C_2-Symmetric Chiral Bis(Oxazoline) Ligands in Asymmetric Catalysis

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1. Introduction

Asymmetric catalysis with chiral metal complexes has received considerable attention in recent years, and its contribution to the art of organic synthesis has become of leading importance.[1,2] In the field of chiral Lewis acid catalysis, the catalyst, in general, consists of a cation coordinated/bound to an optically active ligand to give a chiral complex with at least one vacant Lewis acid site suitable for coordination and activation of the reagent. To induce a good level of enantioselection, the coordinated reagent should be suitably oriented to favor a selective attack to one specific face. One approach to an easier and less costly route to reduce half the variables required for good face selectivity is the use of a C_2-symmetric chiral ligand.

C_2-symmetric bis(oxazolines) (box's) are one of the most popular classes of chiral ligands satisfying all these requirements, which have received a great deal of attention as ligands in coordination chemistry[3] and in asymmetric catalysis.[4a] These ligands have two oxazoline rings separated by a spacer, and C_2-symmetric bis(oxazolines) having a single carbon atom with two identical substituents—different from hydrogen as the spacer—are the topic of this review. The content will try to cover all aspects of these box ligands, except those immobilized on heterogeneous media since a recent review deals with this concept.[5]

In 1991 two back-to-back communications appeared in the *Journal of the American Chemical Society*, one by Evans et al. dealing with asymmetric cyclopropanation of alkenes[6] and one by Corey et al. about enantioselective Diels−Alder reactions,[7] applying chiral Cu(I)− and Fe(III)−box complexes as catalysts, respectively.

These two communications induced a small revolution in the field of asymmetric catalysis. The box ligands quickly became widely adopted bidentate ligands for their easy and flexible synthesis and for the excellent enantioselectivity induced first in two very useful reactions, and later in a large variety of other reactions. The communications also anticipated the usual protocol of research in box chemistry: (a) synthesis of the ligand following a sequence that, for a long time, would become a standard (reaction of dialkylmalonyl dichloride with an optically active 1,2-amino alcohol, conversion of the bis-hydroxyamide to the corresponding bis-chloroamide, and ring closure under basic conditions); (b) preparation of the chiral catalyst by reaction of the box ligand with an inorganic salt (CuOTf and $FeCl_2/I_2$); (c) testing of the chiral Lewis acid complex as a catalyst for asymmetric induction in the reaction; (d) proposal of a reacting intermediate in which the reagent is coordinated to the chiral Lewis acid−box complex to rationalize the stereochemical outcome of the catalytic process.

This historic approach to asymmetric catalysis with chiral Lewis acid−box complexes will be followed in this review that will cover the literature from 1991 to the spring of 2005

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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 at the same university and one year with Alan Katritzky at UEA, in 1975 he joined the Science Faculty at the University of Pavia as a 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 mechanisms 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 Ph.D. at the same university under the supervision of G. Desimoni and he became a researcher in the Desimoni group in the Department of Organic Chemistry. In 2000 he became an associate professor of Organic Chemistry. His research interests concern the optimization of asymmetric catalysts involving Box and Pybox as chiral ligands and solid-phase organic syntheses.

(ca. 400 papers) whose frequency strongly increased in the last years as shown in Figure 1.

2. Syntheses of Box Ligands

The syntheses of box ligands can be roughly classified into three different categories, the last two being modifications of preformed box:

(A) the construction of the oxazolidine rings starting from a symmetrically disubstituted malonic acid derivative (the bis-substituted spacer) and 2 equiv of optically active β-amino alcohol (the chiral messenger), the method followed by Evans and Corey in their pioneering work;

(B) the substitution of two hydrogen atoms with two identical groups on the spacer of a preformed box (followed when the spacer requires substituents other than methyl), a method that is based on the acidity of the methylene protons. This method consists of the formation of a dianion with 2 equiv of NaH or BuLi (rarely with Et_3N) and in the nucleophilic substitution either with 2 equiv of alkyl halide

Karl Anker Jørgensen was born in 1955 in Aarhus, Denmark, and he received his Ph.D. from Aarhus University in 1984. He was a post-doctoral researcher with Professor Roald Hoffmann, Cornell University. In 1985 Karl Anker Jørgensen became an assistant professor at Aarhus University and became a professor in 1992. His research interests are the development, understanding, and application of asymmetric catalysts with a focus on chiral Lewis-acid-catalyzed reactions and organocatalysis.

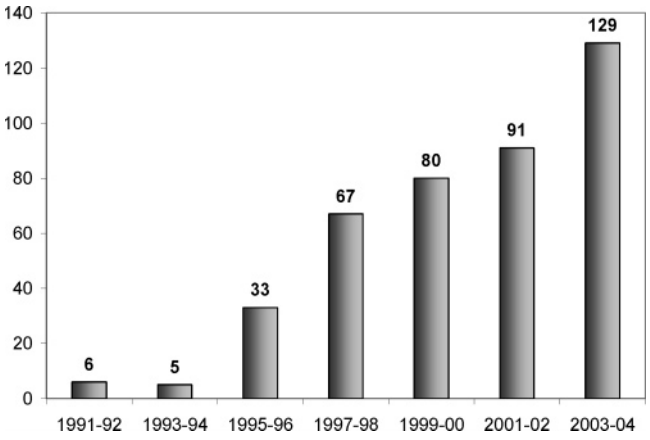


Figure 1. Number of papers dealing with C_2-symmetric chiral box ligands appearing in the literature.

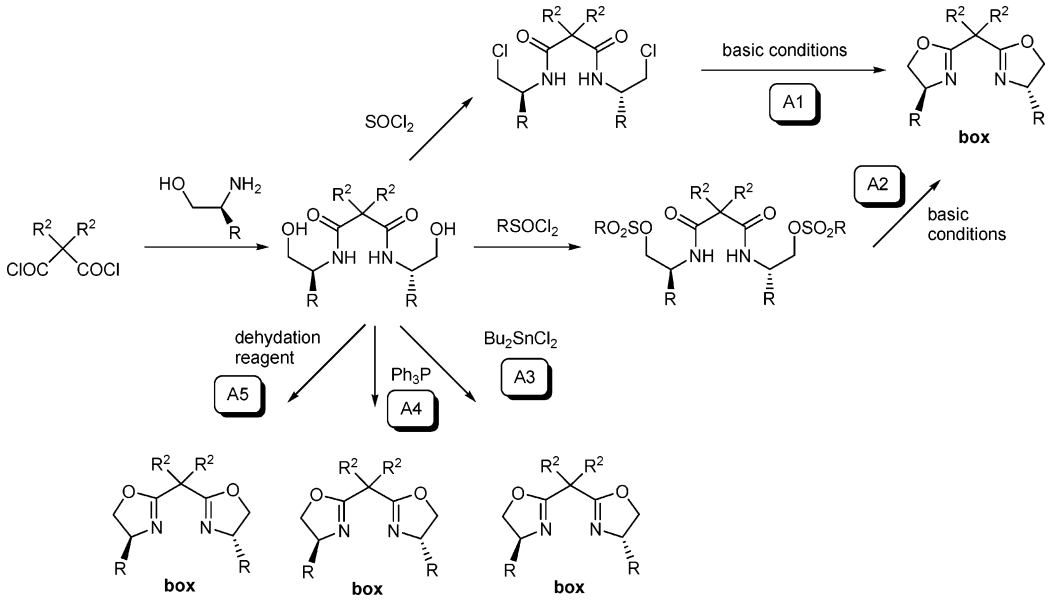
(B1) or with 1 equiv of alkyl dihalide to construct a ring on the spacer (B2);

(C) the manipulations of either the chiral groups on the oxazoline rings (C1) or the groups on the spacer (C2), the former being used to introduce heteroatoms sometimes useful as internal auxiliary ligands to increase the standard bico-ordination of the box ligand and the latter in general being used to introduce functions suitable for grafting the box ligand to a solid surface.

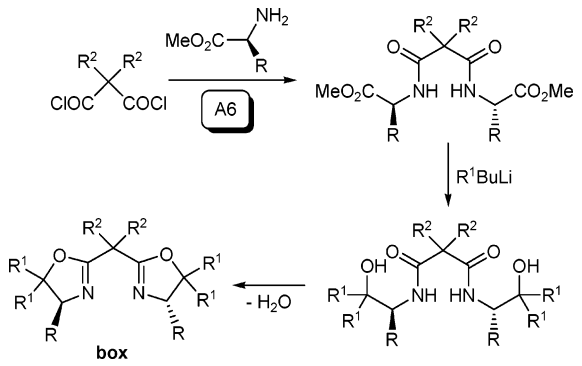
Method A has several variants, some being simple modifications of the original protocol, and some, much more original, may have important drawbacks on the chirality of the ligand. For these reasons method A will be discussed in detail.

Scheme 1 reports the variants of the reaction starting from disubstituted malonyl dichloride that reacts with 2 equiv of β-amino alcohol to give the corresponding bis-amide. This is the key intermediate of the classic approach to box, with several variants. Method A1 was that first used by Corey et al.[7] and consists of the transformation with $SOCl_2$ into the bis-dichloride that is then cyclized to the box under different basic conditions. The hydroxy groups of the bis-amide can also be transformed with mesyl or tosyl chloride into good leaving groups suitable to give box under basic conditions (method A2). Sometimes the bis-amide can be (more or less

Scheme 1



Scheme 2



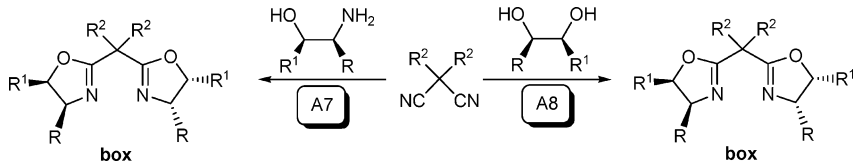
easily) cyclized under other conditions, with Bu_2SnCl_2 in refluxing xylene (the Masamune protocol)[8,9] (method A3) or with $Ph_3P/CCl_4/Et_3N$ (the conditions used by Evans et al.[6,10], method A4). The most direct method consists of the use of dehydration reagents (method A5): methanesulfonic acid in CH_2Cl_2 with continuous removal of H_2O from the refluxing solvent with CaH_2 or molecular sieves (MS) 4 Å, SO_2Cl_2 or $ZnCl_2$ in refluxing $ClCH_2CH_2Cl$, or more sophisticated conditions with diethylaminosulfur trifluoride or the poly(ethylene glycol) (PEG)-linked version of methyl *N*-(triethylammonium-sulfonyl)carbamate (Burgess reagent).

A variant of method A can be used when the targeted 4-substituted box is also 5,5-disubstituted. The malonyl dichloride reacts with a chiral α-aminoester to give the bis-amidoester that with 4 equiv of organolithium reagent and then under dehydrating conditions gives the expected box (method A6, Scheme 2).

The second malonic acid derivative widely used in box synthesis is the symmetrically disubstituted malononitrile (Scheme 3), which may react with 2 equiv of optically active *β*-amino alcohol (method A7) or 1,2-diol (method A8). This approach is useful for 4,5-disubstituted box's, and the important feature of both methods is that the configurations of the diol and amino alcohol are retained in the box.

The configuration of substituents in 4,5-disubstituted box has a relevant importance in both the efficiency and the

Scheme 3



Scheme 4

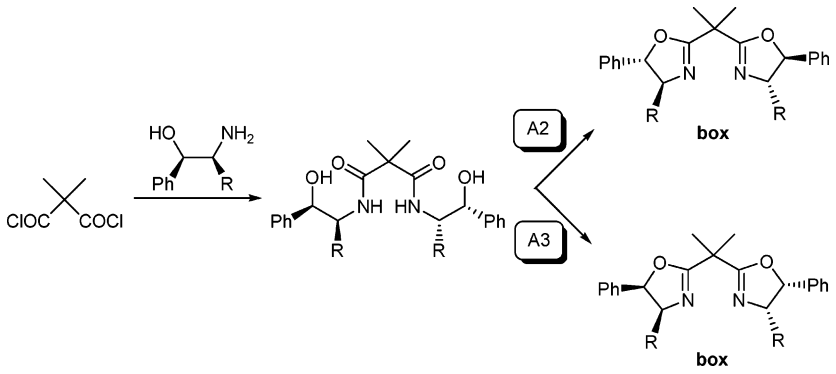
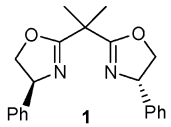
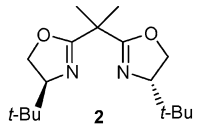
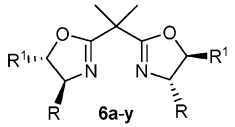
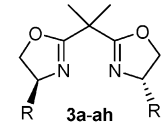


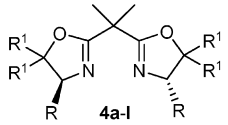
Chart 1











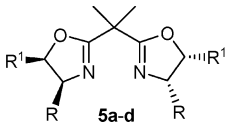
box	R	box	R
3a	Me	**3r**	CMe_2SMe
3b	Et	**3s**	CH(Ph)OH[a]
3c	*i*-Pr	**3t**	CH(Ph)OMe[a]
3d	CH_2Ph	**3u**	$CH(Ph)OCH_2Ph$[a]
3e	CH_2CHMe_2	**3v**	$CH(Ph)OSiMe_2$*t*-Bu[a]
3f	$CH_2C_6H_{11}$	**3w**	CH(Ph)OCOMe[a]
3g	(1-adamantyl)	**3x**	CH(Ph)OCOPh[a]
3h	(1-naphthyl)	**3y**	2-Me-C_6H_4
3i	(2-naphthyl)	**3z**	2-OMe-C_6H_4
3j	CH_2OH	**3aa**	4-OMe-C_6H_4
3k	CH_2OCOPh	**3ab**	4-Cl-C_6H_4
3l	$CH_2OTBDPS$	**3ac**	2-OH-5-*t*-Bu-C_6H_3
3m	CH(Me)OH[a,b]	**3ad**	2-OMe-5-*t*-Bu-C_6H_3
3n	CH(Me)OCOPh[a,b]	**3ae**	2-(OCH_2CH_2Cl)-5-*t*-Bu-C_6H_3
3o	CMe_2OSiMe_3	**3af**	2-OMe-5-Cl-C_6H_3
3p	CH_2SMe	**3ag**	CH_2-1-naphthyl
3q	CH_2CH_2SMe	**3ah**	CH_2-2-naphthyl

[a] Chiral substituent (*S*). [b] Chiral substituent (*R*).

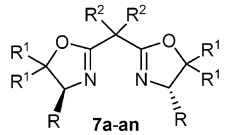
box	R	R^1
4a	*i*-Pr	Me
4b	*i*-Pr	Ph
4c	*i*-Pr	4-tolyl
4d	*i*-Pr	2-naphthyl
4e	*t*-Bu	Me
4f	*t*-Bu	4-tolyl
4g	Ph	Me
4h	Ph	4-tolyl
4i	CH_2Ph	4-tolyl
4j	CH_2Ph	2-naphthyl
4k	CH_2OH	Me
4l	CH_2OCOPh	Me

box	R	R^1	box	R	R^1
6a	Me	Ph	**6m**	CH_2OSiMe_2*t*-Bu	Ph
6b	Ph	Ph	**6n**	CH_2OCOMe	Ph
6c	Ph	CH_2OMe	**6o**	CH_2OCOPh	Ph
6d	Ph	CH_2OCH_2Ph	**6p**	CH_2OCO-$C_8H_{14}O_3$	Ph
6e	Ph	CH_2OCHPh_2	**6q**	CH_2OCODent1[b]	Ph
6f	Ph	CH_2OCPh_3	**6r**	CH_2OCODent2[b]	Ph
6g	Ph	$CH_2OCH_2CH_2OMe$	**6s**	$CH_2OCOCH(Me)NHAc$[c]	Ph
6h	2,4,6-Me_3-C_6H_2	CH_2OCHPh_2	**6t**	$CH_2OCOCH(Me)NHBoc$[c]	Ph
6i	1-naphthyl	CH_2OCHPh_2	**6u**	$CH_2OCOCH(Me)NHTs$[c]	Ph
6j	CH_2OCOAr[a]	Me	**6v**	CH_2OCOCH(*i*-Pr)NHCbz[c]	Ph
6k	CH_2OH	Ph	**6w**	CH_2SMe	Ph
6l	CH_2OMe	Ph	**6x**	CH_2SPh	Ph
			6y	CH_2OH	*p*-SMe-C_6H_4

[a] Ar is 4-benzo-18-crown-6. [b] Dent1 and Dent2 are dentritic substituents whose structure can be taken from the ref. [c] Chiral substituent (*S*).



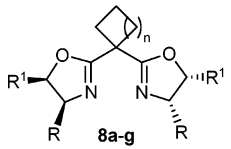
box	R	R^1
5a	Me	Ph
5b	Ph	Ph
5c	Ph	Me
5d	Ph	$CH_2OCHPh2$



box	R	R^1	R^2	box	R	R^1	R^2	box	R	R^1	R^2
7a	*i*-Pr	H	Et	**7o**	*i*-Pr	Me	Et	**7ab**	Ph	H	$CH_2C_6H_4CH{=}CH_2$
7b	*i*-Bu	H	Et	**7p**	*t*-Bu	H	*i*-Pr	**7ac**	*t*-Bu	H	$CH_2C_6H_4CH{=}CH_2$
7c	*t*-Bu	H	Et	**7q**	*t*-Bu	H	*i*-Bu	**7ad**	*t*-Bu	H	$CH_2C_6H_4OH$
7d	CH_2Ph	H	Et	**7r**	$CMePh_2$	H	*i*-Bu	**7ae**	*t*-Bu	H	$CH_2C_6H_4OCH_2CH{=}CH_2$
7e	Ph	H	Et	**7s**	*i*-Pr	H	CH_2Ph	**7af**	*t*-Bu	H	$CH_2C_6H_4OCH_2Ar$[a]
7f	C_6H_4-$O(CH_2)_2Br$	H	Et	**7t**	*t*-Bu	H	CH_2Ph	**7ag**	*i*-Pr	H	$(CH_2)_3C_8F_{17}$
7g	C_6H_4-$O(CH_2)_3Br$	H	Et	**7u**	Ph	H	CH_2Ph	**7ah**	*i*-Pr	H	$(CH_2)_3C_{10}F_{21}$
7h	C_6H_4-$O(CH_2)_4Br$	H	Et	**7v**	Ph	H	$CH_2CH{=}CH_2$	**7ai**	Ph	H	$(CH_2)_3C_8F_{17}$
7i	C_6H_4-$O(CH_2)_5Br$	H	Et	**7w**	*t*-Bu	H	$CH_2CH{=}CH_2$	**7aj**	Ph	H	$(CH_2)_3C_{10}F_{21}$
7j	C_6H_4-OCH_2Ph	H	Et	**7x**	Bn	H	$CH_2CH{=}CH_2$	**7ak**	CH_2OH	H	$(CH_2)_3C_8F_{17}$
7k	$CH_2C_6H_4$-OCH_2Ph	H	Et	**7y**	*t*-Bu	H	$CH_2C(Me){=}CH_2$	**7al**	$CH_2OTBDMS$	H	$(CH_2)_3C_8F_{17}$
7l	CMe_2Ph	H	Et	**7z**	*t*-Bu	H	$CH_2C(CH_2)_2Me$	**7am**	*t*-Bu	H	$CH_2C_6H_4O(CH_2)_3C_8F_{17}$
7m	$CMePh_2$	H	Et	**7aa**	*i*-Pr	H	$C_{11}H_{23}$	**7an**	Ph	H	$(CH_2)_6OTBMS$
7n	CPh_3	H	Et								

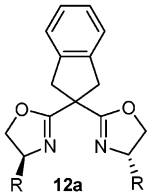
[a] Ar = 3,5-$(C_8F_{17})_2$-C_6H_3

Chart 1 (Continued)



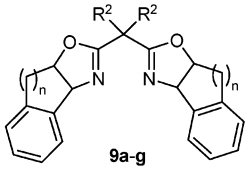
8a-g

box	n	R	R^1
8a	0	Ph	H
8b	0	*t*-Bu	H
8c	1	*t*-Bu	H
8d	2	*t*-Bu	H
8e	3	*t*-Bu	H
8f	0	Ph	Me
8g	0	Ph	Ph



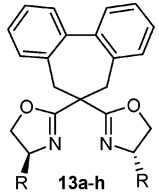
12a

box	R
12a	Ph



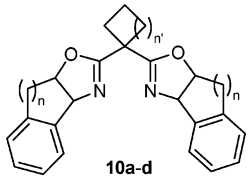
9a-g

box	R^2	n
9a	Me	1
9b	Me	2
9c	CH_2Ph	1
9d	CH_2OH	1
9e	$CH_2C_6H_4OH$	1
9f	$CH_2C_6H_4OCOt$-Bu	1
9g	$CH_2C_6H_4CH{=}CH_2$	1



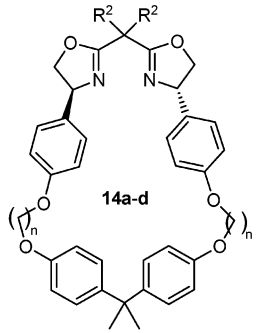
13a-h

box	R
13a	Ph
13b	*i*-Pr
13c	CH_2CHMe_2
13d	*t*-Bu
13e	CH_2Ph
13f	CO_2Me
13g	CMe_2OH
13h	CPh_2OH



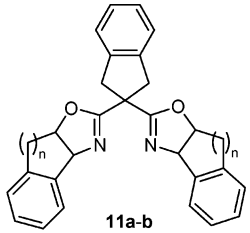
10a-d

box	n	n'
10a	1	0
10b	1	1
10c	1	2
10d	1	3



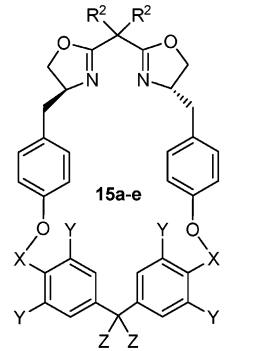
14a-d

box	R^2	n
14a	Et	2
14b	Et	3
14c	Et	4
14d	Et	5



11a-b

box	n
11a	1
11b	2



15a-e

box	R^2	X	Y	Z
15a	Et	CH_2	H	H
15b	Et	$(CH_2)_2O$	H	Me
15c	Et	$(CH_2)_3O$	H	Me
15d	Et	$(CH_2)_2O$	Me	Me
15e	Et	$(CH_2)_3O$	Me	Me

Table 1. Syntheses of Box Ligands

n	box	conf.[a]	method	yield (%)	ref	*n*	box	conf.[a]	method	yield (%)	ref	*n*	box	conf.[a]	method	yield (%)	ref
1	**1**	*S*	A1	76	7	51	**6c**	*R*,*S*	A1	87	30	101	**7af**	*S*	B1	74	42
2	**2**	*S*	A4	60	6, 10	52	**6d**	*R*,*S*	A1	77	30	102	**7ag**	*S*	B1	37	41
3	**2**	*S*	A2	72	11	53	**6e**	*R*,*S*	A1	88	30	103	**7ah**	*S*	B1	62	41
4	**2**	*S*	C2	43	14	54	**6f**	*R*,*S*	A1	95	30	104	**7ai**	*S*	B1	49	41
5	**3a**	*S*	A7	33	12	55	**6g**	*R*,*S*	A1	72	30	105	**7aj**	*S*	B1	46	41
6	**3c**	*S*	*b*	*b*	7	56	**6h**	*R*,*S*	A1	95	30	106	**7ak**	*S*	B1, C1	34	41
7	**3d**	*R*	A1	43	13	57	**6i**	*R*,*S*	A1	93	30	107	**7al**	*R*	B1	24	41
8	**3e**	*S*	A1	46	15	58	**6j**	*R*,*R*	C1	11	31	108	**7am**	*S*	C2	56	43
9	**3g**	*R*	A1	70	16	59	**6k**	*S*,*S*	A7	51	22, 32	109	**7an**	*S*	B1	34	50
10	**3h**	*S*	A2	60	17	60	**6m**	*S*,*S*	*b*	*b*	33	110	**8a**	*S*	B2	48	29
11	**3i**	*S*	A1	39	18	61	**6n**	*S*,*S*	C1	98	32	111	**8b**	*S*	B2	25	15, 14
12	**3i**	*R*	A1	39	18	62	**6o**	*S*,*S*	C1	100	34	112	**8c**	*S*	B2	46	14
13	**3j**	*S*	C1	97	19	63	**6p**	*S*,*S*	C1	63	34	113	**8d**	*S*	B2	72	14
14	**3k**	*R*	A1	65	19	64	**6q**	*S*,*S*	C1	44	34	114	**8e**	*S*	B2	56	14
15	**3l**	*S*	A2	64	20	65	**6r**	*S*,*S*	C1	24	34	115	**8f**	*S*,*R*	B2	50	29
16	**3m**	*R*	C1	88	19	66	**6s**	*S*,*S*	C1	78	32	116	**8g**	*R*,*S*	B2	23	44
17	**3n**	*R*	A1	78	19	67	**6t**	*S*,*S*	C1	96	32	117	**9a**	*S*,*R*	A8	30	45
18	**3o**	*R*	A4	28	21	68	**6u**	*S*,*S*	*b*	*b*	35,32	118	**9a**	*S*,*R*	B1	56	29, 46, 47
19	**3p**	*S*	A7	38	22	69	**6v**	*S*,*S*	C1	86	32	119	**9b**	*S*,*R*	B1	56−72	46
20	**3p**	*S*	A2	41	20	70	**6w**	*R*,*S*	C1	89	22	120	**9c**	*S*,*R*	B1	82	48
21	**3q**	*S*	A7	74	22	71	**6x**	*R*,*S*	C1	47	22	121	**9d**	*R*,*S*	B1	80	49
22	**3q**	*R*	A2	39	20	72	**7a**	*S*	A2	83	36,25,37	122	**9e**	*S*,*R*	C2	100	48
23	**3r**	*S*	A2	66	20	73	**7c**	*S*	A2	74	36,25,37	123	**9f**	*S*,*R*	B1	77	48
24	**3s**	*S*	C1	76	23	74	**7d**	*S*	A2	76	36,25,37	124	**9g**	*S*,*R*	B1	*b*	40
25	**3t**	*S*	C1	83	23	75	**7e**	*R*	A1	*b*	38	125	**10a**	*S*,*R*	B2	50−70	51,29
26	**3u**	*S*	C1	72	23	76	**7f**	*R*	A1	*b*	39a	126	**10b**	*S*,*R*	B2	50−70	51,29
27	**3v**	*S*	C1	95	23	77	**7g**	*R*	A1	*b*	39a	127	**10c**	*S*,*R*	B2	50−70	51,29
28	**3w**	*S*	A1	82	23	78	**7h**	*R*	A1	*b*	39a	128	**10d**	*S*,*R*	B2	50−70	51
29	**3x**	*S*	A1	82	23	79	**7i**	*R*	A1	*b*	39a	129	**11a**	*S*,*R*	B2	56−72	46
30	**3z**	*S*	A2	66	24	80	**7j**	*R*	A1	*b*	39a,b	130	**11b**	*S*,*R*	B2	56−72	46
31	**3ac**	*S*	A2,C1	61	24	81	**7k**	*S*	A1	*b*	39a,b	131	**12a**	*S*	B2	56−72	46
32	**3ad**	*S*	A2	66	24	82	**7l**	*S*	A2	62	36,25	132	**13a**	*R*	A2	59	52
33	**3ae**	*S*	A2	64	24	83	**7m**	*S*	A2	83	36,25	133	**13a**	*S*	A2	55	52
34	**3af**	*R*	A2	65	24	84	**7n**	*S*	A1	54	36,25	134	**13b**	*S*	A2	50	52
35	**4a**	*S*	A5, A6	50	25	85	**7o**	*S*	A5	61	37	135	**13c**	*S*	A2	55	52
36	**4c**	*S*	A5	*b*	26	86	**7p**	*S*	B2	35	14	136	**13d**	*S*	A2	60	53
37	**4d**	*S*	A5	*b*	26	87	**7q**	*S*	A2	59	36,25	137	**13e**	*S*	A2	50	52
38	**4f**	*S*	A5	*b*	26	88	**7r**	*S*	A2	35	25	138	**13f**	*S*	A5	63	53
39	**4g**	*S*	A5	76	27	89	**7t**	*S*	B1	76	40	139	**13g**	*S*	C1	75	53
40	**4h**	*S*	A5	*b*	26	90	**7u**	*S*	B1	88	40	140	**13h**	*S*	C1	71	53
41	**4i**	*S*	A5	*b*	26	91	**7v**	*S*	B1	85	40	141	**14a**	*R*	A1, C1	29	39
42	**4j**	*S*	A5	*b*	26	92	**7w**	*S*	B1	79	40	142	**14b**	*R*	A1, C1	27	39
43	**4k**	*R*	C1	96	19	93	**7x**	*S*	B1	87	40	143	**14c**	*R*	A1, C1	49	39
44	**4l**	*R*	A5	69	19	94	**7y**	*S*	B1	*b*	14	144	**14d**	*R*	A1, C1	25	39
45	**5a**	*R*,*S*	A3	57	9	95	**7z**	*S*	B1	80	14	145	**15a**	*S*	A1	*b*	54
46	**5b**	*R*,*S*	B1	*b*	28	96	**7aa**	*S*	B1	40	41	146	**15b**	*S*	A1	*b*	54
47	**5b**	*R*,*S*	A3	74	9	97	**7ab**	*S*	B1	*b*	40	147	**15c**	*S*	A1	*b*	54
48	**5c**	*S*,*R*	B1	62	29	98	**7ac**	*S*	B1	*b*	40	148	**15d**	*S*	A1	*b*	54
49	**6a**	*R*,*R*	A2	63	9	99	**7ad**	*S*	B1	*b*	42	149	**15e**	*S*	A1	*b*	54
50	**6b**	*R*,*R*	A2	84	9	100	**7ae**	*S*	C2	94	42						

[a] Configuration refers to position 4 or to positions 4,5 of the oxazoline ring. [b] Data not reported as well as other physicochemical data of the box.

enantioselectivity induced in the catalyzed process. From this point of view methods A1 and A2 are complementary to methods A3, A7, and A8. The bis-amides derived from dimethyl malondichloride and (1*S*,2*R*)-norephedrine (R = Me) or from (1*S*,2*R*)-2-amino-1,2-diphenylethanol (R = Ph) (Scheme 4) may be stereodivergently cyclized, either under the Masamune conditions (method A3) with total retention of configuration giving cis-4,5-disubstituted box's or through conversion into the mesylates and cyclization under basic conditions (method A2) with complete inversion of configurations to give trans-4,5-disubstituted box's.[9]

Through methods A−C, more than 140 box ligands with the characteristics and the limits described in the Introduction have been synthesized. These structures are listed in Chart 1, and their respective methods of preparation and the resulting configurations are reported in Table 1.

3. Structures of Box–Metal Complexes

When a chiral box ligand is mixed with an inorganic salt in an organic solvent, a chiral box−metal complex is usually formed, which can spontaneously precipitate or can be isolated by dilution with a less polar solvent. These chiral complexes are the precursors of the reacting intermediate involved in the catalytic cycle, and therefore any information concerning their structure is important to try to understand the configuration of how the molecules involved in the reaction are arranged at the metal center, since this is the source of the chiral discrimination producing the stereoselectivity in the reaction.

The preventive isolation of these precursors is not determinant for their success as enantioselective catalysts; they can be efficiently prepared "in situ", and for this reason, we will not report the protocol of their preparation. Sometimes

Table 2. Reported X-ray Crystal Structures of Box Complexes

entry	no.	metal	box	anion	further ligands	coordination	structure	ref
1		Ag(I)	(*S*)-**1**[a]	OTf	0.5H_2O	single strand	zigzag conformation	55
2		Ag(I)	(*S*)-**3d**[a]	OTf		single strand	helical	55
3		Cu(I)	(*S*)-**2**[a]	OTf		single strand	helical	10
4		Cu(II)	(*S*)-**1**	Cl		4	distorted square-planar	59
5	**16**	Cu(II)	(*S*)-**1**	Br		4	distorted squareplanar	59
6	**17**	Cu(II)	(*S*)-**1**	SbF_6	$2H_2O$	4	distorted square-planar	56−58
7	**18**	Cu(II)	(*S*)-**2**	SbF_6	$2H_2O$	4	distorted square-planar	11, 56−58, 60, 61
8	**19**	Cu(II)	(*S*)-**1**	SbF_6	BM[b]	4	distorted square-planar	63
9	**20**	Cu(II)	(*S*)-**2**	SbF_6	BM[b]	4	distorted square-planar	62, 63
10		Cu(II)	(*S*)-**2**	SbF_6	EM[c]	4	distorted square-planar	63
11		Cu(II)	(*S*)-**2**	Cl		4	distorted square-planar	59, 60
12	**21**	Cu(II)	(*S*)-**2**	Br		4	distorted square-planar	59
13		Cu(II)	(*S*)-**2**	OTf	$2H_2O$	5	distorted square-pyramid	56, 59, 60
14	**22**	Cu(II)	(*S*)-**2**	OTf	DOBET[d]	5	distorted square-pyramid	64
15		Cu(II)	(*S*)-**3c**	SbF_6	$2H_2O$	4	distorted square-planar	56−58
16		Cu(II)	(*R*,*S*)-**9a**	OAc		4	distorted square-planar	65
17		Cu(II)	(*S*,*R*)-**9a**	Cl		4	distorted square-planar	59
18		Cu(II)	(*S*,*R*)-**9a**	Br		4	distorted square-planar	59
19		Cu(II)	(*S*)-**3q**	Cl		5	trigonal bipyramid	20
20		Cu(II)	(*S*)-**3q**	OTf		6	octahedral	20
21		Cu(II)	(*S*)-**3r**	OTf		5	trigonal bipyramid	20
22		Zn(II)	(*S*)-**1**	Cl		4	tetrahedral	59
23		Zn(II)	(*S*)-**2**	Cl		4	tetrahedral	59
24		Ni(II)	(*S*)-**2**	Cl		4	tetrahedral	66
25		Ni(II)	(*S*)-**2**	OTf	$2H_2O$	5	square-pyramid	66
26		Ni(II)	(*S*)-**2**	OTf		4	tetrahedral dimer	66
27		Fe(II)	(*S*)-**2**	Cl		4	distorted tetrahedral	67
28		Fe(II)	(*S*)-**2**	$TMSCH_2$		4	distorted tetrahedral	67
29		W(0)	(*S*)-**2**		4CO	6	octahedral	68
30		W(0)	(*S*)-**3c**		4CO	6	octahedral	69
31		Rh(II)	(*S*)-**3c**	Cl	C_5Me_5	4	distorted tetrahedral	70
32		Ru(II)	(*S*)-**1**	Cl	terpyridine	6	octahedral	71
33		Ru(II)	(*R*)-**1**	Cl	H_2O	4	distorted tetrahedral	72
34		Ru(II)	(*R*)-**1**	Cl	$MeNH_2$	4	distorted tetrahedral	72
35		Ru(II)	(*R*)-**1**		$Ph(CH_2)_3O$	4	distorted tetrahedral	73, 74
36		Ru(II)	(*S*)-**3c**	SbF_6	mesityl, H_2O	4	distorted tetrahedral	75
37		Pd(II)	(*R*)-**3d**	PF_6	allyl	4	pseudo-square-planar	13, 33
38	**23**	Pd(II)	(*R*)-**3d**	PF_6	1,3-diPhall[e]	4	pseudo-square-planar	13, 33
39		Pd(II)	(*S*)-**3s**	BF_4	1,3-diPhall[e]	4	pseudo-square-planar	76
40		Pd(II)	(*S*)-**3t**	BF_4	1,3-diPhall[e]	4	pseudo-square-planar	76
41	**24**	Zn(II)	(*S*)-**1** + (*R*)-**1**[f]	ClO_4		4	tetrahedral	77

[a] Box as a monodentate ligand. [b] BM is benzylidene dimethylmalonate. [c] EM is ethylylidene dimethylmalonate. [d] DOBET is 2,4-dioxobutanoic acid ethylester. [e] 1,3-diPhall is 1,3-diphenylallyl. [f] Racemic complex with two box enantiomers.

their structure can be investigated by spectroscopic methods, and depending on the metal involved in the complex, NMR spectroscopy might be the best tool for these purposes. Furthermore, their structure can be proposed on the basis of various types of calculations. In the following discussion, these data will be mentioned in the specific sections only when their contribution will significantly improve the understanding of the process determining the stereoselectivity of the reactions discussed.

