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An efficient catalyst for highly enantioselective *exo*-Diels–Alder reaction between alkenoyl-1,3-oxazolidin-2-ones and cyclopentadiene

Giovanni Desimoni,* Giuseppe Faita, Matilde Guala and Carmela Pratelli

Dipartimento di Chimica Organica, Università di Pavia, viale Taramelli 10, I-27100 Pavia, Italy

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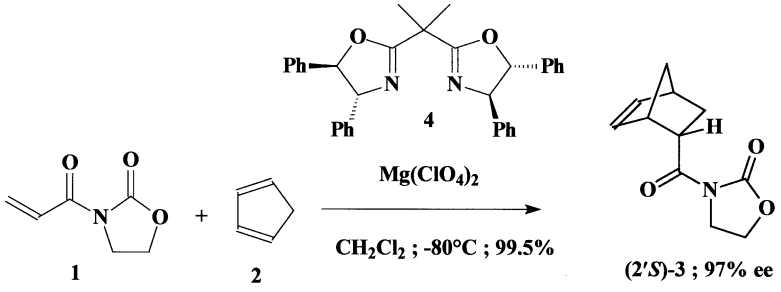
Abstract—The typically *endo*-selective Diels–Alder reactions of cyclopentadiene with acryloyl- and (*E*)-crotonoyl-oxazolidin-2-ones have been studied to find *exo*-selective catalysts. Whereas bis(oxazoline)-based catalysts promote high degree of *endo*-selectivity (with high ee), those derived from 2,6-bis[(4′*R*,5′*R*)-diphenyl-1′,3′-oxazolin-2′-yl]pyridine (pybox) and the triflates of Eu^{III}, La^{III} and Ce^{IV} induce different stereoselectivity. Not only the *exo* products are obtained with Eu^{III} in more than 50% yield, but the enantioselectivity is excellent (more than 99% ee). The absolute configuration of the previously unknown *exo* cycloadduct was unambiguously determined. A stereochemical model is proposed for the activated substrate–catalyst complex which suggests that the excellent efficiency of diphenyl-substituted pybox, compared to that of the corresponding 4-phenyl-substituted ligand, is due to the substituent in the 5-position, suitably placed to blind the *Re*-face of the coordinated reagent.

1. Introduction

The enantioselective catalysis of the Diels–Alder (DA) reaction has been extensively studied by several groups using chiral Lewis acid complexes. Nowadays almost all cations have been used as Lewis acid cores of the catalyst, and a variety of chiral ligands suitable to induce enantioselectivity have been tested.[1] Among the chiral ligands, bis(oxazolines) (box) and 2,6-bis(oxazolidinyl)pyridines (pybox) have found a wide range of application,[2] certainly not limited to DA reactions, for their ability to bind several cations[3] giving complexes that maintain enough free centres of coordination (for at least one reagent of the reaction) to give the activated substrate–catalyst complex.

The important difference between C_2-symmetric box and pybox ligands is that the former ones behave in a bidentate fashion in square-planar, tetrahedral and octahedral complexes, while the latter ones give either hexacoordinate complexes (Ru, Rh, W, Re) or complexes with even larger coordination number (lanthanides).[4]

The prototype of DA reaction used to compare the efficiency of different catalysts is the reaction between acryloyl-1,3-oxazolidin-2-one (**1**) and cyclopentadiene (**2**), a cycloaddition occurring with high *endo*-selectivity. Hence several groups[5] found chiral catalysts suitable to afford the *endo* cycloadduct **3** with ee>95%. Among them, the Mg^{II} complex of 2,2-bis{2-[(4*R*,5*R*)-diphenyl-1,3-oxazolinyl]}propane **4** gave a quantitative yield of **3**, with (*endo*/*exo*) ratio of 99.5:0.5 and ee of 97%[6] (Scheme 1).



Scheme 1.

Keywords: asymmetric catalysis; *exo*-Diels–Alder reaction; lanthanides; pyridine-bis(oxazolines).
* Corresponding author. Tel.: +39-382-507313; fax: +39-382-507323; e-mail: desimoni@chifis.unipv.it

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The *exo*-selectivity in DA reactions is generally observed when α-substituted α,β-enals are used as dienophiles since the substituent in the α position (Me, Br) is the most important factor influencing the stereoselectivity. These reactions can be usefully catalysed with chiral Lewis acids and high *exo* enantioselectivity can be achieved.[7,8] *exo*-Selectivity is rarely observed in cycloadditions involving unsubstituted acrolein or crotonaldehyde. For the reaction between acryloyl-1,3-oxazolidin-2-one (**1**) and cyclopentadiene, only a (phosphino-oxazoline)Cu^{II} complex bearing two bulky substituents (necessarily dianthrylphosphino and *tert*-butyl groups) has been reported to give the *exo* adduct in 69% yield (the ee was 92% of a product whose configuration remained undetermined).[5g] This unfamiliar stereoselectivity provides the reason why the *exo* product was never separated, its NMR spectra were rarely described, the $[\alpha]_D$ value of the enantiomers, as well as their absolute configuration, was never determined.

