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A new and highly efficient catalyst for the enantioselective Mukaiyama–Michael reaction between (*E*)-3-crotonoyl-1,3-oxazolidin-2-one and 2-trimethylsilyloxyfuran

Giovanni Desimoni,[a,*] Giuseppe Faita,[a] Salvatore Filippone,[a] Mariella Mella,[a] Maria Grazia Zampori[a] and Michele Zema[b]

[a]*Dipartimento di Chimica Organica, Università di Pavia, Viale Taramelli 10, I-27100 Pavia, Italy*
[b]*Centro Grandi Strumenti dell'Università di Pavia, Via Bassi 21, 27100 Pavia, Italy*

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Abstract—The Mukaiyama–Michael reaction between 2-trimethylsilyloxyfuran and (*E*)-3-crotonoyl-1,3-oxazolidin-2-one has been stereoselectively catalysed by several optically active complexes based on bis(oxazoline) (box) or pyridine bis(oxazoline) (pybox) chiral ligands and metal cations. The catalysts derived from the newly synthesised 2,6-bis[(4′*R*,5′*R*)-diphenyl-1,3-oxazolin-2′-yl]pyridine and the triflates of Eu^{III}, La^{III}, Ce^{IV} were highly efficient: the diastereoselectivity was entirely *anti* and the enantioselectivity was excellent (ranging from 98 to >99%). A mechanistic insight into the nature of the activated substrate–catalyst complex was inferred studying the lanthanum complexes with ^{1}H and ^{13}C NMR spectroscopy. Based on these results and on the crystallographic structure of the complex between pybox and $La(OTf)_3$, a stereochemical model is proposed to rationalise the crucial role of the substituent in position 5, suitably placed to blind the *Si*-face of the coordinated reagent.

1. Introduction

Among the reactions giving rise to the formation of a new carbon–carbon bond, the Michael reaction is widely recognised as one of the most important in organic synthesis.[1]

Obviously the enantioselective variant has attracted much interest and the most recent approach involves the use of chiral metal complexes as enantioselective catalysts. From the very early example of Brunner and Hammer,[2] several chiral catalysts have been explored: Cu^{II}/salicyclimines,[3a–c] Co^{II} and Ni^{II}/diamines,[4a,b] Rh^{I}/diphosphanes,[5] and the highly efficient La^{III}–Na^{I}/tris(binaphthoxide) heterobimetallic complexes,[6] very recently modified to obtain a stable, storable and reusable catalyst.[7]

An important variant of the Michael reaction was introduced in 1974 by Mukaiyama and co-workers wherein a silylenol-ether reacts with an α,β-unsaturated carbonyl derivative under conditions of Lewis acid catalysis.[8a–c] Later, the asymmetric version of this reaction was the target of several groups. The first successful results were obtained, on different substrates, with (BINOL)Ti–oxo complex,[9] TADDOL-derived titanium chlorides,[10] and bis(oxazoline)–Cu^{II} complexes.[11] An excellent result in terms of chemical yield and enantioselectivity was achieved by Evans[12] for the reaction of silylketene acetals and alkylidene malonates (ee up to 99% in the presence of a suitably substituted ester), with an optically active catalyst derived from $Cu(SbF_6)_2$ and (*S*)-2,2′-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) (*tert*-Bu-box).

One of the leading targets of the Mukaiyama–Michael reaction is the development of an efficient stereoselective synthesis of chirally pure butenolides. Hence, much efforts have been devoted to study the reaction between 2-(trialkylsilyoxy)furans and alkenoyl-1,3-oxazolin-2-ones, and the best stereoselectivities have been obtained with catalysts derived either from optically active 3,3′-bis(diethylaminomethyl)-1,1′-bi-2-naphthol and scandium triflate,[13a,b] or *tert*-Bu-Box and $Cu(OTf)_2$.[13b,14] The former catalyst gave optimised *anti*/*syn* selectivity (>50:1), but only modest enantioselectivity (68% ee for a good chemical yield), the second one gave an excellent control of enantioselectivity (95% ee), but with an *anti*/*syn* selectivity of (8.5:1) only.

With the experience in C_2-symmetric box as ligands for optically active catalysts of Diels–Alder[15a–d] and 1,3-dipolar nitrone cycloadditions,[16a,b] the Mukaiyama–Michael reaction between 2-(trimethylsilyloxy)furan **1** and (*E*)-3-crotonoyl-1,3-oxazolidin-2-one **2** was studied (Scheme 1) to infer the diastereo-and enantiomeric ratio of the four

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* Corresponding author. Tel.: +39-382-507313; fax: +39-382-507323; e-mail: desimoni@chifis.unipv.it

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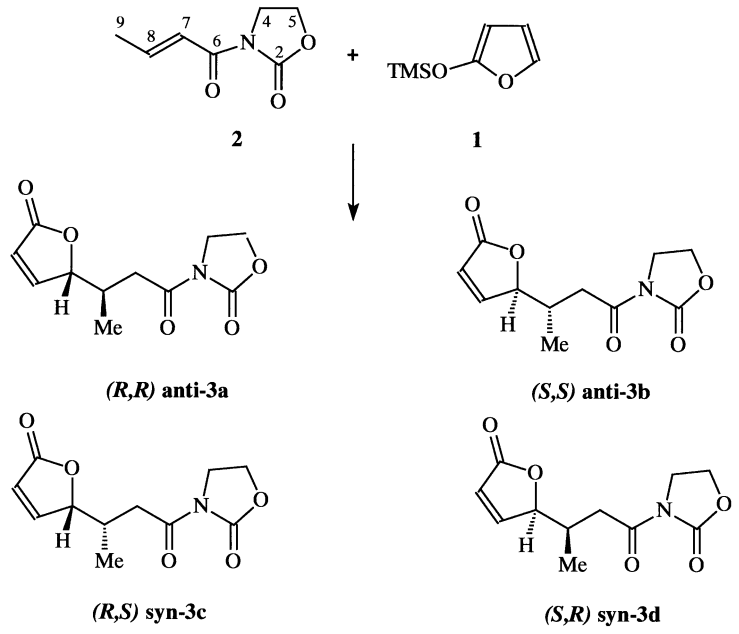
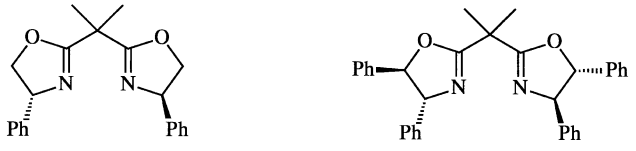


Scheme 1.