When the solid box−metal complex is a crystalline compound suitable for X-ray analysis, key information can be obtained about the coordination number, the nature of the ligand(s) other than box at the cation, which allows one to propose reasonable models of the reacting intermediate participating in the catalytic process.

Table 2 reports the X-ray crystal structures involving the box ligands reported in this review including their most significant structural properties. For some of them, which may be useful models of the reaction intermediates of important enantioselective catalytic processes, we report a homogeneous representation of the crystal structure based on the atomic coordinates. This will give an immediate picture of the coordination at the metal center and the positions of the chiral ligand in the complex, the anions, and the auxiliary ligands that can be replaced by at least one of the reagents to give rise to the reaction intermediate. For this reason, we will always represent the cation and the box in their traditional colors (oxygen, red; nitrogen, blue; metal, violet), whereas all atoms of anions and auxiliary ligands (except H_2O) will be yellow. If an organic molecule involved in a catalytic process is present in the crystal structure, then its carbon atoms will be represented in green, and the other atoms, as far as possible, in their traditional colors.

Box with one carbon atom as the spacer generally behaves as a bidentate ligand through its nitrogen atoms, with few exceptions.

Complexes with Box as a Monodentate Ligand. The crystal structures of {Ag[(*S*)-**1**]OTf(0.5H_2O)} (Table 2, entry 1) and {Ag[(*S*)-**3d**]OTf} (Table 2, entry 2) show both box's behaving as monodentate ligands.[55] The silver cation coordinates two nitrogen atoms, from two different box's, giving rise to single-stranded polymers, with an infinite single-stranded helical coordination, 2-fold symmetry, and left-handed helicity, with an infinitive single strand with a zigzag conformation. A somewhat similar complex was obtained from (*S*)-**2** and CuOTf·0.5C_6H_6 (Table 2, entry 3).[10] The X-ray structure shows a single-stranded helical polymeric structure with 3-fold symmetry, and box occupies a

bridging position between two nearly linear bicoordinated Cu(I) ions.

In general, when box's are involved in the formation of an optically active catalyst in which both nitrogen atoms coordinate to the same cation, this leads to rigid supramolecular devices that efficiently might discriminate the diastereofaces of the coordinated reagent. This discrimination is much more difficult to realize when box behaves as a monodentate ligand, and in comparison to box acting as a bidentate ligand to one metal center, these complexes have not been very successful in enantioselective catalysis. Nevertheless, the above-mentioned [box/Ag(I)] complexes were found to be efficient enantioselective catalysts for the intramolecular insertion of α-diazo compounds into N−H bonds of amines, and the Cu(I) complex is an excellent enantioselective catalyst for the cyclopropanation of alkenes (vide infra).

Complexes with a Single Box as a Bidentate Ligand. This type of complex is by far the most popular in asymmetric catalysis, and Cu(II) is the leading cation involved in their formation. For box's **1** and **2**, the ordinarily found coordination number is four, derived from a distorted square-planar coordination. However, this number may be expanded to five (and the structure becomes a distorted square pyramid) when the counterion is OTf, pointing out the importance not only of the cation but also of the anion in the formation of the reacting intermediate, which is the chiral messenger in the reaction.

The Cu(II) complexes with (*S*)-**1** (Table 2, entries 4−6) are known with SbF_6, Cl, and Br, but the ligands involved in the distorted square planar are two H_2O, Cl, and Br, respectively, since SbF_6 does not enter in the coordination sphere.[56−59] An important point is the value and the sense of the distortion from the ideal box/cation plane. With Cl and Br as the anions (Table 2, entry 5, **16**, Figure 2),[59] the

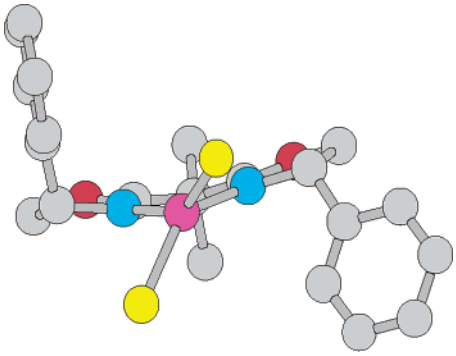


Figure 2. Molecular structure of [(*S*)-**1**·$CuBr_2$] (**16**) (ref 59).

distortions from square planarity are large and nearly equal, and the anions occupy the quadrants free from the substituents. The hydrated complex is more planar (Table 2, entry 6, **17**, Figure 3),[56−58] and the distortion of the H_2O molecules reverses (the dihedral angles O−Cu−N−C (marking how far H_2O is from the oxazoline plane) are −11.3° and −7.2°), with the ligands oriented toward the oxazoline phenyl substituents.

The Cu(II) complexes with (*S*)-**2** (Table 2, entries 7−14) have been studied in detail, and the counterion is of leading importance for the coordination number. The SbF_6 complex (Table 2, entry 7, **18**, Figure 4) has a distorted square-planar structure with two H_2O molecules in the coordination sphere as **17**, but the distortion of the water molecules is large, with the ligands oriented far away from the *tert*-butyl

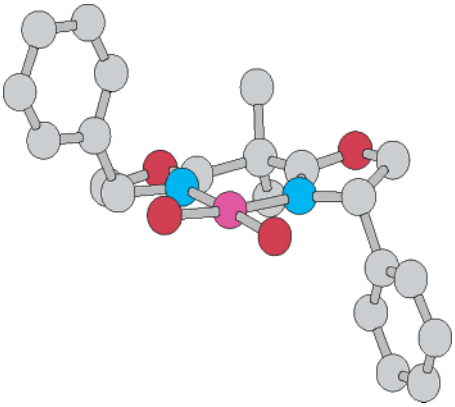


Figure 3. Molecular structure of [(*S*)-**1**·$Cu(SbF_6)_2$·$2H_2O$] (**17**) (refs 56−58).

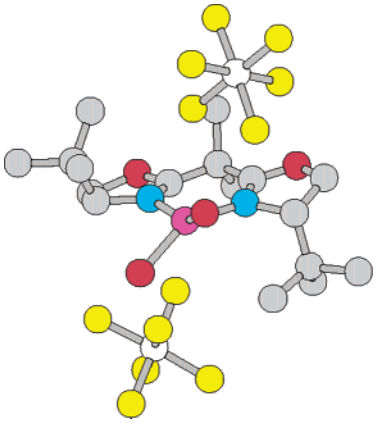


Figure 4. Molecular structure of [(*S*)-**2**·$Cu(SbF_6)_2$·$2H_2O$] (**18**) (refs 12, 56−58, 60, and 61).

groups (the dihedral angles O−Cu−N−C are +30.2° and +35.9°).[12,56−58,60,61]

The importance of structures **17** and **18** can be understood if these complexes, after the coordination of the reagent, become the reacting intermediates of the many different reactions catalyzed by these complexes. If the reagent involved in ligation substitutes the H_2O molecules occupying their sites of coordination, then the opposite distortions of the complexes may have a leading role in the development of the sense of enantioselection. Two of these reacting intermediates, the Cu(II) complexes with (*S*)-**1** and (*S*)-**2**, with benzylidene dimethylmalonate, were isolated, and their crystal structures were determined.[62,63] The dicarbonyl is coordinated at the positions formerly occupied by the H_2O molecules, in the complex of (*S*)-**1** (Table 2, entry 8, **19**, Figure 5). The distortion is small (1.4° and 2.3°), whereas the complex of (*S*)-**2** (Table 2, entry 9, **20**, Figure 6) has the same strong distortion of the corresponding dihydrate, and the sense of the deviation from planarity is the same. Ethylidene dimethylmalonate may substitute the benzylidene analogue in the [(*S*)-**2**/Cu(II)] complex (entry 10),[63] and the resulting crystal structure is nearly superimposable to that of **20**.

The complexes of (*S*)-**2**, with Cl and Br as chelated anions (Table 2, entries 11 and 12 for Br, Figure 7),[59] have distortions from square planarity that are large and nearly equal. The anions occupy the quadrants free from the substituents with the same sense of distortion shown by (*S*)-**1** with the analogous ligands.

When the copper anion is OTf, the complex has a distorted square-pyramidal structure with two H_2O molecules in the

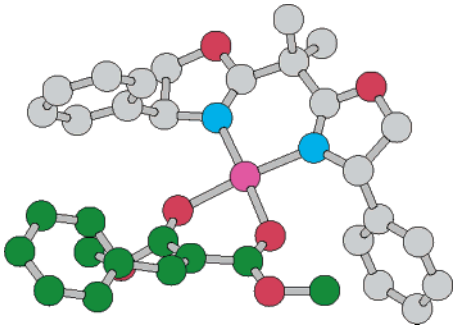


Figure 5. Molecular structure of [(*S*)-**1**·$Cu(SbF_6)_2$·PhCH=$C(CO_2Me)_2$] (**19**) (refs 62 and 63).

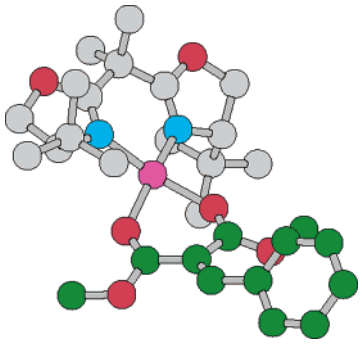


Figure 6. Molecular structure of [(*S*)-**2**·$Cu(SbF_6)_2$·PhCH=$C(CO_2Me)_2$] (**20**) (refs 62 and 63).

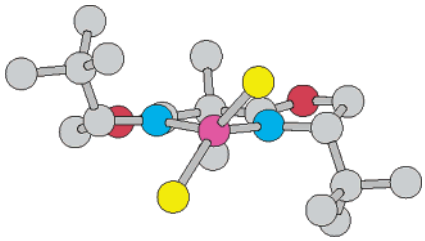


Figure 7. Molecular structure of [(*S*)-**2**·$CuBr_2$] (**21**) (ref 59).

pseudoequatorial positions and one OTf axial (entry 13).[56,59,60] An interesting crystal structure exists with the H_2O molecules substituted by two carbonyl groups. It was obtained from a reaction catalyzed by [(*S*)-**2**·$Cu(OTf)_2$] involving (*E*)-2-oxo-4-ethoxybut-3-enoic acid ethyl ester as a reagent, but the dioxo groups of its hydrolyzed product (2,4-dioxobutanoic acid ethyl ester) were found to be coordinated to copper, together with a OTf anion (Table 2, entry 14, **22**, Figure 8).[64]

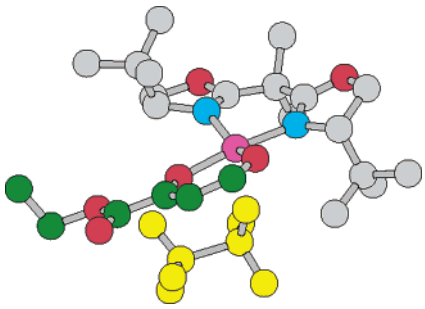


Figure 8. Molecular structure of [(*S*)-**2**·$Cu(OTf)_2$·$HCOCH_2$-$COCO_2Et$] (**22**) (ref 64).

The reason for the inversion of the distortion from square planarity, when moving from (*S*)-**1** to [(*S*)-**2**·$Cu(SbF_6)_2$·$2H_2O$] (**18**), is still an open question, but the strong effect observed in the latter structure can be presumed to be largely due to steric interactions, if the analogous complex [(*S*)-**3c**·$Cu(SbF_6)_2$·$2H_2O$] (entry 15) shows smaller dihedral angles (O−Cu−N−C +6.6° and +7.4° (for isopropyl-box) vs +30.2° and +35.9° (for *tert*-butyl-box)).[56−58]

Several other [box/Cu(II)] crystal structures have been solved (Table 2, entries 16−21). Three of them (entries 16−18) concern indane−box **9a** coordinated by Cu(II)−OAc,[65] −Cl, and −Br.[59] Even if the former is derived from **9a** having (*R*,*S*)-configuration, whereas the latter complexes are derived from the opposite enantiomer (*S*,*R*), the structures are always distorted square-planar, and the sense of the distortion is always the same with anions far away from the indane groups. The distortion is smaller with acetates than with halogens. Three Cu(II) complexes (Table 2, entries 19−21) have box ligands with substituents somewhat involved in the coordination.[20] (*S*)-**3q** has 2-methylthioethyl substituents: If the anions are Cl, then both participate in pentacoordination with a sulfur atom to give a trigonal bipyramid; if the anions are OTf, then both are in the axial positions, and two sulfur atoms in the equatorial plane of the box give an octahedral coordination. (*S*)-**3r** has 1,1-dimethyl-1-methylthiomethyl substituents (Table 2, entry 21): One OTf, one sulfur atom, and one nitrogen atom equatorial, the second nitrogen atom and the second sulfur atom in the axial positions, form a trigonal bipyramidal geometry. Despite the interesting structures generated, the coordination of the substituents seems to have a negative effect on their catalytic efficiency, given the poor enantioselectivity developed in several reactions tested.

Two crystal structures with compositions [(*S*)-**1**·$ZnCl_2$] and [(*S*)-**2**·$ZnCl_2$] (Table 2, entries 22 and 23) have been shown to have a tetrahedral coordination,[59] and a comparison with the corresponding Cu(II) complexes will be adequately considered, discussing their respective catalytic efficiency.

Three Ni(II) and two Fe(II) crystal structures, with (*S*)-**2** as a ligand have been solved (Table 2, entries 24−28). Both [(*S*)-**2**·$NiCl_2$][66] and [(*S*)-**2**·$FeCl_2$][67] have slightly distorted tetrahedral structures as well as [(*S*)-**2**·$Fe(CH_2SiMe_3)_2$].[67] Under different conditions, $Ni(OTf)_2$ gave either the dimeric anhydrous complex [(*S*)-**2**·$Ni(OTf)_2]_2$ with two OTf's bridging two nickel atoms or the hydrated complex [(*S*)-**2**·$Ni(OTf)_2$·$(H_2O)_2$] with one OTf coordinated in a square-pyramidal geometry.[66]

Two different tungsten complexes (Table 2, entries 29 and 30), with (*S*)-**2** and (*S*)-**3c**, have an octahedral structure because of four additional carbonyl ligands each.[68,69] The rhodium complex of (*S*)-**3c** (entry 31) has a tetrahedral structure, because of its [η-C_5Me_5·RhCl·(*S*)-**3c**] structure.[70] The ruthenium complex has attracted much attention, and five structures (Table 2, entries 32−36) are reported. Only the complex of (*S*)-**1** with the tridentate ligand 2,2′:6′,2″-terpyridine (Table 2, entry 32) has an octahedral structure;[71] four other structures, with either (*R*)-**1** or (*S*)-**3c** ligands (Table 2, entries 33−36) and a variety of anions or additional ligands, all have a tetrahedral structure.[71−75]

To close this section, the palladium complexes have to be mentioned as the use of these catalysts in enantioselective allylic substitutions led to the isolation of four complexes with (*R*)-**3d**, (*S*)-**3s**, and (*S*)-**3t** (Table 2, entries 37−40), all with a pseudo-square-planar structure, and all with a bidentate allyl derivative as a ligand.[13,33,76] Because all these complexes may be in principle considered as reaction intermediates of the enantioselective allylic substitution, the crystal structure

of [(*R*)-**3d**·Pd(1,3-diphenylallyl)]$^+$ (**23**, Table 2, entry 38) is reported in Figure 9.

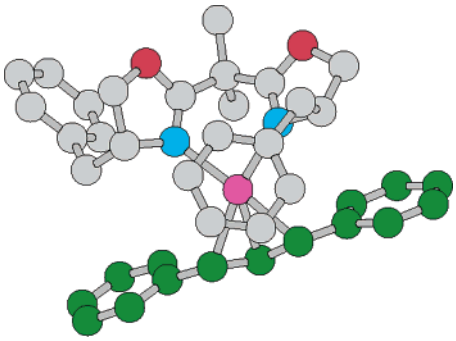


Figure 9. Molecular structure of [(*R*)-**3d**·Pd(1,3-diphenylallyl)]$^+$ (**23**) (refs 13 and 33).

Complexes with Two Box's Coordinated to a Single Cation. When $Zn(ClO_4)_2$ was mixed with equimolecular amounts of (*R*)-**1** and (*S*)-**1**, a complex separated out (entry 41), and the crystal structure shows the tetrahedral arrangement of two box enantiomers at the Zn(II) cation (**24**, Figure 10).[77] The remarkable nonlinear chiral amplification shown

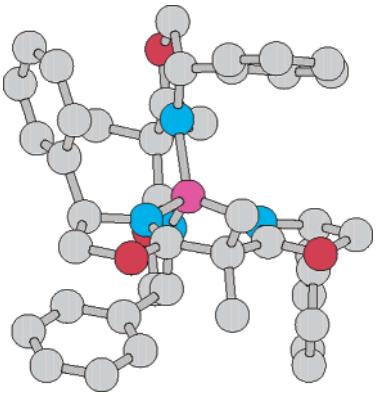


Figure 10. Molecular structure of [(*R*)-**1**·(*S*)-**1**·Zn] (**24**) (ref 77).

by the reactions catalyzed by the chiral [box/Zn(II)] complex is due to the stability of this complex, with the phenyl groups nicely oriented to avoid any steric interaction.

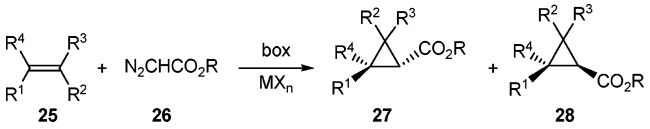
4. Two Commercial Ligands as Box Prototypes: Reactions Using 4-Phenyl- and 4-tert-Butyl-Box-Based Catalysts

At the end of the last century, box ligands became so popular that some of them came on the market as commercial products. Among these **1**, available as (*R*)- and (*S*)-enantiomers, and (*S*)-**2**, sold at a reasonable price, were widely used to test the stereoselective properties of the catalysts derived from this class of ligands versus a large number of reactions. Therefore, these box's belong to the most used ligands in the literature, and their behavior can provide a good representation of the efficiency of 4-aryl- and 4-alkyl-substituted box-based catalysts.

4.1a. Intermolecular Cyclopropanation Reactions

The first application of a new chiral ligand for a given reaction usually focuses on the novel properties of the system with results that can be ameliorated in the proceeding of the field. Rarely, the first report already optimizes the stereoselectivity of the catalytic process, but this occurred with the first use of box's as chiral ligands in metal-catalyzed asymmetric cyclopropanation of alkenes.[6] The reaction between alkenes **25** and diazoacetates **26** (Scheme 5) was

Scheme 5



catalyzed by (*S*)-**2** and CuOTf with excellent yield, diastereoselectivity, and enantioselectivity (Table 3, entries 1 and 4−6) to give *trans*- and *cis*-cyclopropanes, **27** and **28**, respectively. The cyclopropanation of styrene was performed with a complex derived from box **2** and Cu(I) as the catalyst, since the results obtained using either Cu(II) or box **1** (Table 3, entries 2 and 3) were less convincing.[39a,78] Experiments have been performed to investigate the influence of the diazoester structure on the selectivity (entries 4−7). It was found that the increased steric demand displays increased trans selectivity, with the ester derived from 2,6-di-*tert*-butyl-4-methylphenol (BHT, entry 6) giving a **27**/**28** ratio of 94:6. Excellent enantioselectivities were obtained with 3-phenylpropene, 1,1-diphenylethene, and 2-methylpropene (Table 3, entries 8−10), with the symmetrically disubstituted alkenes giving a single enantiomer.[6]

To test the limitations of box's as ligands in Cu-catalyzed enantioselective cyclopropanation, several trisubstituted alkenes were tested (Table 3, entries 12−20).[8,80] (*S*)-**1** and (*S*)-**2** gave the same absolute configuration as the optically active cyclopropanes (Table 3, entries 13 and 14), but enantioselectivity was by far better with the latter ligand (Table 3, entries 13−16). The best trans/cis ratio (91:9) was obtained for the reaction of 3-methyl-2-butenoyl *p*-methoxybenzoate (Table 3, entry 20), and the highest enantioselectivity (95% ee) for 3-methyl-2-butenoyl acetate (Table 3, entry 14), while several substrates gave unsatisfactory results. Vinyl fluorides were a further class of di- and trisubstituted alkenes quite intensively investigated.[81,82] The best results were obtained with the reaction of diazoacetates and α-fluorostyrene, catalyzed by the Cu(I) complex of (*S*)-**2** (Table 3, entries 21−23), since cyclopropanes were obtained with more than 90% ee. The presence of a further substituent or an alkyl group instead of the aryl causes a significantly lower enantioselectivity (Table 3, entries 24−26).

An interesting development led to test the reaction between styrene and ethyl diazoacetate (a benchmark of enantioselective cyclopropanation) catalyzed by copper complexes of (*S*)-**1** and (*S*)-**2**, run in three ionic liquids, 1-ethyl-3-methylimidazolium (EMIM), methyltri-*n*-octylammonium (Oct_3NMe), and 1-butyl-3-methylimidazolium (BMIM) with different anions (Table 4).[83,84] When the reactions were performed with catalysts prepared from $CuCl_2$ and (*S*)-**1** or (*S*)-**2** in ionic liquids a significant improvement of the results was found compared to the disappointing result in CH_2Cl_2 (Table 4, entries 1 and 4 vs 2, 3, and 5). Furthermore, those from $Cu(OTf)_2$ and (*S*)-**2** lower the performance (Table 4, entry 6 vs 7−9), while reactions using CuOTf and (*S*)-**2** significantly ameliorate the enantioselectivity of the reaction run in $CHCl_3$, mainly for the major trans product **27** (Table 4, entry 10 vs 11−14).

Diazoacetates **26** react with enol ethers **29**, some of them with different chiral auxiliaries, to give cyclopropanecarboxylates **30** and **31** (Scheme 6, Table 5).[85,86] The glucose-

Table 3. Asymmetric Cyclopropanations of Alkenes 25 with Diazoacetates 26 Catalyzed by Box Complexes

entry	R^1	R^2	R^3	R^4	R	box	MX_n	yield (%)	**27**/**28**	**27** ee (%) (conf.)	**28** ee (%) (conf.)	ref
1	Ph	H	H	H	Et	(*S*)-**2**	CuOTf	77	73:27	99 (1*R*,2*R*)	97 (1*R*,2*S*)	6, 10, 39a, 78
2	Ph	H	H	H	Et	(*S*)-**2**	$Cu(OTf)_2$	81	71:29	91 (1*R*,2*R*)	88 (1*R*,2*S*)	78
3	Ph	H	H	H	Et	(*R*)-**1**	Cu(I)[a]	77	70:30	65 (1*S*,2*S*)	54 (1*S*,2*R*)	39a
4	Ph	H	H	H	*t*-Bu	(*S*)-**2**	CuOTf	75	81:19	96 (1*R*,2*R*)	93 (1*R*,2*S*)	6
5	Ph	H	H	H	2,6-DMP[b]	(*S*)-**2**	CuOTf	68	86:14	97 (1*R*,2*R*)	96 (1*R*,2*S*)	6
6	Ph	H	H	H	2,6-BHT[c]	(*S*)-**2**	CuOTf	85	94:6	99 (1*R*,2*R*)		6
7	Ph	H	H	H	$CH(C_6H_{11})_2$	(*S*)-**2**	CuOTf	83	88:12	97 (1*R*,2*R*)		79
8	Bn	H	H	H	2,6-BHT	(*S*)-**2**	CuOTf	*d*	99:1	99 (1*R*,2*S*)		6
9	H	Ph	Ph	H	Et	(*S*)-**2**	CuOTf	*d*		99 (1*S*)		6
11	H	Me	Me	H	Et	(*S*)-**2**	CuOTf	*d*		99 (1*S*)		6
12	$C{=}CMe_2$	Me	Me	H	L-menthyl	(*R*)-**2**	Cu(I)P[e]	60	84:16	24 (1*R*,2*R*)	20	8
13	CH_2OAc	Me	Me	H	Et	(*S*)-**1**	CuOTf	47	49:51	69 (1*R*,2*R*)	3	80
14	CH_2OAc	Me	Me	H	Et	(*S*)-**2**	CuOTf	50	80:20	95 (1*R*,2*R*)	47	80
15	CH_2OSiMe_3	Me	Me	H	Et	(*S*)-**1**	CuOTf	52	64:36	66	*d*	80
16	CH_2OSiMe_3	Me	Me	H	Et	(*S*)-**2**	CuOTf	33	76:24	87	*d*	80
17	CH_2OCH_2Ph	Me	Me	H	Et	(*S*)-**2**	CuOTf	74	88:12	93	*d*	80
18	$CH_2OTrityl$	Me	Me	H	Et	(*S*)-**2**	CuOTf	46	82:18	87	*d*	80
19	CH_2OCOPh	Me	Me	H	Et	(*S*)-**2**	CuOTf	82	82:18	92	*d*	80
20	$CH_2OCOC_6H_4OMe$	Me	Me	H	Et	(*S*)-**2**	CuOTf	61	91:9	92	12	80
21	Ph	H	H	F	Et	(*S*)-**2**	CuOTf	62	72:28	89 (1*S*,2*S*)	80	81, 82
22	Ph	H	H	F	*t*-Bu	(*S*)-**2**	CuOTf	56	81:19	93 (1*S*,2*S*)	89	81, 82
23	Ph	H	H	F	L-menthyl	(*S*)-**2**	CuOTf	28	81:19	92 (1*S*,2*S*)	>98	81, 82
24	*p*-ClPh	H	H	F	Et	(*S*)-**2**	CuOTf	64	81:19	93	91	81
25	Ph	Me	H	F	Et	(*S*)-**2**	CuOTf	62	82:18	65	*d*	81
26	C_4H_9	H	H	F	Et	(*S*)-**2**	CuOTf	28	64:36	16	*d*	81

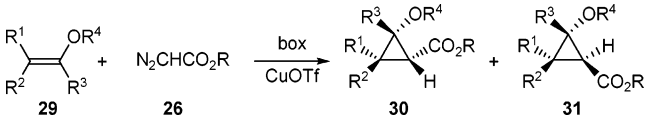
[a] X not reported. [b] 2,6-DMP is 2,6-dimethylphenyl. [c] 2,6-BHT is 2,6-di-*tert*-butyl-4-methylphenyl. [d] Not reported. [e] P is $ClO_4(MeCN)_4$.

Table 4. Asymmetric Cyclopropanations of Styrene (25, R^1 = Ph, R^2 = R^3 = H) with Ethyl Diazoacetate (26, R = Et) Catalyzed by Copper Box Complexes in Ionic Liquids

entry	box	CuX_n[a]	ionic liquid	yield (%)	**27**:**28**[a]	**27** ee (%) (conf.)	**28** ee (%) (conf.)	ref
1	(*S*)-**1**	$CuCl_2$	CH_2Cl_2	19	67:33	17 (1*R*,2*R*)	13 (1*R*,2*S*)	83
2	(*S*)-**1**	$CuCl_2$	(EMIM)(NTf_2)	34	67:33	55 (1*R*,2*R*)	47 (1*R*,2*S*)	83
3	(*S*)-**1**	$CuCl_2$	(Oct_3NMe)(NTf_2)	18	67:33	49 (1*R*,2*R*)	41 (1*R*,2*S*)	83
4	(*S*)-**2**	$CuCl_2$	CH_2Cl_2	24	70:30	2	7	83
5	(*S*)-**2**	$CuCl_2$	(EMIM)(NTf_2)	50	62:38	86 (1*R*,2*R*)	85 (1*R*,2*S*)	83
6	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	61	71:29	91 (1*R*,2*R*)	88 (1*R*,2*S*)	83
7	(*S*)-**2**	$Cu(OTf)_2$	(EMIM)(NTf_2)	38	64:36	66 (1*R*,2*R*)	64 (1*R*,2*S*)	83
8	(*S*)-**2**	$Cu(OTf)_2$	(EMIM)(BF_4)	3	70:30	racemate	racemate	83
9	(*S*)-**2**	$Cu(OTf)_2$	(Oct_3NMe)(NTf_2)	18	63:37	23 (1*R*,2*R*)	22 (1*R*,2*S*)	83
10	(*S*)-**2**	CuOTf	$CHCl_3$	59	73:27	89 (1*R*,2*R*)	96 (1*R*,2*S*)	84
11	(*S*)-**2**	CuOTf	(BMIM)Tf	53	76:24	97 (1*R*,2*R*)	95 (1*R*,2*S*)	84
12	(*S*)-**2**	CuOTf	(BMIM)(PF_6)	47	75:25	95 (1*R*,2*R*)	91 (1*R*,2*S*)	84
13	(*S*)-**2**	CuOTf	(BMIM)(NTf_2)	45	63:37	94 (1*R*,2*R*)	93 (1*R*,2*S*)	84
14	(*S*)-**2**	CuOTf	(BMIM)(BF_4)	61	75:25	95 (1*R*,2*R*)	89 (1*R*,2*S*)	84

[a] **27**, **28**: R = Et, R^1 = Ph, R^2 = R^3 = H.

Scheme 6



and mannose-derived chiral auxiliaries (Table 5, entries 1−4) induce an excellent trans stereoselectivity (**31** being the main product), but diastereoselectivity was moderate.[85] Trimethylsilyloxy (TMSO) alkenes, on the contrary, gave a low cis/trans selectivity, but the enantioselection was excellent for 1-TMSO-styrene (Table 5, entries 5 and 6) and for 1-TMSO-cyclopentene (Table 5, entries 7 and 8), whereas the cyclohexene derivative (Table 5, entry 9) gave poor results under the reaction conditions studied.[86]

The cyclic enol ethers derived from 2,3-dihydrofuran and 2,3-dihydropyran (**32**, n = 1, 2) were useful substrates for the enantioselective cyclopropanation with ethyl diazoacetate (**26**, R = Et), catalyzed by the complex derived from (*S*)-**2** and CuOTf (Scheme 7).[87] If unsubstituted dihydropyran is excluded, the exo/endo diastereoselectivity was up to 95:5, and the enantioselectivity was higher than 95% ee in nearly all cases (Table 6, entries 1−6). This selectivity can be easily rationalized if intermediate **33** is assumed to be the reaction complex, since the attack of **32** following pathway b is disfavored by the strong repulsive steric interaction between the approaching enol ether and the *tert*-butyl group of the ligand.[87] The excellent stereoselectivity of the catalytic stereoselective cyclopropanation reaction leading to **34** (Table 6, entry 4, R^1 = Et, R^2 = H) was used as the key step in the asymmetric synthesis of (+)-quebrachamine, an indole alkaloid of the Aspidosperma family.[87]

Another useful synthon of natural γ-butyrolactone was the product of the enantioselective cyclopropanation of furan-2-carboxylic methyl ester (**35**) with ethyl diazoacetate (**26**, Scheme 8). The catalyst was prepared from (*S*)-**2**, $Cu(OTf)_2$, and phenylhydrazine leading to the formation of cyclopropane **36** with 91% ee (>99% ee after a single crystallization).

Table 5. Asymmetric Cyclopropanations of Enol Ethers 29 with Diazoacetates 26 Catalyzed by CuOTf

entry	R^1	R^2	R^3	R^4	**26** R	box	yield (%)	**30**:**31**	**30** ee (%) (conf.)	**31** ee (%) (conf.)	ref
1	Me	H	H	α-D-Glu	Me	(*S*)-**2**	74	3:97		60	85
2	Me	H	H	α-D-Glu	*t*-Bu	(*S*)-**2**	32	3:97		60	85
3	Me	H	H	α-D-Man	Me	(*S*)-**2**	54	12:88	14	65	85
4	Me	H	H	α-D-Man	*t*-Bu	(*S*)-**2**	71	*a*		63	85
5	H	H	Ph	TMS	Me	(*S*)-**2**	82	48:52	96	89	86
6	H	H	Ph	TMS	Et	(*S*)-**2**	77	44:56	95	90	86
7	H	$(CH_2)_3$		TMS	Me	(*S*)-**2**	56	73:27	92 (1*S*,5*R*,6*R*)	87 (1*R*,5*S*,6*R*)	86
8	H	$(CH_2)_3$		TMS	Et	(*S*)-**2**	46	75:25	85 (1*S*,5*R*,6*R*)	40 (1*R*,5*S*,6*R*)	86
9	H	$(CH_2)_4$		TMS	Me	(*S*)-**2**	7	27:73	11 (1*S*,5*R*,7*R*)	*a*	86

[a] Not determined.

Scheme 7

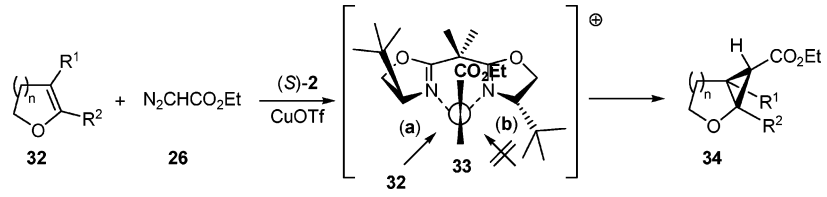


Table 6. [(*S*)-2/CuOTf]-Catalyzed Asymmetric Cyclopropanations of Cyclic Enol Ethers 32 with Ethyl Diazoacetate 26[87]

entry	*n*	R^1	R^2	endo/exo	**34** yield (%)	**34** ee (%) (conf.)
1	1	Me	H	30:70	60	>95 (1*R*,5*S*,6*S*)
2	1	CH_2Ph	H	21:79	77	96 (1*R*,5*R*,6*S*)
3	2	H	H	13:87	77	racemate
4	2	Et	H	9:91	52	>95 (1*R*,6*S*,7*S*)
5	2	*n*-Pr	H	6:94	54	>95 (1*R*,6*S*,7*S*)
6	2	CH_2Ph	H	5:95	67	96 (1*R*,6*R*,7*S*)
7	2	H	CH_2Ph	7:93	45	74 (1*R*,6*R*,7*R*)

This key intermediate was converted to (−)-nephrosteranic acid **37a**,[88] (−)-roccellaric acid **37b**,[88,89] (−)-protolichesterinic acid **38**,[88] and the core nuclei (**39**) of xanthanolides, guaianolides, and eudesmanolides.[90]

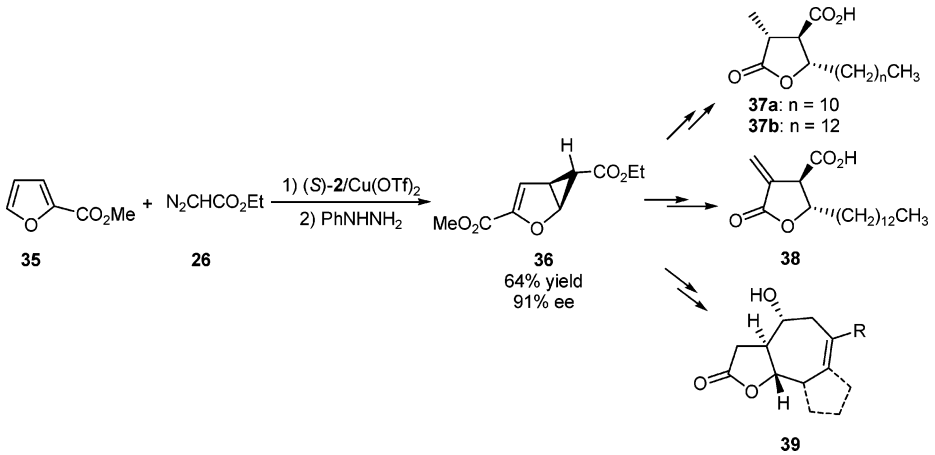
The carbene sources of the previously reported cyclopropanations were diazoacetate esters; therefore the enantioselective cycloadditions with diazomethane **40a** and trimethylsilyldiazomethane **40b** are rather unusual (Scheme 9). The reaction with cinnamate esters was tested with both (*S*)-**1** and (*S*)-**2** in combination with CuOTf (Table 7, entries 1 and 2), and the best result was obtained with the former ligand. Different ester groups (Table 7, entries 1 and 3−6) give comparable results, whereas the effect of substituents at the phenyl group is shown by the linear Hammett correlation between the logarithm of the enantiomeric ratio and the σ^+ parameters (Table 7, entries 1 and 7−9).[91] Trimethylsilyldiazomethane **40b** and styrene react with a remarkably high trans selectivity leading to **41** as the major product (Table 7, entries 10−13), and it was found that substrates with phenyl groups having electron-withdrawing substituents provided an increase in both the trans selectivity and the enantioselectivity (Table 7, entries 11 and 14−16).[92]

To summarize this section, when the carbene sources are diazoalkanes the best catalysts are Cu(I)− or Cu(II)−box complexes, and OTf is a better counterion than PF_6.

