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Chiral Amplification in Diels-Alder and 1,3-Dipolar Cycloadditions Catalyzed by Bis(Oxazoline)-Zn(II)-Based Chiral Complexes

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Abstract - A Zn(II)-bis(oxazoline) chiral complex catalyzes the cycloaddition reactions of alkenoyl-oxazolidinones with both cyclopentadiene and diphenyl nitrone. The 1,3-dipolar cycloaddition becomes *exo* selective with an *ee* of up to 86%. While the Mg(II)-based catalysts give a linear relationship between the ligand's optical purity and the *ee* of the reaction product, a remarkable positive nonlinear effect was observed in both cycloadditions by using Zn(II) as the cationic core of the catalyst. The result may be rationalized by the formation of a stable, insoluble, and catalytically inactive heterochiral complex.

One of the most attractive aspects of asymmetric catalysis is the possibility of preparing products with an *ee* higher than the optical purity of the employed chiral ligand.[1,2] Several examples of either positive (+)- or negative (–)-nonlinear effects were observed in asymmetric catalysis of Diels-Alder (DA) cycloadditions by using BINOL[3,4] and TADDOL[5,6] as chiral ligands. The role of molecular sieves (MS) may be an important factor in determining a non-linear effect.[3]

The observed (+)-nonlinear effects were, in general, rationalized as the result of the so-called *Reservoir Effect*[1] due to the stability of heterochiral dimeric complexes (sometimes they may precipitate during the catalyst preparation) being higher than the homochiral one. More recently, a second mechanism, involving hydrogen bond mediated oligomer formation, has been proposed to explain the extreme chiral amplification observed in asymmetric catalysis of a DA reaction by transition-metal aqua complexes of chiral dibenzofurandiyl-bis(oxazoline).[7]

To our knowledge, the only example of chiral amplification in 1,3-dipolar cycloaddition (1,3-DC) was reported in 1996.[8] The moderate (+)-nonlinear effect observed in catalysis of nitrile oxide cycloaddition mediated by the Zn(II)-tartrate catalyst presumably originated from soluble zinc aggregates with tartrate. In the field of nitrone cycloaddition an example was reported by Seebach,[9] but, contrary to the (+)-nonlinear effect observed in the corresponding DA reaction,[6] the moderate enantioselection induced by the Ti-TADDOLate catalyst was a linear function of the TADDOL optical purity.

Studies on asymmetric catalysis of 1,3-DC[10] have mainly concerned reactions of nitrones with electron poor olefins such as *N*-alkenoyl-oxazolidin-2-one derivatives, and in this paper we wish to report a close comparison of the asymmetric catalysis by chiral bis(oxazoline)-inorganic perchlorates in the DA reaction of acryloyloxazolidinone **1** with cyclopentadiene and in the 1,3-DC of **1** with diphenylnitrone (**2**), Scheme 1.

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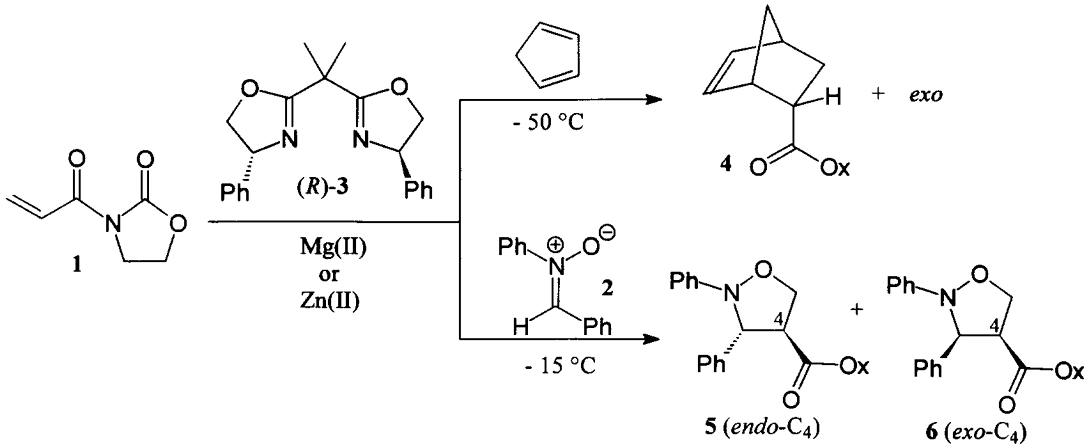
Scheme 1



The cycloaddition between **1** and either cyclopentadiene or **2** can be catalyzed by 10% mol of (*R*)-**3** and magnesium (MgP) or zinc perchlorate (ZnP) chiral catalysts, and the results are reported in the Table.[11] The use of Zn(II) as the Lewis acid instead of Mg(II) results in negligible changes in the DA cycloaddition when run in the presence of MS, but the use of the hydrate salt, as expected, lowers and reverses the enantioselectivity.[12] In the 1,3-DC, the absence of MS gives rise to decomposition products, but the catalysis run in the presence of MS proceeds with high regiocontrol and with an inversion of stereoselectivity allowing the *exo*-**6** adduct to be obtained with up to 84% *ee*.[13]

The shift from *endo* to *exo* selectivity in the 1,3-DC has been observed by Jørgensen in Ti-TADDOLate catalysis as a function of the anionic counterion.[14] In the present study the change in diastereoselectivity is a function of both metal cation and MS and the *exo* adduct **6** is obtained with high enantioselectivity.

