In Search of *exo*-Selective Catalysts for Enantioselective 1,3-Dipolar Cycloaddition between Acryloyloxazolidinone and Diphenylnitrone

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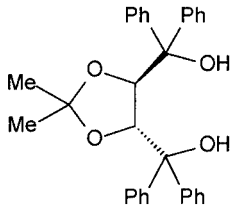
1,3-Dipolar cycloaddition (1,3-DC) between acryloyloxazolidone **1** and diphenylnitrone **2** was catalysed by complexes of three (4*R*)-phenylbis(oxazolines) [box = bis(oxazolines)] – either 5-unsubstituted (**8a**), or 4,5-*cis*- and -*trans*-diphenyl-substituted (**8b**, **8c**) – with several perchlorates of divalent cations. Normal *endo* selectivity was obtained with Mg^{II}- and Ni^{II}-**8a** catalysts, and the formation of the *endo* enantiomers (3′*R*,4′*S*)- or (3′*S*,4′*R*)-**3** depended upon the presence of 4-Å molecular sieves (MS). Different results were observed with the catalysts derived from this ligand and Co^{II} or Zn^{II}, which gave good levels of *exo* enantioselectivity, with 84% *ee* of (3′*S*,4′*S*)-**4**. When **8c** was used as ligand, Mg^{II}, Co^{II} and Ni^{II} give *exo*-selective catalysts, and the enantiomer (3′*R*,4′*R*)-**4** was obtained with good *dr* and excellent *ee*. The unknown absolute configuration of the *exo* enantiomers **4** was established by structure correlation with one *exo* diastereoisomer obtained from the 1,3-DC between **2** and (*S*)-3-acryloyl-4-benzyl-2-oxazolidinone (**10**). The flexibility of the catalysts derived from box **8a** and **8c**, all with 4*R* configuration, is remarkable since a change in the cation allows the *endo*-**3** or the *exo*-**4** enantiomers to be obtained enantioselectively with *ee*s in the 84–99% range.

Introduction

1,3-Dipolar cycloaddition (1,3-DC) between alkenes and nitrones is probably the best method by which to synthesise oxazolidines, useful precursors in the total synthesis of complex natural products deriving from 1,3-amino alcohols.[1] The synthetic relevance of this reaction has been further expanded by developments achieved in asymmetric catalysis, which allow the organic chemist to prepare almost enantiopure cycloadducts.[2]

1,3-DC between acryloyloxazolidinone **1** and diphenylnitrone **2** is a good model with which to study the potential to control three different levels of selectivity (regio-, stereo-, and enantioselectivity), since the uncatalysed reaction proceeds with the formation of all the possible regio- and stereoisomers, each as a pair of enantiomers (Scheme 1).[3]

When the 1,3-DC between **1** and **2** is run under catalysed conditions [$TiCl_2(i\text{PrO})_2$], the reaction becomes highly regioselective (adducts **3** and **4** are obtained with more than 95% selectivity), but the stereoselectivity is negligible, since the *endo*:*exo* ratio is about 50:50.[3] Increased *endo* selectivities are usually observed with the use of asymmetric catalysts involving TADDOL,[3] bis(oxazolines) (box),[4–6] and bis(oxazolinyl)pyridine (pybox)[7–8] as chiral ligands.



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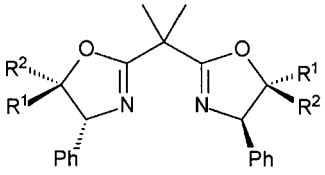
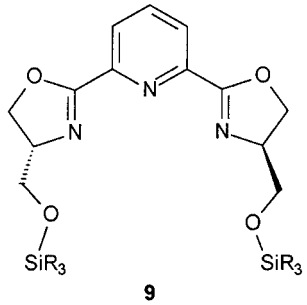


8a: $R^1 = R^2 = H$
8b: $R^1 = H$; $R^2 = Ph$
8c: $R^1 = Ph$; $R^2 = H$



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While TADDOL **7** showed low to moderate enantioselectivities, with *endo*/*exo* ratios depending upon the Ti^{IV} counter-ion, the pybox **9**/Ni^{II} catalysts are highly *endo*-selective and almost completely enantioselective.

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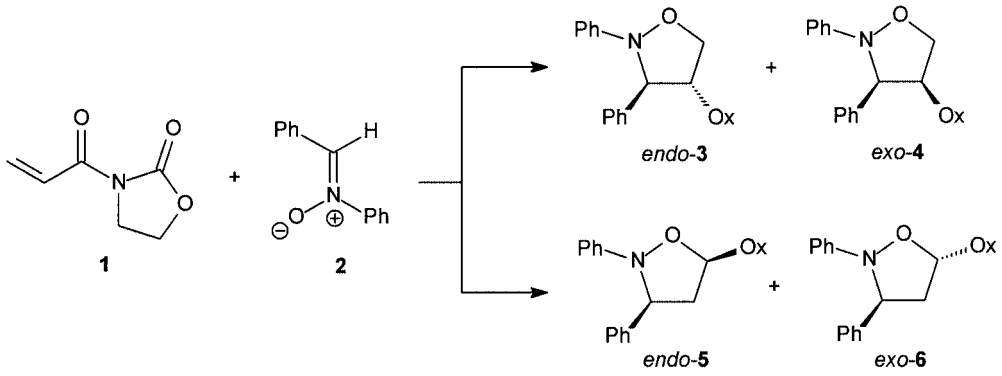


