Pyridine-2,6-bis(oxazolines), Helpful Ligands for Asymmetric Catalysts

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I. Introduction

Asymmetric catalysis with chiral complexes has received considerable attention in recent years, and its contribution to the art of organic synthesis has become of leading importance.[1,2] The catalyst, in general, consists of a cation coordinating an optically active ligand, and great efforts have been done in part to test different cations, mainly to discover new classes of chiral ligands. The ideal ligand,[3] in principle, should offer the user a series of advantages: it has to be easily prepared, cheap, and resistant, and it should give very selective and flexible catalysts. This behavior, as much as possible, requires that a single specific coordination of the reagent should occur onto the chiral catalyst, clearly to favor the attack on a specific face of the coordinated reagent. The easier and less costly route to reduce half this variable is the use of a C_2-symmetric chiral ligand, this being one of the reasons of success behind bis(oxazolines) (box).

Box ligands have two oxazoline rings separated by a spacer (the most commonly used being a single carbon atom), and C_2-bis(oxazolines) received a great deal of attention as ligands in coordination chemistry[4] and in asymmetric catalysis.[5a−c]

In 1989 Nishiyama[6] first synthesized box ligands with a pyridine ring as a spacer. This was a small revolution in the field because a ligand born as bidentate became the widely adopted tridentate pybox ligand, this being due to the presence of the felicitously placed pyridine nitrogen atom. Nishiyama's short communication also anticipated the usual protocol of research in pybox chemistry: (a) synthesis of the ligand following a sequence that, for a long time, would become a standard (reaction of pyridine-2,6-dicarbonyl dichloride with a chiral 1,2-aminol, conversion of the bis-hydroxyamide to the corresponding bis-chloroamide, and ring closure under basic conditions); (b) preparation of the catalyst by reaction of pybox with an inorganic salt ($RhCl_3$ in the cited Nishiyama's paper); (c) when possible, the complex being characterized by a single-crystal X-ray structural study; (d) test of the complex as a catalyst for asymmetric induction in the planned reaction (in the mentioned case the hydrosilylation of ketone); (e) proposal of a reacting complex to rationalize the stereochemical outcome of the catalytic process.

This historic approach to the enantioselective catalysis with pybox complexes will be followed in this review that will cover the literature from 1989 to the end of 2002, around 150 papers, whose frequency strongly increased in the last years as shown in Figure 1.

II. Syntheses of Pybox Ligands

The syntheses of pybox ligands can be roughly classified into two different groups, depending on the starting pyridine derivative. Method A collects all syntheses beginning from pyridine-2,6-dicarbonyl dichloride (**1**), while method B involves 2,6-dicyanopyridine as starting reactant.

As mentioned above, pybox ligands were first described in 1989,[6] the synthesis being outlined in Scheme 1, which shows the reaction of **1** with a chiral aminol, the conversion of the bis-hydroxyamide **2** to

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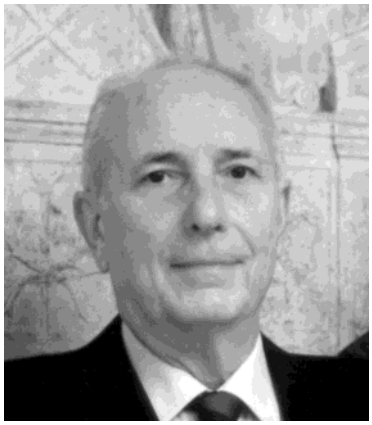


Giovanni Desimoni was born in 1936. He received his laurea degree from the University of Pavia. After a research and teaching period in the same university and one year with Alan Katritzky at UEA, in 1975 he joined the Science faculty at the University of Pavia as full professor. He was Dean of the Faculty and Director of the Department of Organic Chemistry. His recent research interests concern the development of new catalysts for enantioselective reactions, especially those derived from optically active heterocycles used as chiral ligands, and the understanding of their mechanism in inducing selectivity.

Giuseppe Faita was born in 1962 and received his degree in Chemistry in 1986 at the Univeristy of Pavia. In 1990 he obtained his PhD at the same University under the supervision of G. Desimoni and he became Researcher at the Organic Chemistry Department in Desimoni group. In 2000 he became Associate Professor in Organic Chemistry. His research interests concern the optimization of asymmetric catalysts involving box and pybox as chiral ligands and solid-phase organic syntheses.

the corresponding bis-chloroamide **3**, and the ring closure to the pybox derivative **4** under basic conditions.

Method A was followed by Nishiyama[7−12] and other groups[13−16] to synthesize the majority of the ligands reported in Table 1. Simple variants of the methods involved (chloromethylene)dimethylammonium chloride as chlorinating agent and tetra-*n*-butylammonium hydroxide for the ring closure.[17]

Other variants of method A have been reported for the direct ring closure of **2**: the bis-hydroxyamide obtained from (2*S*,3*R*)-threonine was chlorinated and cyclized with PPh_3, imidazole, and CCl_4 (method A1),[10] the bis-amide obtained from (*S*)-serine methyl ester was cyclized with diethylaminosulfur trifluoride and K_2CO_3 (method A2),[18] and a variant of a more flexible application ran the ring closure by simply heating a 15% w/v solution of **2** in $BF_3{\cdot}Et_2O$ at 120 °C (method A3).[19] All 4′-substituted pybox are reported in Table 1.

Paolo Quadrelli was born in 1961. He received his degree in chemistry in 1986 at the University of Pavia. In 1990 he obtained his PhD at the same University under the supervision of G. Desimoni. Then he moved to the R&D Laboratories of ENI Group until 1992, when he returned as Researcher at the University of Pavia in P. Caramella group. In 1996 he joined the group of R. Grigg at the University of Leeds. He currently holds a Docent position at the Department of Organic Chemistry of the University of Pavia. His research interests center around pericyclic reactions, the chemistry of 1,3-dipoles, transition metal catalyzed reactions, and solid-phase syntheses.

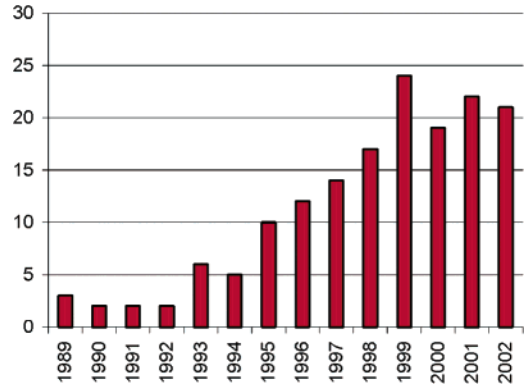
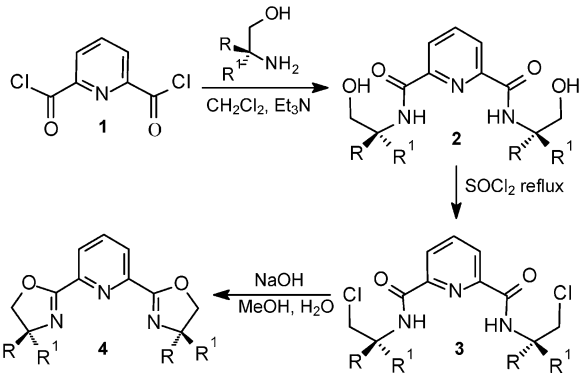


Figure 1. Number of papers dealing with pybox ligands appearing in the literature since their discovery.

Scheme 1

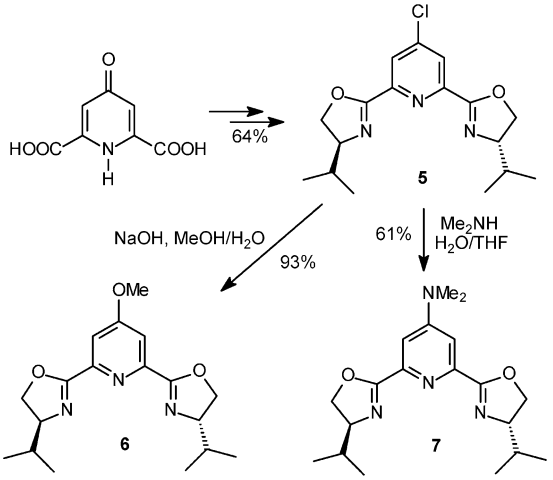


Finally, some modifications of the pyridine ring pattern have been reported. 4-Chloropybox **5**, obtained via method A by trichlorination of chelidamic acid and condensation with (*S*)-valinol, underwent a displacement reaction with either MeOH/NaOH or Me_2NH, to give 4-methoxy- and 4-(dimethylamino)-pybox **6** and **7**, respectively (Scheme 2).[20,21]

Table 1. 4′-Substituted Pybox Ligands

pybox	R	R[1]	starting aminol or amino acid	method	yield (%)	ref
4a	Me	H	(*S*)-2-amino-1-propanol	A	–	16
4b	H	Et	(*R*)-2-amino-1-butanol	A	62	8, 11
4c	i-Pr	H	(*S*)-valinol	A, B1	61	6, 7, 8, 11, 15, 17, 20, 25
4d	H	i-Pr	(*R*)-valinol	A	60–63	8
4e	*s*-Bu	H	(*S*)-*sec*-leucinol	A	70	6, 8, 11
4f	*t*-Bu	H	(*S*)-*tert*-leucinol	A, B1	42	6, 8, 11, 13, 25
4g	H	*t*-Bu	(*R*)-*tert*-leucinol	A	75	19
4h	Ph	H	(*S*)-phenylglycinol	A	–	15
4i	H	Ph	(*R*)-phenylglycinol	A, A2, B1	62–88	8, 11, 19
4j	$PhCH_2$	H	(*S*)-phenylalanilol	A	70	11, 14, 15
4k	*p*-EtO–C_6H_4	H	(*R*)-*p*-ethoxyphenylglycinol	A	78	15
4l	$C_6H_{11}CH_2$	H	(*S*)-2-amino-3-cyclohexyl-propan-1-ol	A	69	13
4m	2-Naph	H	(2*S*)-2-amino-2-(2′-naphthyl)ethanol	B2	43	28
4n	$(CH_2)_2SMe$	H	(*S*)-methioninol	B2	74	28
4o	H	CH_2OH	(*S*)-serine	A	58	9
4p	H	CH_2OSi*t*-$BuMe_2$	(*S*)-serine	A	47	9
4q	H	$CH_2OSi(^iPr)_3$	(*S*)-serine	A	53	12
4r	H	CH_2OSi*t*-$BuPh_2$	(*S*)-serine	A	37	12
4s	H	COOMe	(*S*)-serine methyl ester	A2		18
4t	(*R*)-CHMeOH	H	(2*S*,3*R*)-threonine	A1	40	10
4u	H	H	2-aminoethanol (2-AE)	A	–	11
4v	Me	Me	2,2-dimethyl-2-AE	A, A3	61–66	8, 11, 19

Scheme 2

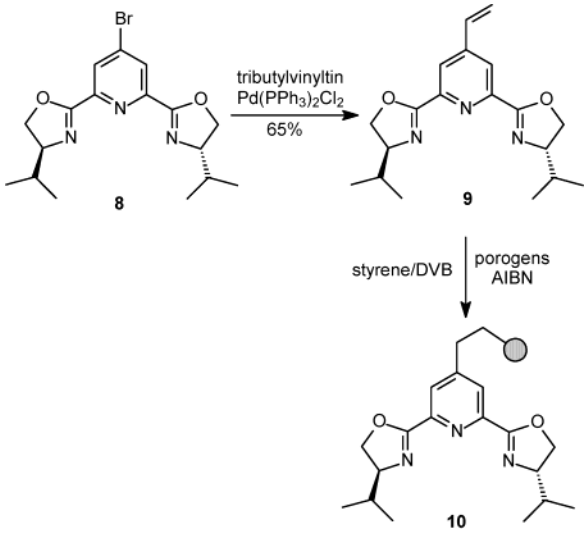


This reaction did not have further developments for almost 10 years when it became the way to link a pybox on a solid support, and two reports on this topic have been published.

The first paper reported that 4′-oxyethanol-pybox-can be covalently attached through 4-(chlorosulfonyl)-benzoic acid to an oxidized silicon surface giving a silica-supported pybox.[22] Possible applications of this supported ligand to organic syntheses are limited by the absence of any experimental details in the cited paper.

The first detailed synthesis of an immobilized pybox chiral ligand has been recently reported.[23] 4-Bromopybox **8**, obtained via method A by monobromination of chelidamic acid, chlorination of 4-bromopyridine-2,6-dicarboxylic acid, condensation with (*S*)-valinol, and ring closure with NaH in THF at 0 °C, was converted into the 2,6-bis[(*S*)-4-isopropyloxazolin-2-yl]-4-vinylpyridine (**9**) with tributylvinyltin in the presence of a palladium catalyst. Monomer **9** was used in different block copolimerization with styrene and divinylbenzene, using toluene or toluene/1-dodecanol as porogens and AIBN as the radical

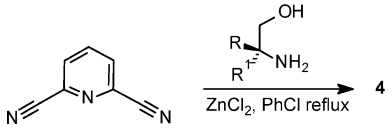
Scheme 3



initiator (Scheme 3). By changing both the degree of cross-linking and the porogen, three different polymers have been obtained, having the general structure **10**, whose ruthenium complexes proved to be useful catalysts in cyclopropanation (as discussed in section IVB1).

2,6-Dicyanopyridine is the starting material used to insert pyridine in the pybox framework when method B is followed. Dinitrile, in accordance with a well-known method used for the synthesis of several mono- and bis-oxazolines,[24a,b] is refluxed in chlorobenzene with 3 equiv of 1,2-aminol, in the presence of $ZnCl_2$, to give **4** as the only reaction product (Scheme 4, method B1).[25]

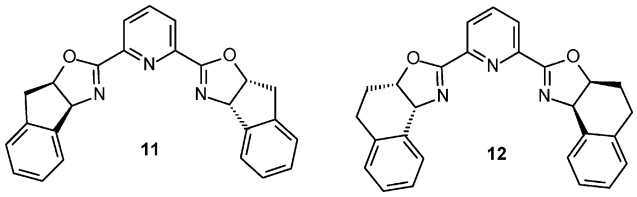
Scheme 4



Even if the substituents on the 4-position of the oxazoline ring are considered to be crucial in determining stereoselectivity, several pybox with substituents on both C-4 and C-5 positions have been synthesized.

Method A3 was used to cyclize bis-amides obtained from (1*S*,2*R*)-aminoindanol and (1*R*,2*S*)-1-amino-2-hydroxytetrahydronaphthalene; following this protocol, pybox **11** and **12**, which retain the configuration of the starting aminols, were synthesized in 73% and 76% yields respectively (Chart 1).[19,26]

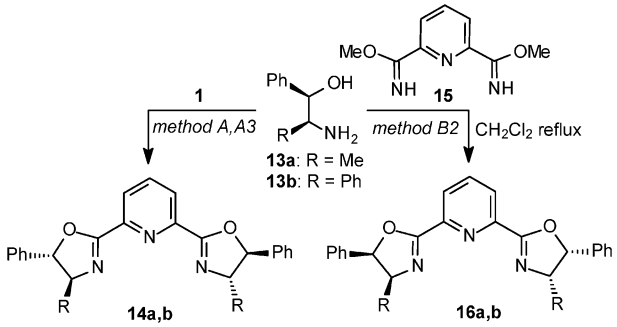
Chart 1



When the same reaction was run on bis-amide derived from (1*R*,2*S*)-norephedrine **13a**, the *trans*-pybox **14a** was formed exclusively [or its enantiomer starting from (1*S*,2*R*)-norephedrine] (Scheme 5),[19] indicating that the ring closure occurred with inversion of configuration. This result could be considered the limit of this synthetic method if an alternative protocol, involving the ring closure with retention of configuration of the starting aminol, would not be available.

These circumstances were studied in detail, and the ring closure following method A was found to be an excellent route to invert the configuration of bis-chloroamide obtained from (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**13b**). Through conversion of bis-hydroxyamide into bis-dichloroamide, the synthesis of *trans*-diphenyl-substituted pybox **14b** was accomplished (Scheme 5).[27]

Scheme 5

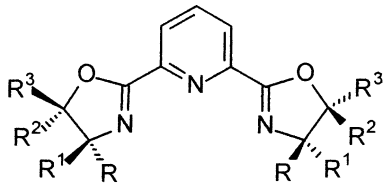


The 1,2-aminols **13a**,**b** were once again the starting products for the stereodivergent synthesis of cis-disubstituted pybox **16a**,**b**.[28] The protocol applied a method already used in the synthesis of four pybox (**17a**−**d**) derived from (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol and dimethyl pyridine-2,6-dicarboximidate **15**, which was prepared from dinitrile **10** (Scheme 5, method B2).[13] This method looks very promising in terms of flexibility, and the mono-substituted pybox **4m** and **4n** were obtained from (2*S*)-2-amino-2-(2′-naphthyl)ethanol and (*S*)-methioninol, respectively.[28]

A pybox with a structure reported to be **16b** had already been described in the literature,[29,30] but all physical and spectroscopic data were reported to be the same for the enantiomer of **14b**. Furthermore, the protocol of preparation (a small variant of method A with NaH instead of NaOH) suggests the inversion of configuration in the ring closure.

Another variant of method A, with the entire synthesis reduced to only two steps, ran the intramolecular condensation of bis-hydroxyamide with methanesulfonic acid (method A4). This protocol was used to prepare several 4′,5′,5′-trisubstituted pybox (**18a**−**e**),[31,32] and all oxazoline pybox derivatives with sub-

Table 2. 4′ and 5′-Substituted Pybox Ligands



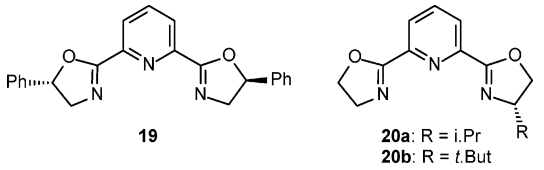
pybox	R	R^1	R^2	R^3	yield %	method	ref
14a	H	Me	Ph	H	70	A3	19
14b	H	Ph	Ph	H	64	A	27
14c	Ph	H	H	Ph	−	A	27
14d	Me	H	H	Ph	−	A3	*a*
16a	H	Me	H	Ph	86	B2	28
16b	H	Ph	H	Ph	75	B2	28
16c	Ph	H	Ph	H	−	B2	28
17a	H	CH_2OH	*p*-NO_2−C_6H_4	H	78	B2	13
17b	H	CH_2O−Si*t*-$BuMe_2$	*p*-NO_2−C_6H_4	H	61	B2	13
17c	H	CH_2O−Si*t*-$BuPh_2$	*p*-NO_2−C_6H_4	H	66	B2	13
17d	H	CH_2O Si(i-Pr)$_3$	*p*-NO_2−C_6H_4	H	62	B2	13
17e	H	CH_2OH	*p*-MeS−C_6H_4	H	67	B1[b]	33
18a	H	i-Pr	Et	Et	68	A4	31
18b	H	i-Pr	Ph	Ph	77	A4	31, 32
18c	H	Me	Ph	Ph	41	A4	32
18d	H	Ph	Ph	Ph	63	A4	32
18e	H	$PhCH_2$	Ph	Ph	72	A4	32

[a] Commercial product. [b] A variant using K_2CO_3 and a mixture of glycerol and ethylene glycol as solvent was used.

stituents in positions 4′ and 5′ are reported in Table 2.

Two exceptions to the structures described above have been reported (Chart 2).

Chart 2



A pybox with the position 4′-unsubstituted and a (*S*)-5′-phenyl substituent (**19**) has been mentioned, but the absence of any chemical and spectral data, as well as of any detail of its preparation, must be apologized.[34]

Two single-chiral pybox ligands have been synthesized, whose preparation involved first the reaction of pyridine-2,6-dicarboxylic acid dimethyl ester with 1 equiv of 2-aminoethanol (to build up the achiral ring), and second the reaction of the monoamide with the chiral 1,2-aminol. Finally, small variants of method A allowed the completion of the synthesis of **20a**,**b**.[35]

III. Pybox–Metal Complexes

When a pybox ligand is mixed with an inorganic salt to prepare a catalyst a pybox−metal complex is usually formed. In this section we will discuss the preparation of complexes that have been isolated, characterized, and investigated either via X-ray crystal structure determinations or through spectroscopic studies. Sometimes, the X-ray crystal structure of the complex was not available, and calculations to various levels of accuracy were used to mime the structure of the complex. This approach is often employed to infer the reacting complex [pybox−cation−reagent] involved in the catalytic cycle of the reaction, but these models will be examined in the section devoted to specific reactions.

A. Syntheses

Solid complexes, prepared from pybox and an inorganic salt, are in certain cases crystalline products suitable for X-ray analysis. In this section we will simply describe the protocols of the preparation along with the information concerning the crude composition of the complex. The problems related to their structure, such as definite number of coordination, relative positions of the ligands, and the various aspects of their configuration, will be discussed in the immediately following section.

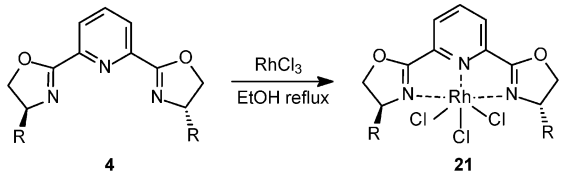
First, pybox complexes can be divided into two main classes, those having a ratio [pybox:cation] of either [1:1] or [2:1].

In addition to three nitrogen atoms arising from pybox, complexes [1:1] commonly have further ligands that may be some counterions of the cation and, sometimes, water molecules. Other complexes, besides the above ligands, have a simple organic molecule coordinated to the inorganic core, which will be considered individually.

The complexes involving two pybox units coordinated to the same cation can be either homochiral or heterochiral. The racemic complex can play an important role in enantioselective catalysis if it is thermodynamically more stable than the homochiral one, as a chiral amplification due to the reservoir effect may be observed.[36]

The early mentioned papers on pybox syntheses[6,8,20,37,38] also reported their reaction with $RhCl_3$ to give the corresponding complexes **21**, the sum of the reagents, as orange solids (Scheme 6).

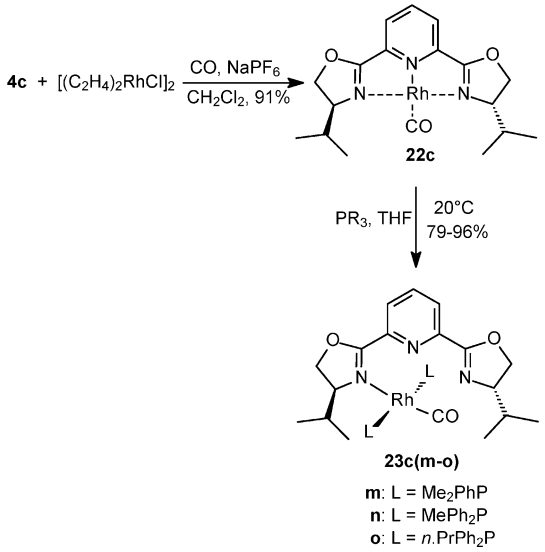
Scheme 6



Normally, pyboxes behave as tridentate ligands, but few examples of pyboxes as mono- and bidentate ligand have been reported.

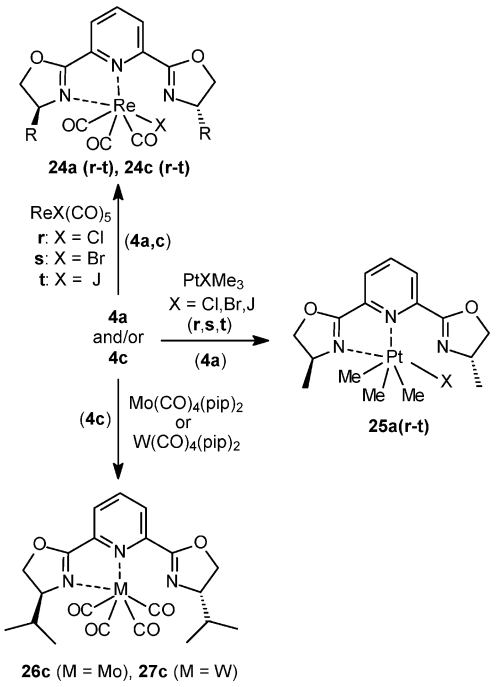
Starting from a tridentate complex, the synthesis of a series of rhodium complexes has been described recently with pybox showing a monohapto coordination through one oxazoline nitrogen atom.[39] Scheme 7 reports the innovative preparation of **23c**(**m**−**o**), air-stable yellow solid complexes, by addition of two equivalents of PR_3 to a solution of **22c**, and in addition to the spectroscopic data, the previously unreported monodentate coordination of **4c** was confirmed by the X-ray crystal structure of **23co**.[39]

Scheme 7



The bidentate coordination mode of pybox involves pyridine and only one oxazoline nitrogen atom, and it occurs when **4a** or **4c** is refluxed with pentacarbonylhalorhenium, $Mo(CO)_4(piperidine)_2$, $W(CO)_4(piperidine)_2$, or halotrimethylplatinum, since the rhenium, platinum, molybdenum, or tungsten complexes [**24a**(**r**−**t**), **24c**(**r**−**t**), **25a**(**r**−**t**), **26c**, or **27c**, respectively] have been isolated (Scheme 8).[16,40]

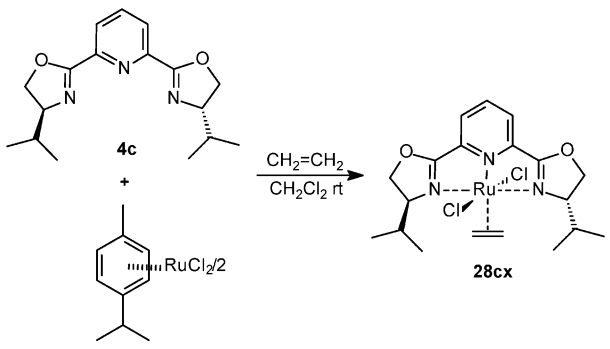
Scheme 8



Besides these exceptions, pybox behaves as a tridentate ligand in several metal complexes, and those coordinated by ruthenium are by far the most studied.