1,1-Diphenylethene (**43**) reacts with styryl-diazoacetate (**44**) to give cyclopropane **45** (Scheme 10). The best ligand with $Cu(OTf)_2$ is (*R*)-**1** (Table 8, entry 2 vs 1); however, the best enantioselectivity (even if the yield is very low) is obtained with (*S*)-**2** and $RuCl_2$ or $Sc(OTf)_3$ (Table 8, entries 4 and 5).[93]

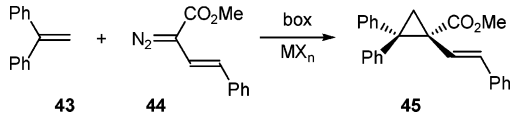
Dimethylsulfonium isopropylide (**47**) can be an interesting alternative to diazoderivatives as the source of carbene, because its reaction with 3-crotonoyl- and 3-cinnamoyl-2-oxazolidinones (**46a**, R = Me; **46b**, R = Ph) can be catalyzed by complexes of (*R*)-**1** with several salts (Table 9, entries 1 and 4−10), and the enantioselectivity with Zn(II) and Mg(II) complexes can be as high as 95% ee.[94] Unfortunately,

Scheme 8



Scheme 9

Scheme 10



the limit of this protocol is the stoichiometric amount of Lewis acid required, because a significant loss of enantioselectivity is observed with less than 1 equiv of catalyst (Table 9, entries 2 and 3).

4.1b. Intramolecular Cyclopropanation Reactions

The intramolecular variant of the box−metal-catalyzed cyclopropanation reaction was first developed by Corey et al. during their enantioselective synthesis of the chemotactic factor sirenin.[95] The starting product was the suitably substituted diazotriene **49** that was submitted to several known catalysts for enantioselective [2 + 1]-cycloaddition (Scheme 12). Many failed, but Cu(I) catalysts in combination with (*S*)-**1** or **(***S*)-**2** as ligands gave **50**, which was easily converted in two steps into the target sirenin (**51**), with promising 68% yield and 60% ee. These results stimulated the authors to develop a new class of more efficient box ligands that increased the enantioselectivity to 90% ee; however, this new class of ligands has a structure far from the topic of this review.

This approach was largely applied to the cyclization of allylic diazoacetates **52** (X = O) that give cyclopropa[*c*]-furans **54** (Scheme 13).[96] With [(S)-**2**/$CuPF_6$] as the catalyst, the enantioselectivity largely depends on the double bond substituents, and the best enantioselectivities are obtained with 2-substituted allyl groups (Table 10, entries 5 and 6) since the steric hindrance of R^1 favors conformation **53** of the substrate. It should be noted also that the absolute configuration of the product depends on substituents, even if this cannot be easily rationalized. An important complementary result is obtained with dirhodium(II)tetrakis(methyl 2-oxopyrrolidine carboxylates) that are the catalysts of choice for products described in entries 1−4, not for those of entries 5 and 6. Even if this is not the topic of this review, it remains an important example of the general phenomenon of selectivity in catalysis.

The same stereochemical result reported in Scheme 13 is also obtained from ethyl (2*Z*)-7-diazo-2-fluoro-6-oxohept-2-enoate (**52**, R^1 = H, R^2 = F, R^3 = CO_2Et, X = CH_2, Table 10, entries 7 and 8)[44] and 1-diazo-7-methyl-6-triethylsyliloxy-6-octen-2-one (**52**, R^1 = OTES, R^2 = R^3 = Me, X = CH_2CH_2, Table 10, entries 9 and 10).[21] These compounds are useful starting products for the preparation of enantiopure fluorobicycloketone and TMSO-bicyclohexanone (**54**), whose structure is that of the CD-ring skeleton of phorbol. The use of a modified box with 4-CMe_2OSiMe_3 substituents enhances the enantioselectivity to an excellent 92% ee, but the effects of substituents other than phenyl and *tert*-butyl will be the topic of the next section.

The intramolecular cyclopropanation works nicely for the construction of large rings: Diazoacetates tethered to the allyl group through 0−3 ethylene glycol units (Scheme 14, **55**) not only give products from the cyclopropanation (**56** and **57**) but also from C−H insertion, intermediate oxonium ylides, and carbene dimers, but the interesting point is that the [(S)-**2**/$CuPF_6$] catalyst increases enantioselectivity as a function of the ring size (Table 11, entries 1−4).[97,98]

If, in addition to the above data, the results of the catalyzed cyclopropanation of homoallylic diazoacetate (**58**, *n* = 1), the homologues with *n* = 3, 4, and 8,[99] and 2-(propen-1-yloxymethyl)benzyl diazoacetate,[100] are considered and the enantioselectivities of the cis-fused cyclopropanes **56** and **59** are plotted versus the ring size, then the above observations appear to be a general trend (Figure 11).[97,99,100] However, the preferred formation of the macrocycle has a negative effect on the reaction stereoselectivity (**56**/**57**).

The catalytic intramolecular cycloaddition prefers a double versus a triple bond, even if the former belongs to an aromatic ring. A naphthalene-1,8-dimethanol derivative carrying a propargilic and a diazoacetate group (**60**, Scheme 15) largely prefers the formation of the norcaradienic derivative **61** (62% yield, 59% ee) instead of the macrocyclic cyclopropene **62** (10% yield, enantiomeric excess not determined).[101] To determine the effectiveness of the box−Lewis-acid-catalyzed cyclopropanation on the naphthalene system, a test was made with compound **60** having no substituent in position 8, and [(*S*)-**2**/$CuPF_6$] was found to

Table 7. Asymmetric Cyclopropanations of Alkenes with Diazomethane Derivatives

entry	R^1	R^2	R	box	MX	yield (%)	**41**:**42**	**41** ee (%)	**42** ee (%)	ref
1	Ph	CO_2Me	H	(*S*)-**1**	CuOTf	80		72		91
2	Ph	CO_2Me	H	(*S*)-**2**	CuOTf	30		24		91
3	Ph	CO_2Et	H	(*S*)-**1**	CuOTf	80		73		91
4	Ph	CO_2i-Pr	H	(*S*)-**1**	CuOTf	43		69		91
5	Ph	CO_2CH_2Ph	H	(*S*)-**1**	CuOTf	79		75		91
6	Ph	CO_2Ph	H	(*S*)-**1**	CuOTf	49		74		91
7	*p*-NO_2Ph	CO_2Me	H	(*S*)-**1**	CuOTf	62		80		91
8	*p*-MePh	CO_2Me	H	(*S*)-**1**	CuOTf	79		60		91
9	*p*-MeOPh	CO_2Me	H	(*S*)-**1**	CuOTf	81		55		91
10	Ph	H	$SiMe_3$	(*S*)-**1**	CuOTf	50	86:14	2	5	92
11	Ph	H	$SiMe_3$	(*S*)-**1**	$CuPF_6$	60	97:3	63	43	92
12	Ph	H	$SiMe_3$	(*S*)-**2**	CuOTf	45	96:4	69	50	92
13	Ph	H	$SiMe_3$	(*S*)-**2**	$CuPF_6$	26	90:10	43	15	92
14	*p*-BrPh	H	$SiMe_3$	(*S*)-**1**	$CuPF_6$	86	100:0	66		92
15	*p*-MePh	H	$SiMe_3$	(*S*)-**1**	$CuPF_6$	54	96:4	58	38	92
16	*p*-MeOPh	H	$SiMe_3$	(*S*)-**1**	$CuPF_6$	80	95:5	49	61	92

Table 8. Asymmetric Cyclopropanations of 1,1-Diphenylethene 43 with Diazoacetate Derivative 44[93]

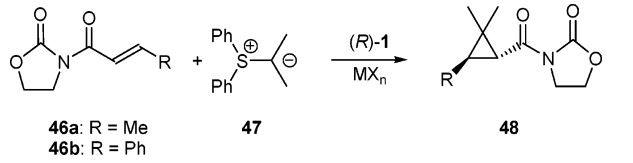
entry	box	MX_n	**45** yield (%)	**45** ee (%)
1	(*R*)-**1**	$Cu(OTf)_2$	62	65
2	(*S*)-**2**	$Cu(OTf)_2$	23	3
3	(*S*)-**2**	$AgSbF_6$	2	24
4	(*S*)-**2**	$RuCl_2$	6	>98
5	(*S*)-**2**	$Sc(OTf)_3$	10	>98

Table 9. Asymmetric Cyclopropanations of Acylidene-Oxazolidinones 46 with Sulfur Ylide 47 Catalyzed by [(*R*)-1/Lewis Acid] Complexes[94]

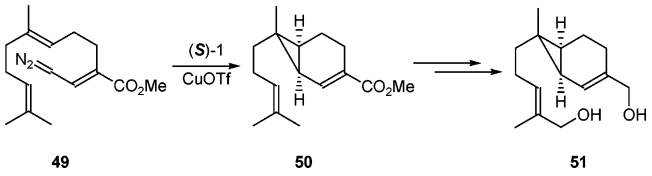
entry	R	MX_n[a]	**48** yield (%)	**48** ee (%)
1	Me	$Zn(OTf)_2$	63	95
2[b]	Me	$Zn(OTf)_2$	65	82
3[c]	Me	$Zn(OTf)_2$	63	55
4	Me	$ZnBr_2$	60	93
5	Me	$ZnCl_2$	53	92
6	Me	$Sn(OTf)_2$	60	81
7	Me	$Mg(OTf)_2$	57	92
8	Me	MgI_2	66	46
9	Ph	$Zn(OTf)_2$	69	36
10	Ph	MgI_2	70	14

[a] 1 equiv of catalyst, except in entries 2 and 3. [b] 0.75 equiv of catalyst. [c] 0.50 equiv catalyst.

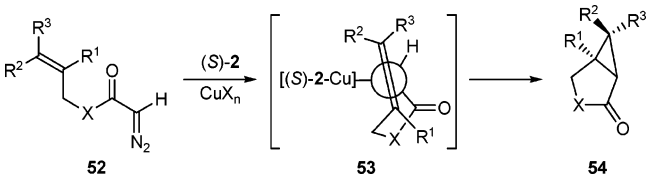
Scheme 11



Scheme 12



Scheme 13



catalyze the aromatic cycloaddition with 83% yield and 42% ee.[101]

When two or more double bonds are present in the substrate, the regioselectivity depends both upon the catalyst and the specific structure of the reagent. The intramolecular cyclopropanation of 4-(2-methyl-2-propenyloxy)-(*Z*)-2-butenyl diazoacetate **63** and the homologous **66**, with [(*S*)-**2**/$CuPF_6$], leads to the formation of the largest cycle as the major product.[102] For the former substrate (Scheme 16), two competing products are formed, with the predominant largest bicyclic derivative (**64**) obtained with the highest enantioselectivity (**64**, 43% yield, 87% ee; **65**, 19% yield, 41% ee), while the reaction of **66** is highly regioselective and the macrocycle **67** is the only reaction product formed (regioisomeric ratio >25:1, 61% yield, 90% ee) (Scheme 17).[102]

A nice application of the intramolecular cyclopropanation is demonstrated by Overman et al. in the enantiodivergent total syntheses of (+)- and (−)-Scopadulcic acid A (Scheme 18). Even if the enantioselective [2 + 1]-cycloaddition is introduced in an early stage of the synthesis, the chiral information is the messenger of half of the total chirality of the process.[103] The key synthon is (1*S*,5*R*)-5-methyl-2-oxo-3-oxabicyclo[3.1.0]hexane (**69**), prepared on a multigram scale in 80% yield and 88% ee (raised to 99% ee by crystallization) by catalytic cyclopropanation of diazoester **68** catalyzed by [(*R*)-**2**/CuOTf]. The bicyclic lactone was opened to 1-(*N*,*O*-dimethylhydroxamido)-2-ethenyl-2-methylcyclopropane **70**, coupled with the messenger of the stereodivergence to give **71** (or its diastereoisomer), submitted first to a Cope rearrangement to give **72**, then to a Heck cyclization to give **73**, the key tricyclic intermediate of the targets (**74** is (−)-Scopadulcic acid A).

Some of the results of this section, concerning both inter- and intramolecular reactions, have been reported in two recent reviews dedicated to the general topic of stereoselective cyclopropanation reactions.[104,105]

4.2. Aziridination Reactions

The first communication dealing with the use of box's as ligands in asymmetric reactions was the catalytic aziridination of styrene leading to optically active aziridines obtained in good yield and promising enantioselectivity.[6] Two years later, a report appeared dealing with the reaction of several alkenes (**75**) with *N*-(*p*-toluensulfonylimino)phenyliodinane (**76**, X = Me) as the nitrene source, catalyzed by both [(*S*)-**1**/CuOTf] and [(*S*)-**2**/CuOTf], to give aziridines **77** (Scheme 19, Table 12).[106]

Four points deserve attention. (i) The best results are obtained with unsaturated esters with enantioselectivties up to 96% ee (Table 12, entries 6−12), and both aryl and ester substituents do not significantly influence the enantioselectivity. (ii) The best box is (*S*)-**1** (Table 12, entry 7 vs 6). (iii) A significant solvent effect is observed, and for styrene and cinnamate esters it has been found that better enantioselectivities are obtained in less polar solvents. (iv) With the same catalyst configuration, the absolute configuration of the chiral carbon atom in the aziridine obtained from from styrene is (*R*), opposite to that in trans disubstituted alkenes (*S*). A similar result is reported for the aziridination of chalcone (**75**, Ar = Ph, R = COPh, Table 12, entry 13).[107]

The data reported in Table 12 are among the best results reported in the literature for the catalysis run under homogeneous conditions. One of the reasons for the limited interest in a field that gives important chiral building blocks is that better overall enantioselectivities have been achieved with heterogenized catalysts than under homogeneous conditions.[5]

For the aziridination of styrene (**75**, R = H) catalyzed by Cu(I) salts in combination with (*R*)-**1** and (*S*)-**2**, a significant effect on the stereochemical outcome of the reaction was observed for various counterions, both achiral and chiral ((*R*)- or (*S*)-$B(binaphthol)_2^-$−$B(BN)_2^-$, in benzene and MeCN (Table 13).[108] In these studies a significant influence of the solvent was also observed. In benzene, the best box was (*S*)-**2**, and enantioselectivity improved when moving from PF_6 to OTf as the counterion (Table 13, entries 7−10). However, this order was inverted for (*R*)-**1** (Table 13, entries 1−4), and a change in enantioselectivity to more than 30%

Table 10. Asymmetric Intramolecular Cyclopropanations of Allylic Diazoacetates, Fluorodiazoenone, and Enol Silyl Ether

entry	box	CuX_n	X	R^1	R^2	R^3	**54** yield (%)	**54** ee (%) (conf.)	ref
1	(*S*)-**2**	$CuPF_6$	O	H	H	H	61	20 (1*R*,5*S*)	96
2	(*S*)-**2**	$CuPF_6$	O	H	Me	Me	80	13 (1*R*,5*S*)	96
3	(*S*)-**2**	$CuPF_6$	O	H	H	Pr	74	29 (1*S*,5*R*)	96
4	(*S*)-**2**	$CuPF_6$	O	H	Pr	H	82	37 (1*S*,5*S*)	96
5	(*S*)-**2**	$CuPF_6$	O	Me	H	H	58	87 (1*S*,5*R*)	96
6	(*S*)-**2**	$CuPF_6$	O	Bu	H	H	73	82 (1*S*,5*R*)	96
7	(*S*)-**1**	CuOTf	CH_2	H	F	CO_2Et	79	65 (1*S*,5*S*,6*S*)	44
8	(*S*)-**1**	$Cu(OTf)_2$	CH_2	H	F	CO_2Et	80	61 (1*S*,5*S*,6*S*)	44
9	(*S*)-**1**	CuOTf	CH_2CH_2	OTES	Me	Me	38	13 (1*R*,6*S*)	21
10	(*S*)-**2**	CuOTf	CH_2CH_2	OTES	Me	Me	82	78 (1*R*,6*S*)	21

Scheme 14

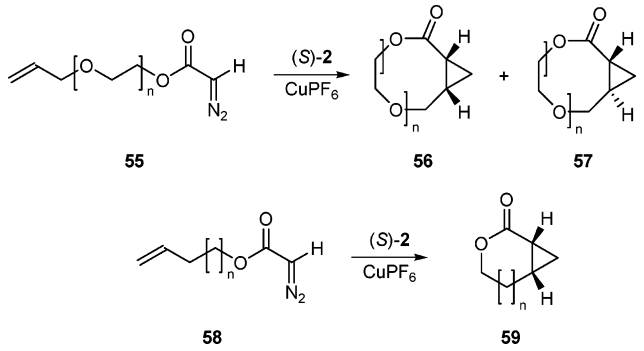


Table 11. Asymmetric Intramolecular Cyclopropanations of Poly(Ethyloxy)-Allyl Diazoacetates 55 Catalyzed by [(*S*)-2/$CuPF_6$]

entry	*n*	conv.[a] (%)	yield[b] (%)	**56**:**57**	**56** ee (%)	**57** ee (%)	ref
1	0		61		20 (1*R*,5*S*)		97
2	1	61	3		71 (1*S*,8*R*)		97
3	2	58	58	86:14	79	85	97
4	3	73	61	40:60	88	80	97, 98

[a] Conversion of **55**. [b] Yield of cyclopropanes **56** and **57**.

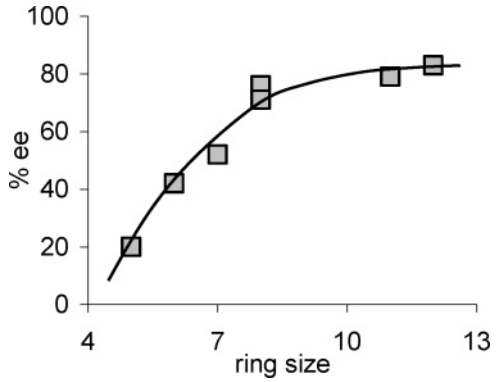
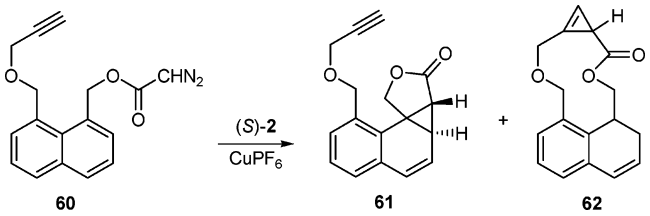


Figure 11. Enantiomeric excess (%) vs ring size of the cis-fused cyclopropanes from the intramolecular reaction of **55** and **58** (refs 97−100).

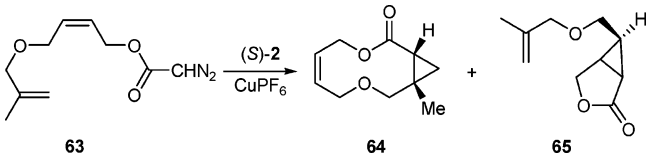
ee was observed. In the more polar MeCN solvent, (*R*)-**1** gave better enantioselection, but no counterion effect was observed (Table 13, entries 1−4 and 7−10). The current disappointing results with both enantiomers of the chiral counterion $[B(BN)_2]^-$ (Table 13, entries 5, 6, 11, and 12) should not prevent further investigations on this original theme.

Recently, the aziridination of styrene derivatives was investigated in detail, varying the substituents both on the substrate (Ar group of **75**)[109,110] and on the nitrene reagent

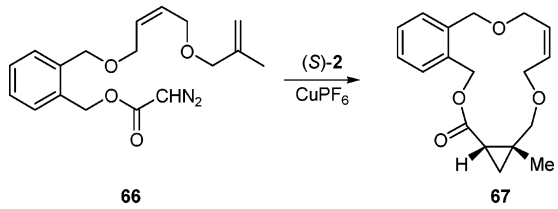
Scheme 15



Scheme 16



Scheme 17

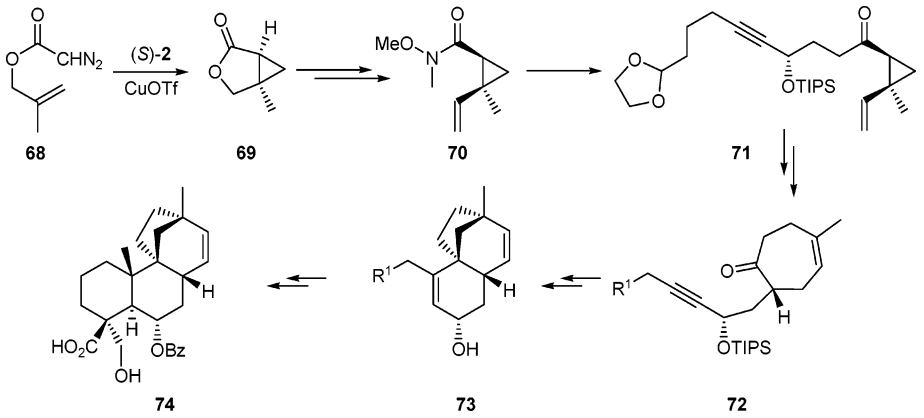


(X group of **76**), prepared in situ from the commercially available $PhI(OAc)_2$ and sulfonamides $X-C_6H_4-SO_2NH_2$, and the results are summarized in Table 14.[109]

With (*S*)-**2**, $Cu(ClO_4)(MeCN)_4$, and benzene as solvent,[109] the enantioselectivity changes with the change of the substituent X on sulfonamide, and it regularly increases with the increase of the electron-withdrawing character of the substituent (Table 14, entries 2−7). Therefore, the best results have been obtained with *p*-nitrobenzenesulfonylnitrene. The comparison of the results with substituted styrene (Table 14, entries 8−10) with those obtained with [(*S*)-**1**/$Cu(OTf)_2$] in MeCN (Table 14, entries 11−19)[110] confirms the features shown by the data in Table 13: Phenyl-box is a better ligand than the *tert*-butyl one; with (*S*)-**1** acetonitrile is the solvent of choice, while (*S*)-**2** prefers benzene. Concerning the specific effect of substituents in styrene, enantioselectivity strongly changes, but no clear relation appears with the electronic properties of the substituent.

An even better preparation of the nitrene precursors **76** was realized in "one pot" from sulfonamides and iodosylbenzene.[111] This protocol was tested on the reaction of styrene catalyzed by [(*S*)-**2**/CuOTf][111] with yield and enantioselectivity comparable to those described previously, but when it was applied to the aziridination of *tert*-butyl-(*R*)-*N*-(9-phenyl-9*H*-fluoren-9-yl)allylglycinate, yield and diastereoselectivity were somewhat unsatisfactory.[112,113]

Scheme 18



Scheme 19

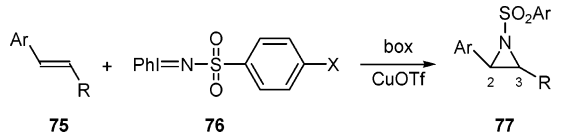


Table 12. Asymmetric Aziridinations of Different Alkenes 75 with 76 (X = Me)

entry	Ar	R	box	solvent	**77** yield (%)	**77** ee (%) (2-conf.)	ref
1	Ph	H	(*S*)-**2**	styrene	89	63 (*R*)	106
2	Ph	H	(*S*)-**2**	benzene	*a*	57 (*R*)	106
3	Ph	H	(*S*)-**2**	CH_2Cl_2	*a*	36 (*R*)	106
4	Ph	H	(*S*)-**2**	MeCN	*a*	6 (*R*)	106
5	Ph	Me	(*S*)-**2**	MeCN	62	70 (*S*)	106
6	Ph	CO_2Me	(*S*)-**2**	MeCN	16	19 (*S*)	106
7	Ph	CO_2Me	(*S*)-**1**	MeCN	21	70 (*S*)	106
8	Ph	CO_2Me	(*S*)-**1**	benzene	63	94 (*S*)	106
9	Ph	CO_2Ph	(*S*)-**1**	benzene	64	97 (*S*)	106
10	Ph	CO_2t-Bu	(*S*)-**1**	benzene	60	96 (*S*)	106
11	1-naphthyl	CO_2Me	(*S*)-**1**	benzene	76	95 (*S*)	106
12	2-naphthyl	CO_2Me	(*S*)-**1**	benzene	73	96 (*S*)	106
13	Ph	COPh	(*S*)-**1**	CH_2Cl_2	38	86 (*S*)	107

[a] Not reported.

Table 13. Asymmetric Aziridinations of Styrene (75, R = H) with 76 (X = Me): Effect of the Counterion[108]

entry	box	Cu(I) counterion	yield (%)	benzene **77** ee (%) (conf.)	MeCN **77** ee (%) (conf.)
1	(*R*)-**1**	OTf	*a*	1 (*S*)	28 (*S*)
2	(*R*)-**1**	ClO_4	*a*	5 (*S*)	28 (*S*)
3	(*R*)-**1**	Cl	*a*	17 (*S*)	28 (*S*)
4	(*R*)-**1**	PF_6	*a*	33 (*S*)	28 (*S*)
5	(*R*)-**1**	(*S*)-B(BN)$_2$[b]	75	22 (*S*)	
6	(*R*)-**1**	(*R*)-B(BN)$_2$[b]	85	24 (*S*)	
7	(*S*)-**2**	OTf	*a*	66 (*R*)	2 (*R*)
8	(*S*)-**2**	ClO_4	*a*	57 (*R*)	2 (*R*)
9	(*S*)-**2**	Cl	*a*	26 (*R*)	2 (*R*)
10	(*S*)-**2**	PF_6	*a*	33 (*R*)	2 (*R*)
11	(*S*)-**2**	(*S*)-B(BN)$_2$[b]	*a*	13 (*R*)	
12	(*S*)-**2**	(*R*)-B(BN)$_2$[b]	*a*	12 (*R*)	

[a] Not reported. [b] BN is binolate.

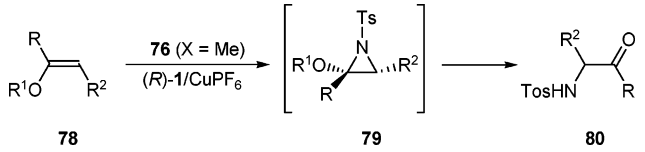
An interesting use of enantioselective aziridination to achieve chiral building blocks is the reaction of enol ethers and esters **78** with **76**, catalyzed by [(*R*)-**1**/$CuPF_6$] (Scheme 20).[114] The alkoxyaziridines **79** are unstable and spontaneously (or under mild hydrolysis) decompose to optically active α-amino ketones **80**. When **78** is a vinyl ether with R = Ph and R^2 = Me, the major product is (*S*)-**80**. When **78** is 1-acetoxy-1-phenylpropene, (*R*)-**80** is obtained with 52% ee (the best enantiomeric excess of the overall experiments), rationalized with a front-side attack of **78** on the coordinated nitrene, under conditions of minimized steric interactions.

Table 14. Asymmetric Aziridinations of Substituted Styrene (75, R = H) with 76: Effect of the Substituents

entry	Ar	X	box	$CuAn_n$	solvent	yield (%)	**77** ee (%) (conf.)	ref
1	Ph	Me	(*S*)-**2**	ClO_4	CH_2Cl_2	82	29 (*S*)	109
2	Ph	Me	(*S*)-**2**	ClO_4	C_6H_6	75	48 (*S*)[a]	109
3	Ph	NO_2	(*S*)-**2**	ClO_4	C_6H_6	94	75 (*S*)	109
4	Ph	Cl	(*S*)-**2**	ClO_4	C_6H_6	90	52 (*S*)	109
5	Ph	H	(*S*)-**2**	ClO_4	C_6H_6	82	50 (*S*)	109
6	Ph	*t*-Bu	(*S*)-**2**	ClO_4	C_6H_6	75	44 (*S*)	109
7	Ph	MeO	(*S*)-**2**	ClO_4	C_6H_6	55	33 (*S*)	109
8	*p*-FC_6H_4	NO_2	(*S*)-**2**	ClO_4	C_6H_6	95	72 (*S*)	109
9	*p*-$CF_3C_6H_4$	NO_2	(*S*)-**2**	ClO_4	C_6H_6	64	51 (*S*)	109
10	*p*-MeC_6H_4	NO_2	(*S*)-**2**	ClO_4	C_6H_6	78	45 (*S*)	109
11	*o*-ClC_6H_4	NO_2	(*S*)-**1**	$(OTf)_2$	MeCN	90	83 (*S*)	110
12	*m*-ClC_6H_4	NO_2	(*S*)-**1**	$(OTf)_2$	MeCN	89	72 (*S*)	110
13	*p*-ClC_6H_4	NO_2	(*S*)-**1**	$(OTf)_2$	MeCN	90	93 (*S*)	110
14	*o*-FC_6H_4	NO_2	(*S*)-**1**	$(OTf)_2$	MeCN	85	71 (*S*)	110
15	*m*-FC_6H_4	NO_2	(*S*)-**1**	$(OTf)_2$	MeCN	80	83 (*S*)	110
16	*p*-FC_6H_4	NO_2	(*S*)-**1**	$(OTf)_2$	MeCN	85	41 (*S*)	110
17	*m*-BrC_6H_4	NO_2	(*S*)-**1**	$(OTf)_2$	MeCN	79	83 (*S*)	110
18	*m*-MeC_6H_4	NO_2	(*S*)-**1**	$(OTf)_2$	MeCN	78	80 (*S*)	110
19	*m*-$NO_2C_6H_4$	NO_2	(*S*)-**1**	$(OTf)_2$	MeCN	48	68 (*S*)	110

[a] This result is in contrast with that in Table 13, entry 8.

Scheme 20

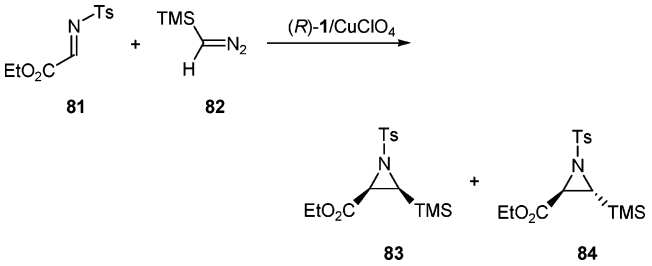


It should be taken into account that reactions listed under entries 11−19 in Table 14 have substituted benzaldehydes as side products and that the aziridination of styrene with [(*S*)-**1**/$Cu(OTf)_2$] may occur with an increase of enantioselectivity with the conversion due to further reactions of the product.[115]

A completely different approach to optically active aziridines can be realized with a chiral catalyst-mediated transfer of carbenes to imines. An early approach, catalyzing the reaction between *N*-arylidene anilines and ethyl diazoacetate **26** with [(*S*)-**1**/$CuPF_6$][116] or [(*R*)-**1**/$Zn(OTf)_2$],[117] gave a low yield (up to 37%) and interesting enantioselectivity (up to 67% ee), but the formation of significant amounts of 1,2-diarylpyrrolidine 2,3,4-triethylcarboxylate (derived from the incorporation of the carbene dimer diethyl fumarate) is a limit for the process. This type of aziridination reaction, but using

N-tosyl α-imino ester **81** and trimethylsilyl-diazomethane **82**, was investigated with [(*R*)-**1**/$CuClO_4$] as the catalyst (Scheme 21).[118] The yield was very low (28%) with a **83**/**84** ratio of

Scheme 21



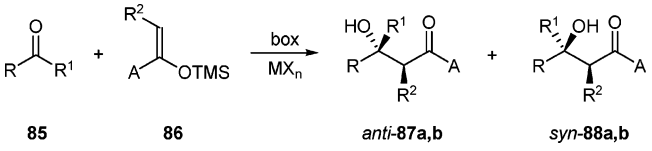
2:1, but promising enantioselectivities were obtained for both isomers (40% and 63% ee, respectively).

4.3. Aldol and Aldol-like Reactions

The aldol addition is one of the main topics of nearly each review dealing with asymmetric catalysis because it is one of the most popular reactions for the construction of C−C bonds and because nearly all chiral ligand families, and the optically active catalysts thereby derived, have been tested on this reaction that, together with the Diels−Alder reaction, can be considered a benchmark of the efficiency of a chiral catalyst.

One of the first tests of box catalysts was the Mukaiyama−aldol variant of the aldol reaction between aldehydes (**85a**,**b**, $R^1 = H$) or activated ketones (**85c**, $R^1 \neq H$) and silylketene acetals (**86**, Scheme 22), and two agile reviews divulgate

Scheme 22

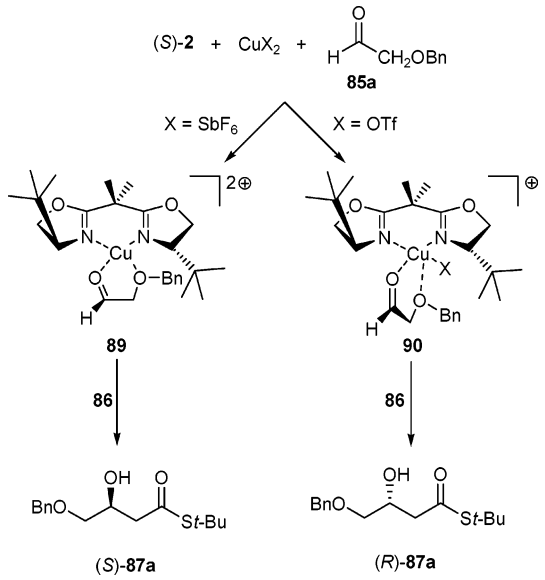


the early applications to the field.[4b,c] The pioneering work of Evans et al. on the use of box and pybox ligands for Mukaiyama−aldol reactions is a cornerstone for the application of these ligands.

In general, the carbonyl derivative **85** has R or R^1 with an atom or a group suitable to induce bidentate coordination to the chiral Lewis acid; hence (benzyloxy)acetaldehyde (**85a**, $R = CH_2OBn$, $R^1 = H$) and ethyl glyoxylate (**85b**, $R = CO_2Et$, $R^1 = H$) were the early aldehydes tested,[119,120] even if, later, the catalyst of choice for the former was found to have pybox as a ligand. Several silylketene acetals were tested in the reaction with aldehydes, and if **86** has $R^2 \neq H$, two products, *anti*-**87a** and *syn*-**88a** were obtained. The overall results with aldehydes are reported in Table 15.