Scheme 1

When the chiral catalyst was based on (4*R*)-phenyl-box **8a**, the choice of the Mg^{II} counter-ion allowed the enantioselective synthesis of both *endo* enantiomers: use of MgI_2 as Lewis acid gave (3′*R*,4′*R*)-**3** as the preferred enantiomer with good stereo- and enantioselectivity,[4] while the use of $Mg(OTf)_2$ with the same (4*R*)-phenyl-box **8a** furnished the opposite (3′*S*,4′*S*)-**3** enantiomer as favoured cycloadduct, again with good *ee*.[5,9]

Catalysis with *exo* selectivity is ordinarily found in 1,3-DC involving crotonoyloxazolidin-2-one as dipolarophile,[4,10−13] or even better when succinimide[14] or pyrazolidinone[15] are used as auxiliaries instead of oxazolidinone. To have good levels of enantioselectivity with acryloyloxazolidin-2-one is much more difficult: the only example of *exo*-selective cycloaddition involving **1** as dipolarophile was observed when the reaction was catalysed by [**8a**-$Zn(ClO_4)_2$][6] (*exo*-**4**/*endo*-**3** was 73:27 with 84% *ee* of **4**), and the absolute stereochemistry of **4** has not yet been reported in the literature.

The theme of this paper is the search for box-based catalysts capable of giving the pair of *exo* enantiomers **4** stereoselectively.

Results

The 1,3-DC reaction between acryloyloxazolidinone **1** and diphenylnitrone **2** was catalysed at −20 °C by 10% mol of complexes consisting of box **8a** and several perchlorates of divalent cations; results are listed in Table 1 together with few closely related data taken from the literature. Nearly all cycloadditions were complete within 20 h, giving quantitative yields of 3,4-disubstituted cycloadducts, with almost complete control over the reaction regioselectivity. The *endo*/*exo* ratio [**3**:**4**] is influenced by several factors: cation, counter-ion, and 4-Å molecular sieves (MS).

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

1) If the cycloaddition is run in the absence of MS, all perchlorates are highly *endo*-selective (Table 1, entries 1,3,5,7), and the stereoselectivity with Mg^{II} is not influenced by the specific counter-ion (perchlorate, iodide, triflate) since the *endo* adduct **3** is always obtained in more than 95% yield (Table 1, entries 1, 11, 13).

2) The use of MS as additive in the reactions catalysed by perchlorates shifts the stereoselectivity towards the for-

Table 1. Selectivity of the 1,3-DC between **1** and **2** with catalysts derived from **8a** (all reactions proceed with quantitative yields)

Entry	Cation	Anion	Additive	*T* /°C (*t*/h)	[**3**+**4**]/[**5**+**6**]	[**3**:**4**]	% *ee endo*-**3** (config.)	% *ee exo*-**4**[a]
1[b]	Mg^{II}	ClO_4	−	−15 (15)	> 98:< 2	95:5	48 (3′*R*,4′*S*)	−
2[b]	Mg^{II}	ClO_4	MS	−15 (15)	> 98:< 2	70:30	70 (3′*S*,4′*R*)	−70
3	Co^{II}	ClO_4	−	−15 (18)	95:5	90:10	47 (3′*R*,4′*S*)	40
4	Co^{II}	ClO_4	MS	−15 (18)	> 98:< 2	24:76	42 (3′*S*,4′*R*)	84
5	Mn^{II}	ClO_4	−	−15 (44)	95:5	93:7	52 (3′*R*,4′*S*)	racem.
6	Mn^{II}	ClO_4	MS	−15 (44)	78:22	48:52	14 (3′*S*,4′*R*)	26
7	Ni^{II}	ClO_4	−	−15 (19)	> 98:< 2	98:2	74 (3′*R*,4′*S*)	−
8	Ni^{II}	ClO_4	MS	−15 (19)	88:12	72:28	85 (3′*S*,4′*R*)	−85
9[c]	Zn^{II}	ClO_4	−	−15 (15)	[d]	−	−	−
10[c]	Zn^{II}	ClO_4	MS	−15 (15)	> 98:< 2	27:73	31 (3′*S*,4′*R*)	84
11[e]	Mg^{II}	I	−	−78 (20)	> 98:< 2	100:0	48 (3′*R*,4′*S*)	−
12[e]	Mg^{II}	I	MS	−78 (20)	> 98:< 2	73:27	82 (3′*S*,4′*R*)	−
13[b]	Mg^{II}	OTf	−	−15 (20)	> 98:< 2	97:3	86 (3′*R*,4′*S*)	−

[a] Positive values refer to the enantiomer of **4** with lower hplc retention time, negative values to the enantiomer with higher retention time (see Exp. Sect.). [b] Data taken from ref.[5]. [c] Data taken from ref.[6]. [d] Decomposition products were mainly observed. [e] Data taken from ref.[4].

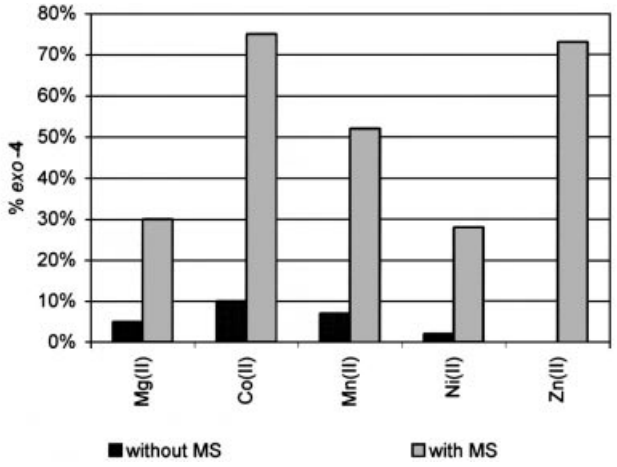


Figure 1. Comparison of the % *exo*-**4** obtained by perchlorate-catalysed cycloaddition in the presence or in the absence of MS

mation of the adduct *exo*-**4** (Figure 1). This effect is particularly evident for Co^{II} and Zn^{II} cations and less pronounced when Mg^{II} and Ni^{II} are used as Lewis acids, with Mn^{II} giving an intermediate result (Table 1, entries 2, 4, 6, 8, 10 vs. 1, 3, 5, 7).