The first complex was obtained by mixing $[RuCl_2(p\text{-cymene})]_2$ and **4c**; the dark-red solution was stirred under ethylene (or carbon monoxide, or *tert*-butylisonitrile), and **28cx**, **28cy**, and **28cz** were obtained respectively, in more than 80% yield (Scheme 9 reports the reaction of **4c** with ethylene).[11,41] Similarly, from **4b**,**e**,**i**,**j**,**r** and ethylene, the analogous complexes **28bx**, **28ex**, **28ix**, **28jx**, and **28rx** have been obtained under the same conditions.[11]

Scheme 9



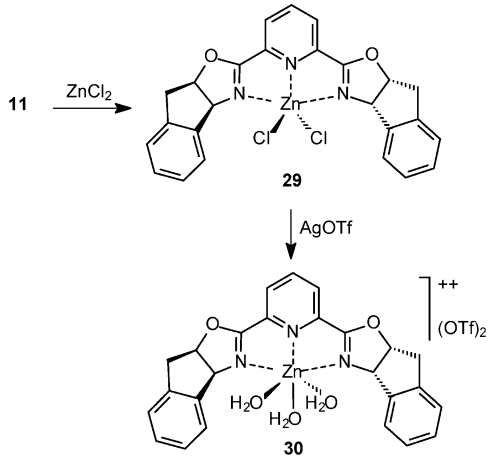
The same protocol allowed the preparation of a large variety of ruthenium complexes starting from different pybox units, with different halogenides or counterions, the main variation being the incorporation of different organic ligands (such as acrolein, methyl vinyl ketone, methyl acrylate, dimethyl fumarate, several mono- and disubstituted carbenes, some pyridines, *trans*-cyclooctene, azine derivatives).[9,11,35,42−53] Through this procedure, the synthesis of **28cx** is amenable to a large-scale preparation.[17] In a similar way, starting from $[OsCl_2(p\text{-cymene})]_2$ complex, $[\mathbf{4a}\cdot OsCl_2\cdot(RCH{=}CH_2)]$ was obtained in more than 70% yield.[47] Ruthenium complexes of **4u**, having Ru and triphenylphosphine in the ratio of either [1:1] or [1:2], were prepared by refluxing the ligand with $Ru(PPh_3)_4Cl_2$ or $Ru(PPh_3)_3Cl_2$.[54]

A series of Pd(II) complexes have been prepared from **4c**,**h**−**k** and $[Pd(CH_3CN)_4](BF_4)_2$. All structures have a square planar geometry, and the fourth ligand can be either acetonitrile, the formate ion, 2,6-dimethylpyridine, methylisocyanate, or even triphenylphosphine.[14,15]

Several copper(II), lanthanide, and silver complexes, the latter giving self-assembled double and triple helicates, will be discussed in the forthcoming section.

Pybox **11** was the ligand of choice for the preparation of a series of Zn(II) and Pd(II) complexes that may involve one or two pybox units coordinated to the same cation. If **11** with $Pd(MeCN)_4(BF_4)_2$ gives, as reported above, a complex with a square planar geometry, $ZnCl_2$ gives the pentacoordinated complex **29** that, with silver triflate, affords the triaquo-complex **30** with six as coordination number (Scheme 10).[26]

Scheme 10



When **11** reacted with zinc triflate, a new complex was obtained, whose composition was $[(\mathbf{11})_2\cdot Zn](OTf)_2$.[26] This complex belongs to the family having a ratio [pybox:cation] of [2:1] that can be either homochiral, as in this case, or heterochiral.

This group of complexes involving two pybox units coordinated to the same cation deserve a short discussion and the cobalt (II) complexes, prepared with a series of enantiopure ligands (**4a**, **4h**, **4j**, and their enantiomers: R = Me, Ph, and CH_2Ph, respectively), allow us to introduce this argument. Cobalt perchlorate reacts with all enantiopure ligands to give the corresponding homochiral complexes (yields around 75%), having an octahedral structure and two pybox units per Co(II) cation. When the same reaction was run on equimolar amounts of (*R*,*R*) and (*S*,*S*) ligands, **4a** and **4j** gave a mixture of homochiral and heterochiral complexes (33:66 and 50:50, respectively), but the phenyl-substituted pybox **4h** gave exclusive formation of the heterochiral species.[55] This remarkable difference in diasteroselectivity may be explained in terms of steric repulsions between the

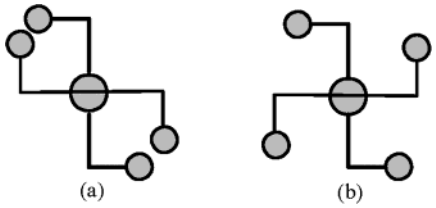


Figure 2. Interpybox interactions in homochiral (a) and heterochiral complexes (b).

substituents that are stronger in the homochiral than in the heterochiral complex (Figure 2).

The lanthanide complexes have been the subject of a recent review that mentions the few pybox structures known.[56] The preliminary results of a research, which deserves much attention in the light of the previous considerations, report that the reaction of $Eu(OTf)_3$ with an equimolar mixture of the pybox enantiomers **4c** and **4d** gives exclusively the heterochiral complex, whereas the same reaction, run with $Yb(OTf)_3$, gives a mixture of both homochiral complexes, with a small amount of the heterochiral one.[57,58] Thus, the ionic radius of the cation may have the same effect on the diastereoselective formation of the complex as the substituent on the oxazoline ring of the pybox.

B. Structures

1. X-ray Crystal Structures

For the purposes of this review, we wish to extrapolate from the X-ray crystallographic data, easily available elsewhere, some outstanding crystal structures that for their specific interest may transmit the key information to gain insight into the structure of the catalyst, such as the coordination number and the nature of ligands other than pybox coordinated to the cation. We hope this will shed some light on the modifications undergone by the catalyst to be transformed into the reacting complex involved in the catalytic cycle, resuming from this the origin of stereoselectivity induced in the catalyzed reaction. Therefore, we will report a homogeneous representation of the crystal structures based on the reported atomic coordinates, which gives an immediate vision of the coordination number around the metal, the pybox, the anions and the auxiliary ligands. For this reason we will always represent the cation and the pybox in the traditional color (e.g., oxygen, red; nitrogen, blue), whereas all atoms of anions and auxiliary ligands (except water) will be yellow. If an organic molecule involved in a catalytic cycle is

Table 3. Reported X-ray Crystal Structure of Pybox Complexes

entry	no.	pybox	metal	coordination	structure	further ligands	ref
1	**23co**	**4c**	Rh	4[a]	square-planar	(*n*-$PrPh_2P)_2$ (CO)	39
2	**24ar**	**4a**	Re	6[b]	octahedral	$(CO)_3$ Cl	16
3	–	**4c**	Mo	6[b]	octahedral	$(CO)_4$	40
4	**21c**	**4c**	Rh	6[c]	octahedral	Cl_3	6,8
5	–	**4c**	Rh	6[c]	octahedral	(CH_3) (CO) J	39
6	**31**	**4u**	Rh	6[c]	octahedral	$O(CH_2C{=}CCO_2Me)_2$ Cl	59
7	–	**4u**	Rh	6[c]	octahedral	$O(CH_2CC)_2PhCO_2Me$ Cl	59
8	–	**4u**	Ru	6[c]	octahedral	ethylene Cl_2	11, 48
9	–	**4c**	Ru	6[c]	octahedral	*trans*-cyclooctene Cl_2	52
10	**32**	**4a**	Ru	6[c]	octahedral	acrolein Cl_2	51, 53
11	–	**4u**	Ru	6[c]	octahedral	acrolein Cl_2	53
12	–	**4h**	Ru	6[c]	octahedral	methyl acrylate Cl_2	53
13	–	**4c**	Ru	6[c]	octahedral	$(MeCOO)_2$ (CO)	11
14	–	**4c**	Ru	6[c]	octahedral	$[{=}C(COOMe)_2]$ Cl_2	47
15	–	**4c**	Ru	6[c]	octahedral	pyridine Cl_2	49
16	–	**4c**	Ru	6[c]	octahedral	*cis*-$(pyridine)_2$ Cl	49
17	–	**4c**	Ru	6[c]	octahedral	*trans*-$(pyridine)_2$ Cl	49
18	–	**4u**	Ru	6[c]	octahedral	(Ph_3P) Cl_2	54
19	–	**4c**	Ru	6[c]	octahedral	(Ph_3P) Cl_2	61
20	–	**4c**	Ru	6[c]	octahedral	(Ph_3P) Cl $(C{=}C{=}CPh_2)$	61
21	–	**4c**	Pd	4[c]	square-planar	MeCN	14
22	–	**4h**	Pd	4[c]	square-planar	MeCN	15
23	–	**4j**	Pd	4[c]	square-planar	Ph_3P	15
24	–	**11**	Zn	5[c]	trigonal-bipyram.	Cl_2	26
25	–	**11**	Zn	6[c]	octahedral	$(H_2O)_3$	26
26	–	**4c**	Cu	5[c]	square-pyramidal	$(H_2O)_2$	62, 63
27	–	**4c**	Cu	5[c]	square-pyramidal	(H_2O) (OTf)	63
28	–	**4c**	Cu	5[c]	square-pyramidal	dimethoxyethane	62
29	**33**	**4h**	Cu	5[c]	square-pyramidal	$BnOCH_2CHO$	62
30	–	**4h**	Sn	6[c]	ψ-octahedral	$(OTf)_2$	64
31	**34**	**14b**	La	9[c]	–	$(H_2O)_4$ $(OTf)_2$	27
32	**35**	**4h**	Sc	7[c]	pentagonal-bipyr.	(H_2O) $(OTf)_3$	65
33	–	**(4i)$_2$**	Co	6[c]	octahedral	–	55
34	–	**(4c)$_2$**	La	9[c]	–	$(OTf)_3$	57, 58
35	–	**(4d)$_2$**	Yb	8[c]	–	$(OTf)_2$	58
36	–	**(4c)(4d)**	Eu	10[c]	–	(H_2O) $(OTf)_3$	58
37	**36**	**(4h)$_2$**	Cu	6[c]	octahedral	–	62
38	**37**	**(4h)(4i)**	Cu	6[c]	octahedral	–	62
39	–	**(11)$_2$**	Zn	6[c]	octahedral	–	26
40	–	**(4j)$_2$**	2Ag	–	double helicate	–	66, 67
41	–	**(4i)$_3$**	3Ag	–	triple helicate	–	66, 67

[a] Pybox as monodentate ligand. [b] Pybox as bidentate ligand. [c] Pybox as tridentate ligand.

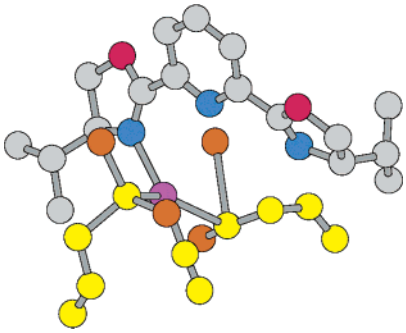


Figure 3. Molecular structure of [**4c**·Rh(CO)($PPrPh_2$)$_2$(Et_2O)(PF_6)] (**23co**) [only the first carbon atom of the phenyl groups (orange) is reported; diethyl ether and hexafluorophosphate anion are omitted for clarity] (ref 39).

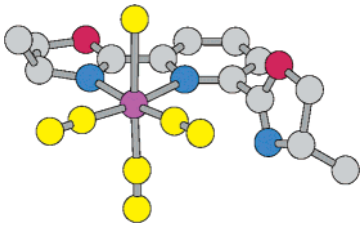


Figure 4. Molecular structure of [**4a**·$ReCl(CO)_3$] (**24ar**) (ref 16).

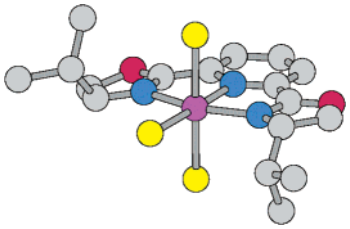


Figure 5. Molecular structure of [**4c**·$RhCl_3$] (**21c**) (refs 6 and 8).

present in the crystal structure, its carbon atoms will be represented in green and the other atoms, as far as possible, in the traditional colors.

The reader should be able to imagine, taking as constant the coordination number, which ligand could be removed to dock the reagent onto the metal and the relative consequences on the selectivity of the catalyzed reaction. Not all the 41 crystal structures will be illustrated, but each one will be listed in Table 3 with its most significant features.

Complexes with Pybox as a Monodentate Ligand. The molecular structure of **23co**,[39] with two phosphines, a carbonyl group, and **4c** (behaving as a monodentate ligand) with a square-planar arrangement around rhodium(I), is the first (and until now the only) example of this class of complexes (Figure 3).

Complexes with Pybox as a Bidentate Ligand. Two octahedral structures, coordinated around Re(I) and Mo(0),[16,40] clearly illustrate the behavior of pybox as a bidentate ligand. The molecular structure of the former complex (**24ar**) is reported in Figure 4.

Complexes with a Single Pybox as a Tridentate Ligand. This is by far the most ordinary behavior of pybox as a ligand with more than 10 metals.

Figure 5 shows the crystal structure of the complex [**4c**·$RhCl_3$] (**21c**) that gave origin to the pybox story

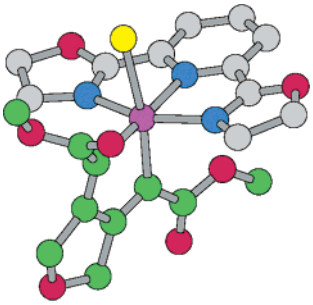


Figure 6. Molecular structure of [**4u**·O($CH_2CC{=}CO_2Me$)$_2$Cl] (**31**) (ref 59).

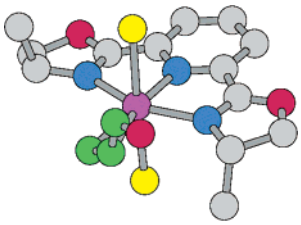


Figure 7. Molecular structure of [**4a**·$RuCl_2$(acrolein)] (**32**)-(ref 51, 53).

where the octahedron positions are held by three chlorine ions and the nitrogen atoms of **4c**.[6,8]

Recently, two nonchiral Rh(I) complexes (Table 3, entries 6 and 7) have been prepared from [Rh(*cis*-cyclooctene)$_2$Cl]$_2$, **4u**, and a diyne that fills an equatorial and an apical position giving a rhodacyclopentadiene moiety, with a chlorine ion in the residual apical position of the octahedral complex (Figure 6 reports the complex **31** with the symmetric diyne).[59]

Thirteen crystal structures of octahedral ruthenium(II) complexes have been determined. In general, the coordination involves one pybox, two anions (chloride or acetate), and a further ligand (pyridine, triphenylphosphine, carbonyl, allenylidene, or a double bond).[11,47−49,51−54,60,61] The most important complexes are those having a double bond with a parallel coordination to the pybox plane due to the back-donation of the electrons of the filled d orbital to the vacant p orbital of the coordinated C=C double bond. Figure 7 represents the complex **32** with the nitrogen atoms of **4a** in three equatorial positions, two apical chlorine ions and acrolein in the fourth equatorial position around ruthenium. Acrolein has an *s*-trans conformation, and the carbonyl group is trans to the pybox methyl substituent.[51,53] The reason of the choice of this crystal structure is because **32** can be regarded as the reacting complex in the catalytic cycle of the asymmetric phenylation of acrolein with phenyllithium. The illustrated enantioface-selective coordination of acrolein rationalizes the 87% ee of the resulting (*S*)-1-phenyl-2-propen-1-ol,[53] a result that will be discussed in the appropriate section.

Palladium(II) complexes[14,15] are always square-planar, whereas Zn(II) may offer a variety of structures[26] being either trigonal-bipyramidal or octahedral and involving one or two pybox in the complex.

If the copper(II) cation coordinates one pybox unit, the complex is square-pyramidal, the residual two positions have two water molecules or one water and one triflate anion,[62,63] and these two ligands may be substituted by one molecule of dimethoxyethane.[62]

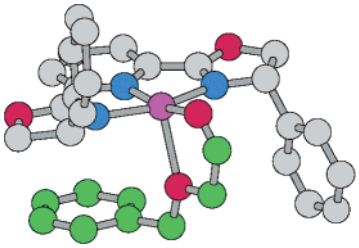


Figure 8. Molecular structure of [**4h**·Cu(BnOCH$_2$CHO)] (**33**) (ref 62).

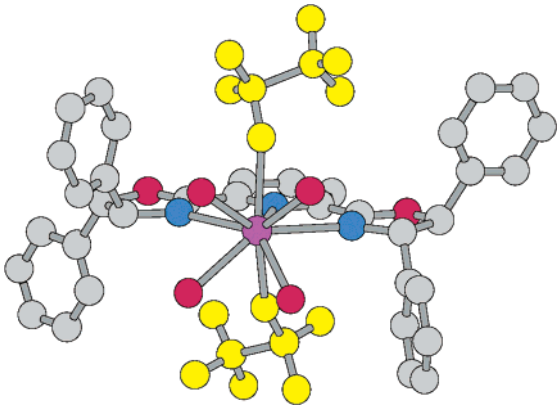


Figure 9. Molecular structure of [**14b**·La(OTf)$_2$(H$_2$O)$_4$] (**34**) (ref 27).

Evans succeeded to isolate the square-pyramidal copper (II) complex of **4h** and (benzyloxy)acetaldehyde, the reacting complex involved in the catalytic enantioselective aldol addition of enolsilanes to the aldehyde. This crystal structure (**33**) shows that the carbonyl group is equatorial and occupies the more Lewis acidic site, while the oxygen ether is in the axial position (Figure 8); the result is that the Re face of the aldehyde carbonyl group is shielded by the phenyl of the pybox.[62]

The tin(II) complex of **4h** catalyzed a similar aldol reaction, and its crystal structure revealed an octahedral geometry with two triflate ligands away from the stereochemically active Sn(II) lone pair laying equatorial with pybox.[64] The effects of these configurations on the enantioselectivity will be discussed in the related section.

The La(III) complex of **14b** has 9 as its coordination number (Figure 9) due to three nitrogen, two triflate anions, and four water molecules (**34**).[27] Quite similar is the Sc(III) complex of **4h**, whose coordination number is 7 (Figure 10) due to three nitrogens, three triflate anions, and one water (**35**).[65] Both these structures had a paramount importance to rationalize the enantioselective catalysis of the Mukaiyama−Michael reaction and the synthesis of homopropargylic alcohols, catalyzed by the pybox complexes **34** and **35**.

Complexes with Two Pybox around a Single Cation. When two pybox ligands are coordinated to the same cation, homochiral or heterochiral complexes are obtained, depending on the enantiomeric composition of the ligand. It has already been reported the effect of different substituents on the homo- versus heterochiral composition of Co(II) complexes.[55] The ionic radius of the lanthanide cations may have the same effect on the diastereoselective

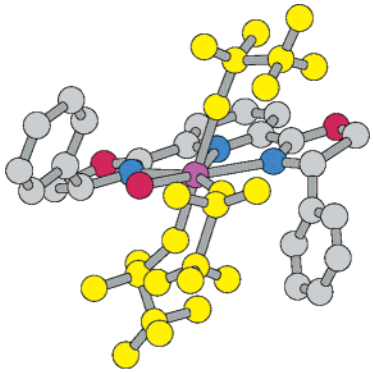


Figure 10. Molecular structure of [**4h**·Sc(OTf)$_3$(H$_2$O)] (**35**)-(ref 65).

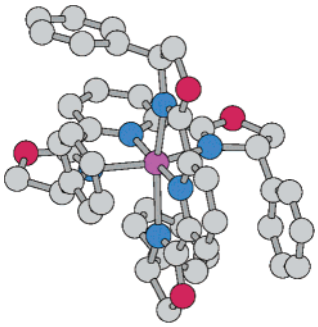


Figure 11. Molecular structure of [(**4h**)$_2$Cu] (**36**) (ref 62).

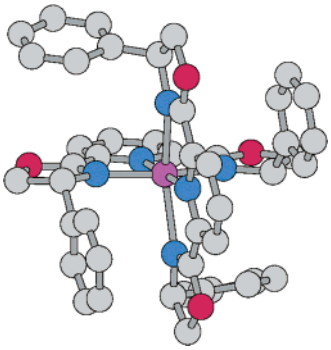


Figure 12. Molecular structure of [(**4h**)(**4i**)Cu] (**37**) (ref 62).

formation of the complex as the substituent on the ligand, and a strictly related effect can be observed in the coordination number of the homochiral complexes of La(III) and Yb(III) (9 and 8, respectively), whereas the heterochiral complex Eu(III) has 10 as its coordination number.[57,58]

If the racemic complex is thermodynamically more stable than the homochiral one, it can play an important role in enantioselective catalysis, and it can give rise to a chiral amplification due to the reservoir effect.[36] Figure 2 represents the steric repulsions between the substituents in the homochiral complex that make this less stable than the heterochiral one. Figures 11 and 12 are the X-ray structures of the homochiral [(**4h**)$_2$Cu(II)] and heterochiral [(**4h**)(**4i**)Cu(II)] complexes (**36**) and (**37**),[62] which clearly support the above considerations.

Helicate Complexes. The formation of helical complexes by simply mixing ligands and metal ions is a fascinating area of coordination chemistry. The

Table 4. Chemical Shift (δ, ppm) of the ^{1}H NMR Spectra of 4a,c and Rh, Al, and Re Complexes

product	coordinat. or free oxazoline	CH_3	$CHMe_2$	4′-H (1H)	5′-H (2H)	3,5-H pyridine	4-H pyridine	ref
4c	–	0.94, 1.06	1.88	4.18	4.23, 4.54	8.21	7.86	68
$RhCl_3$-**4c**	–	0.97, 0.99	3.04	4.62	4.94, 4.98	8.09	8.43	68
$AlCl_3$-**4c**	coordinat.	1.11, 1.15	2.44	4.71	4.91, 5.11	8.14, 8.54	8.13	68
	free	1.02	2.19	4.16	3.78, 3.86		8.13	
4a	–	1.33	–	4.00	4.03, 4.57	7.82[a]	8.13[a]	16
$ReJ(CO)_3$-**4a** (*major*)	coordinat.	1.55	–	4.58	4.42, 4.97	7.91, 7.94	8.05	16
	free	1.41		4.58	4.05, 4.79			
$ReJ(CO)_3$-**4a** (*minor*)	coordinat.	1.67	–	4.58	4.58, 4.96	7.91, 7.94	8.05	16
	free	1.39	–	4.58	4.11, 4.70	–	–	

[a] Data reported in the reference, in general pybox have 3,5-H more deshielded than H-4 (e.g., ref 8).

ligands **4j** and **4i**, with $AgBF_4$ in acetonitrile, give self-assembled dimeric and trimeric complexes that crystallize as double or triple helicates.[66,67]

2. Spectroscopic and Computational Results

Sometimes important information about the structure of the complex can be obtained through ^{1}H- and ^{13}C NMR spectroscopy. A comparison of the ^{1}H NMR spectra of free and coordinated pybox is reported in Table 4.

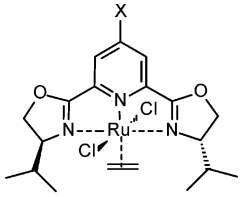
The spectrum of the $RhCl_3$ complex is fully compatible with structure **21**, with **4c** behaving as tridentate ligand. The oxazoline protons (4′,5′a and 5′b) are strongly deshielded, as well as the 4H proton of the pyridine ring. Thus, three N atoms are involved in the coordination, and the complex retains the C_2 symmetry of the ligand. This cannot be assumed from the spectrum of the corresponding $AlCl_3$ complex. Paradigmatic is the 4′-H proton splitted into two signals, one strongly deshielded and one slightly shielded. Therefore, pybox has only one oxazoline N atom involved in the coordination, and this kind of complex is further supported by quantum chemical calculations.[68]

The ^{1}H NMR spectrum of the tricarbonyl-iodorhenium(I) complex of **4a** (**24at**) (the same for the analogous chloro and bromo derivatives **24ar**,**s**) displays two set of signals, in a [74:26] ratio, each of them showing complexed and uncomplexed protons. This not only indicates that pybox behaves as a bidentate ligand, but also that the complexation is more sophisticated than the crude representation given in Scheme 8. **24at** is therefore a mixture of two isomers; to the major one, the structure with the apical iodine cis to the methyl group in the complexed oxazoline ring was tentatively assigned, while the minor isomer was that with the apical iodine trans to the same methyl group.[16]

Spectroscopy sometimes allows us to infer the structure of either the catalyst or the reacting complex involved in the catalytic cycle of the reaction under investigation.

The ruthenium-ethylene complex of **4c** (**28cx**, X = H), a good catalyst for the cyclopropanation reaction, was synthesized with different substituents in position 4 of the pyridine (Chart 3). The ^{1}H NMR spectra[44] show a significant influence of X on the chemical shifts of the ethylene protons. The electron-donating groups induce a downfield shift of Hα and Hβ, the protons of the coordinated ethylene (Table 5), that parallels the remote electronic control of the selectivity discussed in section IVB1.