4 **5**

Scheme 2.

products: (*R*,*R*)-, (*S*,*S*)-, (*R*,*S*)-, and (*S*,*R*)-3-(2′,5′-dihydro-5′oxo-2′-furyl)butanoyl-1,3-oxazolidin-2-ones, **3a**–**d**, respectively, the former pair having the *anti*, the latter one the *syn* configuration.

2. Results and discussion

2.1. Testing of bis(oxazoline) ligands

The bis(oxazoline) ligands (4′*R*)-phenyl-box **4** and (4′*R*,5′*R*)-diphenyl-box **5** (Scheme 2) were tested together with either perchlorates (P) [Mg^{II}, Ni^{II}, Co^{II}, Zn^{II}] or triflates (T) [Sc^{III} and Ce^{IV}]. The catalysts were prepared in the presence of 4 Å molecular sieves (MS) and the reactions were run at 0°C in CH_2Cl_2.

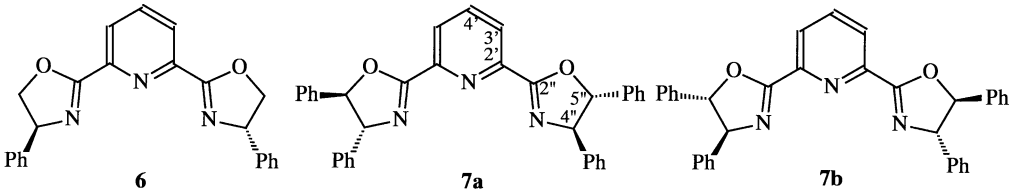
The catalytic conditions were easily achieved since all reactions can be run using low catalyst loadings (5–7 mol%). The results are reported in Table 1 and, whereas chemical yields and *anti* selectivity were in general excellent, the enantioselectivity of the reaction was disappointing.

This screening of box ligands suggests the use of Co^{II} as the best cation to induce enantioselectivity and the *trans* disubstitution on the isoxazoline ring as an important factor to increase stereoselectivity. Even if lanthanides are not the cations of election for complexes with box bidentate ligands,[17] very often they gave **3a**,**b** selectively, and this recommends the choice of rare earths to induce *anti* diastereoselectivity in the catalysed reaction.

Table 1. Mukaiyama–Michael reaction between **1** and **2**, at 0°C in CH_2Cl_2, in the presence of 5 mol% of inorganic salt and chiral ligand **4** or **5**

Entry	Salt[a]	Ligand	Additive[b]	Yield (%)	*Anti*/*syn*	% ee	Configuration
1	MgP	**4**	–	Quant.	82:18	20	*S*,*S*
2	MgP	**4**	MS	Quant.	85:15	20	*S*,*S*
3	NiP.6w	**4**	MS	Quant.	82:18	32	*S*,*S*
4	CoP.6w	**4**	MS	90	>99:1	Racemate	–
5	ZnP.6w	**4**	MS	85	>99:1	31	*S*,*S*
6	ScT.6w	**4**	MS	85	>99:1	Racemate	–
7	CeT.6w	**4**	MS	quant.	>99:1	Racemate	–
8	MgP	**5**	–	95	86:14	10	*S*,*S*
9	MgP	**5**	MS	98	88:12	10	*S*,*S*
10	NiP.6w	**5**	MS	98	85:15	33	*S*,*S*
11	CoP.6w	**5**	MS	97	90:10	55	*S*,*S*
12	ZnP.6w	**5**	MS	90	93:7	13	*S*,*S*
13	ScT.6w	**5**	MS	95	>99:1	Racemate	–
14	CeT.6w	**5**	MS	90	>99:1	Racemate	–

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



Scheme 3.

2.2. Testing of pyridine-bis(oxazoline) ligands

The next step derived from the results obtained in some outstanding papers on the enantioselective Mukaiyama aldol reaction, that has several points in common with the reaction studied in this paper. Evans,[18a–c] Jørgensen,[19] and Kobayashi,[20] studied the reactions between silylenolethers and aldehydes or ketoesters. Box ligands were tested in competition with tridentate bis(oxazolines) pybox and, at least in two cases,[18a,c] the latter ligands were found superior to the former ones.

Thus the known 2,6-bis[(4′*S*)-phenyl-1,3-oxazolin-2′-yl]pyridine **6** (*S*-Ph-pybox) was prepared in accordance to the method reported in the literature,[21] and, taking into account the results derived from the experiments reported in Table 1, which suggested the *trans* disubstitution on the oxazoline ring as an important factor in determining enantioselectivity, 2,6-bis[(4′*R*,5′*R*)-diphenyl-1,3-oxazolin-2′-yl]pyridine **7a** (*R*,*R*-diPh-pybox) was synthesised[22] (Scheme 3).

2,6-Pyridinecarbonyl dichloride was made to react with (1*S*,2*R*)-2-amino-1,2-diphenylethanol, the resulting bis-(amide) **8a** was converted into the dichloro derivative **9a** by treatment with $SOCl_2$, and the ring closure, under basic conditions, occurred with inversion of configuration (Scheme 4).[23]

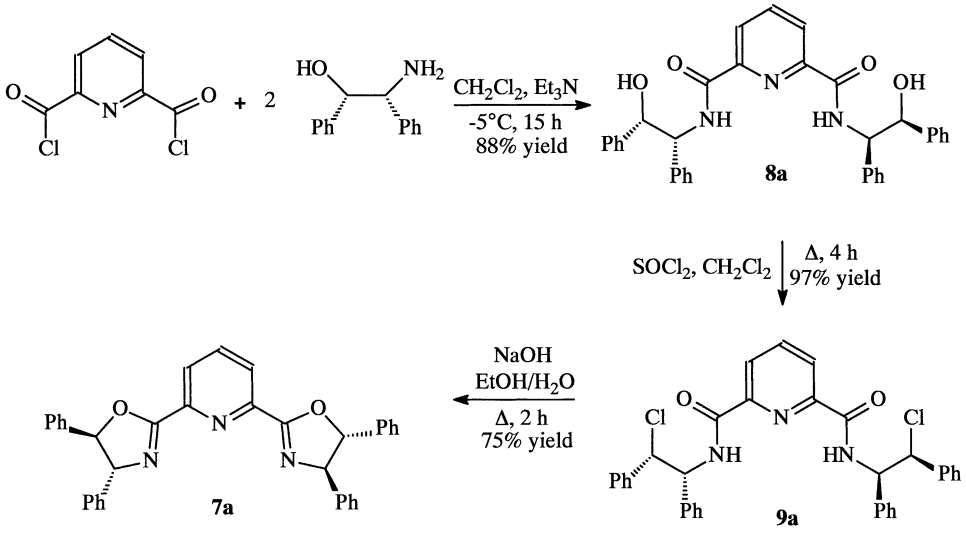
From the similarly available (1*R*,2*S*)-2-amino-1,2-diphenylethanol, following the same sequence of reactions, the enantiomer *S*,*S*-diPh-pybox **7b** (Scheme 3) was obtained.

