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Different Lanthanide Ions and the Pybox Substituents Induce the Reverse of the Sense of Induction in the Enantioselective Diels−Alder Reaction between Acryloyloxazolidinone and Cyclopentadiene

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Received February 19, 2003

The Diels−Alder reaction of cyclopentadiene with acryloyl-1,3-oxazolidin-2-one is catalyzed by (*R,R*)-*i*-Pr- and (*R,R*)-Ph-pybox (**5** and **6**)/lanthanide(III) triflate complexes. The enantioselectivity of the reaction is influenced by 4 Å molecular sieves; moreover, the absolute sense of the enantioselection was found to be a function of the nature of the substituents on the chiral ligand (e.g., aromatic vs alkyl groups) as well as of the specific cation employed. In particular, seven lanthanide triflates were tested and a regular variation of the enantioselectivity as a function of the cation ionic radius was evidenced. The different sense of induction can be rationalized by assuming two competitive reacting complexes with different coordination number, which favor the attack on the opposite heterotopic faces of the coordinated dienophile.

Introduction

Chiral bis(oxazoline) ligands have found a great deal of applications in the construction of chiral catalysts for enantioselective reactions. Depending on the spacer between the heterocyclic rings, they have different cations of choice in the formation of bis(oxazoline)−metal complexes. When the spacer is a pyridine ring, the ligand changes from bidentate (box) to tridentate (pybox), and in general, since the cation must coordinate both ligand and at least one reagent to induce stereoselection, the coordination number required to build the supramolecular complex is greater for the latter than for the former ligand.[1] The structure of the pybox complex is important to gain insight into the factors transmitting the chiral information from the ligand to the reaction product throughout the catalytic process. The search of homogeneous set of reactions, where small modifications of either ligand or cation influence the enantioselectivity, may help to understand the mechanism of the asymmetric catalysis.

In this field, one of the best homogeneous set of reactions is the asymmetric ring opening of cyclohexene oxide with trimethylsilyl cyanide (TMSCN), reaction catalyzed by 2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine [(*S,S*)-*i*-Pr-pybox] and eight different lanthanide trichlorides.[2]

The best ee is obtained with the smallest cation Lu(III), and the enantioselectivity regularly decreases with the decrease of the lanthanide atomic number, with the biggest cation [Ce(III)] giving a racemic product.

Other examples of how lanthanide cations may influence enantioselectivity can be found in the literature. The addition of TMSCN to benzaldehyde[3] and the Diels−Alder (DA) reaction between 3-acryloyl-1,3-oxazolidin-2-one (**1**) and cyclopentadiene (**2**),[4] catalyzed by four *i*-Pr-pybox/lanthanide complexes, gave analogous relationships. In all of these examples, the best results were obtained with catalysts coupling *i*-Pr-pybox with the smallest cation.

The above-reported trends do not appear to be the only kind of relationship between enantioselectivity and cation size. Ethyl glyoxylate reacts both as heterodienophile with the Danishefsky diene[5] and as heteroenophile with alkenes.[6] In both reactions, catalyzed by [(*S,S*)-*i*-Pr-pybox]/lanthanide complexes, too few cations were tested, but the best ee are obtained for a medium-sized cation [Dy(III) and Yb(III), respectively]. The same behavior, with medium-sized cations Tb(III) and Sm(III) giving the best enantioselectivity, was first observed in the Meerwein−Ponndorf−Verley reduction with a chiral aminodiol as ligand.[7]

Since pybox are tailor-made ligands for the DA reaction between **1** and **2** to give *endo*-**3** and *exo*-**4** adducts (Scheme 1), and lanthanides have been proved to be the cations of election not only with *i*-Pr-pybox, but also with phenyl- and diphenyl-substituted pybox,[8] the scope of this paper is to investigate the catalysis of the above DA,

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10.1021/jo034215d CCC: $25.00