The second effect of MS is a change in the absolute configuration of the preferred *endo* adduct. As previously reported in the case of Mg iodide[4] and perchlorate,[5] the reactions run in the presence of MS reverse in enantioselectivity, and (3′*S*,4′*R*)-**3** becomes the favoured enantiomer.

With the chiral ligand kept constant, the catalyst screening depicted in Table 1 allows the best parameters for driving stereo- and enantioselectivity towards the formation of the elusive *exo* enantiomers **4** to be identified. Mg^{II}, Co^{II}, Mn^{II}, Ni^{II} and Zn^{II} perchlorate-based catalysts*, in the presence of MS* (entries 2, 4, 6, 8, 10), give the *exo* adducts with yields in a range from 28−75%. Two cations, Co^{II} and Zn^{II}, give the *exo* enantiomer with the lower hplc retention time (t_R), whereas Mg^{II}- and Ni^{II}-based catalysts give the second *exo* enantiomer; in all cases promising enantioselectivities were evidenced.

Since the use of the *trans* 4,5-diphenyl-disubstituted box **8c** as chiral ligand has been reported to shift stereoselectivity moderately in favour of the *exo* adduct, although enantioselectivity was almost lost,[4] the effect of *cis* and *trans* disubstituted box catalysts **8b** and **8c** was tested with the above perchlorates in the presence of MS, and the results are collected in Table 2.

The results with *cis* diphenyl-substituted box **8b** were disappointing, since all catalysts (Table 2, entries 1−5) gave the *exo* product **4** with enantioselectivity worse than observed in the corresponding experiments described in Table 1 with **8a**.

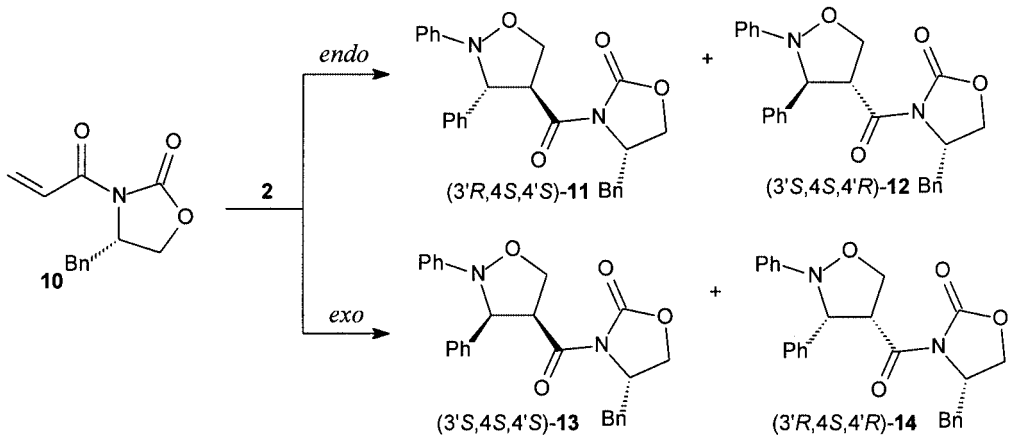
The results with *trans* diphenyl-substituted box **8c** (Table 2, entries 6−10), on the other hand, reveal it as the ligand of choice for the development of *exo*-selective enantioselective catalysts: Mg^{II}, Co^{II} and Ni^{II} provide C4-regioselectivity, with Ni^{II} giving, to the best of our knowledge, the best *exo*-selective catalyst so far reported in the literature for the reaction between **1** and **2** (*dr* 90:10), and all three cations are strongly enantioselective, the best again being Ni^{II}, which gives the second-eluted *exo* enantiomer with 99% *ee*.

The above screening allows testing of the flexibility of the box-based catalysts with the same (4*R*) chiral centre in driving stereo- and enantioselectivity towards the selective formation of all four possible stereoisomers of 3,4-disubstituted regioisomers **3** and **4**. The *endo* enantiomer (3′*S*,4′*R*)-**3** can be obtained in 85% *ee* with [**8a**-$Ni(ClO_4)_2$] catalyst (Table 1 − entry 8), while the (3′*R*,4′*S*)-**3** enantiomer proves to be the main product, with 90% *ee*, with [**8c**-$Zn(ClO_4)_2$] (Table 2 − entry 10). If the *endo* enantioselectivity of these catalytic processes cannot compete with those derived from pybox **9**,[7,8] the *exo* selectivity is competitive with the best catalytic system reported in the literature. The *exo* enantiomer **4** with the lower hplc t_R is obtained in 84% *ee* with the [**8a**-$Zn(ClO_4)_2$] catalyst (Table 1 − entry 10), while the second-eluted *exo* enantiomer is the main product (with 99% *ee*) when complex [**8c**-$Ni(ClO_4)_2$] is the catalyst (Table 2 − entry 9). Unfortunately the absolute stereochemistry of these *exo*-**4** isomers has not yet been determined, and therefore this was our target.

