitron **2a** is shown in the middle. Interaction of the HOMO of **4** with the LUMO of **2a** as outlined on the left in Fig. 1 accounts for the regioselectivity in the reaction, since the LUMO of **4** has the largest amplitude at the β -carbon atom and the HOMO of **2a** has the largest amplitude at the nitron oxygen atom, and thus, by using a frontier-orbital line of reasoning this interaction will be the most favourable, in agreement with the experimental observations. Furthermore, this interaction also has the smallest HOMO–LUMO energy difference and it will thus be the predominant interaction. Coordination of a Lewis acid such as magnesium(II), in a bidentate fashion, to **4** leads to a change in the frontier orbitals of the alkene part of **4**. The LUMO and HOMO of **4** are lowered in energy by coordination to the Lewis acid and, furthermore, the amplitude at the β -carbon atom is increased by coordination to the Lewis acid, compared with **4**. The frontier orbitals of **4** coordinated to magnesium(II) are outlined on the right of Fig. 1. These changes of the frontier orbital energies of **4** lead to a better interaction of the HOMO of the nitron with the LUMO of the alkene part of **4** and account for the catalytic properties of the Lewis acid when coordinated to **4**.

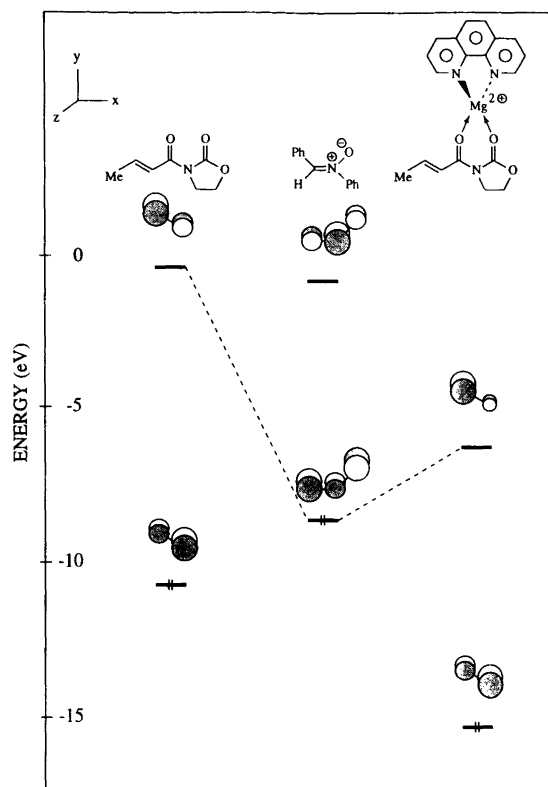
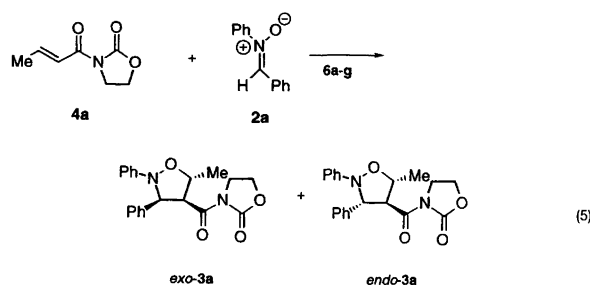


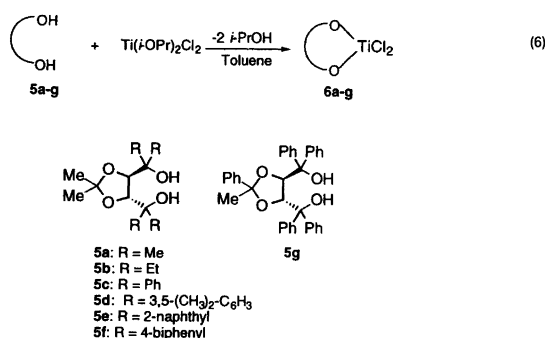
Fig. 1. Frontier orbitals of the alkene **4a** (left-hand side), set up for an interaction with the frontier orbitals of the nitron **2a** (centre). On the right hand-side are the frontier orbitals of **4a** coordinated to Mg^{II} -phenanthroline **9**. The primary interactions are indicated by dotted lines.