Since the complexes with pybox ligands are mainly tetra- or hexacoordinated,[24] Mg^{II} and Co^{II} perchlorates and the rare earths triflates were screened. The reason of the first choice derives from the possibility of the magnesium cation to assume either a tetrahedral or octahedral coordination,[15a,b] the lanthanide choice was the consequence of their use with pybox ligands reported in the literature.[25]

Table 2 summarises the results obtained with catalysts derived from pybox **6** and **7a**.

The *classical* Ph-pybox ligand **6** (entries 1–8) induces a good level of enantioselection, the best result being 63 and 64% ee obtained with La^{III}, Yb^{III} and Eu^{III} (entries 5–7), but the sense of the enantioselection is difficult to predict if the same chiral ligand may give different enantiomers with different cations: Mg^{II}, Co^{II} and, among trivalent lanthanides, Eu^{III}, favour the formation of **3b**, all other trivalent lanthanides and Ce^{IV} the formation of the opposite enantiomer **3a**. This can be mentioned as a further example of reversal of selectivity, which had been observed with the same configuration of the ligand, but changing either the substituent of the ligand,[25–27] or the cation, or its coordination number.[15a,b,28]

Entirely different are the results obtained with *R*,*R*-diPh-pybox **7a** as ligand (entries 9–16). If magnesium perchlorate gave a result that is comparable, for chemical yield, diastereo- and enantioselectivities (ee 78%, entry 9), with those already reported in the literature, better results were obtained when lanthanide cations were tested. These reactions (entries 12–16) gave a quantitative yield of *anti*



Scheme 4.

Table 2. Mukaiyama–Michael reaction between **1** and **2**, at 0°C in CH_2Cl_2, in the presence of 5 mol% of inorganic salt and chiral ligand **6** or **7a**

Entry	Salt[a]	Ligand	Additive	Yield (%)	*Anti*/*syn*	% ee	Configuration
1	MgP	**6**	–	94	82:18	40	*R*,*R*
2	MgP	**6**	MS	88	95:5	49	*R*,*R*
3	CoP.6w	**6**	MS	85	>99:1	15	*R*,*R*
4	ScT.6w	**6**	MS	Quant.	99:1	10	*S*,*S*
5	LaT.6w	**6**	MS	Quant.	95:5	63	*S*,*S*
6	EuT.6w	**6**	MS	97	85:15	64	*R*,*R*
7	YbT.6w	**6**	MS	Quant.	98:2	64	*S*,*S*
8	CeT.6w	**6**	MS	95	90:10	50	*S*,*S*
9	MgP	**7a**	–	Quant.	>99:1	78	*R*,*R*
10	MgP	**7a**	MS	Quant.	99:1	52	*R*,*R*
11	CoP.6w	**7a**	MS	Quant.	93:7	20	*R*,*R*
12	ScT.6w	**7a**	MS	Quant.	>99:1	83	*R*,*R*
13	LaT.6w	**7a**	MS	Quant.	>99:1	>99	*R*,*R*
14	EuT.6w	**7a**	MS	Quant.	>99:1	98	*R*,*R*
15	YbT.6w	**7a**	MS	Quant.	>99:1	92	*R*,*R*
16	CeT.6w	**7a**	MS	Quant.	>99:1	>99	*R*,*R*

[a] Mg and Co are divalent cations, Sc, La, Eu, and Yb trivalent cations, Ce is tetravalent cation, P is perchlorate, T is triflate, w is water.

adducts; three of them gave excellent ee and, among these, both Ce^{IV} and La^{III} satisfy the selective formation of **3a** as a single stereoisomer (quantitative yield, de >98%, ee >99%).

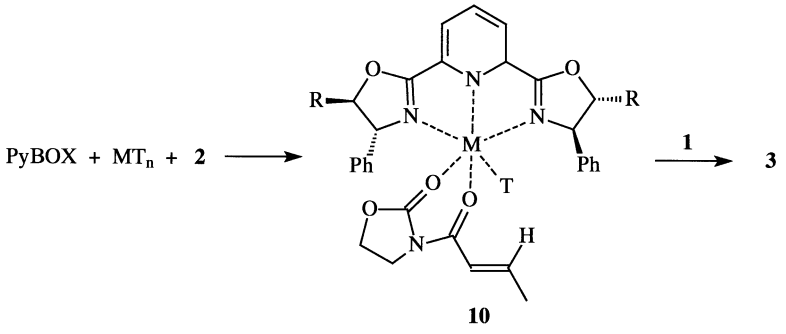
2.3. Reaction mechanism

The catalytic cycle for the pybox/lanthanide cations-catalysed Mukaiyama–Michael reaction should involve the chelation of the crotonoyl-oxazolidinone **2** onto the rare earth cation/pybox complex to give the activated substrate–catalyst complex **10** (Scheme 5), followed by the highly selective addition of **1** to **10**. The catalytic cycle is completed by a ligand substitution where **2** displaces complexed **3** to give again **10**.

The involvement of **10** as reacting complex having a ratio (1:1:1) between cation, reagent and chiral ligand was confirmed by the linear relationship between the ee of the Mukaiyama–Michael adduct and the optical purity of the pybox ligand (see Section 4) and its structure was studied through NMR spectroscopy, by dissolving equimolecular amounts of **2** and **7a** in CD_3CN.

The ^1H and ^{13}C NMR spectra of the mixture (Fig. 1a and Table 3) were registered, and the ^{13}C chemical shift values were assigned through DEPT and heteronuclear shift correlation experiments. When 1 equiv. of $La(OTf)_3$ was added into the NMR tube, the inorganic salt slowly dissolved and the spectra were again registered. The ^1H and ^{13}C NMR spectra (Fig. 1b and Table 3) suggest not only the formation of complex **10**, but also allow some insight into its structure. Crotonoyl oxazolidinone **2** participates to the formation of **10** in the *s-cis* conformation since both 2C and 6C absorptions at 154.1 and 164.7 δ (the carbon peaks of the carbonyl groups) disappear in the ^{13}C spectrum of the chelated species (Table 3), and 7H looses the deshielding of the oxazolidinone carbonyl group, moving upfield in the ^1H NMR spectrum from 7.23 to 6.46 δ (Fig. 1). Furthermore, the behaviour of **2** as a bidentate ligand is consistent with the direction of the chemical shift perturbations, in accordance with the literature data,[29a,b] and also with the NOESY spectrum that shows nOes between 7H and both the oxazolidinone 4H and the methyl group.