One of the methods most frequently used to determine the absolute configuration of 1,3-DC cycloadducts is based on X-ray analysis of a product containing a chiral centre of known configuration. Jørgensen determined the stereochemistry of *endo*-**3a** by correlating this product with that obtained in the 1,3-DC involving (*S*)-3-acryloyl-4-benzyl-2-oxazolidinone (**10**), the structure of which was determined

Table 2. Selectivity of the 1,3-DC between **1** and **2** with catalysts derived from **8b**,**c** (all reactions proceed with quantitative yields)

Entry	Box	Perchlorate cation	*T*/ °C (*t*/h)	[**3**+**4**]/[**5**+**6**]	[**3**:**4**]	% *ee endo*-**3** (config.)	% *ee exo*-**4**
1	**8b**	Mg^{II}	−20 (15)	96:4	84:16	16 (3′*R*,4′*S*)	−50
2	**8b**	Co^{II}	−20 (15)	91:9	44:56	68 (3′*S*,4′*R*)	33
3	**8b**	Mn^{II}	−20 (40)	50:50	39:61	racem.	racem.
4	**8b**	Ni^{II}	−20 (15)	88:12	56:44	77 (3′*S*,4′*R*)	−52
5	**8b**	Zn^{II}	−20 (15)	95:5	39:61	59 (3′*S*,4′*R*)	56
6	**8c**	Mg^{II}	−20 (15)	97:3	26:74	44 (3′*S*,4′*R*)	−94
7	**8c**	Co^{II}	−20 (15)	> 98:< 2	16:84	79 (3′*S*,4′*R*)	−92
8	**8c**	Mn^{II}	−20 (40)	89:11	30:70	37 (3′*S*,4′*R*)	−37
9	**8c**	Ni^{II}	−20 (15)	> 98:< 2	10:90	75 (3′*S*,4′*R*)	−99
10	**8c**	Zn^{II}	−20 (15)	> 98:< 2	85:15	90 (3′*R*,4′*S*)	−40



Scheme 2

by an X-ray analysis, through the conversion of the adducts in the corresponding isopropyl esters.[4]

In order to obtain one of the *exo* adducts **13**/**14** (Scheme 2), the reaction between **10** and **2** was carried out under $Mg(ClO_4)_2$ catalysis conditions, but the results were very similar to those found by Jørgensen[4] under Yb^{III}-catalysis conditions, since **11** was the diastereoisomer obtained in a nearly quantitative yield.

The use of [**8c**-$Mg(ClO_4)_2$] as asymmetric catalyst gave a quantitative yield of three cycloadducts (**12**, **11** and an *exo* isomer) in a ratio of 2:1:1. The mixture was separated by column chromatography and the first-eluted product was the *exo* adduct **13** or **14**.[10] Since every attempt to obtain it in a crystalline form suitable for an X-ray analysis failed, the *exo* adduct was reduced to **15** in a move inspired by the determination of the absolute configurations of adducts between **2** and α-Br- or α-Me-substituted acroleins,[17] and this was esterified with *p*-bromobenzoic acid and DCC to give **16** (Scheme 3).

The *p*-bromobenzoic ester derivative was indeed suitable for X-ray analysis (Figure 2) and it was shown to be

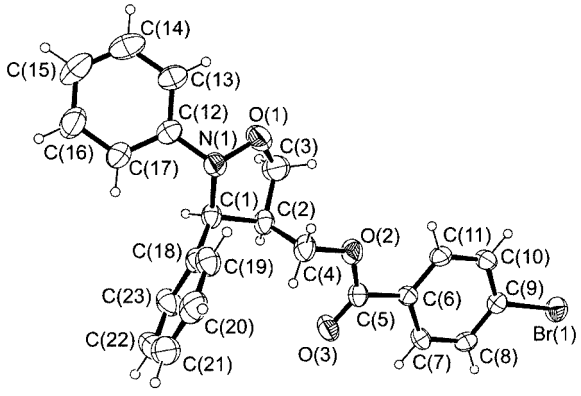
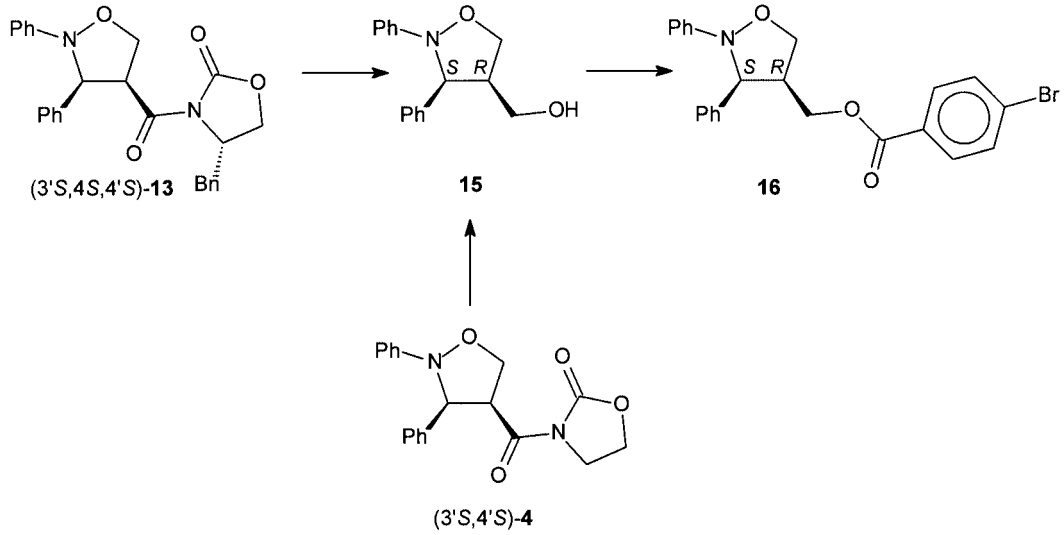


