Synergistic Effect of Pybox Substituents and Lanthanide Cations in Reversing the Asymmetric Induction in the Catalysed Diels–Alder Reaction between 3-Acryloyl-1,3-oxazolidin-2-one and Cyclopentadiene

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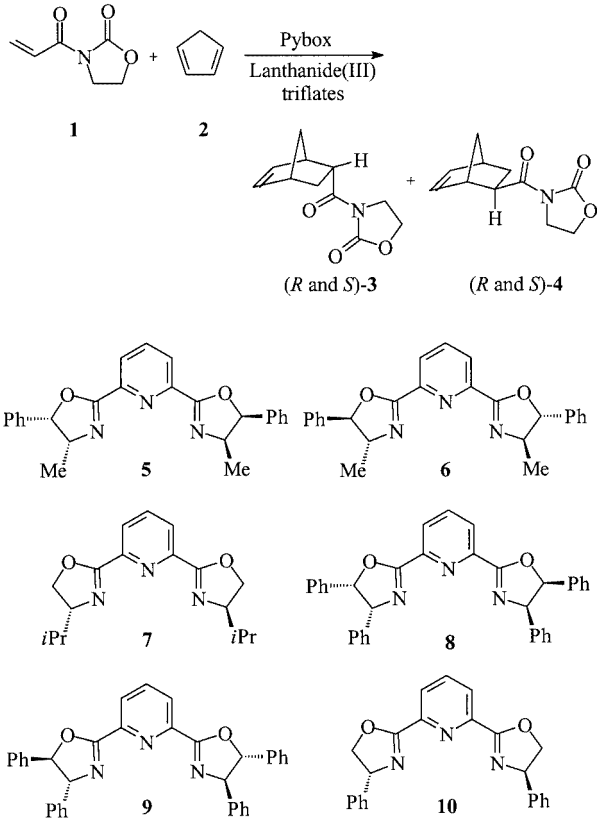
The enantioselectivity in the pybox/lanthanide(III) triflate catalysed Diels–Alder reaction between cyclopentadiene and 3-acryloyl-1,3-oxazolidin-2-one is profoundly influenced by the presence of a phenyl group in the 5′-position of the ligand, since it sometimes amplifies, and sometimes reverses the enantioselectivity induced by the 4′-substituent. The results can be summarised in three points. Of the catalysts derived from (4′*R*,5′*R*)-4-Me-5-Ph-pybox (**6**), the Sc^{III}-based one is both strongly *endo*-selective and strongly enantioselective. Several catalysts derived from (4′*R*,5′*R*)-*trans*-diphenyl-pybox (**9**) give up to 50% yields of *exo*-**4** and, at least with Pr^{III} and La^{III}, induce excellent *ee* values in both *endo* and *exo* adducts. The (4′*R*,5′*S*)-*cis*-diphenyl-pybox (**8**) is a novel and valuable ligand, since opposite enantiomers can be obtained with good selectivity simply by changing the cation from Sc^{III} to La^{III}.

Introduction

The Diels–Alder (DA) reaction between 3-acryloyl-1,3-oxazolidin-3-one (**1**) and cyclopentadiene (**2**) (Scheme 1) is enantioselectively catalysed by several chiral complexes,[1] and those derived from bis(1,3-oxazolidin-2-yl)pyridines (pybox) are particularly appealing for at least three reasons: (i) pybox may induce excellent enantioselectivities when coupled with several cations,[2] (ii) some suitably substituted pybox derivatives may give *exo*-selective catalysts,[3] and (iii) the absolute sense of induction is found to depend both on the nature of the substituent on the chiral ligand (e.g., isopropyl vs. phenyl groups in **7** and **10**) and on the specific lanthanide employed.[4]

Examples of excellent enantioselectivities (*ee* > 99%) were obtained with chiral catalysts derived from (4′*R*,5′*R*)-2,6-bis(4′,5′-diphenyl-1′,3′-oxazolin-2′-yl)pyridine (**9**; Scheme 1) and four lanthanide(III) triflates. Furthermore, the Eu^{III}- and La^{III}-based catalysts were able to shift a typically *endo*-selective cycloaddition towards *exo* selectivity, and for the first time the enantiomerically pure *exo*-**4** was isolated and its absolute configuration determined.[3]

From the X-ray structure of the complex formed between **9** and La^{III},[5] a stereochemical model featuring a crucial role for the phenyl group in the 5′-position of the chiral ligand in determining the observed excellent enantioselectivities was proposed for the substrate–catalyst complex.