The participation of diPh-pybox **7a** as a tridentate ligand in **10** is supported by the strong downfield shift of both the pyridine 4′C and the oxazoline 2″C and by the strong deshielding of the pyridine 4H, from 8.10 δ (free) to 8.50 δ (chelated) (Fig. 1). Whereas **7a** is strongly bound to the cation, **2** exhibit fast exchange between chelated and unchelated species. If **2**, **7a** and $La(OTf)_3$ in the ratio (3:1:1) are mixed, the ^{13}C NMR spectrum (Table 3), registered at +70°C, shows bands at 63.7, 121.5 and 150.3 δ (assigned to 5C, 7C and 8C—Fig. 2a). These singlets are nicely splitted at −30°C into absorptions at 63.2, 64.4, 120.4, 121.5, 146.9 and 157.2 δ, respectively, the upfield absorption of each couple being due to the uncomplexed **2**,



Scheme 5.

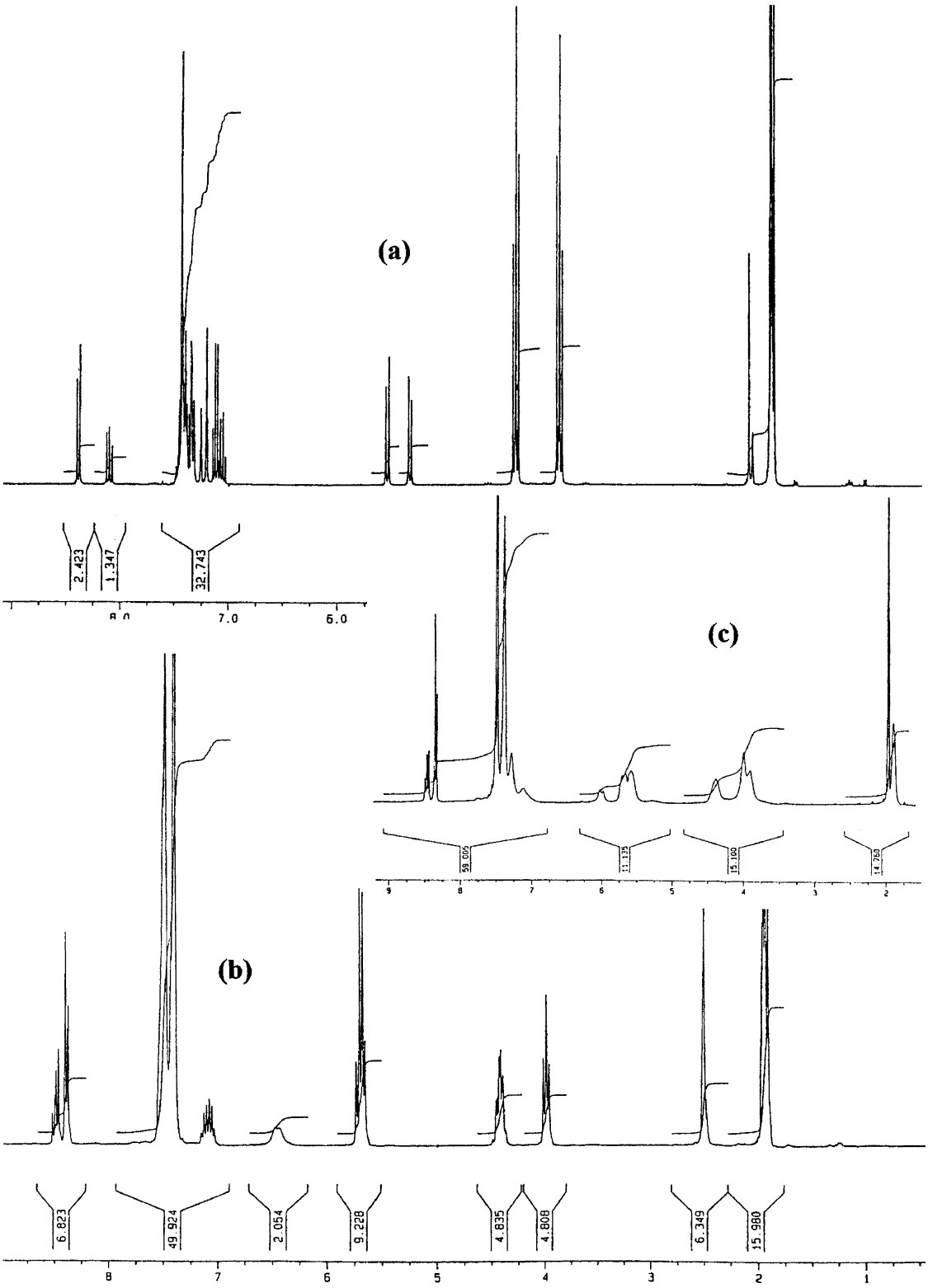


Figure 1. ^{1}H NMR spectra of: (a) equimolecular amounts of **2** and **7a** in CD_3CN; (b) 1 equiv. of lanthanum triflate added to (a), registered at +70°C; (c) the same as (b), but registered at −30°C.

the downfield one to the chelated **2** (Fig. 2b). The carbon chemical shifts of the chelated **2** are nearly coincident with those of the complex obtained from **2** and lanthanium triflate in the ratio (3:1) reported in Table 3.

In conclusion the NMR spectra demonstrate the organisation of three nitrogen and two oxygen atoms, belonging to **7a** and **2**, respectively, around the lanthanum cation in **10**. What lacks to have a direct evidence of the structure of **10** is its crystal structure or, eventually, some other information allowing to propose number and type of coordination around the La^{III} cation. Any attempt to prepare a crystal of

Table 3. ^{13}C NMR spectra of lanthanium triflate complexes between **2** and **7** in CD_3CN

