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1,3-Dipolar Cycloadditions Catalyzed by Bis(Oxazoline)-Magnesium-Based Chiral Complexes. The Importance of a Mg(II) Counterion.

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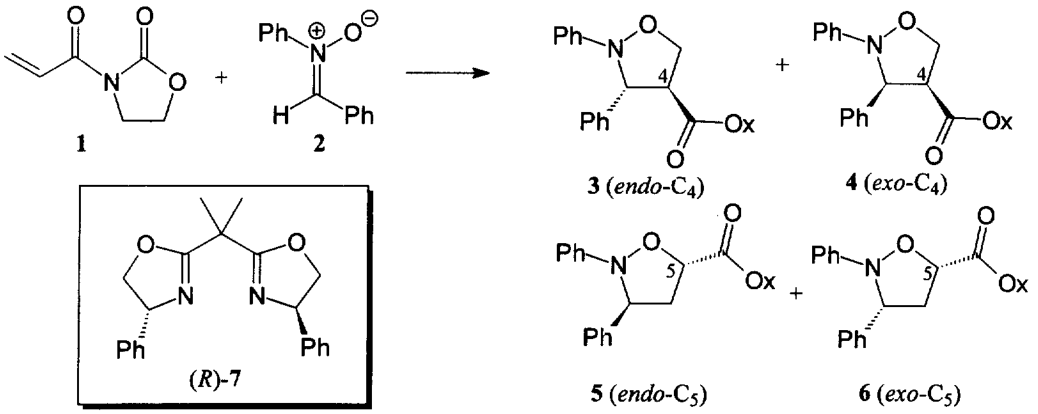
Abstract - The 1,3-dipolar cycloaddition between *N*-acryloyl-oxazolidinone and diphenyl nitrone is catalyzed by chiral catalysts derived from bis(oxazoline) (*R*)-**7** and Mg(II) perchlorate or triflate. In addition to complete regioselectivity, the *endo* cycloadduct can be obtained with up to 86% *ee*. The stereochemical results are due either to the specific counterion or to the presence of molecular sieves (as well as to the relative reagent concentrations). As a consequence, the enantioselecvity is opposite to that induced by the catalyst derived from Mg(II) iodide with the same chiral ligand.

The use of chiral catalysts is one of the most attractive methods of performing asymmetric reactions because, compared to the stoichiometric use of chiral auxiliaries, a smaller amount of chiral material is required, and the target product is directly obtained with no need for further manipulation.

Compared to the Diels-Alder (DA) reaction, the asymmetric catalysis of 1,3-dipolar cycloadditions (1,3-DC) has received less attention,[1,2] and in recent years attempts to develop metal catalyzed asymmetric 1,3-DC have mainly concerned the reaction between alkenes and nitrones.[3-9]

Scheme 1



1 **2** **3** (*endo*-C_4) **4** (*exo*-C_4) **5** (*endo*-C_5) **6** (*exo*-C_5) (*R*)-**7**

The 1,3-DC between monosubstituted alkenes and nitrones often proceeds with lack of regioselectivity,[10] and the reaction of **1** with diphenyl nitrone **2**, which under uncatalyzed conditions, produces all possible regio-

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and stereoisomers **3**-**6** (Scheme 1), is a suitable model to investigate the different selectivities that can be induced by the use of Mg(II)-bis(oxazoline) chiral catalysts and also to perform a direct comparison with the catalysis observed in the DA reaction of **1** with cyclopentadiene.[11,12]

The effect of Ti(IV)-TADDOLate[8] and MgI_2-(*R*)-**7**[9] chiral catalysts on the 1,3-DC in Scheme 1 has been recently investigated by Jørgensen. The reaction between **1** and **2** was found to proceed with high control of the regio- and the stereoselectivity, and, with the Mg(II) based complex, the *endo* adduct was obtained with up to 82% *ee* for the (3*S*,4*R*) enantiomer as shown in entry 7 (together with the data in entries 8 and 9, these report some of Jørgensen's results).[9] An effect of addition of molecular sieves (MS) was also discovered, which reversed the stereochemistry of the main enantiomer obtained.

The cycloaddition between **1** and **2** can be catalyzed by 10% mol of (*R*)-**7** and magnesium perchlorate (MP) or triflate (MT) chiral catalysts and the results are reported in the Table.[13]

The reaction catalyzed by MP and (*R*)-**7**, run in the presence of molecular sieves (MS), was completely regioselective. Even if the *endo*-selectivity was moderate, the enantioface discrimination was good since the *ee* of the *endo* adduct was 70% (entry 1). When the cycloaddition was run without MS complete regioselectivity and increased *endo*-selectivity were observed and the enantio-selectivity was lowered, but *reversed* (entry 2). The addition of 2 equiv of water did not make significant changes in the results, and only a decrease in reactivity was observed (entry 3).