Scheme 1

The effect of the catalyst on the stereochemical outcome of the reaction was tested by the use of seven lanthanide(III) triflates and two pybox ligands with the same (*R*,*R*) con-

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figuration, but with two different substituents: (*R*,*R*)-*i*Pr-pybox (**7**) and (*R*,*R*)-Ph-pybox (**10**). In the presence of molecular sieves (4 Å) (MS), two completely different trends in the enantioselectivity were found within the cation series.[4] With ligand **7**, the Sc^{III}-based catalyst was the best one, giving the (*R*) enantiomer as the major product both for *endo* and *exo* adducts. The *ee* value decreased with increasing cationic ionic radius (*ir*), and nearly racemic mixtures were obtained with Yb and Ho^{III}, while the (*S*) enantiomers then became the preferred products with larger cations. In the case of ligand **10**, the best catalyst was the La^{III}-based one, with the *ee* value systematically changing from (*S*) to (*R*) adducts with increasing cationic radius.[6]

In view of these results, the scope of this paper is to investigate the catalytic efficiency as a function of two variables, ligand substituents and cationic radius, in order to find the best matching between pybox and lanthanides able to drive enantioselectivity towards the selective formation of (*S*) and (*R*) products.

Results and Discussion

Asymmetric catalysis of the reaction between the acryloyloxazolidinone **1** and cyclopentadiene (**2**) was investigated by the testing of seven lanthanide cations, suitably chosen to cover a wide range of different Lewis acidity and cation size,[6] and six pybox ligands (Scheme 1). Two ligands were each characterised by the presence of a methyl substituent on the C-4′ position in the oxazoline ring and by an aromatic group on the 5′-position: (4′*R*,5′*S*)-2,6-bis(4′-methyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**5**)[7,8] and (4′*R*,5′*R*)-2,6-bis(4′-methyl-5′-phenyl-1′,3′-oxazolin-2′-yl)-pyridine (**6**) (to be compared with the 4′-alkyl-substituted pybox **7**). Two other pybox species each had two aromatic substituents on both positions 4′ and 5′ of the oxazoline rings: (4′*R*,5′*S*)-2,6-bis[4′,5′-diphenyl-1′,3′-oxazolin-2′-yl]-pyridine (**8**) and (4′*R*,5′*R*)-2,6-bis[4′,5′-diphenyl-1′,3′-oxazolin-2′-yl]pyridine (**9**) (to be compared with 4′-phenyl-substituted pybox **10**).

All reactions were run in the presence of molecular sieves (4 Å) (MS) at −50 °C in CH_2Cl_2, and Table 1 reports the [*endo*]/[*exo*] ratio, the *ee* value and the absolute configuration of the products obtained from each reaction run with 4′-alkyl-substituted pybox as chiral ligand and lanthanide(III) triflates as Lewis acids.

From the data in Table 1 some features can be pointed out:

(i) All catalysts (Entries 1−21) are *endo*-selective.

(ii) For 4′-alkyl-substituted pybox species **5**−**7**, the best catalyst is always the Sc^{III}-based one.

(iii) Decreased selectivity is observed with increasing the ionic radius, and the selectivity can reverse with the medium-sized cations.

(iv) The sense of the asymmetric induction is clearly influenced by the substituent in the 5′-position: in the case of pybox **5** and **7** the Sc-based catalysts give (*R*) adducts as preferred enantiomers, while the use of **6** as chiral ligand reverses the enantioselectivity and excellent *ee* values of the (*S*) adducts are obtained.

(v) The result reported in Entry 8 makes the Sc^{III} complex derived from the commercially available ligand **6** one of the best catalysts for the DA reaction between **1** and **2**.

