



S0040-4039(96)00460-1

## The First Enantioselective Synthesis of Both Diels-Alder Enantiomers with the Same bis(Oxazoline)-Magnesium Perchlorate Chiral Catalyst.#

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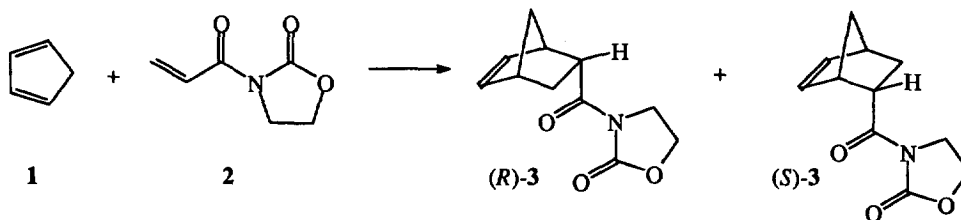
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**Abstract:** the Diels-Alder reaction between cyclopentadiene and 3-acryloyl-1,3-oxazolin-2-one has been found to occur enantioselectively in the presence of catalytic amounts of (*R*)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) and magnesium perchlorate. From a tetrahedral coordination of catalyst and dienophile the (*S*)-enantiomer is obtained. If two equivalents of water are added, the coordination occurs with an octahedral geometry and the same catalyst gives the (*R*)-enantiomer selectively.

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The  $C_2$ -symmetric bis(oxazoline)-Fe(III),<sup>1</sup> -Mg(II),<sup>2</sup> and -Cu(II)<sup>3,4</sup> complexes proved to be excellent chiral Lewis acids for enantioselective Diels-Alder (DA) reactions.<sup>5</sup> Complexes with the same ligand and cation are expected to give adducts with the same enantiomer in excess. The purpose of this communication is to check the limit of this statement.

The typical test for the enantioselective power of the catalysts was the reaction between cyclopentadiene (**1**) and 3-acryloyl-1,3-oxazolidine-2-one (**2**) since, in addition to the *endo:exo* ratio easily determined by nmr, the enantioselectivity of the *endo* adduct [(*R*)-**3** vs (*S*)-**3**] can be determined by hplc analysis using a chiral column or simply by measuring the  $[\alpha]_D^{23}$  value of the product **3**.<sup>1,6</sup>



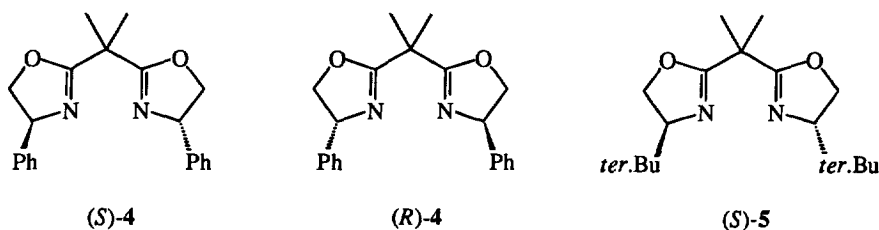
The bis(oxazoline) chiral ligands tested in the Fe(III)-,<sup>1</sup> Mg(II)-,<sup>2</sup> and Cu(II)-catalyzed<sup>3</sup> reaction between **1** and **2** had the same (*S*) configuration at the C-4 oxazoline center: all gave excellent *endo* selectivity, but Fe and Mg gave (*R*)-**3** in 80 and 90.6% e.e. respectively, while Cu gave (*S*)-**3** in 30 and more than 98% e.e. depending on oxazoline substituents. As it will be seen later in details, this depends on the different coordination of the complex between the catalysts and **2**.

#Dedicated to Professor Paolo Grünanger on the occasion of his 70th birthday.

Furthermore, both Cu(II) complexes of 2,2'-isopropylidene-bis[(4*R*)-4-phenyl-2-oxazoline] [(*R*)-4] and its (4*S*)-4-*tert*-butyl analogue [(*S*)-5], catalyzed two competitive reaction pathways between 2,3-dimethyl-1,3-butadiene and ethyl glyoxylate: the ene and the hetero DA reaction. In spite of the opposite configuration of the ligands, both gave the same (*S*)-dihydropyran, adduct of the heterodienic reaction, in 83 and 85% e.e. respectively.

The behaviour of **2** as a bidentate chelating dienophile<sup>8</sup> suggested us to use magnesium perchlorate (MP) as the inorganic core of the catalyst<sup>9</sup> since its cation behaved as an efficient bi-coordinating Lewis acid on 1,3-dicarbonyl compounds and induced significant changes in the reaction chemoselectivity of such derivatives.<sup>10</sup>

Several C<sub>2</sub>-symmetric chiral ligands were tested and the 2,2'-isopropylidene-bis(4-phenyl-2-oxazoline) [**4**, the (*R*) isomer was used in our experiments] was found to be an efficient catalyst.



