Molecular Sieve Dependent Absolute Stereoselectivity in Asymmetric Catalytic 1,3-Dipolar Cycloaddition Reactions

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The absolute stereochemistry of the enantioselective 1,3-dipolar cycloaddition of alkenes with nitrones catalyzed by chiral magnesium(II)−bisoxazoline complexes is shown to be dependent on the presence of molecular sieves. In the presence of powdered molecular sieves 4 Å, the reaction proceeds to give the *endo* product with up to 82% ee, whereas in the absence of molecular sieves the opposite enantiomer of the *endo* product is obtained in up to 73% ee. The influence of additives such as water or different drying agents on the absolute stereoselectivity of the reaction was also studied. The absolute stereochemistry of the products was determined on the basis of an X-ray analysis of a product containing a chiral center with a known configuration. The influence of molecular sieves on the different possible intermediates in the 1,3-dipolar cycloaddition, consisting of the alkenoyloxazolidinone coordinated to the magnesium(II)−bisoxazoline catalyst, is discussed, and it is proposed that molecular sieves are a part of the catalytic system.

Introduction

The formation of nonracemic compounds by the use of chiral metal complexes as the catalyst is a field in rapid development.[1] The chiral metal complexes used to catalyze these reactions are often very sensitive to the reaction conditions, and the outcome can be very dependent on factors such as solvent, counterions, traces of moist air (water and molecular oxygen), and additives such as molecular sieves (MS).[2]

The 1,3-dipolar cycloaddition (1,3-DC) of alkenes with nitrones is one of the reactions that can be catalyzed by various chiral metal complexes to give isoxazolidines with high control of regio-, diastereo-, and enantioselectivity.[3,4] Recently, we observed that the presence of MS was crucial for both reaction rate and diastereoselectivity of $Yb(OTf)_3$-catalyzed 1,3-dipolar cycloaddition reactions.[4o] This has also been observed for other $Yb(OTf)_3$-catalyzed reactions such as the Diels−Alder[5] and Michael reactions.[6]

Often, the role of MS in Lewis acid-catalyzed reactions is ascribed to removal of water from the reaction mixture, although it has been suggested that MS can influence the preparation of especially titanium−BINOL complexes.[7] In earlier work, it was briefly mentioned that the presence or absence of powdered MS 4 Å affected the selectivity of the magnesium(II)−bisoxazoline-catalyzed 1,3-dipolar cycloaddition of alkenes with nitrones.[4d] Desimoni et al. have studied the magnesium(II)−bisoxazoline-catalyzed Diels−Alder reaction of acryloyloxazolidinone with cyclopentadiene.[8] They observed that reactions performed in the presence of H_2O lead to the reverse face-selection compared to dry reaction conditions.

This paper presents a new aspect of MS in metal-catalyzed reactions as the absolute stereochemistry of the isoxazolidine formed by the 1,3-DC reaction of alkenes with nitrones is dependent on MS.

Results

The reaction of crotonoyl- and acryloyloxazolidinones **1a** and **1b**, respectively, with *C*,*N*-diphenylnitrone **2**

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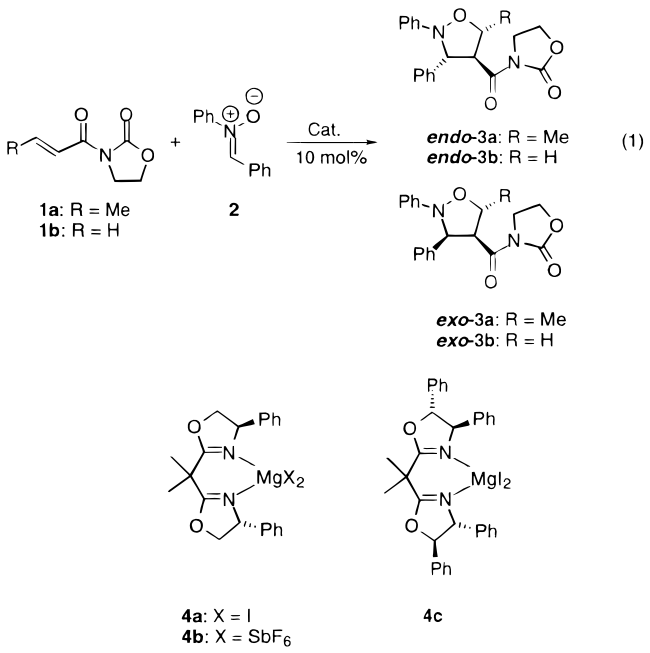
catalyzed by magnesium(II)−bisoxazoline catalysts **4a**−**c** in the presence or absence of MS and other additives has been studied (eq 1) (see the Experimental Section for details). A series of results are presented in Table 1.



