Pergamon

Tetrahedron 55 (1999) 8509–8524

TETRAHEDRON

Control of Diastereoselectivity in Metal-Catalyzed 1,3-Dipolar Cycloaddition between Diphenylnitrone and Chiral Auxiliary-Substituted Crotonyl Amide

Giovanni Desimoni,*[§] Giuseppe Faita,* Mariella Mella, Pierpaolo Righetti and Michele Zema‡

Dipartimento di Chimica Organica, Università di Pavia, V.le Taramelli 10, 27100 Pavia, Italy

‡ *Centro Grandi Strumenti, Università di Pavia, Via Bassi 21, 27100 Pavia, Italy*

Received 1 February 1999; revised 26 April 1999; accepted 20 May 1999

Abstract - The 1,3-dipolar cycloaddition (1,3-DC) between diphenyl nitrone (**1**) and 4-(*S*)-benzyl-((*E*)-2′-butenoyl)-1,3-oxazolidin-2-one (**2**) was studied in the presence of several inorganic salts whose cations behave as Lewis acid. Depending on the salt and the experimental conditions, three products (**3-5**) can be obtained diastereoselectively. The type of conformation assumed by **2** when coordinated to the cation, allows the attack of **1** on either the *Re*- or the *Si*-face of the dipolarophile and rationalizes the resulting diastereoselectivity. The coordination of the reagents around the cation was studied by NMR spectroscopy with 2-acetyl-4-(*S*)-benzyl-1,3-oxazolidin-2-one (**7**) as model compound.

© 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Nitrones; Cycloadditions; Diastereoselection; Catalysis.

Introduction

Asymmetric synthesis by 1,3-dipolar cycloaddition (1,3-DC)[1] between alkenes and nitrones has received increasing attention and it can be approached either by the use of a chiral catalyst,[2-8] or by running the reaction with a dipolarophile having a chiral auxiliary group, in the presence of a suitably choosen Lewis acid (in general an inorganic salt).[1b] The synthetic utility of this process is focused by the conversion of the optically active isoxazolidine either into a 1,3-aminoalcohol[2h] or into a β-lactam,[6b] both retaining the stereochemistry of the stereogenic centers of the heterocyclic cycloadduct.

The cycloaddition between diphenyl nitrone and *N*-alkenoyl-oxazolidinones is the model reaction widely used to test the efficiency of a catalyst in the control of the selectivity.

[§] E-mail address: desimoni@chifis.unipv.it

0040-4020/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.

PII: S0040-4020(99)00469-X

In the absence of any catalyst, 3-crotonoyl-1,3-oxazolidin-2-one reacts slowly at 50 °C and only 39% conversion was observed after 20 h to give a 91 : 9 mixture of *exo*- and *endo*-3-(((5′-methyl-2′,3′-diphenyl)isoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-ones without any trace of the corresponding 4′-methyl regioisomers.[2a] The use of Lewis acid catalysts not only allowed the reaction to proceed smoothly at room temperature, but also strongly influenced the diastereoselectivity of the 1,3-DC. Thus, different achiral catalysts were tested and the results are reported in Table 1.

Some catalysts gave a diastereomer ratio similar to that of the uncatalyzed reaction (Table 1 - entries 1,2,11), some others a poor diastereoselection (entries 7,9), at least three of them invert the diastereoselection (entries 3,4,10) and the *endo* isomer becomes, by far, the main product.

Table 1. Influence of different achiral catalysts on the diastereoselectivity of the reaction between diphenyl nitrone and 3-crotonoyl-1,3-oxazolidin-2-one at ambient temperature.

Entry	Catalyst	Solvent	Yield(%)	*Endo* : *Exo*	Literature
1	Ti(*i*-OPr)$_2$Cl$_2$	$CHCl_3$	68	13 : 87	2a
2	MgI_2-I_2	CH_2Cl_2	>90	15 : 85	2c
3	MgI_2 - Phenanthroline	CH_2Cl_2	>90	>95 : <5	2c
4	MgI_2 - 2,9DMP[a]	CH_2Cl_2	>90	>95 : <5	2c
5	Cu(OTf)$_2$ - Phenanthroline	CH_2Cl_2	63	81 : 19	2c
6	Cu(OTf)$_2$ - 2,9DMP[a]	CH_2Cl_2	<2	-	2c
7	La(OTf)$_3$	PhMe	23	53 : 47	9
8	Sm(OTf)$_3$	PhMe	88	76 : 24	9
9	Eu(OTf)$_3$	PhMe	78	67 : 33	9
10	Yb(OTf)$_3$	PhMe	87	95 : 5	9
11	Yb(OTf)$_3$	MeCN	63	18 : 82	9

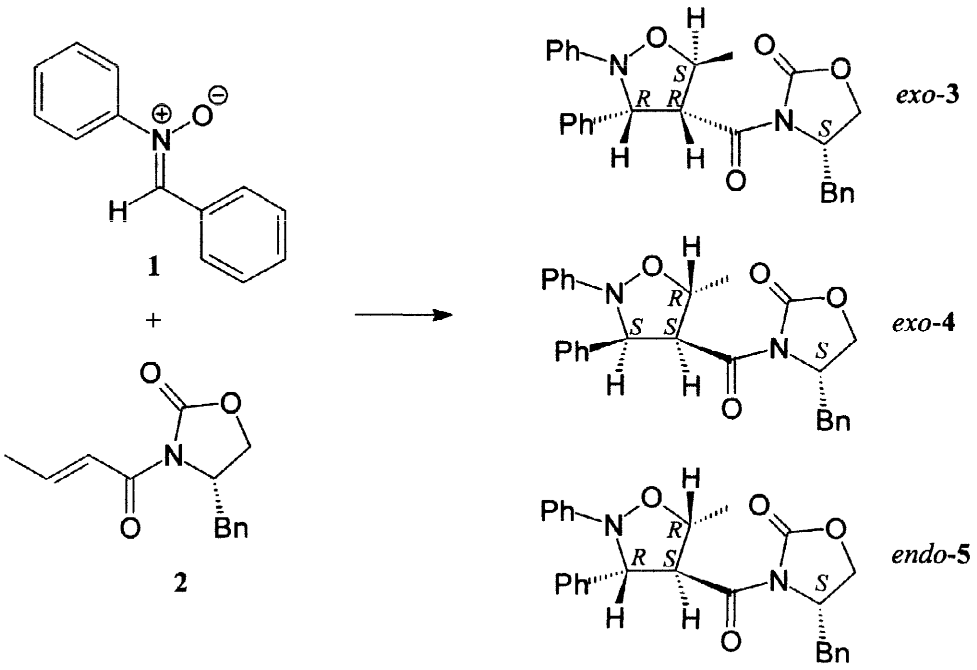
a) 2,9-Dimethylphenanthroline

Several factors may influence diastereoselection. Not only the cation, but also an organic ligand (entry 2 *vs* 3), or the solvent (entry 10 *vs* 11) are important in determining the diastereoselectivity, and its control is important when the 1,3-DC involves a dipolarophile having a chiral auxiliary as substituent since the optically pure isoxazolidines thus obtained are suitable to be used as chiral building blocks.

