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Can a Chiral Catalyst Containing the Same Ligand/Metal Components Promote the Formation of Both Enantiomers Enantioselectively? The Bis(Oxazoline)-Magnesium Perchlorate-Catalyzed Asymmetric Diels-Alder Reaction

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Abstract - The Diels-Alder (DA) reaction between cyclopentadiene (**1**) and 3-acryloyl-1,3-oxazolidin-2-one (**2**), to give the *endo* adduct **5** as the main product, has been found to occur enantiosectively in the presence of catalytic amounts of magnesium perchlorate (MP) and 2,2-bis{2-[(4*R*)-phenyl-, [(4*R*,5*S*)- and [(4*R*,5*R*)-diphenyl-1,3-oxazolinyl]}propanes (**3a-c** respectively). The intermediates are the tetrahedral complexes **4a-c**, with **2** and **3** coordinated around Mg(II), and their structures were investigated by NMR. Whereas **3a** and **3b** gave ee of (*S*)-**5** in the range 28-73%, **3c** was an excellent ligand and 97% ee of (*S*)-**5** was obtained. When two equivalents of hydroxylic ligands (water or alcohols) are added, all these complexes can expand the coordination number of Mg(II) from 4 to 6. The octahedral complexes **6a-c** are again good catalysts of the DA reaction but, with **3a** and **3b**, the enantioselectivity is reversed and (*R*)-**5** is obtained with ee up to 89%. For the first time, achiral auxiliary ligands can be used to invert the enantioselectivity induced by a chiral bis(oxazoline), so that both enantiomers can be synthetized with the same metal cation and chiral ligand. The catalytic enantioselective processes are discussed and a rationalization of the experimental results is proposed.

INTRODUCTION

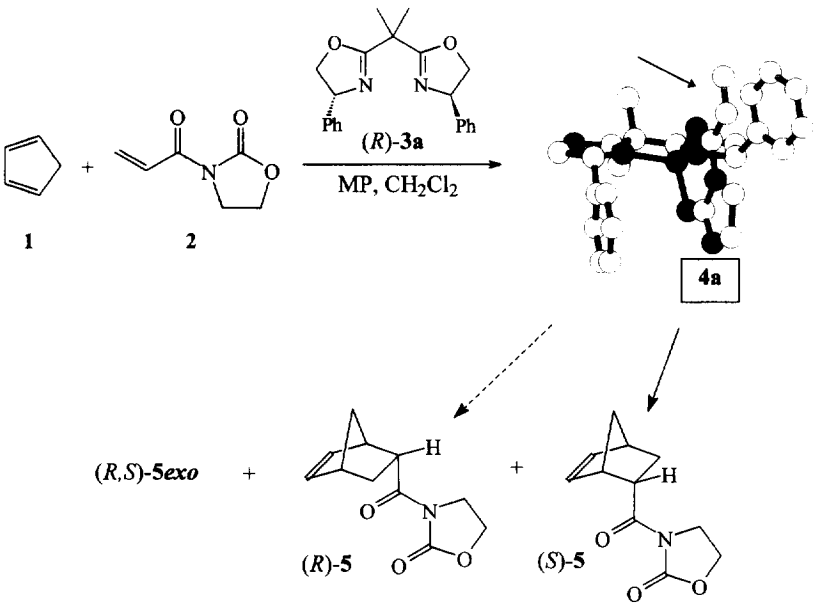
The catalysis of the Diels-Alder (DA) reaction is the target of many research groups due to the wide applications of this reaction to organic synthesis.[1] The formation of the CC bonds in six-membered ring can be enhanced by the development of asymmetric centers, up to a maximum of four adjacent ones, and this promotes the interest in this process.[2] The first approach to asymmetric DA involved the use of a removable chiral auxiliary either on dienophile or on diene, but this requires the stoichiometric use of the chiral messenger. The development of chiral catalysts resulted in a great advantage: the product does not need any further manipulation and the smaller amount of chiral messenger resulted in a multiplication factor of the chirality. The first chiral catalyst for a DA reaction was menthoxyaluminium dichloride.[3] The last decade resulted in an explosion of studies in the field and now this is one of the leading topic of the contemporary research. Several review covered the field[4] and the Lewis-acid core of the catalyst can be: titanium,[5] aluminum,[6] boron,[7] lanthanium and lanthanides,[8] ruthenium,[9] manganese,[10] iron,[11] copper,[12] magnesium[13] and zinc.[12e] Several chiral ligands have been developed, some very simple, some more sophisticated. Among

them three classes have found wide applications: the "so-called" TADDOL derivatives,[5] the binaphthols,[8] and the bis(oxazolines).[11-13]

The C_2-symmetrical bis(oxazoline)-Fe(III),[11a] -Mg(II)[13] and -Cu(II)[12] complexes were found to be excellent chiral catalysts for enantioselective DA reactions. The Mg(II) core of the catalyst was usefully derived from magnesium perchlorate (MP)[13b] and its behaviour as a Lewis acid catalyst for DA reactions gave rise not only to a rate acceleration[14a,b] but, when bound to a chiral ligand, to significant enantioselection.

The standard test for the enantioselective power of the catalyst was the reaction between cyclopentadiene (**1**) and 3-acryloyl-1,3-oxazolidin-2-one (**2**) since the *endo* : *exo* ratio can be easily determined by ^{1}H NMR and the e.e. of the *endo* adduct [(*R*)-**5** *vs* (*S*)-**5**] by HPLC analysis using a chiral column (Scheme 1).

Scheme 1



Some preliminary experiments[13b] showed that 2,2-bis{2-[4(*R*)-phenyl-1,3-oxazolinyl]}propane **3a** was the best commercially available bis(oxazoline) in the Mg(II)-catalyzed DA reaction and, at -50 °C in dichloromethane free from ethanol as solvent, the yield was > 98%, the *endo* : *exo* ratio was 93 : 7, and (*S*)-**5** was obtained in 68-70% ee. This was rationalized as being the result of a tetrahedral coordination of **2** and **3a** around Mg(II) cation that leaves the *Re* diastereoface of the dienophile in **4a** more accessible to the diene and (*S*)-**5** was the preferred enantiomer obtained.