SCHEME 1

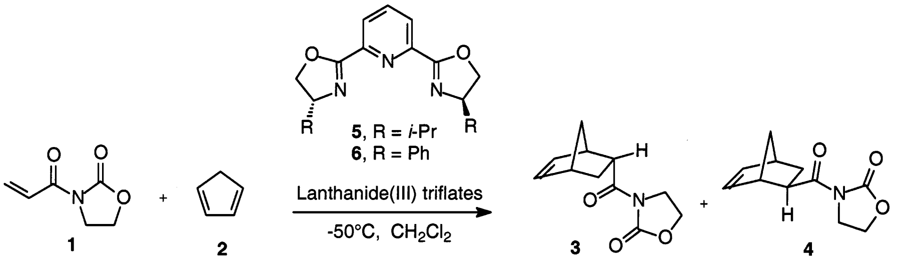

TABLE 1. Diels−Alder Reaction between 1 and 2, at −50 °C in CH_2Cl_2, in the Presence of 10 mol % of Lanthanide^{3+} Triflates and Chiral Ligand 5

				with 4 Å molecular sieves			without molecular sieves		
entry	triflate	ir (Å)	time (h), yield	endo/exo	*endo*-**3** ee (%) (config)	*exo*-**4** ee (%) (config)	endo/exo	*endo*-**3** ee (%) (config)	*exo*-**4** ee (%) (config)
1	Sc^{3+}	0.870	16, quant	96:4[a]	84 (2′*R*)[a]	80 (2′*R*)	96:4	65 (2′*R*)	55 (2′*R*)
2	Yb^{3+}	0.985	16, quant	86:14[b]	racem.[b]	racemic	88:12	13 (2′*R*)	27 (2′*R*)
3	Ho^{3+}	1.015	16, quant	88:12	5 (2′*S*)	racemic	92:8	14 (2′*R*)	4 (2′*R*)
4	Y^{3+}	1.019	16, quant	82:18	30 (2′*S*)	12 (2′*S*)	92:8	15 (2′*R*)	5 (2′*R*)
5	Eu^{3+}	1.066	16, quant	86:14	58 (2′*S*)	24 (2′*S*)	89:11	5 (2′*R*)	20 (2′*S*)
6	Pr^{3+}	1.126	16, quant	90:10	31 (2′*S*)	20 (2′*S*)	91:9	racemic	15 (2′*S*)
7	La^{3+}	1.160	16, quant	90:10[c]	17 (2′*S*)[c]	16 (2′*S*)	86:14	10 (2′*R*)	20 (2′*S*)

[a] Under the conditions reported in ref 4: yield 63%, *endo/exo* 92:8, ee endo 82%. [b] In ref 4: yield 63%, endo/exo 65:35, ee endo 34%. [c] In ref 4: yield 65%, endo/exo 91:9, ee endo 1%.

TABLE 2. Diels−Alder Reaction between 1 and 2, at −50 °C in CH_2Cl_2, in the Presence of 10 mol % of Lanthanide^{3+} Triflates and Chiral Ligand 6

			with 4 Å molecular sieves			without molecular sieves		
entry	triflate	time (h) yield	endo/exo	*endo*-**3** ee (%) (config)	*exo*-**4** ee (%) (config)	endo/exo	*endo*-**3** ee (%) (config)	*exo*-**4** ee (%) (config)
1	Sc^{3+}	16, quant	90:10	19 (2′*S*)	45 (2′*S*)	92:8	20 (2′*S*)	55 (2′*S*)
2	Yb^{3+}	16, quant	84:16	23 (2′*R*)	38 (2′*R*)	88:12	66 (2′*R*)	67 (2′*R*)
3	Ho^{3+}	16, quant	86:14	7 (2′*R*)	28 (2′*R*)	77:23	47 (2′*R*)	70 (2′*R*)
4	Y^{3+}	16, quant	78:22	28 (2′*R*)	42 (2′*R*)	79:21	43 (2′*R*)	67 (2′*R*)
5	Eu^{3+}	16, quant	77:23	racem.	50 (2′*R*)[a]	67:33	38 (2′*R*)	84 (2′*R*)[a]
6	Pr^{3+}	16, quant	72:28	34 (2′*R*)	75 (2′*R*)	69:31	62 (2′*R*)	95 (2′*R*)
7	La^{3+}	16, quant	74:26	71 (2′*R*)	93 (2′*R*)	75:25	78 (2′*R*)	95 (2′*R*)