The interesting feature is that the Sc^{III}-mediated results for **5** are nearly superimposable on those for **7**. Since the

Table 1. Diels−Alder reactions between **1** and **2**, at −50 °C with MS in CH_2Cl_2, in the presence of 10% mol of lanthanide(III) triflates and 4′-alkyl-substituted pybox **5**−**7**

Entry	pybox	Triflate	*ir* [Å]	Time [h]/yield	*endo*/*exo*	*ee* [%] of *endo*-**3** (config.)	*ee* [%] of *exo*-**4** (config.)
1	**5**	Sc^{3+}	0.870	16/quant.	97:3	77 (2′*R*)	50 (2′*R*)
2	**5**	Yb^{3+}	0.985	16/quant.	86:14	9 (2′*S*)	42 (2′*R*)
3	**5**	Ho^{3+}	1.015	18/quant.	88:12	17 (2′*S*)	45 (2′*R*)
4	**5**	Y^{3+}	1.019	24/quant.	78:22	15 (2′*S*)	37 (2′*R*)
5	**5**	Eu^{3+}	1.066	24/quant.	87:13	*rac*	30 (2′*R*)
6	**5**	Pr^{3+}	1.126	16/quant.	87:13	14 (2′*R*)	16 (2′*R*)
7	**5**	La^{3+}	1.160	24/quant.	88:12	25 (2′*R*)	12 (2′*R*)
8	**6**	Sc^{3+}	–	16/quant.	97:3	97 (2′*S*)	> 80 (2′*S*)
9	**6**	Yb^{3+}	–	16/quant.	72:28	7 (2′*R*)	26 (2′*S*)
10	**6**	Ho^{3+}	–	18/quant.	81:19	52 (2′*R*)	30 (2′*R*)
11	**6**	Y^{3+}	–	24/quant.	80:20	58 (2′*R*)	30 (2′*R*)
12	**6**	Eu^{3+}	–	24/quant.	85:15	59 (2′*R*)	29 (2′*R*)
13	**6**	Pr^{3+}	–	16/quant.	87:13	40 (2′*R*)	8 (2′*R*)
14	**6**	La^{3+}	–	24/quant.	88:12	37 (2′*R*)	*rac*
15[a]	**7**	Sc^{3+}	–	–	96:4	84 (2′*R*)	80 (2′*R*)
16[a]	**7**	Yb^{3+}	–	–	86:14	*rac*	*rac*
17[a]	**7**	Ho^{3+}	–	–	88:12	5 (2′*S*)	*rac*
18[a]	**7**	Y^{3+}	–	–	82:18	30 (2′*S*)	12 (2′*S*)
19[a]	**7**	Eu^{3+}	–	–	86:14	58 (2′*S*)	24 (2′*S*)
20[a]	**7**	Pr^{3+}	–	–	90:10	31 (2′*S*)	20 (2′*S*)
21[a]	**7**	La^{3+}	–	–	90:10	17 (2′*S*)	16 (2′*S*)

[a] Data taken from ref.[4]

shielding of a 4′-methyl group (pybox **5**) is certainly smaller than that of a 4′-isopropyl group (pybox **7**), to obtain the same selectivity, the loss of efficiency expected for the smaller alkyl group has to be compensated for by the effect of the phenyl group in the 5′-position. The overall result is the same attack on the *Si* face experienced when the DA reaction is catalysed by the [Sc^{III}-**7**] complex,[4] with the shielding effect of the phenyl group synergistic with that of the 4′-methyl group.

To account for the result of the DA reaction catalysed by the [Sc^{III}-**6**] complex, the reaction intermediate can be derived from the X-ray structure of the [Sc-pybox-$(H_2O)(OTf)_3$] complex.[9] With the same regioselective coordination as previously proposed for **7**-based Sc^{III} catalysts,[4] two vicinal triflates were removed and **1** was bound to the Sc^{III} cation with the oxazolidinone CO group in the apical position, in accordance with the model proposed by Evans for the [Sc(*i*Pr-pybox)]-catalysed aldol reactions between ethyl glyoxylate and enol silanes.[10] The proposed structure is shown in Figure 1; the addition of cyclopentadiene occurs on the *Re* face of the coordinated dienophile (the *Si* face is shielded by the phenyl group of the second oxazoline ring) and (*S*)-**3** is formed as the greatly predominant product. The model in Figure 1 explains the enantioselectivities induced by Sc^{III} complexes of **5**, **6** and **7**, that is, (*R*), (*S*) and (*R*), respectively. The isopropyl group of **7** with the (*R*) configuration, shields the *Re* face of **1**, and (*R*) cycloadducts are obtained. The phenyl groups of **5** and **6**, with an (*S*) and an (*R*) configuration, respectively, dictate the configuration of the DA adducts, (*R*) and (*S*), respectively.