Some significant results can be outlined. All box's tested have (*S*)-configuration, but the chiral information transferred to the adduct is dependent not only on the substituent but also on both cation (Lewis acid, Table 15, entry 1 vs 2) and counterion (Table 15, entry 3 vs 4). This last point is important, because the inversion of the configuration from the reaction in entry 3 to that in entry 4 can be rationalized as being due to a change of the coordination number in the reaction intermediate. If the anion SbF_6 is not involved as an auxiliary ligand, then a square-planar-like coordination is preferred leading to an attack to the Si face of **89**, and (*S*)-**87a** is the major enantiomer formed. However, if the OTf anion behaves as a ligand, a square-pyramidal coordination is favored, and the approach to the Re face of **90** leads to the opposite (*R*)-**87a** enantiomer (Scheme 23).[121]

Scheme 23



The reaction between ethyl glyoxylate **85b** and **86**, performed in CH_2Cl_2 (Table 15, entry 9), gives an excellent 91% ee of **87b**, but more interesting results are obtained with box (*S*)-**3d** as the chiral ligand and will be discussed in a later section.[122] It is notable that when benzaldehyde was reacted with **86** in H_2O (Table 15, entry 10)[123] the reaction is syn-selective, but enantioselectivity with (*S*)-**2** is much lower than that with other box systems.

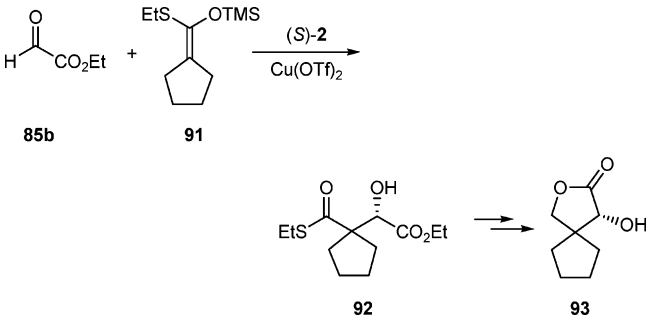
Table 15. Catalyzed Enantioselective Mukaiyama−Aldol Reactions between Aldehydes (85a,b, $R^1 = H$) and Trimethylsilylketene Acetals 86

entry	R	A	R^2	box	MX_n	solvent	yield (%)	anti/syn	**87** ee (%) (conf.)	**88** ee (%)	ref
1	CH_2OBn	S*t*-Bu	H	(*S*)-**1**	$Zn(SbF_6)_2$	CH_2Cl_2	*a*		85 (*S*)		120
2	CH_2OBn	S*t*-Bu	H	(*S*)-**1**	$Cu(OTf)_2$	CH_2Cl_2	*a*		9 (*R*)		121
3	CH_2OBn	S*t*-Bu	H	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	*a*		91 (*R*)		119−121
4	CH_2OBn	S*t*-Bu	H	(*S*)-**2**	$Cu(SbF_6)_2$	CH_2Cl_2	*a*		≤64 (*S*)		121
5	CH_2OBn	OEt	H	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	*a*		50 (*R*)		121
6	CH_2OBn	Me	H	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	*a*		38 (*R*)		121
7	CH_2OBn	Ph	H	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	*a*		51 (*R*)		121
8	CH_2OBn	S*t*-Bu	Me	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	50	81:19	84 (*R*,*S*)	*a*	121
9	CO_2Et	SPh	H	(*S*)-**1**	$Sn(OTf)_2$	CH_2Cl_2	*a*		91 (*S*)		122
10	Ph	Ph	Me	(*S*)-**2**	$Cu(OTf)_2$	H_2O	92	10:90	*a*	15	123

[a] Not reported.

These reactions with aldehydes have interesting applications in the synthesis of two natural products. The Mukaiyama−aldol reaction between ethyl glyoxylate **85b** and silylketene acetal **91** can be catalyzed by [(*S*)-**2**/Cu(OTf)$_2$] to give (*S*)-**92** in 61% yield and 98% ee, which can be easily converted into optically active pantolactone derivative **93** (Scheme 24).[124]

Scheme 24

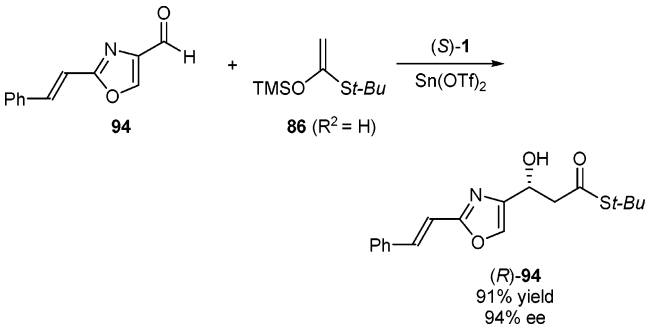


85b **91** **92** **93**

Phorboxazole B is a marine product having a complex macrolactone (C_1−C_{24}) and lactol (C_{33}−C_{37}) ring system, whose total synthesis involved a sequence of aldol- and enolate-bond constructions.[125] The construction of the C_{15}-stereocenter was realized with a [(*S*)-**1**/Sn(OTf)$_2$]-catalyzed Mukaiyama−aldol reaction between aldehyde **94** (that took advantage of the oxazole ring to become part of the final product) and **86** that gave (*R*)-**95** in 91% yield and 94% ee (Scheme 25).

α-Ketoesters **85c** ($R^1 \neq H$) are the second important class of reagents widely submitted to the Mukaiyama−aldol reaction with silylketene acetals **86**, and the reason for this choice is because some of them are commercial products (even if in solutions), but mainly because box, from the early papers,[126,127] proved to be the best ligand for this reaction, with a high yield of adducts and excellent enantioselectivities

Scheme 25



94 **86** (R^2 = H)

of the products. The overall results with α-ketoesters are reported in Table 16.

The results in Table 16 show that the Mukaiyama−aldol reaction was explored in detail: substrate, reagent, ligand, and solvent. With regard to the solvents, it appears that with the exception of $MeNO_2$ and MeCN all other seven solvents gave enantioselectivities >90%, and taking into account yields, tetrahydrofuran (THF), Et_2O, and CH_2Cl_2 can be classified as the best solvents for the reaction between methyl pyruvate and 1-*tert*-butylthio-1-trimethylsyliloxyethene (entries 2 and 4−11). Different ester groups were tested (entries 12−16), some homologous of pyruvic acid, and it was observed that only the isopropyl group in entry 16 lowers the enantioselectivity. A wide choice of silylketene acetals was also tested (changing substituents (at the either α- or *β*-position) and also the double bond configuration), and excellent results were always obtained (entries 17−25), which is a clear sign of the flexibility of the reaction.

All reactions with [(*S*)-**2**/Cu(OTf)$_2$] are (*S*)-enantioselective and, when possible, syn-selective. The X-ray structure of the [(*S*)-**2**−Cu(II)] complex in Figure 4 shows a distorted square-planar geometry, and PM3 semiempirical calculations support this structure when dimethyl pyruvate coordinates at Cu(II) to give the reacting complex **96**.[127] A simple inspection of

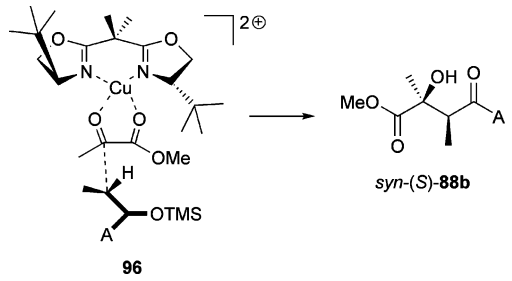
Table 16. Catalyzed Asymmetric Mukaiyama−Aldol Reactions between α-Ketoesters 85c ($R^1 \neq H$) and Trimethylsilylketene Acetals 86

	85c		**86**						yield		**88b** ee (%)	
entry	R	R^1	R^2	A	conf.	box	MX_n	solvent	(%)	syn/anti	(conf.)	ref
1	CO_2Me	Me	H	S*t*-Bu		(*S*)-**1**	Cu(OTf)$_2$	CH_2Cl_2	73		43(*S*)	17, 127
2	CO_2Me	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	CH_2Cl_2	96		99(*S*)	17, 126, 127
3	CO_2Me	Me	H	S*t*-Bu		(*S*)-**2**	Cu(SbF$_6$)$_2$	CH_2Cl_2	*a*		75(*S*)	127
4	CO_2Me	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	Et_2O	94		99 (*S*)	127
5	CO_2Me	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	THF	95		99 (*S*)	127
6	CO_2Me	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	$PhCH_3$	91		96 (*S*)	127
7	CO_2Me	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	hexane	42		96 (*S*)	127
8	CO_2Me	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	$PhCF_3$	88		95 (*S*)	127
9	CO_2Me	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	dioxane	84		92 (*S*)	127
10	CO_2Me	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	$MeNO_2$	95		75 (*S*)	127
11	CO_2Me	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	MeCN	*a*		23 (*S*)	127
12	CO_2Bn	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	THF	95		99 (*S*)	126, 127
13	CO_2t-Bu	Me	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	THF	91		99 (*S*)	126, 127
14	CO_2Me	Et	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	THF	84		94 (*S*)	126, 127
15	CO_2Me	*i*-Bu	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	THF	94		94 (*S*)	126, 127
16	CO_2Et	*i*-Pr	H	S*t*-Bu		(*S*)-**2**	Cu(OTf)$_2$	THF	84		36 (*R*)	126, 127
17	CO_2Me	Me	H	EtS		(*S*)-**2**	Cu(OTf)$_2$	THF	97		97 (*S*)	127
18	CO_2Me	Me	H	Ph		(*S*)-**2**	Cu(OTf)$_2$	THF	77		99 (*S*)	127
19	CO_2Me	Me	H	Me		(*S*)-**2**	Cu(OTf)$_2$	THF	76		93 (*S*)	127
20	CO_2Me	Me	Me	S*t*-Bu	(*Z*)	(*S*)-**2**	Cu(OTf)$_2$	CH_2Cl_2	96	94:6	96 (*S*)	127
21	CO_2Me	Me	Me	S*t*-Bu	(*E*)	(*S*)-**2**	Cu(OTf)$_2$	CH_2Cl_2	90	95:5	98 (*S*)	127
22	CO_2Me	Me	Me	SEt	(*Z*)	(*S*)-**2**	Cu(OTf)$_2$	CH_2Cl_2	95	90:10	95 (*S*)	127
23	CO_2Me	Me	Me	SEt	(*E*)	(*S*)-**2**	Cu(OTf)$_2$	CH_2Cl_2	78	98:2	98 (*S*)	127
24	CO_2Me	Me	*i*-Pr	SEt	(*Z*)	(*S*)-**2**	Cu(OTf)$_2$	CH_2Cl_2	80	90:10	99 (*S*)	127
25	CO_2Me	Me	*i*-Bu	SEt	(*Z*)	(*S*)-**2**	Cu(OTf)$_2$	CH_2Cl_2	88	90:10	93 (*S*)	127
26	CO_2Et	Me	*i*-Bu	SEt	(*Z*)	(*S*)-**2**	Cu(OTf)$_2$	THF	85	90:10	>91 (*S*)	128

[a] Not reported.

this model shows the Re face of the coordinated ketone shielded by a *tert*-butyl group; hence (*S*)-products are easily predicted (Scheme 26). Furthermore, the attack on the

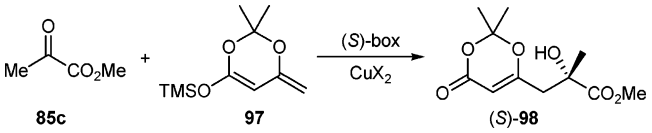
Scheme 26



carbonyl group is favored with the β-alkyl group gauche to the methyl of pyruvic acid to minimize destabilizing interactions; hence the preferred product is *syn*-(*S*)-**88b**.

Methyl pyruvate **85c** may undergo the Mukaiyama−aldol reaction with silylketene acetal **97** to give dioxenone (*S*)-**98** (Scheme 27), a polyfunctionalyzed building block useful for

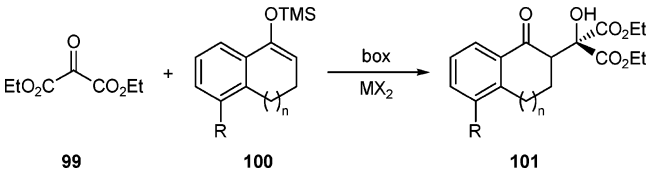
Scheme 27



further transformations. The chiral ligand (*S*)-**2** is much better than the corresponding **1** (but less efficient than **3a,d**), and (rather unusually) the Cl counterion is much better than OTf (91% ee vs 74% ee).[17,24]

Among activated ketones, a specific position can be assigned to diethyl ketomalonate **99**, whose reaction with several silylketene acetals can be catalyzed by box-based complexes with different ligands, cations, and counterions and in different solvents.[129] Adducts **101** are obtained in high yields and excellent enantioselectivties when trimethylsilylketene acetals **100** have a cyclic aromatic structure (Scheme 28, Table 17). Some points deserve attention: The

Scheme 28



double bond in the five-membered ring reduces the enantioselectivity compared to those of six- and seven-membered rings (Table 17, entries 11 and 12), (*R*)-**1** is much better than *t*-Bu-box (Table 17, entry 1 vs 6), $Cu(OTf)_2$ is better than $Cu(SbF_6)_2$ (Table 17, entry 7 vs 8), and furthermore, Zn(II) can be used as the Lewis acid, but the enantiomeric excess is lowered (Table 17, entries 2, 9, and 11). Among other silylketene acetals tested, only (*Z*)-1-phenyl-1-trimethylsilyloxypropene gives 90% ee.

As an alternative to the Mukaiyama−aldol variant, the classic protocol of the aldol reaction assumes the generation of an enolate, coordinated through a Lewis acid to the chiral ligand, which is involved in a catalytic enantioselective addition to the electrophilic center of a carbonyl group.

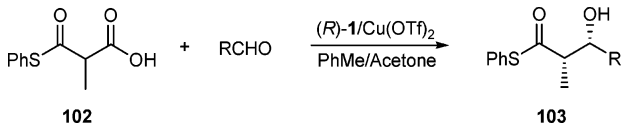
An example of a catalytic enantioselective aldol reaction has methyl malonic acid half thioester **102** as the enolate

Table 17. Catalyzed Enantioselective Mukaiyama−Aldol Reactions between Ketomalonate 99 and Cyclic Trimethylsilylketene Acetals 100[129]

entry	*n*	R	box	MX_2	solvent	*T* (°C)	yield (%)	ee (%)
1	2	H	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	rt	87	1
2	2	H	(*R*)-**1**	$Zn(OTf)_2$	CH_2Cl_2	rt	65	43
3	2	H	(*R*)-**1**	$Cu(OTf)_2$	Et_2O	−78	88	93
4	2	H	(*R*)-**1**	$Cu(OTf)_2$	Et_2O	−10	81	86
5	2	H	(*R*)-**1**	$Cu(OTf)_2$	*t*-BuOMe	−10	77	83
6	2	H	(*R*)-**1**	$Cu(OTf)_2$	CH_2Cl_2	−10	80	78
7	2	H	(*R*)-**1**	$Cu(SbF_6)_2$	CH_2Cl_2	−10	89	37
8	2	H	(*R*)-**1**	$Cu(OTf)_2$	THF	rt	81	71
9	1	H	(*R*)-**1**	$Zn(OTf)_2$	Et_2O	−10	81	77
10	1	H	(*R*)-**1**	$Cu(OTf)_2$	Et_2O	−78	91	86
11	0	H	(*R*)-**1**	$Zn(OTf)_2$	Et_2O	−10	91	45
12	0	H	(*R*)-**1**	$Cu(OTf)_2$	Et_2O	−78	82	58
13	1	OMe	(*R*)-**1**	$Cu(OTf)_2$	Et_2O	−78	90	85

source, which undergoes decarboxylative addition at ambient temperature with a variety of aldehydes catalyzed by [(*R*)-**1**/$Cu(OTf)_2$] to afford *syn*-3-hydroxy-2-methylthiopropionic acid (*S*)-phenyl esters **103** (Scheme 29).[130] Yields are

Scheme 29



in general very good, and enantioselectivity is always excellent (in the range of 89−96% ee), but the syn/anti diastereoselectivity is less satisfactory, since it is seldom >9:1. The absolute configuration of **103** for R = CH_2CH_2Ph was determined to be (2*S*,3*R*).

α-Ketoesters may be both the source of the enolate (usually in the presence of an amine) and the electrophile. The cross-aldol reaction occurs when one of the ketoesters has an activated carbonyl and it cannot give the enolate (e.g., **105**), while the precursor of the enolate **104** has at least one hydrogen atom in the α-position to the carbonyl group (Scheme 30). When R = H, two enantiomers are obtained; if R ≠ H, two diastereoisomers **106a**,**b**, each being a couple of enantiomers, are formed that can be converted to isotetronic derivative **107**.[131] Table 18 reports the results.

Among the cross-aldol reactions, that between ethyl pyruvate and ethyl trifluoropyruvate, catalyzed by [(*S*)-**2**/$Cu(OTf)_2$] (Table 18, entries 1−4), gives low enantiomeric excess independently of the presence and the type of base. Better results in terms of enantioselectivity (up to 96% ee) are obtained with ethyl α-ketobutyrate and its homologues (Table 18, entries 5−12), but the limitation of the reaction is the scarce diastereoselectivity achieved.

An interesting variant is the homo-aldol reaction of ethyl pyruvate, where both the enolate and the electrophile derive from the same source.[131] In Et_2O as the solvent, the optimized conditions for box, cation, and counterion are those reported in Table 18 (entries 13−19), and a crucial factor with [(*S*)-**2**/$Cu(OTf)_2$] as the catalyst becomes the choice of the amine, since *N*,*N*-dimethylaniline (DMA) and *N*,*N*-dibenzylaniline (DBA) give the analogous of (*S*)-**107** (with a methyl group instead of CF_3) in 96% and 93% ee, respectively, while the presence of cyclohexyldimethylamine ($CyNMe_2$) and several other amine bases do not exceed the enantioselectivity obtained without base (Table 18, entry 13 vs 19). The reaction was studied in detail in different solvents. The most

Scheme 30

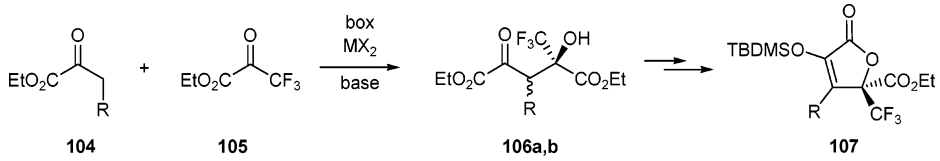


Table 18. Catalyzed Enantioselective Cross-Aldol Reactions between 104 and 105 and Homo-Aldol Reactions of 85c

entry	R	electrophile	amine[a]	box	MX_n	solvent	conv. (%)	dr[b]	ee (%) (conf.)	ref
1	H	**105**		(*S*)-**2**	$Cu(OTf)_2$	Et_2O	40		47	131a
2	H	**105**	DMT	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	40		39	131a
3	H	**105**	DBT	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	40		39	131a
4	H	**105**	$CyNMe_2$	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	40		42	131a
5	Me	**105**		(*S*)-**2**	$Cu(OTf)_2$	Et_2O	>80	45:55	70/93	131a
6	Me	**105**	DMT	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	>80	58:42	82/95	131a
7	Me	**105**	DBT	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	>80	43:57	69/96	131a
8	Me	**105**	$CyNMe_2$	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	>80	52:48	81/93	131a
9	CH_2Cy	**105**	DMT	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	32[c]	45:55	68/84	131a
10	$CH_2CH_2CH{=}CH_2$	**105**	DMT	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	52[c]	42:58	85/96	131a
11	*n*-C_5H_{11}	**105**	DMT	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	28[c]	45:55	92/91	131a
12	*i*-Bu	**105**	DMT	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	66[c]	45:55	62/75	131a
13[d]	H	**85c**		(*S*)-**2**	$Cu(OTf)_2$	Et_2O	>80		65 (*S*)[e]	131a,b
14[d]	H	**85c**		(*S*)-**2**	$Cu(SbF_6)_2$	Et_2O	~80		50 (*S*)[e]	131a,b
15[d]	H	**85c**	DMA	(*S*)-**2**	$Zn(OTf)_2$	Et_2O	>80		16 (*R*)[e]	131b
16[d]	H	**85c**	DMA	(*R*)-**1**	$Cu(OTf)_2$	Et_2O	>80		28 (*R*)[e]	131b
17[d]	H	**85c**	DMA	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	>80		96 (*S*)[e]	131a,b
18[d]	H	**85c**	DBA	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	>80		93 (*S*)[e]	131a
19[d]	H	**85c**	$CyNMe_2$	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	>80		50 (*S*)[e]	131a
20[d]	H	**85c**	DMA	(*S*)-**2**	$Cu(OTf)_2$	toluene	~80		62 (*S*)[e]	131a
21[d]	H	**85c**	DMA	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	~80		21 (*R*)[e]	131a
22[d]	H	**85c**	DMA	(*S*)-**2**	$Cu(SbF_6)_2$	CH_2Cl_2	>80		63 (*R*)[e]	131a
23[d]	H	**85c**	DBA	(*S*)-**2**	$Cu(SbF_6)_2$	CH_2Cl_2	>80		75 (*R*)[e]	131a
24[d]	H	**85c**	$CyNMe_2$	(*S*)-**2**	$Cu(SbF_6)_2$	CH_2Cl_2	>80		77 (*R*)[e]	131a,b

[a] DMT is *N*,*N*-dimethyl-*p*-toluidine; DET is *N*,*N*-dibenzyl-*p*-toluidine; $CyNMe_2$ is cyclohexyldimethylamine; DMA is *N*,*N*-dimethylaniline; DBA is *N*,*N*-dibenzylaniline. [b] Diastereomeric ratio. [c] Isolated yield of corresponding isotetronic acid derivative **107**. [d] Dimerization reaction of **85c**. [e] Enantiomeric excess of the corresponding isotetronic acid derivative **107**.

significant feature, when the catalyst is [(*S*)-**2**/$Cu(SbF_6)_2$], is the strong inversion of the enantioselectivity in CH_2Cl_2 and the reduced importance of the amine (Table 18, entries 22−24).

The important target of a catalyzed aldol reaction is to control diastereo- and enantioselectivity at the same time during the process. The rigid structure of the reacting intermediate, when the reagent coordinates in a bidentate fashion, may help to reach this result. Complex [(*S*)-**2**/$Ni(OTf)_2$] was found to be the best catalyst for the addition of 3-propionoyl-2-thiazolidinethione (**108**) to various aldehydes (Table 19),[66] with 2,6-lutidine as the base suitable to generate the bichelated enolate bound in the reacting intermediate **109**. If the coordination around the nickel center is tetrahedral, similar to that of the X-ray structure reported in Table 2 (entry 24), then the aldehyde addition occurs at the Re face, *syn*-**110** is the main diastereoisomer (Scheme 31), and the silylation and decomplexation of the coordinated product gives substituted (2*R*,3*R*)-3-hydroxy-2-methyl-1-[2-thioxo-(1,3-thiazolidin-3-yl)]propan-1-ones (**110**) with excellent diastereomeric ratios and enantioselectivity (Table 19).

Table 19. Enantioselective Aldol Additions of 108 to Various Aldehydes[66]

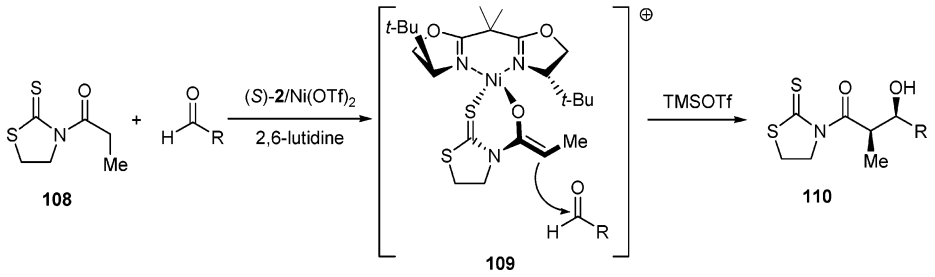
entry	R	box	syn/anti	(*R*,*R*)-**110** ee (%)
1[a]	Ph	(*S*)-**1**	70:30	60
2	Ph	(*S*)-**2**	94:6	97
3	*p*-MeC_6H_4	(*S*)-**2**	93:7	95
4	*p*-ClC_6H_4	(*S*)-**2**	90:10	91
5	1-naphthyl	(*S*)-**2**	93:7	92
6	2-naphthyl	(*S*)-**2**	92:8	93
7	2-furyl	(*S*)-**2**	88:12	95
8	Me−CH=CH	(*S*)-**2**	93:7	97
9	Ph−CH=CH	(*S*)-**2**	88:12	93
10	Me	(*S*)-**2**	97:3	93
11	Et	(*S*)-**2**	97:3	90
12	*i*-Pr	(*S*)-**2**	98:2	90

[a] Reaction catalyzed by $Ni(SbF_6)_2$.

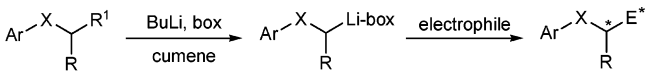
The Toru group studied in detail the formation of α-thio- and α-seleno-carbanions (**112a**,**b)** from derivatives of phenyl or 2-pyridyl sulfide or selenide (**111a**,**b**), (eventually α-selenyl- or α-stannyl-substituted) with BuLi, in the presence of box, and their enantioselective reaction with aldehydes or ketones acting as electrophiles to give products **113a**,**b** (Scheme 32).[132−137]

It is necessary to point out that **1** and **2** are not always the best box ligands, probably because this reaction has an intrinsic diversity with the majority of the catalyses reported in this review. BuLi acts as a base in the generation of the carbanion, and its lithium cation behaves as a Lewis acid that coordinates the carbanion with the chiral ligand, inducing enantioselectivity, and this small, hard cation seldom prefers **3c** (and not the more sterically demanding **2**) in the construction of the reacting intermediate of the catalytic cycle.[133] Among the different reactions reported in Table 20, α-thio-carbanions **112a** give better enantioselectivity if the attached group is 2-pyridyl (entries 2, 3, and 7−11 vs 1, 5, and 6), then there is not a net choice between box **1** and **2**, and the reaction is anti-diastereoselective (Table 20, entries 12−14).[133−135] The reaction can be run with α-lithiated allyl

Scheme 31



Scheme 32



111a: X = S
111b: X = Se

112a,b **113a,b**

aryl sulfides: Enantioselectivity is reasonable, and chemoselectivity unsatisfactory.[137]

Outstanding behaviors of these reagents can be observed in the enantioselective reaction of α-lithio-benzyl-2-pyridyl selenide **112b** (Ar = 2-pyridyl, R = Ph), which gives products with an absolute configuration of the chiral center opposite to that obtained in the reaction of α-lithio-benzyl phenyl selenide **112b** (Ar = R = Ph) (Table 20, entries 15 and 16 vs 18 and 19).[136] Furthermore, the reaction of this last anion with cyclohexanone (Table 20, entry 17) is highly enantioselective. If the same reaction is performed with 4-methyl and 4-*tert*-butyl cyclohexanones, then the excellent enantiomeric excess of both cis and trans diastereoisomers allows the stereospecific elimination of PhSeOH (methanesulfonyl chloride and Et_3N) and the formation of axially chiral benzylidenecyclohexanones with 90% ee.[138a]

The recent extension to *cis*-bicyclo[3.3.0]octane-3,7-dione monoethylene ketals **114** as electrophiles is the development of the reaction with cyclohexanones. The aldol reaction is strongly endo-selective and (*S*)-**115a**,**b** are the products, frequently with a diastereomeric ratio >98:2 and enantioselectivities >90% ee (Scheme 33).[138b] Whereas the different substituents of **114** do not have a strong influence on selectivity, box **2** is by far a ligand better than **1** (Table 21, entry 1 vs 2−7).

The lithiated α-thio-carbanion may derive from *N*-Boc-thiazolidine **116** (Scheme 34), and the enantioselectivity of the reaction with benzophenone depends on box: (*S*)-**1** gives (*R*)-**117** (illustrated in the scheme) in 82% ee, whereas (*S*)-**2** gives its (*S*)-enantiomer in 68% ee.[139]

The addition reaction between carbonyl compounds and nitroalkanes to yield nitro alcohols, in the presence of a base that deprotonates nitroalkanes to nitronates, is known as the Henry reaction, and a recent highlight focused on its asymmetric version.[140] The first test of the capacity of box to be a ligand for useful catalysts in the field was the reaction between α-ketoesters **85c** and $MeNO_2$ (Scheme 35).[141,142] The optimization of the box ((*S*)-**2**), cation (Cu(II), because Zn(II) gives unsatisfactory enantioselectivity of the (*S*)-enantiomer), counterion (OTf, even if SbF_6 gave quite comparable enantioselectivity), and base (Et_3N and *N*-methylmorpholine were by far the best deprotonating agents) led to the exploration in detail of a reaction whose product **118** gives easy access to β-amino-α-hydroxy esters **119**, which allow the assignment of the (*R*)-configuration to the chiral center.[142]

Some effects of the substituents R^1 reported in Table 22 can be pointed out: Unsaturation in the α,β-position reduces enantioselectivity (entry 9 vs 7 and 8), and both yield and enantioselectivity are lowered with the increase of the electron-donating character of the aryl group (entries 10−13).

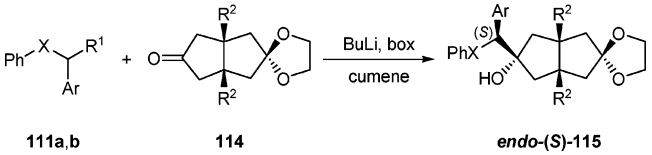
The absolute (*R*)-configuration, which was unambiguously demonstrated for **119** (R^1 = *p*-ClC_6H_4),[142] can be rationalized if both α-ketoester and $MeNO_2$ are coordinated to the copper cation in the equatorial position, while the ester carbonyl

Table 20. Enantioselective Additions of α-Sulfenyl and α-Selenyl Carbanions (112a,b) to Various Carbonylic Electrophiles

entry	Ar	X	R	R^1	box	electrophile	yield (%)	anti/syn	ee (%) (conf.)	ref
1	Ph	S	Ph	$SnBu_3$	(*S*)-**1**	Ph_2CO	60		66 (*S*)	132, 133
2	2-Pyr	S	Ph	H	(*S*)-**1**	Ph_2CO	49		51	133
3	2-Pyr	S	Ph	H	(*S*)-**2**	Ph_2CO	86		90 (*R*)	133
4	2-Quin	S	Ph	H	(*S*)-**2**	Ph_2CO	99		71 (*R*)	134
5	Ph	S	S-Ph	H	(*S*)-**1**	PhCHO	55		6	135
6	Ph	S	S-Ph	H	(*S*)-**2**	PhCHO	99		33	135
7	2-Pyr	S	S*t*-Bu	H	(*S*)-**1**	Ph_2CO	86		61	135
8	2-Pyr	S	S*t*-Bu	H	(*S*)-**2**	Ph_2CO	53		68	135
9	2-Pyr	S	S*i*-Pr	H	(*S*)-**1**	Ph_2CO	92		68	135
10	2-Pyr	S	S-Me	H	(*S*)-**1**	Ph_2CO	80		42	135
11	2-Pyr	S	S-Ph	H	(*S*)-**1**	Ph_2CO	75		18	135
12	2-Pyr	S	S*t*-Bu	H	(*R*)-**1**	PhCHO	91	83:17	85 (1*R*,2*S*)[a]	135
13	2-Pyr	S	S*t*-Bu	H	(*S*)-**1**	MesCHO	83	90:10	85 (1*R*,2*S*)[a]	135
14	2-Pyr	S	S*t*-Bu	H	(*S*)-**1**	2-NaphCHO	92	80:20	83 (1*R*,2*S*)[a]	135
15	Ph	Se	Ph	Se-Ph	(*S*)-**1**	Ph_2CO	62		81 (*S*)	136
16	Ph	Se	Ph	Se-Ph	(*S*)-**2**	Ph_2CO	78		78 (*S*)	136
17	Ph	Se	Ph	Se-Ph	(*S*)-**2**	cyclohexanone	83		95	136
18	2-Pyr	Se	Ph	Se-Ph	(*S*)-**1**	Ph_2CO	77		64 (*R*)	136
19	2-Pyr	Se	Ph	Se-Ph	(*S*)-**2**	Ph_2CO	73		77 (*R*)	136

[a] Enantiomeric excess of the anti product.

Scheme 33

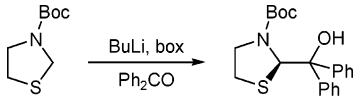


111a,b **114** ***endo*-(*S*)-115**

Table 21. Enantioselective Additions of α-Sulfenyl and α-Selenyl Carbanions from 111a,b to 114[138b]

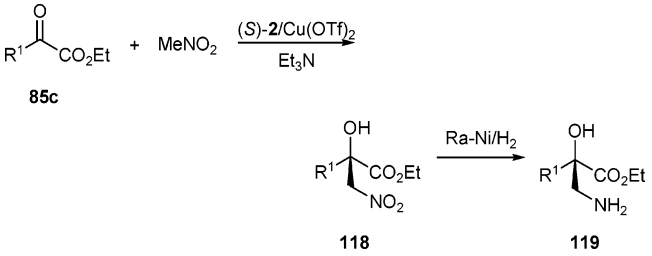
entry	X	R^1	Ar	R^2	box	yield (%)	anti/syn	ee (%) (endo) (conf.)	ee (%) (exo) (conf.)
1	S	$SnBu_3$	Ph	H	(*S*)-**1**	35	>98:2	72 (*S*)	
2	S	$SnBu_3$	Ph	H	(*S*)-**2**	80	>98:2	95 (*S*)	
3	S	$SnBu_3$	Ph	Me	(*S*)-**2**	97	86:14	92 (*S*)	90 (*S*)
4	Se	SePh	Ph	H	(*S*)-**2**	80	>98:2	92 (*S*)	
5	Se	SePh	Ph	Me	(*S*)-**2**	92	82:18	91 (*S*)	86 (*S*)
6	Se	SePh	*p*-Tol	H	(*S*)-**2**	79	>98:2	92 (*S*)	
7	Se	SePh	*p*-Tol	Me	(*S*)-**2**	60	>98:2	91 (*S*)	

Scheme 34



116 **117**

Scheme 35



85c **118** **119**

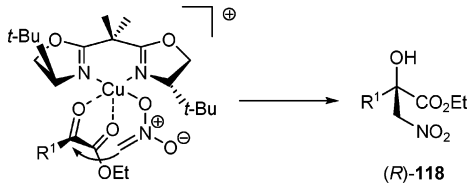
Table 22. Enantioselective Henry Reactions of α-Ketoesters 85c and $MeNO_2$, with Et_3N as the Base, Catalyzed by [(*S*)-2/$Cu(OTf)_2$]

entry	R^1	yield (%)	ee (%) (*R*)	ref
1	Me	>95	92	141, 142
2	Et	73	87	141, 142
3	$PhCH_2CH_2$	47	77	141, 142
4	*n*-hexyl	91	93	142
5	*i*-Bu	99	92	142
6	$Me_2CHCH_2CH_2$	90	94	142
7	CH_2═$CHCH_2CH_2$	97	94	142
8	MeCH═$CHCH_2CH_2$	92	94	142
9	MeCH═CH	>96	60	142
10	*p*-$MeOC_6H_4$	68	57	142
11	Ph	81	86	141, 142
12	*p*-ClC_6H_4	91	88	142
13	*p*-$NO_2C_6H_4$	99	93	141, 142

oxygen atom is coordinated in the axial position (Scheme 36). After deprotonation of $MeNO_2$ to the nitronate the square-pyramidal configuration of **120** allows the attack of the nucleophilic carbon atom of nitronate on the Re face of the keto group to give (*R*)-**118**.