[a] Erroneously described as (2′*S*) in ref 8.

under homogeneous reaction conditions, with catalysts derived from seven lanthanide(III) triflates as cation sources (chosen to cover the widest range of cation size) with two pybox ligands having the same substituent configuration, the above-mentioned [(*R*,*R*)-*i*-Pr-pybox] (**5**) and [(*R*,*R*)-Ph-pybox] (**6**).

Avoiding a target focused on the development of the “best in show” catalyst, our goal is to understand the mechanism of transfer of the chiral information from the catalyst to the products in the enantioselective process.

Results

Preliminary experiments showed that the enantioselectivity of the reaction is strongly influenced not only if this is run with or without 4 Å molecular sieves (MS), but also by their condition of activation. To obtain reproducible results powdered MS have to be heated under vacuum at 300 °C for 5 h and kept in sealed vials in a dryer, and dicloromethane has to be distilled from calcium hydride and used immediately. Therefore, two set of experiments were run with each catalyst, with and without MS, and each reaction was repeated at least three times. Tables 1 and 2 report the ratio [**3**]/[**4**], the ee, and the configuration of each product (**3**, **4**)[8] obtained from each reaction run with **5** and **6** as chiral ligand, with or without MS.

The data in Tables 1 and 2 evidence that both pybox **5** and **6** (with the latter ligand more exo-selective than the former one) can give good ee (80−95%), but with an important difference: whereas *i*-Pr-pybox (**5**) has the best result with Sc(III), Ph-pybox (**6**) shows the best enantioselectivity when La(III) is used as Lewis acid.

To evaluate the role of the lanthanide cations on the catalytic mechanism, the enantioselectivity can be plotted versus the ionic radius (ir)[9,10] that may represent both the variation of the “best fit” of the cation in the pocket of the supramolecular device involving pybox and **1** and the Lewis acidity since ir is related to the charge density (*Z*/*r*). Several sets of values are available in the literature, depending on the coordination number of the complex. Table 1 reports the series of values for 8 as coordination number,[9,10] since this latter seems the best average taking into account that the crystal structures of the lanthanide complexes of pybox have a coordination number in the range 7−10.[3,11−13]

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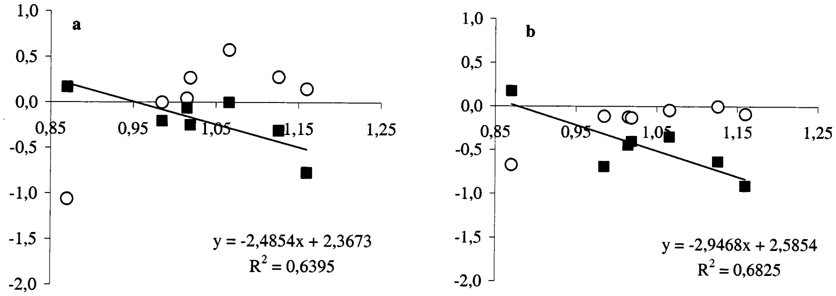

FIGURE 1. Plot of log ee of endo-**3**, with MS (a) or without MS (b), vs the lanthanide ionic radius: (○) with **5** and (■) with **6** as pybox ligand, respectively.

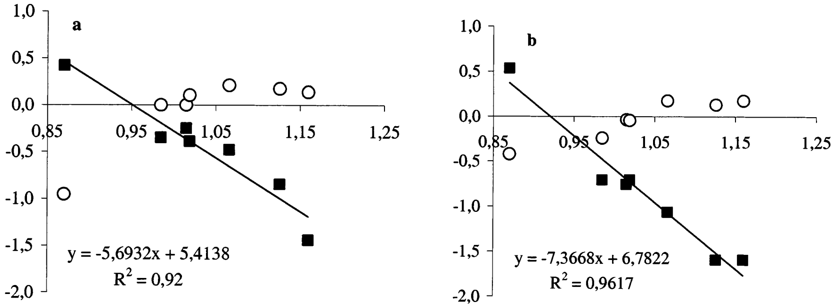

FIGURE 2. Plot of log ee of exo-**4**, with MS (a) or without MS (b), vs the lanthanide ionic radius: (○) with **5** and (■) with **6** as pybox ligand, respectively.