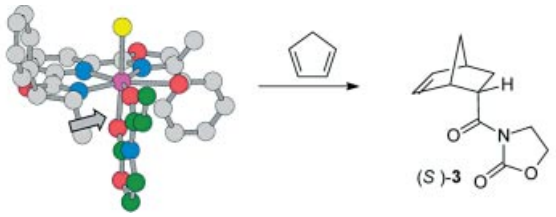

Figure 1. The assumed reacting intermediate for the DA reaction between **1** and **2** catalysed by the complex of $Sc(OTf)_3$ and pybox **6**; the yellow sphere represents the triflate counterion

In this range of ligands, the useful result is that a pybox with a small methyl group at the 4′-position, the position generally considered to be decisive in determining selectivity, gives an excellent stereoselective (97% *ee*) catalyst. This efficiency is similar to that of the most selective catalysts reported in the literature and is undoubtedly due to the presence of the *trans*-phenyl group in the 5′-position. The commercially available ligand **6** also showed its specificity in the DA reaction between methyl 1,4-naphthoquinone-2-carboxylate and *trans*-1,3-pentadiene or -2,4-hexadiene (*ee* = 91%),[11] but the lanthanide of choice for this dienophile was Gd^{III}. Since this cation, when tested in the DA reaction in Scheme 1, gave ordinary results,[12] the specificity of the catalyst required by each coordinating substrate is evident.

The results with 4′,5′-diphenyl-disubstituted pybox **8** and **9** are reported in Table 2 together with those previously obtained with pybox **10**.[4]

Table 2. Diels−Alder reactions between **1** and **2**, at −50 °C with MS in CH_2Cl_2, in the presence of 10% mol of lanthanide(III) triflates and 4′-phenyl-substituted pybox **8**−**10**

Entry	pybox	Triflate	Time [h]/yield	*endo*/*exo*	*ee* [%] of *endo*-**3** (config.)	*ee* [%] of *exo*-**4** (config.)
1	**8**	Sc^{3+}	16/quant.	91:9	55 (2′*S*)	74 (2′*S*)
2	**8**	Yb^{3+}	24/quant.	83:17	13 (2′*R*)	33 (2′*R*)
3	**8**	Ho^{3+}	24/quant.	83:17	rac	40 (2′*R*)
4	**8**	Y^{3+}	24/quant.	74:26	10 (2′*R*)	70 (2′*R*)
5	**8**	Eu^{3+}	24/quant.	72:28	52 (2′*R*)	95 (2′*R*)
6	**8**	Pr^{3+}	24/quant.	63:37	83 (2′*R*)	98 (2′*R*)
7	**8**	La^{3+}	24/quant.	65:35	88 (2′*R*)	98 (2′*R*)
8[a]	**9**	Sc^{3+}	–	98:2	76 (2′*R*)	26 (2′*R*)
9[a]	**9**	Yb^{3+}	–	87:13	82 (2′*R*)	92 (2′*R*)
10	**9**	Ho^{3+}	24/quant.	51:49	86 (2′*R*)	> 99 (2′*R*)
11	**9**	Y^{3+}	24/quant.	59:41	88 (2′*R*)	> 99 (2′*R*)
12[a]	**9**	Eu^{3+}	–	48:52	90 (2′*R*)	> 99 (2′*R*)
13	**9**	Pr^{3+}	16/quant.	64:36	95 (2′*R*)	> 99 (2′*R*)
14[a]	**9**	La^{3+}	–	71:29	96 (2′*R*)	> 99 (2′*R*)
15[b]	**10**	Sc^{3+}	–	90:10	19 (2′*S*)	45 (2′*S*)
16[b]	**10**	Yb^{3+}	–	84:16	23 (2′*R*)	38 (2′*R*)
17[b]	**10**	Ho^{3+}	–	86:14	7 (2′*R*)	28 (2′*R*)
18[b]	**10**	Y^{3+}	–	78:22	28 (2′*R*)	42 (2′*R*)
19[b]	**10**	Eu^{3+}	–	77:23	rac	50 (2′*R*)
20[b]	**10**	Pr^{3+}	–	72:28	34 (2′*R*)	75 (2′*R*)
21[b]	**10**	La^{3+}	–	74:26	71 (2′*R*)	93 (2′*R*)