(1)

The reaction of **1a** with **2** catalyzed by 10 mol % (*R*,*R*)-**4a**, activated by adding 10 mol % I_2,[4d,9] and in the presence of 50 mg of powdered MS 4 Å proceeded to give the *endo*-isoxazolidine *endo*-**3a** as the major diastereomer with an *endo*/*exo* ratio of 96:4 and 79% enantiomeric excess (ee) of *endo*-**3a** (Table 1, entry 1). On the basis of previous work, the absolute stereochemistry of *endo*-**3a** was assigned to be (3*S*,4*R*,5*S*) (Table 1, entry 1).[4e] Performing the same reaction in the absence of MS 4 Å leads also to *endo*-**3a** as the major diastereomer with 46% ee, but now the absolute stereochemistry of *endo*-**3a** has changed to be (3*R*,4*S*,5*R*) (Table 1, entry 2).[10] Performing the reaction in the absence of MS 4 Å but in the presence of various amounts of H_2O does not change the *endo*/*exo* selectivity and the absolute stereochemistry of *endo*-**3a** (Table 1, entries 3 and 4); however, the ee of the product is improved by the addition of H_2O compared to the reaction in the absence of H_2O. Two other magnesium(II)−bisoxazoline catalysts **4b** and **4c** were also tested in order to investigate if the selectivity could be improved. Application of catalyst **4b** for the reaction in the presence of MS 4 Å leads to a change in the *endo*/*exo* ratio to a slight excess of the *exo* isomer (Table 1, entry 5). The enantioselectivity (70% ee) and absolute induction is comparable to the reaction catalyzed by **4a**. Hence, the absolute stereochemistry is independent of the anion at the metal as an exchange of the iodide−iodine combination in **4a**, with antimonate in **4b**, leads to the same absolute stereochemistry of *endo*-**3a** (Table 1, entry 5). The catalyst **4c** gave poor results for the reaction as both low diastereo- and enantioselectivity were observed (Table 1, entry 6).

Table 1. Reaction of Crotonoyl- and Acryloyloxazolidnone, 1a and 1b, Respectively, with *C*,*N*-Diphenylnitrone 2 in the Presence of the Magnesium(II)−Bisoxazoline Catalysts 4a−c under Various Reaction Conditions in the Presence and Absence of MS 4 Å[a]

entry	alkene	catalyst (10 mol %)	additives	amount (additives)	*endo*/*exo*	ee *endo* (%)
1	**1a**[b]	**4a**	MS 4 Å	50 mg	96:4	79 (3*S*,4*R*,5*S*)
2	**1a**[b]	**4a**	*d*		97:3	46 (3*R*,4*S*,5*R*)
3	**1a**[b]	**4a**	H_2O	2 mol %[d]	97:3	50 (3*R*,4*S*,5*R*)
4	**1a**[b]	**4a**	H_2O	20 mol %[d]	94:6	73 (3*R*,4*S*,5*R*)
5	**1a**[b]	**4a**	MS 4 Å	50 mg	40:60	70 (3*S*,4*R*,5*S*)
6	**1a**[b]	**4c**	MS 4 Å	50 mg	63:37	6 (3*S*,4*R*,5*S*)
7	**1b**[c]	**4a**	MS 4 Å	50 mg	73:27	82 (3*S*,4*R*)
8	**1b**[c]	**4a**	*d*		100:0	48 (3*R*,4*S*)
9	**1b**[c]	**4a**	H_2O	40 mol %[d]	90:10	36 (3*R*,4*S*)
10	**1b**[c]	**4a**	MS 4 Å	10 mg	77:23	42 (3*S*,4*R*)
11	**1b**[c]	**4a**	MS 4 Å	25 mg	71:29	78 (3*S*,4*R*)
12	**1b**[c]	**4a**	MS 4 Å H_2O	50 mg 18 mol %[d]	95:5	36 (3*S*,4*R*)
13	**1b**[c]	**4a**	MS 3 Å	50 mg	73:27	82 (3*S*,4*R*)
14	**1b**[c]	**4a**	MS 5 Å	50 mg	73:27	83 (3*S*,4*R*)
15	**1b**[c]	**4a**	$MgSO_4$	50 mg	96:4	52 (3*R*,4*S*)
16	**1b**[c]	**4a**	$CaSO_4$	502 mg	80:20	41 (3*S*,4*R*)

[a] The reactions were carried out on a 0.1 mmol scale in 2 mL of CH_2Cl_2. [b] Reaction temperature: room temperature. [c] Reaction temperature: −78 °C. [d] The water content was measured by a 737 KF coulometer.