If log [(*R*)-**3**]/[(*S*)-**3**] and log [(*R*)-**4**]/[(*S*)-**4**] are plotted vs the ir of the cation, and for each adduct the results of the two ligands are compared under the same conditions, the graphs in Figures 1 and 2 are obtained.

At a first glance, the variation of ee with Ph-pybox **6** is the same in the four graphs. Scandium gives the (*S*) enantiomer as the major product for both endo and exo adducts and the ee changes regularly with the increase of the cation ir giving first a racemic (or nearly racemic) mixture and then the (*R*) enantiomer as the major cycloadduct, with the maximum value obtained with lanthanum. The variations can be represented by linear relationships (R^2 in the range 0.64−0.95), whose negative slopes are 2.49, 2.95, 5.69, and 7.37, with the endo values lower than the exo ones and the presence of MS being a depleting factor.

Scandium with *i*-Pr-pybox **5** always gives the (*R*) enantiomer as the major product both for endo and exo adducts. With the increase of the cation ir, ee decreases and nearly racemic mixtures are obtained with medium cations, and then the (*S*) enantiomer may become the preferred product with larger cations. The variation is very small in three graphs, and it could be represented by linear relationships with small positive slopes if the plot of the ee of *endo*-**3** against ir, in the presence of MS (Figure 1a), would not represent a clear broken line with a maximum for europium (Table 1, entry 5). An analogous point of inversion of the trend may be evidenced by an accurate analysis of the other three graphs.[14]

A further difference between catalysts with ligand **5** and **6** is the different response to the presence of MS: with ligand **5** the reactions in the presence of MS are in general more enantioselective than those run in the absence of MS, while when pybox **6** is used as chiral ligand, the best ee are obtained in the reactions runs without MS.

Discussion and Conclusions

The rationale of the above results requires an explanation of the following points: (a) despite the same configuration, ligands **5** and **6**, with the same cation, give opposite enantioselectivities; (b) both **5**- and **6**-based catalysts reverse the absolute sense of the stereoselection on going from scandium to lanthanum, and the regular variation of the enantioselectivity is about a linear function of the cation radius; (c) MS increase the efficiency of the catalysts derived from **5**, while they decrease that of catalysts derived from **6**.

A reversal of the enantioselectivity has already been observed in reactions catalyzed by complexes with the same cation and **5** or **6** as chiral ligands: the addition of TMSCN to benzaldehyde,[3] catalyzed by $YbCl_3$, and the DA reaction of methacrolein and **2**, catalyzed by Cu(II) (either triflate or hexafluoroantimonate).[15] Thus, the effect is not new and it is not limited to pybox catalysts involving lanthanides. What is new is that the reversal of enantioselectivity, in the same reaction and with the

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(14) The linear relationships of data with **5** as ligand are as follows: Figure 1a, $R^2 = 0.982$ for data 1−5, $R^2 = 0.996$ for data 5−7; Figure 1b, $R^2 = 0.682$ for data 1−7, $R^2 = 0.910$ for data 1−5; Figure 2a, $R^2 = 0.691$ for data 1−7, $R^2 = 0.941$ for data 1−5; Figure 2b, $R^2 = 0.877$ for data 1−5, $R^2 = 0.907$ for data 5−7.