Chart 3



28cx: (X =H)
28cx1: (X = NMe_2)
28cx2: (X = OMe)
28cx3: (X = Cl)
28cx4: (X = COOMe)

Table 5. Chemical Shifts (δ, ppm) of Ethylenic Protons in Complexes 25cx1−4

	28cx1 (X = NMe_2)	**28cx2** (X = OMe)	**28cx** (X = H)	**28cx3** (X = Cl)	**28cx4** (X = COOMe)
Hα	5.05	5.13	5.24	5.27	5.42
Hβ	4.73	4.84	4.94	4.96	5.13

^{1}H and ^{13}C NMR spectroscopy help to infer the structure of the ruthenium complex, formed from **28cx** and 2,6-di-*tert*-butyltolyl diazoacetate, which reacts with styrene to give a mixture of *cis*- and *trans*-cyclopropanes, as discussed in the related section. The NMR spectra[46] show that the methyne group of Ru=*CH*-OCOAr has a clear carbene character: δ 21.67 ppm for $H_{carbene}$, δ 305.7 ppm for $C_{carbene}$, and the C−H coupling constant 142.4 Hz are data indicating that hybridization of the carbene-carbon atom is close to sp^2.

^{1}H and ^{13}C NMR spectroscopy allowed to infer the structure of the complex [**14c**·La(OTf)(3-crotonoyl-1,3-oxazolidin-2-one)],[27] intermediate of the Mukaiyama−Michael reaction discussed in section IVA1.

Finally, the EPR spectra of [**4c**·Cu (benzyloxyacetaldehyde)][69] and [**4c**·Cu (methyl pyruvate)][70] support a square planar structure for the reacting complexes of the Mukaiyama-aldol reactions discussed in the next section.

IV. Reactions

A. Addition to C=O and C=N Double Bonds

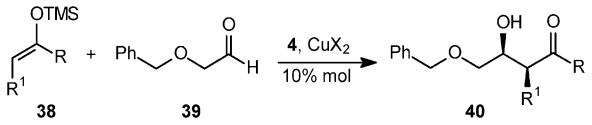
1. Aldol Additions and Related Reactions

The aldol addition is one of the most important reactions for the stereoselective construction of car-

bon−carbon bonds. The aim of organic chemistry is to run the reaction catalytically and enantioselectively, and this goal was approached by using chiral Lewis acids as catalysts in the addition of enolsilanes to aldehydes and α-ketoesters, the commonly known Mukaiyama variant of the aldol reaction. It is mainly merit of Evans and co-workers to have introduced the use of box and pybox as ligands for Cu(II) and for other cations, and recently, an agile review summarized their contribution to this and to nearby fields.[71]

The reaction between silylketene acetals **38** and (benzyloxy)acetaldehyde (**39**) to give **40** was first studied (Scheme 11), and this aldehyde was chosen

Scheme 11



on the assumption that it can behave as a bicoordinating reagent.[62,69] This reaction can be run in the presence of several Cu(II)−pybox complexes, but the most selective catalyst was {[Cu·(**4h**)](SbF$_6$)$_2$} (**41**), which gave (*S*)-**40** with up to 95% ee. Table 6 (entries 5, 9, and 10) shows that this catalyst have a quite general application with respect to the silylketene acetal structure. The experiments described in Table 6 (entries 2−5) were also run with the corresponding zinc complexes, but the results (in term of enantioselectivity) showed the superior efficiency of Cu(II) as a coordinating cation.[72]

With substituted silylketene acetals, syn selectivity (>95:5) was observed (Table 6, entries 11 and 12 as well as other examples mentioned in the references), and silyl crossover experiments indicate that the silyl-transfer step is intermolecular.[62] This was not

Table 6. Effect of Ligand, Counterion, Silylketene Acetal Substituents, and Temperature in the Cu(II)-Catalyzed Reaction between 38 and 39

entry	**4**	X$^-$	R	R^1	*T* (°C)	**40** syn:anti	**40** % ee	ref
1	**4f**	SbF$_6$	S-*t*-Bu	H	−78	−	62	62
2	**4c**	SbF$_6$	S-*t*-Bu	H	−78	−	85	62, 72
3	**4j**	SbF$_6$	S-*t*-Bu	H	−78	−	67	62, 72
4	**4h**	OTf	S-*t*-Bu	H	−78	−	96	62, 72
5	**4h**	SbF$_6$	S-*t*-Bu	H	−78	−	99	62, 72
6	**4h**	SbF$_6$	S-*t*-Bu	H	−50	−	87	62
7	**4h**	SbF$_6$	S-*t*-Bu	H	−20	−	82	62
8	**4h**	SbF$_6$	S-*t*-Bu	H	0	−	78	62
9	**4h**	SbF$_6$	S-Et	H	−78	−	98	62, 69
10	**4h**	SbF$_6$	O-Et	H	−78	−	98	62, 69
11	**4h**	SbF$_6$	S-Et	Me	−78	97:3	97	62
12	**4h**	SbF$_6$	S-Et	i-Bu	−78	95:5	95	62

the sole experiment run to investigate the mechanism. A strong chiral amplification was observed [25% ee **4h** gave 74% ee **40** (R^1 = H, R = (*S*)-*t*-Bu)] that can be assigned to the reservoir effect.[36] For this reason **36** and **37** (the homochiral complex and the heterochiral one responsible for the reservoir effect) were synthesized and their structures determined.

To rationalize the observed sense of induction, a chelation of the aldehyde **39** to the copper ion to give a square pyramidal reacting complex was proposed.[62] Double stereodifferentiating experiments, EPR spectroscopy, and the crystal structure of **33** (in which **39** is bound to the catalyst **41**) supported the proposed reacting intermediate of the catalytic cycle. The mechanism depicted in Figure 13 represents the paradigm of the Mukaiyama-aldol enantioselective catalyzed addition and a good example of the synergetic effect obtained studying a reaction through a multi-information approach.

An example of application of the above reaction is the asymmetric synthesis of the C$_{20}$−C$_{38}$ subunit of

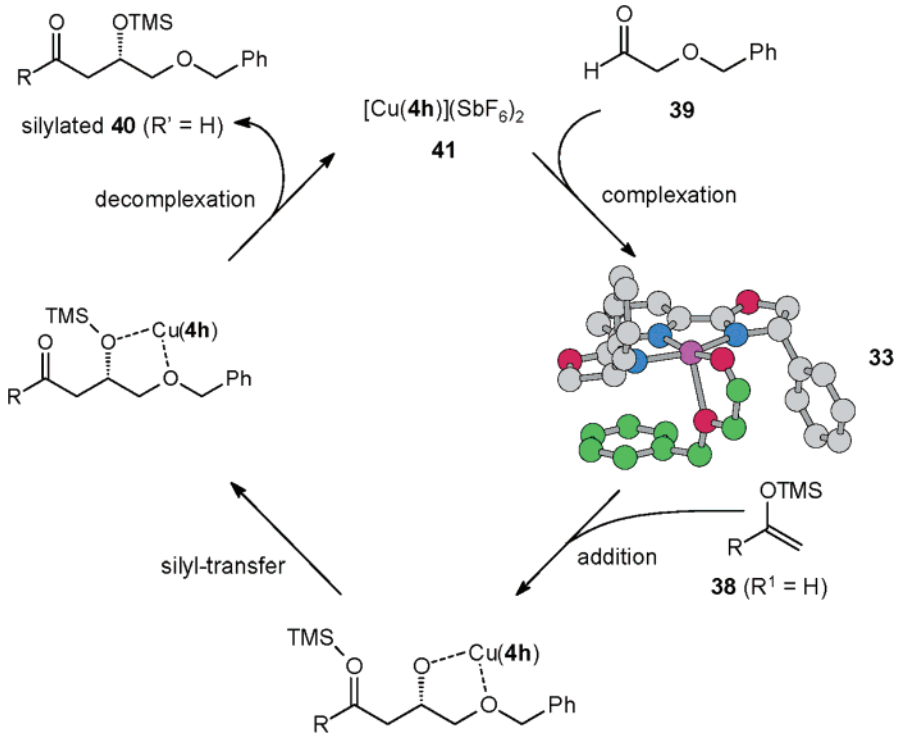


Figure 13. The catalytic cycle of the Mukaiyama-aldol reaction between **38** and **39**.

Table 7. Aldol Reaction between 38 and Pyruvates 42 Catalyzed by Either Cu(II) (Product 43) or Sn(II) Pybox Complex (Product 44)

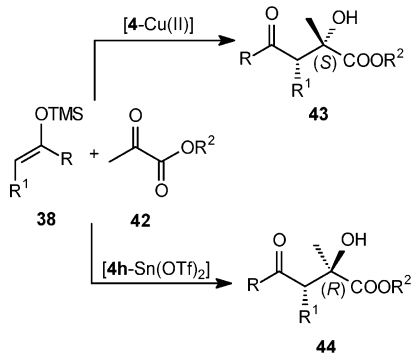
entry	R	R^1	config. of **38**	R^2	pybox	salt	anti:syn [**44**:**43**]	yield (%)	ee % (config.)	ref
1	S-*t*-Bu	H	−	Me	**4c**	$Cu(SbF_6)_2$	−	92	95 (*S*)[a]	70, 74
2	S-*t*-Bu	H	−	Me	**4f**	$Cu(SbF_6)_2$	−	quant.	4 (*S*)[a]	70
3	S-*t*-Bu	H	−	Me	**4h**	$Cu(SbF_6)_2$	−	quant.	62 (*S*)[a]	70
4	S-*t*-Bu	H	−	Me	**4j**	$Cu(SbF_6)_2$	−	quant.	79 (*S*)[a]	70
5	S-*t*-Bu	H	−	Me	**4c**	$Cu(OTf)_2$	−	68	61 (*S*)[a]	70
6	S-*t*-Bu	H	−	Et	**4c**	$Cu(SbF_6)_2$	−	91	91 (*S*)[a]	70
7	S-*t*-Bu	H	−	Bn	**4c**	$Cu(SbF_6)_2$	−	91	84 (*S*)[a]	70
8	S-Et	H	−	Me	**4c**	$Cu(SbF_6)_2$	−	87	82 (*S*)[a]	70
9	S-Et	Me	(*Z*)	Me	**4c**	$Cu(SbF_6)_2$	15:85	quant.	74 (*S*)[b]	70
10	S-*t*-Bu	Me	(*Z*)	Me	**4h**	$Sn(OTf)_2$	99:1	94	99 (*R*)[c]	64
11	S-*t*-Bu	Me	(*E*)	Me	**4h**	$Sn(OTf)_2$	99:1	84	96 (*R*)[c]	64
12	S-*t*-Bu	Et	(*Z*)	Me	**4h**	$Sn(OTf)_2$	98:2	84	97 (*R*)[c]	64
13	S-*t*-Bu	i-Bu	(*Z*)	Me	**4h**	$Sn(OTf)_2$	99:1	81	99 (*R*)[c]	64
14	S-Et	Me	(*Z*)	Me	**4h**	$Sn(OTf)_2$	95:5	91	92 (*R*)[c]	64
15	S-Et	Et	(*Z*)	Me	**4h**	$Sn(OTf)_2$	99:1	94	97 (*R*)[c]	64
16	S-Et	i-Bu	(*Z*)	Me	**4h**	$Sn(OTf)_2$	99:1	76	97 (*R*)[c]	64

[a] ee of **43**. [b] ee of the major diastereomer (**43**). [c] ee of **44**.

Phorboxazole B,[73] incorporating the product of the reaction between **39** and 1-methoxy-1,3-ditrimethylsilyoxybutadiene. The excellent selectivity (85% yield, ee >99%) is due to the catalyst **41**.

The second reaction studied in detail is that between **38** and α-oxo esters, the most important being glyoxylates and pyruvates. The reaction with pyruvates **42** can be catalyzed by pybox with either copper(II) or tin(II) cations (Scheme 12), and Table

Scheme 12

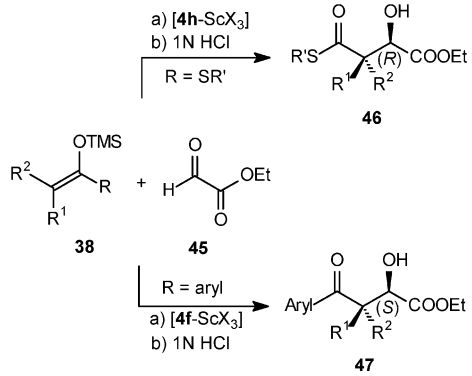


7 collects the results of Cu(II) with different ligands (entries 1−4), counterions (entries 1, 5), representative pyruvate esters (entries 1, 6, 7), and silylketene acetals (entries 1, 8, 9). When **38** has a substituent in the β position (entry 9), the major diastereisomer has the syn configuration.[70,74] The product **43** has a (*S*) configuration at the C-2 carbon atom, and in the absence of an X-ray crystal structure, a semiempirical calculation provides insight into the reasons of the asymmetric induction. With the support of the EPR spectrum of [Cu·**4c**(**42**)]$(SbF_6)_2$, which indicates the presence of a square pyramidal Cu(II) center, a bidentate coordination of **42** with the ketonic oxygen in the equatorial position can be proposed. The attack of **38** on the Si face of the complexed carbonyl group rationalizes both the syn diastereoselectivity and the preferential formation of the (*S*) enantiomer.

When the reaction of methyl pyruvate **42** (R^2 = Me) and silylketene acetals **38** was catalyzed by the tin(II) triflate complex of **4h**, the anti aldol adduct **44** was obtained with a high degree of stereochemical control (Scheme 12 and Table 7, entries 10−16).[64] It is noteworthy that this catalyst serves as a complement to the above-described Cu(II)-based ones. As shown in Table 7, the stereoselectivity of the reaction depends neither from the configuration (*E*) or (*Z*) of **38**, since both isomers react in a stereoconvergent manner, giving the same product (Table 7, entries 10, 11), nor from the type and size of the substituents (entries 10, 12−16). It should be interesting to relate the octahedral geometry of the catalyst, defined by its X-ray structure (Table 3, entry 30), with the coordination of methyl pyruvate to it in order to rationalize the resulting stereoselectivity.

The reaction of **38** (R^2 = H) with ethyl glyoxylate (**45**) was catalyzed by pybox complexes of scandium(III), and the syn adducts **46** were obtained with a high level of enantioselectivity (Scheme 13, Table 8).[75]

Scheme 13



After testing several pybox (**4c**, **4f**, **4j**) the best stereoselectivity was obtained with **4h** when **38** was a silylketene acetal (R = SR: entries 1−6). When **38** was an 1-aryl enolsilane (R = Ar: entries 7−12), the pybox that gave **47** with an excellent stereoselectivity was **4f**. The counterions of the complex were of great importance; the best results with silylketene acetals (entries 13, 14) and ketone enolsilanes (entries 16 and 17) were obtained when two chlorine ions were bound in the complex and SbF_6^- was an uncoordinated

Table 8. Aldol Reaction between Silylketene Acetals or Aryl-Enolsilanes with Ethyl Glyoxylate 45, Catalyzed by Sc(III)/Pybox

entry	R	R^1	R^2	pybox	anions	syn:anti [**46**:**47**]	yield (%)	ee % (config.)	ref
1	S-*t*-Bu	H	H	**4h**	$Cl_2(SbF_6)$	–	92	90 (*R*)[a]	75
2	S-*t*-Bu	Me	H	**4h**	$Cl_2(SbF_6)$	92:8	93	95 (*R*)[a]	75
3	S-*t*-Bu	i-Pr	H	**4h**	$Cl_2(SbF_6)$	95:5	90	99 (*R*)[a]	75
4	S-*t*-Bu	i-Bu	H	**4h**	$Cl_2(SbF_6)$	93:7	94	93 (*R*)[a]	75
5	S-Ph	Et	H	**4h**	$Cl_2(SbF_6)$	92:8	90	95 (*R*)[a]	75
6	S-Et	OBn	H	**4h**	$Cl_2(SbF_6)$	92:8	92	95 (*R*)[a]	75
7	2-Br−C_6H_4	H	H	**4f**[b]	$Cl_2(SbF_6)$	–	91	91 (*S*)[c]	75
8	2,6-Cl_2−C_6H_3	H	H	**4f**[b]	$Cl_2(SbF_6)$	–	96	96 (*S*)[c]	75
9	C_6H_5	Me	Me	**4f**[b]	$Cl_2(SbF_6)$	–	85	95 (*S*)[c]	75
10	4-F−C_6H_4	Me	Me	**4f**[b]	$Cl_2(SbF_6)$	–	85	95 (*S*)[c]	75
11	C_6H_5	$(CH_2)_5$		**4f**[b]	$Cl_2(SbF_6)$	–	80	97 (*S*)[c]	75
12	C_6H_5	$(CH_2)_4$		**4f**[b]	$Cl_2(SbF_6)$	–	81	98 (*S*)[c]	75
13	S-Et	$(CH_2)_4$		**4h**	$(OTf)_3$	–	87	6 (*R*)[a]	76
14	S-Et	$(CH_2)_4$		**4h**	$Cl_2(SbF_6)$	–	90	95 (*R*)[a]	76
15	S-Et	$(CH_2)_4$		**4f**	$Cl_2(SbF_6)$	–	45	62 (*S*)[a]	76
16	C_6H_5	Me	Me	**4h**[b]	$(OTf)_3$	–	90	4 (*R*)[c]	76
17	C_6H_5	Me	Me	**4h**[b]	$Cl_2(SbF_6)$	–	70	32 (*R*)[c]	76
18	C_6H_5	Me	Me	**4f**[b]	$Cl_2(SbF_6)$	–	85	95 (*S*)[c]	76

[a] ee of **46**. [b] 2.0 equiv TMS-Cl. [c] ee of **47**.

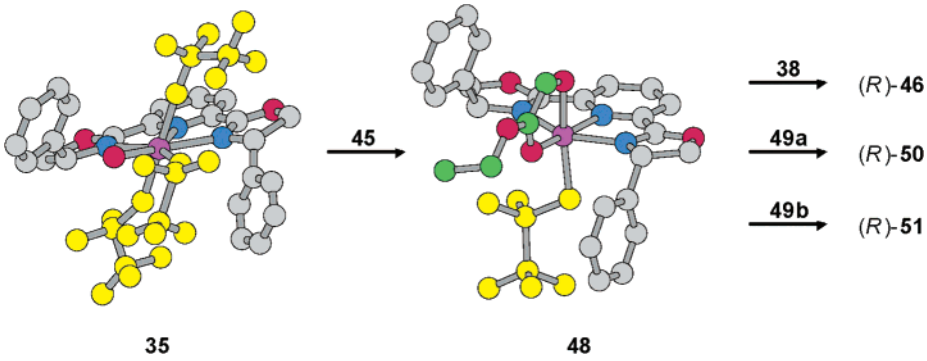


Figure 14. From catalyst, through the reacting complex, to products of the reactions reported in Schemes 13 and 14.

anion.[76] The high enantioselectivity of the above reactions allowed to obtain a series of pantolactone derivatives, isolated in excellent enantiomeric excesses, also useful as chiral auxiliary in asymmetric synthesis.[76]

The stereochemical preference for the (*R*) or (*S*) enantiomer of the product requires the coordination of the aldehyde functionality of glyoxylate in the apical or in the equatorial position respectively; this competitive coordination depends on the pybox substituents. The enantiomer (*R*)-**46** is obtained from **4h**, and the stereochemical course of the reactions can be rationalized by assuming the structure **48**, represented in Figure 14, for the reacting complex involved in the catalytic cycle. This model was computationally created from the pentagonal-bipyramidal crystal structure **35** by replacing the vicinal triflates and the water molecule with **45** to give the octahedral complex **48**.[65] If a further anionic ligand is retained in the equatorial position, a pentagonal-bipyramidal complex is obtained that affords the same sense of induction promoted by **48**, since thiosilylketene acetal **38** cannot add from the Si face shielded by the pybox phenyl group. This model rationalizes the preferred formation of (*R*)-**46**.[75] With **4f** as ligand, steric reasons may induce the coordination of **45** with the aldehyde moiety bound in the equatorial position, thereby favoring addition to its Si face and formation of (*S*)-**46**.[75]

The reaction between ethyl glyoxylate (**45**) and allenylsilanes **49a**,**b**, similar to the Mukaiyama-aldol reaction described above, can be enantioselectively catalyzed by the same scandium complex **35**. Six 1-substituted-1-(trimethylsilyl)allenes (**49a**) gave, after desilylation, homopropargylic alcohols **50** (yields 63−96%, ee 90−98%), while the more sterically demanding *tert*-butyldiphenylsilyl analogues (**49b**) completely altered the course of the reaction and provided dihydrofurans **51** (seven examples: yields 32−91%, ee 85−94%) (Scheme 14).[65]

Scheme 14

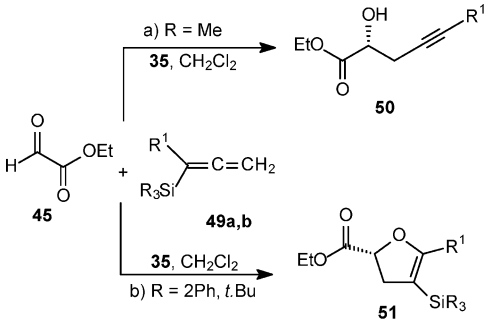


Table 9. Reductive Aldol Reactions between Different RCHOs, Methyl Acrylate (52), and Diethylmethylsilane, Catalyzed by Pybox−[(cod)IrCl]$_2$

entry	R	pybox	yield (%)	syn:anti	**53** ee %
1	Ph	**4a**	<10	63:37	50
2	Ph	**4c**	46	43:57	rac.
3	Ph	**4f**	32	67:33	80
4	Ph	**4h**	30	60:40	70
5	Ph	**11**	48	80:20	92
6	$BnOCH_2$ (**39**)	**11**	49	91:9	96
7	$TBSOCH_2$	**11**	47	89:11	96
8	Et	**11**	<5	−	−
9	$BnOCH_2CH_2$	**11**	65	73:27	82
10	PhCH=CH	**11**	0	−	−

Since the absolute configuration of the products is (*R*), the stereochemical course of the reactions can be rationalized by assuming the same reacting complex **48** represented in Figure 14, the attack of allenylsilane being the last step of the sequence.

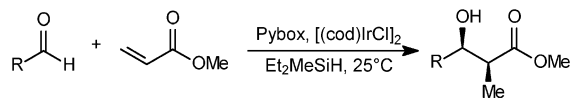
Other examples of aldol reactions catalyzed by pybox complexes of Pd(II),[14] Yb(III),[77] and Cu(II) (run in ethanol/water)[78] have been reported, but discrete enantioselectivities have been obtained only in the Cu(II)-catalyzed reaction between the tributyl tin enolate of cyclohexanone with either benzaldehyde or cinnamaldehyde.[79]

A catalytic enantioselective Mukaiyama addition of silyl enol ethers to diethyl ketomalonate was studied with several Zn− and Cu−box and −pybox complexes. Whereas Cu(II) with box ligands gave excellent enantioselective catalysts, the application of Zn(II)−**4c** and −**4i** gave only moderate yields of the products, accompanied with very low ee.[80]

Two reactions are close to the argument discussed in this section: the reductive aldol and the Mukaiyama−Michael reactions.

The investigation of the catalytic stereoselective reductive aldol reaction between aldehydes and methyl acrylate (**52**) started from an arrayed catalyst evaluation of the variations promoted by three parameters (hydride source, transition-metal salt, and ligand, for a total of 192 combinations).[81] The study revealed **4c** and [(cod) IrCl]$_2$ as the best combination able to induce enantio- and diastereoselectivity in the reaction under discussion. Several experiments were run with benzaldehyde, the Ir(I) salt, diethylmethylsilane, and different pybox ligands to give the adduct **53** (Scheme 15).[82] The nature of the pybox

Scheme 15



52 **53**

substituents has a significant impact on stereoselectivity and the more bulky the substituent, the higher the stereoselectivity, with the best result obtained with indane−pybox **11**. Thus, different aldehydes were tested, and the results are summarized in Table 9.

Even if the yields of **53** are not very good and diastereoselectivity is seldom better than 90:10, the results are interesting inasmuch as enantioselectivity is remarkable with benzaldehyde and with α- and *β*-alkoxy aldehydes (Table 9, entries 5−7, 9) when pybox is **11**. The role of a possible competition between bichelation of the reagent on Ir and inductive effects needs to be further inferred.

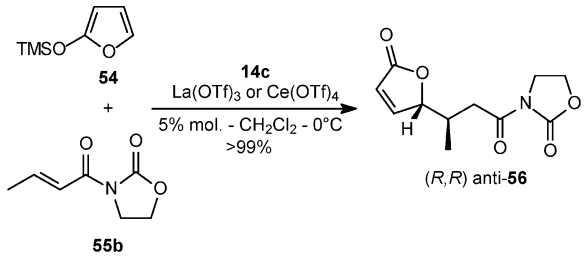
Table 10. Enantioselective Mukaiyama−Michael Reaction between 54 and 55b Catalyzed by 14c-Based Catalysts

entry	salt[a]	anti:syn[b]	**56** ee % (config.)
1	$Mg(ClO_4)_2$	99:1	52 (*R*,*R*)
2	$Co(ClO_4)_2$	93:7	20 (*R*,*R*)
3	$Sc(OTf)_3$	>99:1	83 (*R*,*R*)
4	$La(OTf)_3$	>99:1	>99 (*R*,*R*)
5	$Eu(OTf)_3$	>99:1	98 (*R*,*R*)
6	$Yb(OTf)_3$	>99:1	92 (*R*,*R*)
7	$Ce(OTf)_4$	>99:1	>99 (*R*,*R*)

[a] 4 Å molecular sieves added. [b] Quantitative yields.