The reaction of acryloyloxazolidinone **1b** with *C*,*N*-diphenylnitrone **2** catalyzed by **4a** shows similar trends in both *endo*/*exo* selectivity, ee, and absolute stereochemistry as for alkene **1a** (Table 1, entries 7−16). The reaction of **1b** with **2** catalyzed by **4a** and in the presence of 50 mg of powdered MS 4 Å proceeds to give an excess of the *endo* isomer *endo*-**3b** with 82% ee (Table 1, entry 7). The absolute induction is similar to the one observed for the alkene **1a** (Table 1, entry 1). It should also be noted that the reactions of **1b** with **2** in the presence of the catalyst proceed with complete regioselectivity, which is not the case in the absence of a catalyst.[4k] In the absence of MS, the diastereoselectivity is improved as only the *endo* isomer of the product is observed (Table 1, entry 8), but the enantioselectivity decreases to 48% ee, and the absolute induction is reversed compared to reaction in the presence of MS 4 Å (compare Table 1, entries 7 and 8). Addition of H_2O to the reaction mixture leads to a slight decrease in the selectivities (Table 1, entry 9). The absolute induction is independent of the amount of powdered MS 4 Å; however, the application of only 10 mg as reported in entry 10 (Table 1) causes a decrease in ee compared to the use of 50 mg (Table 1, entry 7) or 25 mg (Table 1, entry 11). To study if the absolute induction is controlled by traces of H_2O or by the MS, the reaction has been performed in the presence of powdered MS 4 Å saturated with H_2O (Table 1, entry

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(10) In a previous investigation (see ref 4d), we reported an *endo*/*exo* ratio of 63:35, and an ee <2% was observed for the reaction in the absence of MS. However, in this reinvestigation of the reaction we found that the opposite enantiomer was obtained and we have not been able to reproduce the first result.

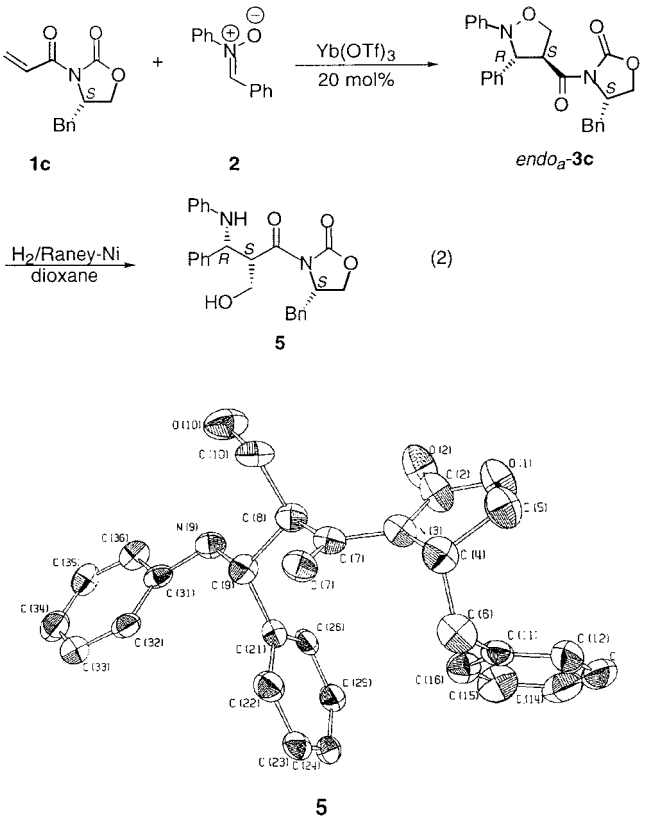


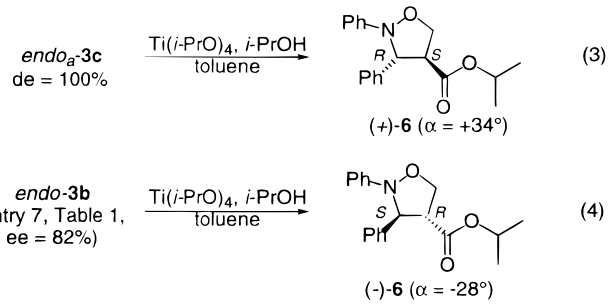
Figure 1. Reaction sequence for the determination of the absolute stereochemistry of *endo*$_a$-**3b** (eq 2) and the X-ray structure of **5**.