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TABLE 3. Diels−Alder Reactions between 1 and 2, at −50 °C, on the NMR Samples in the Presence of Equimolecular Amounts of Pybox and Lanthanide Triflate

entry	solvent	pybox	triflate	endo/exo	*endo*-**3** ee (%) (config)	*exo*-**4** ee (%) (config)
1	CD_3CN	**5**	Sc^{3+}	98:2	7 (2′*S*)	nd (2′*R*)
2	CD_3CN	**6**	Sc^{3+}	98:2	25 (2′*S*)	racemic
3	CD_3CN	**5**	La^{3+}	90:10	3 (2′*S*)	4 (2′*R*)
4	CD_3CN	**6**	La^{3+}	84:16	19 (2′*R*)	49 (2′*R*)
5	$CDCl_3$	**5**	Sc^{3+}	98:2	91 (2′*R*)	nd (2′*R*)
6	$CDCl_3$	**6**	Sc^{3+}	97:3	34 (2′*S*)	74 (2′*S*)
7	$CDCl_3$	**5**	La^{3+}	66:34	4 (2′*S*)	39 (2′*R*)
8	$CDCl_3$	**6**	La^{3+}	66:34	84 (2′*R*)	>95 (2′*R*)

same couple of pybox, can occur or not by simply changing the cation.

The regular variation of the enantioselectivity with the change of the cation cannot be rationalized by proposing for the **5**- and **6**-based catalysts reacting complexes with the same structure, with the selectivity depending upon shielding factors only, and a possible rationale could involve two competing reacting complexes, whose respective contribution to the overall process is maximum with Sc and La, respectively.

To gain insight into the possible competing reacting complexes, the ^1H NMR spectra of equimolecular amounts of **1**, **5**, or **6**, with $Sc(OTf)_3$ or $La(OTf)_3$, were registered in CD_3CN or $CDCl_3$ and compared to those of uncomplexed **1** and pybox. Only in the case of **1**, **5**, and $La(OTf)_3$, the spectra evidenced that both dienophile and pybox are clearly coordinated to the cation, with **1** behaving as a bidentate ligand and its double bond having an s-cis conformation. In all other cases, the NMR spectra showed the selective formation of complexes involving pybox ligands and the lanthanide cation (a behavior already reported for **5** in the presence of $LnCl_3$)[16] in addition to uncomplexed **1**.

To test the relevance of these data and their connections with the enantioselectivity of the reactions, the NMR tubes were cooled at −50 °C, **2** was added, and the DA reactions were run under stoichiometric conditions of reagents and catalyst. CD_3CN proved to be an unfair solvent for reactions catalyzed by chiral Lewis acid complexes, probably because itself behaves as a ligand, and the ee of both **3** and **4** is always low (Table 3, entries 1−4). The $CDCl_3$ solutions gave results (Table 3, entries 5−8) that do not differ from those in CH_2Cl_2 as solvent under catalytic conditions. This is a proof that the reacting intermediate, even if without a NMR detectable concentration, exists and it is the same under both concentration conditions.

Since NMR spectroscopy did not give relevant information on the structure of the reacting complexes, an attempt to rationalize the results has to start from the stereochemical outcome of the catalyzed reactions, taking steady few points: the behavior of **5** and **6** as tridentate ligands, and a bidentate coordination of **1** with its reacting double bond in an s-cis conformation.

A good starting point to propose a model able to rationalize the sense of the stereoselection induced by scandium and lanthanum could be the X-ray structure of the lanthanide complexes. More than 30 crystal structures with different cations and pybox as ligand have been reported in the literature, but only two of them, those with a single pybox coordinated to the rare earth cation, can be used to understand the relationship between structure and enantioselectivity.[17] One has Sc(III) as the cation in a complex with 7 as coordination number and the pentagonal bipyramidal geometry derives from Sc(III) binding [pybox (H_2O) $(OTf)_3$].[11] The second structure has La(III) as the cation in a complex with 9 as coordination number with La(III) binding [pybox $(H_2O)_4$ $(OTf)_2$].[13] Both complexes have a phenyl group in the position 4 of the pybox.