The Mukaiyama−Michael reaction between 2-trimethylsilyloxyfuran (**54**) and (*E*)-crotonoyl-1,3-oxazolidin-2-one (**55b**) has been stereoselectively catalyzed by box- and pybox-based catalysts. If the most significant results are considered, **14c** is far better than other ligands, and the cations of election are lanthanides (Table 10). Of the four possible stereoisomers, $La(OTf)_3$ and $Ce(OTf)_4$ gave (*R*,*R*)-*anti*-**56** with complete stereoselectivity (Scheme 16).[27]

Scheme 16



The structure of the reaction intermediate was studied by ^1H and ^{13}C NMR spectroscopy, and both the spectroscopic data and the linear relationship observed between the ee of the adduct and the optical purity of the ligand supported a reacting complex with a ratio [1:1:1] among La(III), **14c**, and **55b**. Figure 15 shows the proposed structure of the reacting complex **57**, which was derived from the enantiomer of **34** (represented in Figure 9) by removing the water molecules and binding **55b** onto the lanthanum center. This model rationalizes the crucial role of the phenyl group in position 5, suitably placed to blind the Si face of the double bond; the attack of **54** on the opposite Re face gives (*R*,*R*)-*anti*-**56** as the only reaction product.

The conjugate addition of 2-furancarbaldehyde oxime to 1-crotonoyl-3-phenyl-2-imidazolidinone (Scheme 17), marginally related to the above-discussed Mukaiyama−Michael reaction, is mentioned here, even if the chiral metal complex derived from **4i** and $Zn(ClO_4)_2$ was poorly active and the product **58** (a chiral nitrone) was obtained with unsatisfactory yield and enantioselectivity.[83]

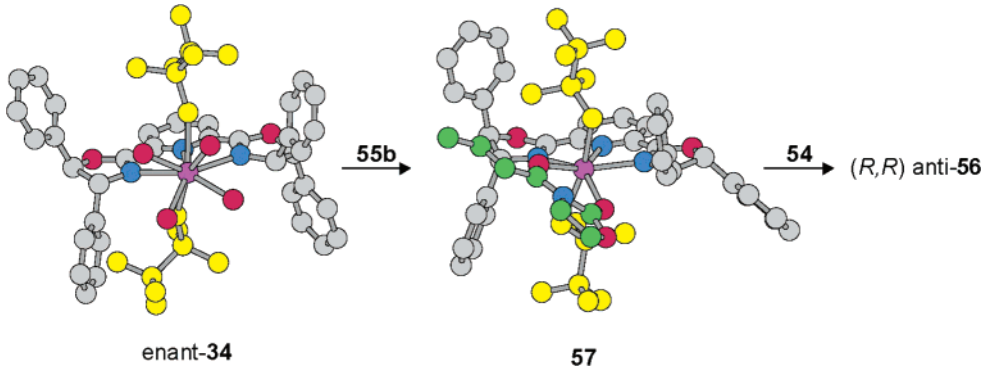
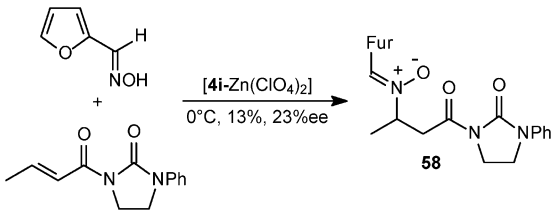
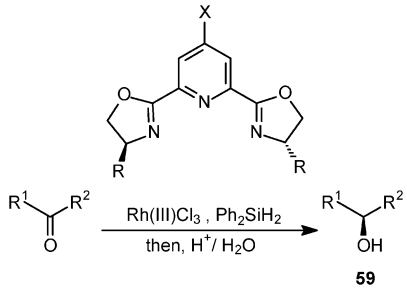


Figure 15. From the structure of the catalyst to the reacting complex, to the product of the Mukaiyama−Michael reaction reported in Scheme 16.

Scheme 17



Scheme 18



2. Reductions of Ketones

The suddenly synthesized pybox−Rh(III)trichloride complexes **21** were tested as chiral catalysts in the asymmetric hydrosilylation of ketones with diphenylsilane, to obtain enantioselectively the secondary alcohols **59** (Scheme 18).[6,8,20,37] The reaction was optimized with acetophenone in the presence of an additive (the most widely used was $AgBF_4$). The catalyst resulted to be very flexible with different ketones often obtaining excellent ee (the best result was 99% ee from 1-tetralone),[8] and a large set of representative results is reported in Table 11.

From Table 11 some trends can be outlined:
(a) the pybox substituents influence the enantioselectivity in the reduction of both acetophenone and ethyl levulinate in the order i-Pr > *s*-Bu > *t*-Bu > Et > Ph (entries 5, 10−13, and 21−25);
(b) the substituent in the 4-position of the pyridine ring does not affect enantioselectivity but increases the rate in the order Cl > H > OMe > NMe_2 (entries 5−8);

Table 11. Asymmetric Hydrosilylation of Ketones with Pybox−Rhodium Catalysts[a]

entry	R^1	R^2	additives	pybox	*T*, °C (time, h)	**59** % yield	% ee (config.)	ref
1	Me	Ph	−	−	rt	−	−	6, 8
2	Me	Ph	BF_3Et_2O	**4c**	0 (14)	90	82 (*S*)	6, 8
3	Me	Ph	$EtAlCl_2$	**4c**	0 (18)	89	67 (*S*)	6, 8
4	Me	Ph	AgOTf	**4c**	−20 (27)	96	89 (*S*)	6, 8
5	Me	Ph	$AgBF_4$	**4c**	0 (2)	91	94 (*S*)	6, 8, 20
6	Me	Ph	$AgBF_4$	**5**	−5 (3)	90	94 (*S*)	20
7	Me	Ph	$AgBF_4$	**6**	10 (18)	86	93 (*S*)	20
8	Me	Ph	$AgBF_4$	**7**	20 (16)	83	90 (*S*)	20
9	Me	Ph	$AgPF_6$	**4c**	−3 (5)	80	87 (*S*)	8
10	Me	Ph	$AgBF_4$	**4e**	−5 (10)	91	91 (*S*)	8
11	Me	Ph	AgOTf	**4f**	0 (18)	92	83 (*S*)	8
12	Me	Ph	$AgBF_4$	**4b**	10 (2)	88	54 (*R*)	8
13	Me	Ph	$AgBF_4$	**4i**	20 (18)	82	19 (*R*)	8
14	Me	α-napht.	$AgBF_4$	**4c**	−5 (5)	87	94 (*S*)	6, 8
15	Me	*β*-napht.	$AgBF_4$	**4c**	−5 (6)	93	93 (*S*)	6, 8
16	Me	*n*-hexyl	$AgBF_4$	**4c**	0 (2)	85	63 (*S*)	6, 8
17	Me	CH_2Ph	$AgBF_4$	**4c**	0 (5)	95	71 (*S*)	8
18	Me	$(CH_2)_2Ph$	$AgBF_4$	**4c**	0 (5)	92	66 (*S*)	8
19	Me	$(CH_2)_2CH{=}CMe_2$	$AgBF_4$	**4c**	20 (20)	94	70 (*S*)	6, 8
20	Me	CH_2COOEt	$AgBF_4$	**4c**	−5 (24)	60	27 (*S*)	6, 8
21	Me	$(CH_2)_2COOEt$	$AgBF_4$	**4c**	0 (7)	91	95 (*S*)	6, 8
22	Me	$(CH_2)_2COOEt$	$AgBF_4$	**4e**	0 (7)	82	94 (*S*)	8
23	Me	$(CH_2)_2COOEt$	$AgBF_4$	**4f**	10 (18)	79	79 (*S*)	8
24	Me	$(CH_2)_2COOEt$	$AgBF_4$	**4b**	10 (4)	80	75 (*R*)	8
25	Me	$(CH_2)_2COOEt$	$AgBF_4$	**4i**	<30	0	−	8
26	Me	$(CH_2)_3OAc$	$AgBF_4$	**4c**	20 (24)	85	68 (*S*)	8
27	Et	Ph	$AgBF_4$	**4c**	5 (4)	73	91 (*S*)	8

[a] 1 mol % with respect to ketone.

Table 12. Enantioselective Addition of TMSCN to Aldehydes Catalyzed by [Pybox/Salt]

entry	R	solvent	pybox	salt	time[a] (h)	**60** % yield	% ee (config.)	ref
1	Ph	CH_2Cl_2	**4c**	$AlCl_3$	16[b]	92	90 (*S*)	68
2	Ph	Et_2O	**4d**	YCl_3	24	85	6 (*R*)	92
3	Ph	$CHCl_3$	**4d**	YCl_3	0.5	81	15 (*R*)	92
4	Ph	PhMe	**4d**	YCl_3	3	97	26 (*R*)	92
5	Ph	CH_2Cl_2	**4d**	YCl_3	3	91	49 (*R*)	92
6	Ph	EtOH	**4d**	YCl_3	24	69	54 (*R*)	92
7	Ph	MeCN	**4d**	YCl_3	1	88	67 (*R*)	57, 58, 92
8	Ph	MeCN	**4d**	$LaCl_3$	3	96	12 (*S*)	57, 58, 92
9	Ph	MeCN	**4d**	$EuCl_3$	16	81	32 (*R*)	57, 58, 92
10	Ph	MeCN	**4d**	$YbCl_3$	1	94	75 (*R*)	57, 58, 92
11	Ph	MeCN	**4i**	$YbCl_3$	0.5	61	89 (*R*)	57, 58, 92
12	Ph	MeCN	**4g**	$YbCl_3$	3	88	14 (*R*)	57, 58
13	Ph	MeCN	**4i**	YCl_3	1	77	80 (*R*)	57, 58, 92
14	Ph	MeCN	**4j**[c]	YCl_3	1	100	60 (*R*)	57, 58, 92
15	4-MePh	MeCN	**4d**	$YbCl_3$	3	93	70 (*R*)	57, 58, 92
16	4-ClPh	MeCN	**4d**	$YbCl_3$	16	60	62 (*R*)	92
17	2-furyl	MeCN	**4d**	$YbCl_3$	2	86	67 (*R*)	57, 58, 92
18	Me	MeCN	**4d**	$YbCl_3$	2	61	45 (*R*)	57, 92
19	*t*-Bu	MeCN	**4d**	$YbCl_3$	2	83	49 (*R*)	92
20	cyclohex	MeCN	**4d**	$YbCl_3$	2	86	60 (*R*)	57, 58, 92
21	1-penten	MeCN	**4d**	$YbCl_3$	2	88	58 (*R*)	58, 92

[a] Reaction run at room temperature. [b] Reaction run at 0−10 °C. [c] The enantiomer of **4j**.

(c) if the configuration of pybox is taken as a constant [(*S*,*S*)], the configuration of the alcohol always derives from the approach to the Re face of the carbonyl group;
(d) the effect of the additive counterions (BF_4, OTf, PF_6) could result in the substitution of the chlorine ions of the catalyst with the new anions in the reacting complex.

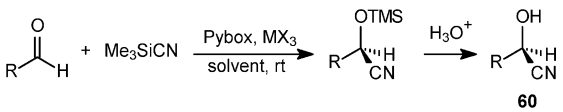
Further investigations on the enantioselective reduction of ketones have been performed.

Again the rhodium complex of **4c** was used to study the stereoselectivity in the reduction of substituted cyclohexanones[84,85] and of aryl- and heteroaryl-alkyl ketones,[86] and a Japanese review probably summarized what has been illustrated above.[87] The cobalt,[88] ruthenium,[89] and boron[90] complexes of **4c** were found to be less selective than the Rh analogue, and the same result was observed when $Sn(OTf)_2$ complexes of **4c**, **4f**, **4i**, **14a**, and **18d** were used to reduce acetophenone [**20**−$Sn(OTf)_2$ gave racemic 1-phenylethanol].[34] The reduction of acetophenone with the titanium complex of **4c**, (in the presence of Ph_2SbH and AIBN) gave (*S*)-1-phenylethanol in 98% ee,[91] and this was the sole result with a pybox in a paper reporting experiments with different ligands.

3. Silylcyanations

The pybox−metal-mediated addition of trimethylsilylcyanide (TMSCN) to aldehydes, followed by the hydrolysis of the protected product, allowed the asymmetric synthesis of cyanohydrins **60** (Scheme 19). The first experiment with **4c**−$AlCl_3$ gave high

Scheme 19



60

yields with several aldehydes, but a significant ee was reported for benzaldehyde only (90%).[68] A more flexible system was found with lanthanide trichlorides, and Table 12 reports the most significant results obtained with these catalysts.[57,58,92]

The results in Table 12 clearly illustrate some trends:
(a) the solvent deeply influences the enantioselectivity (entries 2−7), and even if the best solvent is acetonitrile, a surprising result is obtained with ethanol, since its behavior as a competing ligand in the formation of the reacting complex could be expected;
(b) the best pybox substituent is the phenyl group, then isopropyl and benzyl; *tert*-butyl was briefly investigated, but apparently, is too sterically demanding (entries 7, 13, 14, and 10−12);
(c) the catalyst derived from **4d** and $YbCl_3$ is very flexible and aliphatic (saturated and unsaturated), and aromatic and heteroaromatic aldehydes give quite good ee (entries 15−21);
(d) changing the lanthanides, the ee decreases with the increase of the ionic radius, until the enantioselectivity between La and Eu is reversed.

The most intriguing point is item d, which parallels a result concerning epoxide ring opening that will be discussed in section IVB3. The determination of the relationship between $ee_{product}$ and ee_{ligand} could help to understand if the mechanism of the reaction involves "important structural differences as the lanthanide series is traversed".[58]

4. Other CO and CN Additions

Pybox complexes could be expected to act as enantioselective catalysts in different addition reactions to carbonyl and to similar groups. Some investigations in this field have been done with various results.

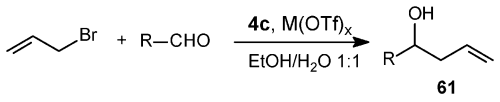
The enantioselective synthesis of α-methylene-β-hydroxy ketones through the chalcogeno-Baylis-Hillman reaction was experienced with the [**4c**−$TiCl_4$] complex;[93] the yield was good, but racemic products

were obtained. Similar results were obtained for the trifluoromethylation of carbonyl compounds with trialkyl(trifluoromethyl)silanes.[94]

A useful field of research could be the alkylation of aldehydes, but few investigations have been reported. The result of a combinatorial test of chiral diols and chiral nitrogen ligands on the enantioselective addition of diethylzinc to aldehydes involved **4c** as a member of the second class of ligands, but the results were not comparable to those obtained with enantiopure diimines of 1,2-diphenylethylenediamine.[95]

Interesting results have been obtained on the enantioselective allylation of aldehydes in ethanol/water medium to give **61** (Scheme 20), even if

Scheme 20



stoichiometric amounts of catalyst are required for the instability of the pybox in the reaction medium.[96] The effect of different triflates with **4c** was tested on benzaldehyde, and the best result was obtained with Ce(IV) (92% ee). Other lanthanides (Pr, Sm, Gd, Dy, Yb) gave ee >80%, while the ee with Zn(II) was only 56%. The good result obtained with triflic acid (76% ee) cannot be easily explained by a model involving [**4c**−cation−aldehyde] as reacting complex. Under the optimized conditions, whereas aromatic aldehydes and cinnamaldehyde gave products with moderate selectivity (51−66% ee), an aliphatic aldehyde (hexanal) gave lower selectivity (34% ee).

The most important result in the field, from the specific point of view of this review, is the asymmetric phenylation of acrolein with phenyllithium and phenylmagnesium bromide.[53] The reaction was run on the ruthenium-acrolein complexes with **4a**,**c**,**h**, hence occurring with a stoichiometric [reagent:catalyst] ratio, and the addition on the carbonyl group gave (*S*)-1-phenyl-2-propen-1-ol (**62**) (Figure 16). The choice

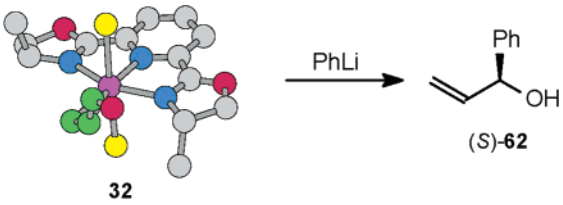


Figure 16. Asymmetric phenylation of acrolein bound to [**4a**·$RuCl_2$] (**32**) to give (*S*)-**62**.

of both the pybox and the solvent is crucial for the enantioselectivity: **4h** is the ligand of election that, in CH_2Cl_2 with PhLi, gives **62** in 89% yield and 87% ee. The emphasis given to this reaction (of no synthetic utility) is due to the structure of the complex [**4a**·$RuCl_2$ (acrolein)] (**32**) that was determined by X-ray analysis,[53] since this latter could be regarded as the reacting complex involved in a nonstoichiometric catalytic process. The formation of (*S*)-**62** is rationalized by the attack of the phenyl anion to the exposed Re face of the *s-trans* acrolein bound to Ru.

Table 13. Enantioselective Addition of Phenylacetylene to ArCH=NAr′ (63), Catalyzed by Pybox−CuOTf, in Water and in Toluene

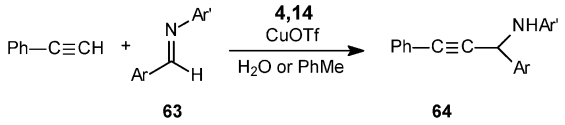
entry	Ar	Ar′	pybox	**64** % yield (% ee) in water	**64** % yield (% ee) in toluene
1	Ph	Ph	**4c**	(a) (45)	(a) (40)
2	Ph	Ph	**4h**	71 (84)	78 (96)
3	Ph	Ph	**14a**	(a) (14)	(a) (21)
4	4-EtC_6H_4	Ph	**4h**	68 (89)	70 (96)
5	4-ClC_6H_4	Ph	**4h**	70 (87)	85 (94)
6	4-PhC_6H_4	Ph	**4h**	48 (84)	81 (94)
7	2-Naph	Ph	**4h**	57 (86)	63 (88)
8	Ph	4-BrC_6H_4	**4h**	82 (83)	93 (91)
9	Ph	4-ClC_6H_4	**4h**	77 (84)	92 (91)
10	Ph	4-MeC_6H_4	**4h**	68 (91)	93 (94)

[a] Yield not reported.

The C=N bond of Schiff bases have close analogies with the carbonyl group, hence enantioselective additions should not be unexpected. The effect of **4c** on the addition of Me- and *n*-BuLi to *N*-benzyliden-*p*-anisidine was disappointing since very good yields of racemic products were obtained.[97]

The synthetic possibilities of this class of reaction is illustrated by a study of the enantioselective addition of phenylacetylene to imines **63** in water or in toluene, catalyzed by Cu(I) triflate and pybox **4c**, **4h**, or **14a**, to give the optically active propargylamines **64** (Scheme 21).[98] The results at 22 °C in

Scheme 21



water and toluene, reported in Table 13, show that **4h** is the best ligand for this reaction. Furthermore the catalyst derived from this pybox and copper(I) triflate has an appreciable flexibility for the Schiff bases with different aryl groups. But what deserves attention for future applications is the excellent behavior of water as a solvent for enantioselective reactions catalyzed by pybox complexes that are not suitably designed to act in this medium under homogeneous conditions.

B. Three-Membered Ring Formation from C=C and C=X Double Bonds

1. Cyclopropanation Reactions

The use of a chiral catalyst to synthesize cyclopropanes enantioselectively from olefins is the topic of an intensive research. Two reviews dealing with this argument appeared in 1998,[99,100] and the report specially devoted to the topic had about 110 references, six concerning pybox-based catalysts. This means that several active chiral ligand/cation couples have been developed as catalysts by different groups, but also that pybox gave an interesting contribution to this research field. The success of pybox as ligand for cyclopropanation reactions was due to the development of several ruthenium complexes by Nishiyama and some of his results were mentioned in a review paper.[101]

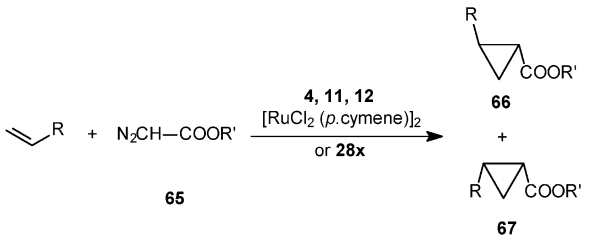
Table 14. Asymmetric Cyclopropanation of Olefins with Diazoacetates (65) Catalyzed by Ru(II)−Pybox

entry	olefin R	**65** R′	catalyst[a]	yield %	[**66**:**67**]	**66**[b] % ee	**67**[c] % ee	ref
1	Ph	Et	**4c**	69	92:8	88	78	11, 41, 48
2	Ph	*t*-Bu	**4c**	81	97:3	94	85	11, 41, 48
3	Ph	D-ment	**4c**	85	95:5	86	95	11, 41, 48
4	Ph	L-ment	**4c**	87	95:5	95	76	11, 41, 48
5	*n*-pent	L-ment	**4c**	40	94:6	99	95	41
6	CH═CMe$_2$	L-ment	**4c**	86	79:21	98	79	11, 41
7	PhCH$_2$	L-ment	**4c**	45	93:7	97	−	11
8	*p*-ClC$_6$H$_4$	L-ment	**4c**	84	96:4	95	83	11
9	*p*-MeOC$_6$H$_4$	L-ment	**4c**	96	95:5	97	−	11
10	Ph	Et	**4h**	30	86:14	76	−	103
11	Ph	Et	**11**	51	90.5:9.5	59.5[d]	−	103
12	Ph	Et	**12**	47	89:11	41[d]	−	103
13	Ph	Et	**28cx**	73	91:9	89	79	11, 41, 48
14	Ph	*t*-Bu	**28cx**	65	97:3	94	87	11, 41, 48
15	Ph	D-ment	**28cx**	82	97:3	87	97	11, 41, 48
16	Ph	D-ment	**28bx**	77	98:2	95[d]	74[e]	11
17	Ph	D-ment	**28ex**	86	97:3	80	93	11
18	Ph	D-ment	**28ix**	51	95:5	84[d]	14[e]	11
19	Ph	D-ment	**28jx**	78	93:7	71	86	11
20	Ph	D-ment	**28ux**	72	94:6	39[d]	5[e]	11
21	Ph	L-ment	**28cx**	83	97:3	96	80	11, 41, 48
22	Ph	L-ment	**28bx**	77	96:4	72[d]	86[e]	11
23	Ph	L-ment	**28ex**	89	99:1	96	66	11
24	Ph	L-ment	**28ix**	56	97:3	14[d]	66[e]	11
25	Ph	L-ment	**28jx**	82	98:2	93	64	11
26	Ph	L-ment	**28ux**	83	97:3	39	17[e]	11
27	Ph	L-ment	**28cx1**[f]	79	94:6	84	38	44
28	Ph	L-ment	**28cx2**[f]	89	96:4	90	67	44
29	Ph	L-ment	**28cx**[f]	93	97:3	93	79	44
30	Ph	L-ment	**28cx3**[f]	93	97:3	94	83	44
31	Ph	L-ment	**28cx4**[f]	95	96:4	97	85	44
32	Ph	Me	**4c**[g]	82	89:11	92	97	35
33	Ph	Me	**20a**[g]	79	89:11	71	48	35
34	Ph	Me	**20b**[g]	88	83:17	86	63	35
35	Ph	Ar[h]	**20b**[g]	91	100:0	90	−	35
36	Ph	D-ment	**20b**[g]	81	96:4	55	69	35
37	Ph	L-ment	**20b**[g]	84	99:1	94	64	35
38	Ph	Et	**10**[i]	26	77:23	54	18	23
39	Ph	Et	**10**[j]	32	78:22	76	41	23
40	Ph	Et	**10**[k,l]	31	85:15	85	41	23
41	Ph	Et	**10**[m]	28	84:16	84	40	23
42	Ph	Et	**10**[n]	11	75:25	45	20	23

[a] The catalysts are pybox and [Ru(II)Cl$_2$(*p*-cymene)]$_2$ (**4**), or the [**4** Ru(II)Cl$_2$ (ethylene)] complexes **28**. [b] The configuration of **65** is (1*R*,2*R*) unless otherwise indicated. [c] The configuration of **66** is (1*R*,2*S*) unless otherwise indicated. [d] (1*S*,2*S*)-**65**. [e] (1*S*,2*R*)-**66**. [f] 40 °C. [g] The catalysts are pybox and [Ru(II)Cl$_2$(*p*-cymene)]$_2$, and the reactions were run at 30−35 °C. [h] Ar is 2,6-(i-Pr)$_2$C$_6$H$_3$. [i] Polymer prepared with a mixture of toluene and dodecanol as porogen. [j] As in footnote i, but with a different degree of cross-linking. [k] Polymer prepared with toluene as porogen. [l] Run 1. [m] As in footnote k, but run 2. [n] As in footnote k, but run 3.