[a] Data taken from ref.[4] [b] Data taken from ref.[3]

Analysis of the reported results reveals some features:
(i) The stereoselectivity is clearly influenced by the change of both cation and pybox; increasing *ir* of the cation and the use of the disubstituted pybox shift stereoselectivity towards the *exo* adduct, which becomes the preferred stereoisomer with the catalyst **9**-Eu^{III} (Entry 12).
(ii) For all 4′-phenyl-substituted pybox compounds **8**−**10**, the best catalysts are those based on the largest lanthanides.
(iii) All the catalysts with the exception of Sc^{III} catalysts give (*R*) adducts as preferred enantiomers and all catalysts based on pybox **9** are extremely efficient, with *endo* and *exo* products always being obtained with *ee* values > 75%, in most cases > 95%.
(iv) pybox **8** gives less efficient catalysts than **9**, but the remarkable result is that the same ligand can allow opposite enantiomers to be obtained in moderate to good *ee* values simply by changing the cation, with a linear relationship between the logs of the enantiomeric ratios (*er*) of both *endo* and *exo* adducts and the *ir* of the cation (Figure 2a,b).[13]

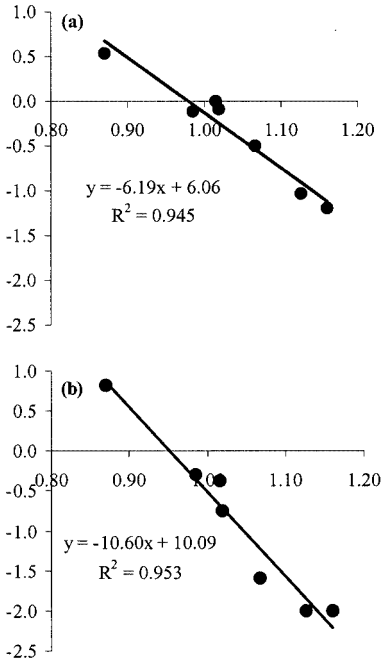

Figure 2. Plot of log *er*(*endo*-**3**) (a) and log *er*(*exo*-**4**) (b) vs. the lanthanide ionic radius with **8** as pybox ligand

Some reports concerning the relationship between enantioselectivity and lanthanide cation,[14] with the pybox ligand taken as a constant, have appeared in the literature; they include the asymmetric ring-opening of cyclohexene oxide with trimethylsilyl cyanide (TMSCN),[15] the addition of TMSCN to benzaldehyde,[16] the DA reaction between **1** and **2**,[4,17] the hetero-DA reaction between ethyl glyoxylate and the Danishefsky diene,[18] the hetero-ene reaction between the same ethyl glyoxylate and 2-phenylpropene,[19] and the DA reaction between methyl 3,6-dioxocyclohexa-1,4-dienecarboxylate and 2,4-hexadiene,[11] but no reversal of the enantioselectivity was observed in any of these examples. The data reported in Table 2 (Entries 1−7) not only provide evidence that the *ee* is a function of the lanthanide cation, but also show that pybox **8** is an original ligand suitable for furnishing opposite enantiomers with good selectivity simply by exchanging Sc^{III} for La^{III}.

The stereoselectivity observed in many different DA[3,4] and Mukaiyama-Michael[5] reactions suggests that the coordination of **1** in Sc^{III} complexes of 4′-Ph-substituted pybox occurs with the acryloyl CO group in the apical position, opposite to that proposed in the complex involving either 4′-*i*Pr-pybox (**7**) or ligand **5** (see Figure 1).