This type of reaction, for the commercial availability of optically pure oxazolidinones and the easy removal and recovery of these auxiliaries, has already been studied by Jørgensen on the oxazolidinone having a 4-(*S*)-isopropyl group on the chiral auxiliary and the (3*S*,4*S*,5*R*)-*exo* isoxazolidine was obtained[2f] under the catalytic conditions described in entry 1 of Table 1, the (3*R*,4*S*,5*R*)-*endo* isoxazolidine[2c] under the conditions of entry 3, both with excellent degrees of diastereoselection.

In an attempt to rationalize the effect of the catalysis on the diastereoselectivity, the reaction between diphenyl nitrone **1** and 4-(*S*)-benzyl-3-((*E*)-2′-butenoyl)-1,3-oxazolidin-2-one **2** (Scheme 1) was studied in the presence of a large number of inorganic perchlorates (P) and triflates (OTf) and eventually with simple additives as H_2O, which was found to change the coordination number around Mg(II),[10] and powdered 4 Å molecular sieves (MS), which were found to have a deep influence on the stereoselectivity of the catalyzed 1,3-DC.[2h]

Scheme 1



Results

The reaction was first run in the absence of any catalyst on 1 mmol scale in CH_2Cl_2 as solvent and, after a long reaction time (Table 2 - entry 1), the conversion was nearly quantitative and three products (**3-5**) were obtained. In all tests the product distribution was determined by hplc analysis on small crops of the reaction mixture (see the Experimental Section for details), the rest was column chromatographed to separate the pure adducts. This protocol was followed when the main adduct had to be isolated; the experiments run to test the reproducibility of yields and product distributions were performed on 0.2 mmol scale.

The product distribution in the uncatalyzed reaction was [**3**] : [**4**] : [**5**] = 76 : 7 : 17. From a comparison of the ^{1}H-NMR spectrum of **3** with those of other isomers and with the NMR spectral data reported in the literature for similar products,[2a] it was easily deduced that H-3 and H-4 are *cis* to each other and, if **1** retains its starting (*Z*) configuration[11] during the reaction, **3** derives from an *exo* attack. Every attempt to correlate with nOe experiments the isoxazolidine stereocenters with that at the oxazolidinone ring, having a known configuration, was unsuccesful. The absolute stereochemistry of *exo*-**3** was therefore assigned by X-ray analysis, and the resulting structure is presented in Figure 1.

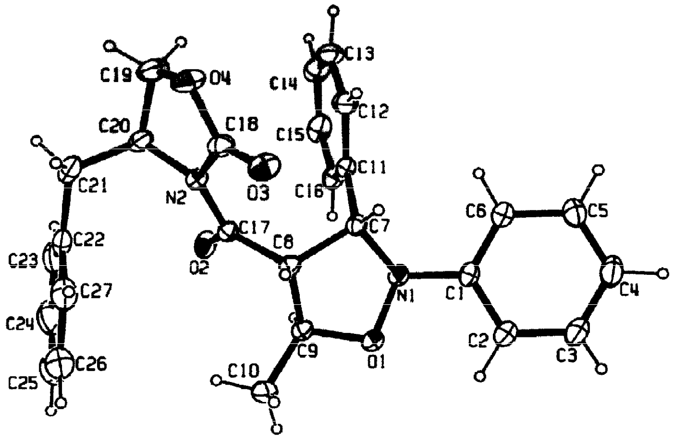


Figure 1. X-Ray structure of *exo*-**3**, labelled with crystallographic atom numbering, showing the absolute stereochemistry of the isoxazolidine ring.

The crystal structure of *exo*-**3** shows that H-3 and H-4 are *cis* to each other as expected and, obviously, H-4 and H-5 are *trans*. Knowing the (*S*) configuration at the benzyl group, the main product of the uncatalyzed reaction between **1** and **2** is (3′*R*,4*S*,4′*R*,5′*S*)-4-benzyl-3-((5′-methyl-2′,3′-diphenylisoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (*exo*-**3**).

The stereochemistry of *exo*-**4** was inferred by ^{1}H-NMR spectroscopy taking advantage from the known structure of *exo*-**3**. The coupling constant between H-3 and H-4 was 11 Hz, very close to 10.5 Hz, the J value between H-3 and H-4 of **3**. Hence *exo*-**4** is (3′*S*,4*S*,4′*S*,5′*R*)-4-benzyl-3-((5′-methyl-2′,3′-diphenylisoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (Scheme 1).

The third product must have an *endo* stereochemistry and this was supported by the J value between H-3 and H-4 (7.2 Hz). The absolute configuration of the oxazolidinic fragment was inferred by converting *endo*-**5** into the isopropyl ester **6** (Scheme 2), and comparing its $[\alpha]_D$ value with those reported by Jørgensen[2c] for both enantiomers. Thus *endo*-**5** is (3′*R*,4*S*,4′*S*,5′*R*)-4-benzyl-3-((5′-methyl-2′,3′-diphenylisoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (Scheme 1).

With these results in hand, the effect of several inorganic salts behaving as Lewis acids was tested, eventually in the presence of additives, and the results are reported in Table 2.

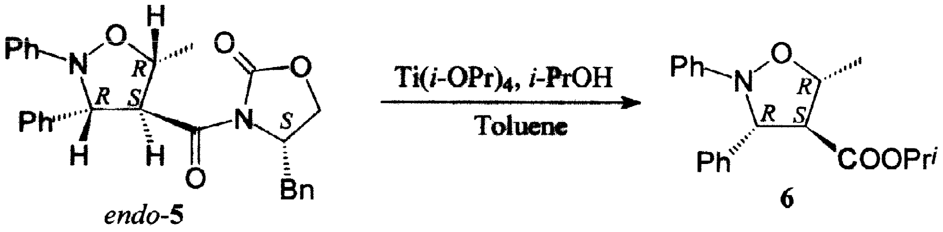
With $Mg(ClO_4)_2$ as catalyst, if the reaction was run in the presence of MS, **5** became by far the major isomer (92% yield, entry 3). This result was not affected by an attempt to test the double asymmetric synthesis

Table 2. Influence of different catalysts on the diastereoselectivity of the reaction between diphenyl nitrone **1** and 4-(*S*)-benzyl-((*E*)-2'-butenoyl)-1,3-oxazolidin-2-one **2** at ambient temperature.