The reaction between olefins and diazoacetates **65** to give *trans*- and *cis*-cyclopropanes, **66** and **67**, respectively (Scheme 22), was enantioselectively catalyzed by pybox and [Ru(II)Cl$_2$(*p*-cymene)]$_2$, or by the [**4**·Ru(II)Cl$_2$ (ethylene)] complexes **28x**.[11,41,42,44,48,102,103]

Scheme 22



The thorough investigation took into account: types of olefins, different diazoacetates, including those with D- and L-menthyl (ment) residues, and the effect of the substituents on pybox ligand. The selectivity obtained with the free ligand and [Ru(II)·Cl$_2$(*p*-cymene)]$_2$ or with the preformed complex is not significantly different, and an extensive selection of the results obtained is reported in Table 14.

From these data, some interesting trends can be outlined:

(a) the trans isomer **66** is largely the major product of the reaction;

(b) the increase in bulkiness of the ester residue increases enantioselectivities (entries 1 and 13 vs 2 and 14);

(c) the best stereochemical matching is L-menthyl ester/**4c** (or **28cx**) for the trans adduct **66** and D-menthyl ester/**4c** (or **28cx**) for the cis adduct **67** (entries 3 and 15 vs 4 and 21);

(d) a weak asymmetric induction occurs in the absence of chirality in pybox (entries 20, 26), and this result can explain the effect of L-menthyl ester in increasing the ee of (1*R*,2*R*)-**66** with (*S*)-**4** (matched pair), while D-menthyl ester decreases it;

(e) the catalysts are quite flexible with different olefins (entries 4−9), but with alkyl-substituted alkenes, poor overall yields are obtained (entries 5, 7); (f) the pybox of election is **4c**, even if **4e** (incorporated into **28ex**) is excellent also in terms of trans/cis selectivity;
(g) the substituents in the 4-position of the pyridine ring strongly influence enantioselectivity: the electron-withdrawing groups give better ee than electron-donating ones, whereas the trans/cis ratio is nearly constant. The enantiomer ratios of L-menthyl cyclopropanes correlate with Hammett's σ_{para} constants with positive ρ values (0.517 for **66** and 0.584 for **67**); (h) assuming the same configuration of the ligand, the pybox derived from aminoindanol and 1-amino-2-hydroxytetrahydronaphthalene (**11** and **12**) induce opposite enantioselectivity (entries 11, 12).

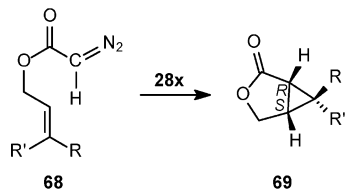
Two single-chiral pybox (**20a**,**b**) have been tested as ligands for the Ru-catalyzed reaction with styrene reported in Scheme 22.[35] Even if excellent results have been obtained (Table 14, entry 37, enantioselectivity of **66** up to 94%), the comparison with the analogous disubstituted pybox (entries 32 vs 33 and 34) shows the lower efficiency of **20**.

Runs 38−42 in Table 14 report the results with the Ru(II) complexes of the polymer-supported pybox **10**.[23] A comparison with the homogeneous phase conditions used as benchmark (entry 1) shows that the activity of the supported catalyst depends on the polymerization conditions (cross-linking and porogen).

The use of dodecanol as porogen is detrimental to selectivity (entries 38, 39 vs 40). The best supported catalyst (entry 40) gives ee of the trans product **66** only slightly lower than the benchmark, in contrast, the enantioselectivity of the cis product **67** is reduced to 41%. The catalyst can be reused twice (entries 40 and 41) with no significant loss of stereoselectivity, then its activity is strongly reduced (entry 42). In conclusion, these results are the first proof of the potential usefulness of a supported pybox-based catalyst, active in enantioselective reactions.

The applicability of the asymmetric catalytic cyclopropanation to intramolecular reactions was investigated on the substituted allyl diazoacetates **68** that, in the presence of complexes **28x**, gave the (1*R*,5*S*)-3-oxabicyclo[3.1.0]hexan-2-one derivatives **69** (Scheme 23).[11,44]

Scheme 23



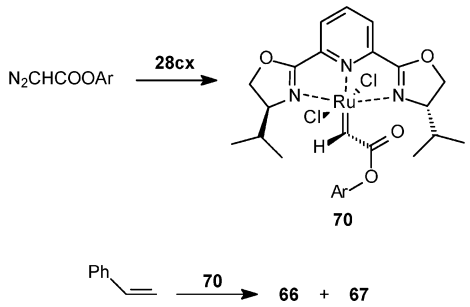
The reaction is stereospecific and again the electron-withdrawing substituents in the 4-position of the pyridine ring increased enantioselectivity, whereas electron-donating ones decreased it (Table 15, entries 2−6). The configuration of the double bond influences selectivity and the (*Z*) isomer cyclizes less enantioselectively than the (*E*) one (entries 2 vs 7).

Table 15. Intramolecular Asymmetric Cyclopropanation of 68 to 69 Catalyzed by Complexes 28x

entry	R	R′	28	yield %	ee %	ref
1	Ph	H	**28cx**[a]	93	86	11
2	Ph	H	**28cx**[b]	83	86	44
3	Ph	H	**28cx1**[b]	67	52	44
4	Ph	H	**28cx2**[b]	73	78	44
5	Ph	H	**28cx3**[b]	80	85	44
6	Ph	H	**28cx4**[b]	72	89	44
7	H	Ph	**28cx**[b]	79	24	11
8	Me	Me	**28cx**[b]	91	76	11

[a] r.t. [b] 30 °C.

Scheme 24



The mechanism of the reaction was proposed to involve the formation of a carbene coordinated to [Ru−pybox] and the attack of the olefin to its less hindered face could rationalize the observed enantioselectivity. A support of this mechanism came from the stable aryloxycarbonylcarbene−ruthenium complexes (**70**) isolated from the reaction of **28cx** with substituted aryl diazoacetates (Scheme 24).[46] The structure of these complexes, as mentioned in section IIIB2, was characterized by NMR spectroscopy. The stretching of the CO double bond of the ester group in the carbene complexes involved in the cyclopropanation reaction was found to be of paramount importance to investigate the nature of the metal−carbene carbon bond as a function of both metal and ligand.[104]

Since the important feature of the process is the asymmetric carbene transfer from **70** to styrene to give **66** and **67**,[46] the yields of **70**, the temperatures required to transfer carbenes to styrene, and the stereoselectivity of the reactions are collected in Table 16.

The last piece of the puzzle was the configuration of the complex with the carbene fragment in the equatorial position and perpendicular to the pybox plane as resulting from the X-ray structure of [**4c**·$RuCl_2$ $C(COOMe)_2$] (Table 3, entry 14).[47] Again, this ruthenium complex transferred the dicarbomethoxycarbene to styrene at 110 °C, giving the corresponding cyclopropane [very low yield (11%) and 36% ee].[47]

This model was further confirmed by simple MO calculation on [**4u** $RuCl_2$ CH_2].[101] The LUMO possesses the vacant π-orbital of the carbene fragment lying in the pybox plane that can be attacked by olefin's π-electrons, and derived from this structure, Figure 17 reports the reacting complexes when **4c** is the ligand of both the intermolecular (Scheme 22) and the intramolecular cyclopropanation (Scheme 23). In

Table 16. Formation of [4c−Ru−Carbene] Complexes 70 and the Enantioselective Transfer of Carbenes to Styrene To Give 66 and 67

entry	Ar	**70** (%)	*T* (°C)[a]	**66** + **67** yield (%)	[**66**:**67**]	**66** ee %	**67** ee %
1	2,6-(i-Pr)$_2$C$_6$H$_3$	90[b]	60	82	100:0	97	–
2	2,4,6-Me$_3$C$_6$H$_2$	92[c]	40	91	99:1	97	99
3	2,6-(*t*-Bu)$_2$-4-MeC$_6$H$_2$	94[d]	80	80	100:0	55	–
4	Ph	30[e]	–	–	–	–	–

[a] Temperature of the carbene transfer. [b] 45 °C. [c] 40 °C. [d] 50 °C. [e] 0 °C.

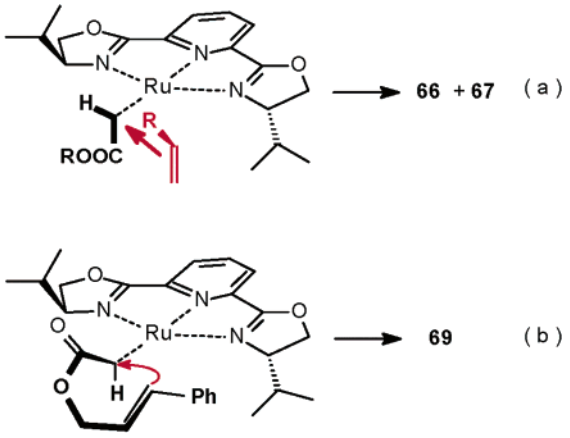


Figure 17. (a) The reacting complex of the intermolecular cyclopropanation in Scheme 22 and (b) that of the intramolecular reaction in Scheme 23.

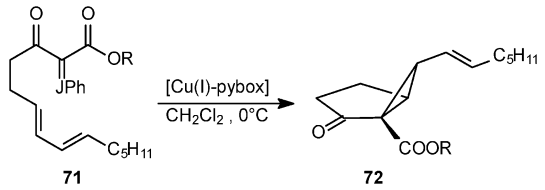
the intermolecular process, the favored attack of styrene with its Re face occurs on the Re face of the metal-carbene center, and this gives the major product of the reaction, (1*R*,2*R*)-**66** (Figure 17a and Table 14). In the intramolecular cyclization, the favored attack again occurs on the Re face of carbene center, giving (1*S*,5*R*)-**69** as the major reaction product (Figure 17b and Table 15).

Also the additions of diphenylvinylcarbene[45] and trimethylsilylcarbene[43] to styrene are based on the formation of rutenium-carbene complexes, but only the former reaction gave a good yield (74%) even if the enantioselectivity was moderate (53−56% ee).

The Nishiyama [**4c**−Ru] catalyst was tested on the reaction of methyl diazoacetate with trimethylsilyl enol ethers.[105] Only the unsubstituted ether and 1-trimethylsilyloxy-1-phenylethene reacted, but the induced stereoselectivities were lower than those obtained with box-based copper catalysts.

Several experiments of asymmetric cyclopropanation were run with pybox−copper complexes. The Cu(I) derivatives of **18a** and **18b** were tested as catalysts in the reaction between diazoformates and styrene:[31] the yields of the cyclopropanes were excellent, but stereoselectivity was poor. Müller and Boléa examined the Cu(I) complexes of several pybox as catalysts of both inter- and intramolecular cyclopropanation reactions.[13,106] The results of the former reaction were disappointing, but the intramolecular cyclopropanation of phenyliodonium ylides **71** gave **72** with yields in the range 36−63% (Scheme 25). The most reactive ester was the methyl derivative: the best ee was 42% with **11** as the chiral ligand, while ee in the range 32−39% were obtained with **4f** and **17b**−**d**. The *t*-butyl ester gave 40% ee again with **11**, whereas the

Scheme 25



enantioselectivity of the more crowded 2-methyl-1-(1-methylethyl)propyl derivative was only 10%.

As the result of a catalyst library screening, **4c** matched Sc(III) as the best pybox complex in the cyclopropanation of 1,1-diphenylethene and methyl stiryldiazoacetate.[107] Even if the reaction yield was very low, the 86% ee suggests that this cation, useful in other reactions, cannot be neglected for cyclopropanation.

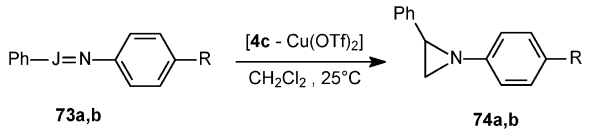
Finally, an impelling demand for the organic chemist is to change the halogenated media with a safe, nontoxic, environmentally friendly solvent, such as water, to realize clean chemical processes. The cyclopropanation described in Scheme 22 between styrene and D-menthyl diazoacetate, chosen as matching the configuration of the pybox, was catalyzed by the Ru complex of the highly water-soluble pybox **4o**.[10] The results in toluene (or THF) were 8% ee for **66** and 28% ee for **67** (yield, 38%; **66**:**67** ratio, 89:11). By addition of water, the reaction was run in a two-phase system and the ee were 94% and 78% for **66**, 76% and 45% for **67**, respectively, in water/toluene and water/THF (yields 57% and 46%; ratios **66**:**67** were 97:3 and 95:5). When alcohols were adopted in place of water to provide homogeneous protic media,[10] toluene/2-propanol gave the best enantioselectivities: 96% ee for **66** and 88% ee for **67**. If the results in toluene/2-propanol conditions with the ruthenium catalyst derived from **4c** are taken as a reference, **4o** gave a comparable selectivity, while **4t** was less efficient.

2. Aziridination Reactions

Aziridines can be obtained either by addition of nitrenes onto olefins or by addition of carbenes onto imines. Even if enantioselective catalyzed aziridinations are not so extensively studied as cyclopropanations, some examples of both processes have been reported.

It was found that copper (II)-exchanged zeolite is a highly active catalyst for the aziridination of alkenes. The modification using bis(oxazolines) lead to the first enantioselective aziridination catalyst.[108,109] Pybox **4c** was tested with Cu(OTf)$_2$ on the reaction of styrene with two nitrene donors: [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane (**73a**) and [*N*-(*p*-

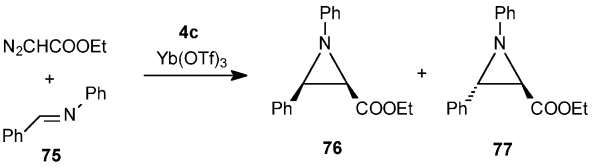
Scheme 26



nitrophenylsulfonyl)imino]phenyliodinane (**73b**) and the aziridines **74a**,**b** (Scheme 26) were obtained in good yields (70 and 42% respectively), but with negligible enantioselectivity (11% and 15% ee).[110−113]

The metal-catalyzed aziridination of *N*-phenylimine (**75**) with ethyl diazoacetate as carbene fragment donor to afford *cis*- and *trans*-aziridines **76** and **77** was investigated in the presence of a chiral ligand and various Lewis acids as catalysts (Scheme 27).[114]

Scheme 27

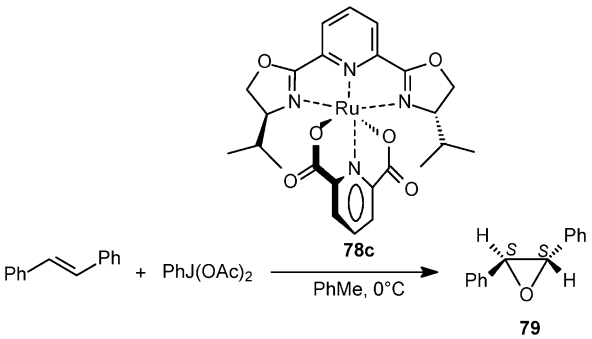


At 0 °C $Yb(OTf)_3$ gave an overall yield of 52% with a [**76**:**77**] ratio of 25:1, but attempts to perform asymmetric aziridinations by using **4c**−$Yb(OTf)_3$ as chiral catalyst were unsuccessful (the ee was in the range 5−15%).

3. Epoxidations and Epoxide Ring Opening

The first enantioselective epoxidation of *trans*-stilbene with pybox-based catalysts was run with **4c**, $RuCl_2$, and $NaIO_4$ as oxidant, but a very low yield of epoxide was obtained in nearly racemic form.[115] The reaction gave better results with [**4c** (or **4h**)−Ru(pyridine-2,6-dicarboxylate)] complexes (**78c**,**h**), prepared from $[Ru(p\text{-cymene})Cl_2]_2$, disodium pyridine-2,6-dicarboxylate and the corresponding ligand **4** in 78% and 71% yield, respectively.[50,60] The complex **78c**, with PhJO or $PhJ(OAc)_2$, gave the epoxide **79** with the (2*S*,3*S*) configuration in 40−80% yield and 24−74% ee, the best result being obtained with $PhJ(OAc)_2$, at 0 °C in toluene (Scheme 28). Under the same experimental conditions, **78h** gave **79** in 84% yield, but with a lower enantioselectivity (58% ee).

Scheme 28



The design of a catalyst for epoxidation must take into account the behavior of complex [**4c** $Ru(OAc)_2$(pyridine)] that, under the conditions described for **78**, gave racemic epoxide. Therefore, a rigid O,N,O ligand must be introduced in the complex to help pybox to maintain the chiral environment during the whole catalytic process.

If the asymmetric synthesis of epoxides with pybox-based chiral catalyst has not yet given significant level of enantioselectivity, their ring opening showed more interesting results.

Meso epoxides **80** can be asymmetrically opened with TMSCN, lanthanide trichlorides, and pybox, yielding β-trimethylsilyloxy nitriles **81** with a very good enantioselectivity (Scheme 29, Table 17).[116] The

Scheme 29

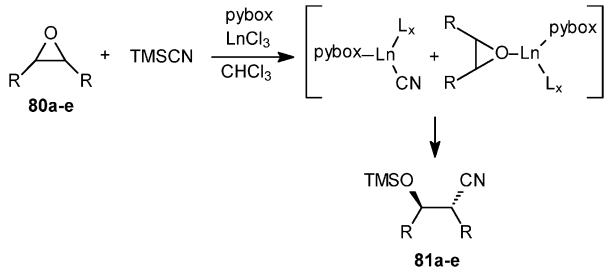


Table 17. Asymmetric Epoxide Opening by TMSCN, Pybox, and Lanthanide Trichlorides

entry	epoxide	pybox	Ln(III)	*T* (°C)	**81** yield (%)	**81** ee % (config.)
1	**80a**	**4c**	Ce	r.t.	68	0
2	**80a**	**4c**	Pr	r.t.	96	2 (1*S*,2*R*)
3	**80a**	**4c**	Nd	r.t.	88	10 (1*S*,2*R*)
4	**80a**	**4c**	Eu	r.t.	91	25 (1*S*,2*R*)
5	**80a**	**4c**	Dy	r.t.	89	31 (1*S*,2*R*)
6	**80a**	**4c**	Er	r.t.	88	40 (1*S*,2*R*)
7	**80a**	**4c**	Yb	r.t.	96	47 (1*S*,2*R*)
8	**80a**	**4c**	Lu	r.t.	94	51 (1*S*,2*R*)
9	**80a**	**4f**	Yb	r.t.	93	57 (1*S*,2*R*)
10	**80a**	**4h**	Yb	r.t.	96	67 (1*R*,2*S*)
11	**80a**	**4j**	Yb	r.t.	96	28 (1*S*,2*R*)
12	**80a**	**11**	Yb	r.t.	93	28 (1*S*,2*R*)
13	**80a**	**4h**	Yb	−45	90	91 (1*R*,2*S*)
14	**80b**	**4f**	Yb	−10	83	92 (1*R*,2*S*)
15	**80c**	**4h**	Yb	−40	80	90 (2*S*,3*R*)
16	**80d**	**4f**	Yb	0	86	83 (1*R*,3*S*,4*R*)
17	**80e**	**4f**	Yb	−10	72	87 (3*R*,4*R*)

reaction of cyclohexene epoxide (**80a**) was studied in detail both to optimize the conditions and to clear the mechanism. Among the different tested ligands, pybox proved to be the best. A systematic evaluation of different lanthanides (Table 17, entries 1−8) revealed a linear increase of the enantioselectivity with the increase of the lanthanide atomic number, with the highest ee obtained for Lu (entry 8). It is not surprising that the same behavior was observed in the enantioselective addition of TMSCN to aldehydes (section IVA3).[58,92]

To identify the best catalyst for the ring opening of **80a**, a series of pybox with the same (*S*,*S*) configuration was evaluated with $YbCl_3$ as Lewis acid (Table 17, entries 7, 9−12). At r.t., **4h** gave the best result (entry 10), and it is important to underline that the configuration of **81** hereby obtained was opposite to that given by all other pybox. Finally, the optimized conditions were found not only for **80a** (yield 90% and 91% ee, entry 13), but also for cyclopenten

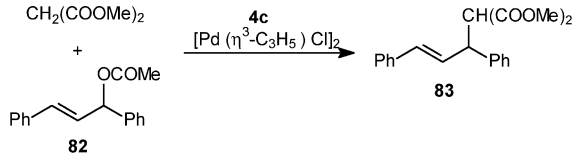
epoxide (**80b**), *cis*-2,3-epoxibutane (**80c**), *trans*-ethyl 3,4-epoxy-ethyl-1-cyclopentancarboxylate (**80d**), and 3,4-epoxy-1-trifluoroacetylpyrrolidine (**80e**) (entries 14−17).

The reaction exhibited a second-order kinetic dependence on the catalyst concentration and first-order on the epoxide concentration. This is consistent with a catalytic pathway involving the coordination of both epoxide and cyanide (Scheme 29), a mechanism supported by a significant positive nonlinear effect in the correlation between ee_{pybox} and $ee_{product}$. What still deserves attention is the rationalization of the variation of ee as a function of the lanthanide atomic number, to understand if this has a "geometric" or a "mechanistic" origin, as well as the anomalous reversal of enantioselectivity observed by using the "aromatic" pybox **4h**.

C. Other Addition and Substitution Reactions

Several experiments have been performed to catalyze enantioselectively both ordinary and unusual reactions by using pybox complexes, with different degree of success. The copper-catalyzed Meerwein reaction of methyl acrylate with *p*-tolyldiazonium tetrafluoroborate in the presence of tetrabutylammonium chloride, leading to the formal addition of tolyl chloride to the double bond, was tentatively catalyzed by [**4c**/CuOTf], the yield was 40%, but the ee was only 2.7%.[117] Lithium was a bad partner of pybox for the enantioselective carboxylation of α-methoxybenzyllithium, generated via asymmetric lithiation with [**4c**/*t*-BuLi]. Under these conditions, α-methoxy phenylacetic acid (obtained with excellent ee by using suitably chosen box ligands) was obtained as a racemate in a disappointing yield.[118] The allylic substitution of 1,3-diphenylprop-2-enyl acetate (**82**) with dimethyl malonate to afford dimethyl 1,3-diphenylprop-2-enyl malonate (**83**) (Scheme 30) was enantioselectively catalyzed by $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and **4c**, but the results [both in terms of yield (45%) and enantioselectivity (26%)] were remarkably lower than those obtained with 2-cyano-6-oxazolylpyridines.[25]

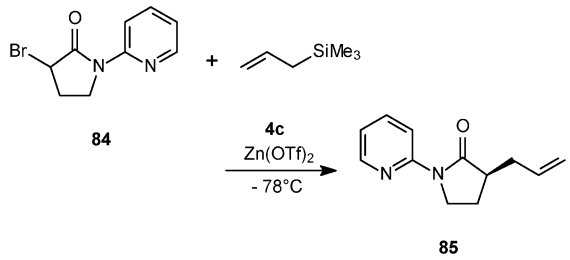
Scheme 30



Few examples of radical reactions are known to be catalyzed by pybox complexes. The atom transfer radical cyclization of *N*-allyl and homoallyltrichloroacetamides to afford γ- and δ-lactams is catalyzed by [**4c**−CuCl], but an influence on diastereoselectivity was only observed.[119]

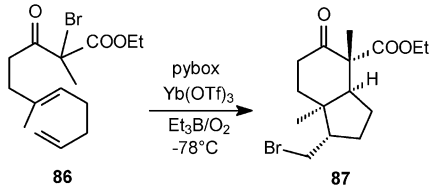
The radical reactions of 1-(1-pyridyl)-3-bromo-2-pyrrolidone (**84**) with allyltrimethylsilane (Scheme 31)[120] was catalyzed by **4c** and $Zn(OTf)_2$. Following these conditions, **85** was obtained in a good yield (42%), but the enantioselectivity (75% ee) could not compete with that obtained with suitably chosen box ligands (ee >99%).

Scheme 31



An intramolecular radical cyclization, followed by bromine transfer, allowed the ring closure of **86** to **87** (Scheme 32).[121] With Yb(III) triflate and different

Scheme 32



pybox as catalysts, **87** was obtained with yields in the range 11−60%, beside variable amounts of debrominated starting product. The phenyl-substituted pybox **4i** gave the best result [(2*R*,3*S*,4*S*,5*S*)-**87** was obtained in 66% ee], while the alkyl-substituted ligands **4c**,**f** afforded products with negligible ee. Probably the most intriguing result is the effect of the addition of 4 Å molecular sieves, since a clear decrease in reactivity was observed (11% reaction yield), together with a remarkable reversal in enantioselectivity (56% ee of the opposite enantiomer). In any case, the important limit of this cyclization was the stoichiometric amount of catalyst required.

D. Allylic Oxidations

The enantioselective allylic oxidation of olefins is a topic of great interest and the reaction can be run either using peresters (or *tert*-butyl hydroperoxide and carboxylic acids) to synthesize allylic esters (the Kharasch reaction),[122] or *tert*-butyl hydroperoxide alone to introduce a peroxy group.[123] The synthetic utility of the Kharasch reaction derives from its use as alternative route to chiral allylic alcohols; the peroxides may serve as useful substrates for highly stereoselective functionalization of the residual double bond through epoxidation or bishydroxylation.

The enantioselective allylic peroxidation was studied with *tert*-butyl hydroperoxide, **4c**, and Cu(I) triflate in acetonitrile as solvent.[123] Cyclohexene, cyclopentene, α-angelica lactone, allylbenzene, and *rac*-2-phenylbutane gave a single regioisomer in good yield, but the enantioselectivity was low (ee in the range 4−20%): starting from cyclohexene, (*S*)-**88** was obtained in 75% yield and 9% ee (R = H, Scheme 33).