The enantiodivergent results obtained by use of **8** with Sc and La (Table 2, Entries 1 and 7) can be interpreted by starting from the X-ray structures of Sc^{III} [9] and La^{III} [5] complexes. If these geometries are assumed for the corresponding reacting complexes, a pentagonal-bipyramidal coordination is obtained for Sc^{III}, while La^{III} has nine as coordination number. The former complex has two phenyl groups shielding the *Re* face, so the Sc cation preferentially gives (*S*)-**3** and (*S*)-**4** (*er* = 77.5:22.5 and 87:13, respectively), while the latter has both 4′- and 5′-phenyl groups that induce shielding of the *Si* face, so (*R*)-**3** and (*R*)-**4** are formed as the major products (*er* = 94:6 and 99:1, respectively) (Figure 3).

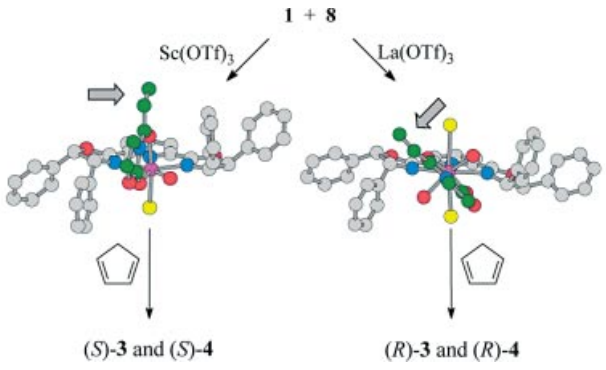

Figure 3. The enantiodivergent DA reaction between **1** and **2**, catalysed by the complexes of pybox **8** with $Sc(OTf)_3$ or $La(OTf)_3$, respectively

The linear relationships observed in Figure 2 for reactions catalysed by intermediate-sized lanthanides may be interpreted as the result of competition between two reaction pathways each involving one of the reacting complexes illustrated in Figure 3.

When the ligand is pybox **9**, the strong increase in the enantioselectivity demonstrates the specific effect of the second phenyl group. Each lanthanide cation that coordinates **9** always favours the formation of (*R*)-**3** and (*R*)-**4** through a preferred attack to the *Si* face, and the *ee* value is frequently > 95%. The La^{III}-coordinated reacting intermediate derived from the X-ray crystal structure of [La^{III}-**9**·$(H_2O)_4$·$(OTf)_3$],[5] binding **1** in place of two water molecules, has already been reported as a rationale for the attack at the *Si* face in both the DA[3] and Mukaiyama−Michael[5] reactions.

Conclusion

In conclusion, this research deals with the influence induced by pybox substituents and lanthanide cations on the enantioselectivity of the DA reaction. Two results deserve attention: of the catalysts derived from the easily available pybox **6** obtained from norephedrine, the Sc^{III}-based one is *endo*-selective, whereas several catalysts derived from (4′*R*,5′*R*)-*trans*-diphenylpybox **9** give significant amounts of *exo* adduct, all these catalysts affording products with excellent *ee* values. The (4′*R*,5′*S*)-*cis*-diphenylpybox **8** is an original ligand able to change the selectivity systematically with changing lanthanide radius, and suitable to give opposite enantiomers, both with good selectivity, by exchanging Sc^{III} for La^{III}. The overall effect of several efficient catalysts of the DA reaction described in this paper, which, having the same configuration of the chiral centre in the 4′-position of the ligand, may promote divergent enantioselectivity depending on the pybox substituents and the lanthanide cation, is summarised in Figure 4.