Carbon atoms[a]	**2**, **7a** free[b]	$La(OTf)_3$ complexes						**11**[c] **7b** and LaT	**2** and LaT[d]
		e	b,e	f	b,f	g	h		
2	154.1	–	–	–	–	154.9	155.7	–	155.8
4	42.4	43.8	+1.4	44.2	+1.8	43.5	43.6	–	43.5
5	62.2	64.0	+1.8	64.7	+2.5	63.2, 64.4	63.7	–	63.6
6	164.7	–		–		165.7	166.5	–	166.6
7	121.6	120.5	−1.1	120.0	−1.6	120.4, 121.5	121.5	–	121.0
8	145.3	[i]	[i]	157.3	+12.0	146.9, 157.2	150.3	–	151.1
9	17.4	18.1	+0.7	18.9	+1.5	18.6	18.0	–	17.6
2′	146.7	144.9	−1.8	144.8	−1.9	144.8	145.0	144.7	–
3′	126.4	127.8	+1.4	128.1	+1.7	128.5	128.4	128.7	–
4′	137.9	143.1	+5.2	143.4	+5.5	143.5	143.1	143.4	–
2″	162.5	167.6	+5.1	167.6	+5.1	167.9	167.7	167.5	–
4″	78.4	77.3	−1.1	77.1	−1.3	77.2	77.2	77.3	–
5″	89.2	93.5	+4.3	93.1	+3.9	92.9	93.3	93.4	–
[j]	139.7	137.8	−1.9	137.8	−1.9	137.6	137.7	137.8	–
[j]	141.5	140.1	−1.4	139.8	−1.7	139.4	140.0	139.9	–

[a] Numbering in accordance to Schemes 1 and 3.
[b] Registered at +23°C.
[c] **7b** and $La(OTf)_3$, ratio (1:1) at +23°C, the crystal structure of this complex is shown in Fig. 3.
[d] **2** and $La(OTf)_3$, ratio (3:1) at +70°C.
[e] **2**, **7a** and $La(OTf)_3$, ratio (1:1:1) at +70°C.
[f] As in b, but at −30°C.
[g] **2**, **7a** and $La(OTf)_3$, ratio (3:1:1) at −30°C.
[h] As in f, but at +70°C.
[i] δ impossible to determine at +70°C.
[j] Phenyls quaternary carbons.

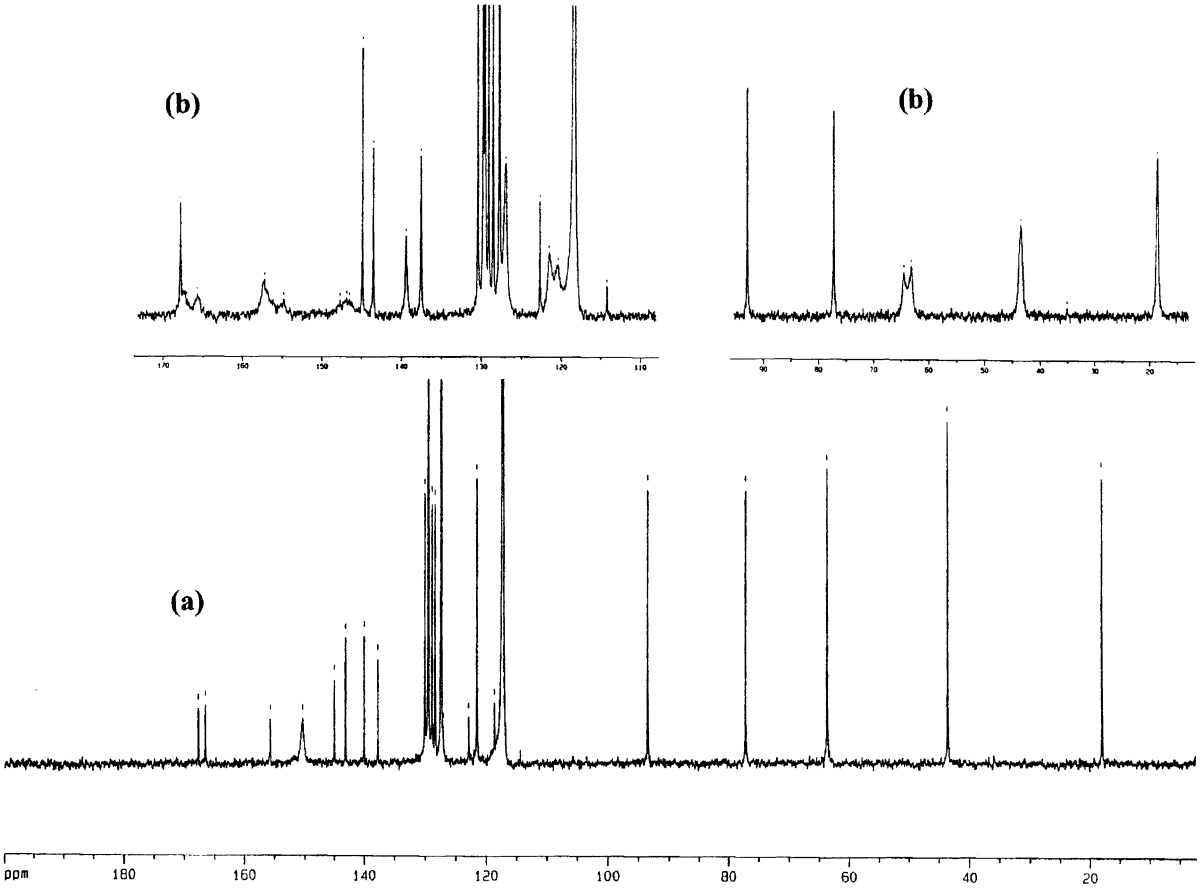


Figure 2. ^{13}C NMR spectra of: (a) **2**, **7a** and lanthanum triflate in the ratio (3:1:1) in CD_3CN, registered at +70°C; (b) the same as (a), but registered at −30°C.