Exo-selective and enantioselective reactions

Titanium complexes have been found to be very efficient catalysts for the 1,3-dipolar cycloaddition between alkenes and nitrones and with these catalysts one can control both the diastereo- and enantio-selectivity of the reaction.⁹

The catalytic effect of different chiral dichlorotitanium diolates has been tested for the reaction of **4a** with **2a** [reaction (5)]. The following ligands were investigated: dialkyl tartrates, 1,1'-binaphthols and $\alpha, \alpha', \alpha', \alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs). The TiCl_2 -TADDOLates **6a-g** showed the most promising properties, and their preparations are outlined in reaction (6).¹⁰



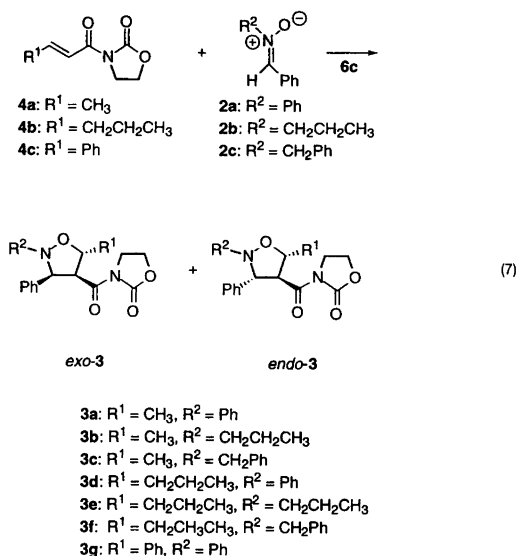


The reaction of alkene **4a** with nitronone **2a** in the presence of some of the TiCl₂-TADDOLates **6a-g** are presented in Table 1 together with the results for the uncatalyzed- and Ti(*i*-OPr)₂Cl₂ catalyzed reactions.⁹

The uncatalyzed 1,3-dipolar cycloaddition reaction of **4a** with **2a** requires elevated temperature, but even at 50 °C a low conversion is observed (Table 1, entry 1). The reaction of **4a** with **2a** in the absence of a catalyst gives an *exo*-**3a**:*endo*-**3a** ratio of 91:9. Addition of Ti(*i*-OPr)₂Cl₂ (100 mol%) to this reaction leads to smooth reaction at room temperature with a conversion of 68% and an *exo*-**3a**:*endo*-**3a** ratio of 87:13 (entry 2). A ligand-accelerating effect¹¹ is observed if catalyst **6b** is used leading to a significant improvement in both the conversion and the *exo*-**3a**:*endo*-**3a** ratio. The *exo*-**3a**:*endo*-**3a** ratio, 95:5, is the highest *exo*-selectivity observed in the reaction of **4a** with **2a**. Furthermore, an ee of 29% is found, which is the highest ee observed when alkyl substituents are present in the α-position of the TADDOL ligands. If aromatic substituents are introduced into the α-position of the TADDOL ligands an improvement of the ee of the reaction is found, and a similar high *exo*:*endo* ratio is maintained. The TiCl₂-TADDOLate catalyst **6c** in equimolar amount gives 56% ee and the properties can be improved by changing the solvent from CH₂Cl₂ (entry 4) to toluene (entry 5), while the latter reaction takes place in the presence of 10 mol% of catalyst **6c**. Introducing other aromatic substituents as 3,5-dimethylphenyl (entry 6) or 2-naphthyl (entry 7) in the α-position of the TADDOL ligand leads to a lower *exo*:*endo* ratio, as well as a lower ee of *exo*-**3a**. However, 45% ee of *endo*-**3a** is formed

with **6c** as the catalyst. It is interesting to note that the TiCl₂-TADDOLate catalyst **6g** which has been applied with success in titanium-catalyzed asymmetric Diels-Alder reactions¹² leads to a reduction in the ee when used for the 1,3-dipolar cycloaddition reactions of alkenes with nitrones.

The catalytic properties of **6c** (10 mol%) on the reaction of some alkenes **4a,b** with some nitrones **2a-c** [reaction (7)] are presented in Table 2.⁹



The use of the TiCl₂-TADDOLate catalyst **6c** to control the *exo*-selectivity and the enantioselectivity of the 1,3-dipolar cycloaddition reaction of **4a,b** with **2a-c** shows that the diastereoselectivity is most dependent on the nitronone and the best results are obtained with the *N*-phenylnitronone **2a** where an ee of 60% is found (Table 2, entry 1). Replacing the *N*-phenyl substituent with alkyl or benzyl substituents leads to a reduction of both the diastereo- and enantio-selectivity. It should be noted that the ee of the minor *endo*-diastereomers are always higher than for the *exo*-diastereomers, with the best ee in the range of 59–62% (entries 1–3).