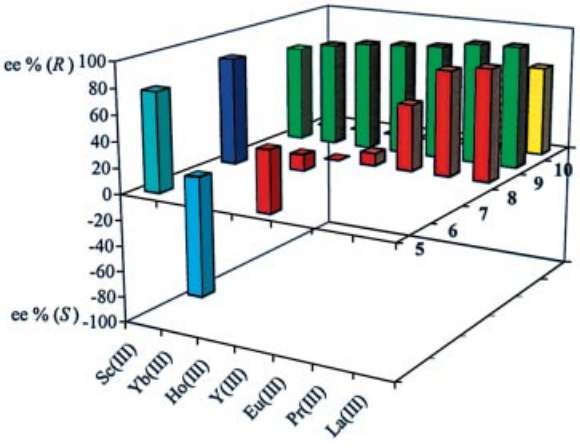

Figure 4. Distribution of enantioselectivities (*ee* > 70%) with different pybox and lanthanide based catalysts

Three simple points are evident:
(i) With 4′-alkyl-substituted pybox (**5**−**7**), Sc^{III} is by far the best lanthanide.
(ii) *trans*-diphenyl-pybox **9** and larger *ir* lanthanides give catalysts that induce the best enantioselectivities.
(iii) *cis*-diphenyl-pybox **8** is the ligand of choice for more flexible catalysts.

The attractive possibility that a (4′*R*)-pybox may induce opposite enantioselectivities in the DA reaction by judicious choice of substituent or lanthanide cation may help chemists in successful enantioselective syntheses.

Experimental Section

General Remarks: Melting points were determined by the capillary method and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. Dichloromethane was the hydrocarbon-stabilised Aldrich ACS grade, distilled from calcium hydride and used immediately; inorganic salts were Aldrich ACS reagents; powdered molecular sieves (4 Å) (MS) was Aldrich reagent 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 by a literature method.[20] (4′*R*,5′*R*)-2,6-Bis(4′-methyl-5′-phenyl-1′,3′-oxazolin-2′-yl)pyridine (**6**) was an Aldrich commercial product, (4′*S*,5′*R*)-2,6-bis(4′-methyl-5′-phenyl-1′,3′-oxazolin-2′-yl)pyridine (*ent*-**5**),[8] (4′*R*,5′*R*)-2,6-bis(4′,5′-diphenyl-1′,3′-oxazolin-2′-yl)pyridine (**9**),[5] and (4′*R*,5′*S*)-2,6-bis(4′,5′-diphenyl-1′,3′-oxazolin-2′-yl)pyridine (**8**),[8] were prepared as described in the literature.

General Procedure for Enantioselective Diels−Alder Reactions between 1 and 2: 3-Acryloyl-1,3-oxazolidin-2-one (**1**; 0.042 g, 0.30 mmol), pybox (**5**, **6**, **8** or **9**; 0.03 mmol), the inorganic triflate (0.03 mmol) and the molecular sieves (about 0.040 g) were added to anhydrous CH_2Cl_2 (0.3 mL) at ambient temperature in a sealed (rubber septum) vial, and the mixture was stirred and then cooled to −50 °C. After 1 h, cyclopentadiene (100 μL; ca. 1.5 mmol) was added by microsyringe and stirring was continued at −50 °C until TLC showed all dienophile had reacted. The reaction was decomposed in water, extracted with CH_2Cl_2 and dried, and the mixture of adducts **3** and **4** was separated from the pybox by column chromatography (silica gel; *l* = 30 cm, diameter = 1.5 cm; cyclohexane/ethyl acetate, 70:30 was the eluent), and subjected to HPLC analysis on a Chiralcel OD column with hexane/2-propanol (9:1) as eluent (1.0 mL/min). The average retention times − 20 and 21 min for (*R*)- and (*S*)-**4**, respectively; 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. The data reported in Tables 1 and 2 are the average of at least three determinations on independently run reactions.

Acknowledgments

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Sect. with $Gd(OTf)_3$ and pybox **6**, after 24 h, gave [*endo*]/[*exo*] = 84:16, *ee*[(*R*)-**3**] = 57%, *ee*[(*R*)-**4**] = 26%.

[13] The 4′-alkyl-substituted pybox compounds **5** and **6** (as well as **7**, see ref.[4]) give a relation between log *er* and *ir* (*er*: enantiomeric ratio; *ir*: ionic radius) represented in general by two broken linear relationships; the same linear relationships found for **8** can be observed for **10** (see ref.[4]) and **9**, although in the case of *exo*-**4** a plateau (*er* > 99.5:0.5) is observed in the Ho^{III}–La^{III} range.

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