12). Using this additive in the reaction, the *endo* selectivity increases, whereas the enantioselectivity is lowered to 36% ee, and what is most notable, the absolute induction is similar to the dry reactions where MS have been applied. The presence of MS 3 Å and MS 5 Å instead of MS 4 Å leads to similar high enantioselectivity (82−83% ee) of the reaction and the same *endo*/*exo* selectivity (Table 1, entries 13 and 14). Finally, two drying agents, $MgSO_4$ and $CaSO_4$, have been applied as additives in the reaction of **1b** with **2** in the presence of **4a** as the catalyst (Table 1, entries 15 and 16). Interestingly, the application of $MgSO_4$ leads to an absolute induction similar to that of the reactions in the absence of MS, whereas the application of $CaSO_4$ as the additive leads to an absolute induction similar to that of the reactions in the presence of MS (Table 1, entries 15 and 16).

Various procedures have been used to dry (oven or flame under vacuum) the MS. However, the absolute stereochemistry of the isoxazolidines formed in the 1,3-DC reaction is independent of the drying procedure of the MS, and furthermore, both activated and unactivated MS 4 Å give the same results. However, the highest ee's were obtained when activated powdered MS were dried with a flame in a vacuum prior to reaction, and this was used as the standard procedure for the reactions in Table 1. It should also be noted that the absolute stereochemistry is independent of the solvent, as CH_2Cl_2, Et_2O, and toluene all give the same enantiomer of *endo*-**3a**. Another important feature is that for the reactions of **1b** with **2** catalyzed by **4a** the absolute induction of the *exo* isomers (determined for reactions in entries 7 and 9−16: 51−83% ee) is *independent* of the presence or absence of MS. In all reactions, the same enantiomer was obtained in excess.

The absolute stereochemistry of *endo*-**3b** has been determined on the basis of X-ray analysis. The chiral acryloyloxazolidinone **1c**, which is derived from (*S*)-phenylalanine, has a known configuration,[11] and in the reaction of **1c** with **2**, $Yb(OTf)_3$ was an excellent catalyst since *endo*$_a$-**3c** was obtained as the only observable diastereomer in high yield (Figure 1, eq 2).[4n,o] Unfortunately, several attempts to crystallize *endo*$_a$-**3c** failed, and therefore, *endo*$_a$-**3c** was subjected to a reductive ring opening using H_2/Raney nickel.[12] The 3-amino alcohol **5** obtained in this manner was crystallized, and the absolute structure could now be determined by X-ray crystallography. The structure of **5** is shown in Figure 1.

With the knowledge of the absolute structure of *endo*$_a$-**3c**, it is now possible to determine the absolute structure of *endo*-**3b** by conversion of both products into the corresponding isopropyl esters, (+)-**6** and (−)-**6**, respectively, and comparison of the optical rotations (eqs 3 and 4).[4d,e,k] The product *endo*$_a$-**3c** in Figure 1, eq 3, is obtained



from attack of the nitrone **2** to the *si*-face of the alkene **1c**, while *endo*-**3b** described in eq 4 is obtained from attack of **2** to the *re*-face of the alkene **1b**. This *re*-face attack is general for all the reactions reported in Table 1, where MS are present.

Discussion

The present results have shown that MS strongly affect the absolute stereoselectivity in the magnesium(II)−bisoxazoline-catalyzed 1,3-DC reaction. It is assumed that the reaction proceeds via an intermediate in which the bisoxazoline ligand and the alkenoyloxazolidinone are both bidentately coordinated to magnesium(II), thus occupying four sites of magnesium.[8,9] Furthermore, it is also assumed that the iodide and triiodide ligands at magnesium are dissociated to give a highly activated 2+-cationic intermediate.[9] When alk-2-enoyloxazolidinones such as **1a** and **1b** are bidentately coordinated to a Lewis acid, it is generally accepted that the alkenoyl moiety possesses an *s-cis* conformation.[9] On the basis of these assumptions, six intermediates of the catalyst−substrate complex are possible (Scheme 1). The six structures in Scheme 1 are based on MM2 optimizations, and L indicates a binding of a ligand to magnesium.