Scheme 33

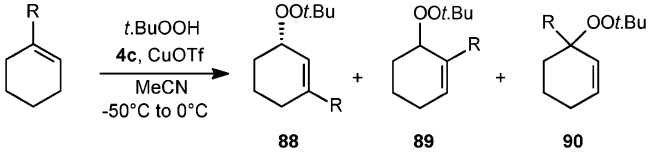


Table 18. Asymmetric Catalytic Allylic Oxidation of Cycloalkenes 91 (n = 1−4) with Pybox−Copper Complexes, at Room Temperature

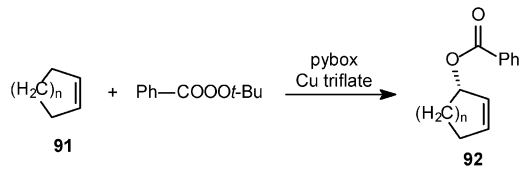
entry	**91** $(CH_2)_n$	pybox	Cu triflate	additive	solvent	time	yield (%)	**92** ee % (config.)	ref
1	2	**4c**	(I)	−	MeCN	3 d	80	71(*S*)	124
2	2	**4c**	(II)	−	MeCN	10 d	35	13(*S*)	125
3	2	**4c**	(II)	MS[a]	MeCN	20 d	63	45(*S*)	125
4	2	**18b**	(I)	−	acetone	6 d	87	73(*S*)	32
5	2	**18b**	(I)	MS[a]	acetone	21 d	88	86(*S*)	32
6	2	**18b**	(I)[b]	PH	acetone	5 h	78	70(*S*)	32
7	2	**18b**	(I)[b]	MS, PH	benzene	72 h	70	35(*S*)	32
8	2	**18b**	(I)[b]	MS, PH	MeCN	15 d	58	80(*S*)	32
9	2	**18b**	(I)[b]	MS, PH	acetone	24 h	73	75(*S*)	32
10	2	**18c**	(I)[b]	MS, PH	acetone	2 d	69	23(*S*)	32
11	2	**18d**	(I)[b]	MS, PH	acetone	36 h	57	11(*S*)	32
12	2	**18e**	(I)[b]	MS, PH	acetone	24 h	79	62(*S*)	32
13	2	**18b**	(I)[c]	−	MeCN	5 d	48	42(*S*)	125
14	2	**11**	(I)[d]	−	MeCN	24 h	66	52(*S*)	126
15	1	**4c**	(I)	−	MeCN	6 d	48	45(*S*)	125
16	1	**18b**	(I)	−	acetone	48 h	90	51(*S*)	32
17	1	**18b**	(I)[b]	MS, PH	acetone	4 h	80	60(*S*)	32
18	3	**18b**	(I)	−	acetone	6.5 d	63	71(*S*)	32
19	3	**18b**	(I)[b]	MS, PH	acetone	24 h	42	82(*S*)	32
20	4	**18b**	(I)	−	acetone	30 d	28	80(*S*)	32
21	4	**18b**	(I)[b]	MS, PH	acetone	72 h	28	81(*S*)	32

[a] 4 Å molecular sieves. [b] Cu(I)OTf was prepared in situ from Cu(II)$(OTf)_2$ and phenylhydrazine (PH). [c] CuCN, *t*-BuOOH, and PhCOOH. [d] $Cu(MeCN)_4PF_6$ at 40 °C.

The reaction was studied in details on 1-substituted-cyclohexenes (R = Me, Ph, *t*-Bu; Scheme 33), but regioselectivity was the limit in the synthetic applications since two further regioisomers (**89** and **90**) were obtained in different amounts depending on the substituents. The highest ee (84%) was obtained for (*S*)-**88** when R was a methyl group.

The Kharasch reaction was studied in detail on cycloalkenes. The first use of a pybox (**4c**) was reported by Pfaltz, and even if he privileged a deep investigation with box as chiral ligands, the enantioselective allylic oxidation of cyclohexene **91** with *tert*-butyl perbenzoate and [**4c**/Cu(I) triflate] in acetonitrile gave (*S*)-**92** in a very good yield (80%) and with a promising 71% ee (n = 2, Scheme 34).[124]

Scheme 34



91 **92**

This is the first of a series of papers of different groups, the major contribution coming from Singh,[32,125] and the most significant results with different pybox, under a variety of experimental conditions, are reported in Table 18.

From these results, some interesting trends can be outlined:

(a) pybox **18b** gives better results than both its 5′-unsubstituted analogue **4c** and other trisubstituted pybox **18c**−**e**;

(b) in terms of reaction time (see, e.g., entry 4 vs 6), Cu(I) triflate, prepared in situ from Cu(II)$(OTf)_2$ and phenylhydrazine, gives more active catalysts than those derived from stable Cu(I) salts;

(c) molecular sieves have a positive effect on rate and stereoselectivity, if they are used mainly with phenylhydrazine to generate Cu(I);

(d) acetone is the solvent of choice, better than acetonitrile and benzene (entries 7−9);

(e) the flexibility of **18b** versus different cycloalkenes is good if the protocols described in points c and d are followed (entries 9, 17, 19 and 21).

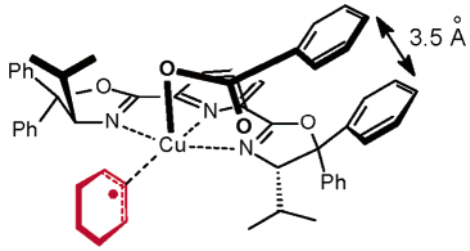


Figure 18. Working model of the reacting complex in the Kharasch reaction between cyclohexene and *tert*-butyl perbenzoate, catalyzed by Cu(I)−**18b** complex.

The mechanism of the enantioselective Kharasch reaction occurs through cleavage of the perester by Cu(I) to give *tert*-butoxy radical, which abstracts an allylic hydrogen to give the corresponding radical and Cu(II) benzoate. If a square-pyramidal coordination of three ligands around the copper(II) (5′,5′-diphenyl-substituted pybox, benzoate, and the allylic radical) is assumed,[32] the attack of the benzoate to the radical will give ester (*S*)-**92** enantioselectively. In the proposed model, a crucial role is played by π-stacking interactions between the two suitably placed aromatic rings of benzoate and chiral ligand (Figure 18). The reduction of Cu to its original oxidation state allows the catalytic cycle to continue.

E. Diels−Alder and Hetero-Diels−Alder Reactions

Diels−Alder (DA) reactions always cover a leading chapter in each review dedicated to enantioselective

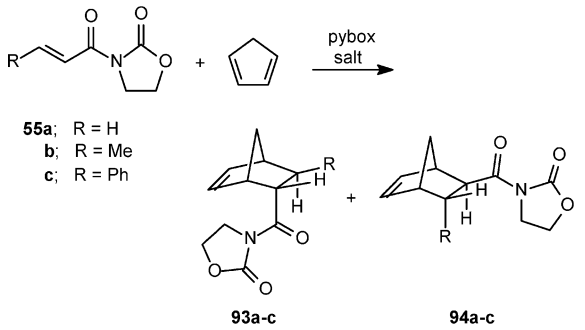
Table 19. Enantioselective Diels−Alder Reactions between Cyclopentadiene and Alkenoyl-1,3-oxazolin-2-ones (55a−c), Catalyzed by Pybox Complexes

entry	**55**	pybox	salt[a]	add.	solv.	*T* (°C)	yield (%)	**93**:**94**	**93** ee % (config.)	**94** ee% (config.)	ref
1	**a**	**4h**	$Cu(SbF_6)_2$	−	CH_2Cl_2	−78	quant	*b*	90 (*S*)	*b*	72
2	**a**	**4h**	$Zn(SbF_6)_2$		CH_2Cl_2	−78	quant	*b*	90 (*S*)	*b*	72
3	**a**	**4i**	$Ni(ClO_4)_2$		CH_2Cl_2	−40	79	95:5	2 (b)	*b*	128
4	**a**	**4i**	$NiBr_2$	$AgClO_4$	CH_2Cl_2	−40	95	87:13	38 (b)	*b*	128
5	**a**	**4c**	$La(OTf)_3$	MS[c]	CH_2Cl_2	0	65	91:9	1 (*S*)	*b*	129
6	**a**	**4c**	$Sm(OTf)_3$	MS[c]	CH_2Cl_2	0	59	86:14	7 (*S*)	*b*	129
7	**a**	**4c**	$Yb(OTf)_3$	MS[c]	CH_2Cl_2	0	63	65:35	34 (*S*)	*b*	129
8	**a**	**4c**	$Sc(OTf)_3$	MS[c]	CH_2Cl_2	−78	60	98:2	90 (*S*)	*b*	129
9	**a**	**4c**	$Sc(OTf)_3$	MS[c]	BTF[d]	0	61	96:4	70 (*S*)	*b*	129
10	**a**	**4c**	$Sc(OTf)_3$	−	$scCO_2$[e]	40	67	91:9	65 (*S*)	*b*	129
11	**b**	**4c**	$Sc(OTf)_3$	MS[c]	CH_2Cl_2	−78	94	91:9	83 (*S*)[f]	*b*	129
12	**b**	**4c**	$Sc(OTf)_3$	MS[c]	BTF[d]	0	89	88:12	76 (*S*)[f]	*b*	129
13	**b**	**4c**	$Sc(OTf)_3$	−	$scCO_2$[e]	40	68	88:12	63 (*S*)[f]	*b*	129
14	**c**	**4c**	$Sc(OTf)_3$	MS[c]	CH_2Cl_2	25	27	78:22	75 (*S*)[g]	*b*	129
15	**a**	**14c**	$Mg(OTf)_2$	MS[c]	CH_2Cl_2	−50	quant	98:2	84 (*R*)	*b*	130
16	**a**	**14c**	$Sc(OTf)_3$	MS[c]	CH_2Cl_2	−50	quant	98:2	76 (*R*)	*b*	130
17	**a**	**14c**	$Yb(OTf)_3$	MS[c]	CH_2Cl_2	−50	quant	87:13	82 (*R*)	*b*	130
18	**a**	**14c**	$La(OTf)_3$	MS[c]	CH_2Cl_2	−50	quant	71:29	96 (*R*)	>99 (*R*)	130
19	**a**	**14c**	$Eu(OTf)_3$	MS[c]	CH_2Cl_2	−50	quant	48:52	90 (*R*)	>99 (*R*)	130
20	**a**	**14c**	$Ce(OTf)_4$	MS[c]	CH_2Cl_2	−50	quant	69:31	88 (*R*)	>99 (*R*)	130
21	**a**	**4i**	$Eu(OTf)_3$	MS[c]	CH_2Cl_2	−50	quant	78:22	racemate	36 (*R*)[h]	130
22	**a**	**4i**	$Ce(OTf)_4$	MS[c]	CH_2Cl_2	−50	quant	70:30	72 (*R*)	94 (*R*)[h]	130
23	**b**	**14c**	$Yb(OTf)_3$	−	CH_2Cl_2	−20	quant	71:29	84 (*R*)[i]	90 (*R*)[j]	130
24	**b**	**14c**	$La(OTf)_3$	MS[c]	CH_2Cl_2	−20	quant	69:31	>99 (*R*)[i]	>99 (*R*)[j]	130
25	**b**	**14c**	$Eu(OTf)_3$	MS[c]	CH_2Cl_2	−20	quant	33:67	92 (*R*)[i]	>99 (*R*)[j]	130
26	**b**	**14c**	$Ce(OTf)_4$	MS[c]	CH_2Cl_2	−20	quant	64:36	92 (*R*)[i]	94 (*R*)[j]	130

[a] w is water. [b] Not reported. [c] 4 Å molecular sieves. [d] BTF benzotrifluoride. [e] $scCO_2$ supercritical carbon dioxide at 100 atm. [f] (2*S*,3*R*). [g] (2*R*,3*R*). [h] Erroneously reported as (*S*). [i] (1*R*,2*R*,3*R*,4*S*). [j] (1*S*,2*R*,3*S*,4*R*).

catalyzed syntheses. The transition from chiral auxiliary control to optically active catalyst control was developed in the DA reaction between cyclopentadiene and alkenoyl-1,3-oxazolidin-2-ones (**55**) affording endo and exo adducts **93** and **94**, respectively (Scheme 35). From the very first research of Narasaka with

Scheme 35



Taddol catalysts,[127] through the box era,[5,71] to this review devoted to pybox, the above reaction is the "fil rouge" that binds the research on this mile-stone of organic synthesis.

The first report of a pybox catalyzed DA reaction appeared as a marginal part in an Evans's communication where **4h**−copper(II) or −zinc(II) complexes were found to be good catalysts for the reaction of cyclopentadiene with **55a**, affording (*S*)-**93a** in a very promising 90% ee (Table 19, entries 1, 2).[72] Then Kanemasa, in his investigation on 4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) as chiral ligand, mentioned the [**4i**−Ni(II)] complex as a catalyst of the same reaction (entries 3, 4), but its efficiency was unsatisfactory.[128]

The best results have been obtained with lanthanides as coordinating Lewis acids.[129,130] The catalysts derived from **4c** and different lanthanide triflates showed Sc(III) as the best cation for the reaction with acryloyl dienophile **55a** (Table 19, entries 5−7 vs 8). Sc(III) was also found to be significantly selective with (*E*)-crotonoyl and cinnamoyl derivatives **55b**,**c** with ee ranging from 75% to 90% (entries 8, 11, 14).

However, the most interesting result was the behavior of the [**4c**−Sc(III)] complex as efficient catalyst of the reaction involving **52a**,**b** in environmentally friendly solvents such as benzotrifluoride and supercritical carbon dioxide (entries 9, 10, 12, 13). The good enantioselectivity (65−75% ee) makes this catalyst a promising Lewis acid complex in green chemistry synthesis.[129]

All the DA catalysts mentioned above, as well as (by far) the large majority of those reported in the literature, are strongly endo-selective. The catalysts derived from *trans*-4′,5′-diphenyl-substituted pybox **14c** and some lanthanides induce a different stereoselectivity. The enantioselectivity is strongly increased by the presence of the second phenyl group in 5′ as shown by the comparison of the results of **4i** and **14c** (Table 19, entries 21 and 22 vs 19 and 20). Far from the behavior of Sc and Yb, that again favor the endo t.s., La(III), Eu(III), and Ce(IV) give the exo adduct **94a** in 31−52% yield, but its ee is >99%. For the first time these protocols allow the separation of enantiomerically pure **94a**, and its absolute configuration was unambiguously determined to be (1′*S*,2′*R*,4′*S*) (Table 19, entries 18−20). The same behavior was observed in the La(III)− and Eu(III)−**14c**-catalyzed reaction of (*E*)-crotonoyl-1,3-oxazolidin-2-one (**55b**)

Table 20. Enantioselective Diels−Alder Reactions Catalyzed by Pybox Complexes of Cyclopentadiene with Acrylates and Enals in Dichloromethane

entry	**95** (R)	**95** (R′)	**95** (Z)	pybox	salt	additive	*T* (°C)	time	yield (%)	[**96**:**97**]	**96** ee % (config.)	**97** ee % (config.)	ref
1	OMe	H	H	**4j**	$Cu(SbF_6)_2$[a]		−20	12 h	>95	95:5	85 (*R*)	−	63
2	OPh	H	H	**4j**	$Cu(SbF_6)_2$[a]		−20	12 h	>95	92:8	44 (*R*)	−	63
3	O*t*-Bu	H	H	**4j**	$Cu(SbF_6)_2$[a]		−20	12 h	>95	98:2	92 (*R*)	−	63
4	O*t*-Bu	H	H	**4c**	$Cu(SbF_6)_2$[a]		−20	12 h	>95	98:2	88 (*R*)	−	63
5	O*t*-Bu	H	H	**4f**	$Cu(SbF_6)_2$[a]		−20	12 h	>95	96:4	84 (*R*)	−	63
6	O*t*-Bu	H	H	**4h**	$Cu(SbF_6)_2$[a]		−20	12 h	>95	96:4	83 (*R*)	−	63
7	H	H	H	**4f**	$Cu(SbF_6)_2$[a]		−20	18 h	>95	94:6	85	−	131
8	H	H	Br	**4f**	$Cu(OTf)_2$		−40	60 h	>95	3:97	−	87 (*R*)	63, 131
9	H	H	Br	**4f**	$Cu(SbF_6)_2$[a]		−78	12 h	>95	2:98	−	96 (*R*)	63, 131
10	H	H	Br	**4j**	$Cu(SbF_6)_2$[a]		−78	12 h	>95	2:98	−	95 (*R*)	63
11	H	H	Me	**4f**	$Cu(OTf)_2$		−20	5 d	>95	3:97	−	85 (*S*)	63, 131
12	H	H	Me	**4f**	$Cu(SbF_6)_2$[a]		−40	8 h	>95	3:97	−	92 (*S*)	63, 131
13	H	H	Me	**4j**	$Cu(SbF_6)_2$[a]		−40	6 h	>95	4:96	−	90 (*S*)	63
14	H	H	Me	**4c**	$Cu(SbF_6)_2$[a]		−40	6 h	>95	4:96	−	72 (*S*)	63
15	H	H	Me	**4h**	$Cu(SbF_6)_2$[a]		−40	6 h	>95	4:96	−	49 (*R*)	63
16	H	Me	H	**4i**	$TaCl_5$		−40	24 h	15	82:18	27 (*R*)	−	132
17	H	Me	H	**4i**	$TaCl_5$	PF[b]	−40	24 h	18	87:13	20 (*R*)	−	132
18	H	H	Me	**4i**	$TaCl_5$		−40	48 h	33	9:91	−	43 (*R*)	132
19	H	H	Me	**4c**	$NbCl_5$	MS[c]	−40	24 h	43	2:98	−	52 (*S*)	132
20	H	H	Me	**4e**	$NbCl_5$	MS[c]	−40	24 h	35	6:94	−	20 (*S*)	132
21	H	H	Me	**4i**	$NbCl_5$	MS[c]	−40	24 h	41	2:98	−	35 (*R*)	132
22	H	H	Me	**4j**	$NbCl_5$	MS[c]	−40	24 h	33	3:97	−	17 (*S*)	132

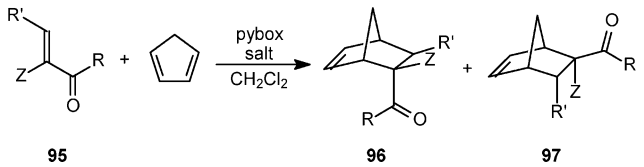
[a] In situ from $CuCl_2$ and $2AgSbF_6$. [b] PF is NH_4PF_6. [c] 4 Å molecular sieves.

since its exo product **94b** was obtained in 31% and 67% yields, respectively, with ee >99% (entries 24 and 25).[130]

These results can be rationalized through the reacting complex **57** (Figure 15), the same stereochemical model of the complex involved in the Mukaiyama−Michael reaction of **55b** reported in Scheme 16.[27] A comparison between the enantioselectivity observed with **14c**-based catalysts with the lower ee of (*R*)-**94** obtained with the monophenyl-substituted ligand **4i** suggests that the specific efficiency of **14c** is due to the phenyl group in the 5′-position of the oxazoline ring, suitably placed to blind the Re face of coordinated **55b** (complex **57** in Figure 15).

Alkenoyloxazolidinones **55** behave in the catalytic cycle of the DA reaction as bidentate dienophiles. The second topic of this section concerns the pybox-catalyzed reaction with acrylates and enals, two classes of monodentate dienophiles whose cycloadditions with cyclopentadiene afforded cycloadducts *endo*-**96** and *exo*-**97** (Scheme 36 and Table 20).

Scheme 36



Evans investigated in detail the reactions of cyclopentadiene with acrylates, methacrolein and 2-bromoacrolein, catalyzed by Cu(II)−pybox complexes,[63,131] and Table 20 reports the most significant results.

The reaction of cyclopentadiene with acrylates (**95**: R′ = Z = H; R = OMe, OPh, O*t*-Bu) was stereoregular and endo-selective and gave **96** with always the same (*R*) configuration, regardless of the [pybox−$Cu(SbF_6)_2$] complex used as catalyst (Table 20, entries 1−6). The best dienophile was *tert*-butyl acrylate that gave 92% ee with the catalyst derived from **4j**.

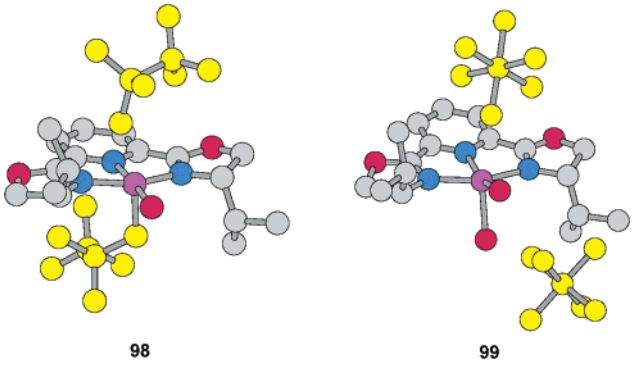
The core of the research was the reaction with α-substituted acrolein derivatives, since many factors influenced the selectivity. As known acrolein is endo-selective (entry 7), whereas methacrolein and α-bromoacrolein (**95**: R = R′ = H, Z = Me, Br) are strongly exo-selective (entries 8−15).

Four different pybox were tested in the DA reaction with methacrolein, and under the same experimental conditions, **4f**, **4j**, and **4c** gave (*S*)-**97** in 92%, 90%, and 72% ee respectively, while an anomalous reversal of enantioselectivity was observed by using the "aromatic" pybox **4h** and (*R*)-**97** was obtained in 49% ee (Table 20, entries 12−15).[63]

An important effect of the Cu(II) counterion was also evidenced: the catalyst derived from SbF_6 was more efficient than that incorporating OTf (Table 20, entries 8 and 11 vs 9 and 12). In terms of rate, after about 6 h, the conversion of methacrolein at −20 °C with Cu(II)−$(BF_4)_2$, −$(OTf)_2$, −$(PF_6)_2$, and −$(SbF_6)_2$ was 7%, 15%, 25%, and 100%, respectively.[131]

The reason of this behavior is the different degree of interaction between anion and Cu(II) center that is illustrated by the X-ray structures of [**4c**Cu(OTf)-H_2O](OTf) and [**4c**$Cu(H_2O)_2$]$(SbF_6)_2$ complexes (Figure 19: **98** and **99** respectively),[62,63] (Table 3, entries 26 and 27): both adopt a square-pyramidal geometry, but the residual two positions have either one water molecule and one triflate anion, or two water molecules, respectively.

On the basis of the geometry of **99**, it is presumed that the aldehydes can easily displace water to coordinate Cu(II) in a square planar geometry and, if the dienophiles adopt the *s*-cis conformation, cyclopentadiene attacks acrolein through an endo t.s., while methacrolein and α-bromoacrolein through exo t.s.; the model is illustrated in Figure 20 and rationalizes the experimental results (with the exception



98 99

Figure 19. Molecular structure of [**4c**Cu(H_2O)(OTf)](OTf) (**98**) and [**4c**Cu(H_2O)$_2$](SbF_6)$_2$ (**99**).

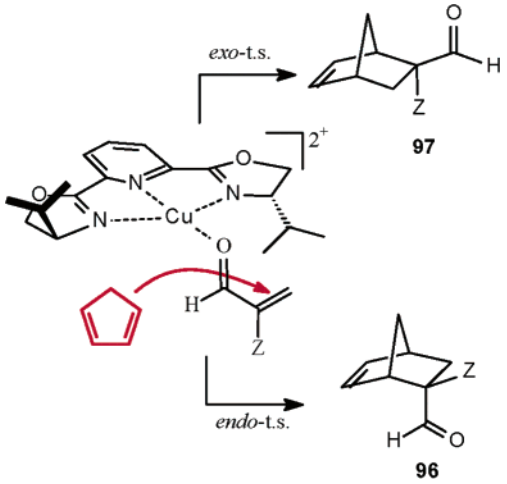


Figure 20. Working model of the reacting complex in the Diels−Alder reaction between cyclopentadiene and enals (Z = H, Me, Br) catalyzed by the Cu(II)−**4c** complex.

of **4h**). The same model leads to the wrong prediction for the acrylate (since its reacting geometry is *s*-trans), and only a 90° rotation of the complexed dienophile allows the exposure of the Si enantioface to the diene attack to give (*R*)-endo cycloadducts.

Howarth and Gillespie[132] studied the cycloadditions involving methacrolein and crotonaldehyde catalyzed by pybox−tantalum(V) and niobium(V) complexes. The efficiency of these catalysts was rather unsatisfactory (Table 20, entries 16−22), and the best yield and enantioselectivity (43% yield and 52% ee) was obtained for the reaction of methacrolein catalyzed by [**4c** Nb(V)].