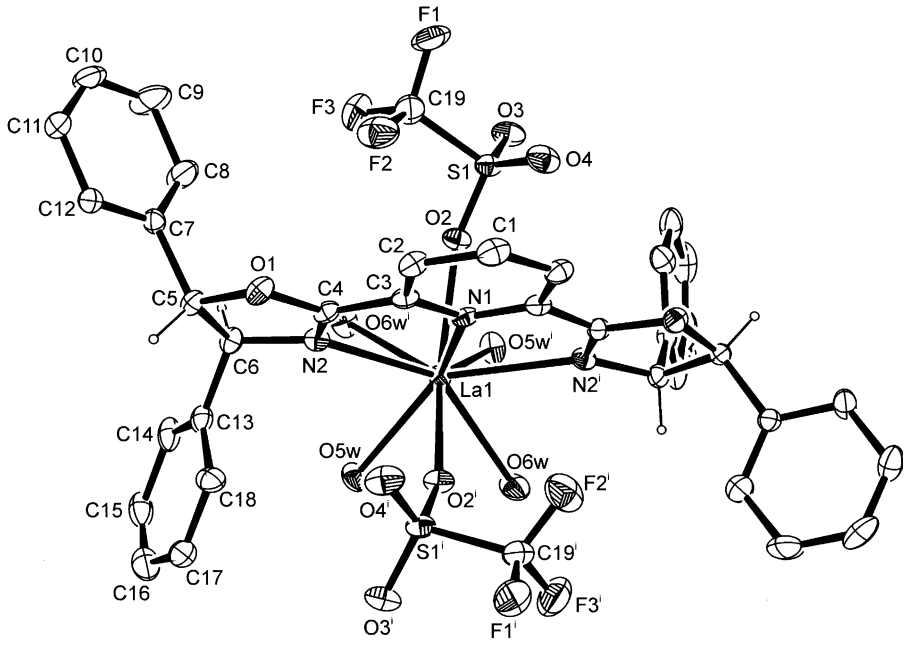


Figure 3. ORTEP view of **11**, [La^{III}(**7b**)](CF$_3$SO$_3$)$_2$(H$_2$O)$_4$ molecular cation, with 20% ellipsoids probability displacement ellipsoids. The asymmetric unit, the triflate anions, the water molecules and all N atoms have been labelled. Selected bond distances: La1–N1 2.714(8) Å; La1–N2 2.680(6) Å; La1–O2 2.505(6) Å; La1–O5w 2.537(7) Å; La1–O6w 2.551(8) Å. Selected angles: N1–La1–N2 61.5(1)°; N1–La–O2 68.8(1)°; N1–La1–O5w 132.5(2)°; N1–La1–O6w 119.9(2)°; N2–La1–N2^i 123.0(3)°; N2–La1–O2 77.2(2)°; N2–La1–O5w 83.4(2)°; N2–La1–O5w^i 139.5(2)°; N2–La1–O6w 142.0(2); N2–La1–O6w^i 71.8(2)°; O2–La1–O5w 141.0(2); O2–La1–O5w^i 73.2(2)°; O2–La1–O6w 134.8(3)°; O2–La1–O6w^i 69.9(3)°; O5w–La1–O5w^i 95.0(3)°; O5w–La1–O6w 71.2(3)°; O5w–La1–O6w^i 69.4(3); O6w–La1–O6w^i 120.2(5)°. Symmetry codes: (i) $x-y$, $-y$, $-z+5/3$.

10 was unsuccessful, but it was possible to obtain a crystal of the complex **11**, between **7b** and La(OTf)$_3$, whose X-ray structure is reported in Fig. 3 and its ^{13}C NMR spectrum is listed in Table 3.

This result is important in as much as, for the first time, a pybox complex[24] with a lanthanide cation was obtained, that can elucidate the basic coordination geometry of these complexes, and provide a stereochemical model for **10**. The first consideration concerns the number of pybox ligands involved in the coordination. Probably for steric reasons, **11** is a (1:1) ligand/metal complex, different from the (2:1) Ph-pybox/copper complexes.[18a] In addition to three nitrogen atoms deriving from **7a**, La^{III} coordinates two triflate ions (the third anion is free) and four water molecules, thus giving a total coordination number of nine. The triflate ligands have positions similar to those in the complex between **6** and Sn(OTf)$_2$ which is a useful catalyst for enantioselective Mukaiyama–aldol reactions.[30] A coordination number of La^{III} in the range 8–10 is not unusual[31a,b] and water takes a part to this organisation. The necessary participation of **2**, the intrinsic overcrowding around La^{III} in **10**, and its formation in the presence of MS, makes highly probable the loss of the majority of the ancillary ligands of **11** in the formation of **10**.

The nucleophilic addition of trimethylsilyloxyfuran **1** to **10** determines the stereoselectivity of the entire process. The

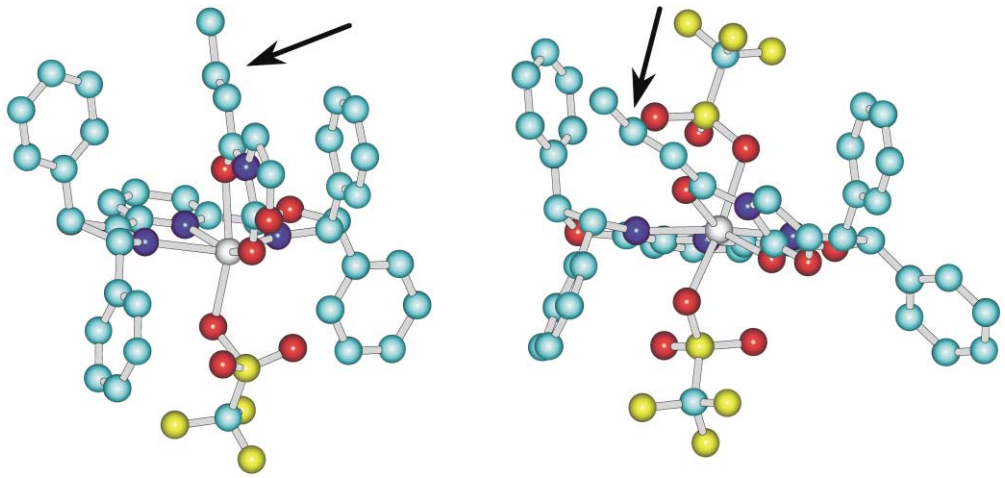


Figure 4. Proposed structures of **10**: (a) with an octahedral configuration, a triflate ion is one apical ligand; (b) with seven as coordination number.

anti selectivity observed is the result of a preference for the less hindered transition state with the hydrogen atoms (H-5 furan and H-β crotonoyl) *anti*, a disposition which minimises the number of repulsive *gauche* interactions, relative to the more hindered transition state with the same hydrogen atoms *gauche*.

To rationalise the observed enantioselectivity, two models of **10**, with six and seven as coordination number, can be proposed by addition of **2**, in the *s-cis* conformation, to **11** (Fig. 4).

As may be observed, trimethylsilyloxyfuran should attack the more easily accessible *Re*-face of the double bond of both structures to give the formation of (*R*,*R*) *anti*-**3a** since the *Si*-face results blinded by the (5′*R*)-phenyl group. For the first time the enantioselective control of a reaction catalysed by a pybox-based catalyst is not only a function of the substituent in position 4 of the oxazoline ring. The lack of the crucial substituent in position 5 makes **6** a less efficient chiral ligand than **7a**.

3. Conclusions

This paper reports a study of the Mukaiyama–Michael reaction between (*E*)-3-crotonoyl-1,3-oxazolidin-2-one **2** and 2-trimethylsilyloxyfuran **1**, which can be easily catalysed by different chiral complexes prepared by inorganic perchlorates or triflates and optically active ligands. With lanthanide cations and tridentate *R*,*R*-diPh-pybox the reaction results completely stereospecific and only the *anti* product with the (*R*,*R*) configuration is obtained. This is a significant improvement of the efficiency of the catalysts if these results are compared with those previously reported in the literature.