Figure 2. Crystal structure of **16** showing the atom-numbering scheme of non-H atoms: thermal ellipsoids are drawn at the 30% probability level

(3*S*,4*R*)-**16**, hence deriving from (3′*S*,4*S*,4′*S*)-**13**. HPLC comparison with several samples of reduced and esterified *exo* mixtures obtained from the catalysed 1,3-DC reactions allowed the (3′*S*,4′*S*) configuration to be assigned to the



Scheme 3

Table 3. Best selectivities and preferred face approach with box **8a** and **8c** and four cations in the 1,3-DC between **1** and **2**

Cation	Box **8a**			Box **8c**		
	[*endo:exo*]	%*ee* **3** (conf.)	%*ee* **4** (conf.)	[*endo:exo*]	%*ee* **3** (conf.)	%*ee* **4** (conf.)
Mg^{II}	70:30	70 (3′*S*,4′*R*) *Re*-face	70 (3′*R*,4′*R*) *Re*-face	26:74	44 (3′*S*,4′*R*) *Re*-face	94 (3′*R*,4′*R*) *Re*-face
Ni^{II}	72:28	42 (3′*S*,4′*R*) *Re*-face	85 (3′*R*,4′*R*) *Re*-face	10:90	75 (3′*S*,4′*R*) *Re*-face	99 (3′*R*,4′*R*) *Re*-face
Co^{II}	24:76	47 (3′*S*,4′*R*) *Re*-face	84 (3′*S*,4′*S*) *Si*-face	16:84	79 (3′*S*,4′*R*) *Re*-face	92 (3′*R*,4′*R*) *Re*-face
Zn^{II}	27:73	52 (3′*S*,4′*R*) *Re*-face	84 (3′*S*,4′*S*) *Si*-face	85:15	90 (3′*R*,4′*S*) *Si*-face	40 (3′*R*,4′*R*) *Re*-face

exo enantiomer with the shorter hplc t_R (Table 1 − entries 4 and 10), and the (3′*R*,4′*R*) configuration to the second-eluted *exo* enantiomer (Table 2 − entries 6,7,9,10).

Discussion and Conclusion

From the data reported in Table 1 and 2, some main features can be derived.

a) The presence of MS clearly shifts the stereoselectivity in favour of the *exo* adducts and influences the enantioselectivity of the cycloaddition.

b) The use of *trans*-disubstituted box **8c** in place of **8a** usually increases the *exo* selectivity; the only exception is represented by the Zn^{II}-based catalyst.

c) If the absolute configurations of the *endo* and *exo* adducts are compared (Table 3), it is evident that:

i) the Mg^{II}- and Ni^{II}-based catalysts exhibit parallel behaviour, with both *endo*- and *exo*- favoured enantiomers deriving from the same nitrone approach to the *Re* face of the coordinated dipolarophile (in the *s*-*cis* conformation);

ii) the Zn^{II}-based catalysts show different behaviour, since the preferred enantiomer of the predominant stereoisomer (*exo*-**4** with **8a**, and *endo*-**3** with box **8c**) derives from a *Si* face approach, while the minor stereoisomer (*endo*-**3** with **8a**, and *exo*-**4** with box **8c**) derives from preferential approach to the *Re* face.

iii) the Co^{II}-based catalysts give intermediate results: when the ligand is **8a**, the stereochemical outcome is analogous to that obtained by use of the Zn^{II}-**8a** complex as catalyst; if the box employed is **8c**, the results are similar to those obtained with Mg^{II}- and Ni^{II}-based catalysts.

An interpretation of the above findings requires that different catalyst geometries have to be proposed, structures that are functions of ligand, cation, and MS. Furthermore, the potential coordinating ability of nitrone **2** may also influence the structure of the reacting complex.

The role of MS has been a matter of a discussion and cannot yet be fully explained. Jørgensen[4] proposed that MS can directly participate in the Mg^{II} coordination, while Kanemasa[18] preferred the more traditional behaviour as dehydrating agent. Probably both hypotheses may be operative, but the active role of MS with Mg^{II} was evidenced only in the 1,3-DC of **1** and not in the corresponding Diels−Alder (DA) cycloaddition.[5] As a consequence, a possible interaction between nitrone **2** and MS cannot be excluded.

To explain the stereochemical outcomes collected in Table 3, some models can be tentatively proposed, taking as guidelines the experimental results as well as the use of the simplest model compatible with the cation involved in the coordination.

In the case of the Ni^{II}- and Mg^{II}-based catalysts, the enantioselectivity can be interpreted by regarding a tetrahedral complex[18] as the more reactive intermediate with the *Si* face of the coordinated dipolarophile in the *s*-*cis* conformation shielded by the phenyl group at the C-4 position of **8a**. In this case the *endo* approach is favoured, resulting in the formation of (3′*S*,4′*R*)-*endo* **3** as the favoured stereoisomer (Figure 3, a). The shift towards *exo* selectivity observed when **8c** is the chiral ligand can be explained by considering the steric interactions between the phenyl groups, one on the C-5 position of the ligand and one on the nitrogen atom of the nitrone, in the *endo* transition state (ts). The nitrone *exo* approach will not suffer from this unfavourable contribution, and (3′*R*,4′*R*)-*exo* **4** will be the preferred stereoisomer (Figure 3, b).