Although the ee of the reactions of alkenes **4a,b** with nitrones **2a-c** is moderate, it can be improved for *exo*-

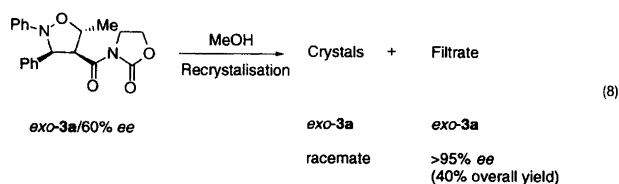
Table 1. Catalytic effects of Ti(*i*-OPr)₂Cl₂ and some TiCl₂-TADDOLates **6a-g** on the 1,3-dipolar cycloaddition of **4a** with **2a**.⁹

Entry	Catalyst (mol%)	Conversion (%)	<i>exo</i> : <i>endo</i> ratio	Ee (%) <i>exo</i> - 3a (<i>endo</i> - 3a)
1	—	39	91:9	—
2	Ti(<i>i</i> -OPr) ₂ Cl ₂ (100)	68	87:13	—
3	6b (100)	85	95:5	29
4	6c (100)	85	89:11	56
5	6c (10)	94	90:10	58
6	6d (100)	81	77:23	20
7	6e (100)	78	57:43	27 (45)
8	6g (100)	93	88:12	22

Table 2. Enantioselective 1,3-dipolar cycloaddition reactions of alkenes **4a,b** with nitrones **2a–c** catalyzed by **6c**.⁹

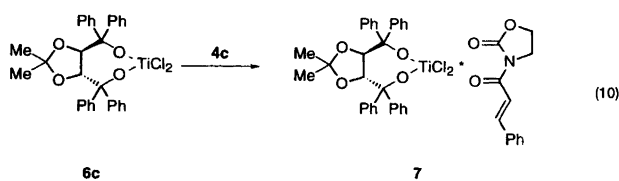
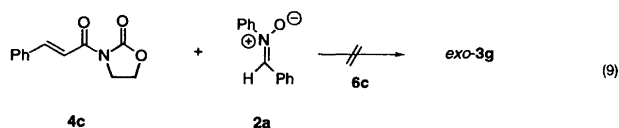
Entry	Alkene	Nitrone	Product	Yield (<i>exo:endo</i>) (%)	Ee (%) <i>exo-3</i> / <i>endo-3</i>
1	1a	2a	3a	94 (85:9)	60/62
2	1a	2b	3b	84 (51:33)	15/62
3	1a	2c	3c	71 (38:33)	27/59
4	1b	2a	3d	71 (62:9)	39/48
5	1b	2b	3e	80 (40:40)	10/35
6	1b	2c	3f	85 (44:41)	24/53

3a by recrystallization from MeOH as outlined in reaction (8).



The recrystallization procedure leads to *exo-3a* with an ee >95% as the filtrate, while the racemate precipitates. The crystals of racemic *exo-3a* have been subjected to an X-ray structural determination, in order to confirm the *exo*-selectivity.¹³

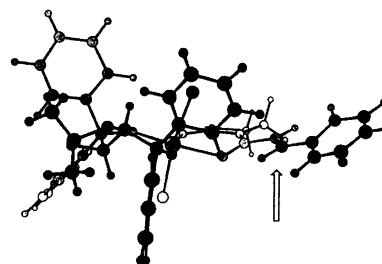
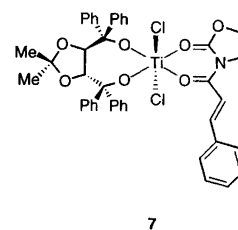
Attempts to perform a 1,3-dipolar cycloaddition reaction of the cinnamoyl oxazolidinone **4c** with nitrone **2a** in the presence **6c** as the catalyst [reaction (9)] under a variety of different reaction conditions were unsuccessful.



Unexpectedly, another interesting reaction took place. The catalyst **6c** precipitated with the cinnamoyl oxazolidinone **4c** as a 1:1 complex **7** [reaction (10)].¹⁴ The complex formed by chelation of **4c** to the titanium centre in **6c** is probably an important intermediate, not only in the 1,3-dipolar cycloaddition reactions of alkenes with nitrones, but probably also in the TiCl₂-TADDOLate catalyzed asymmetric Diels–Alder reaction.¹⁴ The complex precipitated as crystals which were subjected to an X-ray analysis.¹⁴

The crystal structure of **7** shows an octahedral complex with the chiral diol **5c** and the alkene **4c** in the equatorial plane and the two chloride ligands in the axial positions, *trans* to each other. The alkene plane of the dienophile

is tilted 33° out of the plane containing the titanium atom and the four equatorial oxygen atoms. The X-ray structure shows that one of the phenyl substituents of the TADDOL ligand seems to block the upper face of the alkene forcing the reactant to approach the α -*Re*-face of the alkene as illustrated by the arrow below.