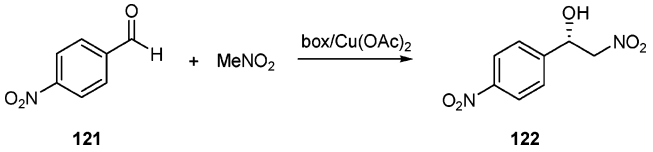
The Henry reaction was carried out with $MeNO_2$ and various aldehydes.[65] The best cationic source was $Cu(OAc)_2$ whereas both (*S*)-**1** and (*S*)-**2** gave unsatisfactory enantiomeric excesses of (*S*)-**122** (43% and 37%, respectively), the product of the reaction with *p*-nitrobenzaldehyde **121** (Scheme

Scheme 36



120 (*R*)-**118**

Scheme 37



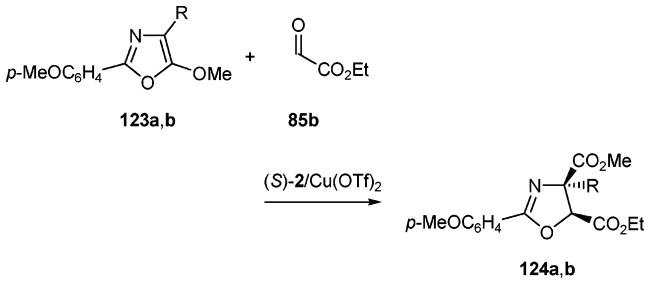
121 **122**

37). The box of choice for this reaction is (*R,S*)-**9a**, which gives excellent enantiomeric excesses of the products, but this will be discussed in the next section. We can anticipate that the reacting complex has a square-pyramidal configuration similar to that of **120**, with the oxygen atom of the aldehyde and nitronate both coordinated to Cu(II) together with an acetoxy group.

The Henry reaction can take place with a variant similar to the Mukaiyama−aldol reaction, with silyl nitronates instead of nitroalkanes. $Cu(OTf)_2$ is the best Lewis acid; however, (*S*)-**1** and (*S*)-**2** are not the best box's (with benzaldehyde 19% ee);[143] the reactions are threo-selective, and the good stereoselectivity obtained with a different box makes the reaction promising.

Ethyl glyoxylate **85b** (R^1 = CO_2Et) undergoes enantioselective aldol reaction with 5-alkoxyoxazoles **123a**,**b**, efficiently catalyzed by [(*S*)-**2**/$Cu(OTf)_2$·$(H_2O)_2$]. Assuming as a reacting model the analogue of **96** represented in Scheme 26, the electrophilic 4-position of **123** attacks the Si face of the Lewis-acid-coordinated glyoxylate to give (4*R*,5*S*)-**124a**,**b** (Scheme 38) with excellent yields, diastereoselectivities, and

Scheme 38



123a,**b** **85b** **124a**,**b**

enantioselectivities (**a** (R = H), >99%, cis/trans 95:5, 97% ee (cis); **b** (R = Me), 94%, cis/trans 94:6, 99% ee (cis).[144]

The oxazole fragment −O−C_5(═C_4)−OMe has several analogies with ketene diethylacetal **125**; hence its aldol reaction with either α-ketoesters or α-diketones **85c**,**d** is not unexpected, but the ratio (2:1) of the reactants affording **126** and their hydrolysis to optically active unsaturated lactones **127** makes the reaction both synthetically and mechanistically attractive (Scheme 39).[145] Sometimes the monoaddition product of ethyl benzoylformate **85c** (R^1 = Ph, R = OEt) (2-hydroxy-2-phenylsuccinic acid) is the side product of the reaction (6−30% yield, up to 99% ee), but its known absolute (*R*)-configuration again allows the assumption of **96** as the reaction model, with the attack of the ketene acetal to the Si face of the bound α-ketoesters. The reaction, when optimized

Scheme 39

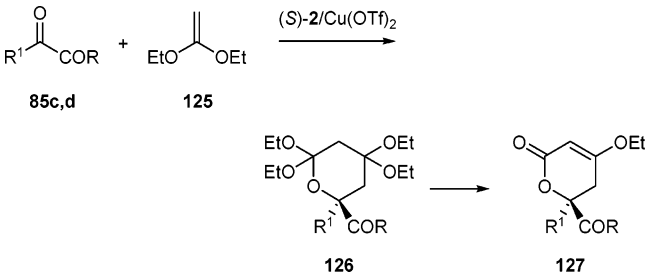


Table 23. Enantioselective Aldol Additions of 85c,d to Ketene Diethylacetal 125[145]

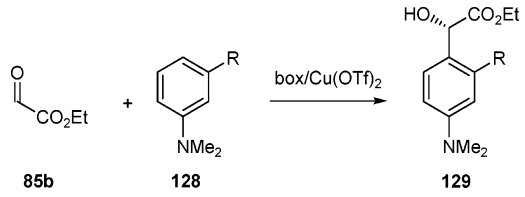
entry	R^1	R	box	CuX_2	solvent	yield (%)	(*R*)-**126** ee (%)
1	Ph	OEt	(*S*)-**2**	OTf	Et_2O	80[a]	93
2	Ph	OEt	(*S*)-**2**	SbF_6	CH_2Cl_2	<20	*b*
3	Ph	OEt	(*S*)-**2**	OTf	THF	61[a]	77
4	Ph	OEt	(*R*)-**1**	OTf	Et_2O	79[a]	12
5	Me	OMe	(*S*)-**2**	OTf	Et_2O	74	83
6	Et	OMe	(*S*)-**2**	OTf	Et_2O	70	77
7	*i*-Pr	OEt	(*S*)-**2**	OTf	Et_2O	58	80
8	Me	Me	(*S*)-**2**	OTf	Et_2O	71	95
9	Me	Et	(*S*)-**2**	OTf	Et_2O	70	90
10	Me	Ph	(*S*)-**2**	OTf	Et_2O	58	90

[a] 2-Hydroxy-2-phenylsuccinic acid as a side product (6−14% yield). [b] Not determined.

with [(*S*)-**2**/Cu(OTf)$_2$] and Et_2O as the solvent (Table 23, entries 1−4), is flexible and can be performed with different α-ketoesters **85c** (Table 23, entries 1 and 5−7) and α-diketones **85d** (Table 23, entries 8−10).

When the nucleophile is an aromatic or a heterocyclic compound, the addition to the activated carbonyl group of ethyl glyoxylate (**85b**, R = CO_2Et, R^1 = H) can be considered as an enantioselective Friedel−Crafts reaction. Obviously, the aromatic ring must be activated for the electrophilic substitution by suitable substituents (e.g., *N*,*N*-dimethylaniline and its substituted derivatives **128**), and the products **129** (Scheme 40) are obtained in very good yields

Scheme 40



and excellent enantioselectivities only with Cu(OTf)$_2$ and the solvents reported in Table 23.[146,147] Three points deserve attention: A sharp regioselectivity, dictated by dimethylamino group, is always observed, box (*S*)-**2** gives better enantioselectivity than (*R*)-**1** (Table 24, entries 1−3 vs 4−6), and both catalysts derived from (*R*)-**1** and (*S*)-**2** give (*S*)-**129** (R = H).

The reaction can be performed with *N*,*N*-(dimethylamino)-1-naphthalene, *N*,*N*-(dimethylamino)-1-anthracene, and several heterocycles, *N*-methylindoline, *N*-methyl-tetrahydroquinoline, julolidine, and 2-methyl- or 2-TMS-furan; the best enantioselectivities are obtained with the first two heterocycles (83% and 93% ee, respectively), with regioselectivity in the carbocyclic ring recalling that of *N*,*N*-dimethylaniline.[146]

Table 24. Enantioselective Friedel−Crafts Reactions of Ethyl Glyoxylate 85b with *N*,*N*-Dimethylanilines 128[146]

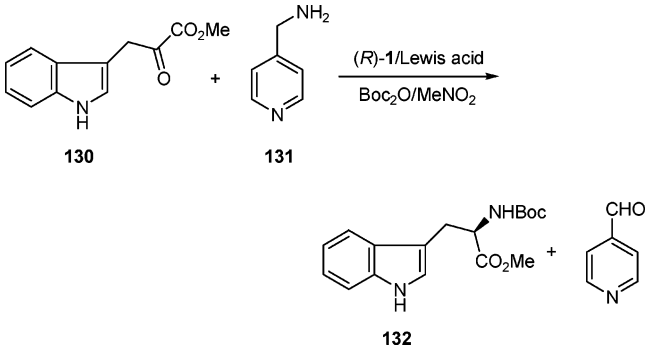
entry	R	box	solvent	yield (%)	ee (%) (conf.)
1	H	(*R*)-**1**	CH_2Cl_2	70	54 (*S*)
2	H	(*R*)-**1**	Et_2O	76	42 (*S*)
3	H	(*R*)-**1**	THF	81	22 (*S*)
4	H	(*S*)-**2**	CH_2Cl_2	81	80 (*S*)
5	H	(*S*)-**2**	Et_2O	78	89 (*S*)
6	H	(*S*)-**2**	THF	72	90 (*S*)
7	F	(*S*)-**2**	THF	58 (80)[a]	81 (85)[a]
8	Cl	(*S*)-**2**	THF	41 (84)[a]	95 (93)[a]
9	Br	(*S*)-**2**	THF	36 (68)[a]	89 (88)[a]
10	Me	(*S*)-**2**	THF	76 (77)[a]	92 (80)[a]
11	OMe	(*S*)-**2**	THF	19 (21)[a]	86 (77)[a]

[a] Yields and enantiomeric excesses in CH_2Cl_2.

The general synthesis of enantiomerically enriched amines and amino acids in organic chemistry through a catalytic process has attracted the interest of several groups, many strategies have been followed, and at least two deserve attention in this review: the amination of activated carbonyls and the addition of nucleophiles to imines.

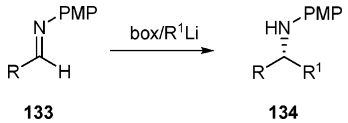
The enantioselective transamination of an α-ketoester is a suggestive strategy, for its analogy to the well-known enzymatic reaction, whose potentiality has not yet been fully disclosed. The reaction of ethyl pyruvate and pyridoxamine, catalyzed by [(*S*)-**1**/Zn(OTf)$_2$], gives 66% yield of Boc-protected alaninate whose enantiomeric excess cannot not be determined for technical reasons. Changing to methyl 3-indole pyruvate **130** and 4-picolylamine **131**, the reaction, catalyzed by both Zn(OTf)$_2$ or $CuPF_6$ complexes of (*R*)-**1** (Scheme 41), affords **132** in moderate yield and low enantioselectivity (20% ee).[148]

Scheme 41



Within the additions of organometallic reagents to imines, the effect of the box structure in the asymmetric addition of MeLi was studied in detail, taking (*S*)-**2** as a reference; for this reason the results of the addition of organolithium to **133** to give amine **134** (Scheme 42 and Table 25) are

Scheme 42



considered in this section,[14,149] whereas the comparison with other box ligands will be considered elsewhere.

The strictly analogous enantioselective addition of *i*-BuLi to the aldimine derived from methylamine and 1-(4-chlorophenyl)cyclobutanecarboxaldehyde is the key step in the

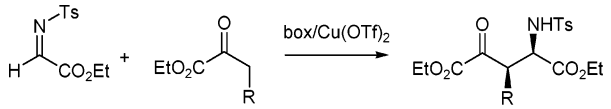
Table 25. Asymmetric Additions of Organolithiums to Imine 133

entry	R	R^1	box	solvent	yield (%)	ee (%) (conf.)	ref
1	Ph	Me	(*S*)-**2**	toluene	90	67 (*R*)	14
2	Ph	Me	(*S*)-**1**	toluene	93	44 (*R*)	149
3	(*E*)-PhCH=CH	Me	(*S*)-**2**	toluene	73	94 (*R*)	14
4	$PhCH_2CH_2$	Me	(*S*)-**2**	toluene	81	93 (*R*)	14
5	Ph	*n*-Bu	(*S*)-**2**	toluene	96	29 (*R*)	149
6	Ph	*n*-Bu	(*S*)-**1**	toluene	74	3 (*R*)	149

asymmetric synthesis of (*R*)-desmethylsibutramine, a pharmacologically active metabolite of the antiobesity drug sibutramine. It is important to notice as reported in Table 25 (entries 1 and 5 vs 2 and 6) that (*S*)-**2** gave an excellent yield of amine in a satisfactory enantioselectivity (95% yield and 40% ee), while (*S*)-**1** does not catalyze the reaction.[150] An attempt to use Et_2Zn instead of organolithium was disappointing.[151]

The best strategy to substituted α-aminoesters is the Mannich reaction by which the α-iminoester **135** reacts with enol nucleophiles derived from α-ketoesters **104** (Scheme 43) to give **136** with excellent syn-diastereo- and enantioselectivity (Table 26).[152a]

Scheme 43



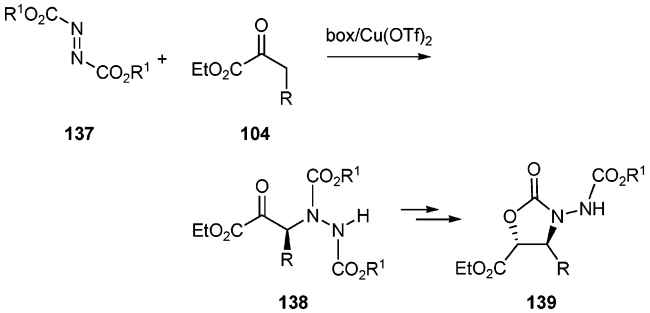
135 **104** **136**

Table 26. Catalytic Diastereo- and Enantioselective Mannich Reactions between α-Ketoesters 104 and *N*-Tosyl-α-Iminoester 135[152a]

entry	R	box	solvent	yield (%)	syn/anti	syn ee (%) (conf.)	anti ee (%)
1	H	(*S*)-**2**	CH_2Cl_2	76		33 (*R*)	
2	H	(*R*)-**1**	CH_2Cl_2	70		89 (*R*)	
3	H	(*R*)-**1**	THF	45		76 (*R*)	
4	H	(*R*)-**1**	Et_2O	<5			
5	Me	(*R*)-**1**	CH_2Cl_2	89	>98:2	>98 (*R*)	>90
6	Bn	(*R*)-**1**	CH_2Cl_2	94	>98:2	97 (*R*)	
7	Br	(*R*)-**1**	CH_2Cl_2	79	75:25	78	

The [box/Cu(II)] complexes have the specific properties first to promote the keto to enol tautomerization of the β-ketoester, then to catalyze the diastereo- and enantioselective C−C bond formation. This methodology has been extended to the reaction of α-ketoesters **104** with azodicarboxylic esters **137** with formation of a C−N bond, which is the core of product **138** (Scheme 44).[152b] The acidity of the proton next to keto group makes this product unstable; therefore, a stereoselective reduction with L-Selectride,

Scheme 44



137 **104** **138** **139**

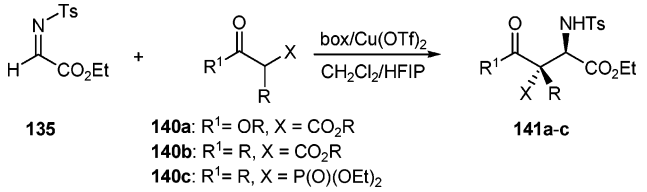
Table 27. Catalytic Asymmetric Mannich Reactions between α-Ketoesters 104 and Azodicarboxylic Esters 137[152b]

entry	R	R^1	box	solvent	yield (%)	ee (%) (conf.)
1	Bn	Bn	(*S*)-**2**	THF	31	7 (4*S*,5*R*)
2	Bn	Bn	(*R*)-**1**	THF	60	82 (4*S*,5*R*)
3	Bn	Bn	(*R*)-**1**	CH_2Cl_2	39	90 (4*S*,5*R*)
4	Bn	Et	(*R*)-**1**	CH_2Cl_2	55	68
5	Me	Bn	(*R*)-**1**	CH_2Cl_2	33	78
6	pentyl	Bn	(*R*)-**1**	CH_2Cl_2	40	93

cyclization, and esterification with TMS-diazomethane gave *N*-amino oxazolidinones **139**. Table 27 reports yields and enantioselectivities of these reactions, the best catalyst being [(*R*)-**1**/$Cu(OTf)_2$] (Table 27, entry 1 vs 2), and the configuration of the product described in entries 1−3 was demonstrated to be (4*S*,5*R*)-**139**.

The Mannich reaction with *N*-tosyl-α-iminoester **135** can be performed for malonates **140a**,[153a] β-ketoesters **140b**,[153a] and β-ketophosphonates **140c**,[153b] to give **141a−c** (Scheme 45). Reactions involving malonates **140a** (R^1 = OR, X = CO_2R) may be catalyzed by either [(*R*)-**1**/$Cu(OTf)_2$] or [(*S*)-**2**/$Cu(OTf)_2$], the former catalyst requires the addition of hexafluoroisopropanol (HFIP) as an additive that may assist the catalytic turnover (Table 28, entries 1 vs 2−6), and the latter gives better yields and enantioselectivities without an additive (Table 28, entries 7 vs 8−12). The same absolute configuration (*R*) was found for the Mannich adducts of diethyl malonate (Table 28, entries 1, 2, 8, and 9) prepared with [(*R*)-**1**/$Cu(OTf)_2$] and [(*S*)-**2**/$Cu(OTf)_2$], although the ligands have the opposite configurations. In the reaction of β-ketoesters **140b** (X = CO_2R) there is a good correlation between size of the ester moiety and selectivity (Table 28, entries 13−19). β-Ketoesters derived from primary alcohols (Table 28, entries 13 and 14) gave products with good yields and diastereoselectivities but low enantioselectivities, while β-ketoesters derived from tertiary alcohols (Table 28, entries 15−19) were the best substrates, and even if yields were moderate, diastereo- and enantioselectivities were good. The more bulky substituents on the ester moiety invert the absolute configuration of the products (Table 28, entries 15 and 16).[153a] After an extensive screening of diffferent box's, inorganic salts, and other reaction conditions, [(*S*)-**2**/$Cu(OTf)_2$] was found to be the best catalyst, in the presence of a Brønsted base, of the reaction between **135** and β-ketophosphonates **140c** (X = $P(O)(OEt)_2$).[153b] The absolute configuration of **141c** (R = R^1 = Me) (Table 28, entry 27) was found to be (2*R*,3*R*) and derives from the attack on the Re face of coordinated enolized **140c**.

Scheme 45



135 **141a-c**

The catalytic enantioselective α-amination through the enolate form of β-ketoesters **140b**[154a] and β-ketophosphonates **140c**[154b] with azodicarboxylates **137** is achieved with box-based catalysts, without the necessity of the base as sometimes required in the reaction with the *N*-tosyl-α-iminoester. The aminated products **142b,c** (Scheme 46) are obtained with excellent yields and enantioselectivities as

Table 28. Catalytic Asymmetric Mannich Reactions of *N*-Tosyl-α-Iminoester 135 with Malonates 140a, *β*-Ketoesters 140b, and *β*-Ketophosphonates 140c

entry	R^1	R	X	box	additive	yield (%)	dr[a]	ee (%) (conf.)[b]	ref
1	OEt	H	CO_2Et	(*R*)-**1**		95		39 (*R*)	153a
2	OEt	H	CO_2Et	(*R*)-**1**	HFIP	63		80 (*R*)	153a
3	OEt	Me	CO_2Et	(*R*)-**1**	HFIP	71		79	153a
4	OEt	*n*-Bu	CO_2Et	(*R*)-**1**	HFIP	80		82	153a
5	OEt	*i*-Bu	CO_2Et	(*R*)-**1**	HFIP	60		79	153a
6	OEt	CH_2Ph	CO_2Et	(*R*)-**1**	HFIP	65		79	153a
7	OEt	H	CO_2Et	(*S*)-**2**	HFIP	80		45 (*R*)	153a
8	OEt	H	CO_2Et	(*S*)-**2**		80		74 (*R*)	153a
9	OEt	Me	CO_2Et	(*S*)-**2**		99		85	153a
10	OEt	*n*-Bu	CO_2Et	(*S*)-**2**		63		91	153a
11	OEt	*i*-Bu	CO_2Et	(*S*)-**2**		64		96	153a
12	OEt	CH_2Ph	CO_2Et	(*S*)-**2**		54		94	153a
13	Me	Me	CO_2Et	(*R*)-**1**		90	90:10	42	153a
14	Et	Me	CO_2Et	(*R*)-**1**		76	84:16	23 (2*R*,3*R*)	153a
15	Et	Me	CO_2-1-adamantyl	(*R*)-**1**		43	>95:<5	66 (2*S*,3*S*)	153a
16	Et	Me	CO_2t-Bu	(*R*)-**1**		33	>95:<5	68 (2*S*,3*S*)	153a
17	Me	Me	CO_2t-Bu	(*S*)-**2**		87	93:7	88 (2*R*,3*R*)	153a
18	Et	Me	CO_2t-Bu	(*S*)-**2**		80	98:2	92 (2*R*,3*R*)	153a
19	*i*-Pr	Me	CO_2t-Bu	(*S*)-**2**		55	84:16	91 (2*R*,3*R*)	153a
20	Ph	Me	$P(O)(OEt)_2$	(*R*)-**1**		70	60:40	50	153b
21	Ph	Me	$P(O)(OEt)_2$	(*R*)-**1**	Et_3N	>98	79:21	56	153b
22	Ph	Me	$P(O)(OEt)_2$	(*S*)-**2**		32	67:33	55	153b
23	Ph	Me	$P(O)(OEt)_2$	(*S*)-**2**	Et_3N	>98	71:29	84	153b
24	Ph	Me	$P(O)(OEt)_2$	(*S*)-**2**	DMA[c]	>98	66:34	64	153b
25	Ph	Me	$P(O)(OEt)_2$	(*S*)-**2**	2,6-lutidine	78	84:16	72	153b
26	2-naphthyl	Me	$P(O)(OEt)_2$	(*S*)-**2**	Et_3N	88	91:9	51	153b
27	Me	Me	$P(O)(OEt)_2$	(*S*)-**2**	Et_3N	61	63:37	43 (2*R*,3*R*)	153b
28	Pr	Me	$P(O)(OEt)_2$	(*S*)-**2**	Et_3N	87	62:38	70	153b
29	*t*-Bu	Me	$P(O)(OEt)_2$	(*S*)-**2**	Et_3N	44	86:14	67	153b
30	EtO	Me	$P(O)(OEt)_2$	(*S*)-**2**	Et_3N	72	82:18	79	153b

[a] Diastereomeric ratio. [b] Enantiomeric excess of the major diastereoisomer. [c] *N*,*N*-Dimethylaniline.

Scheme 46

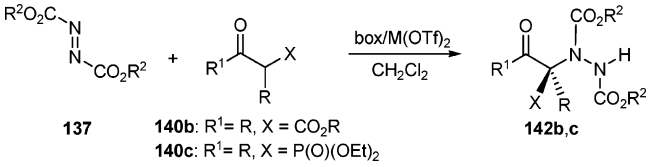


Table 29. Catalytic Enantioselective Mannich Reactions of Azodicarboxylates 147 with *β*-Ketoesters 140b and *β*-Ketophosphonates 140c

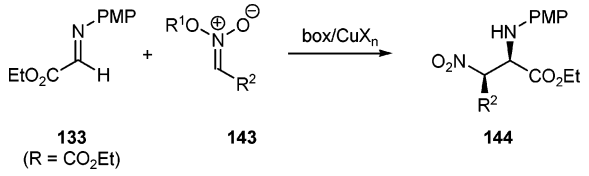
entry	R	R^1	X	R^2	box	M	yield (%)	ee (%) (conf.)	ref
1	Me	Me	CO_2Et	Bn	(*S*)-**1**	Cu	98	98 (*R*)	154a
2	Me	Me	CO_2Et	Et	(*S*)-**1**	Cu	87	>95	154a
3	Me	Et	CO_2Et	Bn	(*S*)-**1**	Cu	94	98	154a
4	Me	Ph	CO_2Et	Bn	(*S*)-**1**	Cu	85	95	154a
5	Me	*i*-Pr	CO_2tBu	Bn	(*S*)-**1**	Cu	96	98	154a
6	Me	Bn	CO_2tBu	Bn	(*S*)-**1**	Cu	84	98	154a
7	allyl	Me	CO_2tBu	Bn	(*S*)-**1**	Cu	80	98	154a
8	Me	Me	CO_2tBu	Bn	(*S*)-**1**	Cu	86	98	154a
9	Me	Ph	$P(O)(OEt)_2$	Et	(*S*)-**2**	Zn	20	12	154b
10	Me	Ph	$P(O)(OEt)_2$	Et	(*S*)-**1**	Zn	80	92	154b
11	Me	Ph	$P(O)(OEt)_2$	Bn	(*S*)-**1**	Zn	85	92 (*S*)	154b
12	Me	2-naphthyl	$P(O)(OEt)_2$	Bn	(*S*)-**1**	Zn	93	92	154b
13	Me	Bn	$P(O)(OEt)_2$	Bn	(*S*)-**1**	Zn	60	95	154b
14	Me	Me	$P(O)(OEt)_2$	Bn	(*S*)-**1**	Zn	75	85	154b
15	Allyl	Ph	$P(O)(OEt)_2$	Bn	(*S*)-**1**	Zn	85	98	154b
16	Me	Ph	$P(O)(OMe)_2$	Bn	(*S*)-**1**	Zn	97	94	154b

reported in Table 29. The best box is (*S*)-**1** in combination with $Cu(OTf)_2$ for *β*-ketoesters, while $Zn(OTf)_2$ turned out to be the best Lewis acid for *β*-ketophosphonates. The absolute configurations were determined to be (*R*)-**142b** (Table 29, entry 1) and (*S*)-**142c** (Table 29, entry 11) by X-ray crystal structure analysis of oxazolidinone derivatives analogous to **139**.

The Mannich reaction was also attempted between *N*-tosyl-α-iminoester **135** and benzophenone imine glycine methyl ester, but the product was obtained as a racemate using [(*S*)-**2**/$CuClO_4$] as the catalyst.[155]

The reaction between the α-iminoester **133** (R = CO_2Et) and nitronates **143** (either derived from nitroalkanes in the presence of a base or as TMS derivatives)—the aza-Henry reaction—is an interesting approach to optically active *β*-nitro-α-amino acid derivatives **144** (Scheme 47).[156] The

Scheme 47



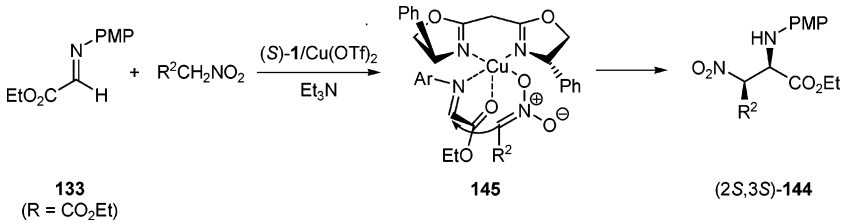
reaction is catalyzed by Cu(I)- or Cu(II)-based box complexes, and it is strongly erythro-selective. The solvent of choice is CH_2Cl_2 if the reaction is performed with nitroalkanes and Et_3N (R^1 = H), or THF with trimethylsilyl nitronates (R^1 = TMS). The results of the diastereo- and enantioselective aza-Henry reactions are reported in Table 30.

The aza-Henry reaction gives optically active **144** with a good yield and excellent diastereo- and enantioselectivity either with nitroalkanes and Et_3N or with preformed trimethylsilyl nitronates (Table 30, entry 4 vs 14). Among the chiral ligands, **1** is better than **2**, since the latter gives either lower yield, diastereoselectivity, or enantioselectivity compared to the application of the former chiral ligand (Table 30, entries 3, 10, and 11). The reaction is flexible, and selectivity is excellent with several nitroalkanes (Table 30,

Table 30. Catalytic Aza-Henry Reactions between *N*-(*p*-Methoxyphenyl)-α-Iminoester 133 and Nitronates 143

entry	R^1	R^2	box	CuX_n	yield (%)	erythro/threo	erythro ee (%) (conf.)	threo ee (%)	ref
1	H	H	(*R*)-**1**	$Cu(OTf)_2$	38		87 (2*R*,3*R*)		156a
2	H	Me	(*R*)-**1**	$Cu(OTf)_2$	61	70:30	97 (2*R*,3*R*)	95	156a
3	H	Et	(*S*)-**2**	$Cu(OTf)_2$	8	95:5	89 (2*R*,3*R*)	70	156a
4	H	Et	(*R*)-**1**	$Cu(OTf)_2$	81	95:5	97 (2*R*,3*R*)	87	156a
5	H	Et	(*R*)-**1**	$Cu(SbF_6)_2$	85	60:40	26 (2*R*,3*R*)	21	156a
6	H	Et	(*R*)-**1**	$CuBr_2$	69	95:5	93 (2*R*,3*R*)	86	156a
7	H	pentyl	(*R*)-**1**	$Cu(OTf)_2$	52	93:7	97 (2*R*,3*R*)	89	156a
8	H	$PhCH_2$	(*R*)-**1**	$Cu(OTf)_2$	80	95:5	95 (2*R*,3*R*)	88	156a
9	H	Ph	(*R*)-**1**	$Cu(OTf)_2$	59	55:45	74 (2*R*,3*R*)	77	156a
10	TMS	Et	(*S*)-**2**	$CuClO_4$	99	92:8	12 (2*S*,3*S*)		156b
11	TMS	Et	(*S*)-**2**	$Cu(OTf)_2$	58	88:12	56 (2*R*,3*R*)		156b
12	TMS	Et	(*S*)-**1**	$CuClO_4$	90	75:25	90 (2*S*,3*S*)		156b
13	TMS	Et	(*S*)-**1**	$CuPF_6$	63	83:17	56 (2*S*,3*S*)		156b
14	TMS	Et	(*S*)-**1**	$Cu(OTf)_2$	67	95:5	89 (2*S*,3*S*)		156b
15	TMS	Et	(*S*)-**1**	$Cu(SbF_6)_2$	92	86:14	70 (2*S*,3*S*)		156b
16	TMS	Me	(*S*)-**1**	$CuClO_4$	67	83:17	>98 (2*S*,3*S*)		156b

Scheme 48

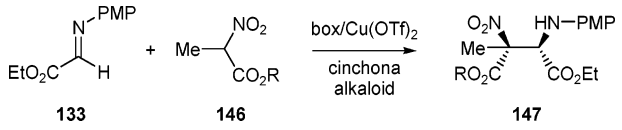


133 (R = CO_2Et) **145** (2*S*,3*S*)-**144**

entries 1, 2, 4, and 6−8, the exception is R^2 = Ph (entry 9)). Scheme 48 shows the proposed intermediate for the aza-Henry reaction. The α-iminoester **133** coordinates in a bidentate fashion, with the nitrogen atom in the equatorial postion, to the catalyst derived from [(*S*)-**1**/$Cu(OTf)_2$]. This accounts for the diastereo- and enantioselectivity of the aza-Henry reaction, and it cannot be ignored that the similarity of **145** to the reacting intermediate **120** accounts for the stereoselectivity observed in the Henry reaction.

The development of the catalytic aza-Henry reaction not only points to the formation of optically active quaternary centers, as in **147**, by the reaction of (*p*-methoxyphenylimino)acetic acid ethyl ester **133** with esters of 2-nitro propanoic acid **146** (Scheme 49), but also to the combination of a box-

Scheme 49



133 **146** **147**

based Lewis acid and chiral base catalysis (the former to coordinate **133**, the latter to form nitronate from **146**) through a chiral molecular regnition approach.[156c] The data in Table 31 show the increasing selectivity with a bulky ester group (entry 1 vs 2) and the great improvement of both diastereomeric ratio and enantiomeric excess with cinchona alkaloids (entries 3−6). The best chiral bases are quinidine and quinine, and these were tested with both (*R*)- and (*S*)-**1** (Table 31, entries 5 and 6 vs 7 and 8). Selectivity with both bases decreases with (*S*)-**1**; hence the enantioselectivity is governed by the chiral Lewis acid ligand.

Table 31. Catalytic Aza-Henry Reactions between α-Iminoester 133 and Nitroesters 146[156c]

entry	R	box	base	yield (%)	dr[a]	**147** ee (%)
1	Et	(*R*)-**1**	Et_3N	95	50:50	
2	*t*-Bu	(*R*)-**1**	Et_3N	>90	67:33	80
3	*t*-Bu	(*R*)-**1**	cinchonine	76	88:12	94
4	*t*-Bu	(*R*)-**1**	hydroquinine	90	91:9	95
5	*t*-Bu	(*R*)-**1**	quinidine	80	90:10	96
6	*t*-Bu	(*R*)-**1**	quinine	90	93:7	98
7	*t*-Bu	(*S*)-**1**	quinidine	90	89:11	−91
8	*t*-Bu	(*S*)-**1**	quinine	76	90:10	−93

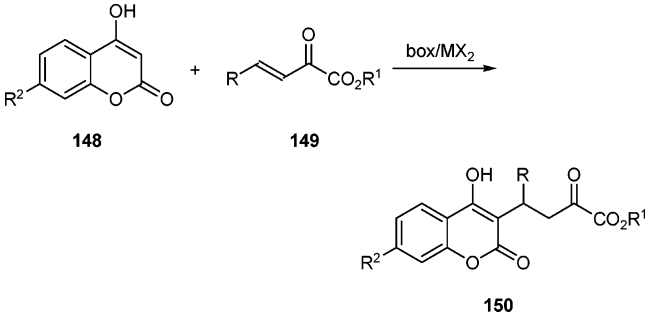
[a] Diastereomeric ratio.

4.4. Michael and Mukaiyama–Michael Reactions

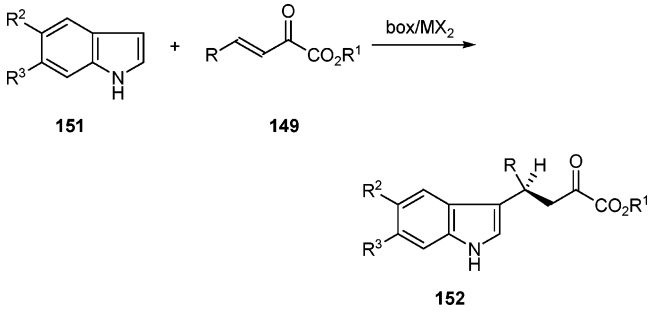
The addition of active methylene compounds to electrophilic π-systems, the Michael reaction, is one of the most useful C−C bond-forming reactions, whose catalytic enantioselective version has been extensively studied also for the construction of quaternary stereocenters.[157] This classic approach has several variants involving either the formation of a C−C bond or the formation of a C−X bond if the nucleophilic site is localized on a heteroatom.