Entry	Catalyst				Time	Yields[a] %	Diastereoisomer ratio[a] %		
	Salt[b]	MS	H_2O	Ligands[c]			*exo*-**3**	*exo*-**4**	*endo*-**5**
1	-	-	-	-	15 d	95	**76**	7	17
2	$Mg(ClO_4)_2$	-	-	-	60 h	>95	3	**82**	15
3	$Mg(ClO_4)_2$	d	-	-	60 h	>95	-	8	**92**
4	$Mg(ClO_4)_2$	-	2 eq.	-	3 d	>95	3	**71**	26
5	$Mg(ClO_4)_2$	-	4 eq.	-	4 d	>95	3	68	26
6	$Mg(ClO_4)_2$	d	-	(*R*)-DPBO	3 d	>95	2	8	**90**
7	$Mg(ClO_4)_2$	d	-	(*S*)-DPBO	3 d	>95	-	8	**92**
8	$Mg(OTf)_2$	–	-	-	2 d	85	11	66	23
9	$Mg(OTf)_2$	-	2 eq	-	2 d	90	12	**71**	17
10	$Mg(OTf)_2$	d	-	-	2 d	88	12	**76**	12
11	$Mg(OTf)_2$	d	-	(*R*)-DPBO	2 d	88	17	66	17
12	$Mg(OTf)_2$	d	-	(*S*)-DPBO	2 d	86	12	**74**	14
13	$Sc(OTf)_3$	-	-	-	5 h	>95	2	22	76
14	$Sc(OTf)_3$	d	-	-	5 h	>95	-	5	**95**
15	$Sc(OTf)_3$	-	6 eq.	-	12 h	80	5	10	85
16	$Sc(OTf)_3$	-	e	-	6 d	80	**74**	6	20
17	$Eu(OTf)_3$	d	-	-	12 h	>95	4	6	**90**
18	$Yb(OTf)_3$	d	-	-	12 h	>95	-	6	**94**
19	$Eu(OTf)_3$	-	6 eq.	-	10 h	25	66	9	25
20	$Yb(OTf)_3$	-	6 eq.	-	10 h	75	56	14	30
21	$Fe(ClO_4)_2 \cdot xH_2O$	d	-	-	24 h	90	18	34	48
22	$Ni(ClO_4)_2 \cdot 6H_2O$	d	-	-	40 h	>95	1	20	79
23	$Co(ClO_4)_2 \cdot 6H_2O$	d	-	-	48 h	>95	1	14	85
24	$Mn(ClO_4)_2 \cdot 6H_2O$	d	-	-	60 h	>95	1	18	81
25	$Zn(ClO_4)_2 \cdot 6H_2O$	d	-	-	5 d	>95	4	58	38

[a]These are the average of at least three independent determinations. [b]Ratio [**1**] : [**2**] : [Salt] = 10:10:1. [c](*R*)DPBO- and (S)-DPBO are 1 eq. 2,2-bis{2-[4(*R*)-phenyl-1,3-oxazolinyl]}propane and its 4(*S*) enantiomer, respectively. [d]50 mg in the reaction run on 0.2 mmol scale. [e]about 100 equiv.

Scheme 2



of the isoxazolidines, running the reaction (entries 6,7) in the presence of either 2,2-bis{2-[4(*R*)-phenyl-1,3-oxazolinyl]}propane or its 4(*S*) enantiomer, that are known to be excellent chiral ligands for enantioselective 1,3-DC catalyzed by Mg(II).[2c,2h,8] If the reaction was run without MS, or in the presence of 2-4 eq H_2O, the diastereoselectivity changed and the main product became **4**, (yield 68-82% - entries 2,4,5). With $Mg(OTf)_2$ as salt, **4** was always the main product of the reaction, independently from the presence of MS, H_2O or any other ligand (yield 66-76% - entries 8-12).

When the triflates of the rare earths [Sc(III), Eu(III) and Yb(III)] were tested, three types of results were obtained. With each of them, the reactions run with MS gave **5** as the main product (yield 84-95% - entries 14,17,18). If 6 equivalents of H_2O were added to Eu(III) and Yb(III), **3** was the main adduct (entries 19,20). Apparently, the same result was obtained with Sc(III), but only in the presence of a large excess (about 100 eq.) of H_2O and after a longer reaction time (entry 16), hence under conditions, and with a result, which are reminiscent those described in entry 1 for the uncatalyzed reaction. As a whole, Sc(III) is the best Lewis acid in terms of reaction time (entries 13,14), capable of supporting 6 eq. H_2O without a significant loss of both catalytic effect and stereoselectivity (entry 15).

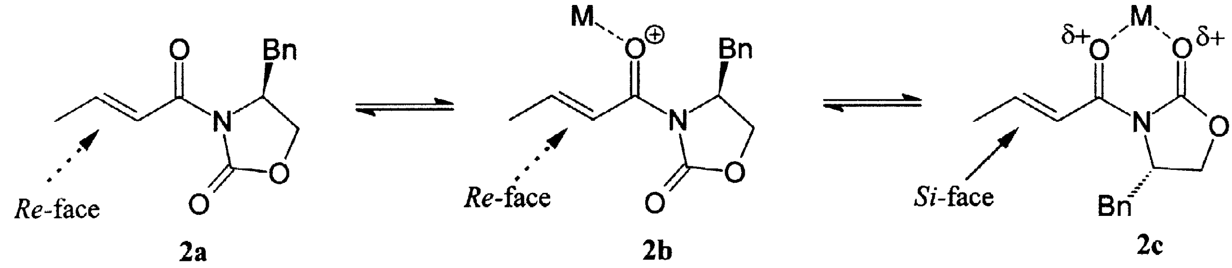
The last set of experiments was a test of five metal(II) perchlorates, commercially available in their hydrate form. The yields were excellent only in the presence of MS, otherwise the decomposition of the reagents was the main process. Furthermore, only Ni(II), Co(II) and Mn(II) gave **5** selectively (yield 79-85% - entries 22-24); Fe(II) and Zn(II) (entries 21,25) gave mixtures of two or three diastereoisomers in comparable yields.

Discussion

As can be seen, the products of all these reactions are always **3** - **5**, but the diastereomer distribution changes strongly. Three main classes of reaction can be observed, depending on which is the main product, and it remains to discuss the rationale of the products formation that depends on the type of reagents involved in the reaction.

Evans[12] discussed in detail the topographical relationship between the chiral center of the oxazolidinone and the prochiral dipolarophile in chiral *N*-alkenoyloxazolidinones. This depends on the various rotational degrees of freedom around N3-C1′ and C1′-C2′ single bonds. The conformation around the C1′-C2′ bond is always *s-cis* either in the uncomplexed (**2a**) or in the Lewis acid-complexed molecule. The conformation around the N3-C1′ may be either (*E*) in **2a** and in complexes with monocoordinating Lewis acids (**2b**) or (*Z*) if bidentate chelation involves both carbonyl groups (**2c**) (Scheme 3).

Scheme 3

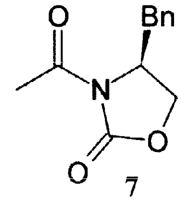


Given the *s-cis* conformation of the α,β-unsaturated carbonyl fragment, it seems reasonable to assume an approach of **1** to the dipolarophile always from its less sterically hindered face: the *Re* face of **2a,b** and the *Si* face of **2c**. Since *exo*-**3** derives from the attack of diphenyl nitrone **1** to the *Re* face of the double bond and both *exo*-**4** and *endo*-**5** from the *Si* face, this requires different reacting substrates for the different reaction conditions. Under uncatalyzed conditions involving **2a** as substrate, the main attack of **1** occurs from the *Re* face of the dipolarophile. This is what happens in the reaction described in entry 1 and *exo*-**3** is the main product.