For the analogous TiCl₂-TADDOLate catalyzed asymmetric Diels–Alder reaction the absolute configuration of the product of the reaction between cyclopentadiene with **4c** catalyzed by **6c** tells us that the product is formed by approach of cyclopentadiene to the α -*Re* face of **4c** coordinated to **6c**.¹⁴ This is in accordance with the approach indicated by the arrow in **7**.^{14,15}

Endo-selective and enantioselective reactions

The diastereoselectivity (*exo/endo* selectivity) of the 1,3-dipolar cycloaddition of alkenes with nitrones can be controlled by (i) using metal complexes which form tetrahedral complexes, rather than octahedral complexes,¹³ or (ii) by an exchange of the axial ligand in the TiX₂-TADDOLate catalyst with bulkier ligands.¹⁶

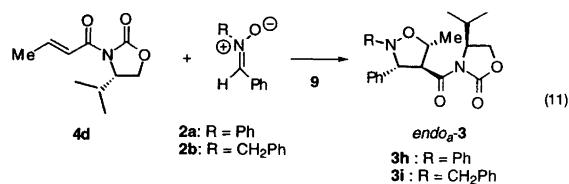
The diastereoselectivity of the 1,3-dipolar cycloaddition reaction between alkene **4a** and nitrone **2a** [reaction (5)] has been performed in the presence of different Lewis acid complexes in order to study the influence on the *endo:exo* ratio (Table 3).¹³

Table 3. Diastereoselective 1,3-dipolar cycloaddition reaction of alkene **4a** with nitrone **2a** in the presence of different Lewis acid complexes as catalysts.¹³

Entry	Catalyst	Conversion (%)	<i>endo</i> : <i>exo</i>
1	Ti(<i>i</i> -OPr) ₂ Cl ₂	68	13:87
2	6b	85	5:95
3	Cu ^{II} -phenanthroline 8	63	81:19
4	MgI ₂ ·I ₂	>90	15:85
5	Mg ^{II} -phenanthroline 9	>90	>95:<5

The Ti(*i*-OPr)₂Cl₂ catalyst give a relative low conversion and an *endo*-**3a**:*exo*-**3a** ratio of 13:87 (Table 3, entry 1). The highest *exo*-selectivity of 90% is obtained with catalyst **6b**, and in this reaction a conversion of 85% is found (entry 2). Use of a Cu^{II}-phenanthroline catalyst **8** leads to a change in the *endo*-**3a**:*exo*-**3a** ratio to 81:19 with a conversion of 63% (entry 3). Use of MgI₂·I₂ as the catalyst changes the *endo*-**3a**:*exo*-**3a** ratio to nearly the same as obtained with the Ti(*i*-OPr)₂Cl₂ catalyst, but a much higher conversion is found (entry 4). However, when Mg^{II}-phenanthroline **9** is used a significant change towards *endo*-selectivity is observed; an *endo*-**3a**:*exo*-**3a** ratio of >95:<5 is obtained together with a high conversion (entry 5) comparable to that of MgI₂·I₂. Substitution with bulky groups at the 2- and 9-positions in the phenanthroline ligand did not increase the *endo*-**3a**:*exo*-**3a** ratio further.

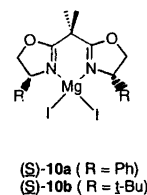
The Mg^{II}-phenanthroline catalyst **9** was applied to a series of *endo*-selective 1,3-dipolar cycloaddition reactions of alkenes **4a,b** with nitrones **2a,b**. In small-scale reactions where the catalyst was present in 10 mol% the conversions were generally very high (>90%) as were the *endo*:*exo* ratios >95:<5.¹³ The catalytic properties of **9** were further extended to a double diastereoselective reaction of a chiral oxazolidinone **4d** with the nitrones **2a,b** [reaction (11)].¹³



The results for reaction (11) are outlined in Table 4.¹³

The reaction of nitrone **2a** with alkene **4d** in the presence of the Mg^{II}-phenanthroline catalyst **9** led to a highly selective reaction as evidenced by the formation of only one of the four diastereomers (according to ¹H NMR spectroscopy) in excellent yield (Table 4, entry 1). The reaction proceeded well for small-scale reactions, as well as on a larger scale (entries 1,2). The *N*-benzyl nitrone **2b** also reacted with the alkene **4d** giving mainly one of the four diastereomers in a fair yield (entry 3). These results show that **9** induces a very high degree of double diastereoselectivity in the 1,3-dipolar cycloaddition reaction between the chiral alkene **4d** and the nitrones.

The *endo*- and enantio-selective 1,3-dipolar cycloaddition reactions of alkenes with nitrones can also be performed with chiral catalysts, especially Mg^{II}-bisoxazolines (*S*)-**10a** and (*S*)-**10b**.



The results for some *endo*- and enantio-selective 1,3-dipolar cycloaddition reactions catalyzed by the Mg^{II}-bisoxazoline (*S*)-**10a** are presented in Table 5.¹³

The catalyst (*S*)-**10a** has proved to be efficient for the control of both the diastereo- and enantio-selectivity in the reaction between *N*-phenyl nitrone **2a** and alkene **4a**.