The proposed reacting intermediates do not involve the nitrone or the MS in the cation coordination sphere,[4] since these possible complexes, even if present in higher concentrations, should be less active than the tetrahedral ones.[19]

To explain the results from **8a**-Co^{II} and -Zn^{II} catalysts, an expansion of the coordination from 4 to 5 or 6 is required,[20] and Figure 3 (c) shows the pentacoordinate Zn^{II} complex. The *endo* approach is disfavoured due to the steric interaction between the nitrone *N*-phenyl group and the apical ligand, the shielded face is now the *Re* one, and the preferential approach from the opposite *Si* face will furnish (3′*S*,4′*S*)-*exo* **4** as the predominant stereoisomer.

When the *trans*-disubstituted box **8c** is coordinated to Co^{II}, the steric hindrance of the second phenyl group on the oxazoline ring inhibits the coordination of the fifth ligand and the observed results may be easily explained by considering a ts structure similar to that represented in Figure 3 (b).

The three models proposed can serve as explanation for seven of the eight catalytic systems reported in Table 3. The last [**8c**-Zn^{II} complex] can be explained with difficulty, even

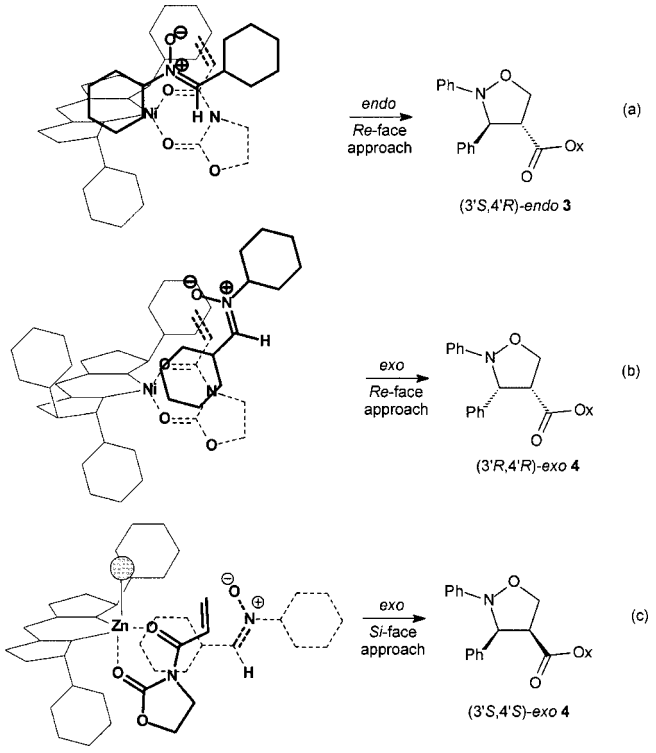


Figure 3. Proposed favoured transition state structures for the 1,3-DC between **1** and **2** catalysed by Ni^{II} with **8a** (a) or **8c** (b) and [**8a**-Zn^{II}] (c) complexes

if the similarity of its results with those obtained by use of Mg^{II} triflate as Lewis acid (*endo-Si* face approach strongly favoured − Table 1, entry 13) could be interpreted in terms of a structurally analogous complex.

In conclusion, the results reported in the paper demonstrate the high flexibility and efficiency of box complexes as catalysts of 1,3-DC reactions. The screening of several catalysts with mono- or disubstituted box and several perchlorates allowed identification of the best catalytic system with which to obtain each of the four possible stereoisomers of 3,4-disubstituted isoxazolidines with good selectivity.

Experimental Section

General Remarks: 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. Dichloromethane was the hydrocarbon-stabilised Aldrich ACS grade, distilled from calcium hydride and used immediately, inorganic salts were Aldrich ACS reagents, silica gel was Merck 230−400 mesh, powdered molecular sieves (4 Å) were Aldrich reagent heated under vacuum at 300 °C for 5 hours and kept in sealed vials in a dryer, 2,2-bis[2-(4*R*)-phenyl-1,3-oxazolinyl]propane (**8a**) was Aldrich commercial product, and 3-acryloyl-1,3-oxazolidin-2-one (**1**),[21] benzylidenephenylamine *N*-oxide (**2**),[22] 2,2-bis[2-(4*R*,5*S*)-diphenyl-1,3-oxazolinyl]-propane (**8b**),[23] 2,2-bis[2-(4*R*,5*R*)-diphenyl-1,3-oxazolinyl]propane (**8c**),[23] and (*S*)-3-acryloyl-4-benzyl-2-oxazolidinone (**10**)[24] were prepared by the literature methods.

General Procedure for the Enantioselective 1,3-Dipolar Cycloaddition Between 1 and 2: 3-Acryloyl-1,3-oxazolidin-2-one (**1**, 0.028 g, 0.20 mmol), the box (**8a**−**c**, 0.02 mmol), the inorganic perchlorate (0.02 mmol) and the molecular sieves (4 Å, 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 for about 30 minutes. The mixture was then cooled to −20 °C and after about 10 minutes **2** (0.040 g, 0.20 mmol) was added and stirring was continued at −20 °C until TLC showed all dipolarophile had reacted. The reaction mixture was decomposed in water, extracted with CH_2Cl_2 and dried, and the mixture of adducts **3** and **4** was subjected, without any further purification, to HPLC analysis on a Chiralpack AD column with hexane/2-propanol (8:2) as eluent (1.0 mL/min). The quality of 2-propanol was crucial for the separation; C. Erba solvent was the best. The average retention times were 17 and 19 min for (3′*S*,4′*S*)- and (3′*R*,4′*R*)-**4**, respectively, and 20.5 and 24.4 min for (3′*R*,4′*S*)- and (3′*S*,4′*R*)-**3**, respectively. The data reported in Table 1 and 2 are averages of at least three determinations on independently run reactions. From the reaction described in Table 2 (entry 9), column chromatography on silica gel (elution with cyclohexane/ethyl acetate, 80:20) allowed **4** to be isolated slightly contaminated with **3**. A fractional crystallisation from ligroin gave pure **4**, the ^1H NMR spectrum of which was identical to that described in the literature.[6] ^{13}C NMR ($CDCl_3$): δ = 42.5 (4-C), 53.8 (4′-C), 62.0 (5-C), 67.0 (5′-C), 71.4 (3′-C), 115.1, 122.3, 128.0, 128.1, 128.3, 128.8, 149.8, 153.0 (C=O), 169.2 (C=O) ppm.