The attack to **2b** should again occur on the *Re* face, therefore, to account for the *Si* attack giving rise either to *exo*-**4** or *endo*-**5** products, the bidentate chelation giving **2c** must be involved in the major part of the catalyzed reactions described in Table 2. Furthermore **2c** could give either a tetrahedral or an octahedral complex, depending on the different cations and the ligands eventually added.

NMR spectroscopic studies with model compound

In order to investigate by NMR spectroscopy the structure of the complex involved in the catalyzed reaction between **1** and **2**, an unreactive model compound for the latter derivative was required. The suitable product was assumed to be 2-acetyl-4-(*S*)-benzyl-1,3-oxazolidin-2-one (**7**) and some ^{1}H- and ^{13}C-NMRspectroscopic experiments were performed[13] with this and MgP or ScOTf, two of the most effient catalysts (Table 2), whose complexes with **1** and **7** were soluble in $CDCl_3$.



7

When 7 and MgP, in the ratio 2 : 1, were mixed in the NMR tube, the salt slowly dissolved and the ^{1}H-NMR spectra showed the clear formation of a complex.[14] Some

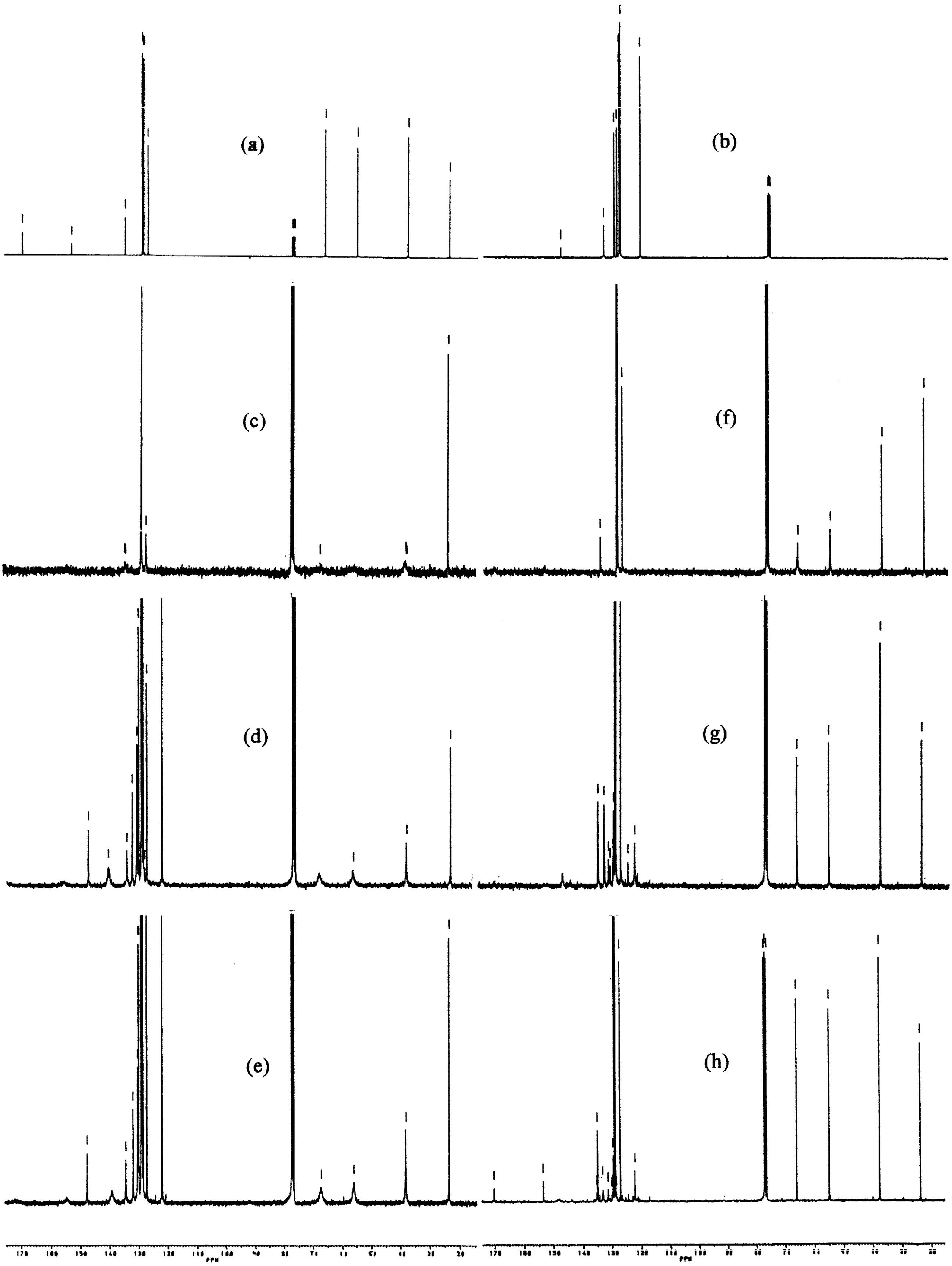
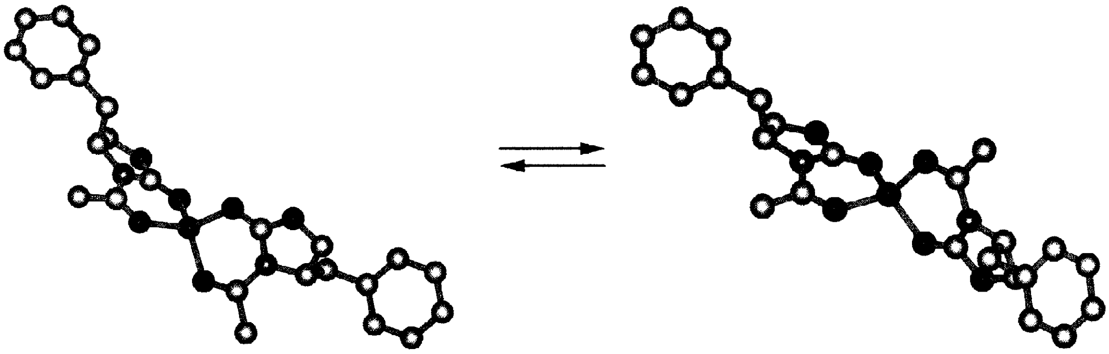


Figure 2. ^{13}C-NMR spectra of: (a) **7**; (b) **1**; (c) MgP and **7** (ratio 1:2); (d) MgP, **1**, and **7** (ratio 1:2:2); (e) MgP, **1**, and **7** (ratio 1:2:3); (f) ScOTf and **7** (ratio 1:3); (g) ScOTf, **1**, and **7** (ratio 1:2:2); (h) ScOTf, **1**, and **7** (ratio 1:2:3).

important information on its structure can be derived from the ^{13}C-NMR spectrum (Figure 2c) compared with that of the free ligand (Figure 2a).[15] In the presence of 0.5 equiv MgP, the absorptions at δ 135.5, 66.0, 55.0 and 38.5 became weak and broad, the methyl at δ 24.5 moved downfield by 1 ppm and the carbonyl carbon atoms, resonating at δ 170.5 and 154.0 in free **7**, disappeared. This can be interpreted in terms of the formation of two interconverting equivalent tetrahedral stereoisomers **8a,b** (Scheme 4).