In the tetrahedral intermediate *tet*-**7**, addition to the *re*-face is favored, and thus, the products (3*S*,4*R*,5*S*)-*endo*-**3a** and (3*S*,4*R*)-*endo*-**3b**, obtained in the presence of MS 4 Å, could be obtained in this manner. There are

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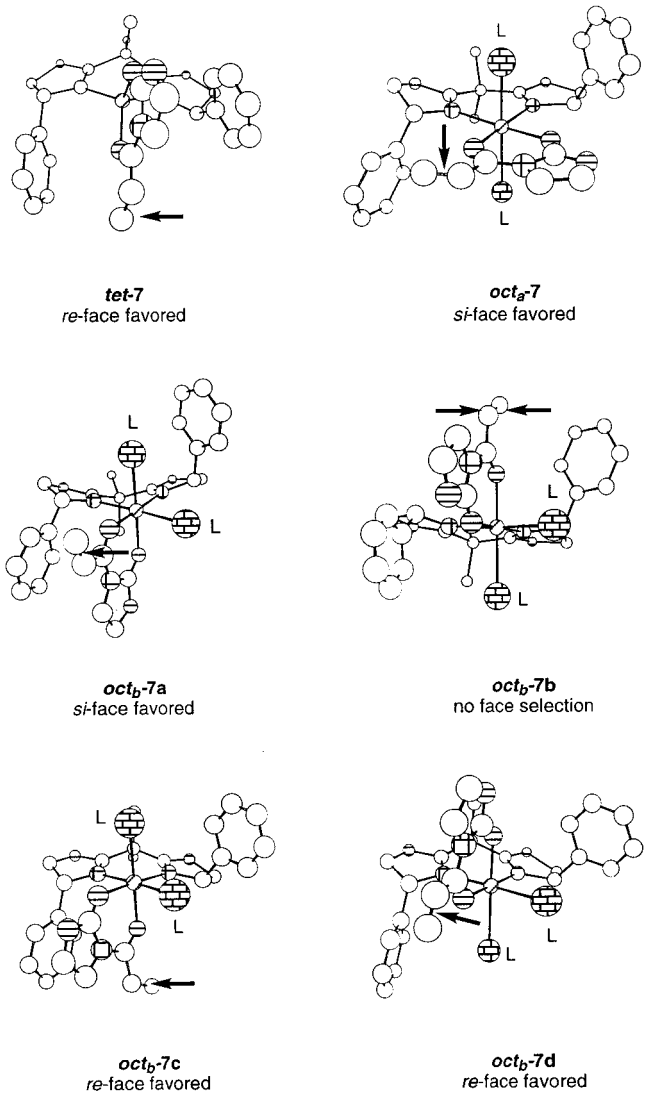
Scheme 1



five possible octahedral structures containing two additional ligands. In one of these, *oct*$_a$-**7**, the ligands are located *trans* to each other, and in this intermediate attack to the *si*-face is favored. Thus, the products obtained in the absence of MS 4 Å could arise from this intermediate. Finally, there are four possible octahedral intermediates *oct*$_b$-**7a**−**d**, in which L is located *cis* to each other. In *oct*$_b$-**7a**, attack to the *si*-face is also favored, whereas in *oct*$_b$-**7b**, there is no obvious face-shielding. In *oct*$_b$-**7c**,**d**, attack to the *re*-face is favored, and the products obtained in the presence of MS 4 Å might thus be obtained from these intermediates.

Desimoni et al. have studied the intermediates for the Diels−Alder reaction with cyclopentadiene catalyzed by magnesium(II)−bisoxazolines.[8a] When the reaction was performed in the absence of ligands, such as H_2O or alcohols, the absolute structure of the products indicated that cyclopentadiene added to the *re*-face of the alkene. On the basis of these observations and NMR experiments, the tetrahedral intermediate *tet*-**7** was proposed to account for the Diels−Alder reaction in the absence of ligands. The opposite enantiomer of the Diels−Alder product arising from attack of cyclopentadiene to the *si*-face of the alkene was obtained in the presence of a ligand, especially H_2O. Addition of a bidentate ligand such as ethylene glycol also led to a product with the same absolute configuration as obtained in the presence of H_2O.[8a] As a conclusion of this result and NMR experiments, *oct*$_a$-**7** was ruled out and *oct*$_b$-**7a** was proposed to account for the absolute selectivity of the products obtained in the presence of a ligand.