This data cannot compete in terms of enantioselective efficiency with some results reported in the literature [using bis(oxazolines) as ligands and Cu(II) as inorganic core of the catalyst, (*R*)-**5** was obtained by Evans[12c] in 98% ee], but one important property of the catalytic system was observed. When the same

reaction was run in the presence of two moles water per mole catalyst, the opposite enantiomer (*R*)-**5** was obtained in 59-65% ee. This was the first example of enantioselective synthesis of both DA enantiomers using the same bis(oxazoline)-based catalyst and the second one reported in the field. In fact $Yb(OTf)_3$ / (*R*)-(+)-binaphthol was found to give either one enantiomer or the other one in the presence of a suitably chosen β-dicarbonylic achiral ligands.[8d,e]

The effect of water in inverting the enantioselectivity of the reaction was tentatively assigned to a change in the coordination around Mg(II) from tetrahedral to octahedral. Since the synthesis of both enantiomers of chiral compounds from the same chiral messenger is a very important task in organic synthesis, this topic was studied in details with two main goals: to increase enantioselectivity making these results competitive with those reported in the literature; to infer the mechanism of the inversion of the enantioselectivity.

RESULTS

*DA Reaction of **1** and **2** with MP and 4(R)-phenylsubstituted bis(oxazoline) **3a** as ligand.* From the early experiments,[13b] the most important change of the protocol was the determination of the stereo- and enantioselectivity of the reaction in Scheme 1 by HPLC using a chiral Daicel OD column. Dichloromethane was the solvent of choice having care to avoid samples stabilized with alchohols that have a dramatic influence on the enantioselectivity of the reaction. The effect of temperature was tested and Table 1 shows the time required for the complete conversion to **5** and the change of stereo and enantioselectivity for the reaction. The best results were obtained for temperature in the range -50/-80 °C (Table 1 - entries 1,2).

Dienophile **2**, bis(oxazoline) **3a**, and MP in the ratio (10-20) : 1 : 1 were stirred in dichloromethane at ambient temperature for about 1 hour in a rubber septum sealed vial, then **1** was added to the chilled solution. The typical experiment reported in this paper was run on 0.5 mmoles **2**, and **1** was added in excess (about 1.5 mmoles). After decomposition in water and extraction with dichloromethane, the organic layer was briefly dried and then tested at HPLC. Under the conditions reported in details in the experimental part, the enantiomers of *exo*-**5** were eluted first, then *endo (S)*-**5** and *endo (R)*-**5** were eluted in the order. Both *endo* : *exo* ratio and the *endo* ee were thus determined and the former data, from time to time, were confirmed by ^1H NMR.

The mechanism of the catalysis was inferred. If **4a** (Scheme 1) is the tetrahedral intermediate in the catalytic cycle, using catalysts with different enantiomeric purities, a linear relationship between the $ee_{product}$ and the ee of the catalyst (hence the ee_{ligand}) is expected.[15] This was tested with four samples prepared from (*R*)- and (*S*)-**3a** and the results are reported in Table 2 (entries 3-6). When the ee of *endo*-**5** was plotted *vs* the ee of the ligand (*R*)-**3a**, a good linear relationship was obtained (Figure 1A).

Table 1. Effect of the temperature on *endo* : *exo* ratio, and ee of *endo*-**5** for the DA reaction between **1** and **2** with 0.1 equivalents of the catalyst obtained from **3a** and MP in dichloromethane.[a]

Entry	T/°C	Time[b]	*endo* : *exo*	*endo* **5**% ee[c]
1	-80	48 h	96 : 4	73 (*S*)
2	-50	18 h	93 : 7	68-70(*S*)[d]
3	-40	12 h	93 : 7	57 (*S*)
4	0	15 min	88 : 12	52(*S*)
5	25	10 min	87 : 13	49(*S*)

[a]Hydrocarbon-stabilized solvent. [b]Reaction time for complete conversion to **5**. [c]The e.e. reported is the average of at least two independent experiments, the major enantiomer obtained is in parenthesis. [d]Ref.[13b].

Table 2. Enantioselectivity of the DA reaction between **1** and **2** with the catalyst from **3a**, MP and the eventual auxiliary ligands.

Entry	Enant. purity **3a**	Auxiliary ligand (AL)	**2**	Ratio [**3a**-MP]	AL	T/°C	*endo*: *exo*	ee% *endo* **5**[a]
1	*b*	---	*10*	*1*	---	*-80*	*96 : 4*	*73 (S)*
2	b	---	20	1	---	-50	93 : 7	70 (*S*)
3	100[b]	---	10	1	---	-50	92 : 8	72 (*S*)
4	80	---	10	1	---	-50	90 : 10	50 (*S*)
5	50	---	10	1	---	-50	90 : 10	36 (*S*)
6	25	---	10	1	---	-50	90 : 10	21 (*S*)
7	*b*	*H_2O*	*10*	*1*	*2*	*-80*	*95 : 5*	*73 (R)*
8	*b*	*H_2O*	*10*	*1*	*2*	*-50*	*93 : 7*	*64-70 (R)*
9	*b*	*MeOH*	*10*	*1*	*2*	*-50*	*91 : 9*	*42(R)*
10	b	MeOH	20	1	2	-50	92 : 8	44(*R*)
11	b	MeOH	10	1	1	-50	92 : 8	7-15 (*S*)
12	b	MeOH	10	1	8	-50	92 : 8	22 (*R*)
13	*b*	*EtOH*	*10*	*1*	*2*	*-50*	*91 : 9*	*16(R)*
14	*b*	*2-propanol*	*10*	*1*	*2*	*-50*	*92 : 8*	*12(S)*
15	*b*	*tert-BuOH*	*10*	*1*	*2*	*-50*	*92 : 8*	*33(S)*
16	b	$HOCH_2CH_2OH$	20	1	1	-50	91 : 9	58(*R*)
17	*100[b]*	*$HOCH_2CH_2OH$*	*10*	*1*	*1*	*-50*	*90 : 10*	*55(R)*
18	80	$HOCH_2CH_2OH$	10	1	1	-50	89 : 11	45(*R*)
19	50	$HOCH_2CH_2OH$	10	1	1	-50	90 : 10	26(*R*)
20	25	$HOCH_2CH_2OH$	10	1	1	-50	88 : 12	15(*R*)

[a]The ee reported is the average of 2-3 independent experiments; when the variation is larger than ±2%, the range is reported. The major enantiomer is in parenthesis. [b]The purity of the commercial samples (*R*)- and (*S*)-**3a** (98%) was taken as 100%, hence the values of the *endo* **5** ee are not corrected.