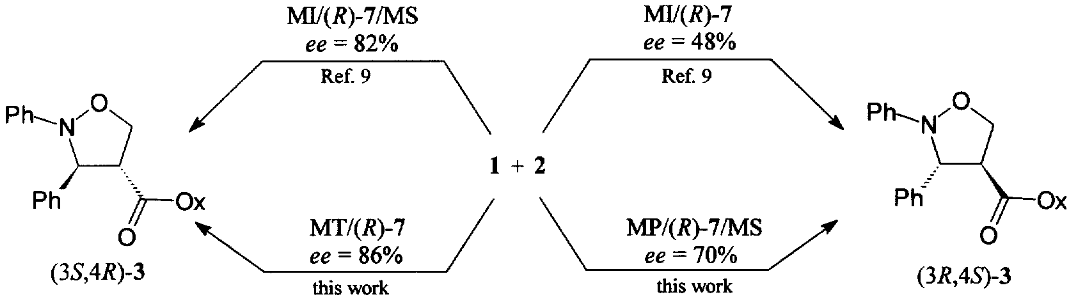
Table. Enantioselectivity of the 1,3-dipolar cycloaddition between **1** and **2** run in CH_2Cl_2 with the catalysts formed from (*R*)-**7** and MP, MT or MI[9], and an additive (all reactions proceed with quantitative yields).

Entry	Salt	Additives	[Mg]: [**7**] : [**1**] : [**2**]	T/°C	t/h	[**3**+**4**]:[**5**+**6**]	[**3**] : [**4**]	*ee endo* **3**
1	MP	MS 4 Å	1 : 1 : 10 : 10	-15	15	>98 : <2	70 : 30	70 (3*R*,4*S*)
2	MP	---	1 : 1 : 10 : 10	-15	15	>98 : <2	95 : 5	48 (3*S*,4*R*)
3	MP	H_2O	1 : 1 : 10 : 10	-15	48	>98 : <2	96 : 4	45 (3*S*,4*R*)
4	MT	MS 4 Å	1 : 1 : 10 : 10	-15	20	74 : 26	56 : 44	2 (3*R*,4*S*)
5	MT	---	1 : 1 : 10 : 10	-15	20	>98 : <2	97 : 3	86 (3*S*,4*R*)
6	MT	H_2O	1 : 1 : 10 : 10	-15	60	38 : 62	17 : 83[a]	0
7[b]	MI	MS 4 Å	1 : 1 : 10 : 15	-78	20	(c)	73 : 27	82 (3*S*,4*R*)
8[b]	MI	---	1 : 1 : 10 : 15	-78	20	(c)	100 : 0	48 (3*R*,4*S*)
9[b]	MI	H_2O	1 : 1 : 10 : 15	-78	20	(c)	90 : 10	36 (3*R*,4*S*)
10	MP	---	1 : 1 : 1 : 2	r.t.	0.2	>98 : <2	92 : 8	84 (3*S*,4*R*)
11	MP	---	1 : 1 : 10 : 2	r.t.	0.5	>98 : <2	77 : 23	14 (3*R*,4*S*)
12	MP	---	1 : 1 : 1 : 10	r.t.	0.5	>98 : <2	91 : 9	54 (3*S*,4*R*)
13	MT	---	1 : 1 : 1 : 2	r.t.	1	>98 : <2	97 : 3	82 (3*S*,4*R*)
14	MT	---	1 : 1 : 10 : 2	r.t.	1	>98 : <2	94 : 6	72 (3*S*,4*R*)
15	MT	---	1 : 1 : 1 : 10	r.t.	1	>98 : <2	91 : 9	58 (3*S*,4*R*)

a)The ratio [**5**]:[**6**] was 38 : 62. b)Data taken from Ref. 9. c)The reaction proceeds with the complete regioselective formation of **3**,**4**.

When the Mg(II) core of the chiral catalyst was derived from the corresponding triflate, the cycloaddition in the presence of MS was slower and selectivities also dropped (entry 4), compared to the reaction run without MS when the *endo* selectivity became excellent, and *endo*-**3** was obtained in 86% *ee* (entry 5). If 2 equiv H_2O were added the results were completely different (entry 6) since the cycloaddition became slow and unselective; the racemic adducts were obtained in a ratio very close to that of the uncatalyzed cycloadditon run at room temperature in dichloromethane (**3** : **4** : **5** : **6** = 7 : 32 : 26 : 35).