Since *endo*/*exo* stereoselectivity in other pericyclic reactions (e.g. 1,3-dipolar cycloadditions)[9] may be deeply influenced by the catalysts structure, and with the experience in C_2-symmetric box and pybox as ligands for optically active catalysts, the DA cycloaddition between **1** and **2** was studied in order to design a chiral catalyst tailored to favour *exo*-selectivity.

2. Results and discussion

Any attempt to use the bis(oxazoline) (4′*R*)-phenyl-box and (4′*R*,5′*R*)-diphenyl-box as ligands with either perchlorates (P) (Mg^{II}, Co^{II}, Mn^{II}, Ni^{II}, Zn^{II}) or triflates (T) (Mg^{II}, Sc^{III}, Eu^{III}, Yb^{III}) to induce *exo*-selectivity was unsuccessful since the (*endo*/*exo*) ratio was always greater than 9:1 (the ee of *endo* was sometimes greater than 95%). Only Eu^{III} and Yb^{III}T gave a modest amount of *exo* product (17 and 28%, respectively), but in a nearly racemic form.

Since the Mukaiyama–Michael reaction between crotonoyl-1,3-oxazolidin-2-one and 2-trimethylsilyloxyfuran was catalysed by 2,6-bis[(4′*R*,5′*R*)-diphenyl-1′,3′-oxazolin-2′-yl]pyridine-based complexes,[4] whose 5′-phenyl group determines the stereoselective attack to a coordinated reagent which is very similar to **2**, the pybox ligand **5** was tested in the presence of different inorganic salts, among them the lanthanide triflates.

2.1. The Diels–Alder reaction between acryloyl-1,3-oxazolidin-2-one and cyclopentadiene

The DA reactions were run by mixing **1**, **5** and the inorganic salt in a ratio (10:1:1) in CH_2Cl_2 (with MS when required) at ambient temperature in a rubber septum sealed vial, under stirring for about 1 h. Then the mixture was cooled at −50°C and **2** was added with a microsyringe. After completion of the reaction, this was worked up, and the stereo- and enantioselectivity of the reaction were determined by ^{1}H NMR spectroscopy and HPLC (Chiralcel OD column). Table 1 summarises the results obtained under the above conditions.

The Mg^{II}, Co^{II} and Zn^{II} cations give catalysts that are strongly *endo*-selective (entries 1–4), with a significant ee of the (2′*R*) enantiomer.

When lanthanide triflates were tested, Yb^{III} and Sc^{III}, gave *endo*-selective catalysts (entries 5–7), but La^{III}, Eu^{III} and Ce^{IV} triflates (entries 8–12) gave very different results. The reactions were complete within one night, the *exo* product **6** was obtained with up to 50% yield, and HPLC analysis showed that these three catalysts led to the formation of a single enantiomer of the *exo* adduct (Scheme 2). Since the configuration of this *exo* enantiomer was unknown, the reaction with EuT was run on 2.00 mmol scale in order to separate the product to identify its absolute configuration.

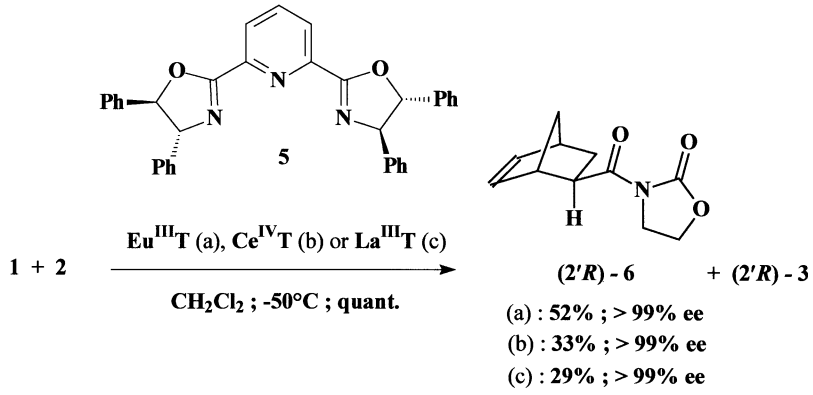
The result obtained on 10 times scale was identical to that described in Table 1 (entry 10), *exo*-**6** and *endo*-**3** products were separated by column chromatography, the former being that eluted first with cyclohexane/ethyl acetate 93:7 as eluant. The structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy (see Section 4) and the stereochemical identity of the enantiomer having $[\alpha]_D^{25}=-17.3$ (*c* 0.54 in $CHCl_3$) was subsequently determined.