The reaction of α,β-unsaturated carbonyl derivatives, or unsaturated nitro compounds, with different types of carbanions has been tested with (*S*)-**1** or (*S*)-**2** and several Cu, Ni, Fe, or Mg salts,[50,158,159] but the reaction with these catalysts gave nearly racemic products, whereas other box's, which will be considered in a later section, gave excellent selectivities. The reaction between cyclic and heterocyclic 1,3-dicarbonyl compounds with α,β-unsaturated carbonyls is more appealing and, together with the reaction of pyrones, phenalen-2-one, 1,4-naphthoquinone, and various enamines of cyclic 1,3-diketones, was the topic of an investigation of the Michael reaction between a series of different 4-hydroxycoumarins **148** with 2-oxo-3-butenoate esters **149** (Scheme 50).[160] To achieve a high enantiomeric excess of the Michael adduct **150**, Et_2O was the best solvent, and the Lewis acids $Cu(SbF_6)_2$, $Zn(OTf)_2$, and $Ni(ClO_4)_2$ proved to be inferior to $Cu(OTf)_2$. The results under the optimized

Scheme 50



Scheme 51



conditions with applying (*R*)-**1** and (*S*)-**2** as the chiral ligands are reported in Table 32.

The interesting results are: (i) the product configuration is (*R*), which suggests **149** coordinates in a bidentate fashion to copper leaving the Si face shielded by the *tert*-butyl group of (*S*)-**2**; hence coumarin attacks the Re face; (ii) box **1** promotes the same enantioselection with $Cu(OTf)_2$, not with $Zn(OTf)_2$ (Table 32, entries 1 and 2); (iii) aryl groups on **149** always induce (*R*)-enantioselectivity.

The enantioselective catalytic Friedel−Crafts-type addition of aromatic and heteroaromatic C−H bonds to 4-substituted 2-oxo-3-butenoate **149** has been tested with 1,3-dimethoxybenzene, 2-methylfuran, and (in detail) with indoles **151**, which give 4-substituted 4-(3-indolyl)-2-oxobutanoates **152** (Scheme 51).[147,161]

Table 33 reports the results of a Michael reaction that, in analogy to the reaction of the activated carbonyl compounds acting as electrophiles with electron-rich aromatic compounds reported in Scheme 40, can be also regarded as a Friedel−Crafts alkylation/Michael reaction of the indole with the α,β-unsaturated carbonyl compounds. The best enantioselectivities are obtained with Et_2O as the solvent (Table 33, entries 2−4), even if CH_2Cl_2 gives somewhat comparable results, and the enantioselectivity is always that reported in Scheme 51 ((*R*)-**152** for R = Ph) except with [(*S*)-**1**/$Cu(OTf)_2$] (Table 33, entry 1). Excellent enantiomeric excesses are also obtained with [(*S*)-**2**/$Cu(OTf)_2$] for any kind of substituents both in the indole ring (either electron-withdrawing or electron-donating substituents, Table 33, entries 7−11) and in the α,β-unsaturated carbonyl compound (Table 33, entries 6 and 10−12).

The Friedel−Crafts alkylation/Michael reaction of indoles **151** can be performed with arylidene malonates **153** (Scheme 52) and the decarboxylation of products **154** to monoesters, allowing the formal transformation of the reaction into a Friedel−Crafts alkylation of indoles with cinnamates.[147,162,163] The most significant results are obtained with THF as the solvent and [(*S*)-**2**/$Cu(OTf)_2$] as the catalyst, but the enantiomeric excesses are somewhat lower than those of the 2-oxo-3-butenoates reported in Table 33. Negligible enan-

Table 32. Enantioselective Catalyzed Michael Additions of 4-Hydroxycoumarin 148 and 2-Oxo-3-Butenoate Esters 149[160]

entry	R	R^1	R^2	box	MX_2	solvent	yield (%)	ee (%) (conf.)
1	Ph	Me	H	(*S*)-**1**	$Zn(OTf)_2$	CH_2Cl_2	98	25 (*S*)
2	Ph	Me	H	(*R*)-**1**	$Cu(OTf)_2$	Et_2O	85	77 (*S*)
3	Ph	Me	H	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	98	60 (*R*)
4	Ph	Me	H	(*S*)-**2**	$Cu(OTf)_2$	THF	98	13 (*R*)
5	Ph	Me	H	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	98	86 (*R*)
6	*p*-ClC_6H_4	Me	H	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	98	73 (>99.5) (*R*)[a]
7	*p*-MeC_6H_4	Me	H	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	95	78 (*R*)
8	*p*-$MeOC_6H_4$	Me	H	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	98	64 (*R*)
9	2-furyl	Et	H	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	95	81 (*S*)
10	Ph	Me	OMe	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	47	91 (*R*)
11	Ph	Me	F	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	45	91 (*R*)

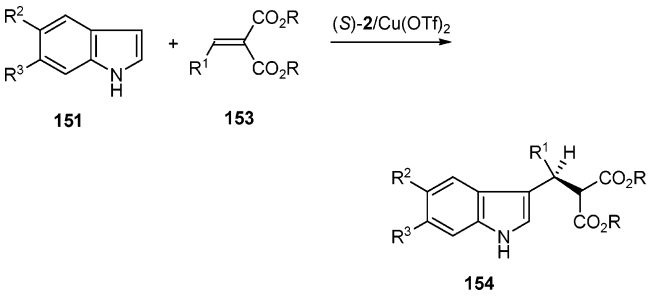
[a] Enantiomeric excess after crystallization; the absolute configuration was assigned by X-ray analysis.

Table 33. Enantioselective Catalyzed Michael Additions of Indoles 151 and 2-Oxo-3-Butenoate Esters 149

entry	R	R^1	R^2	R^3	box	MX_2	solvent	yield (%)	ee (%) (conf.)	ref
1	Ph	Me	H	H	(*S*)-**1**	$Cu(OTf)_2$	Et_2O	100	42 (*S*)	161
2	Ph	Me	H	H	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	100	99.5 (*R*)	147, 161
3	Ph	Me	H	H	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2[a]	99	89 (*R*)	161
4	Ph	Me	H	H	(*S*)-**2**	$Cu(OTf)_2$	THF	100	74 (*R*)	161
5	Ph	Me	H	H	(*S*)-**2**	$Zn(OTf)_2$	Et_2O	100	87 (*R*)	161
6	Me	Et	H	H	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	96	95 (*S*)	147, 161
7	Ph	Me	OMe	H	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	95	>99.5 (*R*)	147, 161
8	Ph	Me	H	Cl	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	69	97 (*R*)	147, 161
9	Ph	Me	H	CO_2Me	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	82	94 (*R*)	161
10	Me	Et	OMe	H	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	95	>99.5 (*S*)	147, 161
11	CH_2OBn	Et	OMe	H	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	98	95 (*S*)	147, 161
12	CH_2OBn	Et	H	Cl	(*S*)-**2**	$Cu(OTf)_2$	Et_2O	70	80 (*S*)	161

[a] CH_2Cl_2 and pentane (1:2).

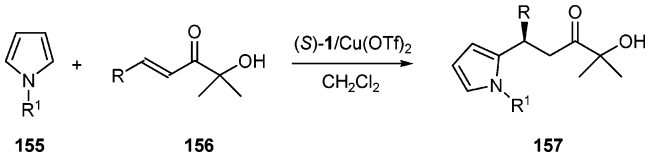
Scheme 52



tioselectivities have been obtained running the reaction with 2-methylfuran and pyrrole instead of **151**.

Excellent electrophiles for the enantioselective Friedel−Crafts alkylation/Michael reaction of pyrroles **155** were found to be α′-hydroxy enones **156**, which give a bidentate coordination, through their oxygen atoms, to [(*S*)-**2**/Cu(OTf)$_2$] and easily afford **157** (Scheme 53).[164] Table 34 reports some

Scheme 53



results showing the great flexibility of a reaction that, besides pyrroles, can also be performed with a variety of indoles, always with excellent yields and enantioselectivities (>90% ee). The absolute configuration of **157** (R = *i*-Pr, R^1 = Me, Table 34, entry 5) was determined to be (*R*).

Table 34. Enantioselective Catalyzed Friedel−Crafts Alkylations of Pyrroles 155 with α-Hydroxy Enones 156[164]

entry	R	R^1	yield (%)	ee (%) (conf.)
1	$PhCH_2CH_2$	H	83	90
2	$PhCH_2CH_2$	Me	86	92
3	$CH_3(CH_2)_5$	H	87	91
4	$CH_3(CH_2)_5$	Me	82	96
5	*i*-Pr	Me	86	95 (*R*)
6	cyclohexyl	Me	84	97
7	Et	Me	88	94
8	$(CH_3)_2CHCH_2$	Me	86	94

Two important variants of the Michael reaction involve the formation of C−O or C−N bonds, if the nucleophile is localized on a heteroatom. An example of the oxa-Michael reaction is the first step of the tandem reaction of 2-oxo-3-butenoate esters **149** (R = Ar, R^1 = Me) with phenols **158**. The adducts **159** then undergo an intramolecular Friedel−Crafts alkylation to the optically active chromans **160** (Scheme 54).[28] Other box-based catalysts give enantioselectivities up to 81% ee and will be discussed in a later section; [(*S*)-**1**/Mg(OTf)$_2$] limits enantioselectivities to 44% ee.

The aza-Michael reaction, tested for the addition of aromatic amines to 3-alkenoyl-1,3-oxazolidin-2-one as a route to β-amino acid derivatives, catalyzed with [(*S*)-**2**/Zn(OTf)$_2$], gave a good yield but disappointing enantioselectivity.[165] More appreciable results, in terms of yield and enantioselectivity, have been obtained in the addition of α′-hydroxy enones **156** to carbamates **161** to give β-amino-protected hydroxyketones **162** (Scheme 55), which can be easily oxidized to N-protected β-amino acids.[166] The reaction proceeds for a variety of enones and carbamates, and Table 35 reports a representative selection of the results. The catalyst of choice was [(*S*)-**2**/Cu(OTf)$_2$] (Table 35, entries 1 and 2), and optically active **162** was obtained with excellent enantioselectivities (generally >90% ee). The corresponding Mg(II)- and Zn(II)-based catalysts were uneffective.

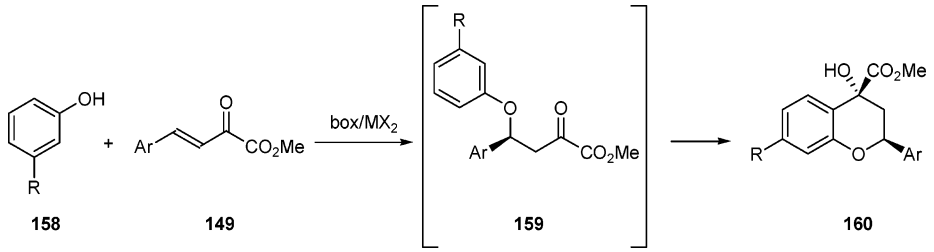
Among the different activated double bonds that have been the topic of extensive research in enantioselective box-catalyzed additions and cycloadditions, special attention has been devoted to substituted *N*-alkenoyl-oxazolidinones. These substrates are characterized by a β-dicarbonyl functionality (one carbonyl belonging to the unsaturated chain and the other one to the heterocycle) that allows the molecule to behave as a bidentate reagent during the catalytic cycle. Some of them have been employed in the aza-Michael reaction, and their reactions are discussed below.

3-(*E*)-Crotonoyl-4,4-dimethyl-2-oxazolidinone **163** (R = R^1 = Me) undergoes conjugate addition of *O*-benzylhydroxylamine (Scheme 56), and even if (*S*)-**1** and (*S*)-**2** do not represent the best catalysts for this reaction, (*S*)-**164** is obtained with excellent yield; unfortunately, the enantioselectivities are only 14% and 47% ee, respectively.[167]

The reaction of 1-(*E*)-crotonoyl-3-phenyl-2-imidazolidinone **165** and 2-furancarbaldehyde oxime gives an addition product with a nitrone structure (**166**, Scheme 57); again the yields with catalysts [(*R*)-**1**/Cu(OTf)$_2$] and [(*S*)-**2**/Cu(OTf)$_2$] are very good, but the enantioselectivities are only 15% and 29% ee, respectively.[168]

1-Substituted 2-alkenoyl-4,4-dimethylpyrazolidin-3-ones **167** are interesting substrates, which will be considered several times along this review, developed by Sibi et al. for a novel protocol termed "chiral relay". This strategy focuses on the design of achiral templates that may relay and amplify the stereochemistry induced by the box. The essence of this strategy is that the chiral catalysts would convert an achiral template like **167** into a chiral nonracemic template.[169] The chiral relay methodology was applied to the enantioselective aza-Michael reaction studying the addition of *N*-(4-methoxybenzyl)-hydroxylamine to **167**. The results in terms of enantioselectivity with (*S*)-**1** or (*S*)-**2** and Mg(ClO$_4$)$_2$ or Zn(OTf)$_2$ cannot be compared to those obtained with (*S*)-**3c** and (4*S*,5*R*)-**10a**, but the addition product **168**, which undergoes elimination of the template to give chiral isox-

Scheme 54



Scheme 55

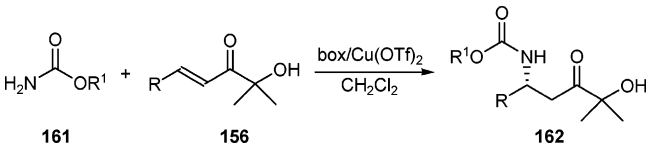
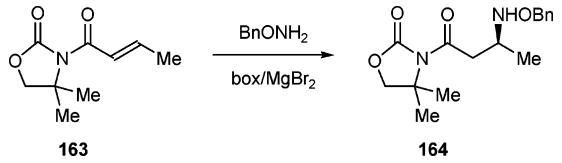


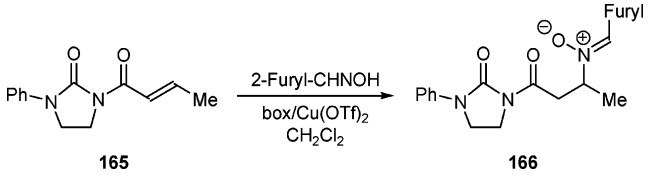
Table 35. Enantioselective Catalyzed Aza-Michael Additions of Enones 156 to Carbamates 161[166]

entry	R	R^1	box	yield (%)	ee (%) (conf.)
1	$PhCH_2CH_2$	$PhCH_2$	(*S*)-**1**	49	83 (*S*)
2	$PhCH_2CH_2$	$PhCH_2$	(*S*)-**2**	86	96 (*S*)
3	$PhCH_2CH_2$	Me	(*S*)-**2**	51	99
4	$PhCH_2CH_2$	Et	(*S*)-**2**	74	96
5	$PhCH_2CH_2$	*t*-Bu	(*S*)-**2**	92	88
6	Et	$PhCH_2$	(*S*)-**2**	83	96
7	*i*-Pr	$PhCH_2$	(*S*)-**2**	53	98
8	*i*-Bu	$PhCH_2$	(*S*)-**2**	71	96 (*S*)
9	*t*-Bu	$PhCH_2$	(*S*)-**2**	65	94
10	*n*-hexyl	*t*-Bu	(*S*)-**2**	76	96
11	*c*-C_6H_{11}	*t*-Bu	(*S*)-**2**	85	91
12	*c*-C_6H_{11}	$PhCH_2$	(*S*)-**2**	57	94

Scheme 56



Scheme 57



azolidine (*S*)-**169** with enantiomeric excess up to 41% ee (Scheme 58) allows the illustration of this attractive process.[170]

The aza-Michael reaction of *N*,*O*-bis(trimethylsilyl)hydroxylamine with arylidene malonates **153** is catalyzed by several box-based catalysts and some of them give enantioselectivities up to 76% ee. However, catalyst [(*S*)-**1**/$Cu(OTf)_2$] is not among them, and both yield and enantioselectivity afforded by this complex are unsatisfactory.[171]

The Mukaiyama−Michael reaction is probably the most important variant of the Michael reaction and occurs between an activated α,*β*-unsaturated carbonyl derivative (the electrophilic *π*-systems) and silylketene acetals (**86**), and the first applications of the catalysis by box-based complexes have been reported in two agile highlights.[4c,56]

The first example of the catalytic asymmetric Mukaiyama−Michael reaction was the reaction between 2-carbomethoxycyclopentanone and 1-TMSO-1-*tert*-butoxypropene using the combination of (*R*)-**1** and $Cu(OTf)_2$ or $Cu(SbF_6)_2$ as the catalyst to give the syn and anti adducts in ratios of 9:1 and 60:1 and enantiomeric excesses of 66% and 60% ee, respectively.[172] Detailed and important developments were by Evans et al., who focused on the Mukaiyama−Michael reaction of **86** (A = S*t*-Bu) with alkylidene malonates **153**, leading to the formation of 3-substituted *tert*-butyl 4,4-dicarbomethoxy-butanethioate **170** (Scheme 59).[62,63]

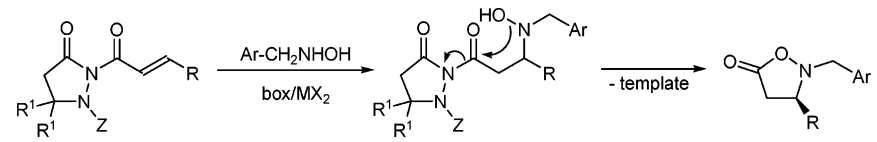
Several parameters were investigated, and Table 36 reports the most significant results for each variable. Catalysts derived from box ligands (*S*)-**1** or (*S*)-**2** gave adducts with opposite configurations (Table 36, entries 1 and 14 vs 2 and 15), and the latter provided the highest enantiomeric excess. For $R^2 \neq H$ in **86**, the diastereoselectivity was found to depend on the enolsilane geometry (Table 36, entries 16−19). Arylidene and heteroarylidene malonates gave excellent enantiomeric excesses (Table 36, entries 2 and 6−8), while alkylidene malonates with branched alkyl substituents give adducts in high enantioselectivities with the stereochemistry reported in Scheme 59 (Table 36, entries 9−11). Unbranched alkyl substituents in the malonate are far less effective, and the configuration of ethylidene (Table 36, entry 14) is the result of an opposite facial attack, probably as other unbranched alkyl groups (Table 36, entries 12 and 13). In conclusion, it seems reasonable to propose that the absolute stereochemistry of the Mukaiyama−Michael adducts derived from benzylidene and ethylidene malonates correspond to the opposite facial attack of the nucleophile, and substituents larger than methyl provide intermediate selectivity between the extremes.

On the basis of the crystal structures of [(*S*)-**1**·$Cu(SbF_6)_2$·$PhCH{=}C(CO_2Me)_2$] (**19**) and [(*S*)-**2**·$Cu(SbF_6)_2$·$PhCH{=}C(CO_2Me)_2$] (**20**) reported in Figures 5 and 6, respectively, which have been proposed for the reacting intermediates in the catalytic cycles of **153** with these box's as ligands, Figure 12 reports the simple rationale of the opposite configuration obtained in these reactions. The attack of the nucleophiles to coordinated benzylidene malonate occurs on the Re face in **19** and on the Si face of **20**.[63]

The excellent enantioselectivity of the Mukaiyama−Michael reaction with alkylidene malonates, obtained with catalysts based on box ligands **1** and **2**, was only in part confirmed (<60% ee) with the reaction of *β*-enamidomalonates **153** (R^1 = ROCHN) and **86**.[173]

3-Alkenoyl-2-oxazolidinones **163** (R^1 = H) are also excellent substrates for the Mukaiyama−Michael reaction since they easily undergo conjugate addition of enolsilanes **86** (Scheme 60). Monitoring the reaction by in situ IR spectroscopy showed that the reaction occurs through the dihydropyran intermediate **171**, which then converts to the Michael products *anti*-**172** (plus the syn diastereoisomer) in the presence of small amounts of protic additives (the best is HFIP) that serve to facilitate the catalyst turnover.[61,174] This reaction is discussed in this section for traditional

Scheme 58



Scheme 59

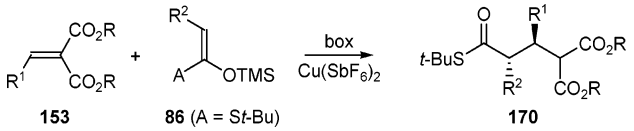


Table 36. Diastereo- and Enantioselectivity in the Catalyzed Mukaiyama−Michael Reactions of Enolsilanes 86 and Alkylidene Malonates 153

entry	R^1	R	R^2 (conf.)	box	yield (%)	anti/ syn	anti ee (%) (conf.)	syn ee (%)	ref
1	Ph	Me	H	(*S*)-**1**	99		52 (*S*)		63
2	Ph	Me	H	(*S*)-**2**	>98		93 (*R*)		62,63
3	Ph	Et	H	(*S*)-**2**	>98		88 (*R*)		63
4	Ph	*i*-Pr	H	(*S*)-**2**	80		58 (*R*)		63
5	Ph	*t*-Bu	H	(*S*)-**2**					63
6	2-furyl	Me	H	(*S*)-**2**	88		94		62
7	3-Ts-indolyl	Me	H	(*S*)-**2**	99		86		62
8	*o*-MeOPh	Me	H	(*S*)-**2**	92		99 (*R*)		62
9	*t*-Bu	Me	H	(*S*)-**2**	89		90 (*R*)		62,63
10	cyclohexyl	Me	H	(*S*)-**2**	95		95 (*S*)		62,63
11	*i*-Pr	Me	H	(*S*)-**2**	93		93 (*S*)		62,63
12	*n*-Pr	Me	H	(*S*)-**2**	87		27		63
13	Et	Me	H	(*S*)-**2**	82		22		63
14	Me	Me	H	(*S*)-**1**	91		40 (*R*)		63
15	Me	Me	H	(*S*)-**2**	91		44 (*S*)		62,63
16	Ph	Me	Me (*E*)	(*S*)-**2**		55:45	<5	<5	63
17	Ph	Me	Me (*Z*)	(*S*)-**2**		92:8	80	70	63
18	Me	Me	Me (*E*)	(*S*)-**2**		95:5	68	30	63
19	Me	Me	Me (*Z*)	(*S*)-**2**		29:71	10	62	63

reasons, even if it is clear that the formation of dihydropyran **171** can be regarded as an example of a hetero Diels−Alder reaction between **163**, acting as a heterodiene, and **86**, behaving as an electron-rich dienophile.

The most significant results are reported in Table 37. The best catalyst is [(*S*)-**2**/Cu(OTf)$_2$] (Table 37, entries 1 vs 2), and this complex was widely used in different experiments. Excellent enantioselectivities were obtained with 2-unsubstituted enolsilane **86** when reacting with **163** (Table 37, entries 2−4 and 17−19). If 2-substituted enolsilane **86** has the (*Z*)-configuration, then the product is largely syn, and diastereoselectivity increases with the increase in the size of A; if the configuration is (*E*), then the product is largely anti, but diastereoselectivity decreases with the increase in the size of A (Table 37, entries 5−7 and 8−10). Different substituents in the β-position of enolsilane do not change enantioselectivity, which is always >90% ee (Table 37, entries 10−13). For 1-phenyl- or 1-(1-pyrrolyl)-enolsilanes, and even changing other substituents in the reactants, excellent diastereo- and enantioselectivities are always obtained (Table 37, entries 14−16 and 20−22). A last point deserves attention: Dihydropyran intermediate **171** can be isolated (even if in only 6% yield) in the experiment reported in Table 37, entry 20, and its (4*S*,5*S*,6*S*)-configuration is consistent with that of **172** obtained under the same conditions.

3-Alkenoyl-2-oxazolidinones **163** (R^1 = H) give also excellent results in the Mukaiyama−Michael reaction with 2-(trimethylsilyloxy)furans **173** catalyzed by box−metal complexes (Scheme 61).[175,176] Table 38 presents some interesting results; one needs attention: The catalysts derived from (*R*)-**1** with either Mg(II), Ni(II), or Zn(II) and that from (*S*)-**2** with Cu(II), which involves ligands with an opposite configuration, induce the same chiral induction (Table 38, entries 2 and 3 vs 4−6).

The optically active adducts of the Michael reaction can be useful synthons for natural products: An example is *anti*-(*S*,*S*)-**174** (from entry 2 in Table 38) that is converted within five steps into *trans*-whisky lactone.[177]

The Mukaiyama−Michael reaction of enolsilanes **86** was performed with [(2-oxo-1,3-oxazolidin-3-yl)carbonyl]diazenyl formates **175** (Scheme 62).[178] A survey of [box/Cu(II)] complexes revealed that [(*S*)-**2**/Cu(OTf)$_2$] is the catalyst of choice affording (*R*)-hydrazino adducts **177** in excellent yields and enantioselectivities as shown in Table 39.

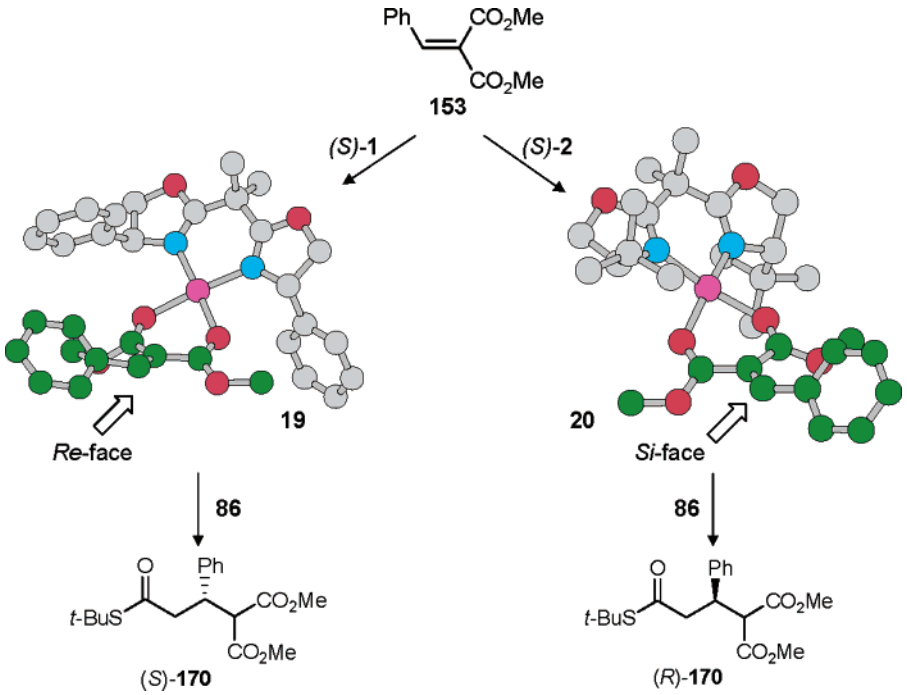
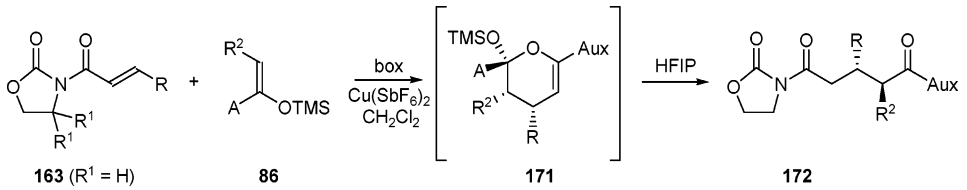


Figure 12. Different reaction complexes of **153** with (*S*)-**1** and (*S*)-**2** and their influence on the configuration of the Mukaiyama−Michael adducts with **86**.

Scheme 60



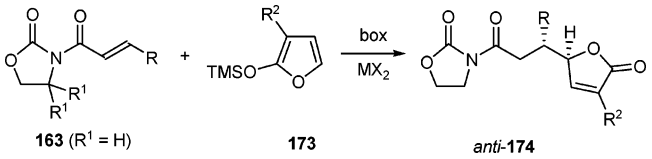
163 (R^1 = H) **86** **171** **172**

Table 37. Diastereo- and Enantioselective Catalyzed Mukaiyama−Michael Reactions of Enolsilanes 86 and 3-Alkenoyl-2-Oxazolidinones 163

entry	R	A	R^2 (conf.)	box	yield (%)	anti/syn	anti ee (%) (conf.)	syn ee (%) (conf.)	ref
1	CO_2Et	S*t*-Bu	H	(*S*)-**1**	n.d.		57 (3*S*)		61
2	CO_2Et	S*t*-Bu	H	(*S*)-**2**	86		89 (3*S*)		61
3	CO_2Et	Ph	H	(*S*)-**2**	54		98		61
4	CO_2Et	Cyhex	H	(*S*)-**2**	31		99		61
5	CO_2Et	S*t*-Bu	Me (*Z*)	(*S*)-**2**	94	1:>99		99 (3*S*,4*R*)	61, 174
6	CO_2Et	SEt	Me (*Z*)	(*S*)-**2**	91	25:75		92 (3*S*,4*R*)	61
7	CO_2Et	SMe	Me (*Z*)	(*S*)-**2**	90	34:66		90 (3*S*,4*R*)	61, 174
8	CO_2Et	S*t*-Bu	Me (*E*)	(*S*)-**2**	65	78:22	96 (3*S*,4*S*)		61, 174
9	CO_2Et	SEt	Me (*E*)	(*S*)-**2**	77	86:14	91 (3*S*,4*S*)		61
10	CO_2Et	SMe	Me (*E*)	(*S*)-**2**	90	95:5	90 (3*S*,4*S*)		61, 174
11	CO_2Et	SMe	Et (*E*)	(*S*)-**2**	89	95:5	90 (2*S*,3*S*)		61, 174
12	CO_2Et	SMe	*i*-Pr (*E*)	(*S*)-**2**	93	>99:1	98 (3*S*,4*S*)		61, 174
13	CO_2Et	SMe	CH_2Cy[b] (*E*)	(*S*)-**2**	84	96:4	97 (3*S*,4*S*)		61
14	CO_2Et	Ph	Me (*Z*)	(*S*)-**2**	99	95:5	92 (3*S*,4*S*)		61, 174
15	CO_2Et	Ph	Et (*Z*)	(*S*)-**2**	99	99:1	94 (2*S*,3*S*)		61, 174
16	CO_2Et	Ph	*i*-Pr (*Z*)	(*S*)-**2**	99	99:1	94 (2*S*,3*S*)		61, 174
17	Me	1-Pyr[b]		(*S*)-**2**	90		91 (3*R*)		61
18	CO_2Et	1-Pyr[b]		(*S*)-**2**	92		95 (2*R*)		61
19	Ph	1-Pyr[b]		(*S*)-**2**	94		90 (3*R*)		61
20	Me	1-Pyr[b]	Me (*Z*)	(*S*)-**2**	88	99:1	98 (2*S*,3*S*)		61, 174
21	CO_2Et	1-Pyr[b]	Me (*Z*)	(*S*)-**2**	91	97:3	94 (2*S*,3*S*)		61, 174
22	Ph	1-Pyr[b]	Me (*Z*)	(*S*)-**2**	97	99:1	98 (2*S*,3*S*)		61

[a] Cy is cyclopentyl. [b] 1-Pyr is 1-pyrrolyl.

Scheme 61



163 (R^1 = H) **173** *anti*-**174**

Table 38. Diastereo- and Enantioselective Catalyzed Mukaiyama−Michael Reactions of 3-Alkenoyl-2-Oxazolidinones 163 and 2-TMSO-Furans 173

entry	R	R^2	box	MX_2	additive[a]	yield (%)	anti/syn	anti ee (%) (conf.)	ref
1	H	H	(*S*)-**2**	$Cu(OTf)_2$	HFIP, MS	71		64 (*S*)	176b
2	Me	H	(*S*)-**2**	$Cu(OTf)_2$	HFIP, MS	89	89:11	95 (*S*,*S*)	176
3	Me	H	(*S*)-**2**	$Cu(OTf)_2$	MS	37	91:9	92 (*S*,*S*)	176b
4	Me	H	(*R*)-**1**	$Mg(ClO_4)_2$	MS	94	85:15	20 (*S*,*S*)	175
5	Me	H	(*R*)-**1**	$Ni(ClO_4)_2$	MS	91	82:18	32 (*S*,*S*)	175
6	Me	H	(*R*)-**1**	$Zn(ClO_4)_2$	MS	90	>99:1	31 (*S*,*S*)	175
7	Me	Me	(*S*)-**2**	$Cu(OTf)_2$	HFIP, MS	95	96:4	91 (*S*,*S*)	176

[a] Molecular sieves are 4 Å.

The use of trifluoroethanol as an additive is critical to achieve a good catalyst turnover (Table 39, entry 1 vs 2). Enolsilanes afford the (*R*)-hydrazino products independently from substituents (Table 39, entries 2−6 and 8), but (*E*)- and (*Z*)-thioester silylketene acetals give the opposite enantiomers (Table 39, entry 6 vs 7). The investigation was extended to silylketene aminals of acylpyrroles, and the nature of the β-substituent is crucial: The steric hindrance of *tert*-butyl-substituted **86** does not allow the β-attack (easy for R^1 = Me), and amination occurs exclusively on the pyrrole ring (Table 39, entry 9 vs 8). Monitoring the reaction by in situ IR spectroscopy allowed the discovery that the reaction occurs through an intermediate, proposed to be the dihydropyran **176** in analogy with the Mukaiyama−Michael reaction illustrated in Scheme 60.

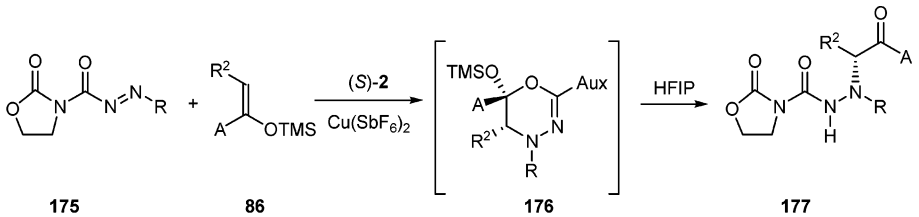
4.5. Allylic Substitution Reactions

The palladium-catalyzed nucleophilic allylic substitution reaction was an early test of the possible applications of box ligands in enantioselective catalysis; however, neither **1** nor **2** have been considered as starting compounds for the construction of the catalysts, and box's with different substituents (sometimes even more sophisticated) were mainly studied.[13,179] The generally accepted mechanism, in the most simple intermolecular version, is outlined in Scheme 63. The first step is the complexation of the racemic X-allyl-substituted reagent **178** to the box−palladium complex **179** to give, after ionization, two diastereomeric palladium complexes **180a**,**b**, which react with a nucleophile to give, after decomplexation, the optically active allyl-substituted product **181**.

This reaction differs from other box-catalyzed reactions for the facile preparation, isolation, and characterization (frequently through an X-ray crystal structure, Table 2, entries 37−40, and Figure 9) of the reacting intermediate(s) **180a**,**b**, which allow the inference of the mechanism of the enantiodiscrimination. In this section, discussion will be limited to Ph- and *t*-Bu-box; other important box's will be discussed later.