The protocol was in accordance to the following procedure: **2** (1 mmol), (*R*)-**4** (0.1 mmol) and commercial anhydrous MP (0.1 mmol) were added to CH<sub>2</sub>Cl<sub>2</sub> (0.7 ml) dried according to the standard procedure, and the mixture was stirred in a rubber stoppered vial at ambient temperature. In about two hours MP dissolved, the clear solution was cooled to -50 °C and about 3 equiv. of freshly distilled cyclopentadiene were added with a microsyringe. The reaction completed within 3 hours; a small amount of the solution was evaporated to dryness and <sup>1</sup>H-nmr gave *endo/exo* ratio of the adducts. The residue was chromatographed on silica gel and the [α]<sub>D</sub><sup>23</sup> (c = 1, chloroform) of the *endo* isomer **3** was determined.<sup>11</sup>

The enantiomeric excess, determined on several independent runs, was in the range 68-70% and the main enantiomer, obtained with (*R*)-**4** as ligand of the catalyst, was (*S*)-**3**. The sense of the asymmetric induction in the preceding reaction can be rationalized by assuming a tetrahedral bis(oxazoline)-Mg(II)-dienophile complex, already proposed by Corey<sup>2</sup> for Mg(II)-catalyzed DA reaction. A square planar coordination analogous to that proposed by Evans<sup>3,4</sup> for the Cu(II)-complex should give (*R*)-**3** as main enantiomer, the same enantiomer that is obtained with the octahedral coordination around Fe(III), **2** being chelated at an axial and equatorial site.<sup>1</sup>

In order to test the efficiency of the catalyst few experiments were run with a ratio [catalyst]:[dienophile] of 1:100. The DA reaction runs well at -50 °C in about 18 hrs but, surprisingly, the main enantiomer became the (*R*)-**3** one with the e.e. in the range 50-60%.<sup>12</sup> The opposite enantioselectivity of the reaction can be rationalized by assuming a change of the coordination number of the metal cation in the complex induced by small amounts of moisture.

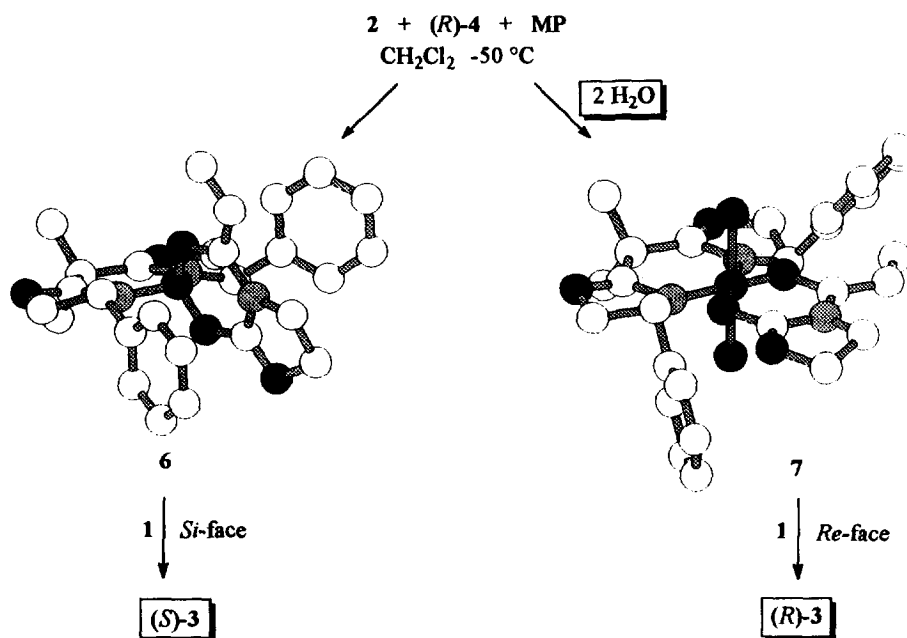
To test the effect of water new experiments were run. Using a ratio [catalyst]:[dienophile] 1:10, two equivalents of water were added, stirring was continued further 3 hours, the reaction mixture was cooled at -50 °C and **1** was added. Invariably (*R*)-**3** was obtained as the main enantiomer and the e.e. was in the range 59-65%.<sup>13</sup>

Table. Enantioselective DA reaction of 1 and 2.