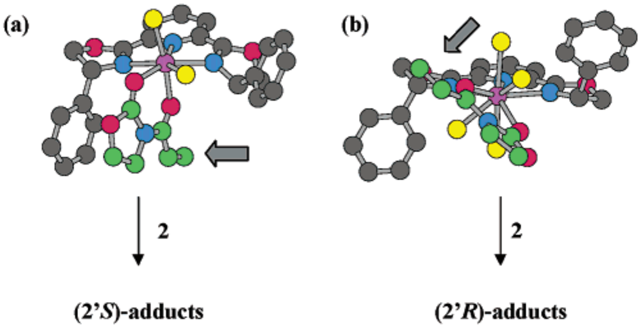

FIGURE 3. Assumed reacting intermediates for the DA reaction between **1** and **2** catalyzed by complexes of pybox **6** and $Sc(OTf)_3$ **(a)** or $La(OTf)_3$ **(b)**; yellow balls are either triflates or water.

For this reason, the results with **6** as ligand (Table 2) will be discussed first, starting from the X-ray structure of the above complexes. The Sc(III) with 7 as coordination number has three triflates (two axial and one equatorial) and one water molecule equatorial.[11] If two adjacent triflates are removed from the complex and **1** is docked to scandium with the ketonic carbonyl group in the apical position (Figure 3a), as proposed for the reacting complex with ethyl glyoxylate,[11,18] the phenyl group of the ligand shields the *Si* face, the addition of cyclopentadiene occurs to the *Re* face of the reacting double bond and the (*S*) adducts are preferentially obtained.

The La(III) complex should have two triflates in the apical positions and four water molecules with a coordination number of 9, in analogy with the X-ray structure of the lanthanum complex with tetraphenyl pybox.[13] If two water molecules are removed and **1** is bound onto lanthanum, the less hindered reacting complex (Figure 3b) has now the *Si* face more available to the attack of cyclopentadiene and the (*R*) adducts are obtained.

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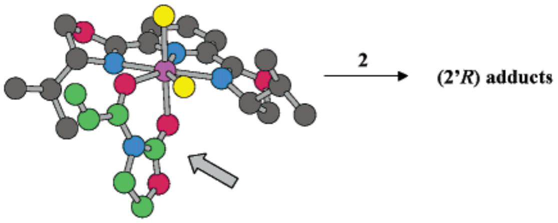

FIGURE 4. Assumed reacting intermediate for the DA reaction between **1** and **2** catalyzed by the complex of pybox **5** and Sc(OTf)$_3$; yellow balls are either triflates or water.

To rationalize the results reported in Table 2, a mechanism involving a competition between the complexes in Figure 3 can be proposed, competition that becomes evident when lanthanides with values of the ir intermediate between Sc(III) and La(III) are used as Lewis acids.

If the role of MS is the removal of water,[19] this has a low effect on the scandium catalyzed process (Table 2, entry 1) since structures with 6 or 7 as coordination number induce a similar selectivity.[11,18] When the reacting complex with 9 as coordination number is preferred (La and higher molecular weight lanthanides) the loss of water decreases the rigidity of the complex and selectivity is lowered.

The data reported in Table 1 show that a significant enantioselectivity is obtained only if the cation coordinating **5** is Sc(III) (entry 1). To obtain (*R*)-**3** and (*R*)-**4** as favored products, the catalyst has to induce the attack of cyclopentadiene to the *Si* face of the double bond, but a model of the reacting complex cannot be easily found since only X-ray structures of (*S*)-*i*-Pr-pybox coordinated to La(III) or Yb(III) in dimeric [Ln(OTf)$_n$(*i*-Pr-pybox)$_2$] complexes have been reported in the literature.[16]

Assuming again the coordination number of seven for the Sc(III) complex with **5**, to afford the opposite sense of induction mediated by the [Sc(III) **6**] catalyst, the addition of cyclopentadiene to the *Si* face of the double bond requires the binding of **1** to the Sc cation with the oxazolidinone CO in the apical position (Figure 4).