Scheme 4



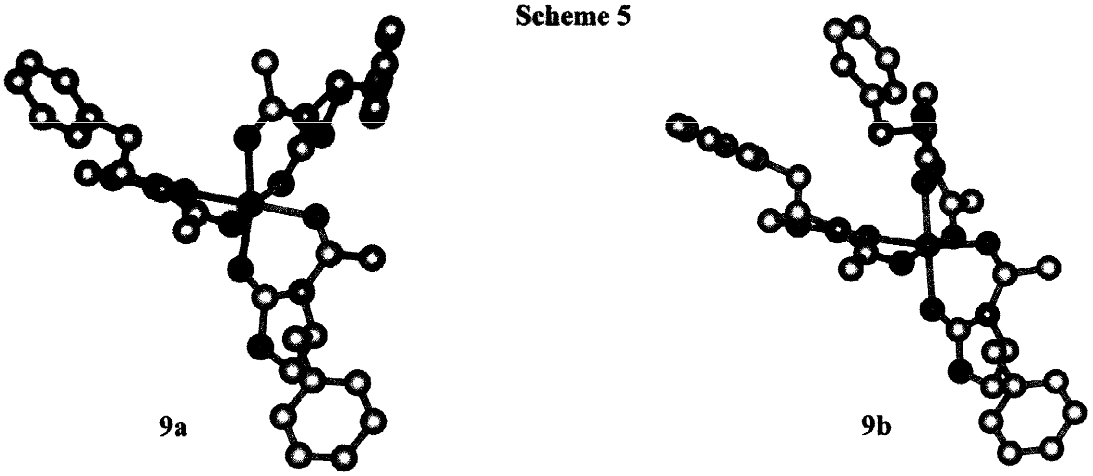
8a **8b**

When **1** was added to the above sample, with **1**, **7** and MgP being in the ratio 2 : 2 : 1, the structure of the complex, clearly detected by ^{1}H-NMR spectroscopy, was inferred by its ^{13}C-NMR spectrum (Figure 2d). The signals of 7 did not significantly change (again no absorption of carbonyl carbon atoms was observed); those of **1** (Figure 2b) had the C-1′ absorption (adjacent to N) moving from δ 149.0 to 147.9 and the methyne carbon absorption broadened and moved from δ 134.4 to 138.9. This data can be rationalized only by assuming that diphenyl nitrone enters in the coordination sphere of Mg(II) with formation of an octahedral complex where two acetyloxazolidinones (**7**) behave as bidentate ligands and two nitrones (**1**) as monodentate ligands. Nitrone is coordinated in the *Z*-configuration since the saturation of the methyne H induces a positive nOe on both H-2,6 and H-2′,6′. The addition of a further equiv. of 7, (ratio between **1**, **7** and MgP = 2 : 3 : 1) gave a ^{13}C-NMR spectrum (Figure 2e) nearly unchanged. This indicates that both free and complexed **1** and **7** are rapidly exchanging, and complexes of different compositions can simultaneously exist.

ScOTf and 7, dissolved in $CDCl_3$ in the ratio 1 : 3, had a ^{1}H-NMR spectrum very similar to that of uncomplexed 7, whereas the ^{13}C-NMR spectrum was significantly different since the absorptions of the carbonyl carbon atoms disappeared and the methyl was at δ 23.5 (Figure 2f). This data can be interpreted in terms of 7 behaving as a bidentate ligand in an octahedral complex, the symmetric structure **9a**[16] being probably favoured over the unsymmetric one **9b** for steric reasons (Scheme 5).

When 2 equiv. of **1** were added into the NMR tube, the ^{1}H-NMR spectrum showed that the nitrone became involved in the coordination (methyne H; H-2,6 and H-2′,6′ were all deshielded by at least δ 0.1) and this assumption was further supported by the ^{13}C-NMR spectrum (Figure 2h) since the C-1′ and the methyne

Scheme 5



9a

9b

C resonances (at δ 149 and 134.4 in uncomplexed **1**) disappeared. No evidence of rapid exchange of ligands was observed since two sharp carbonyl carbons resonating at δ 170.3 and 153.5 (identical to those of free **1**) appeared and this can be interpreted in terms of exchange of 1 equiv. **7** to allow the coordination of **1** around the Sc(III) cation in an octahedral structure. The octahedral complex with no ligand in excess was obtained by mixing ScOTf, **7** and **1**, in the ratio 1 : 2 : 2, in CDCl$_3$ and the ^{13}C-NMR spectrum (Figure 2g) was as expected.

Conclusions

The above described NMR spectroscopic experiments suggest that:

1) the catalyzed 1,3-DC between diphenyl nitrone (**1**) and 4-(*S*)-benzyl-((*E*)-2′-butenoyl)-1,3-oxazolidin-2-one (**2**) occurs with the latter in the bicoordinated conformation **2c**, hence attack of **1** should occur on the *Si* face of the dipolarophile;

2) a tetrahedral structure [*e.g.* around a Mg(II) cation] is unlikely in the presence of both **1** and **2** and, by far, octahedral coordination seems to be involved in the configuration of the reacting species;

3) the octahedral complex involved in the 1,3-DC has two dipolarophile molecules, as bidentate ligands, and two nitrone units, behaving as monodentate ligands, organized around the inorganic core of the catalyst.[17]