To convert the amide product into the benzyl ester, the removal of the oxazolidin-2-one residue should be achieved by following one of the known protocols: the recently

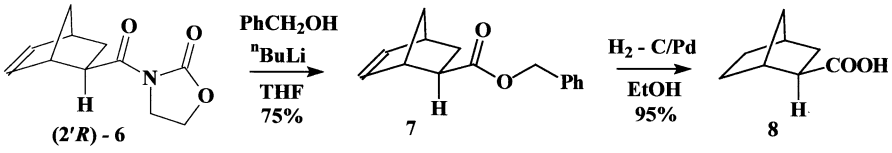
Table 1. Diels–Alder reaction between **1** and **2**, at −50°C in CH_2Cl_2, in the presence of 10 mol% of inorganic salt and chiral ligand **5**

Entry	Salt[a]	Additive[b]	Time (h)—yield (%)	*endo*/*exo*	*endo*-**3** ee% (configuration)	*exo*-**6** ee% (configuration)
1	Mg^{II}P	–	16—quant.	97:3	80 (2′*R*)	[c]
2	Mg^{II}T	MS	72—quant.	98:2	84 (2′*R*)	[c]
3	Co^{II}P·6w	MS	16—quant.	96:4	74 (2′*R*)	[c]
4	Zn^{II}P·6w	MS	16—quant.	97:3	82 (2′*R*)	[c]
5	Sc^{III}T·6w	MS	48—quant.	98:2	76 (2′*R*)	[c]
6	Yb^{III}T·6w	–	16—quant.	90:10	87 (2′*R*)	[c]
7	Yb^{III}T·6w	MS	16—quant.	87:13	82 (2′*R*)	[c]
8	La^{III}T	MS	16—quant.	71:29	96 (2′*R*)	>99 (2′*R*)
9	Eu^{III}T·6w	–	16—quant.	50:50	87 (2′*R*)	>99 (2′*R*)
10	Eu^{III}T·6w	MS	16—quant.	48:52	90 (2′*R*)	>99 (2′*R*)
11	Ce^{IV}T.nw	–	16—quant.	67:33	92 (2′*R*)	>99 (2′*R*)
12	Ce^{IV}T.nw	MS	16—quant.	69:31	88 (2′*R*)	>99 (2′*R*)

[a] P is perchlorate, T triflate, and w water.
[b] MS is 4 Å molecular sieves.
[c] Not determined.



Scheme 2.



Scheme 3.

reported transesterifications with benzyl alcohol promoted by either lanthanum iodide[10] or scandium triflate,[11] or the treatment of **6** with lithium benzyl oxide in tetrahydrofuran.[12]

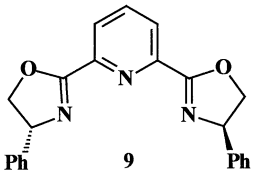
All protocols were tested on *endo* (2′*R*)-**3** adduct and the conversion always occurred with excellent yields and in the absence of any epimerisation. When the reactions were tested on *exo*-**6**, only the Evans' procedure[12] gave *exo*-benzyl ester **7** as a single enantiomer in a satisfactory yield, fully characterised by spectroscopic methods. The benzyl ester was hydrogenated to give the corresponding saturated *exo* acid of known absolute configuration,[13] and proved to be (1*R*,2*R*,4*S*)-bicyclo[2.2.1]heptane-2-carboxylic acid **8**. Therefore, the configuration of the *exo* adduct obtained in the experiments reported in Table 1 (entries 8–11) is (1′*S*,2′*R*,4′*S*)-**6** (Scheme 3).

Hence, both *endo*-**3** and *exo*-**6** adducts of the DA reactions reported in entries 8–11 (Table 1) have a (2′*R*) configuration. This has an important implication in the mechanism of the catalysis if the result reported in Scheme 1 is compared with those in Table 1.

Even if the catalysts derived from both box-**4** and pybox-**5** have the same (4*R*,5*R*) configuration of the phenyl substituents at the oxazoline rings, the enantioselectivity is reversed. The catalyst derived from box ligand (Scheme 1) gives the (2′*S*)-*endo* product, while those from pybox ligand give both *endo* and *exo* products with the opposite (2′*R*)-configuration. This means that different coordination modes are involved in box and pybox reacting complexes: the box catalyst blinds the *Si*-face of coordinated **1** and the attack of cyclopentadiene occurs at the *Re*-face, whereas the pybox catalysts blind the *Re*-face of coordinated **1** and cyclopentadiene attacks the more easily accessible *Si*-face.

To rationalise the shielding observed in pybox-based catalysts, a crucial role of the substituent in position 5 of the chiral oxazoline has to be considered.

This working hypothesis was tested by running the DA reaction in the presence of pybox-based catalysts without the phenyl group in position 5 of the oxazoline rings, hence with catalysts derived from **9** (Scheme 4) and Eu^{III} or Ce^{IV} triflates.



Scheme 4.

If the results reported in Table 2 are compared with those in Table 1, some interesting features are evidenced. The ligand **9** gives catalysts that are always less stereoselective than those derived from pybox **5**. The preferred (2′*R*)-*endo* adduct is the result of a cyclopentadiene attack to the *Si*-face of the coordinated dienophile as pybox **5** does, whereas the (2′*S*)-*exo* adduct derived from a diene approach to the *Re*-face, just the opposite of the behaviour found for **5**. In conclusion, the results with **9** could be defined as disappointing if they would not support, at least for the *exo*-attack, the proposed model of catalysis.