Table 4. Double diastereoselective 1,3-dipolar cycloaddition reactions of alkene **4d** with nitrones **2a,b** in the presence of Mg^{II}-phenanthroline **9** as the catalyst.¹³

Entry	Nitron	Molar scale/mmol	Yield (%)	<i>endo</i> _a (%)	Other diastereomers
1	2a	0.1	95	3h (98)	<2
2	2a	0.5	99	3h (98)	<2
3	2b	0.5	67	3i (93)	7

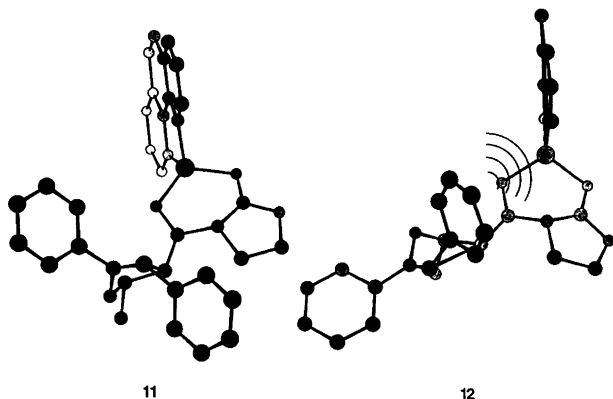
Table 5. Some examples of metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions of alkenes **4a,b** with nitrones **2a,b** in the presence of (*S*)-**10a** as the catalyst.¹³

Entry	Alkene	Nitron	Product	Conversion (%)	<i>endo</i> : <i>exo</i>	Ee <i>endo</i> (%)
1	4a	2a	3a	72	92:8	79
2	4a	2c	3c	82	89:11	0
3	4b	2a	3d	>95	>95:<5	82

By the application of 10 mol% of (*S*)-**10a** in the above reaction an *endo*-**3a**:*exo*-**3a** ratio of 92:8 was obtained, the *endo*-isomer having an ee of 79% (Table 5, entry 1). The *N*-benzylnitronone **2c** also reacts with **4a** in the presence of (*S*)-**10a** to give primarily the *endo*-isomer, but unfortunately the product was racemic (entry 2). In the reaction of the hexenoyloxazolidinone **4b** with **2a** catalysed by 10 mol% of (*S*)-**10a** an excellent *endo*-**3a**:*exo*-**3a** ratio of >95: <5 is obtained, with an ee of 82% of the *endo* diastereomer of **3b** (entry 3).

The chiral centres in *endo*-**3a** have been assigned as 3*R*,4*S*,5*R* on the basis of the isolation and characterisation of *endo*_a-**3h** formed by reaction of **4d** with **2a** in the presence of Mg^{II}-phenanthroline **9** as the catalyst.¹³

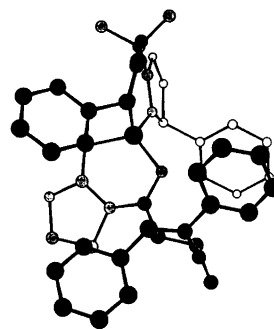
In order to understand the rate enhancement and diastereo- and enantio-selectivity observed in the Mg^{II}-complex catalyzed 1,3-dipolar cycloaddition reactions of alkenes with nitrones, a series of semiempirical calculations using the MOPAC-PM3 method were carried out.¹³ The transition states for the reaction of alkene **4a** with nitronone **2a** in the absence of a catalyst, and in the presence of the Mg^{II}-phenanthroline **9** and the Mg^{II}-bisoxazoline (*S*)-**10a**, have been examined. The transition state energies for the formation of *exo*-**3a** and *endo*-**3a** were calculated to be 40 kcal mol⁻¹ and 65 kcal mol⁻¹, respectively,¹³ indicating that the former should be expected as the major product, which is in accordance with the experimental results, as a ratio of *exo*-**3a**:*endo*-**3a** = 91:9 is obtained.⁹ If the calculations were performed to take into account the presence of **9** coordinated to **4a** both the transition state energies for the *endo*- and *exo* approaches of nitronone **2a** to the alkene and the relative location of the transition states are altered. The calculated transition state for the formation of *endo*-**3a** is shown in **11**, while the one leading to *exo*-**3a** is outlined in **12**.



The transition state energy for the formation of *endo*-**3a** (**11**) is calculated to be 20 kcal mol⁻¹, while that for the formation of *exo*-**3a** (**12**) is calculated to be 35 kcal mol⁻¹. These transition state energies show that, in the presence of **9** as the catalyst, *endo*-**3a** should be formed, which is in accordance with the experimental results.¹³ The calculated transition state energy for the formation

of *endo*-**3a** also nicely accounts for the catalytic effect of **9**. The reason for the *endo*-selectivity in the presence of **9** is obvious from the transition states illustrated in **11** and **12** where significant steric repulsion between the incoming *C*-phenyl substituent of nitronone **2a** and the phenanthroline ligand coordinated to Mg^{II} is seen in the latter.