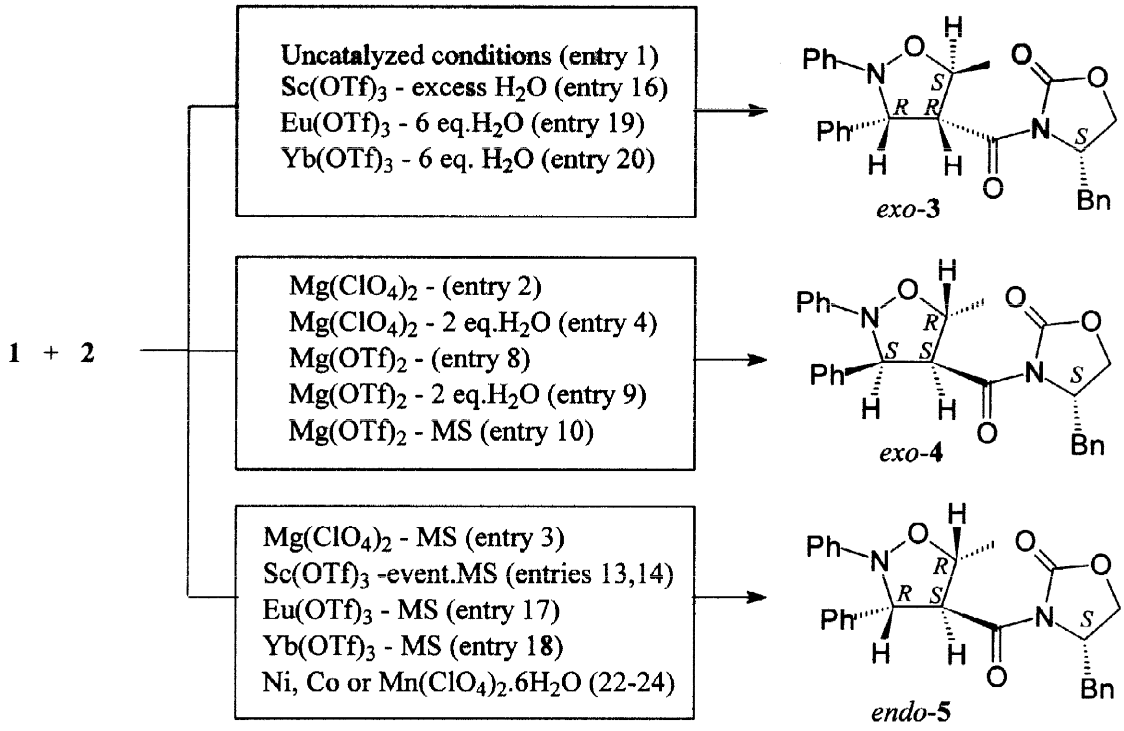
This data allows us to rationalize the diastereoselectivity observed in the 1,3-DC between **1** and **2** under the experimental conditions that, to simplify the further discussion, are collected in Scheme 6.

This data can be rationalized as follows:

a) The uncatalyzed reaction occurs through the attack of **1** onto **2a** from the less hindered *Re* face and the favoured transition state is *exo*.

b) If the attack of **1** occurs on the *Si* face of the bicoordinated dipolarophile (**2c**), the formation of *exo*-**4** or *endo*-**5** as the main products in nearly all catalyzed experiments described in Table 2 is the expected result.

Scheme 6



c) The diastereoselectivity of the 1,3-DC between **1** and **2** is substrate-controlled since there is an absence of any significant affects of the chiral ligands added to the reaction (entries 6,7,11,12). This excludes a catalyst-dominated process, as observed in the Diels-Alder reaction.[18]

d) The coordinated nitrone that behaves as a ligand should not be the reacting dipole. In addition to some obvious considerations on the effect of coordination on the MO energy levels of **1** (HOMO should be lowered and the reagents FMO separation increased), some previous studies[4] on the reactivity of the Pd-coordinated nitrone support its inertness *versus*.**2**.

e) When, in the presence of a salt, the main product of the 1,3-DC is *exo*-**3**, two possible reaction pathways can rationalize this result. In the presence of excess H_2O (about 100 eq. - entry 16) the reaction conditions (6 days) and the product composition suggest this is not a catalyzed reaction and **2a** is the substrate. When 6 eq. of H_2O are added to Eu- or Yb-OTf (entries 19,20), a significant catalytic effect is still found in terms of increased reactivity and the formation of *exo*-**3** could be due to the solvation of the cation that can monocoordinate the dipolarophile with formation of **2b** as the reacting substrate. This is not the case of ScOTf which, under the same experimental conditions (entry 15), still retains a strong preference for the bicoordination of **2**.

f) The reasons of *exo vs endo* attack of **1** to **2c** are not easy to be rationalized. If the uncatalyzed reaction gives the *exo* attack preferentially (entry 1), this, for intrinsic reasons, should be the favoured pathway in these 1,3-DC. It could be argued that *endo* attack occurs when steric (or different) interactions disfavour the *exo* approach. If the reactions catalyzed by MgOTf are for the moment not taken into account, *endo*-**5** is obtained when the reactions, independently of the type of catalyst, are run in the presence of MS (entries 3,8,9,14,17,18,22-24). It could be easy to assume that the molecular sieves are involved in the formation of the catalytic complex[2h] and that their steric hindrance disfavours an *exo* approach whereas, in their absence (entries 2,4,5), the *exo* attack again favours the formation of **4**. This does not rationalize the reaction catalyzed by MgOTf that, *with or without MS*, always gives *exo*-**4** with the same good diastereoselection (entries 8-12). Thus the choice between the formation of *endo*-**5** *vs* *exo*-**4** can be due to octahedral complexes that differ for the possible presence of water or triflate anions as ligands.

In conclusion, the 1,3-DC between diphenyl nitrone and a dipolarophile with a β-dicarbonyl substituent can be usefully catalyzed by different salts whose cation behaves as a Lewis acid; the rate can be strongly increased and, if the dipolarophile has a good chiral auxiliary, a suitable choice of the catalytic system allows three of the four possible diastereomeric cycloadducts to be obtained selectively.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were made on C. Erba CHN analyzer mod. 1106. ^{1}H- and ^{13}C-NMR spectra (TMS as standard) were recorded on a Bruker AC 300 spectrometer, IR spectra on a Perkin Elmer 881 spectrophotometer; optical rotation at room temperature on a Perkin Elmer 241 polarimeter with a 1 dm cell.

Dichloromethane was hydrocarbon-stabilized Aldrich ACS grade, distilled on calcium hydride and immediately used. All the inorganic salts were Aldrich ACS reagents. 2,2-Bis{2-[4(*R*)-phenyl-1,3-oxazolinyl]}propane and its 4(*S*) isomer were commercially available from Aldrich.

Diphenyl nitrone (1), 4-(S)-benzyl-((E)-2'-butenoyl)-1,3-oxazolidin-2-one (2) and 2-acetyl-4-(S)-benzyl-1,3-oxazolidin-2-one (7) were prepared as described in the literature.[12,15,19]