In the present case concerning the 1,3-DC reaction, a different picture emerges. Both in the absence and presence of H_2O (in the absence of MS) attack to the *si*-face is favored (Table 1, entries 2−4, 8, and 9). A possible explanation for this behavior may be that the nitrone is a very efficient ligand L. The tetrahedral coordination mode is then avoided both in the presence and absence of H_2O. According to Desimoni et al., intermediate *oct*$_b$-**7a** may account for these results,[8a] but intermediate *oct*$_a$-**7** cannot be completely ruled out. The nitrone is a very bulky ligand, and the two nitrone ligands might prefer a *trans* coordination to magnesium. Why is the opposite *re*-face attack then favored in the presence of MS? In a previous investigation, we proposed the tetrahedral intermediate *tet*-**7** to account for these reactions; however, this explanation may have to be revised on the basis of the present results. The *re*-face selection observed for the reactions involving MS is in agreement with the tetrahedral intermediate, but in this case the nitrone should also act as a ligand and avoid the tetrahedral intermediate. Another fact that disagrees with a tetrahedral coordination is that the reaction conducted in the presence of MS saturated with H_2O leads to a preferred *re*-face selection. One of the intermediates, *oct*$_b$-**7c**,**d**, is therefore proposed to account for the absolute stereoselectivity obtained in the reactions in which MS are involved.

There may be several explanations for the role of MS in the reaction, and one possibility could be that the MS are taking part in the catalytic process. MS 4 Å are known to exchange sodium(I) with calcium(II), and similar ion exchange is possible with magnesium(II) ions.[13] These ion-exchange reactions are mainly measured in H_2O, and the behavior may be different in organic solvents. However, it might be possible that the metal center of the magnesium(II)−bisoxazoline catalyst is attached to two oxygen atoms at the surface of the MS.[13,14] If mangesium(II) is bound to the surface of the MS, it is most likely that the binding to the surface is by a *cis* coordination to the surface oxygen atoms. In the presence of the alkenoyloxazolidinone, formation of an octahedral complex with a structure as *oct*$_b$-**7c** and/or *oct*$_b$-**7d** (two oxygen atoms from the MS occupy the L positions) may be favored as these two structures account for the absolute stereochemistry of the reaction.

The experimental results found for the 1,3-DC reaction catalyzed by the magnesium(II)−bisoxazoline catalyst in the presence and absence of MS show that MS are highly involved in the catalytic process. The MS have a complex structure,[13a,b] and the exact structure of the binding of the magnesium(II)−bisoxazoline to the surface of the MS is very difficult to predict due to complexity of the system. The two octahedral complexes *oct*$_b$-**7c** and/or *oct*$_b$-**7d** are

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(14) See also: (a) Davis, M. E. *Acc. Chem. Res.* **1993**, *26*, 111. (b) Thomas, J. K. *Chem. Rev.* **1993**, *93*, 301.

proposed intermediates on the basis of the absolute stereochemistry of the 1,3-DC reaction.

The present results have shown a new and very important aspect of MS in catalytic asymmetric chemistry. If the observation that MS can be involved in the catalytic process is more general when using cationic catalysts, which can exchange with the cations located in the MS, precautions should be taken with regard to interpretation of the catalytic process, as the reaction course is then much more complex than first anticipitated. However, it also allows for a new entry to asymmetric catalysis as MS might be an important part of the reaction's course.

Summary

A new effect of molecular sieves has been discovered. In the magnesium(II)−bisoxazoline-catalyzed 1,3-DC reaction of a nitrone with crotonoyl- or acryloyloxazolidinone, one enantiomer of the *endo* product with up to 82% ee is obtained in the presence of powdered MS 4 Å, whereas in the absence of MS the mirror image enantiomer is obtained with up to 73% ee. The absolute structure of the *endo* products was determined on the basis of an X-ray analysis. The products obtained in the magnesium(II)−(*R*,*R*)-bisoxazoline-catalyzed 1,3-DC reaction in the presence of MS arises from attack of the nitrone to the *re*-face of the alkenoyloxazolidinone, and in the absence of MS attack to the *si*-face of the alkene is favored. The magnesium(II)−(*R*,*R*)-bisoxazoline−alkenoyloxazolidinone intermediates of the reaction have been discussed, and it was rationalized that the two octahedral intermediates oct_a-**7** and/or oct_b-**7a** may account for the reactions in the absence of MS. The intermediates oct_b-**7c** and/or oct_b-**7d** were proposed to account for the absolute stereoselection of the reactions conducted in the presence of MS. It was demonstrated that MS was an important part of the reaction in which the magnesium(II)−(*R*,*R*)-bisoxazoline−alkenoyloxazolidinone intermediate is probably bound to the surface of the MS.