This model is analogous to that proposed by Evans in the aldol reaction of ethyl glyoxylate with enolsilanes, where opposite enantioselectivities were observed by using Sc(III) complexes with (*S*,*S*)-*t*-Bu-pybox or (*S*,*S*)-Ph-pybox:[18] the *t*-Bu-pybox ligand gives a complex that binds the aldehyde carbonyl group in the equatorial position, while the complex with Ph-pybox binds the same CO group in the axial position of the pentagonal-bipyramidal structure. If the Sc(III) results in Table 1 can be rationalized by this model, a competition between different intermediates can be the reason of the low enantioselectivity reported in Table 1 with the other lanthanides.

In conclusion, an experimental evidence of the importance to choose the suitable chiral ligand/cation pair has been presented: from the reported data the best cation to be used with the alkyl substituted pybox **5** is Sc(III), while the best catalyst with aromatic substituted pybox **6** is formed by the La(III) cation.

Experimental Section

General Methods and Materials. Melting points were determined by the capillary method and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. Dichloromethane was the hydrocarbon-stabilized ACS grade, distilled from calcium hydride and used immediately; inorganic salts were ACS reagents; powdered molecular sieves 4 Å were heated under vacuum at 300 °C for 5 h and kept in sealed vials in a dryer; 3-acryloyl-1,3-oxazolidin-2-one (**1**) was prepared following the literature method.[7] 2,6-Bis[(*S*)-4-isopropyloxazolin-2-yl]pyridine (**5**) and 2,6-bis[(*S*)-4-phenyloxazolin-2-yl]pyridine (**6**) were obtained from commercial suppliers.

General Procedure for the Enantioselective Diels−Alder Reaction between 1 and 2. 3-Acryloyl-1,3-oxazolidin-2-one (**1**) (0.042 g, 0.30 mmol), pybox (**5** or **6**) (0.03 mmol), the inorganic triflate (0.03 mmol), and when required, the molecular sieves (0.040 g) were added to anhydrous CH$_2$Cl$_2$ (0.3 mL) at ambient temperature in a rubber septum sealed vial, and the mixture was stirred and then cooled at −50 °C. After 1 h, cyclopentadiene (100 μL, ~1.5 mmol) was added with a microsyringe, and stirring was continued at −50 °C for 16 h, until TLC showed all dienophile reacted. The reaction was decomposed in water, extracted with CH$_2$Cl$_2$, and dried, and the mixture of adducts **3** and **4** was separated from pybox by column chromatography (silicagel, 30 cm l, 1.5 cm diameter, cyclohexane/ethyl acetate 70:30 was the eluant) and submitted to HPLC analysis using a Chiralcel OD column with hexane/2-propanol (9:1) as eluant (1.0 mL/min). The average retention times, 20 and 21 min for (*R*)- and (*S*)-**4**, respectively, and 22.5 and 25 min for (*S*)- and (*R*)-**3**, respectively, largely depend on small variations of the solvents and were checked with reference mixtures.

General Procedure for the ^{1}H NMR Spectra of Samples with 1, 5 (or 6) and Sc or La(OTf)$_3$, Followed by Diels−Alder Reactions with 2. Equimolecular mixtures of **1** with **5** and **1** with **6** (0.025 mmol) were dissolved in NMR tubes with CDCl$_3$ or CD$_3$CN (0.4 mL), and the ^{1}H NMR spectra of the four solutions were registered. Sc(OTf)$_3$ (0.025 mmol) was added to each solution, the solutions were homogenized in an ultrasonic bath, and the ^{1}H NMR spectra of the resulting mixtures were again registered. To four similar solutions was added La(OTf)$_3$ (0.025 mmol), and the ^{1}H NMR spectrum of each sample was registered. The eight tubes were cooled at −50 °C, cyclopentadiene (10 μL, ~0.15 mmol) was added to each sample, and cooling was continued for 2 days. The reaction mixtures were chromatographed using a Pasteur pipet as the column, and the composition of each mixture was determined by HPLC under the conditions described above. The results are reported in Table 3.

Acknowledgment. This work was supported by MIUR (PRIN 2002), the University of Pavia (FAR 2002), and the National Research Council (CNR).

Supporting Information Available: NMR spectral data and significant chromatographic analyses of the DA mixtures of adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034215D

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