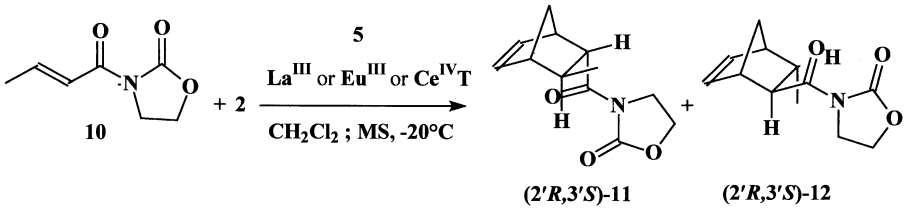
2.2. Diels–Alder reaction between crotonoyl-1,3-oxazolidin-2-one and cyclopentadiene

To test the compatibility of the catalysts derived from **5** with the structure of the dienophile, the DA reaction of **2** with (*E*)-3-crotonoyl-1,3-oxazolidin-2-one **10** was investigated.

Table 2. Diels–Alder reaction between **1** and **2**, at −50°C in CH_2Cl_2, in the presence of 10 mol% of inorganic salt and chiral ligand **9**

Entry	Salt[a]	Additive[b]	Time (h)—yield (%)	*endo*/*exo*	*endo*-**3** ee% (configuration)	*exo*-**6** ee% (configuration)
1	Eu^{III}T·6w	–	16—quant.	67:33	34 (2′*R*)	84 (2′*S*)
2	Eu^{III}T·6w	MS	16—quant.	78:23	Racemate	36 (2′*S*)
3	Ce^{IV}T.nw	–	16—quant.	80:20	48 (2′*R*)	76 (2′*S*)
4	Ce^{IV}T.nw	MS	16—quant.	70:30	72 (2′*R*)	94 (2′*S*)

[a] T is triflate, and w water.
[b] MS is 4 Å molecular sieves.



Scheme 5.

In general the catalysed reaction is *endo*-selective;[14] also the catalyst that behaves as *exo*-selective in the reaction of acryloyl-1,3-oxazolidin-2-one becomes *endo*-selective with **10**.[5g] Only a few experiments giving significant amounts of *exo* adduct are reported in the literature,[15] and only one catalyst[15f] (that was *endo*-selective with the DA between **1** and **2**) provides good *exo*-selectivity (ee of the *exo* adduct 75%).

The reactions between **2** and **10** were run at −20°C due to the lower reactivity of the dienophile, and the results of the experiments with some lanthanide triflates (Scheme 5) are reported in Table 3.

Again significant amounts of the *exo* product **12** are obtained with the majority of lanthanide cations and the best *exo* selectivity (67%) was obtained in the reaction run with EuT. *Endo*-(1′*R*,2′*R*,3′*S*,4′*S*)-**11** is obtained as a single enantiomer with LaT (entry 2) and very good ee are also obtained with Eu^{III} and Ce^{IV} triflates. *Exo*-**12** is obtained as a single enantiomer running the reaction either with La^{III} or Eu^{III}, and a very good ee is obtained with Ce^{IV} also.

The stereochemical identity of the *exo* isomer isolated as above described (see Section 4 for details) cannot be related to the absolute configuration of a known 2-*exo* 3-methylbicyclo[2.2.1]heptane-2-carboxylic acid. Since the same catalyst gives *endo* products with the same configuration [(1′*R*,2′*R*,4′*R*)-**3** and (1′*R*,2′*R*,3′*S*,4′*S*)-**11**] starting either from **1** or **10**, the known configuration (1′*S*,2′*R*,4′*S*) of the major *exo* enantiomer **6** obtained from **1**, suggests the configuration (1′*S*,2′*R*,3′*S*,4′*R*) for *exo*-**12**. This attribution is further supported by the $[\alpha]_D^{25}=+94.1$ (*c* 0.97 in $CHCl_3$), since the supposed (1′*R*,2′*S*,3′*R*,4′*S*) enantiomer (whose configuration was proposed in the literature)[15f] in 75% ee has $[\alpha]_D^{25}=-67.7$ (*c* 0.80 in $CHCl_3$).[16]

3. Conclusions

Whereas box ligands were widely applied in the asymmetric catalysis of the DA cycloaddition, pybox ligands found only few applications. To the best of our knowledge, only three examples have been reported in the literature. Evans[7] used different mono-substituted pybox-Cu^{II} chiral complexes to catalyse the DA reaction between cyclopentadiene and acrylate esters, and all cycloadditions were *endo*-selective. Again, Evans[17] reported the use of (4′*S*)-**9**/Cu^{II} and Zn^{II} for the reaction between **1** and **2**, both catalysts are strongly *endo*-selective and the ee of (2′*S*)-**3** was 90%. Recently, Fukuzawa[18] reported the chiral Sc^{III} triflate/*i*-Pr-pybox complex as an efficient *endo*-selective catalyst for the DA reaction between cyclopentadiene and **1** or **10**, giving (2′*S*)-**3** or (2′*S*,3′*R*)-**12**, respectively. Other lanthanides were less enantioselective by far and a clear shift of the stereoselectivity towards the formation of the *exo*-cycloadduct was observed: La^{III}, (*endo*/*exo*)=(91:9); Sm^{III}, (86:14); Yb^{III}, (65:35).