A second relevant difference of the Zn(II)/MS catalyst was evidenced when the *ee* of cycloadducts was determined by using (*R*)-**3** with different optical purities.

Table. Enantioselectivity of the DA reaction and 1,3-DC of **1** in CH$_2$Cl$_2$ with the catalysts formed from (*R*)-**3** and MgP or ZnP with or without MS.[a]

Entry	Diene/1,3-dipole	Salt	Additive	[*endo*]: [exo]	*ee endo* **4**	*ee endo* **5**	*e.r. exo* **6**[b]	Ref.
1	Cyclopentadiene	MgP	MS 4 Å	92 : 8	70 (*S*)			c
2	Cyclopentadiene	MgP	---	92 : 8	72 (*S*)			15
3	Cyclopentadiene	ZnP[d]	MS 4 Å	92 : 8	73 (*S*)			c
4	Cyclopentadiene	ZnP[d]	---	92 : 8	20 (*R*)			c
5	**2**	MgP	MS 4 Å	70 : 30		70 (3*R*,4*S*)	15 : 85	16
6	**2**	MgP	---	95 : 5		48 (3*S*,4*R*)	---	16
7	**2**	ZnP[d]	MS 4 Å	27 : 73		31 (3*S*,4*R*)	92 : 8	c
8	**2**	ZnP[d]	---	e		---	---	c

[a]All reactions, except entry 8, gave quantitative yields of the products. [b]The absolute configuration is not assigned and the e. r. refers to the elution order. [c]This work. [d]The zinc perchlorate was the hexahydrate. [e]Decomposition products were mainly observed.

While the Mg(II)-based catalyst, with or without MS, gives in both reactions nice linear relationships, the DA reaction and the 1,3-DC catalyzed by Zn(II)/MS show a strong chiral amplification (Figure 1). With 10% *ee* of (*R*)-**3**, cycloadducts with *ee* up to 50% (DA) and 62% (1,3-DC) were obtained.

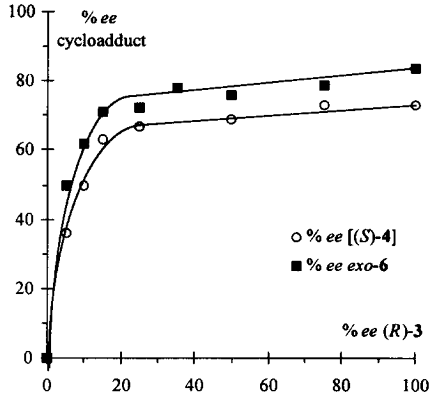


Figure 1. (+)-Nonlinear effect in the Zn(II)/MS catalysis of the DA reaction and 1,3-DC of **1**.

A possible rationale of these (+)-nonlinear effects derives from the formation of a precipitate during the preparation of the catalytic species. The solid had $[\alpha]_D = 0$ and it was stable enough to be crystallized from methanol. The ^{1}H-NMR spectrum was recorded in CD_3CN and found to be identical to that obtained by mixing equimolecular amounts of (*R*) and (*S*)-**3** with ZnP both in the presence or in the absence of MS (Figure 2a). The proton absorptions of the aromatic protons are split into two distinct absorptions at δ 7.2 and 7.6, while the signals of the oxazolidine ring are shielded by δ 0.5-0.7.[17]

The crystal structure of the complex was determined by X-ray analysis[18] (Figure 2b - the atom numbering is that of the crystal structure) and it clearly shows the tetrahedral arrangement of the two chiral ligands around the Zn(II) cation with Zn-N bond lengths ranging from 1.970 to 1.980 Å. The H-4 and H-5 protons of the oxazoline ring fit in the shielding cone of the phenyl group belonging to the second chiral unit in full accordance with the spectroscopic evidence.

The ^{1}H-NMR spectrum obtained by mixing 2 equiv. of (*R*)-**3** and ZnP was completely different and strongly dependent on the presence of MS. The spectrum registered before MS addition shows all the signals of the heterocyclic ring deshielded by 0.4-0.5 ppm, while the aromatic proton adsorption is split into two distinct signals at δ 6.95 and 7.35. The signals of the spectrum recorded in the presence of MS are broader and at least three different species, one being the complex present in the absence of MS, are detectable.