The enantioselective hetero-DA reaction of carbonyl compounds as dienophiles is an important tool to prepare heterocyclic building blocks bearing a chiral quaternary center and easily transformable functions. The reactions of glyoxylate and pyruvate esters with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (the Danishefsky's diene) **100** to afford 2,3-dihydropyran-4-ones (**101**) (Scheme 37) are known to be efficiently catalyzed by box-based catalysts.[71]

Scheme 37

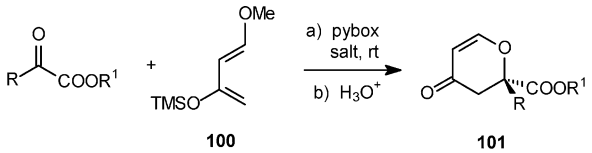


Table 21. Enantioselective Hetero-Diels−Alder Reaction between Glyoxylate and Pyruvate Esters with the Danishefsky's Diene (100) at Room Temperature To Give 101

entry	R	R′	pybox	triflate	**101** yield (%)	**101** ee % (config.)	ref
1	Me	Et	**4c**	Cu(II)[a]	29	9 (*S*)	133
2	Me	Et	**4f**	Cu(II)[a]	15	27 (*S*)	133
3	Me	Et	**4h**	Cu(II)[a]	23	55 (*S*)	133
4	H	Et	**4c**	Yb(III)[b]	41	72	29
5	H	Et	**4h**	Yb(III)[b]	52	4	29
6	H	Et	**14b**	Yb(III)[b]	49	34	29
7	H	Me	**4c**	Yb(III)[b]	73	77	29
8	H	Bu	**4c**	Yb(III)[b]	73	71	29
9	H	Et	**4c**	Sc(III)[b]	46	18	29
10	H	Et	**4c**	La(III)[b]	46	6	29
11	H	Et	**4c**	Sm(III)[b]	46	29	29
12	H	Et	**4c**	Dy(III)[b]	48	58	29

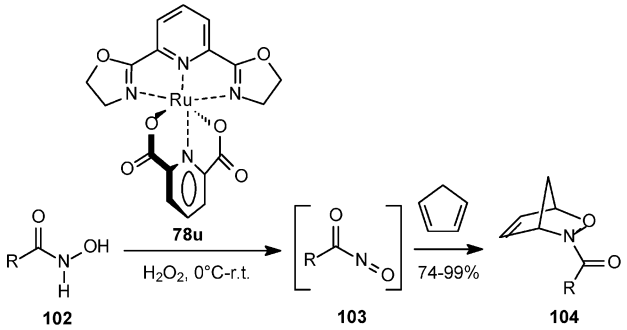
[a] Methylene chloride as solvent. [b] 4 Å molecular sieves and methylene chloride/diethyl ether in the ratio 1:3 as solvent.

Attempts were made to test pybox-based catalysts on this reaction, but both copper[133] and lanthanides[29] catalysts (Table 21) gave results that are not comparable, in terms of yields, enantioenrichments, and flexibility, to those given by Cu(II)−box complexes.[133]

With ethyl pyruvate, the best copper (II) catalyst is that obtained with **4h**; with glyoxylic esters, the best enantioselectivity can be obtained by using the sterically less demanding methyl group and Yb(III), coupled with **4c**, to afford **101** in a significant 77% ee.

The ruthenium(II)−pyridine-2,6-dicarboxylate complex of **4u** (**78u**) catalyzed the H_2O_2 oxidation of hydroxamic acids **102** to give transient acyl nitroso derivatives **103** (Scheme 38).[134] This reaction, which

Scheme 38



occurs even in 1% mol catalyst loading, is discussed in this section because **103** is easily trapped by cyclopentadiene through an hetero Diels−Alder reaction to give **104** in high yields. For the enantioselective development of this reaction, the pybox-catalyzed step should be involved into the generation of chiral centers in the product.

F. 1,3-Dipolar Cycloaddition Reactions

Enantioselective catalyzed 1,3-dipolar cycloaddition reactions between electrophilic nitrones (*N*-benzyl-α-ethoxycarbonylmethanimine *N*-oxide) and electron-rich alkenes, have been usefully run employing copper(II)− and zinc(II)−box chiral catalysts. When the reaction of the above bidentate coordinating nitrone was attempted with **4f**− and **4i**−Cu(II)

Table 22. Asymmetric 1,3-Dipolar Cycloadditions of Nitrones Catalyzed by Pybox-Based Complexes

entry	**55** (R)	**105** (R′)	**105** (X)	pybox	salt[a]	solvent	*T* (°C)	time	yield (%)	[**106**:**107**] endo:exo	**106** endo ee % (config. 3,4,5)	ref
1	Me	Ph	H	**4c**	$Yb(OTf)_3$	toluene	r.t.	20 h	82	94:6	67	136
2	Me	Bn	H	**4c**	$Yb(OTf)_3$	toluene	r.t.	4 d	52	97:3	8	136
3	Me	Ph	Me	**4c**	$Yb(OTf)_3$	toluene	r.t.	5 d	54	96:4	73	136
4	*n*-Pr	Ph	H	**4c**	$Yb(OTf)_3$	toluene	r.t.	2 d	69	92:8	69	136
5	*n*-Pr	Bn	H	**4c**	$Yb(OTf)_3$	toluene	r.t.	7 d	52	96:4	28	136
6	*n*-Pr	Ph	Me	**4c**	$Yb(OTf)_3$	toluene	r.t.	3 d	58	97:3	67	136
7	Me	Ph	H	**4c**	$Ni(ClO_4)_2$	CH_2Cl_2	r.t.	–	89	97:3	66 (*R*,*S*,*R*)	12
8	Me	Ph	H	**4f**	$Ni(ClO_4)_2$	CH_2Cl_2	r.t.	–	98	97:3	86 (*R*,*S*,*R*)	12
9	Me	Ph	Me	**4f**	$Ni(ClO_4)_2$	CH_2Cl_2	r.t.	–	99	99:1	82 (*R*,*S*,*R*)	12
10	H	Ph	H	**4f**	$Ni(ClO_4)_2$	CH_2Cl_2	r.t.	–	97	98:2	90 (*R*,*S*)[d]	12
11	H	Ph	Me	**4f**	$Ni(ClO_4)_2$	CH_2Cl_2	r.t.	–	99	96:4	86 (*R*,*S*)[d]	12
12	H	Ph	H	**4o**	$Ni(ClO_4)_2$	CH_2Cl_2	25	24 h	0	–	–	12
13	H	Ph	H	**4p**	$Ni(ClO_4)_2$	CH_2Cl_2	0	24 h	96	94:6	95[b] (*S*,*R*)[d]	12, 137
14	H	Ph	H	**4q**	$Ni(ClO_4)_2$	CH_2Cl_2	0	4 h	99	>99:1	>99 (*S*,*R*)[d]	12, 137
15	H	Ph	H	**4r**	$Ni(ClO_4)_2$	CH_2Cl_2	0	1.5 h	99	97:3	>99 (*S*,*R*)[d]	12, 137
16	H	Ph	Me	**4p**	$Ni(ClO_4)_2$	CH_2Cl_2	0	24 h	93	>99:1	96 (*S*,*R*)[d]	12, 137
17	H	Ph	Me	**4q**	$Ni(ClO_4)_2$	CH_2Cl_2	0	4 h	95	>99:1	>99 (*S*,*R*)[d]	12, 137
18	H	Ph	OMe	**4p**	$Ni(ClO_4)_2$	CH_2Cl_2	0	24 h	94	>99:1	98 (*S*,*R*)[d]	12, 137
19	H	Ph	OMe	**4q**	$Ni(ClO_4)_2$	CH_2Cl_2	0	4 h	98	>99:1	>99 (*S*,*R*)[d]	12, 137
20	Me	Ph	H	**4p**	$Ni(ClO_4)_2$	CH_2Cl_2	r.t.	24 h	60	>99:1	95 (*S*,*R*,*S*)	12
21	Me	Ph	Me	**4p**	$Ni(ClO_4)_2$[a]	CH_2Cl_2	0	72 h	56	98:2	93 (*S*,*R*,*S*)	12
22	Me	Ph	OMe	**4p**	$Ni(ClO_4)_2$[a]	CH_2Cl_2	r.t.	72 h	71	>99:1	92 (*S*,*R*,*S*)	12
23	Me	Ph	Br	**4p**	$Ni(ClO_4)_2$[a]	CH_2Cl_2	r.t.	72 h	77	>99:1	94 (*S*,*R*,*S*)	12
24	Me	Ph	H	**4r**	$Ni(ClO_4)_2$	CH_2Cl_2	r.t.	72 h	99	>99:1	97 (*S*,*R*,*S*)	12
25	Me	Ph	H	**4q**	$Ni(ClO_4)_2$	CH_2Cl_2	r.t.	24 h	95	98:2	96 (*S*,*R*,*S*)	12
26	Me	Ph	H	**4q**	$Ni(ClO_4)_2$[a]	*s*-BuOH	r.t.	24 h	50	83:17	86 (*S*,*R*,*S*)	138
27	Me	Ph	H	**4q**	$Ni(ClO_4)_2$[a]	*t*-BuOH	r.t.	24 h	85	>99:1	95 (*S*,*R*,*S*)	138
28	Me	Ph	Me	**4q**	$Ni(ClO_4)_2$[a]	*t*-BuOH	r.t.	5 h	87	>99:1	90 (*S*,*R*,*S*)	138
29	Me	Ph	OMe	**4q**	$Ni(ClO_4)_2$[a]	*t*-BuOH	r.t.	5 h	86	>99:1	90 (*S*,*R*,*S*)	138
30	H	Ph	H	**4q**	$Ni(ClO_4)_2$[a]	*t*-BuOH	r.t.	4 h	97	91:9	93 (*S*,*R*)[d]	138
31	H	Ph	Me	**4q**	$Ni(ClO_4)_2$[a]	*t*-BuOH	r.t.	4 h	95	92:8	95 (*S*,*R*)[d]	138
32	H	Ph	OMe	**4q**	$Ni(ClO_4)_2$[a]	*t*-BuOH	r.t.	4 h	94	90:10	93 (*S*,*R*)[d]	138

[a] Hydrate, 4 Å molecular sieves (MS) as additive. [b] Without MS. [c] 98% ee if T is −15 °C. [d] Configurations of 3 and 4 positions.

triflate, the result was a complete absence of diastereo- and enantioselectivity.[135]

The reactions of aryl nitrones with electron-poor alkenes were successfully investigated, and if dipolarophiles may behave as bidentate ligands, the dipolar cycloaddition can be usefully catalyzed by pybox-based chiral complexes. The best dipolarophiles having these features are alkenoyl-1,3-oxazolidin-2-ones **55**; hence their reactions with *C*-aryl nitrones **105** (Scheme 39) were catalyzed by [**4c**−Yb(OTf)$_3$] to give selectively the *endo*-isoxazolidines **106**.[136]

Scheme 39

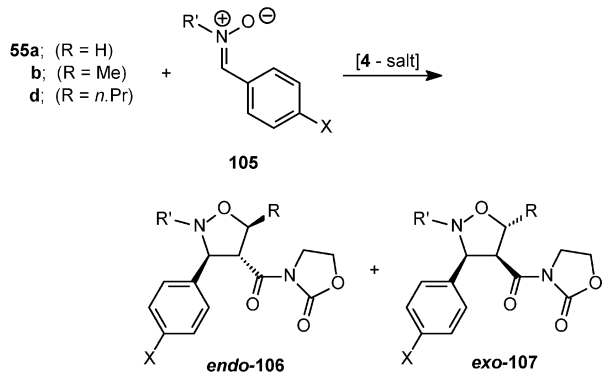


Table 22 reports the experiments run following this protocol, and the ee was in the range 67−73% if the nitrone is *N*-phenyl-substituted, while the enantioselectivity dropped with *N*-benzyl-substituted nitrones (entries 2 and 5 vs 1 and 4). When the same reaction was catalyzed by [**4c**−Ni(ClO$_4$)$_2$], an identical result was obtained (entry 7 vs 1).[12]

The change of the pybox coordinating Ni(II) to **4f** ameliorated the efficiency of the catalyst since yields were nearly quantitative, endo-selectivity was excellent, and the ee of **106** was in the range 82−90% with both acryloyl- and crotonoyl-1,3-oxazolidin-2-ones (**55a**,**b**; R = H, Me) (Table 22, entries 7−11).[12]

Important new ligands in the field were obtained by modifying bis(oxymethyloxazolinyl)pyridine (**4o**) that gave completely inactive catalysts (Table 22, entry 12).[12,137] When the hydroxy groups of **4o** were protected with a series of sterically encumbered trialkyl silyl groups, three new very efficient pybox ligands (**4p**, **4q**, and **4r**) were obtained, which were tested on the 1,3-dipolar cycloaddition of **55a**,**b** with different diarylnitrones (Table 22, entries 14−25), using the traditional methylene chloride as solvent. The tri-isopropylsilyloxymethyl ligand **4q** (as well as ligand **4r**) exhibits reaction-rate acceleration with **55a** to give at 0 °C (within 4 h) (3*S*,4*R*,5*S*)-**106** in 99% yield (Table 22, entry 14). Both cycloadditions of *p*-tolyl and *p*-methoxyphenylnitrones with acryloyl dipolarophile **55a** gave excellent results with either **4p**- or **4q**-based catalysts (Table 22, entries 16−19), while those with the crotonoyl derivative **55b** (a less reactive dipolarophile) had to be run at 40 °C with **4p**, **4q**, and **4r** to give cycloadducts with slightly lower selectivities (>90% ee; Table 22, entries 20−25). Incidentally, the relationship between enantio-

Table 23. Asymmetric 1,3-Dipolar Cycloadditions in CH_2Cl_2 of Carbonyl Ylide 109 with Different Dipolarophiles, Catalyzed by Pybox−Lanthanide Triflate Complexes

entry	dipolarophile C=X	M	pybox	additive (a)	*T*, °C (time, h)	yield, %	endo:exo	endo ee %	exo ee %
1	**39**	Sc	**4c**	−	−10 (2)	91	55:45	85	16
2	**39**	Sc	**4c**	MS	−10 (2)	96	88:12	91	18
3	**39**	Sc	**4h**	MS	−10 (2)	57	86:14	92	14
4	**39**	Sc	**4p**	−	−10 (2)	92	71:29	75	18
5	**39**	Yb	**4c**	−	−10 (2)	99	9:91	40	40
6	**39**	Yb	**4c**	MS	−10 (2)	98	9:91	35	36
7	**39**	Yb	**4h**	MS	−10 (2)	quant.	14:86	38	7
8	**42** (R^2 = Me)	Sc	**4c**	−	−10	84	12:88	*b*	45
9	**42** (R^2 = Me)	Sc	**4c**	MS[c]	−10 (1)	88	4:96	*b*	78
10	**42** (R^2 = Bn)	Sc	**4c**	−	−10	82	18:82	*b*	11
11	**42** (R^2 = Bn)	Sc	**4c**	MS[c]	−10	88	7:93	*b*	87
12	**55a**	Sc	**4c**	MS	−10 (1)	65	90:10	8	1
13	**55a**	Sc	**4h**	MS	−10 (1)	86	89:11	7	14
14	**55a**	Yb	**4c**	MS	−10 (1)	90	88:12	13	22
15	**55a**	Yb	**4h**	MS	−10 (1)	94	46:54	*b*	89
16	**55a**	Yb	**4h**	MS	−25 (6)	89	12:88	*b*	98

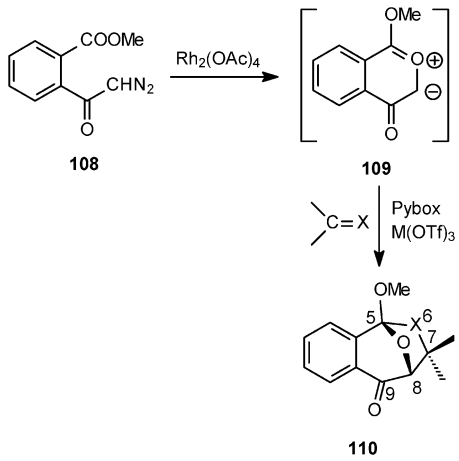
[a] MS is 4 Å molecular sieves. [b] ee not determined. [c] Catalytic amounts of pyruvic acid.

meric excess of pybox and endo product **106** was checked for both **4c** and **4q** chiral ligands. The former relationship showed a weak positive chiral amplification, while the latter was linear. A rationale in terms of reservoir effect, possible for **4c** and impossible for the bulky **4q**, was proposed.[12]

The search of environmentally friendly solvents is an important topic of contemporary organic synthesis, and enantioselective catalyzed 1,3-dipolar cycloadditions have been investigated with this aim. Protic solvents have been found usefull media for the above-described nitrone cycloadditions catalyzed by Ni-$(ClO_4)_2$ with the sterically tuned pybox **4q**.[138] Whereas 2-propanol gives solvolysis derivatives as byproducts, the reaction in *s*-BuOH and (better) *t*-BuOH proceeds smoothly to give the corresponding isoxazolidines with very good yields. With both acryloyl- and crotonoyl-oxazolidinones **55a**,**b**, the [endo/exo] ratios ranged from 90:10 to >99:1, and the ee of **106** was in the range 90−98% (Table 22, entries 26−32). These results, which are comparable to those obtained with alogenated solvents, make sterically hindered alcohols possible media for these Lewis-acid catalyzed enantioselective reactions. Excellent results have also been obtained with 1-acryloyl and 1-crotonoyl-2-pyrrolidones as dipolarophiles.[138]

The chiral pybox complexes of Sc(III) and Yb(III) were usefully applied to the enantioselective 1,3-dipolar cycloaddition of 2-benzopyrylium-4-olate (**109**), a carbonyl ylide generated by rhodium-catalyzed intramolecular carbenoid−carbonyl cyclization of *o*-methoxycarbonyl-α-diazoacetophenone (**108**) (Scheme 40).[139] The reaction was initially run, under different conditions, with benzyloxyacetaldehyde (**39**) as dipolarophile that gave the regioisomer **110** with the oxygen atom in position 6 (Table 23, entries 1−7). The best ligand was **4c** (followed by **4h**), Sc and Yb gave opposite endo/exo selectivity, and the presence of 4 Å molecular sieves with Sc greatly increased both endo selectivity and the level of enantioselectivity of this cycloadduct (entry 3). Substituted benzyloxyacetaldehydes gave similar results, whereas the enantioselectivity with benzaldehyde was very low [3% ee (endo), 14% ee (exo)], a result that indicates how important is bidentate coordination of the dipolarophile on the catalyst for selectivity.

Scheme 40



The reaction with methyl and benzyl pyruvate (**42**), catalyzed by the Sc complex of **4c**, was strongly regio- and exo-selective and the maximum enantioselectivity was observed when the reaction was run in the presence of pyruvic acid as additive (Table 23, entries 9, 11). Finally, 3-acryloyl-1,3-oxazolidin-2-one (**55a**) was tested as dipolarophile: the regioisomer **110** has the acyl residue in position 6, and selectivity was excellent only when the [**4h** Yb] catalyst was used at low temperature (Table 23, entry 16).

In conclusion, 1,3-dipolar cycloadditions can be enantioselectively catalyzed by pybox complexes, and in addition to widely investigated nitrones, carbonyl ylides (at least **109**) give excellent levels of selectivity, a promising result for future researches.

G. Other Pericyclic Reactions

Three examples of sigmatropic rearrangements catalyzed by pybox-based complexes have been reported in the recent literature, but the efficiency of these catalysts was disappointing (low reactivity and enantioselectivity) if compared to that obtained by using the other ligands reported in the references.[140−142]

The asymmetric sulfur ylide [2,3]-sigmatropic rearrangement of carbenoid generated from methyl phen-

Table 24. The Glyoxylate-Ene Reactions between Glyoxylate Esters and 113, Catalyzed by Pybox−Lanthanide Complexes

entry	**113** (Ar)	R	pybox	Ln(III)	solvent	time (h)	**114** yield (%)	ee % (config.)
1	Ph	Et	**4c**	Yb	PhMe	40	4	31 (*R*)
2	Ph	Et	**4c**	Yb	THF	40	6	48 (*R*)
3	Ph	Et	**4c**	Yb	CH_2Cl_2	8	31	46 (*R*)
4	Ph	Et	**4c**	Sc	CH_2Cl_2	40	26	27 (*R*)
5	Ph	Et	**4c**	Dy	CH_2Cl_2	40	44	20 (*R*)
6	Ph	Et	**4c**	Sm	CH_2Cl_2	40	42	16 (*R*)
7	Ph	Et	**4f**	Yb	CH_2Cl_2	36	75	1 (*R*)
8	Ph	Et	**4h**	Yb	CH_2Cl_2	36	71	50 (*R*)
9	Ph	Et	**14b**	Yb	CH_2Cl_2	36	73	37 (*R*)
10	Ph	Et	**18d**	Yb	CH_2Cl_2	36	81	5 (*R*)
11	*p*-ClC_6H_4	Et	**4h**	Yb	CH_2Cl_2	45	69	54 (*R*)
12	2-naph	Et	**4h**	Yb	CH_2Cl_2	36	78	38 (*R*)
13	Ph	Ment[a]	—[b]	Yb	CH_2Cl_2	20	88	6[c]
14	Ph	Ment[a]	**4h**	Yb	CH_2Cl_2	30	76	81[c]

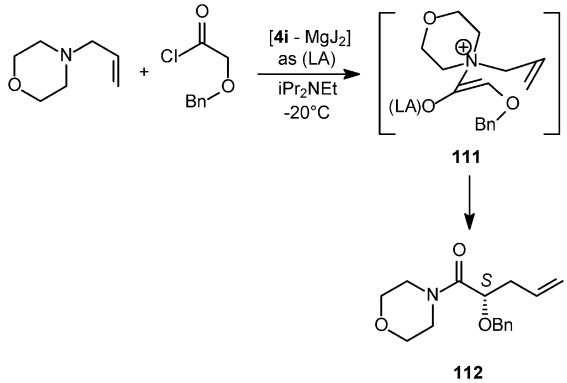
[a] Ment is (−)-menthyl. [b] Absence of pybox, with $Yb(OTf)_3$. [c] de, the configuration of the new stereogenic center is (*R*).

yldiazoacetate with *o*-tolyl allyl sulfide was inter alia catalyzed by [**4c**−$Cu(MeCN)_4PF_6$], but methyl 2-phenyl-2-[(2-methylphenyl)thio]-4-pentenoate was obtained with 57% yield and 8% ee.[140]

The aza-Claisen rearrangement of *N*-(4-trifluoromethyl-phenyl)benzimidic acid hex-2-enyl ester was run in the presence of {**4c**−$[Pd(MeCN)_4](BF_4)_2$}, and the ee of the resulting allylic amide was a promising 55%, despite a disappointing 4% yield.[141]

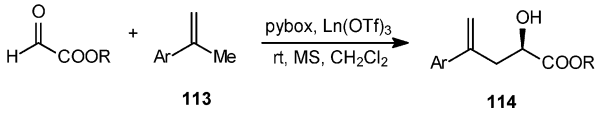
A different result is obtained in the enantioselective acyl-Claisen rearrangement that utilizes benzyloxyacetyl chloride (via the in situ formation of benzyloxyketene) and *N*-allylmorpholine to give α-substituted-*γ*,*δ*-unsaturated amide **112** through the reacting complex **111** (Scheme 41). The selectivity with [**4i**−MgJ_2] was quite good (87% yield and 56% ee), but the "catalysis" required 200% mol of chiral Lewis acid complex.[142]

Scheme 41



The glyoxylate-ene reaction is an interesting route to α-hydroxy esters that has been catalyzed by both BINOL-[143,144] and box-based catalysts.[145,146] Recently, the reaction between glyoxylic esters and 2-arylpropenes **113** has been reported to be catalyzed by pybox and lanthanide triflates to afford **114** (Scheme 42).[30]

Scheme 42



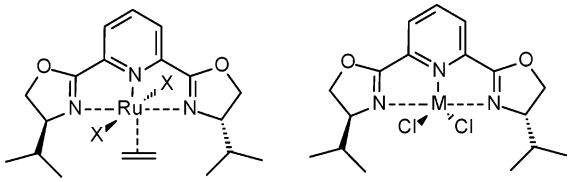
The experimental results are summarized in Table 24: methylene chloride was the best solvent tested (entries 1−3), ytterbium was the best lanthanide (entries 3−6), and phenyl-substituted pybox **4h** gave the best balance between yield and ee for α-methylstyrene (entries 3, 7−10).

Different alkenes were tested, and two examples are reported (Table 24, entries 11, 12) showing a reasonable flexibility of the catalyst versus propene substituents. Among the different esters tested (e.g., R = Me, Et, Bu), the most interesting result was reported with (−)-menthyl ester, since the stereoselectivity (that in the absence of pybox was poor, entry 13) was significantly higher than that of alkyl esters (entry 14 vs 8). A conversion of menthyl into the methyl ester and the comparison of its [α] value with the literature data allowed to determine the configuration of the new stereocenter as (*R*).