The pybox **5**, with Mg^{II}, Co^{II}, Zn^{II} and Sc^{III} cations, gives

Table 3. Diels–Alder reaction between **10** and **2**, at −20°C in CH_2Cl_2, in the presence of 10 mol% of inorganic salt and chiral ligand **5**

Entry	Salt[a]	Additive[b]	Time (h)—yield (%)	*endo*/*exo*	*endo*-**11** ee% (configuration)	*exo*-**12** ee% (configuration)
1	Yb^{III}T·6w	–	48—95	71:29	84 (2′*R*,3′*S*)	90 (2′*R*,3′*S*)
2	La^{III}T	MS	48—quant.	69:31	>99 (2′*R*,3′*S*)	>99 (2′*R*,3′*S*)
3	Eu^{III}T·6w	–	48—90	41:59	94 (2′*R*,3′*S*)	98 (2′*R*,3′*S*)
4	Eu^{III}T·6w	MS	48—quant.	33:67	92 (2′*R*,3′*S*)	>99 (2′*R*,3′*S*)
5	Ce^{IV}T.nw	–	48—quant.	62:38	94 (2′*R*,3′*S*)	96 (2′*R*,3′*S*)
6	Ce^{IV}T.nw	MS	48—quant.	64:36	92 (2′*R*,3′*S*)	94 (2′*R*,3′*S*)

[a] T is triflate, and w water.
[b] MS is 4 Å molecular sieves.

endo-selective catalysts that also induce a good level of enantioselection (Table 1, entries 1–5). In all cases, as well as in the already mentioned examples reported in the literature,[17,18] the favoured *endo*-enantiomer derives from a diene approach to the *Si*-face of the coordinated dienophile.

The results are significantly different when the rare earth cations are involved in the formation of the chiral complexes with pybox **5**. The catalysts derived from La^{III}, Eu^{III} and Ce^{IV} cations (less that derived from Yb^{III}) not only give the *exo* adducts with even more than 50% yield, but the reactions are highly enantioselective: the *endo* products **3** and **11** are formed in 96 and >99% ee, respectively, both *exo* products (**6** and **12**) are obtained in >99% ee.

The reason why a catalyst determines *exo*-selectivity is considered to be a steric repulsion between the activated substrate–catalyst complex and the approaching diene.[5g,15f,19] This certainly rationalises the *exo*-selectivity promoted by the above based pybox catalysts, but the intriguing stereochemical course of the reaction deserves attention.

When pybox behaves as a tridentate ligand,[3] the geometry of the complex depends on the cation. The Pd^{II} give a square planar coordination,[20] Cu^{II} is square pyramidal,[7] Rh^{III} and Ru^{II} are octahedral[21,22] as well as Sn^{II};[23] the most important data for this paper derive from the crystallographic structures of pybox–lanthanide complexes. The (*S*)-Ph-pybox (the enantiomer of **9**)/Sc^{III} complex has a pentagonal bipyramidal geometry,[24] the metal–ligand complex between **5** and La^{III} triflate has nine as coordination number.[4]

This information allows us to propose for the DA cycloaddition the same reacting complex involved in the Mukaiyama–Michael reaction,[4] having a (1:1:1) ratio between cation, reagent and chiral ligand (Fig. 1). This complex not only is crowded enough to rationalise the *exo*-selectivity, but clearly illustrates the reason why cyclopentadiene attacks the *Re*-face of the double bond to give

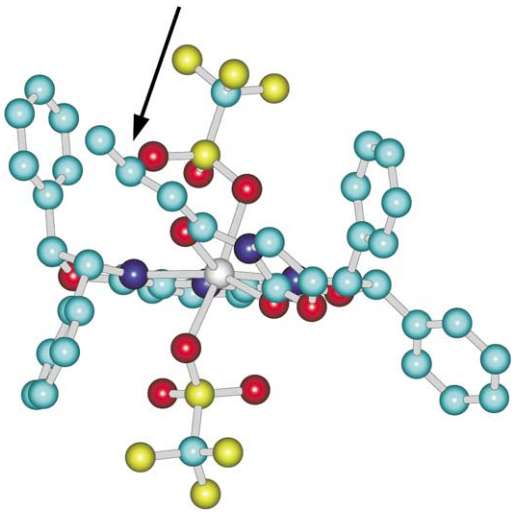


Figure 1. Proposed structure for the activated substrate complex, with seven as coordination number, formed between the dienophile and the lantanide–pybox complex derived from **5**.

(2′*R*)-**6** and (2′*R*,3′*S*)-**11**. As it may be observed, the substituent in the 5-position has a stronger effect to determine the face selectivity of the attack than that in the 4-position, even if the latter is closer to the cationic centre.

Table 2 reports the results obtained from the catalysts with pybox **9**, a ligand without the phenyl group in the 5-position. Even if the oxazoline chiral centres in the 4-position have the same configuration in **5** and **9**, the less selective behaviour of the latter must be due to a lower shielding of the coordinated dienophile. The ee of the adduct *endo*-**3** is lower even if the configuration is the same. On the contrary, the adduct *exo*-**6** is formed with lower enantioselectivity and the major enantiomer has the opposite configuration.