Enantioselective 1,3-Dipolar Cycloaddition between 2 and 10: (*S*)-3-Acryloyl-4-benzyl-2-oxazolidinone (**10**, 0.208 g, 0.90 mmol), the box **8c** (0.036 g, 0.074 mmol), magnesium perchlorate (0.016 g, 0.072 mmol) and the molecular sieves (4 Å, 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 for about 30 minutes. The mixture was then cooled to −20 °C and after about 10 minutes **2** (0.177 g, 0.90 mmol) was added and stirring was continued at −20 °C for 3 days until TLC showed all **10** had reacted. The reaction mixture was decomposed in water, extracted with CH_2Cl_2 and dried, and a sample of the mixture was subjected to HPLC analysis on a Chiralcel OD column with hexane/2-propanol [8:2] as eluent (1.0 mL/min). The composition was **11** (t_R 21 min), **13** (t_R 26.5 min) and **12** (t_R 49 min) in the ratio 43:31:26. The reaction mixture was column chromatographed on silica gel and eluted with cyclohexane/ethyl acetate, 85:15. The order of elution was **13**, **12**, **11**, and the products have the following physico-chemical properties.

(3′*R*,4*S*,4′*S*)-4-Benzyl-3-[(2′,3′-diphenylisoxazolidin-4′-yl)carbonyl]-1,3-oxazolidin-2-one (11): Yield: 0.170 g (44%); white crystals, m.p. 116−117 °C from diisopropyl ether. $[\alpha]_D$ = +43 (*c* = 1.0, $CHCl_3$), ref.[4] $[\alpha]_D$ = +40.8; ^1H- and ^{13}C NMR spectra were identical to those reported in the literature.[4]

(3′*S*,4*S*,4′*R*)-4-Benzyl-3-[(2′,3′-diphenylisoxazolidin-4′-yl)carbonyl]-1,3-oxazolidin-2-one (12): Yield: 0.060 g (16%); soft white needles, m.p. 146 °C from hexane. $[\alpha]_D$ = +109.3 (*c* = 0.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 2.82 (dd, *J* = 13.5, 9.2 Hz, 1 H, benzyl-H), 3.21 (dd, *J* = 13.5, 3.1 Hz, 1 H, benzyl-H), 4.14 (dd, *J* = 5.3, 8.7 Hz, 1 H, 5′-H), 4.25 (m, 2 H, 5-H), 4.45 (m, 1 H, 4′-H), 4.68 (m, 1 H, 4-H), 4.73 (t, *J* = 8.7 Hz, 1 H, 5′-H), 5.29 (d, *J* = 5.7 Hz, 1 H, 3′-H), 6.95−7.55 (m, 15 H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$): δ = 37.6 (benzyl-C), 55.1 (4-C), 59.3 (4′-C), 66.5 (5-C), 69.6 (5′-C), 70.3 (3′-C), 115.9, 122.4, 127.1, 127.5, 127.8, 128.6, 128.8, 128.9, 129.3, 134.6, 140.7, 150.1, 153.0 (C=O), 170.0 (C=O) ppm. $C_{26}H_{24}N_2O_4$: calcd. C 72.88, H 5.65, N 6.54; found C 73.00, H 5.60, N 6.52.

(3′*S*,4*S*,4′*S*)-4-Benzyl-3-[(2′,3′-diphenylisoxazolidin-4′-yl)carbonyl]-1,3-oxazolidin-2-one (13): Yield: 0.075 g (19%); soft white crystals, m.p. 140−141 °C from diisopropyl ether/hexane. $[\alpha]_D = -17.7$ (c = 0.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.46 (dd, J = 13.5, 11.7 Hz, 1 H, benzyl-H), 2.34 (dd, J = 13.5, 3.1 Hz, 1 H, benzyl-H), 3.94 (dd, J = 9.1, 2.8 Hz, 1 H, 5-H), 4.03 (dt, J = 9.1, 1.0 Hz, 1 H, 5-H), 4.31 (m, 1 H, 5′-H), 4.35 (m, 1 H, 4-H), 4.86 (m, 1 H, 4′-H), 4.89 (dd, J = 6.3, 11.1 Hz, 1 H, 5′-H), 5.39 (d, J = 9.4 Hz, 1 H, 3′-H), 6.9−7.6 (m, 15 H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$): δ = 36.1 (C-benzyl), 53.8 (4′-C), 55.0 (4-C), 66.3 (5-C), 67.2 (5′-C), 71.3 (3′-C), 115.0, 122.2, 127.1, 128.2, 128.6, 128.8, 128.9, 129.0, 135.5, 138.3, 149.7, 152.9 (C=O), 168.6 (C=O) ppm. $C_{26}H_{24}N_2O_4$: calcd. C 72.88, H 5.65, N 6.54; found C 72.95, H 5.70, N 6.60.