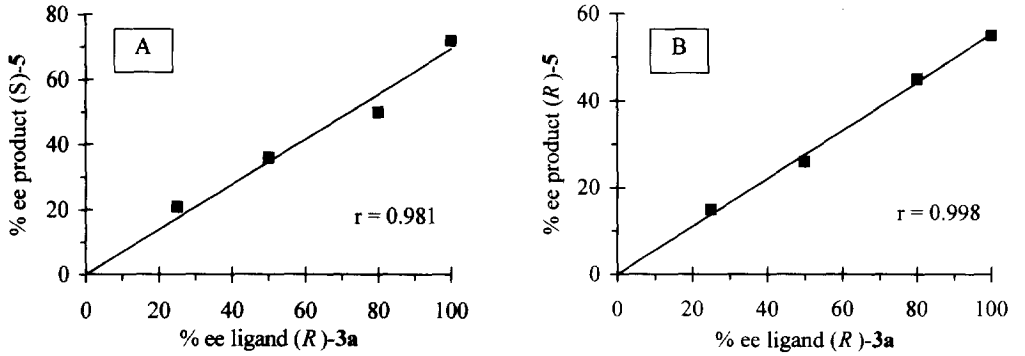


Figure 1. Linear relationships between: (A) the ee of the *endo* product (*S*)-**5** and that of the ligand (*R*)-**3a**; (B) the ee of the *endo* product (*R*)-**5** and that of the ligand (*R*)-**3a** in the presence of 1 equiv ethylene glycol.

When two moles water were added to the catalyst, as previously tested,[13b] the opposite enantiomer (*R*)-**5** was obtained and the ee was in the range 64-73% (Table 2 - entries 7,8). A similar result was obtained when the catalyst was left for a few hours unstoppered, allowing a spontaneous absorbance of moisture.

It is known that magnesium tends to adopt octahedral coordination with a preference for oxygen ligands.[16a,b] It is therefore expected that not only water but alcohols too may behave as auxiliary ligands affecting the enantioselectivity of the reaction. Methanol, ethanol, 2-propanol, and *tert*-butyl alcohol were tested (Table 2 - entries 9,13-15) and a rationale result was obtained if the increasing steric hindrance of the alkyl group increases the overcrowding around the Lewis acid center making the octahedral catalyst less competitive than the tetrahedral one [the ee are in the order: water ≅70(*R*), methanol 42(*R*), ethanol 16(*R*), 2-propanol 12(*S*), *tert*-butyl alcohol 33(*S*), no hydroxylic ligand 73%(*S*)].[17]

Some further experiments were performed with methanol. If only one equivalent of MeOH is used (Table 2 - entry 11) the result is that expected, when two catalysts, one tetrahedral and one octahedral, are in competition. If MeOH is used in excess (Table 2 - entry 12), this begins to give substitution of ligands **3a** or **2** around the cationic center, giving rise either to an achiral or to an inactive species.

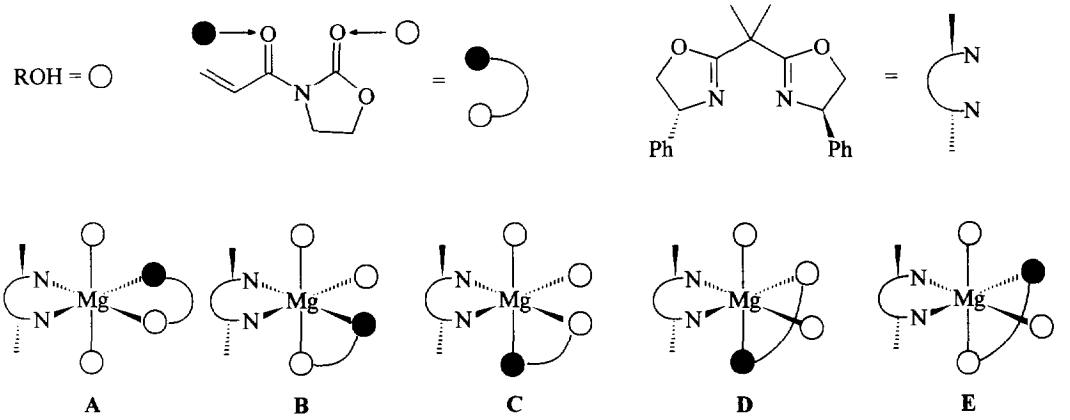
A further hydroxylic ligand was tested for stereochemical reasons discussed later. When one equivalent of ethylene glycol was added to **4a** (Table 2 - entry 16), 58% ee of (*R*)-**5** was obtained, a value lying between those of water and methanol, suggesting that the same octahedral complex is the intermediate of all these reactions. Experiments to test the aging of the catalyst showed that the same ee was obtained if the reaction is run immediately after the addition of glycol, after 1 hour or after 8 hours stirring at ambient temperature. Only after 24 hours the catalyst became somewhat less enantioselective [38% ee (*R*)].

If an homogeneous octahedral complex is in the catalytic cycle to give *endo* (*R*)-**5** enantiosectively, again a linear relationship is expected to be obtained by plotting $ee_{product}$ *vs* ee_{ligand}. The results determined on four

mixtures of different (*R*)-, and (*S*)-**3a** composition, each with one equivalent ethylene glycol, are reported in Table 2 (entries 17-20) and are plotted in Figure 1B.

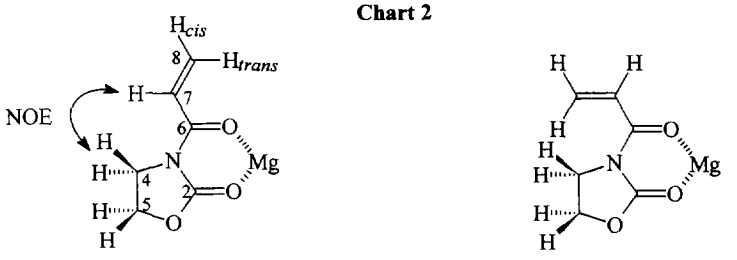
Given that the hydroxylic ligands, the bidentate dienophile **2**, and the bis(oxazoline) **3a** develop a supramolecular device around the Mg(II) cation, the octahedral complexes **A** - **E**, reported in Chart 1, could result. The structure **A** was excluded having performed the reaction with ethylene glycol that, for geometrical constrain, cannot have the hydroxylic groups *trans* to each other as required by structure **A**.

Chart 1



A further crucial factor determining the enantioselectivity of the process has to be taken into account: the dienophile **2**, complexed either in the tetrahedral intermediate **4a** or in one of the octahedral complexes **B-E**, can have the double bond *s-cis* or *s-trans* relative to the carbonyl function (Chart 2).

Chart 2



s-cis-**2** bound to Mg(II)

s-trans-**2** bound to Mg(II)

Some information about the structure of the Magnesium(II) complex can be obtained by ^{1}H NMR spectroscopy. In the literature three ^{1}H NMR investigations of the complex between *trans* alkenoyl-oxazolidinones and $SnCl_4$,[18a] Et_2AlCl,[18b] and TADDOL-$TiCl_2$ have been reported.[5e] These have H-7 always shielded in the range 0.99-1.36 ppm, and H-8_{trans} deshielded in the range 0.48-0.82 ppm.