Some interesting results of the tailor-made catalyst prepared from lantanide triflates and diPh-pybox ligands can be emphasised. Good cations are La^{III}, Ce^{IV} and Eu^{III}. The same result is obtained with two cations (La^{III} and Ce^{IV}) that have identical electronic configuration but different cation size (1.032 and 0.87 Å for six-coordinated species, respectively)[32] and different Lewis acid character. This seems to suggest that the ability to organise at least five ligands, three nitrogen and two oxygen atoms, is the important factor to induce stereoselectivity.

If the efficiency of the 4,5-diphenyl substituted pybox-based catalysts is compared with that of the catalysts derived from 4-phenyl substituted pybox ligand, the enantioselectivity strongly ameliorates with the former ligand. Thus, the substituent in position 5 has a stronger effect in determining the face selectivity of the attack than that in position 4, even if this is closer to the cation.

Probably the reason why a Michael reaction is not easily catalysed enantioselectively is because a catalyst suitable to blind a face of the coordinated reagent is difficult to design. At least for the reaction discussed in this paper, 2,6-bis[(4′*R*,5′*R*)-diphenyl-1,3-oxazolin-2′-yl]pyridine **7a** is the tailor-made ligand for it.

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 MHz, respectively; IR spectra were recorded on a Perkin Elmer 881 spectrophotometer; optical rotations were measured at room temperature 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; 2-(trimethylsilyloxy)furan (**1**) was the Aldrich reagent used without any further purification; (*E*)-3-crotonoyl-1,3-oxazolidin-2-one (**2**) was prepared following the literature method.[15c,33]

4.2. Preparation of the chiral ligands

4.2.1. 2,2-Bis{2-[(4*R*)-phenyl-1,3-oxazolinyl]}propane (4). This compound was a commercial Aldrich product.

4.2.2. 2,2-Bis{2-[(4*R*,5*R*)-diphenyl-1,3-oxazolinyl]}propane (5). This compound was prepared as described in the literature.[23]

4.2.3. 2,6-Bis[(4′*S*)-phenyl-1,3-oxazolin-2′-yl]pyridine (6). This compound was prepared as described in the literature.[21]

4.2.4. 2,6-Bis[(1*R*,2*S*)*N*,*N*′-2-hydroxy-1,2-diphenylethyl]-pyridinedicarboxamide (8a). Pyridine-2,6-dicarbonyl dichloride (1.15 g, 5.64 mmol), dissolved in anhydrous dichloromethane (20 mL), was added dropwise to a cooled (−5°C) and stirred mixture of (1*S*,2*R*)-2-amino-1,2-diphenylethanol (2.5 g, 11.7 mmol) and triethylamine (2.9 g, 29 mmol) in anhydrous dichloromethane (40 mL). The reaction was stirred at room temperature overnight. The white precipitate was filtered and washed with water to give **8a** (2.6 g) and a second crop (0.18 g, total yield 88%) of the same product was obtained from the evaporated mother liquors after crystallisation of the residue from acetic acid; mp 276–277°C; $[\alpha]_D^{20}=+5.7$ (c=1.1 in dimethylformamide); IR (Nujol) ν 3410, 3440, 1655 cm^{-1}; ^1H NMR (300 MHz, [D$_6$]DMSO, 25°C, TMS): δ 5.14–5.25 (m, 4H; N–CH–CH–O), 5.85 (d, ^3J(H,H)= 4.3 Hz, 2H; OH), 7.1–7.5 (m, 20H), 8.05–8.13 (m, 3H; H pyridine), 9.00 (d, ^3J(H,H)=8.5 Hz, 2H; NH); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO) δ 59.3, 74.7, 125.0, 127.0, 127.4, 128.0, 128.8, 139.9, 140.0, 143.1, 149.2, 162.5. Elemental analysis calcd (%) for $C_{35}H_{31}N_3O_4$ (557.6): C 75.38, H 5.60, N 7.54; found C 75.31, H 5.48, N 7.62.

4.2.5. 2,6-Bis[(1*R*,2*S*)*N*,*N*′-2-chloro-1,2-diphenylethyl]-pyridinedicarboxamide (9a). To a suspension of diamide **8a** (1.4 g, 2.5 mmol) in anhydrous dichloromethane (5 mL), a solution of $SOCl_2$ (3 mL=4.8 g, 40 mmol) in the same solvent (3 mL) was added dropwise, and the mixture was refluxed 3 h. The solvent and excess $SOCl_2$ were removed under vacuum and water was added to the residue. **9a** was obtained as a white solid (1.45 g, yield 97%), pure enough for the next step. It crystallised from ethyl acetate as small

white crystals: mp 222–223°C; $[\alpha]_D^{20}$=+252.0 (c=0.5 in chloroform); IR (Nujol) ν 3410, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ 5.60 (d, ^3J(H,H)= 4.5 Hz, 2H; CHCl), 5.70 (dd, ^3J(H,H)=4.5, 9.5 Hz, 2H; CHN), 7.1–7.3 (m, 20H), 8.05 (t, ^3J(H,H)=7.5 Hz, 1H; 4H pyridine), 8.35 (d, ^3J(H,H)=7.5 Hz, 2H; 3,5H pyridine), 8.78 (d, ^3J(H,H)=9.5 Hz, 2H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 58.6, 67.0, 125.4, 127.8, 128.0, 128.1, 128.3, 128.6, 135.6, 136.8, 139.3, 148.4, 162.2. Elemental analysis calcd (%) for $C_{35}H_{29}Cl_2N_3O_2$ (594.5): C 70.71, H 4.92, N 7.07; found C 70.56, H 5.04, N 6.98.

4.2.6. 2,6-Bis[(4*R*,5*R*)-diphenyl-1,3-oxazolin-2-yl]pyridine (7a). To a suspension of **9a** (0.89 g, 1.5 mmol) in ethanol (20 mL), an aqueous solution of 2N NaOH (10 mL) was added and the mixture was refluxed untill the starting product disappeared (about 3 h—TLC, eluant cyclohexane/ethyl acetate (7:3)). The hot suspension was filtered and the white solid, washed with water, gave pure **7a** (0.59 g, yield 75%). It crystallised from ethyl acetate as white crystals: mp 201–202°C; $[\alpha]_D^{20}$=+41.4 (c=0.5 in chloroform) (**7b**, $[\alpha]_D^{20}$=−41.4); HPLC analysis using a Chiralpak AD column with hexane/2-propanol (2:1) as eluant (0.7 mL min^{-1}), retention time 16.9 min (**7b**, same conditions, retention time 13.8 min); IR (Nujol) ν 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ 5.35 (d, ^{3}J(H,H)=8.5 Hz, 2H; CHN), 5.55 (d, ^3J(H,H)= 8.5 Hz, 2H; CHO), 7.3–7.5 (m, 20H), 8.00 (t, ^3J(H,H)= 9.5 Hz, 1H; 4H pyridine), 8.42 (d, ^3J(H,H)=9.5 Hz, 2H; 3,5H pyridine); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 78.9, 89.9, 126.1, 126.5, 126.8, 127.8, 128.5, 128.7, 137.3, 139.7, 141.2, 147.0, 162.9; elemental analysis calcd (%) for $C_{35}H_{27}N_3O_2$ (521.6): C 80.59, H 5.22, N 8.06; found C 80.66, H 5.13, N 8.15.