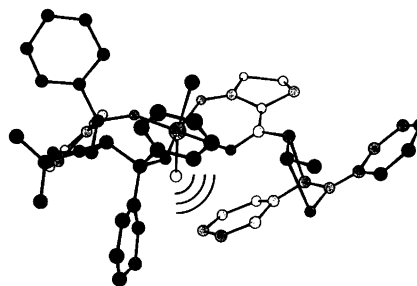
The calculated transition state for the approach of nitronone **2a** to the alkene coordinated to the Mg^{II}-bisoxazoline (*S*)-**10a** catalyst is depicted in **13**.



13

The transition state energy for **13** is calculated to be 32 kcal mol⁻¹ and is significantly lower in energy than those for the three other possible approaches of the nitronone to the alkene. The transition state, as outlined in **13**, accounts for the catalytic effect and for the regio-, diastereo- and enantio-selectivity observed in the Mg^{II}-bisoxazoline-catalyzed reactions of alkenes with nitrones.

Returning to the titanium catalysts we have found that, on the basis of an alteration of the TiCl₂-TADDOLate catalyst, a highly *endo*- and enantio-selective titanium catalyst, for the 1,3-dipolar cycloaddition reaction between alkenes and nitrones could be developed.¹⁶ The development of this reaction was based on the crystal structure of the TiCl₂-TADDOLate-alkene complex **7** from which one can propose the transition state model outlined in **14** for the reaction of alkene **4a** with nitronone **2a** in the presence of catalyst **6c**.

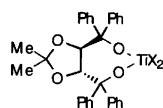


14

It appears from **14** that no significant steric repulsion between the α -phenyl group of the nitronone and the chloride ligand on the titanium atom is apparent for the

exo approach of the nitron. Since the *exo*-transition state is generally of lower energy than the *endo*-transition state when no steric repulsion is present, the *exo*-diastereomer is primarily obtained from this reaction. However, the axial ligands at the titanium atom have been found to be of significant importance for both the diastereo- and enantio-selectivity of the reaction of alkenes with nitrones.¹⁶ According to **14** it appears that the *exo*-approach would be less favoured if the chloride ligands on the titanium atom are replaced by bulkier groups, owing to increased steric hindrance between the new bulky ligands and the α -phenyl group of the nitron (this increased steric repulsion is indicated by the curved lines).

In order to verify this hypothesis a series of experiments, where the bulkiness of the axial ligands was increased, was performed.¹⁶ The titanium complexes **6c,h,i** are examples of the catalysts that were tested in the reaction between alkene **4a** and nitron **2a**.¹⁶



6c: X = Cl
6h: X = Br
6i: X = OTs

The catalyst **6c** induced, as previously mentioned, *exo*-selectivity in the 1,3-dipolar cycloaddition reaction, whereas with **6h**, the bromide analogue of **6c**, the diastereoselectivity changed giving *endo*-**3a** as the major diastereomer and with improved ee (Table 6, entries 1,2). The reaction of **4a** and **2a** in the presence of 50 mol% of the bulky tosylato analogue Ti(OTs)₂-TADDOLate **6i** gave good *endo*-selectivity and high enantioselectivity; a 90% ee was obtained (entry 3). The *endo*-selectivity of the latter reaction was excellent, and for the first time a more than 90% ee could be obtained in a metal-catalysed 1,3-dipolar cycloaddition reaction between nitrones and alkenes.

Thus, the high *endo*-selectivity observed for the 1,3-dipolar cycloaddition reaction of alkene **4a** with nitron **2a** is in nice agreement with the model predicted from **14**.

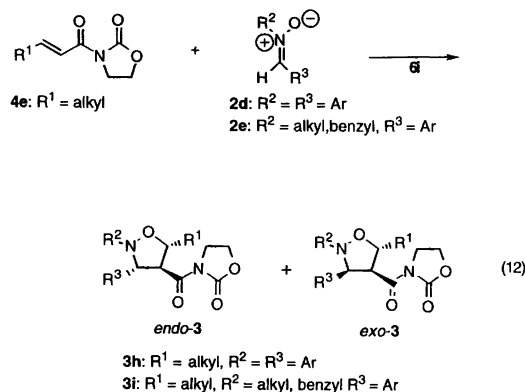
The Ti(OTs)₂-TADDOLate catalyst **6** was then exam-

Table 6. Application of different TiX₂-TADDOLates as catalyst for the 1,3-dipolar cycloaddition reaction between **4a** and **2a**.¹⁶

Entry	Catalyst	Conversion (%)	<i>endo:exo</i>	Ee <i>endo</i> (%) ^a
1	6c	98	10:90	62 (60)
2	6h	98	64:36	76 (64)
3	6i	99	>95:<5	93