When 1 equivalent MP was added to an equimolecular mixture of **2** and **3a** (Figure 2a - $CDCl_3$ was the solvent for solubility reasons), the spectrum in Figure 2b was obtained. The spectral data of these and of the forthcoming spectra, Figure 3, are reported in the experimental section. This spectrum is clearly consistent with the formation of the [1:1:1] tetrahedral complex **4a**, it is nicely resolved at 50 °C and it does not change significantly with the lowering of the temperature. From the comparison of the spectra in Figures 2a and 2b, it is evident the deshielding of both methyl groups and H-4 of **3a** by about 0.2 ppm and the shielding of H-7 and H-8_{trans} by 1.44 and 0.38 ppm respectively while H-8_{cis} remains almost unaltered (the δ values are reported in Table 5 in the experimental section for this and all other ^{1}H NMR spectra together with the absorptions of some secondary species observed). A negative NOE between H-7 of the acryloyl subunit and the oxazolidinone H-4 supports the *s-cis* conformation of the α,β-unsaturated carbonyl fragment as represented in **4a**. In such structure the H-8_{trans} is placed in the shielding cone of the phenyl group of the bis(oxazoline) and this offers a rationalization of the observed results.

When 2 equiv of CH_3OD were added a spectrum nicely resolved at 52 °C (Figure 2c) was obtained. When the temperature was lowered, the spectrum broadened and, at -35 °C, not only the methyl absorption of bound **3a** was splitted into two singlets, but two well separated methoxy singlets appeared, again not consistent with two methanol molecules *trans* to each other as type-**A** complex requires. If the spectra in Figures 2b and 2c are compared, the protons of the bis(oxazoline) **3a** do not change significantly and are deshielded by less than 0.1 ppm. The protons of bound **2** are all deshielded (in the range 0.15-0.38 ppm), both those of the acryloyl group and, more important, *those of the oxazolidinone ring*. This is consistent only if the oxazolidinone ring is close to a phenyl group as the stereochemistry of complex **B** brings, and the double bond is *s-cis* relative to the carbonyl functionality. The above stereochemistry is supported by a negative NOE observed between H-7 of the acryloyl subunit and both H-4 and the *ortho* protons of the phenyl group.

The different octahedral structures, all with the acryloyl group in the *s-cis* conformation, are expected to give opposite results in terms of enantioselectivity. Even if it is evident that the most abundant complex is not necessarily the most reacting one, only the complex **B** will give the (*R*) enantiomer preferentially, while **C-E** will give the opposite enantiomer.

DA reaction of 1 and 2 with MP and 4,5-diphenylsubstituted bis(oxazolines) as ligands. The limits of **3a** as chiral ligand to build an enantioselective catalyst for the DA reaction have been described in the previous section. To reach an enantioselective efficiency comparable with the results reported in the literature, a different bis(oxazoline) has to be used. Several bis(oxazolines) with an alkyl group in position 4: [(4*S*)-benzyl-,[(4*S*)-isopropyl-,[(4*S*)-*tert*-butyl- and [(4*S*)-methyl-(5*R*)-phenyl-derivatives] were tested, and unsatisfactory results were obtained. Since a phenyl group in position 4 seems to be crucial for the enantioselective efficiency of the catalyst, 2,2-bis{2-[(4*R*,5*S*) and [(4*R*,5*R*)-diphenyl-1,3-oxazolinyl]}propanes (**3b** and **3c** respectively),[19a,b] were tested (Chart 3).

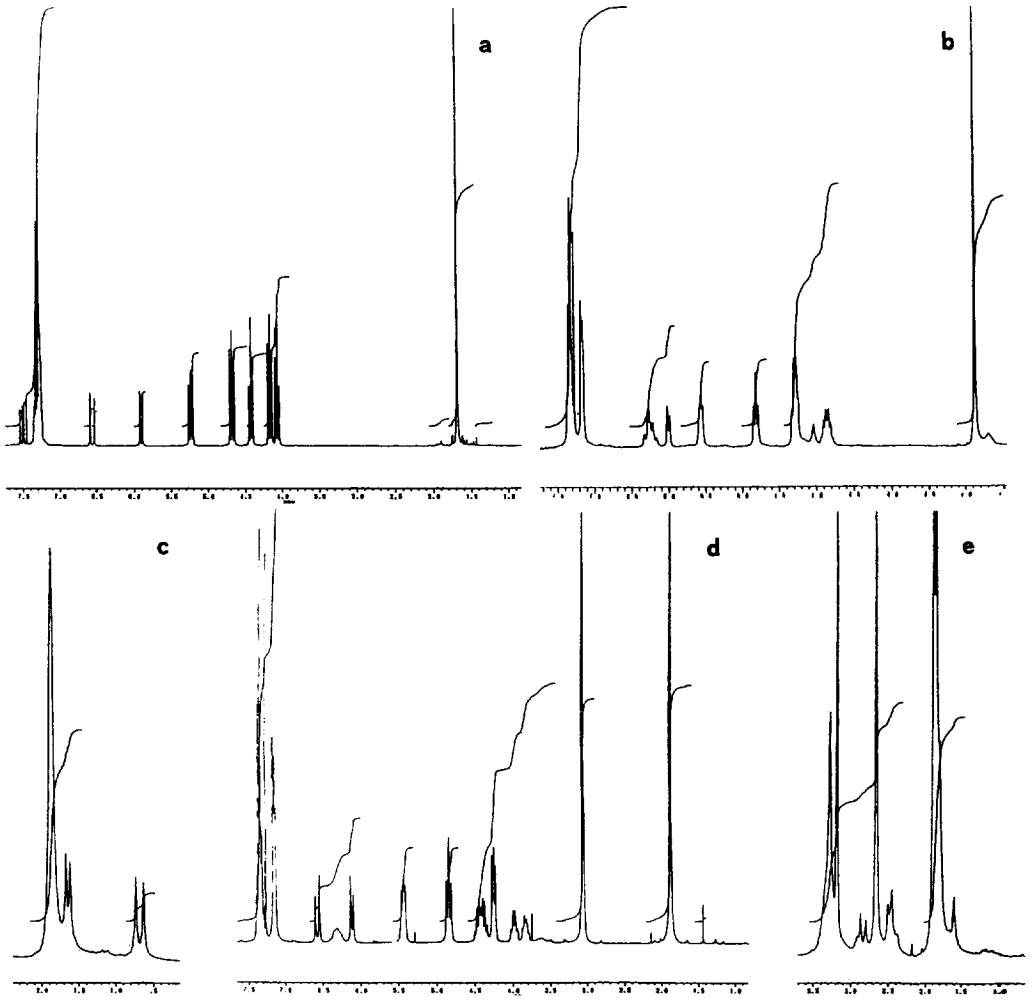
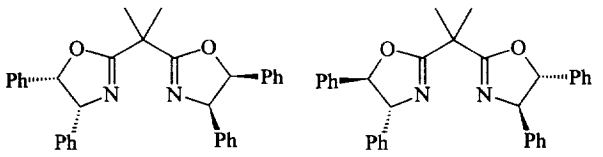


Figure 2. (a) H^1 NMR spectrum of equimolecular amounts of **2** and **3a** in $CDCl_3$ at 25 °C. Spectrum (a) after the addition of 1 equiv of $Mg(ClO_4)_2$, registered at 50 (b) and -50 °C (c). Spectrum (b) after the addition of 2 equiv of CH_3OD, registered at 52 (d) and -50 °C (e).