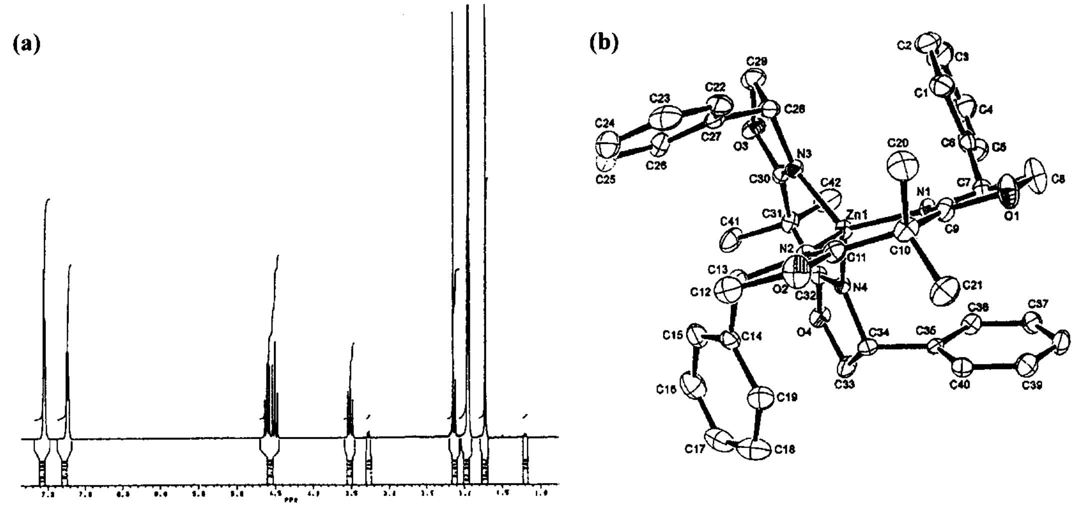


Figure 2. ^{1}H-NMR spectra in CD_3CN (a) and X-ray structure (b) of the complex from (*R*)-**3**, (*S*)-**3**, and ZnP.

The absence of a (+)-nonlinear effect in the case of the Mg(II)-based catalyst is due to the lower affinity of the magnesium cation for the bis(oxazoline) as demonstrated by NMR spectra of the heterochiral complex recorded in CD_3CN either with or without MS. Both spectra exhibit free and complexed ligand, while the addition of 1 equiv of 3-acetyl-1,3-oxazolidin-2-one (a unreactive model compound for **1**)[19] determined the formation of a 1:1:1 complex between this latter, Mg(II), and **3**, the second equiv. of **3** being uncomplexed. In the case of Zn(II)-heterochiral complexes, the addition of 3-acetyl-1,3-oxazolidin-2-one is without any effect.

Hence the strong chiral amplification observed in the Zn(II) catalyzed reaction is rationalized by considering the formation of a heterochiral *meso* complex, which is almost insoluble in dichloromethane, thermodynamically more stable than the homochiral one, and catalytically inactive. Even if this is a quite general mechanism to rationalize (+)-nonlinear effects, the reported example represents the first case in the field of 1,3-DC catalysed by bis(oxazoline)-based chiral complexes.

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13. The racemic *exo*-**6** was prepared in accordance with the literature[20] and was isolated after column chromatography (eluent: cyclohexane:ethyl acetate 8:2) as crystals from ligroine, m.p. 49°. ^1H NMR, δ ($CDCl_3$): 7.48 (2H, dd, aromatic protons), 7.43 (2H, m, aromatic protons), 7.17 (3H, m, aromatic protons), 7.03 (2H, dd, aromatic protons), 6.96 (1H, t, aromatic proton), 5.19 (1H, d, J = 9.5 Hz, $H_{3'}$), 4.97 (1H, ddd, J = 6.0, 8.0, and 9.5 Hz, $H_{4'}$), 4.83 (1H, dd, J = 6.0 and 8.0 Hz, $H_{5'}$), 4.26 (1H, t, J = 8.0 Hz, $H_{5'}$), 4.22 (1H, dt, J = 6.0 and 9.0 Hz), 3.90 (1H, ddd, J = 7.5, 9.0, and 9.0 Hz), 3.74 (1H, ddd, J = 7.5, 9.0, and 10.0), 3.08 (1H, ddd, J = 6.0, 9.0, and 11.0 Hz). Elem. anal.: calc. for $C_{19}H_{18}N_2O_4$: C, 67.4; H, 5.4; N, 8.3. Found C, 67.2; H, 5.2; N, 8.1. The e.e.s of the optically active samples from entries 5-8 in the table were determined by HPLC (Chiralpack AD column; eluent: *n*-hexane:*i*-PrOH 8:2); t_R: 17.1 (major) and 19.5 min (minor).
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17. The spectrum of (*R*)-**3** in CD_3CN is: δ 1.58 (s, 3H, Me), 4.08 (1H, t, H_5), 4.62 (1H, t, H_5), 5.18 (1H, dd, H_4), 7.2-7.4 (5H, m, aromatic protons).
18. Crystal data: $C_{42}H_{44}Cl_2N_4O_{12}Zn$, M=933.10; monoclinic, space group $P2_1/c$, a = 16.395(5) Å, b=15.700(4) Å, c= 17.047(5) Å, β=94.27(3)°, V=4376(2) $Å^3$, Z=4, Absorption coefficient=0.749 mm^{-1}, calculated density 1.416 mg/m^3, R=0.0500. Atomic coordinates have been deposited to the Cambridge Crystallographic Data Centre.
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