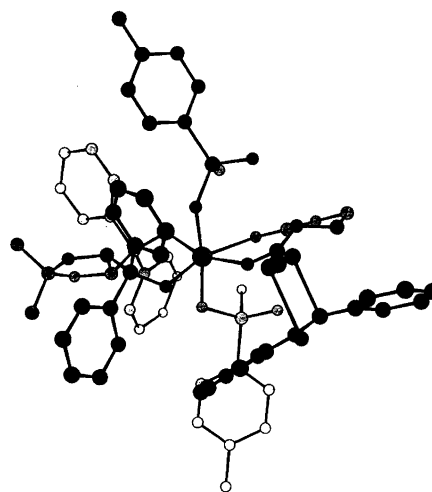
^a Ee of *exo*-diastereomer in parentheses.

ined in a series of reactions employing alkenes **4a,b** and nitrones **2d,e** [reaction (12)].¹⁶



For all reactions in which **6i** was the catalyst, *endo:exo* ratios >90% were obtained, and most remarkably, when R²=R³ was phenyl or substituted phenyl, *endo*-**3h** was formed with >90% ee and in relatively good isolated yield.¹⁶ The *N*-benzyl- and *N*-alkyl-nitrones **2e** reacted with **4a** in the presence of **6i** to give products with moderate enantioselectivities (40–60%). The enantioselectivities obtained for the reactions of **4e** with **2d** are the highest reported for 1,3-dipolar cycloaddition reactions between alkenes and nitrones.

On the basis of the crystal structure of **7**, an MM2 model of the approach of **2a** to **4a** coordinated to **6i** is illustrated below in **15** which accounts for both the *endo*- and enantio-selectivity of this 1,3-dipolar cycloaddition reaction of alkenes with nitrones. This approach is in agreement with the absolute configuration of the product which has been determined.¹⁶



15

Epilogue

At the present stage of the development of metal-catalyzed 1,3-dipolar cycloaddition reactions of alkenes

with nitrones one can, to a relatively high extent, control the diastereoselectivity of the reaction and obtain a >90% ee of the *endo*-isoxazolidines, whereas up to 60% ee has been obtained for the *exo*-isoxazolidines. There are certain restrictions as to which substrates can be used as only alkenes having alkyl substituents at the β -carbon atom are reactive. For the nitrone, especially, the *N*-phenylnitrones give both high *endo*- and enantioselectivities, whereas for the *exo*-selective reactions there are also some limitations. In order to improve the metal-catalysed 1,3-dipolar cycloaddition reaction of alkenes with nitrones and to make this reaction a synthetically useful procedure it will be necessary to develop catalysts or substrates which allow one to introduce a variety of different substituents such as aryl, alkyl and benzyl in different positions of the isoxazolidine ring. We are now in the process of tackling these problems.

Acknowledgements. Thanks are expressed to *Forskningsrådene, Statens Tekniske Videnskabelige Forskningsråd, Carlsbergfondet* and *Aarhus Universitets Forskningsfond* for financial support.