Chart 3



3b

3c

The results with the catalyst prepared from **3b** and MP in the presence of **2** were disappointing since the ee of (*S*)-**5** was in the range 22-43% (Table 3 - entries 1,2) and the results seems to be reproducible with difficulty.[20]

When the DA reaction between **1** and **2** was catalyzed with 0.05 equivalents of **3c** and MP, the results were excellent. Not only the *endo : exo* ratio was 99.5 : 0.5, but the ee of (*S*)-**5** was 97% at -80°C and 94% at -50 °C (Table 4 - entries 1,2). These, in terms of both stereo- and enantioselectivities, are among the best results reported in the literature[5d,12e] for the DA reaction of **1** and **2**.

Stimulated by these results, **3b** and **3c** were studied in details and the effect of ROH as auxiliary ligands was investigated. To the catalyst prepared from 1 equivalent of the *trans* bis(oxazoline) **3c** and MP in the presence of **2**, two equivalents of water, methanol, ethanol, 2-propanol or *tert*-butyl alcohol, or 1 equivalent of ethylene glycol were alternatively added, then the reactions were run at -50 °C (Table 4 - entries 3-9). Water lowers the enantioselective power of the catalyst; only at -80 °C the ee of (*S*)-**5** remains 78%; at -50 °C the ee is reduced to 49% (Table 4 - entries 3,4). All alcohols gave ee of (*S*)-**5** but the larger the steric hindrance of the alkyl residue, the lower is the reduction of enantioselectivity. Results comparable to those given by two equivalents of methanol are obtained with the addition of one equivalent of ethylene glycol (Table 4 - entries 5 and 9).

The octahedral complex assembled by **2**, **3c** and two hydroxylic ligands around Mg(II) seems to be formed with increased difficulty with the increase of the steric hindrance of the hydroxylic ligands; furthermore, this seems to be less enantioselective than the tetrahedral one given by **2**, **3c** and MP.

Table 3. Enantioselectivity of the DA reaction between **1** and **2** with the catalyst from **3b**, MP and the eventual auxiliary ligands.

Entry	Auxiliary ligand (AL)	Ratio **2**	Ratio [**3b**-MP]	Ratio AL	T/°C	*endo:exo*	ee% *endo* **5**[a]
1	---	10	1	---	-80	96 : 4	28-34(*S*)
2	---	10	1	---	-50	92 : 8	22-43(*S*)
3	*H_2O*	*20*	*1*	*2*	*-80*	*94 : 6*	*89(R)*
4	*H_2O*	*20*	*1*	*2*	*-50*	*95 : 5*	*82(R)*
5	*MeOH*	*20*	*1*	*2*	*-50*	*93 : 7*	*78(R)*
6	*EtOH*	*20*	*1*	*2*	*-50*	*94 : 6*	*74(R)*
7	2-propanol	20	1	2	-50	92 : 8	18(*R*)
8	*tert*-BuOH	20	1	2	-50	92 : 8	5(*R*)
9	*$HOCH_2CH_2OH$*	*10*	*1*	*1*	*-50*	*93 : 7*	*64(R)*

[a]The ee reported is the average of 2-3 independent experiments, when the variation is larger than ±2%, the range is reported. The major enantiomer is in parenthesis.

Table 4. Enantioselectivity of the DA reaction between **1** and **2** with the catalyst from **3c**, MP and the eventual auxiliary ligands.

Entry	Auxiliary ligand (AL)	**2**	Ratio [**3c**-MP]	AL	T/°C	*endo:exo*	ee% *endo* **5**[a]
1	---	*20*	*1*	---	*-80*	*99.5 : 0.5*	*97(S)*
2	---	*20*	*1*	---	*-50*	*98 : 2*	*94(S)*
3	H_2O	20	1	2	-80	98 : 2	78(*S*)
4	H_2O	20	1	2	-50	95 : 5	49(*S*)
5	MeOH	20	1	2	-50	96 : 4	76(*S*)
6	EtOH	20	1	2	-50	96 : 4	80(*S*)
7	2-propanol	20	1	2	-50	97 : 3	86(*S*)
8	*tert*-BuOH	20	1	2	-50	96 : 4	84(*S*)
9	$HOCH_2CH_2OH$	10	1	1	-50	97 : 3	79(*S*)

[a]The ee reported is the average of 2-3 independent experiments. The major enantiomer is in parenthesis.

When the hydroxylic auxiliary ligands (2 equivalents) were added to the catalyst prepared from 1 equivalent of the *cis* bis(oxazoline) **3b** and MP in the presence of **2**, more interesting results were obtained. The DA reaction that gave a low ee of (*S*)-**5** with the tetrahedral complex formed from **2**, **3b** and MP as catalyst, became strongly enantioselective and the main enantiomer was (*R*)-**5**. Two equivalents of water give ee in the range 82-89% (Table 3 - entries 3,4) depending on the temperature. This *effect of strong inversion of the enantioselectivity* remains important for methanol or ethanol (2 equivalents) and ethylene glycol (1 equivalent), the ee of (*R*)-**5** being 78, 74 and 64% respectively (Table 3 - entries 5,6 and 9), it becomes very low with 2-propanol and *tert*-butyl alcohol (18 and 5% ee respectively - entries 7,8 in Table 3).

The ^{1}H NMR spectra of the tetrahedral Mg(II) complexes of **2** and **3b** or **3c** (**4b** and **4c** respectively) are reported in Table 5. The spectra are well resolved at about 50 °C and, when compared with the spectrum of **4a**, these have all δ values consistent for the proposed structures. Lowering the temperature, the spectra begin broadening but, even at -50 °C, only one largely predominant species is observed.

The addition of 2 equivalents methanol to **4b** gave a spectrum consistent for an octahedral complex (Figure 3a - Table 5). The methanol ligands are *cis* to each other since at -50 °C the spectrum (Figure 3b) shows two nicely separated singlets for two methanol molecules in deeply different environments and two singlets for the methyl groups (coalescence temperature -16 °C).