4. Experimental

4.1. General methods and materials

Melting points were determined by the capillary method and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively; IR spectra were recorded as neat products on a Perkin–Elmer FT-Paragon 1000 spectrophotometer; optical rotations were measured at 25°C on a Perkin–Elmer 241 polarimeter with a 1 dm cell. 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 was Aldrich reagent activated in an oven 12 h at 150°C and kept in a dryer; (3)-acryloyl-1,3-oxazolidin-2-one (**2**) and (*E*)-3-crotonoyl-1,3-oxazolidin-2-one (**10**) were prepared following the literature method.[12,14g] 2,6-Bis[(4′*R*,5′*R*)-diphenyl-1′,3′-oxazolin-2′-yl]pyridine (**5**) was prepared as described in the literature.[4] 2,6-Bis[(4′*R*)-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**9**) was prepared as described in the literature.[25]

4.2. General procedure for the enantioselective Diels–Alder reaction between 1 and 2

3-Acryloyl-1,3-oxazolidin-2-one (**2**) (0.042 g, 0.30 mmol), the chiral ligand pybox (**5** or **9**) (0.03 mmol), the inorganic perchlorate or triflate (0.03 mmol) and, when required, the molecular sieves (0.040 g) were added to anhydrous CH_2Cl_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, about 1.5 mmol) was added with a microsyringe and stirring was continued at −50°C for the times reported in Tables 1 and 2.

The reaction was decomposed in water, extracted with CH_2Cl_2 and dried. If TLC (cyclohexane/ethyl acetate 7:3 as eluant) showed some unreacted starting product **2**, the yield of the reaction (as well as the *endo*/*exo* ratio, Tables 1 and 2) was determined by ^1H NMR taking the region of the olefinic protons at 6.55 (one of the vinylic protons of **2**), 6.26 (one of the olefinic proton of the *endo* adduct) and 6.18 δ (both olefinic protons of the *exo* adduct) to determine **3** and **6** vs. **2**. In each case the mixture of adducts **3** and **6** was separated by column chromatography (silicagel, 30 cm l, 1.5 cm diameter), 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, 29.5 and 31 min for (*S*)- and (*R*)-**6**, respectively; 34 and 37 min for (*S*)- and (*R*)-**3**, respectively, largely depend from the small variations of the solvents and were checked with reference mixtures (literature: 19.9, 20.7, 21.9 and 24.6 min for the same products).[26]

The adducts **6** can be isolated from a reaction run on 2.00 mmol scale in accordance to entry 10—Table 1, by column chromatography (silica gel 230–400 mesh, 60 cm l, 2,5 cm diameter, cyclohexane/AcOEt 97:3 as eluant).

4.2.1. (1′*S*,2′*R*,4′*S*)-3-(Bicyclo[2.2.1]hept-5′-ene-2′-carbonyl)-2-oxazolidinone (6). The titled compound was isolated as colourless oil; $[\alpha]_D^{25}=-17.3$ (c=0.54 in $CHCl_3$); IR (film) ν 1778, 1694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ=1.39 (m, 1H, H7′), 1.47 (m, 1H, H3′*exo*), 1.54 (m, 1H, H7′), 1.96 (m, 1H, H3′*endo*), 2.95 and 3.03 (2s, 1H+1H, H1′ and H4′), 3.29 (dd, ^3J(H,H)=4.6, 8.8 Hz, 1H; H2′), 4.04 (t, ^3J(H,H)=8.4 Hz, 2H; H4), 4.42 (t, ^{3}J(H,H)=8.4 Hz, 2H; H5), 6.18 (s, 2H, H5′ and H6′); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 30.3 (C3′), 41.8 (C1′ or C4′), 42.9 (C2′ and C4), 46.1 (C7′), 46.7 (C4′ or C1′), 61.9 (C5), 135.9 (C5′ or C6′), 138.1 (C6′ or C5′), 153.3 (C2), 176.1 (CO); elemental analysis calcd (%) for $C_{11}H_{13}NO_3$ (207.2): C 63.75, H 6.32, N 6.76; found C 63.59, H 6.48, N 7.01. The second fraction was (1′*R*,2′*R*,4′*R*)-3-(bicyclo[2.2.1]hept-5′-ene-2′-carbonyl)-2-oxazolidinone (contaminated by (1′*S*,2′*S*,4′*S*) enantiomer) **3**, isolated as colourless solid, whose ^1H NMR spectrum was identical to that reported in the literature.[5f]