Comparison between the results obtained by using MT or MP with those obtained by using the corresponding I^-/I_2 (MI) system[9] shows the great versatility of Mg(II) as an inorganic core of bis(oxazoline)-based enantioselective catalysts. Furthermore, the importance of the Mg(II) counterion in determing the geometry of the reactive complex is shown (entries 1-6 *vs* 7-9). Jørgensen, with MI, changes the enantioselectivity of the reaction by adding MS, the results reported here are complementary to this, since by using the same chiral source and the same cation, opposite enantiomers can be obtained, with comparable enantioselectivity, just by changing the anionic counterion.



Comparison of the results reported in the Table with those obtained for the analogous asymmetric catalysis of DA reactions between **1** and cyclopentadiene, shows some relevant differences.

- The absolute stereochemistry of **3** is derived from a nitrone approach to coordinated **1** from the opposite face to that observed in the DA reactions (*e.g.*: a catalyst from MT alone favoured a *Si*-face approach in DA reaction,[12] a *Re*-face approach in the reaction described in entry 5).
- In respect to the asymmetric DA catalysis, the addition of MS has an important effect on the nitrone addition.
- In the DA reactions the addition of 2 equiv of water to the MP-based chiral catalyst brought about an inversion of the stereochemical result, while the MP-based catalysis of 1,3-DC was almost insentive to water.
- In the catalysis with MT based complexes, the addition of water was without effect in the DA reactions, while it destroyed the catalytic effect in 1,3-DC.

A possible rationale of these results may involve the role of the second cycloaddition partner since in the switch from a DA reaction to a 1,3-DC a non-coordinating reagent (cyclopentadiene) is replaced by a potentially coordinating 1,3-dipole (nitrone).

To determine the role of **1** and **2** in the formation of the reactive complex, some further experiments with either **1** or **2** in excess, were performed. The results, reported in entries 10-15, can be summarized in the following points.

- The use of equimolecular amounts of the MP-based chiral catalyst allowed a significant increase in the enantioselectivity, and *endo*-**4** was obtained with up to 84% *ee* (entry 10 *vs* 2). In the case of MT-based catalyst, no relevant variation was observed (entry 13 *vs* 5).
- The use of an excess oxazolidinone **1** caused an inversion in the stereochemistry of the *endo* adduct for the MP-based chiral catalysts (entries 11 *vs* 2), but had no significant effect on the MT-based catalysis (entries 14 *vs* 5).
- The cycloadditions run in the presence of a 10 fold excess of nitrone, independantly from the Mg(II) salt (Table, entries 12 and 15) give the same results in terms of regio-, stereo-, and enantioselectivity, suggesting formation of the same reacting complex.

Contrary to DA catalysis, the results here reported clearly show the possibility that more than one reagent is involved in coordination around the Lewis acid core of the catalyst, and the catalytic cycle may be different depending on several variables such as the specific counterion, the presence of MS, and the relative ratio of the cycloaddends.

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13. Dipolarophile **1**, bis(oxazoline) **7**, and the inorganic salt in the ratio 10 : 1 : 1 (two equiv water or 0.05 g MS were also added when required), were stirred in dichloromethane at ambient temperature for about 1 hour in a rubber septum sealed vial. The mixture was then chilled to -15 °C and, after 30 min, an equimolar amount of **2** was added (the typical experiment reported in this paper was run on 0.3 mmol scale). After completion of the cycloaddition, the reaction mixture was treated with water, extracted with dichloromethane, and briefly dried on $MgSO_4$. The organic layer was evaporated to dryness and the residue was analyzed. The reaction yields as well as the product distributions in Table 1 were determined by integration of the characteristic NMR signals (data in parentheses are the corresponding retention times of hplc analyses: Chiralpack AD column; eluent: *n*-hexane:*i*-PrOH 8:2); **1**: 6.58 and 5.91 δ (t_R, 11.1 min); **2**: 7.92 δ (t_R, 12.5 min); **3**: 5.26 δ (t_R, 21.1 and 25.6 min); **4**: 5.18 δ (t_R, 17.1 and 19.5 min); **5**: 5.65 δ (t_R, 28.1 and 35.0 min); **6**: 5.78 δ (t_R, 30.7 and 33.1 min). The absolute configuration of **3** was determined by transformation to the corresponding *i*-propyl ester (see Ref. 9).