The addition of 2 equiv methanol to **4c** gave a different result. At -50 °C the region of the methyl signals shows at least five different singlets and a similar shape is observed in the regions of the methoxy groups (Figure 3d - Table 5; all values listed under **6c**). When the spectrum is heated at 0 °C a coalescence of the

different singlets is observed, at 60 °C the spectrum (Figure 3c) sharpened and the different protons are all well resolved. This behaviour can be rationalized assuming the existence at low temperature of *at least two configurationally different octahedral complexes.* Increasing the temperature, the exchange of ligands becomes fast on the ^{1}H NMR time scale and the result is the spectrum of a fluxional structure.

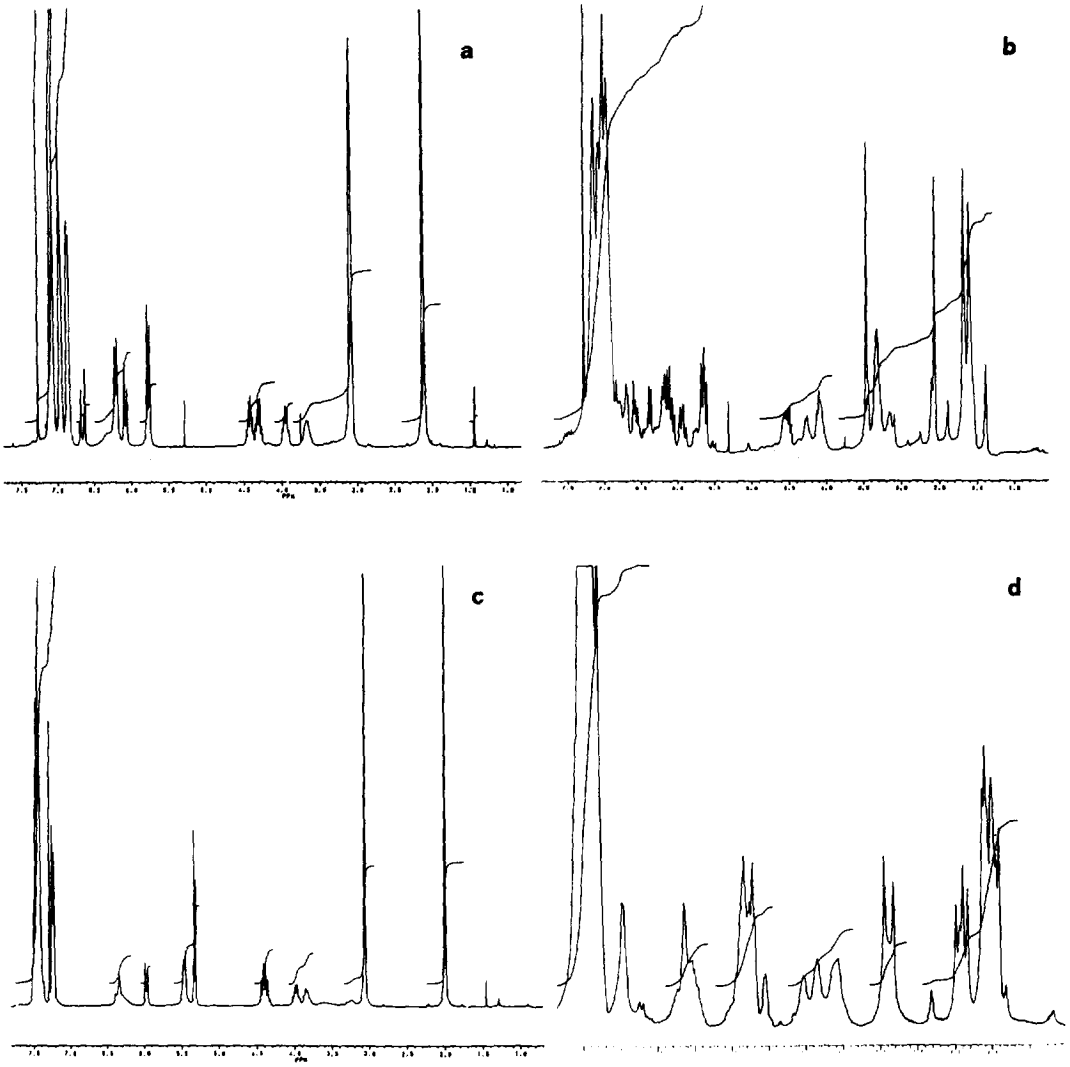


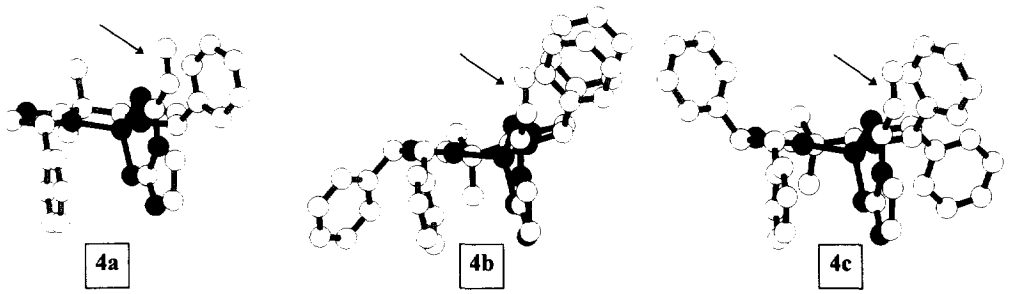
Figure 3. (a) H^1 NMR spectrum of **3b**, **2**, MP, and CH_3OD in the ratio [1:1:1:2], registered at 52 °C. (b) Spectrum a registered at -50 °C. (c) H^1 NMR spectrum of **3c**, **2**, MP, and CH_3OD in the ratio [1:1:1:2], registered at 60 °C. (d) Spectrum c registered at -50 °C.

DISCUSSION

The tetrahedral complexes formed from MP and bis(oxazolines) **3a-c** in the presence of **2**, gave an enantioselective DA reaction with **1** as diene, and (*S*)-**5** was the major enantiomer; but the ee was deeply different: excellent with **3c**, good with **3a**, and poor with **3b**. All these bis(oxazolines) have the same (*R*) configuration of the 4-phenyl-substituted chiral center, but the addition of a second phenyl group in position (5) lowers the efficiency of the catalyst if this is ***cis***, has a synergic effect if it is ***trans***. This point needs to be discussed since the steric effects alone do not rationalize the results.