4.2.2. (1*S*,2*R*,4*S*)-(Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid benzyl ester (7). To a stirred and cooled (−70°C) solution of benzyl alcohol (0.100 mL 0.97 mmol) in anhydrous tetrahydrofuran (3.5 mL) a 1.6 M hexane solution of *n*-butyllithium (0.500 mL, 0.8 mmol) was added. After few minutes, a solution of (1′*S*,2′*R*,4′*S*)-**6** (0.070 g, 0.34 mmol) in anhydrous tetrahydrofuran (0.35 mL) was added with a microsyringe, the reaction mixture was warmed to 0°C, and stirring was continued for 3 h. The solution was quenched with excess saturated aqueous solution of ammonium chloride and extracted with CH_2Cl_2. The organic layers, dried with sodium sulphate, were evaporated and the residue was column chromatographed over silicagel (eluant cyclohexane/ethyl acetate 96:4). The first fraction gave **7** (0.058 g, 75% yield) as a colourless liquid; $[\alpha]_D^{25}=-18.7$ (c=0.975 in $CHCl_3$); IR (film) ν 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 1.41 (m, 2H; H3*exo* and H7), 1.56 (m, 1H, H7), 1.97 (m, 1H, H3*endo*), 2.31 (m, 1H, H2), 2.95 and 3.09 (2s, 1H+1H, H1 and H4), 5.16 (s, 2H, CH_2 benzyl), 6.14 (m, 2H, H5 and H6), 7.3–7.4 (m, 5H, aromatic protons); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.3 (C3), 41.6 (C1 or C4), 43.1 (C2), 46.3 (C7), 46.5 (C4 or C1), 66.2 (C benzyl), 128.0, 128.0, 128.5 (aromatic C), 135.6 (C5 or C6), 136.2 (aromatic C), 138.0 (C6 or C5), 176.0 (CO); Elemental analysis calcd (%) for $C_{15}H_{16}O_2$ (228.3): C 78.92, H 7.06; found C 78.78, H 6.97.

4.2.3. (1*S*,2*R*,4*S*)-Bicyclo[2.2.1]heptane-2-carboxylic acid (8). Pd 10% on charcoal (0.010 g) was added to a solution of **7** (0.050 g, 0.22 mmol) in ethanol (4 mL). The stirred mixture was submitted to hydrogenation at room temperature and the uptake of hydrogen was completed within 3 h. The mixture was filtered and concentrated under vacuum to give the known acid (**8**) as a white solid (0.029 g, 95% yield): mp 44–45°C, (lit[13] mp 42–45°C); $[\alpha]_D^{25}=-25.2$ (c=0.73 in $CHCl_3$), {lit[13] $[\alpha]_D^{25}=-25.5$ (c=3.7 in $CHCl_3$}. The ^1H NMR was identical to that reported in the literature;[13] ^{13}C NMR ($CDCl_3$): δ 28.5, 29.8, 36.9 (C5, C6 and C7), 34.5 (C3), 36.4 (C1 or C4), 41.3 (C2), 46.7 (C4 or C1), 182.1 (CO).

4.3. General procedure for the enantioselective Diels–Alder reaction between 10 and 2

(*E*)-3-Crotonoyl-1,3-oxazolidin-2-one (**10**) (0.046 g, 0.30 mmol), the chiral ligand pybox (**5**) (0.018 g, 0.03 mmol), the inorganic triflate (0.03 mmol) and, when required, the molecular sieves (0.040 g) were added to anhydrous CH_2Cl_2 (0.3 mL) at ambient temperature in a rubber septum sealed vial, and the mixture was stirred and then cooled to −20°C. After 1 h cyclopentadiene (100 μL, about 1.5 mmol) was added and the reaction was worked up as previously described for the reaction between **1** and **2** except the HPLC analysis was performed on a Chiralpak AD column with hexane/2-propanol (95:5) as eluant (0.5 mL/min). The average retention times: 43 (−) and 47 (+) min for *exo*-**12** adducts, 45 and 51 min for (1′*S*,2′*S*,3′*R*,4′*R*)- and (1′*R*,2′*R*,3′*S*,4′*S*)-3-(3-methylbicyclo-[2.2.1]hept-5′-ene-2′-carbonyl)-2-oxazolidinone (**11**), respectively, largely depend from the small variations of the solvents and were checked with reference mixtures.[14g]

The adduct **12** having lower HPLC retention time can be isolated from a reaction run on 2.00 mmol scale run in accordance to entry 4—Table 3, by column chromatography (silica gel 230–400 mesh, 60 cm l, 2.5 cm diameter, cyclohexane/AcOEt 85:15 as eluant).