The asymmetric allylic alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene **182** with dimethyl malonate, catalyzed

Scheme 62



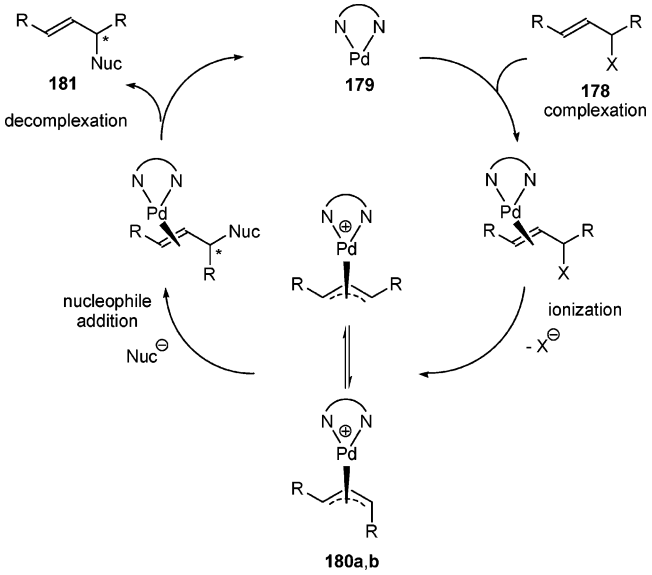
175 (R = $CO_2CH_2CCl_3$) 86 176 177

Table 39. Enantioselective Catalyzed Mukaiyama−Michael Reactions of Enolsilanes 86 and Azodicarbonyl Derivatives 175[178]

entry	R^2 (conf.)	A	box	additive	yield (%)	ee (%) (conf.)
1	Me	Ph	(*S*)-**2**		60	90 (*R*)
2	Me	Ph	(*S*)-**2**	TFE[b]	95	99 (*R*)
3	Me	6′-MeONaph	(*S*)-**2**	TFE[b]	96	99 (*R*)
4	*i*-Bu	Ph	(*S*)-**2**	TFE[b]	92	98 (*R*)
5	Ph	4′-MeOPh	(*S*)-**2**	TFE[b]	94	97 (*R*)
6	Me (*E*)	S*t*-Bu	(*S*)-**2**	TFE[b]	85	96 (*R*)
7	Me (*Z*)	S*t*-Bu	(*S*)-**2**	TFE[b]	89	84 (*S*)
8	Me	1-Pyrrole	(*S*)-**2**	TFE[b]	96	99 (*R*)
9	*t*-Bu	1-Pyrrole	(*S*)-**2**	TFE[b]	*a*	

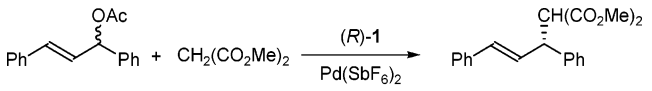
[a] An 80% yield of amination in position 2 of the pyrrole ring. [b] TFE is trifluoroethanol.

Scheme 63



181 179 178 180a,b

Scheme 64

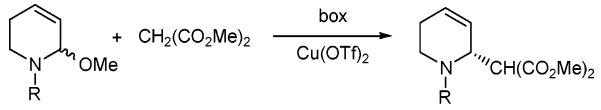


182 183

by [(*R*)-**1**/$Pd(PF_6)_2$], gives (*R*)-**183** with 95% ee (Scheme 64).[30] Beside this result, the use of new 4,5-disubstituted box's (whose behavior as ligands for catalysts of the above reaction will be discussed later) and the isolation of their palladium complexes have been reported, and even if none of these complexes was suitable for X-ray analysis, their structures were solved by ^{1}H NMR spectroscopy. The complex [(*R*)-**1**/$Pd(PF_6)_2$·(CH_2CHCH_2)] deserves specific interest, and the most significant characteristic of this complex is the loss of symmetry of both the box and the allyl ligand upon coordination. The reaction reported in Scheme 64 can be also catalyzed by [(*S*)-**2**/$Pd(PF_6)_2$], and (*S*)-**183** is obtained with 33% ee.[180]

Dimethyl malonate is the alkylating agent of 1-substituted 3,4-dehydro-2-methoxypiperidines (**184**, R = COAr and CO_2Me), and (*R*)-**185** are the products when [(*S*)-**1**/$Cu(OTf)_2$] is used as the catalyst: 34−78% yields and 41−53% ee were obtained, while [(*S*)-**2**/$Cu(OTf)_2$] gave lower enantiomeric excesses (Scheme 65).[181]

Scheme 65



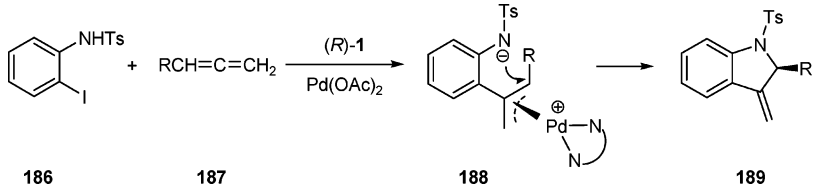
184 185

The allylic substitution reaction has an intramolecular version, and the reagent undergoing the cyclization may derive from different routes. The aryl compound **186** (or vinylic iodides) with a nucleophilic substituent in the ortho (or, respectively, in the allylic) position reacts with allenes **187** under a palladium-catalyzed coupling to give palladium complex **188**, which undergoes intramolecular allylic substitution reaction to give the heterocyclic product **189** (Scheme 66).[182] The result of a throughout screening of several ligands revealed that (*R*)-**3d** was the optimal ligand for this reaction. With this catalyst several heterocycles, either monocyclic or bicyclic such as **189**, have been obtained with enantioselectivities often >80% ee (e.g., **189** is obtained in 94% yield and 82% ee), and their configurations were found to be (*S*), whose rationale is the backside nucleophilic displacement of **188**.

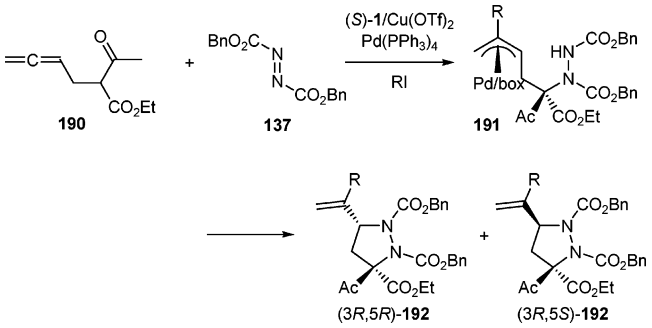
The reaction of allene-*β*-ketoester **190** with dibenzyl azodicarboxylate **137** (R^2 = Bn) is an alternative way to introduce the nucleophile, via a [(*S*)-**1**/$Cu(OTf)_2$]-catalyzed enantioselective amination, suitably placed to give the intramolecular allylic substitution reaction. The carbopalladiation reaction of the allene with an aryl (or vinyl or heteroaryl) iodide (RI) affords the *π*-allyl palladium intermediate **191**, which can be trapped by the NH in the diastereoselective step to give the pyrazoline derivatives (3*R*,5*R*)- and (3*R*,5*S*)-**192** (Scheme 67).[183] The solvent is very important in both steps, CH_2Cl_2 is required with copper complexes, THF with palladium complexes, and the reaction can be run in "one pot" by diluting the first solvent with 1,4-dioxane to allow the reaction to be run at 100 °C. The reaction suffers an important limitation; with each R group, the enantioselectivity of both pyrazolidines is very high (97−99% ee), but diastereoselectivity is disappointing (in the range of 1:1−1:2).

In the intramolecular allylic substitution reaction, the nucleophile can be obtained from a triple bond, whose attack from an external nucleophile (AcO^-, the palladium counterion), gives the carbon nucleophile. This promotes the ring closure on the box−palladium-coordinated allylic group

Scheme 66

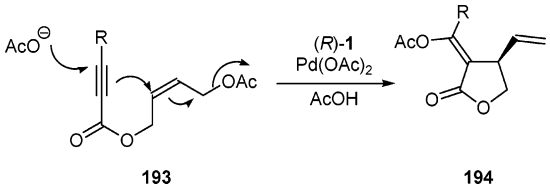


Scheme 67



having AcO as the leaving group.[184−186] The sequence reported in Scheme 68 starts from (*Z*)-4′-acetoxy-2′-butenyl-

Scheme 68



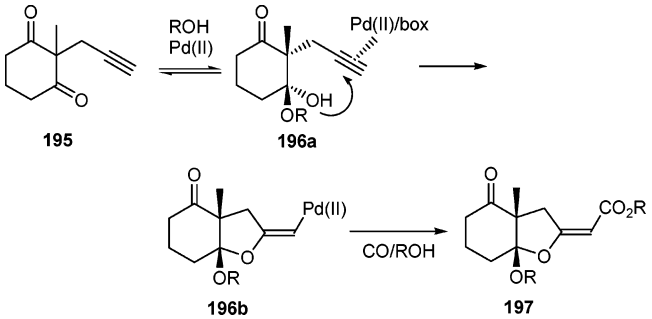
2-alkynoates **193**, which affords, with catalyst [(*R*)-**1**/Pd(OAc)$_2$] in AcOH, α-(*Z*)-acetoxyalkylidene-*β*-vinyl-*γ*-butyrolactones **194**, and the results with different R groups are reported in Table 40.

Table 40. Asymmetric Cyclizations of 193[184,185]

entry	R	yield (%)	ee (%) (conf.)
1	Me	78	92 (*R*)
2	*n*-Pr	80	80 (*R*)
3	Ph	58	79 (*R*)
4	*i*-C_7H_{15}	77	85 (*R*)
5	$MeOCH_2$	67	87 (*R*)

Another version of the intramolecular allylic substitution reaction has a triple bond attacked from an internal nucleophile (OH^-), formed in situ from an alcohol and the carbonyl group of **195** (Scheme 69), this being the step that induces enantioselectivity because of the coordination of the triple

Scheme 69



bond in **196a** with [(*S*)-**1**/Pd(CF$_3$CO$_2$)$_2$]. The resulting organo-palladium **196b** is then carbonylated and esterified to **197**. The effect of ROH is crucial since the use of bulky alcohols increases the enantiomeric excess, which goes from 8% ee of (*R*)-**197** with MeOH to 43% ee (*S*)-**197** with *i*-BuOH.[187] If cyclic 2-methyl-2-propargyl-1,3-diol is used instead of dione **195**, then the reaction follows again Scheme 63, and the good enantioselectivity with MeOH (65% ee) proves that the effect of ROH has its influence on the formation of **196a**.[188] These products may be converted in useful intermediates for the synthesis of natural products.

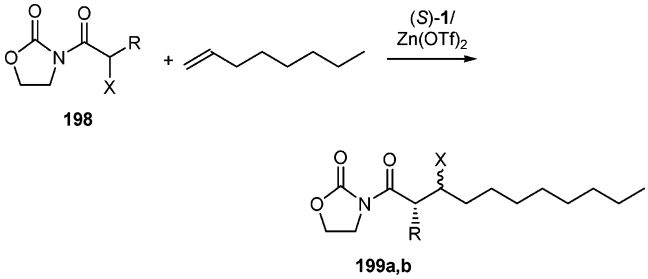
4.6. Radical Reactions

A recent review covered the enantioselective radical processes, and since the authors of this review are highly engaged in box chemistry, this review is strongly recommended to those interested to the field.[189]

As all previous catalytic enantioselective processes, a box-complexed Lewis acid gives either the substrate-bound or the radical-bound species, which determines the approach of the second reagent (the enantioselectivity-determining step) and, due to its specific effect as a Lewis acid, the increase of the rate of the chiral pathway versus the background reaction. Since the majority of the box-catalyzed radical processes involve N-acyl-substituted oxoheterocycles, which behave as bidentate reagents during the catalytic cycle, their reactions will be discussed first.

If 3-acyl-2-oxazolidinone **198** has an α-iodine atom in the chain (R = Me, X = I), then homolysis of the C−X bond gives two radicals (one bound), which can be transferred (reagent-bound process) to the unsaturated group of 1-octene, giving two diastereomers **199a** (X = I), which can be dehalogenated with Zn/AcOH giving a couple of enantiomers **199b** (X = H) (Scheme 70).[190] The optimized conditions with [(*S*)-**1**/Zn(OTf)$_2$] give (*S*)-**199b** in 40% ee.

Scheme 70



The couple of radicals derived by bromo derivatives **198** with Et$_3$B (an efficient initiator at low temperatures) may be trapped with allylsilanes or allylstannanes in the presence of box-based Lewis acids (reagent-bound process) to give *β*-bromo silane (or stannane) **200**, which undergoes the elimination of ZBr to give **201** that is formally the result of an allyl transfer (Scheme 71).[15] Some of the appreciable results are reported in Table 41; among them, Zn(OTf)$_2$ (the

Scheme 71

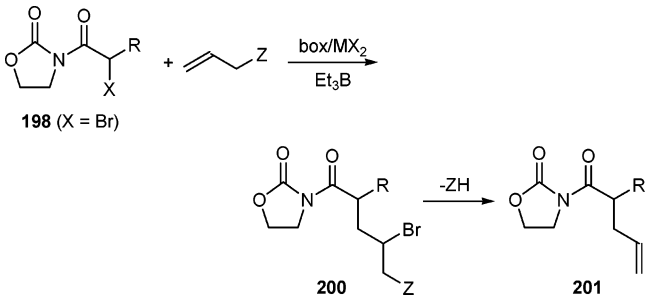
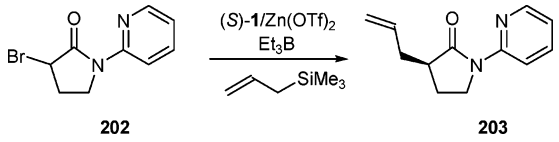


Table 41. Reactions of 3-(α-Bromoacyl)-2-Oxazolidinone 198 with Allyl Silanes and Stannanes[15]

entry	R	Z	box	MX_2	yield (%)	ee (%) (conf.)
1	Et	$SnBu_3$	(*R*)-**1**	$Zn(OTf)_2$	84	42 (*S*)
2	Et	$Si(OEt)_3$	(*R*)-**1**	$Zn(OTf)_2$	65	60 (*S*)
3	CH_2t-Bu	$SnBu_3$	(*R*)-**1**	$Zn(OTf)_2$	63	74 (*R*)
4	CH_2t-Bu	$SiMe_3$	(*R*)-**1**	$Zn(OTf)_2$	88	90 (*R*)
5	CH_2t-Bu	$SiMe_3$	(*R*)-**1**	MgI_2	86	68 (*S*)
6	CH_2t-Bu	$SiMe_3$	(*S*)-**2**	MgI_2	61	78 (*R*)

Scheme 72



Scheme 73

best enantiomeric excess) and MgI_2 under identical conditions give opposite enantiomers (entries 4, 5).

The same reaction can be performed with allyltrimethylsilane on 3-bromo-1-(2-pyridyl)-2-pyrrolidone **202**, which behaves as a bidentate ligand with [(*S*)-**1**/$Zn(OTf)_2$] (reagent-bound process), to give (*S*)-**203** in 59% ee (Scheme 72).[191]

In the absence of any radical trap, the radical derived from **198** (R = Ph, X = H) under oxidative conditions dimerizes to **204** (Scheme 73), the D,L/meso ratio is ~1:1, and it is noteworthy that both (*R*)-**1** and (*S*)-**2** give the same (*S*,*S*)-**204** enantiomer despite their opposite configurations.[192]

Porter et al. achieved one of the earliest examples of a substrate-bound process activated by a [box/Lewis acid] complex.[193] This process describes the addition of a radical generated from alkyl iodides to 3-acryloyl-2-oxazolidinone **163**, the resulting new radical being then trapped by allyltributylstannane, with the intermediate (as reported in Scheme 71) that loses Bu_3SnBr to give **205**. Under the stoichiometric conditions reported in Scheme 74, for R^2 = cyclohexyl and *tert*-butyl, the yields of (*S*)-**205** are 61% and 78%, and the enantiomeric excesses 80% and 88%, respectively, whereas [(*S*)-**2**/$Zn(OTf)_2$] gives a racemic product.[193]

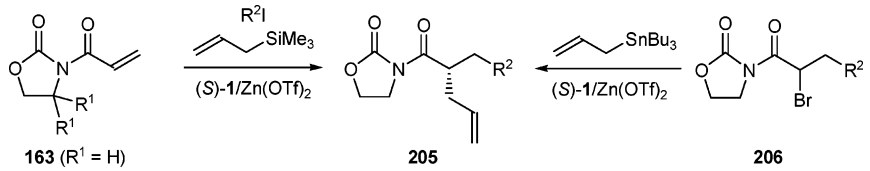
The stereochemical efficiency of the reactions in Scheme 74 can be compared, the substrate-bound addition/trapping process from **163** to **205** versus the reagent-bound process involving fragmentation of **206** and addition of allyl stannate to the radical.[194] In both cases the selectivity increases with the increase of Lewis acid equivalents, and the substrate-bound addition/trapping sequence gives a higher enantiomeric excess than the corresponding reagent-bound fragmentation reaction. Both processes give a higher enantioselectivity with the increase of the steric hindrance of R (74% and 90% ee, respectively, for R = *t*-Bu), and a linear relationship is obtained by plotting log(*R*/*S*) vs Taft E'_s steric parameters.

The above substrate-bound process was further developed by Sibi and Porter: Compound **163** (R^1 = H) reacts with the radical derived from the cleavage of R^2I promoted by Et_3B/O_2, but the new radical was quenched with Bu_3SnH to give **207**, which is formally the product of the conjugate addition of R^2H (Scheme 75).[29,195] The results for this reaction are reported in Table 42; these are obtained by using stoichiometric amounts of [box/MX_2], except entry 9, which is carried out under catalytic conditions (0.2 equiv of Lewis acid). The box ligand (*S*)-**1** gives the best enantioselectivities with $Zn(OTf)_2$ (Table 42, entries 3 and 7−9), and (*S*)-**2** the best enantioselectivitity with $MgBr_2$ (Table 42, entries 5 and 10). It is also observed that box ligands having identical absolute configurations give opposite product enantiomers.

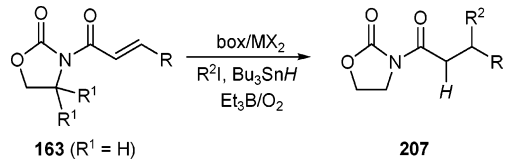
An attempt was made to use optically active Lewis acids derived from metal triflamides under catalytic conditions; the complexes were tested in the reaction in Scheme 75 between **163** (R = Ph, R^1 = H) and *i*-PrI.[196] (*S*)-**2** gives interesting results (94% yield and 80% ee) only with $Fe(NTf_2)_2$, but it cannot compete with box **10a** and MgI_2,[29] which (together with **9a**, **10b**,**c**, and MgI_2, $Mg(NTf_2)_2$, and $Fe(NTf_2)_2$)[196] gives **207** (R = Ph, R^2 = *i*-Pr) in yields between 82% and 99% and enantioselectivities up to 98% ee, under substoichiometric conditions.[29]

The substrate-bound conjugate radical addition can be carried out on several substrates. The reaction of R^2I and 3-(β-acyloxy)-acryloyl-2-oxazolidinones **163** (R = acyloxy, R^1 = H) gives excellent yields and enantioselectivities when catalyzed with stoichiometric amounts of [(*S*)-**2**/MgI_2] (enantioselectivities regularly increase with catalyst loadings from 59% ee for 50 mol % catalyst to 93% ee for 100 mol % catalyst) suggesting either a slow turnover of the catalyst or a competition with the uncatalyzed process.[197] The absolute stereochemistry was determined for two products (Table 43, entries 2 and 9), and it is consistent with a Si face radical addition to the s-cis conformer of the substrate. This is the same sense of selectivity as that obtained with cinnamate and crotonate oxazolidinones (Table 42) suggesting the presence of similar reacting intermediates. The success, or not, of the catalytic version probably depends on the stability of the reaction intermediate that influences the turnover rate; for the reactions with 3-(β-acyloxy)-acryloyl-2-oxazolidino-

Scheme 74



Scheme 75



163 (R^1 = H) **207**

Table 42. Enantioselective Radical Additions of 3-Alkenoyl-2-Oxazolidinones 163 with R^2I.[195]

entry	R	R^2	box	MX_2	yield (%)	ee (%) (conf.)
1	Ph	*i*-Pr	(*R*)-**1**	$MgBr_2$	84	32 (*R*)
2	Ph	*i*-Pr	(*S*)-**1**	MgI_2	88	47 (*S*)
3	Ph	*i*-Pr	(*R*)-**1**	$Zn(OTf)_2$	88	61 (*R*)
4	Ph	*i*-Pr	(*S*)-**2**	$Zn(OTf)_2$	61	37 (*R*)
5	Ph	*i*-Pr	(*S*)-**2**	$MgBr_2$	92	77 (*R*)
6	Ph	*i*-Pr	(*S*)-**2**	MgI_2	88	61 (*R*)
7	Me	Cyhex	(*R*)-**1**	$Zn(OTf)_2$	66	72 (*R*)
8	Me	*t*-Bu	(*R*)-**1**	$Zn(OTf)_2$	90	82 (*R*)
9[a]	Me	*t*-Bu	(*S*)-**1**	$Zn(OTf)_2$	71	70 (*S*)
10	Me	*t*-Bu	(*S*)-**2**	$MgBr_2$	78	82 (*R*)

[a] Under catalytic conditions (0.2 equiv of Lewis acid).

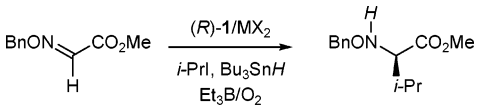
Table 43. Enantioselective Radical Additions of 3-(β-Acyloxy)-Acryloyl-2-Oxazolidinones 163 with R^2I in the Presence of 1 Equiv of Lewis Acid [(*S*)-2/MgI_2][197]

entry	R	R^2	yield (%)	ee (%) (conf.)
1	OCOMe	*i*-Pr	70	89
2	OCOPh	*i*-Pr	90	93 (*R*)
3	OCO(4-FC_6H_4)	*i*-Pr	94	62
4	OCO(4-$MeOC_6H_4$)	*i*-Pr	83	82
5	1-naphthoyloxy	*i*-Pr	87	46
6	1-naphthoyloxy	*i*-Pr	79	80
7	OCOPh	Et	90	50
8	OCOPh	Cyhex	70	84
9	OCOPh	*t*-Bu	91	89 (*R*)
10	OCOMe	*t*-Bu	73	95

nes the presence of an additional donor atom in the substrate must be considered.

The substrate-bound radical addition can also take place on the C=N bond of glyoxylic oxime methyl ester **208** with *i*-PrI in the presence of Lewis acids derived from (*R*)-**1**. $Mg(OTf)_2$, $Zn(OTf)_2$, $Yb(OTf)_3$, and $MgBr_2$ were tested, and the enantiomeric excesses of (*R*)-**209** were 2%, 10%, 24%, and 52% ee, respectively (Scheme 76).[198] This

Scheme 76

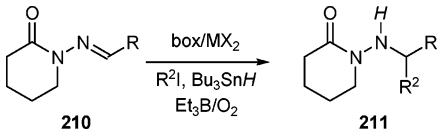


208 **209**

potentially useful asymmetric synthesis of α-amino acids has a limit in the stoichiometric amount of chiral Lewis acid required. This is probably due to the difficult substitution of product **209** by **208** in the reacting complex (which is the key step to promote the catalysis turnover) for the increased binding properties developed in the product with the formation of the NH group.

The substrate-bound radical addition of alkyl iodides to 1-iminoaryliden-2-piperidinone **210** gives **211** (Scheme 77): Yields are in the range of 44−88%, and the enantiomeric excess of ∼90% ee, but stoichiometric conditions are

Scheme 77



210 **211**

required.[199] The reaction with 1-iminobenzylidene derivative and *i*-PrI was optimized with [(*S*)-**2**/$Cu(OTf)_2$] in benzene/CH_2Cl_2 as the solvent and gave (*R*)-**211** with an excellent yield and 95% ee.

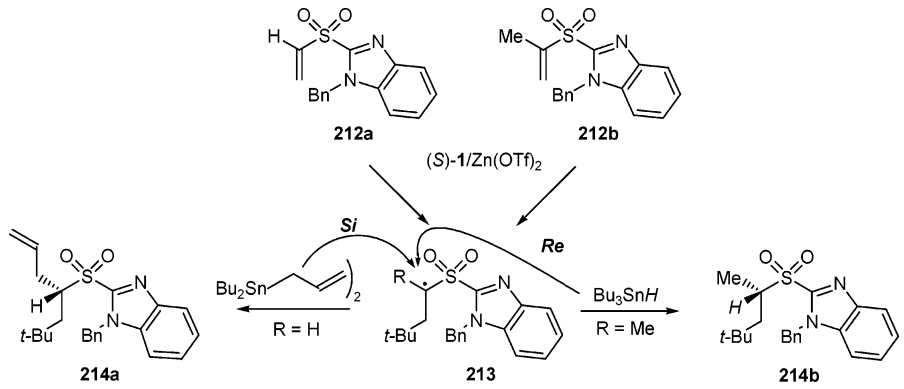
Alkylidene sulfones bound to pyridyl, or better to benzimidazolyl moiety **212a**,**b**, achieve a bidentate chelation with [box/$Zn(OTf)_2$] complexes, and a substrate-bound radical addition derived from R^2I (in the presence of Et_3B as the initiator) gives bound radical **213** (R = H or Ph from **212a**,**b**, respectively) (Scheme 78).[200,201] This intermediate can be trapped either by allylation (with $Bu_2Sn(allyl)_2$) or by hydrogen (with Bu_3SnH); surprisingly diallylbutyltin approaches the Si face of the carbon radical to give 84% ee of (*S*)-**214a**, whereas the tin hydride approaches the Re face of the radical center to achieve 38% ee of (*S*)-**214b**. All reactions occur under stoichiometric conditions, with suitable substituents may furnish products with up to 91% ee, and with **212b** as starting reagent, the Lewis acids derived from (*S*)-**2** give only negligible enantioselectivity (5% ee).

If both the radical source and the radical trap are in the same molecule, then the resulting intramolecular reaction promotes a cyclization, which is an interesting reaction as multiple stereocenters are formed. When the radical is created by cleavage of the C−Br bond of **215**, which incorporates a C=C bond, the intramolecular version of the reaction already reported in Scheme 64 gives **216** (Scheme 79).[202] In the catalytic version with [(*S*)-**2**/$Mg(ClO_4)_2$] and 4 Å MS, the yields and enantiomeric excesses of **216** are reported in Table 44. The presence of a further double bond (Scheme 79, **217** (n = 1)) promotes a radical cyclization cascade with formation of (2*R*,3*S*,4*S*,5*S*)-**218** (24% yield and 33% ee).[203] The homologous **218** (n = 2) is obtained in 16% yield and 84% ee, but its absolute configuration is unknown.

If α,β-unsaturated sulfones, bound to the benzimidazolyl moiety, are tethered to a potential radical source, the C−I bond in **219**, then its cleavage promotes a radical cyclization that can be accomplished by a hydrogen atom donor to give **220** (Scheme 80). The reaction is run under stoichiometric conditions, and the coordination of one of the sulfonyl oxygen atoms and the unsubstituted benzymidazole nitrogen atom by [(*S*)-**1**/$Zn(OTf)_2$] gives (*R*)-**220** in 93% yield and 70% ee; the same reaction with (*S*)-**2** gives a racemate.[204]

If susceptible positions of organic compounds (e.g., the allylic position) can be acyloxylated by *tert*-butyl peresters in the presence of a trace of Cu(I) in accordance to the Kharasch reaction, then why not experiment with the enantioselective variant running the reaction in the presence of chiral ligands such as box? This has been done with cyclopentene or cyclohexene **221** (n = 1, 2), *tert*-butyl perbenzoate, (*S*)-**1** or (*S*)-**2**, and CuOTf, to give cycloalkenyl-2-benzoate **222**. The mechanism starts with the cleavage of the peroxy bond, which gives [box/Cu(II) benzoate] **223** and a *tert*-butoxy radical that abstracts an allylic hydrogen atom to give *t*-BuOH and the allyl radical. The addition of the radical to **223** generates the Cu(III) species **224**, which undergoes fragmentation to **222** and [box/Cu(I)] (Scheme 81).[205] The first results were good enough to stimulate the interest of several groups since [(*S*)-**1**/CuOTf] gave with

Scheme 78



Scheme 79

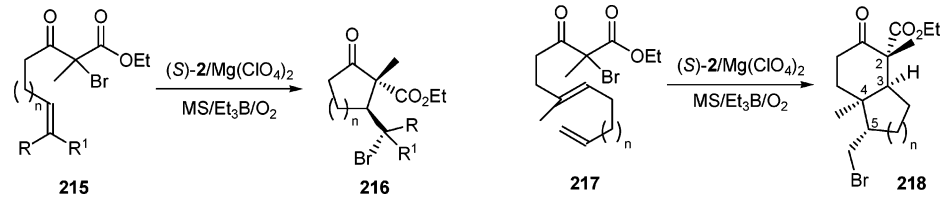
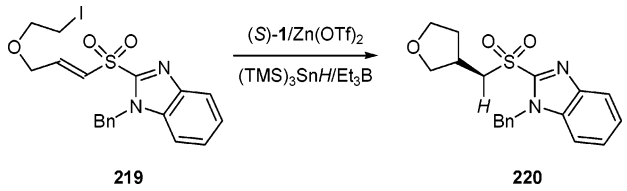


Table 44. Enantioselective Radical Cyclizations of 215 in Toluene[202]

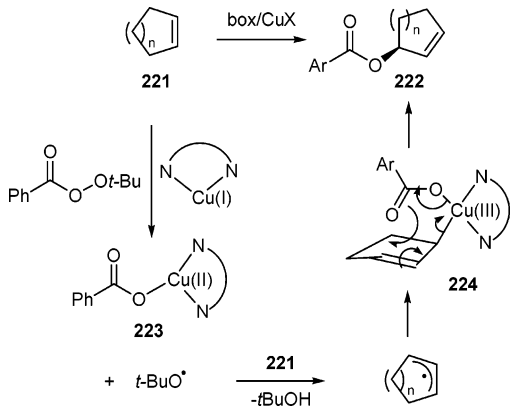
entry	*n*	R	R^1	yield (%)	dr	ee (%) (conf.)
1	1	Me	Me	68		92 (2*R*,3*S*)
2	2	Me	Me	53		94 (2*R*,3*S*)
3	2	Et	H	81	1:1.4	74 (2*R*,3*S*), 95 (2*R*,3*S*)[a]
4	2	H	Et	58	1:1	74 (2*R*,3*S*), 87 (2*R*,3*S*)[a]

[a] The enantiomeric excesses of the diastereomers and the absolute configurations of the ring stereocenters.

Scheme 80



Scheme 81



cyclopentene and cyclohexene 84% and 77% yields of **222** with 71% and 67% ee, respectively. The same reactions performed with [(*S*)-**2**/CuOTf] gave 61% and 64% yields, with 84% and 77% ee, respectively.

The asymmetric Kharasch reaction was tested on several alkenes, with different aromatic perester oxidants, box ligands, copper salts, and solvents, and a selection of the most significant results is reported in Table 45. MeCN is the best solvent, *tert*-butyl *p*-nitroperbenzoate the best oxidant, both (*S*)-**1** and (*S*)-**2** give the same enantiomer, the best enantiomeric excess is obtained with the latter box (Table 45, entries 1, 10, 13, and 16 vs 4, 12, 14, and 17), and three Cu(I) salts give comparable results even if the most frequently used is PF_6.

The Kharasch oxidation can be performed on acetylenes having a propargylic hydrogen atom (**225**), and the benzoyl esters of the corresponding propargylic alcohols **226** are obtained in high yields and reasonable levels of induction (Scheme 82).[211] [(*S*)-**1**/$CuPF_6$] gives better enantioselectivities than the corresponding catalysts derived from (*S*)-**2**, and enantioselectivities of about 50% ee are obtained only with 1-trimethylsilyl- and 1-phenyl-2-hexyne.

tert-Butyl hydroperoxide, box, and CuOTf are the conditions for the asymmetric peroxidation of cycloalkenes **221**; the peroxides **227** are obtained in good yields, but enantioselectivity is in the range of 4−20% ee. An interesting result is obtained with *t*-BuO_2H/AcOH since cyclohexene **221** (*n* = 2) gives both the peroxide **227** and the acetate **228** (Scheme 83); while (*S*)-**2** gives both products in good yields but in nearly racemic form, (*S*)-**1** gives again peroxide as a racemate, but (*S*)-**228** is obtained in 47% ee.[212]

The Baeyer−Villinger reaction of 3-phenylcyclobutanone, catalyzed by [(*S*)-**2**/Pd],[213] is the only other example of box-catalyzed oxidation reported in the literature. It should not be considered in this section because it does not involve radicals, but certainly the modest 15% ee does not justify a specific section dedicated to it.

4.7. Diels−Alder Reactions

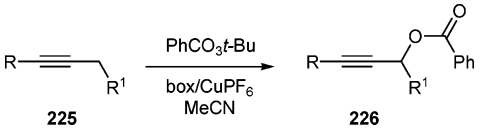
It has already been mentioned that in 1991 two short successive communications appeared in the *Journal of the American Chemical Society* describing the early use of box's as ligands for the preparation of optically active catalysts, and one of them, by Corey et al.,[7] performed the enantioselective Diels−Alder reaction of 3-acryloyl-2-oxazolidinone **163** (R = R^1= H) with cyclopentadiene, catalyzed by [(S)-**1**/Fe(III)X_3] (X = halogens) complexes. The reaction

Table 45. Asymmetric Allylic Oxidations of Alkenes

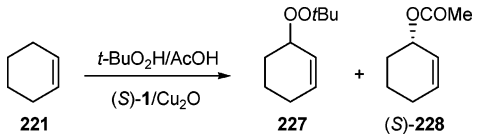
entry	alkene	Ar	box	CuX_n	solvent	yield (%)	ee (%) (conf.)	ref
1	cyclopentene	Ph	(*S*)-**2**	CuOTf	MeCN	44	70 (*S*)	206
2	cyclopentene	*p*-$NO_2C_6H_4$	(*S*)-**2**	CuBr	MeCN	52	53 (*S*)	207
3	cyclopentene	*p*-$NO_2C_6H_4$	(*S*)-**2**	$CuPF_6$	MeCN	52	79 (*S*)	210
4	cyclopentene	Ph	(*S*)-**1**	$CuPF_6$	MeCN	72	69 (*S*)	208
5	cyclopentene	*p*-$NO_2C_6H_4$	(*S*)-**1**	CuBr	MeCN	37	54 (*S*)	207
6	cyclopentene	*p*-$NO_2C_6H_4$	(*S*)-**1**	$CuPF_6$	MeCN	49	82 (*S*)	210
7	cyclohexene	Ph	(*S*)-**2**	CuOTf	MeCN	43	80 (*S*)	206, 207
8	cyclohexene	Ph	(*S*)-**2**	$CuPF_6$	MeCN	74	40 (*S*)	208
9	cyclohexene	Ph	(*S*)-**1**	$CuPF_6$	MeCN	71	59 (*S*)	208
10	cyclohexene	*p*-$NO_2C_6H_4$	(*S*)-**2**	$CuPF_6$	MeCN	61	84 (*S*)	210
11	cyclohexene	*p*-$NO_2C_6H_4$	(*S*)-**2**	CuBr	MeCN	53	63 (*S*)	207
12	cyclohexene	*p*-$NO_2C_6H_4$	(*S*)-**1**	$CuPF_6$	MeCN	44	96 (*S*)	207, 210
13	cycloheptene	*p*-$NO_2C_6H_4$	(*S*)-**2**	$CuPF_6$	MeCN	3	95 (*S*)	210
14	cycloheptene	*p*-$NO_2C_6H_4$	(*S*)-**1**	$CuPF_6$	MeCN	23	56 (*S*)	210
15	cyclooctene	Ph	(*S*)-**2**	CuOTf	MeCN	44	13 (*S*)	207
16	1,5-cyclooctadiene	*p*-$NO_2C_6H_4$	(*S*)-**2**	$CuPF_6$	MeCN	13	94 (*S*)	210
17	1,5-cyclooctadiene	*p*-$NO_2C_6H_4$	(*S*)-**1**	$CuPF_6$	MeCN	46	74 (*S*)	210
18	allylbenzene	Ph	(*S*)-**2**	CuOTf	PhH	34	36 (*R*)	206
19	bicyclopentadiene	Ph	(*S*)-**2**	$Cu(OTf)_2$	MeCN	14	87[a]	209

[a] 1-Benzoyloxy; 3a-benzoyloxy as a byproduct (7% yield, 13% ee).