(3*S*,4*S*)-(2,3-Diphenylisoxazolidin-4-yl)methanol (15): $NaBH_4$ (0.020 g) was dissolved in water (0.1 mL), and a solution of (3′*S*,4*S*,4′*S*)-4-benzyl-3-[(2′,3′-diphenylisoxazolidin-4′-yl)carbonyl]1,3-oxazolidin-2-one (**13**, 0.020 g, 0.06 mmol) in tetrahydrofuran (0.6 mL) was added whilst stirring. After 12 h TLC showed all starting product had disappeared, the organic solvent was evaporated, some more water was added, and the mixture was extracted with CH_2Cl_2. The mixture was column chromatographed on silica gel, eluted with cyclohexane/ethyl acetate, 80:20, and (3*S*,4*S*)-**15** (0.011 g, 92% yield) was isolated; soft white needles m.p. 100−101 °C from hexane. HPLC: Chiralcel OD column, hexane/2-propanol (8:2) as eluent (1.0 mL/min), t_R 5.9 min. $[\alpha]_D = -186$ (c = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.1(m, 1 H, 4-H), 3.33 (dd, J = 10.9, 6.0 Hz, 1 H, -C*H*HOH), 3.47 (dd, J = 10.9, 8.1 Hz, 1 H, C*H*HOH), 4.13 (dd, J = 8.2, 5.0 Hz, 1 H, 5-H), 4.27 (dd, J = 8.2, 6.6 Hz, 1 H, 5-H), 4.83 (d, J = 8.0 Hz, 1 H, 3-H), 6.9−7.6 (m, 10 H, aromatic protons) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.9(4-C), 61.3 (CH_2OH), 69.3 (5-C), 71.6 (3-C), 114.6, 121.4, 126.7, 127.2, 127.5, 127.6, 127.9, 128.6, 128.7, 128.9, 138.1, 151.6 ppm. $C_{16}H_{17}NO_2$: calcd. C 75.27, H 6.71, N 5.49; found C 75.15, H 6.77, N 5.58.

(3*S*,4*S*)-(2,3-Diphenylisoxazolidin-4-yl)methyl 4-Bromobenzoate (16): (3*S*,4*S*)-(2,3-Diphenylisoxazolidin-4-yl)methanol (**15**, 0.010 g, 0.04 mmol) was added at 0 °C to a solution of *p*-bromobenzoic acid (0.012 g, 0.06 mmol), 1,3-dicyclohexylcarbodiimide (0.010 g, 0.05 mmol) and 4-(dimethyamino)pyridine (0.003 g, 0.02 mmol) in anhydrous CH_2Cl_2 (3 mL). The solution was stirred at 0 °C for 10 min, and then overnight at room temperature. The suspension was evaporated on a pinch of silica gel and column chromatographed on silica gel with cyclohexane/ethyl acetate, 90:10 as eluent. Compound **16** soon separated and crystallised from pentane m.p. 113−114 °C. HPLC: Chiralcel OD column, hexane/2-propanol (8:2) as eluent (1.0 mL/min), t_R 65 min. [the (3*S*,4*S*) enantiomer has t_R 11 min.], $[\alpha]_D = -40.3$ (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.4 (m, 1 H, 4-H), 4.07 (m, 2 H, −C*H*$_2$OH), 4.14 (dd, J = 8.3, 5.1 Hz, 1 H, 5-H), 4.31 (dd, J = 8.3, 6.5 Hz, 1 H, 5-H), 4.87 (d, J = 8.1 Hz, 1 H, 3-H), 6.9−7.6 (m, 10 H, aromatic protons), 7.58 (d, J = 8.5 Hz, 2 H, 3-H bromophenyl), 7.80 (d, J = 8.5 Hz, 2 H, 2-H bromophenyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.8 (4-C), 63.5 (CH_2O), 69.3 (5-C), 71.5 (3-C), 114.6, 121.8, 127.2, 127.8, 128.8, 130.9 (2-C bromophenyl), 131.6 (3-C bromophenyl), 137.4, 151.4, 165.2 (C=O) ppm. $C_{23}H_{20}BrNO_3$: calcd. C 63.03, H 4.60, N 3.20; found C 62.93, H 4.25, N 3.23.

X-ray Crystallography: Data for X-ray structure analysis were collected at ambient temperature with an Enraf−Nonius CAD4 four-circle diffractometer, with the use of graphite-monochromatized Mo-K_α X-radiation (λ = 0.7107 Å). Crystal data for **16**: $C_{23}H_{20}BrNO_3$, M = 438.30, monoclinic $P2_1$ (no. 4), a = 13.6216(22) Å, b = 5.8575(15) Å, c = 14.3712(24) Å, β = 116.278(20)°, V = 1028.2(4) Å^3, Z = 2, $\rho_{calcd.}$ = 1.416 g·cm^{-3}, μ = 2.022 mm^{-1}, $2\theta_{max.}$ = 54°, 4476 independent reflections, 2905 strong reflections [$I_0 > 2\sigma(I_0)$], 253 parameters refined, $R1$ = 0.0446 (strong data) and 0.0800 (all data), R_2w = 0.0955 (strong data) and 0.1083 (all data), GOF 0.996, largest difference peak and hole 0.38 and −0.19 e·Å^{-3}. Data reduction (including intensity integration, background, Lorentz and polarization corrections) was performed with the WinGX package.[25] Absorption effects were evaluated with the psi-scan method[26] and absorption correction was applied to the data (min. and max. transmission factors were 0.617 and 0.902). Crystal structure was solved by direct methods (SIR 97)[27] and refined by full-matrix, least-square procedures on F^2 with use of all reflections (SHELXL 97).[28] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at calculated positions with the appropriate AFIX instructions and refined by use of a riding model.

CCDC-246506 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.): +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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