Experimental Section

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts for ^{1}H and ^{13}C NMR are reported in ppm downfield from tetramethylsilane (TMS). HPLC was performed using a 4.6 mm × 25 cm Daicel Chiralcel OD or column. Mass spectra were recorded at 70 eV with a direct inlet. Preparative thin-layer chromatography (PTLC) was performed on 200 × 200 × 1.8 mm silica gel (60 $HP_{254+366}$, Merck) on glass plates. The magnesium(II)−bisoxazoline-catalyzed reactions were carried out using Schlenk conditions.

Materials. The starting materials 3-((*E*)-2′-butenoyl)-1,3-oxazolidin-2-one (**1a**), 3-((*E*)-2′-propenoyl)-1,3-oxazolidin-2-one (**1b**), 4-(*S*)-benzyl-3-((*E*)-2′-propenoyl)-1,3-oxazolidin-2-one (**1c**), and benzylidenephenylamine *N*-oxide **2** were synthesized according to the literature.[4a,d,e,j] The ligands (*R*)-(+)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) and (*R*)-4,(*R*)-5-(2,2′-isopropylidenebis(4,5-diphenyl-2-oxazoline), magnesium (99%), and powdered MS 3 Å, 4 Å, and 5 Å were received from Aldrich. Millix Filter Unit 45 were received from Fluka.

Preparation of the Magnesium(II)−Bisoxazoline Catalyst 4a (0.1 M in CH_2Cl_2). Magnesium (48 mg, 2.0 mmol) and I_2 (253 mg, 1.0 mmol) were placed in a 10 mL flask with a magnetic stirring bar under N_2. Et_2O (10 mL) was added, and the mixture was stirred at room temperature until the iodine color disappeared (2−3 h). The mixture was filtered through a Millix Filter Unit 45 μm via syringe and into a flask containing a N_2 atmosphere and a magnetic stirring bar. The solvent was removed in a vacuum at room temperature and the white MgI_2 dissolved in CH_2Cl_2 (10 mL). To the resulting solution was added the bisoxazoline (1.5 mmol). After the solution was stirred for 2 h, I_2 (253 mg, 1 mmol) was added, and the deep red suspension was stirred for 2 h before use.

General Procedure for the Magnesium(II)−Bisoxazoline-Catalyzed Reactions. In a Schlenk flask containing glass wool in the vacuum outlet was placed a magnetic stirring bar, and in some reactions additives (see Table 1), and the flask was dried with a flame under vacuum. After the mixture was cooled to room temperature, CH_2Cl_2 (1.9 mL) and the alkene **1a**,**b** (0.1 mmol) were added. For the reactions of **1b**, the flask was cooled to −78 °C. The catalyst **4a**−**c** (0.1 mL, 0.1 M in CH_2Cl_2, 0.01 mmol) and the nitrone **2** (30 mg, 1.52 mmol) were added, and the reaction mixture was stirred for 20 h. For the reactions of **1b**, the mixture was allowed to warm to room temperature over 20 h. After the appropriate reaction time, the reaction mixture was stirred with 1 mL of 5% MeOH in CH_2Cl_2 and filtered through a 20 mm layer of silica gel. After the silica gel layer was washed with another 2 mL of 5% MeOH in CH_2Cl_2, the solvent was evaporated. The crude material was purified by preparative TLC (PTLC) (silica gel, 1% MeOH in CH_2Cl_2) to give a mixture of the diastereomers of **3a** and **3b**. All reactions proceeded quantitatively as measured by ^{1}H NMR with only small amounts (<5%) of byproducts. The physical data for compounds *endo*-**3a**[4d] and *endo*-**3b**[4k] have been reported previously. The products *endo*-**3b** were converted into the corresponding isopropyl esters for the determination of the ee.[4d,e,k]

(−)-(3′*S*,4′*R*,5′*S*)-3-(((5′-Methyl-2′-*N*,3′-diphenyl)isoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (*endo*-3a) was synthesized according to the general procedure under the conditions in entry 1 in Table 1: ee = 79% HPLC (Diacel Chiralcel OD, hexane/*i*-PrOH = 8/2, flow rate = 1.0 mL/min); t_R = 28 min (minor), t_R = 39 min (major).

(−)-Isopropyl (3*S*,4*R*)-2,3-Diphenylisoxazolidine-4-carboxylate ((−)-6). A mixture of (3*S*,4*R*)-*endo*-**3b** (82% ee) and *exo*-**3b** (73:27) (52 mg, 0.15 mmol) were refluxed in a mixture of a Ti(*i*-PrO)$_4$ (0.1 M) and *i*-PrOH (0.2 M) in toluene (2 mL) from a stock solution. After 2 h and cooling, CH_2Cl_2 (25 mL) was added, and the solution was extracted three times with H_2O and dried over $MgSO_4$. After evaporation, the residue was purified by PTLC (silica gel, petroleum ether/EtO 4:1, R_f = 0.4) to give the pure *endo*-**6** (25.5 mg, 0.082 mmol, 55%): $[\alpha]_D$ = −28.7° (*c* 1.0, $CDCl_3$); HPLC (Diacel Chiralcel OD, hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min); t_R = 21 min (major), t_R = 26 min (minor).