Taking into account the computer generated (Hyperchem-Chemplus representations) tetrahedral complexes **4a-c** (Chart 4), it is evident that the diastereoface of **4a** accessible to diene is the *Re* one. This could be the result of the steric encumbrance of the *Si* face due to the phenyl group, but when this was substituted by the more steric-demanding *tert*-butyl group, the enantiomeric efficiency resulted strongly lowered.[21]

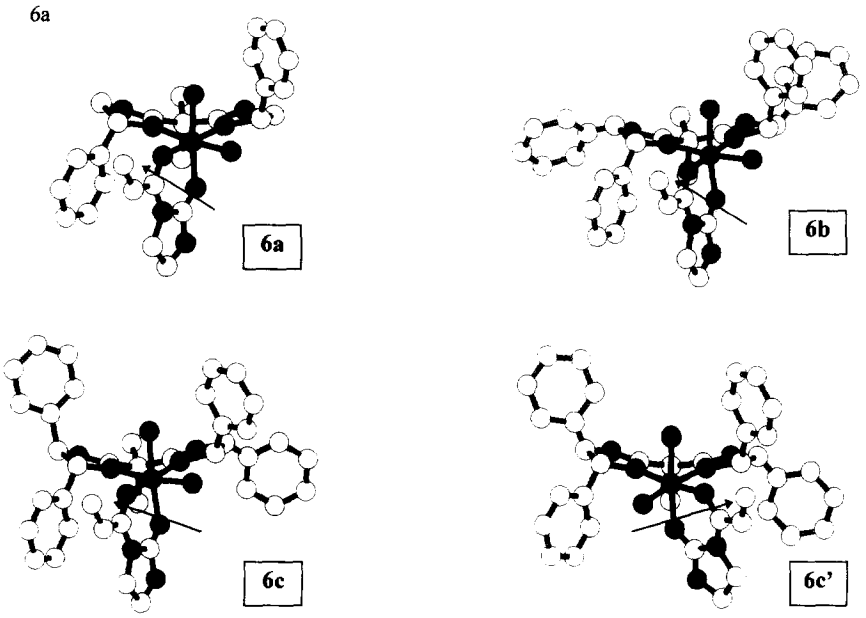
Chart 4



The reduced importance of the steric hindrance becomes evident if **4b**, the tetrahedral complex with *cis* bis(oxazoline) **3b**, is considered. The steric shielding of the *Si* face in **4b** should be increased by the second phenyl ring, nevertheless the diene adds less enantioselectively. The electronic effects (donor/acceptor interactions), involving both one phenyl group with the oxazolidinone ring and the second phenyl group with the acryloyl double bond can rationalize the results. These electronic interactions, recently suggested to be involved in the catalytic mechanism of aryl-substituted complexes,[12e,13c] are significant in **4a**, are reduced in **4b** due to the competitive phenyl/phenyl interactions, are again important in **4c** with, in addition, a synergic effect of the 5(*R*)-phenyl group which drives the approach of cyclopentadiene to the *Re* face of the dienophile. The same effect was observed with the same catalyst in the intramolecular ene reaction.[22]

After the addition of two equivalents of hydroxylated auxiliary ligands, Mg(II) changes its coordination number and the tetrahedral complex becomes octahedral. The reasons for the preference of the **B** configuration (Chart 1) for **6a** and **6b** have already been discussed and these complexes are reported in Chart 5 with an oxygen atom in the position of the auxiliary ligands for sake of simplicity.

Chart 5



The addition of cyclopentadiene to **6a** occurs at the *Si* diastereoface and this rationalizes the inverted sense of the asymmetric induction when two equivalents of water or alohol are added to the catalyst prepared from **3a**.

If two equivalents of auxiliary ligands are added to **4b**, a catalyst with low (*S*) enantioselectivity is transformed into a good (*R*)-inducing one. This can be represented by the structure **6b** that, in spite of the electronic effects, cannot add cyclopentadiene other than to the *Si* diastereoface producing high ee of (*R*)-**5**.

When the auxiliary ligands are added to **4c**, the catalyst results less enantioselective. The ^{1}H NMR experiments have shown that (in $CDCl_3$) at least two configurationally defined species are obtained. In Chart 5 two octahedral complexes are represented: **6c** and **6c'**. The experimental results are better rationalized if the latter is more efficient than the former in the catalytic cycle.

SUMMARY AND CONCLUSIONS

The complex prepared from C_2-symmetric bis(oxazolines) and MP is a chiral Lewis acid very efficient as catalyst for the DA reaction. This coordinates 3-acryloyl-1,3-oxazolidin-2-one (**2**) around Mg(II) and the bound dienophile reacts easily and enantioselectively with cyclopentadiene (**1**).

The tetrahedral coordination in the presence of 4(*R*)-phenyl substituted bis(oxazoline) (**3a**), makes the *Re* diastereoface more accessible to the diene and (*S*)-**5** is preferentially obtained. This enantioselectivity cannot be rationalized only in terms of steric effects, but electronic (donor/acceptor) interactions between the

different π-systems in the complex must be taken into account. The catalytic system was studied and an intermediate with **3a**, MP and **2** in the ratio 1:1:1 was demonstrated to be involved in the catalytic cycle. Furthermore the structure of this complex was checked by ^{1}H NMR.

When a second chiral center, again carrying a phenyl group, was introduced in the bis(oxazoline), its configuration had a dramatic influence on the enantioselectivity. *Cis*-diphenyl substituted bis(oxazoline) **3b** and MP is a catalyst with a low enantioselective efficiency; its *trans* isomer **3c** results to be one of the best enantioselective catalysts for the DA reaction between **1** and **2.**

All these complexes can expand the coordination number of Mg(II) from 4 to 6 when two equivalents of hydroxy derivatives (water or alcohols) are added and again the Mg(II) complex behaves as a catalyst of the DA reaction. The structure of the resulting octahedral complexes was investigated by ^{1}H NMR and their importance in the catalytic cycle was underlined. The change from tetrahedral to octahedral coordination has a strong influence on enantioselectivity and **3a,b** give the opposite (*R*)-**5** adduct, preferentially.

For the first time, achiral auxiliary ligands can be used to invert the enantioselectivity induced by a chiral bis(oxazoline) so that both enantiomers can be synthetized enantioselectively with the same Mg-based chiral catalyst. While the above studies focussed the influence of the structure of the Mg(II) complex involved in the catalytic process on the enantioselectivity of the DA reaction, and the possible use of achiral auxiliary ligands to change the sense of the asymmetric induction of a catalytic process seems to open wide horizons, additional theoretical and experimental studies are necessary to rationalize every experimental result.