1,3-DC of diphenyl nitrone (1) and 4-(S)-benzyl-((E)-2'-butenoyl)-1,3-oxazolidin-2-one (2). General procedure. Nitrone **1** (0.20 g, 1.0 mmol) and dipolarophile **2** (0.15 g, 1.0 mmol) were dissolved in a rubber septum sealed vial in anhydrous dichloromethane (1.0 mL). The required inorganic salt (0.1 mmol), powdered 4 Å molecular sieves (MS) (0.25 g), H_2O (the required amount, measured with a microsyringe), 2,2-bis{2-[4(*R*)-phenyl-1,3-oxazolinyl]}propane or its 4(*S*) enantiomer (0.033 g, 0.1 mmol), all as reported in the entries of Table 2, were eventually added and the resulting mixture was stirred at room temperature for the time reported in Table 2. After completion of the cycloaddition, the reaction mixture was decomposed in water, extracted with dichloromethane and dried. The organic layer was evaporated to dryness and a portion of the residue was analyzed. The standard analysis of the reaction mixture was performed by hplc analyses using a Chiralpak AD column with *n*-hexane/2-propanol 9:1 as eluant [1 mL/min; average retention times: *exo*-**3** (9.5 min), *exo*-**4** (10.7 min), **2** (13.0 min), **1** (25.4 min), *endo*-**5** (53.8 min)]. When the yield was not quantitative a portion of the crude mixture was monitored by ^{1}H-NMR spectroscopy and the amount of unreacted **2** was determined by integrating the doublet of the methyl group at δ 1.96. The reaction mixture was then column chromatographed on silica gel 230-400 mesh and eluted with cyclohexane/ethyl acetate 9:1. The order of elution was: *exo*-**3**, *exo*-**4**, **2** (when present), **1** (when present) and finally *endo*-**5**. The chemical and spectroscopic characters of the products will be subsequently described in detail. This protocol was followed in any other experiment when the adducts had to be isolated; the further experiments, run to test the reproducibility of yields and product distributions (at least three independent experiment for each condition described in entries 1-26 of Table 2), were performed on 0.2 mmol scale. The products have the following physico-chemical properties.

(3'R,4S,4'R,5'S)-4-benzyl-3-((5'-methyl-2',3'-diphenylisoxazolidin-4'-yl)carbonyl)-1,3-oxazolidin-2-one (exo-3). White crystals, mp = 161 °C from ethanol. IR (nujol mulls), ν: 1775 and 1709 cm^{-1}. $[\alpha]_D$ = +91.4 (c = 0.2; chloroform). Elem. anal.: calc. for $C_{27}H_{26}N_2O_4$: C, 73.3; H, 5.9; N, 6.3. Found: C, 73.6; H, 6.0; N, 6.2%.

(3'S,4S,4'S,5'R)-4-benzyl-3-((5'-methyl-2',3'-diphenylisoxazolidin-4'-yl)carbonyl)-1,3-oxazolidin-2-one (exo-4). Soft white crystals, mp = 130-131 °C from ethanol. IR (nujol mulls), ν: 1780 and 1693 cm^{-1}. $[\alpha]_D$ = +35.5 (c = 0.15; chloroform). Elem. anal.: calc. for $C_{27}H_{26}N_2O_4$: C, 73.3; H, 5.9; N, 6.3. Found: C, 73.5; H, 5.6; N, 6.0%.

(3'R,4S,4'S,5'R)-4-benzyl-3-((5'-methyl-2',3'-diphenylisoxazolidin-4'-yl)carbonyl)-1,3-oxazolidin-2-one (endo-5). White crystals , mp = 96-97 °C from ethanol. IR (nujol mulls), ν: 1782, 1765 and 1691 cm^{-1}. $[\alpha]_D$ = +74.0 (c = 0.3; chloroform). Elem. anal.: calc. for $C_{27}H_{26}N_2O_4$: C, 73.3; H, 5.9; N, 6.3. Found: C, 73.4; H, 6.2; N, 6.1%.

The ^{1}H-NMR spectra of the above described three products are reported in Table 3.

*Conversion of (3'R,4S,4'S,5'R)-4-benzyl-3-((5'-methyl-2',3'-diphenylisoxazolidin-4'-yl)carbonyl)-1,3-oxazolidin-2-one (endo-**5**) into the corresponding isopropyl ester **6**.* Following the procedure described in the literature,[2c] to **5** (49 mg, 0.11 mmol) dissolved in toluene (2 mL) Ti(*i*-OPr)$_4$ (1.1 mmol) and *i*-PrOH (2.2 mmol) were added, and the mixture was refluxed for 5 h. The solvent was evaporated and the residue was column chromatographed (eluant: cyclohexane/ethyl acetate 85:15) to give (*3R,4S,5R*)-5-methyl-2,3-diphenyl-4-(isopropoxycarbonyl)isoxazolidine (**6**) as a colourless oil (33 mg, yield 91%). IR (neat), ν: 1728 cm^{-1}. The ^{1}H-NMR spectrum was identical to that reported in the literature.[2c] $[\alpha]_D$ = +110.8 (c = 0.6; chloroform) {lit.,[2c] $[\alpha]_D$ > 35}.

Table 3. ^{1}H-NMR chemical shift and coupling constants of the products of the 1,3-DC between **1** and **2**.

H no.	**3** δ (J)	**4** δ (J)	**5** δ (J)
CH_3-5′	1.53 d (6.3)	1.50 d (6.2)	1.58 d (6.1)
CH_2-benzyl	2.65 dd, 3.13 dd (3.5, 9.7, 13.5)	1.41 dd, 2.32 dd (3.0, 11.3, 13.5)	2.77 dd, 3.23 dd (3.3, 9.2, 13.5)
H_2-5	3.38 t, 3.89 dd (2.2, 8.5)	3.92 dd, 4.03 dd (2.8, 8.0, 8.8)	4.18 m
H-4	3.77 m	4.35 m	4.78 m
H-4′	4.48 dd (9.4, 10.5)	4.31 dd (9.8, 11.0)	4.91 t (7.3)
H-3′	4.88 d (10.5)	5.12 d (11.0)	5.25 d (7.3)
H-5′	5.15 dq (6.3, 9.4)	5.15 dq (6.2, 9.8)	4.53 dq (6.1, 8.7)
aromatic H	6.85-7.5 (15 H)	6.9-7.6 (15 H)	6.9-7.55 (15 H)

^{1}H- and ^{13}C-NMR spectra of complexes between 1, 7, and MgP or ScOTf. The NMR tube was filled with the required amount of $CDCl_3$, and an exact amount of salt was weighed into (about 0.03 mmol). To this, the required amount of $CDCl_3$ solution of **1** and/or **7** (1.0 mmol in 2.0 mL volumetric flask) was added with a microsyringe and the salt dissolved with the aid of a microwave bath.

Table 4. Crystal and refinement data.