References

- See, e.g., Noyori, R. *Asymmetric Catalysis in Organic Chemistry*, Wiley: New York, 1994.
- (a) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH, New York 1988; (b) Tufariello, J. J. In: Padwa, A., Ed., *1,3-Dipolar Cycloaddition Chemistry*, Wiley, New York, 1984, Vol. 2, pp. 83–168.
- Mulzer, J. In: Mulzer, J., Altenbach, H.-J., Braun, M., Krohn, K. and Reissig, H.-U., Eds., *Organic Synthesis Highlights*, VCH, New York 1991, p. 77.
- Houk, K. N. *Top. Curr. Chem.* 79 (1979) 1.
- Woodward, R. B. and Hoffmann, R. *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim 1970.
- For recent 1,3-dipolar cycloaddition reactions with chiral nitrones, see: (a) Kiers, D., Moffat, D., Overton, K. and Tomanek, R. *J. Chem. Soc., Perkin Trans. 1* (1991) 1041; (b) Brandi, A., Cicchi, S., Goti, A., and Pietrusiewicz, K. M. *Tetrahedron: Asymmetry* 2 (1991) 1063; (c) Goti, A., Cicchi, S., Brandi, A. and Pietrusiewicz, K. M. *Tetrahedron: Asymmetry* 2 (1991) 1371; (d) McCaig, A. E. and Wightman, R. H. *Tetrahedron Lett.* 34 (1993) 3939; (e) Saito, S., Ishikawa, T., Kishimoto, N., Kohara, T. and Moriwake, T. *Synlett* (1994) 282; (f) Oppolzer, W., Deerberg, J. and Tamura, O. *Helv. Chim. Acta* 77 (1994) 554.
- For recent 1,3-dipolar cycloaddition reactions with chiral alkenes, see: (a) Olsson, T., Stern, K., Westman, G. and Sundell, S. *Tetrahedron* 46 (1990) 2473; (b) Ito, M. and Kibayashi, C. *Tetrahedron* 47 (1991) 9329; (c) Carruthers, W., Coggins, P. and Weston, J. B. *J. Chem. Soc., Chem. Commun.* (1991) 117; (d) Takahashi, T., Fujii, A., Sugita, J., Hagi, T., Kitano, K., Arai, Y., Koizumi, T. and Shiro, M. *Tetrahedron: Asymmetry* 2 (1991) 1379; (e) Panfil, I., Belzecki, C., Urbanczyk-Lipkowska, Z. and Chmielewski, M. *Tetrahedron* 47 (1991) 10087; (f) Krol, W. J., Mao, S., Steele, D. L. and Townsend, C. A. *J. Org. Chem.* 56 (1991) 728; (g) Brandi, A., Cicchi, S., Goti, A., Pietrusiewicz, K. M., Zablocka, M. and Wisniewski, W. *J. Org. Chem.* 56 (1991) 4382; (h) Annunziata, R., Cinquini, M., Cozzi, F., Giaroni, P. and Raimondi, L. *Tetrahedron Lett.* 32 (1991) 1659; (i) Ito, M., Maeda, M. and Kibayashi, C. *Tetrahedron Lett.* 33 (1992) 3765; (j) Bravo, P., Bruché, L., Farina, A., Fronza, G., Meille, S. V. and Merli, A. *Tetrahedron: Asymmetry* 4 (1993) 2131; (k) Saito, S., Ishikawa, T. and Moriwake, T. *Synlett* (1994) 279; (l) Rispens, M. T., Keller, E., Lange, B., Zijlstra, R. W. J. and Feringa, B. L. *Tetrahedron: Asymmetry* 5 (1994) 607; (m) Ina, H., Ito, M. and Kibayashi, C. *J. Chem. Soc., Chem. Commun.* (1995) 1015; (n) Langlois, N., Bac, N. V., Dahuron, N., Delcroix, J.-M., Deyne, A., Griffart-Brunet, D., Chiaroni, A. and Riche, C. *Tetrahedron* 51 (1995) 3571.
- For 1,3-dipolar cycloaddition reactions involving metal-complexes, see: (a) Kanemasa, S., Uemura, T. and Wada, E. *Tetrahedron Lett.* 33 (1992) 7889; (b) Kanemasa, S., Tsuruoka, T. and Wada, E. *Tetrahedron Lett.* 34 (1993) 87; (c) Kanemasa, S., Nishiuchi, M., Kamimura, A. and Hori, K. *J. Am. Chem. Soc.* 116 (1994) 2324; (d) Kanemasa, S. and Tsuruoka, T. *Chem. Lett.* (1995) 49; (e) Murahashi, S.-I., Imada, Y., Kohno, M. and Kawakami, T. *Synlett* (1993) 395; (f) Tamura, O., Yamaguchi, T., Noe, K. and Sakamoto, M. *Tetrahedron Lett.* 34 (1993) 4009; (g) Tamura, O., Yamaguchi, T., Okabe, T. and Sakamoto, M. *Synlett* (1994) 620; (h) Gilbertson, S. R., Dawson, D. P., Lopez, O. D. and Marshall, K. L. *J. Am. Chem. Soc.* 117 (1995) 4431; (i) Seerden, J.-P. G., Scholte op Reimer, A. W. A. and Scheeren, H. W. *Tetrahedron Lett.* 35 (1994) 4419; (j) Seerden, J.-P., Kuypers, M. M. M. and Scheeren, H. W. *Tetrahedron: Asymmetry* 6 (1995) 1441.
- Gothelf, K. V. and Jørgensen, K. A. *J. Org. Chem.* 59 (1994) 5687.
- Ito, Y. N., Ariza, X., Beck, A. K., Bohác, A., Ganter, C., Gawley, R. E., Kühnle, F. N. M., Tuleja, J., Wang, Y. M. and Seebach, D. *Helv. Chim. Acta* 77 (1994) 2071.
- Berrisfield, D. J., Bolm, C. and Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* 34 (1995) 1059.
- Narasaka, K., Iwasawa, N., Inoue, M., Yamada, T., Nakashima, M. and Sugimori, J. *J. Am. Chem. Soc.* 111 (1989) 5340.
- Gothelf, K. V., Hazell, R. G. and Jørgensen, K. A. *J. Org. Chem.* 61 (1996) 346.
- Gothelf, K. V., Hazell, R. G. and Jørgensen, K. A. *J. Am. Chem. Soc.* 117 (1995) 4435.
- Gothelf, K. V. and Jørgensen, K. A. *J. Org. Chem.* 60 (1995) 6847.
- Gothelf, K. V., Thomsen, I. and Jørgensen, K. A. *J. Am. Chem. Soc.* 118 (1996) 59.

Received September 20, 1995.