EXPERIMENTAL SECTION

Dichloromethane was the hydrocarbon-stabilized Aldrich ACS grade, distilled on calcium hydride and immediately used. Magnesium perchlorate was the anhydrous Aldrich ACS reagent. 3-Acryloyl-1,3-oxazolidin-2-one (**2**) was prepared following the literature method.[23] 2,2-Bis{2-[4(*R*)-phenyl-1,3-oxazolinyl]}propane **3a** and its 4(*S*) isomer were commercially available by Aldrich; 2,2-bis{2-[4(*R*),5(*S*)- and [4(*R*),5(*R*)-diphenyl-1,3-oxazolinyl]}propanes (**3b** and **3c** respectively) were prepared as described in the literature.[19a,b] The *endo* : *exo* ratios were measured by HPLC and confirmed by ^{1}H NMR; the enantiomer compositions were determined by HPLC (Daicel Chiralcel OD column).

^{1}H NMR Spectra. All ^{1}H NMR spectra were measured in $CDCl_3$ on a Bruker AC 300 spectrometer and the probe temperatures were determined by the chemical shift difference of the two absorptions of methanol. The chemical shift data are reported in Table 5; the following spectra have been registered at low temperature and the most significant chemical shift values are hereto reported. **4a:** at -51 °C δ 1.89 {s, Me; in addition 4

singlets at 0.63, 0.74, 1.62 and 1.67δ due to the complex $[(\mathbf{3a})_2 \cdot Mg(ClO_4)_2 \cdot \mathbf{2}]^{24}$ in the ratio 26:74 with **4a** are observed}. **6a:** at -58 °C δ 1.88 and 1.91 (s, Me; in addition a singlet at 1.61δ due to free **3a** in the ratio 5:95 with **6a** is observed); 2.67 and 3.20 (s, OMe; in addition a broad singlet at 3.30δ is observed). **4b:** at -50 °C δ 2.10 and 2.14 {s, Me; in addition 4 singlets at 0.70, 0.78, 1.88 and 1.91δ due to the complex $[(\mathbf{3b})_2 \cdot Mg(ClO_4)_2 \cdot \mathbf{2}]^{24}$ are observed}. **6b:** at -50 °C δ 2.11 and 2.19 (s, Me; in addition a singlet at 1.89δ due to free **3b** in the ratio 10:90 with **6b** is observed); 2.57 and 3.46 (s, OMe; in addition a broad singlet at 3.31 δ is observed). **4c:** at -50 °C δ 1.98 and 2.07 (s, Me). **6c:** at -50 °C δ 1.92, 1.96, 2.03, 2.12 and 2.15 (s, Me; in addition a singlet at 1.89δ due to free **3c** in less than 10% amount is observed); 2.35, 2.40, 2.50, 3.32 and 3.44 (s, Ome).

Table 5. ^{1}H NMR chemical shift data for **2**, **3a-c** and their Magnesium tetrahedral (**4a-c**) and octahedral complexes in $CDCl_3$[a]

H no.	**2**	**3a**	**4a**[b]	**6a**[c]	**3b**	**4b**[c]	**6b**[c]	**3c**	**4c**[b]	**6c**[e]
H-8*cis*	5.91	-	5.95	6.10	-	5.92	6.06	-	5.82	5.95
H-8*trans*	6.55	-	6.17	6.55	-	6.24	6.65	-	5.96	6.34
H-7	7.50	-	6.06	6.30	-	6.09	6.3	-	6.10	6.3
H-4	4.10	-	3.64 3.75	3.82 3.98	-	3.63 3.75	3.66 3.94	-	3.78 3.81	3.82 3.97
H-5	4.44	-	4.16	4.38 4.45	-	4.01	4.31 4.43	-	4.21	4.36 4.42
Me	-	1.71	1.85	1.87	1.93	2.12[d]	2.12	1.89	1.97	2.00
H-4'	-	5.28	5.54	5.43	5.60	5.88	5.76	5.11	5.30	5.31
H-5'*cis*	-	4.69	4.75	4.83	5.98	6.17	6.20	-	-	-
H-5'*trans*	-	4.15	4.21	4.24	-	-	-	5.33	5.60	5.45
OMe	-	-	-	3.05	-	-	3.10	-	-	3.06

[a]Registered at 25 °C unless otherwise stated.[b]Registered at 50 °C. [c]Registered at 52 °C. [d]In addition 4 singlets at 0.86, 0.94, 1.89 and 1.91δ are observed due to the complex $[(\mathbf{3b})_2 \cdot Mg(ClO_4)_2 \cdot \mathbf{2}]^{24}$ whose ratio with **4b** is 8:92. [e]Registered at 60 °C.

DA Reaction of cyclopentadiene (1) and 3-acryloyl-1,3-oxazolidin-2-one (2) catalyzed by magnesium perchlorate and bis(oxazolines) 3a-c. General procedure. Anhydrous magnesium perchlorate (11 mg - 0.05 mmol), bis(oxazoline) **3** (0.05 mmol) and 3-acryloyl-1,3-oxazolidin-2-one (**2**) (72 mg - 0.5 mmol, or a double amount in accordance with the indications in Tables 2-4) were added to anhydrous CH_2Cl_2 (0.3-0.5 mL) under stirring at ambient temperature in a rubber septum sealed vial. Within one hour the inorganic salt

dissolved and a dusty white solid can precipitate. At this stage, *when required,* the auxiliary ligand [water or alcohols (0.1 mmol) or ethylene glycol (0.05 mmol)] was added with a microsyringe and stirring was continued for two additional hours. The vial was chilled at the temperature reported in the Tables and after 20 minutes cyclopentadiene [(0.1 mL - about 1.5 mmol) or eventually a double amount for the reactions run on 1 mmol of **2**] was added. Stirring was continued overnight (for the reactions run at -80°C the time was 48 hours), then the reaction was decomposed in water, extracted with CH_2Cl_2 and dried In at least one experiment for each reaction, a portion of the crude mixture was monitored by ^1H NMR and the *endo : exo* ratio was determined. The standard analysis of the reaction mixture was performed by HPLC analysis using a Diacel OD column with 10% 2-propanol in hexane as eluant [1 mL/min; average retention times: 19.9 and 20.7 min for *exo* enantiomers, 21.9 min for (*S*)-**5** and 24.6 min for (*R*)-**5**]. The *exo : endo* ratio, determined by HPLC, was identical with that determined by ^1H NMR. The chemical yields were determined running a single experiment for each reaction on 1 mmol **2**, the reaction mixture was then column chromatographed on silicagel 230-400 mesh and eluted with cyclohexane/ethyl acetate 8:2. The total yield of *exo* and *endo* adducts was nearly quantitative.

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20) Since water heavily changes the enantioselectivity of the reaction, traces of moisture may easily induce significant variations of the e.e.

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24) The ^{1}H NMR spectra of these complexes can be registered if the stoichiometric amounts of reagents are mixed and are found to be in equilibrium with the corresponding **3** and **4**.

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