H. Polymerization and Oligomerization of Alkenes and Alkynes

From the point of view of chemists involved in organic synthesis, it is difficult to understand the choice of a chiral ligand to prepare nonoptically active polymers, but the topic has such an industrial relevance that deserves adequate comment. Pybox **4c** was the starting ligand for three ruthenium complexes: one was the already mentioned **28cx**, and two were prepared from $[RuX_2(p\text{-cymene})]_2$ and had X = J^- or $CF_3SO_3^-$ instead of chlorides. From the same ligand **4c** and $FeCl_2$, the pentacoordinated Fe(II) complex **115a** was isolated (Chart 4).[147,148]

Chart 4



28cx (X = Cl) **115a:** M = Fe **b:** M = Co

The ruthenium complexes exhibited moderate catalytic activity for ethylene homopolymerization and

ethylene/1-hexene (E/H) copolymerization in the presence of solid methylaluminoxane (MAO) as cocatalyst. The resultant polyethylene had high molecular weight ($M_w = 208.8 \times 10^4$), and the molecular weight distribution was narrow ($M_w/M_n = 2.93$). The study of the monomer sequence distribution in the copolymer showed that copolymerization does not proceed in a random manner since a strong preference (95%) for triads containing (3E) or (2E1H) was observed. Also the iron complex **115a** exhibited catalytic activity for ethylene (E) polymerization, but the attempted copolymerization of E with H gave linear polyethylene without incorporation of H.[147−150]

Other metals have been tested for the preparation of pybox complexes active in olefin oligomerization and polymerization. The properties of Cr complexes were not inferred in details, probably for their nonsignificant activity.[151] The jade-green solid [**4c**−$CoCl_2$] (**115b**) was prepared in 76% yield in THF and used, with MAO as cocatalyst, for the preparation of oligomers of ethylene ($M_w = 336$).[152]

A rhodium−pybox complex was found to catalyze a mechanistically interesting cycloaddition of diynes with several alkynes, a reaction that can be regarded as related to the topic of this section. Even if the isobenzofuran derivatives **118** have no chiral centers, the interest in such a reaction derives from its catalytic cycle illustrated in Figure 21. At 80 °C the

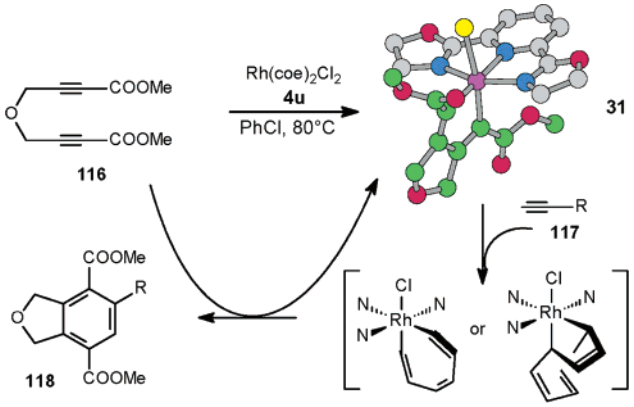


Figure 21. The catalytic cycle of the cycloaddition between diyne **116** and alkynes **117**.

reaction between 4-(3-methoxycarbonyl-prop-2-ynyloxy)-but-2-ynoic acid methyl ester (**116**) and an excess alkyne **117**, in the presence of either **4u** and [Rh (*cis*-cyclooctene)$_2$Cl]$_2$ (0.05 mol) or the same amount of **31**,[59] gives 5-substituted-1,3-dihydro-4,7-isobenzofurandicarboxylic acid dimethyl esters (**118**) in fair yields (Table 25).

Table 25. The Cycloaddition of 116 with Different Alkynes (116), Catalyzed by [Rh-4u] Complex

entry	catalyst	**117** (R)	time (h)	**118** yield %
1	**4u** + Rh[a]	Ph	5	72
2	**31**	Ph	4	74
3	**4u** + Rh[a]	$SiMe_3$	72	23
4	**31**	$SiMe_3$	72	47
5	**31**	*n*-Bu	30	68
6	**31**	COOMe	24	0

[a] [Rh(*cis*-cyclooctene)$_2$Cl]$_2$.

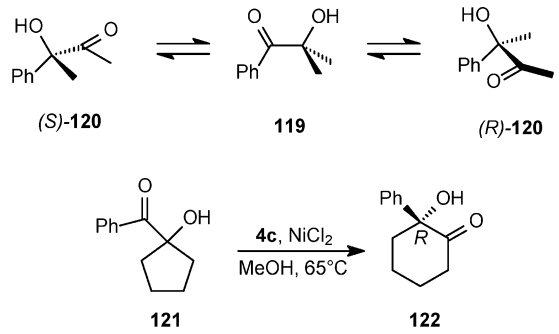
The comparable results obtained either with **4u** and Ru, or with **31**, illustrate the importance of this complex (whose crystal structure has been illustrated in Figure 6) as one of the reacting intermediates in the catalytic cycle (Figure 21), since it may react with **117** either via a concerted cycloaddition of alkyne to the diene moiety of the rhodacyclopentadiene, or via insertion giving a rhodacycloheptatriene, both possible precursors of **118**.

I. Miscellaneous Reactions

More than thirty types of reactions have been reported to be catalyzed by pybox complexes, the majority of them having been reviewed in previous sections, nevertheless, several papers have not yet been considered. This makes the current section difficult to organize because it is not easy to find a logical connection between papers with different methodologies and targets; the following discussion may also become a source of new ideas and suggestions since what has been done once on a specific reaction may perhaps have useful and much more general applications.

In the presence of catalytic amounts of Ni(II), the tertiary α-hydroxy ketones undergo α-ketol rearrangement, that may occur with asymmetric induction if a chiral ligand is used. An example of this is the reaction of 2-hydroxy-2-methyl-1-phenylpropan-1-one (**119**) that, with **4c** and $NiCl_2$, gives the couple of enantiomers **120** (Scheme 43). At 130 °C the

Scheme 43

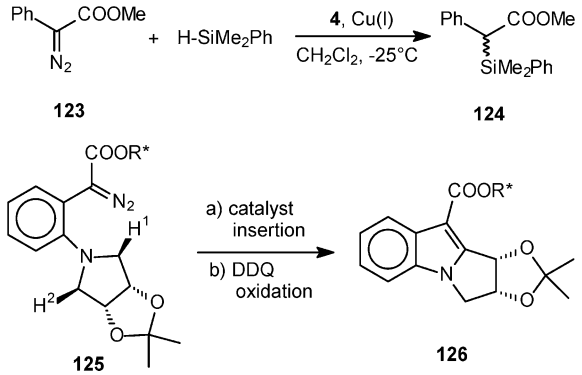


enantiomeric excess rises to a maximum of 19.3% of (*R*)-**120** after 4 h, and then it decreases rapidly.[153] An interesting extension of this reaction was tested with 1-benzoyl-1-cycloalkanols. The reaction of cyclopentanol **121**, under the reported conditions, gives **122** in 91% conversion, and the ee of the *(R)* enantiomer was 34.2% (Scheme 43). The analogous cyclobutanol derivative reacted at 25 °C, and the ee was 33.6%, while the corresponding cyclohexanol, even at 130 °C, was unreactive.[154]

The pybox **4c** had some occasional uses as a candidate in the construction of combinatorial libraries, none of them successful: it was one of the 96 bases tested in the Ullmann ether formation,[155] one of the five chiral activators added to five chiral ligands for the catalytic addition of dialkylzinc to aldehydes,[156] and also failed in the desymmetrization of *meso*-1,2-cyclopentandiol attempted with [**4c**−Cu(OCOMe)$_2$] complex (60% yield).[157]

Three insertion reactions, one intramolecular onto a Si−H bond and two intermolecular on a C−H bond, were performed under pybox-catalyzed conditions. Two were based on the decomposition of α-diazoesters, and the intermolecular insertion consisted in the reaction of methyl phenyldiazoacetate **123** with dimethylphenylsilane to give **124** (Scheme 44).[158] Catalysts based on Cu(I) and **4f**,**h** (or their enantiomers **4g**,**i**; curiously this is not specified), gave ee of 53% and 49% respectively.

Scheme 44

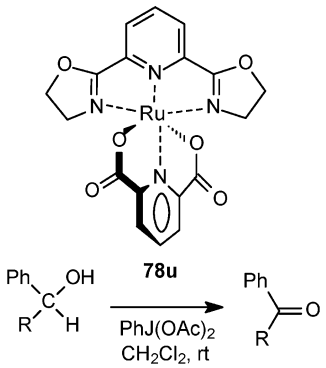


The intramolecular insertion was realized by decomposition of **125** [R = (−)-menthyl], with **4c** and different cations in different solvents, to investigate the diastereomeric ratio originated from the attack on (H^1), giving **126** after oxidation with DDQ, versus that on (H^2), giving the diastereoisomer of **126** (**d-126**) (Scheme 44). The selectivity was not very high, nevertheless Ag(I) or Cu(I) in THF gave a ratio [**126**:**d-126**] of [2.0:1], whereas with Rh in toluene the ratio was reversed to [1:2.3].[159] The second intramolecular insertion consisted in the ring closure of phenyliodonium 1-[2-methyl-1-(1-methylethyl)propoxy]-1,3-dioxo-6-phenylhexylite with the complex of $Cu(OTf)_2$ and the enantiomer of **11**. After decomposition of the resulting keto ester, the yield of 3-phenylcyclopentanone was discrete (42%), but the ee [16% (*R*)] was too low if compared with the enantioselectivity induced by other catalysts.[160]

Two papers discuss catalytic reactions that at a first glance do not generate chirality.

Primary and secondary alcohols were oxidized with diacetoxyiodobenzene to the corresponding aldehydes and ketones, in the presence of ruthenium[bis-(oxazolinylpyridine)−(pyridine-2,6-dicarboxylate)] **78u**

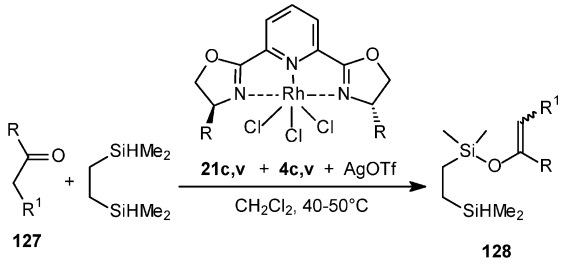
Scheme 45



(Scheme 45), and the yield of 10 very different samples was in the range 44−96%.[161] Obviously, a possible chiral development of this reaction could consist in the kinetic resolution of secondary alcohols by using chiral catalyst **78c** (with pybox **4c** as ligand).

The dehydrogenative silylation of ketones **127** with 1,2-bis(dimethylsilyl)ethane was catalyzed by a mixture of the rhodium complexes **21c** (or **21v**), the corresponding pybox **4c** (or **4v**), and silver triflate. Only one Si−H group is converted to the corresponding silyl enol ether **128**, and the yields of seven very different samples were in the range 67−97% (Scheme 46). The chiral development of the process was

Scheme 46



discovered running the reaction on *t*-butylcyclohexanone with the chiral catalyst: the optically active **128**, derived from the 4-substituted ketone, was formed in 7% ee, whereas the kinetic resolution of 2-*t*-butylcyclohexanone provided it with up to 11% ee after 60% conversion.[162]

The last argument does non fit the topic "catalysis"; it deals better with "chiral recognition", but this may be used as a fruitful model both for the "reagent/catalyst" and "artificial enzymes" interactions and may probably have future important applications in analytic techniques.[163,164]

The wide possibilities of application of the above concept can be found in the NMR study of the association between **4c** and **4j** with (*R*)- and (*S*)-1,1′-bi-2-naphthols [(*R*)-**129** and (*S*)-**129**]. The chiral recognition arises from the hydrogen bonds given by hydroxy groups with oxazoline nitrogen atoms (Figure 22 illustrates the interactions of **4c**). The titration

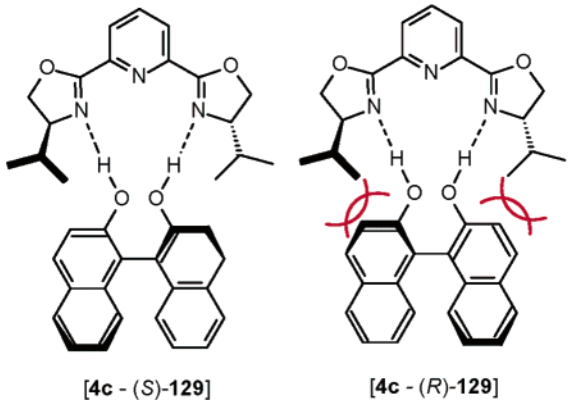


Figure 22. Matched and mismatched pairs between **4c** and **129**.

of each binaphthol with the pybox in the NMR tube gave the respective association constants (K_R and K_S) and the energy difference between the couples of

Table 26. Association Constants of Pybox 4c,j with Binaphthols (*R*)-129 and (*S*)-129

pybox	binaphthol	K (L mol^{-1})	K_S/K_R	$\Delta(\Delta G)$ (kJ mol^{-1})
4c	(*S*)-**129**	14	4.0	−3.5
4c	(*R*)-**129**	3.4		
4j	(*S*)-**129**	42	8.0	−5.1
4j	(*R*)-**129**	5.3		

diastereoisomers $\Delta(\Delta G)$ (Table 26).[165] Figure 22 illustrates the steric interactions involved in [**4c**/(*R*)-**129**] that makes it a mismatched base-acid pair, and Table 26 quantifies these interactions both for **4c** and **4j**.

V. The Coordination and the Mechanism of the Chirality Transfer

The mechanism of the chirality transfer in asymmetric catalysis requires a diastereofacial discrimination of the coordinated reagent in the reacting complex, whose structure is not often known in detail. Furthermore, no less than 30 reactions have been described to be catalyzed by pybox complexes, and very often a catalyst is selective only for a limited number of reagents in a specific reaction.

A pragmatic possibility to infer the catalytic cycle, and hence to rationalize the chirality transfer, is based on the comparison of the experimental data obtained by small variations of those parameters influencing the selectivity (pybox structure, Lewis acid, additives, sometimes solvent, and temperature). The aim of this section is to describe how some homogeneous classes of reactions modify their selectivity upon changing the above considered parameters.

The paradigm that a low temperature increases stereoselectivity, since a decrease of the degree of freedom of the reacting intermediate is expected, must be mediated with the eventual low reactivity of the substrate. In consideration of this, the temperature of the pybox-catalyzed reactions is in the range −50/+40 °C, and the higher the temperature the lower the selectivity; hence, the reactions run below 0 °C are commonly found.

The solvent of election with box and pybox ligands is methylene chloride, sometimes toluene or acetonitrile, but three exceptions deserve a mention.

The 1,3-dipolar cycloaddition of nitrones shown in Scheme 39, catalyzed by [**4q**−Ni(II)] complexes, can be run in *tert*-butyl alcohol, without loss of the excellent selectivity observed when methylene chloride is the solvent.[138] The cyclopropanation of styrene with diazoacetates (Scheme 22), catalyzed by the Ru complex of (*R*,*R*)-4,4′-bis(hydroxymethyl)pybox (**4o**), is run in a mixture of water and toluene. The reason is because bis-hydroxy ligand, which is freely soluble in water, is almost insoluble in aprotic solvents. Thus, the reaction run in THF or toluene occurs in low yield and low stereoselectivity, but when performed in water/toluene, the cyclopropanation gives better yield and diastereoselectivity, and the enantioselectivity dramatically increases.[10] The reaction between phenylacetylene and Schiff bases (Scheme 21) can be run in water or toluene and the enantioselectivity in water is comparable to that in the more traditional solvent (Table 13).[98] The aim of this protocol is to find environmentally friendly conditions, since the pybox of this reaction is the phenyl-substituted **4h**, whose standard conditions involve its use in more pollutant aprotic solvents.

The development of the concept of green asymmetric synthesis led to the search of environmental benign solvents compatible with chiral catalysts, and the Diels−Alder reaction in Scheme 35, catalyzed by [**4c**−Sc(III)] complex, was run either in benzotrifluoride (a solvent less toxic than dichloromethane) or in supercritical carbon dioxide with good selectivity (Table 19).[129]

The relationship between the ee of the reaction product and that of the ligand involved in the catalyst gives important information on the stoichiometric composition of the reacting intermediate. A linear relationship supports a ratio [ligand:cation:reagent] of [1:1:1], while a nonlinear effect (NLE) can be due either to a different composition of the reacting intermediate or to the reservoir effect.[36] When reported in the literature, this point has been discussed in previous specific sections and NLEs have been observed in the following reactions:

(a) the Mukaiyama-aldol reaction (Scheme 11) catalyzed by [**4h**−Cu(II)] complex,[62]

(b) the epoxide ring opening (Scheme 29) catalyzed by [**4f**−Yb(III)] complex,[116]

(c) the nitrone 1,3-dipolar cycloaddition (Scheme 39) catalyzed by [**4c**−Ni(II)].[12]

The NLE of the reactions a and c is due to the reservoir effect since the X-ray structure of the racemic complex has been determined,[62] while the 1,3-dipolar cycloaddition gives a linear effect when the ligand was the bulky **4q**.[12] The NLE of the reaction b is due to the catalyst playing a dual role, coordination of epoxide and delivery of cyanide.[116] A settled point in the structure of the reacting complex is that no example with a stoichiometry other than [1:1:1] for [ligand:cation:reagent] has been reported.

The best homogeneous set of reactions, taking constant everything except the cation acting as Lewis acid, is the asymmetric ring opening of cyclohexene oxide with TMSCN, catalyzed by **4c** and lanthanide trichlorides.[116] Figure 23a illustrates the variation of enantioselectivity as a function of the ionic radius

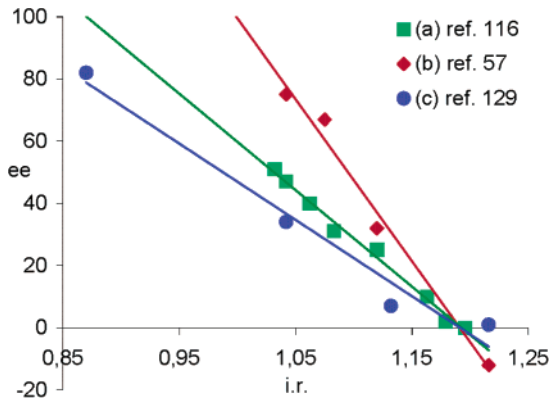


Figure 23. Variations of the ee of the reactions in Schemes 29 (**a**, ref 116), 19 (**b**, ref 57), and 35 (**c**, ref 129) vs the ionic radius of the lanthanide (III).

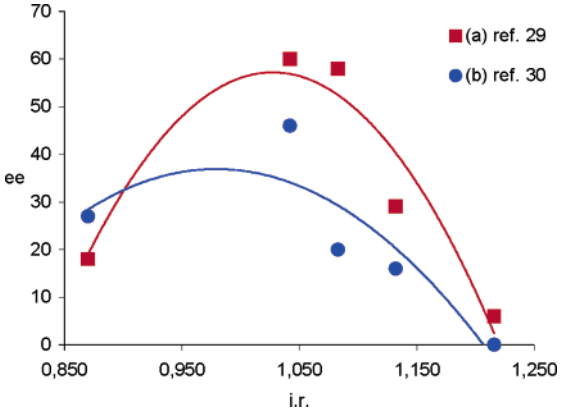


Figure 24. Variations of the ee of the reactions with ethyl glyoxylate in Schemes 37 (**a**, ref 29) and 42 (**b**, ref 30) vs the ionic radius of the lanthanide (III).

(i.r.) of the trivalent cation involved in a 9-coordination.[166] The best ee is obtained with lutetium, the smallest cation; unfortunately the research does not takes into account scandium. Other examples of variation of enantioselectivity, changing the lanthanide cation, have been encountered along this review. Even if the number of cations is limited, Figure 23b,c reports the variations of the ee both in the addition of TMSCN to benzaldehyde,[57] catalyzed by [**4d**−lanthanide] complexes, and in the Diels−Alder reaction, catalyzed by [**4c**−lanthanide],[129] versus the i.r. of the lanthanides (8-coordination for Sc). The trend is the same as that in the Figure 23a, and it rationalizes the inversion of configuration observed for product **60** on going from La(III) to Eu(III).

The above illustrated trends are not the only type of relationship between ee and i.r.. Ethyl glyoxylate reacts as heterodienophile with the Danishefsky diene (Scheme 37)[29] and with alkenes in the hetero-ene reaction (Scheme 42).[30] In both reactions, catalyzed by [**4c**−lanthanide] complexes, the number of cations tested is low, but the relationships are clearly not linear (Figure 24a,b), with the best ee obtained for a value of i.r. around 1.05 Å (ytterbium and dysprosium).

The question as to whether this is due to a geometrical factor (a suitable i.r. fits correctly the site of coordination of pybox) or to the Lewis acidity is at the moment hard to state mainly because the latter parameter is a function of the charge density.

A diverse rationale cannot be excluded. If two competitive reacting complexes are assumed for rare earth cations allowing different coordination number, each favoring the attack on the opposite heterotopic faces of the coordinated reagent, the observed different sense of induction can be understood.

More examples with a significant number of cations are required, and this will certainly be the argument of future experiments.

The second important parameter to be considered is the change of stereoselectivity changing the pybox substituent. If the selectivity depends only from shielding factors, the ee should be a function of the substituent steric effects and could be quantified by the corresponding steric constants. It is not simple to find a homogeneous set of reactions run under identical conditions with a sufficiently large series of substituents on the pybox ligand as the unique variant. As a general trend, from the several series of values listed in the tables, it can be said that selectivity roughly increases in the order Me < Et ≈ Bn < *i*-Pr, which largely respects the steric hindrance. Phenyl and *t*-butyl are excluded from the series because these substituents gives rise to major variations.

To appreciate this, Figure 25 represents the variations of the ee in eight reactions when pybox is **4c** (isopropyl), **4f** (*t*-butyl) and **4h** (phenyl), taking as a constant the configuration of the pybox for an homogeneous lecture of the graph.

4c-Based chiral complexes give homogeneously good results in seven of the eight reactions considered, while the HDA reaction has an unusually poor enantioselectivity.[133]

The reactions catalyzed by **4f** complexes have random selectivity: four give from good to very good results (57−90%) and four very low ee (1−26%). A rationale is not easy since two Mukaiyama-aldol reactions, both catalyzed by Cu(II) cations, give opposite results: (benzyloxy)acetaldehyde **39** reacts with **38** to give **40** in 62% ee,[62] while methyl pyruvate reacts again with **38** to give **43** in 4% ee[70] (but the reaction of **38** with the Danishefsky diene gives **101** in 26% ee).[133]

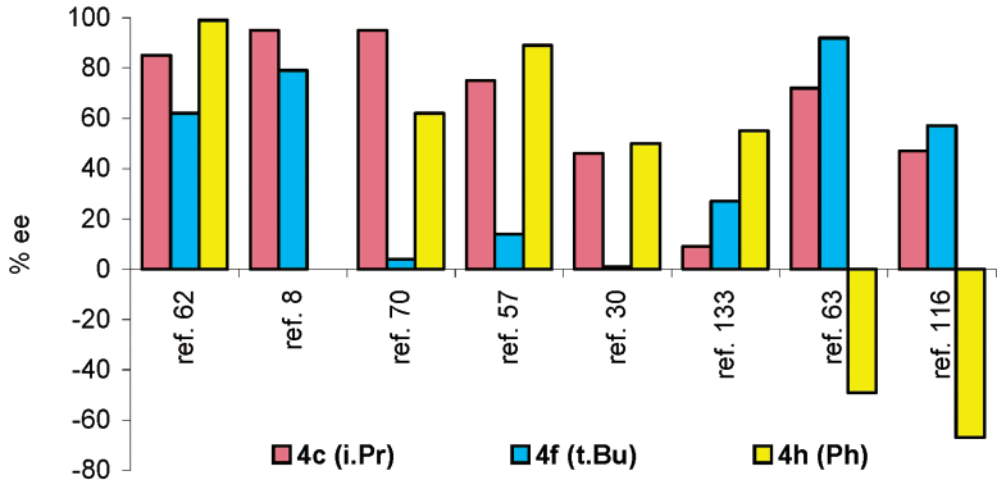


Figure 25. Variation of the ee in eight reactions, as a function of three substituents in pybox-based chiral catalysts.

The most interesting results is given by **4h**-based complexes. Some reactions are excellently catalyzed by phenyl-substituted pybox (the best enantioselectivity in Figure 25 is 99% ee obtained in the reaction between **38** and **39**),[62] but ethyl levulinate, which is reduced by other catalysts, with [**4h**−Rh(III)] complex does not react.[8] The most intriguing point is that in the DA reaction of methacrolein[63] and in the ring opening of cyclohexene oxide with TMSCN,[116] the selectivity is reversed in respect to that obtained with alkyl-substituted pybox ligands. A further case is found in the reaction of **11** and **12** to give the cyclopropane **66**, obtained as the (1*S*,2*S*) enantiomer.[103]

Finally, more attention should be devoted to the important effect of the substituent in the 5′-position of the oxazoline ring, as shown by pybox **14c**, whose 5′-phenyl group makes this ligand the tailor-made one for both Ln-catalyzed Mukaiyama−Michael and DA reactions on **55**.[27,130]

VI. Conclusion

This review reports the history of pybox since their introduction in 1989 in the scientific literature.

Pyboxes are a direct evolution of box ligands and take advantage from the C_2-symmetry to reduce the number of possible configurations of the reacting complex formed from ligand, Lewis acid (a cation), and one of the reagents involved in the reaction.

A comparison of complexed box and pybox shows the following: (a) the binding site of pybox is suitable to host Ln cations that become the Lewis acids of election in pybox-based chiral catalysts, in contrast to the failure of Ln−box complexes;[56] (b) the increased rigidity of the pybox scaffold when the ligand behaves as tridentate, rigidity that is further increased in the reacting complex with reagents behaving as bidentate. Under these assumptions, the tetrahedral coordination becomes impossible, and a coordination number of 4 corresponds to a square-planar structure. Much more easy to find are structures with square-pyramidal, octahedral, and other geometries with coordination number higher than 6.

Despite its rigidity, the versatility of these ligands has been demonstrated in numerous catalytic asymmetric syntheses, and the reason of this success derives from the simple preparation of pybox that makes the projects of new derivatives easily realisable.

Some questions concerning the mechanism of the chirality transfer from the catalyst to the product have been discussed and, hopefully, rationalized in the above chapters. In the enantioselective catalysis with pybox complexes there are still unanswered questions that will probably be solved in the future only through an integrated approach where computations will play a fundamental role.

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