| Entry            | Ligand                      | Cation  | Anion                             | T/°C    | Yield % | <i>endo:exo</i> | e.e. %                          | Coordination <sup>a</sup> |
|------------------|-----------------------------|---------|-----------------------------------|---------|---------|-----------------|---------------------------------|---------------------------|
|                  |                             |         |                                   |         |         |                 | (major enantiomer)              |                           |
| A <sup>b</sup>   | ( <i>S</i> )-4              | Fe(III) | (Cl <sub>2</sub> l) <sup>3-</sup> | -50     | 85      | 97 : 3          | 80 ( <i>R</i> )                 | Octahedral <sup>c</sup>   |
| B <sup>d</sup>   | ( <i>S</i> )-4 <sup>e</sup> | Mg(II)  | I <sup>-</sup>                    | -50     | 82      | 97 : 3          | 90.6 ( <i>R</i> )               | Tetrahedral               |
| C <sup>f</sup>   | ( <i>S</i> )-4              | Cu(II)  | OTf <sup>-</sup>                  | -78/-50 | 92      | 95 : 5          | 30 ( <i>S</i> )                 | Square-planar             |
| D <sup>f</sup>   | ( <i>S</i> )-5              | Cu(II)  | OTf <sup>-</sup>                  | -78     | 86      | 98 : 2          | >98 ( <i>R</i> )                | Square-planar             |
| E <sup>g</sup>   | ( <i>R</i> )-4              | Mg(II)  | ClO <sub>4</sub> <sup>-</sup>     | -50     | >98     | 93 : 7          | 68-70 ( <i>S</i> ) <sup>h</sup> | Tetrahedral               |
| F <sup>g,i</sup> | ( <i>R</i> )-4              | Mg(II)  | ClO <sub>4</sub> <sup>-</sup>     | -50     | >98     | 93 : 7          | 59-65 ( <i>R</i> ) <sup>h</sup> | Octahedral <sup>j</sup>   |

<sup>a</sup>)Proposed structure of the [Ligand-cation-2] complex. <sup>b</sup>)Ref. 1. <sup>c</sup>)Chelation of the dienophile 2 occurs at an axial and equatorial site. <sup>d</sup>)Ref. 2. <sup>e</sup>)5,5,5',5'-tetramethyl. <sup>f</sup>)Ref. 3. <sup>g</sup>)This work. <sup>h</sup>)The e.e. are based on the  $[\alpha]_D^{20} = 126.7^\circ$ , value corresponding to 80% e.e. given in ref. 1 and are determined on five independent experiments. <sup>i</sup>)With 2 eq. of H<sub>2</sub>O. <sup>j</sup>)Chelation of 2 at two equatorial sites.

The rationalization of the observed enantioselectivities results if the tetrahedral complex 6<sup>14</sup> is formed from 2, MP, and (*R*)-4. Here the sterically accessible dienophile diastereoface is the *Si* one, and (*S*)-3 is enantioselectively obtained. In the presence of water, the same reactants give the octahedral complex 7, the water molecules being the axial ligands,<sup>15</sup> the sterically accessible diastereoface of complexed 2 now becomes *Re* and (*R*)-3 is enantioselectively formed.



The above described reaction cannot compete in terms of enantioselective efficiency with the Corey<sup>1,2</sup> and Evans<sup>3,4</sup> protocols.

The opposite enantiomers have been obtained either from the same chiral ligand changing the cation [Fe(III) or Mg(II) vs Cu(II)]<sup>1-4</sup> or from the same cation changing the substituents on the ligand.<sup>7</sup>

For the first time, the same chiral ligand with the same cation can give both enantiomers selectively, simply in the presence or in the absence of an achiral ancillary ligand.

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

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10. Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron Lett.* **1995**, *36*, 2855.
11. If chromatography (cyclohexane-ethyl acetate 8:2 was the eluant) is performed on the whole reaction sample, the total yield of *exo* and *endo* adducts was nearly quantitative (more than 98%). The *exo* isomer was isolated first (*endo/exo* ratio determined by nmr was 93:7), then **3** was separated as a colourless oil that soon crystallized. The  $[\alpha]_D^{23}$  value was determined on this sample, without any further purification.
12. The opposite configuration was confirmed by <sup>1</sup>H-nmr spectroscopy on the olefinic protons of **3** with chiral [Eu(tfc)<sub>3</sub>].
13. The amount of water strongly influence the enantioselectivity of the catalyst as shown by an experiment with 1 equivalent of H<sub>2</sub>O that gave (*S*)-**3** with 24% e.e..
14. For the importance of the octahedral coordination of magnesium ion see: Black, C.B.; Huang, H.-W.; Cowan, J.A. *Coord. Chem. Rev.* **1994**, *135/136*, 165.
15. If the water molecules are in the equatorial and axial sites, again the *Si*-face becomes the sterically more accessible as reported by Corey in ref. 1. Structures **6** and **7** are Hyperchem-Chemplus representations.

(Received in UK 10 January 1996; revised 1 March 1996; accepted 8 March 1996)