4.3.1. (1′*S*,2′*R*,3′*S*,4′*R*)-3-(3-Methylbicyclo[2.2.1]hept-5′-ene-2′-carbonyl)-2-oxazolidinone (12). The titled compound was isolated as a colourless oil: $[\alpha]_D^{25}=+94.1$ (c=0.97 in $CHCl_3$); IR (film) ν 1778, 1694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.87 (d, ^3J(H,H)=6.8 Hz, 3H, CH_3), 1.39 (m, ^{gem}J(H,H)=8.5 Hz, 1H, H7′), 1.67 (m, ^{gem}J(H,H)=8.5 Hz, 1H, H7′), 2.69 (m, ^3J(H,H)=4.9, 6.8 Hz, 1H, H3′), 2.75 (s, 1H, H1′ or H4′), 2.89 (dd, ^3J(H,H)=4.9 Hz, 1H, H2′), 2.91 (s, 1H, H4′ or H1′), 4.05 (t, ^3J(H,H)=8.5 Hz, 2H, H4), 4.42 (t, ^3J(H,H)=8.5 Hz, 2H, H5), 6.17 (dd, ^3J(H,H)=5.7 Hz, 1H, H5′ or H6′), 6.34 (dd, ^{3}J(H,H)=5.7 Hz, 1H, H6′ or H5′); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.7 (CH_3), 37.3 (C3′), 43.0 (C4), 46.6 (C7′), 47.4 (C1′ or C4′), 49.4 (C4′ or C1′), 50.6 (C2′), 61.7 (C5), 135.4 (C5′ or C6′), 136.8 (C6′ or C5′), 153.3 (C2), 175.5 (CO). Elemental analysis calcd (%) for $C_{12}H_{15}NO_3$ (221.3): C 65.14, H 6.83, N 6.33; found C 65.20, H 7.01, N 6.19. The second fraction was (1′*R*,2′*R*,3′*S*,4′*S*)-3-(3-methylbicyclo[2.2.1]hept-5′-ene-2′-carbonyl)-2-oxazolidinone (eventually contaminated by its enantiomer) **11**, isolated as colourless solid, whose ^1H NMR spectrum was identical to that reported in the literature.[5f]

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References

1. For a review on catalytic asymmetric Diels–Alder reaction, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (b) Evans, D. A.; Johnson, J. S. In *Diels–Alder Reaction*, Jacobsen, E. N., Pfalts, A., Yamamoto, H., Eds.; *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vol. III Chapter 33.1. (c) Carmona, D.; Lamata, M. P.; Oro, L. A. *Coord. Chem. Rev.* **2000**, *222–202*, 717.
2. For a review on chiral box and pybox metal complexes in catalytic asymmetric synthesis, see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.
3. For a review on coordination chemistry of oxazoline ligands, see: Gòmez, M.; Muller, G.; Rocamora, M. *Coord. Chem. Rev.* **1999**, *193–195*, 769.
4. Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *57*, 10203.
5. (a) Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991**, *32*, 6289. (b) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559 and references therein. (c) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. *J. Chem. Commun.* **1996**, 1753. (d) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815. (e) Davies, I. W.; Gerena, L.; Cai, D.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 1145. (f) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074. (g) Sagasser, I.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 261. (h) Oi, S.; Kashiwagi, K.; Inoue, Y. *Tetrahedron Lett.* **1998**, *39*, 6253. (i) Brunel, J. M.; Del Campo, B.; Buono, G. *Tetrahedron Lett.* **1998**, *39*, 9663.
6. Desimoni, G.; Faita, G.; Gamba Invernizzi, A.; Righetti, P. *Tetrahedron* **1997**, *53*, 7671.
7. Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582.
8. (a) Kundig, E. P.; Saudan, C. M.; Bernardinelli, G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1220. (b) Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem.* **1999**, 527 and references therein.
9. Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59.
10. Fukuzawa, S.; Hongo, Y. *Tetrahedron Lett.* **1998**, *39*, 3521.
11. Orita, A.; Nagano, Y.; Hirano, J.; Otera, J. *Synlett* **2001**, 637.
12. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
13. Eda, M.; Takempto, T.; Ono, S.; Okada, T.; Kosaka, K.; Gohda, M.; Matzno, S.; Nakamura, N.; Fukaya, C. *J. Med. Chem.* **1994**, *37*, 1983.
14. Enantioselectivities in excess of 90% have been reported in: (a) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109. (b) Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991**, *32*, 6289. (c) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535. (d) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (e) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815. (f) Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *J. Org. Chem.* **1997**, *62*, 7937. (g) Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099. (h) Nishida, A.; Yamanaka, M.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 1555.
15. Yields of the *exo* product at least of 20% have been reported in: (a) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027. (b) Altava, B.; Burguete, M. I.; Escuder, B.; Luis, S. V.; Salvador, R. V.; Fraile, J. M.; Mayoral, J. A.; Royo, A. J. *J. Org. Chem.* **1997**, *62*, 3126. (c) Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron* **1998**, *54*, 15721. (d) Ref. 14g. (e) Ref. 14h. (f) Matsukawa, S.; Sugama, H.; Imamoto, T. *Tetrahedron Lett.* **2000**, *41*, 6461.
16. Tsuneo Imamoto, personal communication.
17. Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481.
18. Fukuzawa, S.; Matsuzawa, H.; Metoki, K. *Synlett* **2001**, 709.
19. Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 6438.
20. Nesper, R.; Pregosin, P. S.; Pünterer, K.; Wörle, M. *Helv. Chim. Acta* **1993**, *76*, 2239.
21. Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horlhata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846.
22. Nishiyama, H.; Naitoh, T.; Motoyama, Y.; Aoki, K. *Chem. Eur. J.* **1999**, *5*, 3509 and references therein.
23. Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *123*, 10859.
24. Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *119*, 12095.
25. Nishiyama, H.; Kondo, M.; Nakamura, T.; Park, S. B.; Itoh, K. *Organometallics* **1991**, *10*, 500.
26. Desimoni, G.; Faita, G.; Gamba Invernizzi, A.; Righetti, P. *Tetrahedron* **1997**, *53*, 7671.