Formula	$C_{27}H_{26}N_2O_4$	Reflections measured	$-12 < h < 12$ $0 < k < 21$ $0 < l < 24$
Molecular weight	442.52	Standard reflections	3 every 300 reflections
Crystal colour	colourless	T_{max}, T_{min}	0.999, 0.982
Crystal size (mm)	0.50 × 0.72 × 0.79	Tot. reflns measured	7252
Crystal system	orthorhombic	Unique reflections	3834
Space group	$P2_12_12_1$	R_{int}[a]	0.027
a (Å)	8.794(2)	Refinement type	F^2
b (Å)	15.541(6)	Obs. Reflns [$I > 2\sigma_I$]	2618
c (Å)	17.210(3)	R_1[b]	0.040
V (Å^3)	2352.1(11)	GOF[c]	1.023
Z	4	$wR2_{all}$[d]	0.095
d_{calc} (g × cm^{-3})	1.250	R_{all}	0.071
T (K)	293(2)	Extinction coefficient	0.0158(14)
Radiation, λ (Å)	MoK$_\alpha$ (λ = 0.71073Å)	Refined parameters	394
Monochromator	graphite	θ range (°)	2 - 30
μ (mm^{-1})	0.084	(shift/e.s.d.)$_{max}$	0.000
Scan type	ω - 2θ	min., max. $\Delta\rho$ (e × Å^{-3})	0.233, -0.172
Weighting scheme	$1/[\sigma^2 F_o^2 + (0.0478\,P)^2 + 0.241\,P$ where $P = [\mathrm{Max}\,(F_o^2, 0) + 2\,F_c^2)/3$		

[a] $R_{int} = = \Sigma\,|F_o^2 - F_o^2(\mathrm{mean})|\,/\,\Sigma\,[F_o^2]$. [b] $R_1 = \Sigma\,||F_o| - |F_c||\,/\,\Sigma\,|F_o|$. [c] GOF = S = $\{\Sigma\,[w(F_o^2 - F_c^2)^2]\,/\,(n - p)\}^{0.5}$, where n is the number of reflections and p is the total number of parameters refined. [d] $wR2_{all} = \{\Sigma\,[w(F_o^2 - F_c^2)^2]\,/\,\Sigma\,[w(F_o^2)^2]\}^{0.5}$

X-ray data collection and processing. Unit cellparameters and intensity data were obtained on an Enraf-Nonius CAD-4 diffractometer. Calculations were performed with the WinGX-97[20] software. Crystal data and the most relevant parameters used in the crystallographic study are reported in Table 4. Cell dimensions were determined by least-squares fitting of 25 centred reflections monitored in the range 9.68° $< \theta <$ 14.58°. Corrections for Lp and empirical absorption were applied.[21] The structure was solved by SIR92.[22] The non-hydrogen atoms were refined anisotropically by full-matrix least-squares using SHELXL-93.[23] All the hydrogen atoms were located in the difference Fourier maps and refined isotropically. Secondary extinction[24] was applied. Atomic scattering factors were taken from *International Tables for X-ray Crystallography.*[25] Diagrams of the molecular structure were produced by the ORTEP program[26] showing 20% probability displacement ellipsoid.

Acknowlwdgment Financial support for this work was provided by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), by the Consiglio Nazionale delle Ricerche (CNR), and by the University of Pavia.

References and Notes

1) For recent reviews on the argument see: a) Gothelf, K.V.; Jørgensen, K.A. *Acta Chem. Scand.* **1996,** *50,* 652; b) Gothelf, K.V.; Jørgensen, K.A. *Chem. Rev.* **1998**, *98*, 863.

2) a) Gothelf, K.V.; Jørgensen, K.A. *J. Org. Chem.* **1994,** 59, 5687; b) Gothelf, K.V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996,** 118, 59; c) Gothelf, K.V.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* **1996,** *61*, 346; d) Sanchez-Blanco, A.I.; Gothelf, K.V.; Jørgensen, K.A. *Tetrahedron Lett.* **1997,** 38, 7923; e) Gothelf, K.V.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 2* **1997,** 111; f) Jensen, K.B.; Gothelf, K.V.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* **1997,** *62*, 2471; g) Jensen, K.B.; Gothelf, K.V.; Jørgensen, K.A. *Helv. Chim. Acta* **1997,** *80,* 2039; h) Gothelf, K.V.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* **1998,** *63*, 5483.

3) Seerden, J.P.G.; Kuypers, M. M. M.; Scheeren, H.W. *Tetrahedron: Asymmetry* **1995,** *6*, 1441.

4) Hori, K.; Kodama, H.; Otha, T.; Furukawa, I. *Tetrahedron Lett.* **1996,** *37*, 5947.

5) Seebach, D.; Marti, R.E.; Hintermann, T. *Helv. Chim. Acta* **1996,** *79*, 1710.

6) a) Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett.* **1997,** 1039; b) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998,** *120*, 5840.

7) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998,** *120*, 12355.

8) Desimoni, G.; Faita, G.; Martoni, A.; Righetti, P.P. *Tetrahedron Lett.* **1999,** *40*, 2001.

9) Minakata, S.; Ezoe, T.; Nakamura, K.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998,** *39*, 5205.

10) a) Desimoni, G.; Faita, G.; Invernizzi Gamba, A.; Righetti, P.P. *Tetrahedron* **1997,** *53,* 7671; b) Desimoni, G.; Faita, G.; Righetti, P.P. *Tetrahedron Lett.* **1996,** *37*, 3027.

11) Gothelf, K.V.; Hazell, R.G.; Jørgensen, K.A. *J. Acta Chem. Scand.* **1997,** *51,* 1234.

12) Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.***1988,** *110,* 1238.

13) ^{1}H-NMR spectroscopic studies with 3-acetyl-2-oxazolidinone as model compound of Diels-Alder dienophile showed the formation of an octahedral structure around Zn(II) in the presence of *(R,R)*-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline): Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *Tetrahedron Lett.* **1998,** *39,* 7521.

14) All signals of **7** broadened after the addition of MP, but their chemical shifts were not significantly changed

15) Ager, D.J.; Allen, D.R.; Schaad, D.R. *Synthesis* **1996**, 1283.

16) The ^{1}H-NMR spectrum, δ: 2.57 (3H, s, Me), 2.87 (1H, dd, J = 9.5, 13.5, CH_2Ph), 3.32 (1H, dd, J = 3.3, 13.5, CH_2Ph), 4.2 (2H, m, CH_2O), 4.75 (1H, m, CHN), 7.2-7.4 (5H, m, aromatic protons) does not change at -50°C.

17) K. A. Jørgensen (Aarhus) very recently discussed the coordination of nitrone to the catalyst in two Cu(II)- and Al(III)-catalysed 1,3-dipolar cycloadditions (personal communication).

18) Evans, D.A.; Miller, S.J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460

19) Wheeler, O.H.; Gore, P.H. *J. Am. Chem. Soc.* **1956**, *78*, 3363.

20) Farrugia, L.J. WinGX-97, An integrated system of Publicly Available Windows Programs for the Solution, Refinement and Analysis of Single-Crystal X-Ray Diffraction, University of Glasgow, **1997**.

21) North, A.C.T.; Philips, D.C.; Mathews, F.S. *Acta Crystallogr.* **1968,** *A24*, 351.

22) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Gualardi, A. *J. Appl. Cryst.* **1993**, *26*, 343.

23) Sheldrick, G.M. SHELXL-93, A program for Crystal Structure Refinement, University of Goettingen, **1993**.

24) Zachariasen, W.H. *Acta Crystallogr.* **1963,** *A16*, 1139.

25) *International Tables for X-ray Crystallography*, Kynochn Birmingham, England, *Vol. 4*, **1974**, pp. 99-101 and 149-150.

26) Farrugia, L.J. *J. Appl. Cryst.* **1997**, 565.