(+)-(3′*R*,4*S*,4′*S*)-4-Benzyl-3-(((2′-*N*,3′-diphenyl)isoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one ($endo_a$-3c). A mixture of Yb(OTf)$_3$·H_2O (128 mg, 0.2 mmol) and powdered MS 4 Å (250 mg) in dry CH_2Cl_2 (5 mL) was stirred for 0.5 h, and subsequently, the alkene **1c** (1.0 mmol) and nitrone **2** (1.5 mmol) were added. The mixture was stirred for 16 h. Then 5% MeOH in CH_2Cl_2 was added, and the mixture was filtered through a 20 mm layer of silica gel. The silica gel layer was washed with 10 mL of 5% MeOH in CH_2Cl_2 and the solvent evaporated. The crude product was purified by preparative PTLC (silica gel, MeOH/CH_2Cl_2 1:99) to give $endo_a$-**3c** (376 mg, 0.88 mmol, 88%): [α] = +40.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.78 (dd, J = 13.2, 8.8 Hz, 1H), 3.16 (dd, J = 13.2, 2.8 Hz, 1H), 4.17 (m, 3H), 4.65 (m, 3H), 5.37 (d, J = 4.4 Hz, 1H), 6.97−7.63 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 37.4, 55.3, 59.3, 66.4, 69.6, 71.1, 115.7, 122.4, 127.1, 127.5, 128.0, 128.8, 129.0, 129.1, 129.4, 134.7, 141.0, 150.41, 153.1, 170.3.

(2′*S*,3′*R*,4*S*)-4-Benzyl-3-(3′-(phenylamino)-2′-(hydroxymethyl)hydrocinnamoyl)-1,3-oxazolidin-2-one (5). A suspension of Raney nickel (∼0.5 g) in a small amount of H_2O is saturated with an H_2 atmosphere. A solution of $endo_a$-**3c** (180, mg, 0.42 mmol) in dioxane (10 mL) was added, and the mixture was stirred under an H_2 atmosphere for 3 h. After filtration through a Celite pad, the solvent was removed. The residue was purified by PTLC (silica gel, MeOH/CH_2Cl_2 5:95, R_f = 0.5). The product was crystallized from EtOAc as thin pale plates:

^{1}H NMR δ 2.35 (dd, J = 13.8, 9.3 Hz, 1H), 2.87 (dd, J = 13.8, 3.3 Hz, 1H), 3.94 (dd, J = 12.1, 4.9 Hz, 1H) 4.02 (dd, J = 12.0, 3.3 Hz, 1H), 4.09 (dd, J = 8.7, 3.3 Hz, 1H), 4.21 (t, J = 8.8 Hz, 1H), 4.21 (m, 1H), 4.72 (m, 1H), 5.25 (d, J = 6.1 Hz, 1H), 6.64−7.53 (m, 15H); MS m/z = 430 (M^+).

X-ray Analysis of 5. Crystals of **5** ($C_{26}H_{25}N_2O_4$) were very thin, twinned needles. X-ray diffraction analysis was carried out on a Siemens SMART CCD diffractometer at room temperature. A crystal of dimensions 1.0 × 0.2 × 0.02 mm^3 was monoclinic, space group $P2_1$, with unit cell a = 11.972(1) Å, b = 6.147(1) Å, c = 15.132(1) Å, β = 100.941(1)°, V = 1093.4(1) Å^3, Z = 2, D_x = 1.30 g·cm^{-3}, μ = 0.083 mm^{-1}. Mo Kα radiation (λ = 0.710 73 Å). A total of 1491 reflections with $I > 2\sigma(I)$ gave R = 0.113 in a constrained refinement with only 147 parameters. The primary alcohol group was disordered over three sites, phenyl rings were held alike with $mm2$ symmetry, and thermal parameters were approximated by four rigid groups. The twinning necessitated a separate scale factor for $hk0$ reflections; otherwise, there did not seem to be complete overlap, and only one twin was accounted for. The high R value signifies that this was not quite correct.

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Supporting Information Available: Copies of X-ray materials (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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