4.2.7. General procedure for the enantioselective Mukaiyama–Michael reaction between 1 and 2. (*E*)-3-Crotonoyl-1,3-oxazolidin-2-one (**2**) (0.039 g, 0.25 mmol), the chiral ligand box (**4**, **5**) or pybox (**6**, **7**) (0.013 mmol), the inorganic perchlorate or triflate (0.013 mmol) and, when required, the molecular sieves (0.040 g) were added to anhydrous CH_2Cl_2 (0.5 mL) at ambient temperature in a rubber septum sealed vial, and the mixture was stirred and then cooled at 0°C. After 1 h (trimethylsilyloxy)furan (**1**) (0.047 g=50 μL, 0.30 mmol) was added with a microsyringe and stirring at 0°C was continued for 3 days. The reaction was decomposed in water, extracted with CH_2Cl_2 and dried. If TLC (cyclohexane/ethyl acetate 6:4 as eluant) showed some unreacted starting product **2**, the yield of the reation (Tables 1 and 2) was determined by ^1H NMR from the ratio 3:2, taking the methyl doublets at 1.09, 0.94 and 1.95 δ to determine **3a**,**b** and **3c**,**d** vs **2**, respectively. In each case the standard analysis of the reaction mixture was performed by HPLC analysis using a Chiralpak AD column with hexane/2-propanol (2:1) as eluant (0.5 mL min^{-1}). The average retention times, 68 and 75 min for (*R*,*R*) *anti*-**3a** and (*S*,*S*) *anti*-**3b**, respectively; 57 and 82 min for *syn*-**3c**,**d**, largely depend from the small variations of the solvents and were checked on the products of a reaction run under non-enantioselective conditions (literature: 42.5 and 49.6 min for **3a** and **3b**, respectively).[13b] When the ligand was **7**, to avoid its large absorption, the CH_2Cl_2 residue was chromatographed on silica gel (cyclohexane/AcOEt 3:7), the ligand separated first and the products mixture was submitted to the previously described HPLC analysis. The adducts **3** can be isolated from a reaction run on 1.00 mmol scale by column chromatography on silica gel 230–400 mesh (cyclohexane/AcOEt 3:7 as eluant) and, depending on the diastereomeric composition of the reaction mixture, pure **3a**,**b** or this in admixture with **3c**,**d** was isolated. The *anti*-**3a**,**b** has ^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ 1.09 (d, ^3J(H,H)=6.9 Hz, 3H; Me), 2.45–2.55 (m, 1H; CHMe), 2.85 (dd, ^3J(H,H)=7.35, 16.9 Hz, 1H; CHCO), 3.15 (dd, ^3J(H,H)=5.9, 16.9 Hz, 1H; CHCO), 4.00–4.05 (m, 2H; NCH_2), 4.40–4.45 (m, 2H; OCH_2), 5.02 (ddd, ^3J(H,H)=1.5, 2.0, 6.4 Hz, 1H; 5′H), 6.15 (dd, ^3J(H,H)= 2.0, 5.8 Hz, 1H; 3′H), 7.59 (dd, ^3J(H,H)=1.5, 5.8 Hz, 1H; 4′H). This spectrum is in accordance with that reported in the literature for **3a**.[13b] Some absorptions can be assigned to the *syn*-**3c**,**d**, ^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ 0.94 (d, ^3J(H,H)=7.0 Hz, 3H; Me), 2.60–2.70 (m, 1H; CHMe), 2.90 (dd, 1H; CHCO), 5.18–5.20 (m, 1H; 5′H), 6.18 (dd, ^3J(H,H)=3.7, 5.8 Hz, 1H; 3′H), 7.47 (dd, ^3J(H,H)=1.5, 5.8 Hz, 1H; 4′H).

4.3. Mukaiyama–Michael reaction between 1 and 2 carried out with different enantiomeric purity of the catalyst from lanthanium triflate and 7

From reactions carried out following the general procedure described earlier but with mixtures of **7a**/**7b** having known enantiomeric purities of 100, 80, 60, 40 and 20%, **3a** was obtained with ee of ≥99.5, 72, 60, 43 and 20%, respectively. The relationship between the $ee_{product}$ and ee_{ligand} was linear (r=0.993).

4.3.1. X-Ray data collection and processing of the (1:1) 7b/lanthanium triflate complex (11). Lanthanum triflate (0.039 g, 0.066 mmol) was added to a solution of **7b** (0.035 g, 0.066 mmol) in acetonitrile (0.5 mL) at ambient temperature. The colourless solution was let aside for 1 week then toluene was added until incipient turbidity. Within 1 week colourless crystals of **11** separated that were filtered: mp about 200°C after softening; ^1H NMR (300 MHz, CD_3CN, 25°C, TMS): δ 5.62 (d, ^3J(H,H)= 7.8 Hz, 2H; CHN), 5.79 (d, ^3J(H,H)=7.8 Hz, 2H; CHO), 7.4–7.5 (m, 20H), 8.41 (d, ^3J(H,H)=8.5 Hz, 1H; 3H pyridine), 8.42 (d, ^3J(H,H)=6.8 Hz, 1H; 3′H pyridine), 8.52 (dd, ^3J(H,H)=6.8, 8.5 Hz, 1H; 4H pyridine); ^{13}C NMR reported in Table 3.

X-Ray data were obtained on an Enraf–Nonius CAD4 diffractometer. Calculations were performed with the WinGX-97 software.[34] The structure was solved by direct methods (SIR92)[35] and refined by full-matrix least-squares using SHELXL-97[36] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were inserted in calculated positions with isotropic displacement parameters proportional to those of their neighbouring atoms. Atomic scattering factors were taken from *International Tables for X-ray Crystallography*.[37] Diagrams of the molecular structures were produced by the ORTEP program.[38] Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-156651.

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