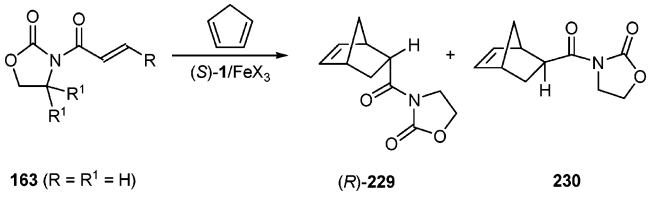
Scheme 82



Scheme 83



Scheme 84



(Scheme 84) was found to be endo-selective (**229**/**230** = 96:4), and (1*R*,2*R*,4*R*)-**229**, whose configuration from now on is simplified as (2*R*), was obtained in 82% ee. This was the beginning of a long story: Box complexes were found to function as asymmetric Diels−Alder catalysts with alkenoyl imide dienophiles,[56] and especially 3-acryloyl- and 3-crotonoyl-oxazolidinones were used as the benchmark to compare the efficiencies of different catalysts in asymmetric Diels−Alder reactions. The next paragraphs are the summary of the story, and Table 46 starts to summarize the results obtained within these years, investigating the reaction between 3-acryloyl-2-oxazolidinone and cyclopentadiene with different catalysts (changing the cations and their counterions with phenyl- and *tert*-butyl-box's), different solvents, and the effects of several additives that sometimes have a dramatic effect on enantioselectivity.

From the investigations by Evans et al., it appears that the best combination is box **2** and Cu(II)[46,60,120,214,215,222] and the best counterions are OTf and SbF_6 (Table 46, entries 3−8). Among the tests with different cations (Table 46, entries 9−16), only cobalt and manganese gave discrete enantiomeric excesses, by far not comparable to copper. The sense of asymmetric induction ((*S*)-**2** gives (*S*)-**229** as the main product) can be rationalized through a square-planar rather than a tetrahedral reaction intermediate (Figure 13).[214] Double stereodifferentiating experiments with dienophiles having a further chiral center on the oxazolidinone ring support this model since the catalysis with [(S)-**2**/$Cu(OTf)_2$] is a matched pair if **163** has R^1 = (*R*)-benzyl and a mismatched pair with its (*S*)-enantiomer (Table 46, entries 17 and 18). The solvent effect (Table 46, entries 3−6) suggests to exclude not only protic solvents but also MeCN, which significantly reduces enantioselectivity.

The best Lewis acid for **1** is $Zn(SbF_6)_2$ (Table 46, entry 34),[60,120] but the most interesting cation is Mg(II).[216,217,220] With (*R*)-**1**, enantioselectivity is dependent on both counterion and additives that behave as auxiliary ligands. When the counterion is perchlorate, the product is (*S*)-**229**, but if 2 equiv H_2O, 1 equiv of ethylene glycol, or 2 equiv of tetramethylurea are added, then (*R*)-**229** is obtained (Table 46, entries 19, 20, 24, and 25). When the counterion is OTf, the reaction product is (*R*)-**229**, and the enantioselectivity does not change if H_2O or tetramethylurea (TMU) are added (Table 46, entries 27−29). This unusual behavior (the same chiral box with the same cation and the same counterion may give opposite enantiomers if an achiral component is added) can be rationalized if H_2O, TMU, or $(CH_2OH)_2$ behave as ligands that expand the coordination number from 4 (tetrahedral) to 6 (octahedral with two oxygen atoms of auxiliary ligands, one axial and one equatorial) when the counterion is perchlorate. This change of coordination is supported by ^1H NMR spectroscopy, and the position of the auxiliary ligands by the result with diethylene glycol. With the more coordinating OTf anions, the reaction intermediates always have octahedral coordination (with two OTf's in the axial positions), and this complex does not change by addition of either H_2O or TMU. Figure 14 gives a representation of the three reacting intermediates; the tetrahedral one makes the Re face of the dienophile available to the attack of cyclopentadiene; those with the octahedral structures allow the attack to the Si face.

The three reacting intermediates represented in Figure 14 involve a ratio of (*R*)-**1**/**163** of 1:1; hence, through the use of catalysts with different enantiomeric purities, linear relationships between the enantiomeric excess of **229** and

Table 46. Enantioselective Diels−Alder Reactions between Cyclopentadiene and 3-Acryloyl-2-Oxazolidinones 163 (R = H) Catalyzed by [Box/MX_n]

entry	R^1	box	MX_n	additives	solvent	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	H,H	(*S*)-**1**	FeI_3/I_2		CH_2Cl_2	85	96:4	82 (*R*)	7
2	H,H	(*S*)-**1**	$Cu(OTf)_2$		CH_2Cl_2	92	95:5	30 (*S*)	60, 214
3	H,H	(*S*)-**2**	$Cu(OTf)_2$		CH_2Cl_2	86	98:2	>98 (*S*)	60, 214, 218, 222
4	H,H	(*S*)-**2**	$Cu(OTf)_2$		THF	>98	97:3	98 (*S*)	60
5	H,H	(*S*)-**2**	$Cu(OTf)_2$		$MeNO_2$	>98	92:8	84 (*S*)	60
6	H,H	(*S*)-**2**	$Cu(OTf)_2$		MeCN	87	92:8	58 (*S*)	60
7	H,H	(*S*)-**2**	$Cu(SbF_6)_2$		CH_2Cl_2	>95	96:4	>98 (*S*)	60, 120
8	H,H	(*S*)-**2**	$Cu(ClO_4)_2$[a]		CH_2Cl_2	85	97:3	6 (*S*)	221
9	H,H	(*S*)-**2**	$Co(OTf)_2$		CH_2Cl_2	85	90:10	50 (*S*)	60
10	H,H	(*S*)-**2**	$Mn(OTf)_2$		CH_2Cl_2	80	85:15	50 (*S*)	60
11	H,H	(*S*)-**2**	$Ni(OTf)_2$		CH_2Cl_2	75	90:10	40 (*S*)	60
12	H,H	(*S*)-**2**	$Zn(OTf)_2$		CH_2Cl_2	85	95:5	38 (*S*)	60
13	H,H	(*S*)-**2**	LiOTf		CH_2Cl_2	89	85:15	14 (*S*)	60
14	H,H	(*S*)-**2**	$Cd(OTf)_2$		CH_2Cl_2	80	90:10	10 (*S*)	60
15	H,H	(*S*)-**2**	$Sm(OTf)_3$		CH_2Cl_2	78	80:20	racemate	60
16	H,H	(*S*)-**2**	$Lu(OTf)_3$		CH_2Cl_2	75	75:25	racemate	60
17	(*R*)-Bn	(*S*)-**2**	$Cu(OTf)_2$		CH_2Cl_2	100	99:1	>98 (*S*)[b]	60, 214
18	(*S*)-Bn	(*S*)-**2**	$Cu(OTf)_2$		CH_2Cl_2	20	>95:5	36 (*S*)[b]	60, 214
19	H,H	(*R*)-**1**	$Mg(ClO_4)_2$		CH_2Cl_2	>98	93:7	73 (*S*)	216, 217, 220
20	H,H	(*R*)-**1**	$Mg(ClO_4)_2$	$2H_2O$	CH_2Cl_2	>98	95:5	73 (*R*)	216, 217, 220
21	H,H	(*R*)-**1**	$Mg(ClO_4)_2$	2MeOH	CH_2Cl_2	>98	91:9	42 (*R*)	217
22	H,H	(*R*)-**1**	$Mg(ClO_4)_2$	2EtOH	CH_2Cl_2	>98	91:9	16 (*R*)	217
23	H,H	(*R*)-**1**	$Mg(ClO_4)_2$	2*t*-BuOH	CH_2Cl_2	>98	92:8	33 (*S*)	217
24	H,H	(*R*)-**1**	$Mg(ClO_4)_2$	$(CH_2OH)_2$	CH_2Cl_2	>98	91:9	58 (*R*)	217
25	H,H	(*R*)-**1**	$Mg(ClO_4)_2$	TMU[c]	CH_2Cl_2	>98	96:4	51 (*R*)	220
26	H,H	(*R*)-**1**	$Mg(ClO_4)_2$	Py or Et_3N	CH_2Cl_2	0	0	0	220
27	H,H	(*R*)-**1**	$Mg(OTf)_2$		CH_2Cl_2	>98	92:8	88 (*R*)	218,220
28	H,H	(*R*)-**1**	$Mg(OTf)_2$	$2H_2O$	CH_2Cl_2	>98	92:8	86 (*R*)	220
29	H,H	(*R*)-**1**	$Mg(OTf)_2$	TMU[c]	CH_2Cl_2	>98	93:7	88 (*R*)	220
30	H,H	(*S*)-**1**	MgI_2/I_2		CH_2Cl_2	>98	94:6	76 (*R*)	60
31	H,H	(*R*)-**1**	$Zn(OTf)_2$		CH_2Cl_2	>98	90:10	32 (*R*)	218
32	H,H	(*R*)-**1**	$Zn(ClO_4)_2$[a]		CH_2Cl_2	>98	92:8	20 (*R*)	77
33	H,H	(*R*)-**1**	$Zn(ClO_4)_2$	MS[d]	CH_2Cl_2	>98	92:8	73 (*S*)	77
34	H,H	(*S*)-**1**	$Zn(SbF_6)_2$		CH_2Cl_2	>90	98:2	92 (*R*)	60, 120
35	H,H	(*R*)-**1**	$Ni(ClO_4)_2$[a]		CH_2Cl_2	97	88:12	52 (*R*)	219
36	H,H	(*S*)-**1**	$Cu(ClO_4)_2$[a]		CH_2Cl_2	84	97:3	41 (*S*)	221

[a] Hexahydrate salt. [b] Major endo diastereoisomer. [c] TMU is tetramethylurea. [d] Molecular sieves are 4 Å.

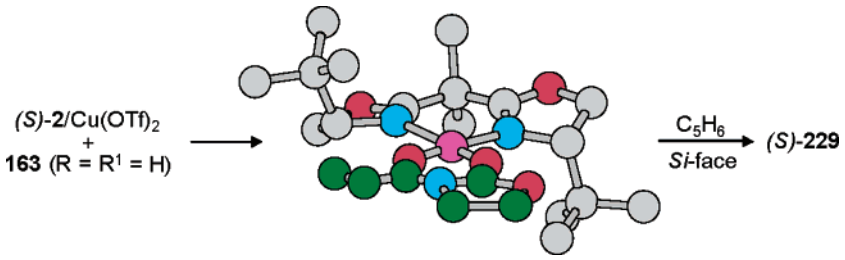


Figure 13. Square-planar intermediate complex of the Diels−Alder reaction catalyzed by [(*S*)-**2**/$Cu(OTf)_2$] between **163** (R = R^1 = H) and cyclopentadiene.

the enantiomeric excess of the catalysts (hence the enantiomeric excess of **1**) should be obtained. This was tested and punctually observed.[217,220] When the same experiment was done with the [(*R*)-**1**/$Zn(ClO_4)_2$/MS]-catalyzed reaction (Table 46, entry 33), a strong chiral amplification was observed,[77] and Figure 15 illustrates the relationships between the enantiomeric excess of (*R*)-**1** and the enantiomeric excess of (*S*)-**229** for the reactions in Table 46 entries 19 (linear) and 33 (curve). The rationale for the positive nonlinear effect derives from the thermodynamic stability of the racemic complex [(*R*)-**1**/(*S*)-**1**/Mg(II)] **24**, which was isolated, and its X-ray structure determined (Figure 10), and is much more stable and insoluble than the corresponding chiral complex [2(*R*)-**1**/Mg(II)]. This behavior, known as the "reservoir effect", is one of the possible reasons for chiral amplification.

Several examples of enantioselective catalyzed Diels−Alder reactions between cyclopentadiene and *β*-substituted 3-acryloyl-2-oxazolidinone **163** (R^1 = H), catalyzed by [box/MX_n], have been reported, and some significant results are reported in Table 46. The reaction of the crotonoyl derivative (R = Me) is best catalyzed by [(*S*)-**2**/$Cu(OTf)_2$] or [(*S*)-**2**/$Cu(SbF_6)_2$] (Table 47, entries 7 and 9)[60,214] and tolerates ionic liquids (Table 47, entry 8).[223] With (*R*)-**1** and Mg(II) as the catalyst, enantioselectivity is again a function of the counterion eventually coupled with TMU as the auxiliary ligand (Table 47, entries 1−4).[220] The enantioselectivity of the reaction with 3-(acyloxy)acrylates (Table 47, entries 12 and 13) inverts by changing the substituent of the box ligands (**1** or **2**), taking constant their (*S*)-configuration.[224]

Several examples have been reported of enantioselective Diels−Alder reactions between various dienes and 3-acryloyl-2-oxazolidinone **163** (R = R^1 = H), and Table 48 reports the most significant results. The majority of them have (*S*)-**2** and CuX_2 (X = OTf or SbF_6) as catalysts, which have been

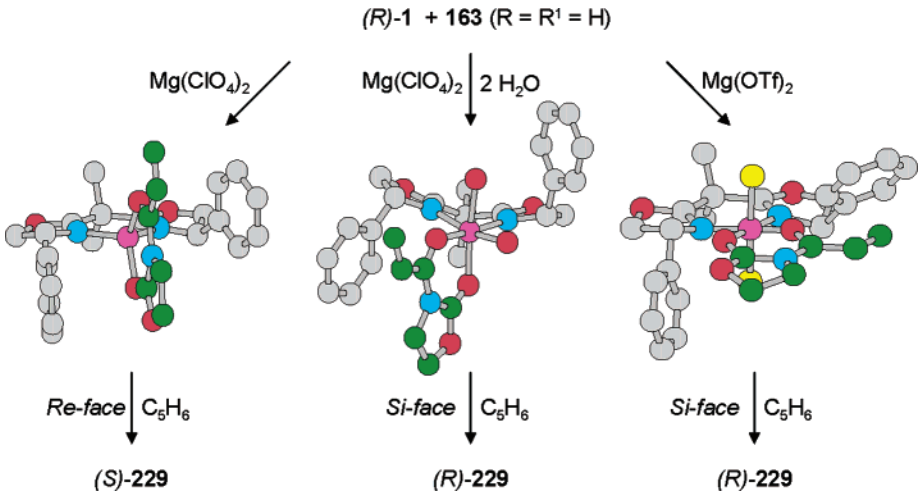


Figure 14. Tetrahedral or octahedral intermediate complexes of the Diels−Alder reactions catalyzed by [(*R*)-**1**/$Mg(ClO_4)_2$] or [(*R*)-**1**/$Mg(OTf)_2$] between **163** (R = R^1 = H) and cyclopentadiene, with or without H_2O.

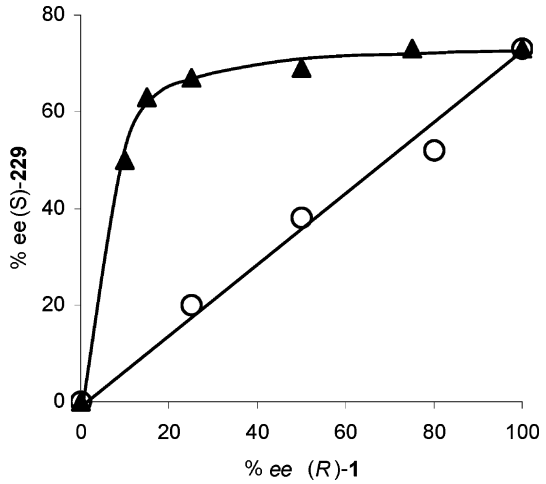


Figure 15. Relationships between the enantiomeric excess of (*R*)-**1** and the enantiomeric excess of (*S*)-**229** for the reactions in Table 46 entries 19 (○) and 33 (▲).

isolated as anhydrous or aquo complexes, and their X-ray structures have been determined (Table 2, entries 7 and 13). $Cu(SbF_6)_2$ gives the most efficient catalysts with 1,3-pentadiene (either anhydrous or hydrated (bis-aquo complex from OTf is inactive)) (Table 48, entries 8 and 9 vs 5 and 6); the addition of MS regenerates the aquo-triflate catalysts, while suppressing the activity of the aquo-hexafluoroantimonate one (Table 48, entries 6, 7, 10, and 11).[60,215,228] The Diels−Alder reaction with furan equilibrates rapidly at −20 °C, but the endo product can be isolated enantiomerically pure at −78 °C (Table 48, entry 21).[226,228]

Several dienophiles have been tested in the enantioselective Diels−Alder reaction, the majority with cyclopentadiene as the diene, and Table 49 reports the most significant results.

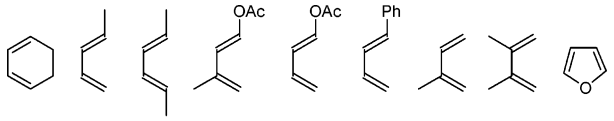
It is not astonishing that the majority of dienophiles have either a β-dicarbonyl system (**231**, **234**, **236**, and **237**) or a group β to the carbonyl that, through lone pairs, makes the dienophile suitable to behave as a bicoordinating reagent. In some cases the new group ameliorates the binding properties of the carbonyl; e.g., **233** (Table 49, entries 9−11) is 20−30 times more reactive than the corresponding oxazolidinone.[60] α-Thioacrylates **232** display higher enantioselectivity with phenylthio- compared to that with methylthio-derivatives and that with small or moderately sized ester substituents (Me ≈ Et ≈ *i*-Pr ≪ *t*-Bu) (Table 49, entries 3 and 8 vs 4−7). The effect induced by the phenyl group is due to the coordination involving only one of the two enantiotopic lone pairs of sulfur, which becomes asymmetric,

Table 47. Enantioselective Diels−Alder Reactions between Cyclopentadiene and β-Substituted 3-Acryloyl-2-Oxazolidinones 163 (R^1 = H) in CH_2Cl_2 Catalyzed by [Box/MX_n]

entry	R	box	MX_n	additive	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	Me	(*R*)-**1**	$Mg(ClO_4)_2$		>98	85:15	28 (4*S*,5*R*)	220
2	Me	(*R*)-**1**	$Mg(ClO_4)_2$	TMU[b]	93	84:16	87 (4*R*,5*S*)	220
3	Me	(*R*)-**1**	$Mg(OTf)_2$		94	81:19	84 (4*R*,5*S*)	220
4	Me	(*R*)-**1**	$Mg(OTf)_2$	TMU[b]	88	81:19	84 (4*R*,5*S*)	220
5	Me	(*S*)-**1**	$Zn(SbF_6)_2$		>98	86:14	64 (4*R*,5*S*)	60
6	Me	(*S*)-**1**	FeI_3/I_2		>98	76:24	32 (4*R*,5*S*)	60
7	Me	(*S*)-**2**	$Cu(OTf)_2$		85	96:4	97 (4*S*,5*R*)	60, 214
8[a]	Me	(*S*)-**2**	$Cu(OTf)_2$		65	93:7	92 (4*S*,5*R*)	223
9	Me	(*S*)-**2**	$Cu(SbF_6)_2$		99	85:15	99 (4*S*,5*R*)	60
10	Ph	(*S*)-**2**	$Cu(OTf)_2$		85	90:10	90 (4*R*,5*R*)	60, 214, 215
11	Ph	(*S*)-**2**	$Cu(SbF_6)_2$		96	81:19	96 (4*R*,5*R*)	60, 215
12	*p*-$CF_3C_6H_4CO_2$	(*S*)-**1**	$Cu(OTf)_2$		99	94:6	89 (4*S*,5*S*)	224
13	*p*-$CF_3C_6H_4CO_2$	(*S*)-**2**	$Cu(OTf)_2$		99	90:10	54 (4*R*,5*R*)	224
14	CO_2Et	(*S*)-**2**	$Cu(OTf)_2$		92	94:6	95 (4*R*,5*R*)	60, 214
15	CO_2Et	(*S*)-**2**	$Cu(SbF_6)_2$		88	82:18	87 (4*R*,5*R*)	60
16	Cl	(*S*)-**2**	$Cu(OTf)_2$		96	93:7	53 (3*S*,4*R*)	60, 215
17	Cl	(*S*)-**2**	$Cu(SbF_6)_2$		96	86:14	95 (3*S*,4*R*)	60, 215

[a] Reaction run in 1,3-dibutylimidazolium tetrafluoborate (DiBuIm). [b] TMU is tetramethylurea.

Table 48. Enantioselective Diels−Alder Reactions in CH_2Cl_2 between Various Dienes and 3-Acryloyl-2-Oxazolidinones 163 (R = R[1]= H) Catalyzed by [(*S*)-2/MX_n]



entry	diene	MX_n	additive	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	A	$Cu(OTf)_2$		90	98:2	82 (2*S*)	215, 225, 228
2	A	$Cu(SbF_6)_2$		90	95:5	93 (2*S*)	215, 225, 228
3[a]	A	$Cu(OTf)_2$		90		92 (2*S*)	225
4[a]	A	$Cu(SbF_6)_2$		87		96 (2*S*)	225
5	B	$Cu(OTf)_2$		72	75:25	86	60, 215, 228
6	B	$Cu(OTf)_2 \cdot 2H_2O$		<10	n.d.	n.d.	60
7	B	$Cu(OTf)_2 \cdot 2H_2O$	MS	95	74:26	85	60
8	B	$Cu(SbF_6)_2$		89	83:17	94	60, 215, 228
9	B	$Cu(SbF_6)_2 \cdot 2H_2O$		100	83:17	94	60
10	B	$Cu(SbF_6)_2 \cdot 2H_2O$	MS	10	n.d.	n.d.	60
11	C	$Cu(OTf)_2$		66	78:22[b]	84	215, 228
12	C	$Cu(SbF_6)_2$		59	77:23[b]	93	215, 228
13	D	$Cu(SbF_6)_2$		57	27:73	98 (3*S*,4*S*)[c]	227
14	E	$Cu(SbF_6)_2$		75	85:15[b]	96 (3*R*,4*S*)	228
15	F	$Cu(OTf)_2$		89	67:33[b]	84 (3*R*,4*S*)	228
16	F	$Cu(SbF_6)_2$		95	85:15[b]	97 (3*R*,4*S*)	228
17	G	$Cu(OTf)_2$		95	97:3[d]	60 (4*S*)	228
18	G	$Cu(SbF_6)_2$		81	96:4[d]	59 (4*S*)	228
19	H	$Cu(OTf)_2$		95		60	228
20	H	$Cu(SbF_6)_2$		78		65	228
21	I	$Cu(SbF_6)_2$		97	80:20	97 (3*S*)	226, 228

[a] Reaction performed in $MeNO_2$. [b] The cis/trans ratio. [c] Enantiomeric excess of exo product. [d] The (1,4)/(1,3) regioisomer ratio.

and whose orientation forces the phenyl below the plane of the reacting complex **238**, inducing shielding of the Si face of the dienophile and giving the endo product (*S*)-**239** (Scheme 85).[230,231] This is another example of the Sibi et al. strategy termed chiral relay,[169] whose essence is that the chiral catalysts convert an achiral template like **232** into a chiral nonracemic template.

A similar effect controlling enantioselectivity is induced by R in **234** since, under chelation control with the [(*R*)-**1**/Mg(II)] complex, the acryloyl group cannot be coplanar with the aromatic ring (dihedral angle Φ CN−CO ≠ 0°) and the template becomes chiral. If the counterion (ClO_4) favors a tetrahedral reacting intermediate, then (*R*)-**1** box intrinsically shields the Si face, but the different twisting induced when R = H or = Me ($\Phi_{(AM1)}$ = 14° and 43°, respectively) favors the Si (H) or the Re face (Me), giving opposite enantiomers (Table 49, entries 12 and 14). If the counterion (Br) favors an octahedral complex, then enantioselectivity correlates with the increase of Φ around the CN−CO bond and to an increase of the steric bulk near the reacting olefinic moiety. The lower enantioselectivities observed for larger substituents are due to the too large twist that does not allow an efficient chelation of the metal ion (Table 49, entries 13 and 15−18).[232] An excellent efficiency is obtained with a variety of α′-hydroxy enones **156** because, in addition to the Diels−Alder reactions with cyclopentadiene (Table 49, entries 20−22), several other dienes give products with enantioselectivities in the range of 90−99% ee. Compounds **236** and **237** are, at the moment, promising dienophiles, **237** because it is the unique example of an acetylenic dienophile and **236** because the exo adducts (exo selectivity with 2,4-disubstituted butadienes is >99:1 and enantioselectivities in the range of 97−98% ee, larger than the Diels−Alder reaction with cyclopentadiene) could become useful synthons for marine natural toxins.[235]

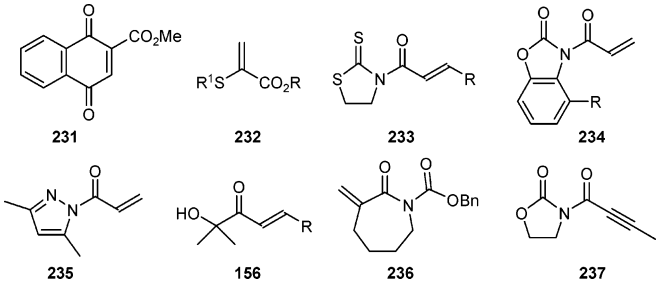
The intramolecular enantioselective Diels−Alder reaction is based on a structure (**240**) having a diene tethered at the β-position of acryloyl-oxazolidinone (Scheme 86).[228,236] If the catalyst is [(*S*)-**2**/$Cu(SbF_6)_2$], then the square-planar bicoordination of the carbonyl groups to copper allows application of the concept previously illustrated in Figure 13 to the intramolecular variant, and the absolute configuration (4′*R*,5′*R*,6′*S*)-**241a** of the bicyclo[4.3.0]non-1′-ene-4′-carbonyl-2-oxazolidinone is consistent with the proposed reacting intermediate. To illustrate the excellent potentials developed by the above reaction, with diastereo- and enantioselectivity up to >99:1 and 96%, respectively, and with as many as four contiguous stereogenic centers created in a single step, **241c** was transformed within few steps and 62% overall yield into the marine toxin (−)-isopulo'upone.[228,236]

To close this section, it has to be mentioned that computational studies related to Diels−Alder reactions of acryloyl-oxazolidinone and cyclopentadiene have been carried out, mainly focused on the reaction catalyzed by box and copper, which appear with increasing frequency in the literature.[237−240] To emphasize the possible future developments of the field, research tends either to identify the smallest fragment of the reaction intermediate that carries the information on molecular chirality[237] or to understand the geometric and energetic consequences of the box substituents (in particular the *tert*-butyl group) to create a steric barrier, suggestively christened the "axial gateway", that maintains the electrophilicity of the catalyst by shielding the copper center from nucleophilic attack.[239]

4.8. Hetero Diels−Alder Reactions

As seen in the previous section, the catalytic enantioselective Diels−Alder reaction is the most powerful option offered to the organic chemist for the construction of chiral

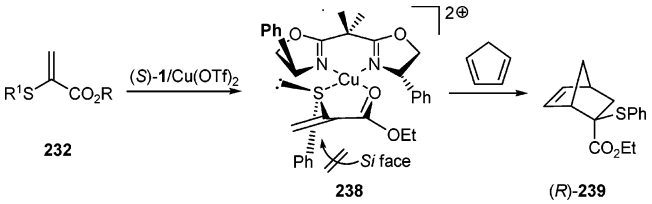
Table 49. Enantioselective Diels−Alder Reactions in CH_2Cl_2 between Various Dienophiles and Cyclopentadiene Catalyzed by [Box/MX_n]



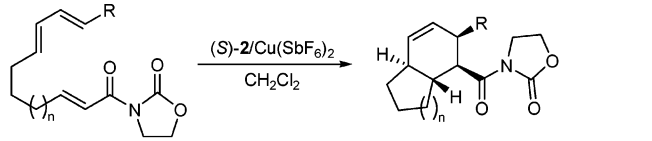
entry	dienophiles	box	MX_n	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	**231**	(*R*)-**1**	$Cu(OTf)_2$	60		18	229
2	**231**	(*S*)-**2**	$Cu(OTf)_2$	51		14	229
3	**232** R = Et, R^1 = Me	(*S*)-**1**	$Cu(OTf)_2$	53	71:29	40 (*R*)	230, 231
4	**232** R = Me, R^1 = Ph	(*S*)-**1**	$Cu(OTf)_2$	44	79:21	84 (*R*)	230, 231
5	**232** R = Et, R^1 = Ph	(*S*)-**1**	$Cu(OTf)_2$	76	88:12	>95 (*R*)	230, 231
6	**232** R = Et, R^1 = Ph	(*S*)-**1**	$Cu(SbF_6)_2$[a]	92	94:6	>95 (*R*)	230, 231
7	**232** R = *i*-Pr, R^1 = Ph	(*S*)-**1**	$Cu(OTf)_2$	70	70:30	85 (*R*)	230, 231
8	**232** R = *t*-Bu, R^1 = Ph	(*S*)-**1**	$Cu(OTf)_2$	91	71:29	26 (*R*)	230, 231
9	**233** R = Me	(*S*)-**2**	$Cu(OTf)_2$	82	96:4	94 (4*S*,5*R*)	60, 214
10	**233** R = Ph	(*S*)-**2**	$Cu(OTf)_2$	86	92:8	97 (4*R*,5*R*)	60, 214
11	**233** R = CO_2Et	(*S*)-**2**	$Cu(OTf)_2$	88	84:16	96 (4*R*,5*R*)	60, 214
12	**234** R = H	(*R*)-**1**	$Mg(ClO_4)_2$[b]	97	92:8	70 (*R*)	232
13	**234** R = H	(*R*)-**1**	$MgBr_2$	98	96:4	14 (*S*)	232
14	**234** R = Me	(*R*)-**1**	$Mg(ClO_4)_2$[b]	98	97:3	86 (*S*)	232
15	**234** R = Me	(*R*)-**1**	$MgBr_2$	97	97:3	74 (*S*)	232
16	**234** R = Et	(*R*)-**1**	$MgBr_2$	97	97:3	76 (*S*)	232
17	**234** R = Bn	(*R*)-**1**	$MgBr_2$	97	92:8	86 (*S*)	232
18	**234** R = CH_2t-Bu	(*R*)-**1**	$MgBr_2$	98	95:5	10 (*S*)	232
19	**235** R = H	(*S*)-**1**	$Mg(ClO_4)_2$	80	86:14	60	233
20	**156** R = H	(*S*)-**2**	$Cu(OTf)_2$	99	>99:1	>99	234
21	**156** R = Et	(*S*)-**2**	$Cu(SbF_6)_2$	90	>98:2	>99	234
22	**156** R = Ph	(*S*)-**2**	$Cu(SbF_6)_2$	86	94:6	>99	234
23	**236**	(*S*)-**2**	$Cu(OTf)_2$	66	38:62	94[c]	235
24	**237**	(*S*)-**2**	$Cu(SbF_6)_2$	65		52	60

[a] From $CuBr_2$ and $AgSbF_6$. [b] Freshly dried. [c] The exo enantiomeric excess, endo 93% ee.

Scheme 85



Scheme 86



240a: n = 1; R = H
240b: n = 1; R = Ph
240c: n = 1; R = $(CH_2)_4$OTBS
240d: n = 2; R = H
240e: n = 2; R = Ph

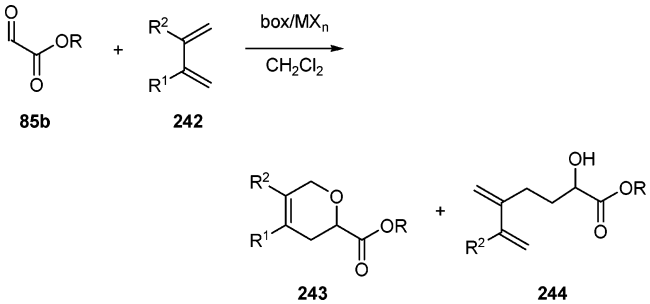
241a: 89% yield; *endo*:*exo*>99:1; 86% ee
241b: 86% yield; *endo*:*exo*>95:5; 92% ee
241c: 81% yield; *endo*:*exo*>99:1; 96% ee
241d: yield<20%
241e: 97% yield; *endo*:*exo*=84:16; 97% ee

six-membered rings. Its variant with heteroatoms either on the diene or on the dienophile, the hetero Diels−Alder reaction, is the parallel way to chiral heterocycles.

For the cycloadditions of dienes to carbonyls and those of α,β-unsaturated carbonyl compounds to olefins, great progress has been achieved in developing box-based catalysts that allow enantioselective reactions for unactivated and activated carbonyl compounds, and the field has been the topic of two specific reviews.[4b,241]

The first C=O dienophile tested was the glyoxylate ester **85b** because of its high reactivity in the catalyzed hetero Diels−Alder reactions with dienes **242**, even those unactivated.[242] The expected product of the reaction is dihydropyran **243**, but when the diene contains an allylic C−H bond, both hetero Diels−Alder and hetero ene reactions can take place, the latter with the formation of **244** (Scheme 87).

Scheme 87



The first paper on box-catalyzed reactions of dienes with glyoxylate esters allows illustration of this behavior that forces the discussion in this section of the formation of some products that strictly should be discussed later (Table 50).[243,244] After some experiments with different solvents (CH_2Cl_2 was the best) and Lewis acids (Table 50, entries 1−3), [(*S*)-**2**/$Cu(OTf)_2$] was found to be the best catalyst (Table 50, entries 4−6 vs 7−9), and the methyl ester was the best glyoxylate. Obviously, the absence of any methyl

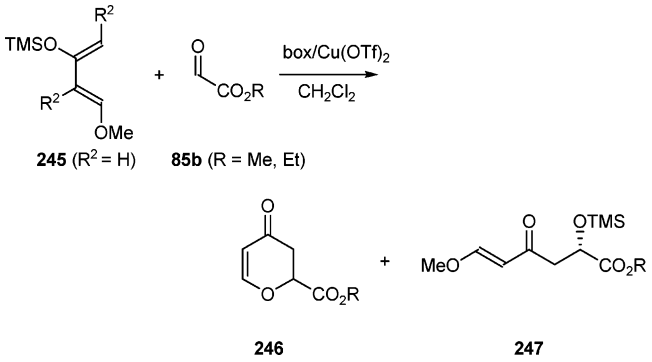
Table 50. Enantioselective Hetero Diels−Alder and Hetero Ene Reactions between Dienes 242 and Glyoxylate Esters 85b

entry	R	R^1	R^2	box	MX_n	yield (%)	**243**/**244**	**243** ee (%) (conf.)	**244** ee (%)	ref
1	Et	Me	Me	(*S*)-**2**	MgI_2	30	33:67	5 (*S*)	10	243
2	Et	Me	Me	(*S*)-**2**	$Zn(OTf)_2$	66	63:37	23 (*S*)	31	244
3	Et	Me	Me	(*R*)-**1**	$Zn(OTf)_2$	67	63:37	81 (*S*)	68	244
4	Me	Me	Me	(*S*)-**2**	$Cu(OTf)_2$	64	39:61	90 (*S*)	85	243
5	Et	Me	Me	(*S*)-**2**	$Cu(OTf)_2$	56	36:64	85 (*S*)	83	243
6	*i*-Pr	Me	Me	(*S*)-**2**	$Cu(OTf)_2$	24	50:50	77 (*S*)	83	243
7	Me	Me	Me	(*R*)-**1**	$Cu(OTf)_2$	86	42:58	81 (*S*)	85	243
8	Et	Me	Me	(*R*)-**1**	$Cu(OTf)_2$	81	39:61	83 (*S*)	88	243
9	*i*-Pr	Me	Me	(*R*)-**1**	$Cu(OTf)_2$	71	43:57	87 (*S*)	90	243
10	Et	Me	H	(*R*)-**1**	$Cu(OTf)_2$	67	50:50	80	91	243
11	*i*-Pr	H	H	(*R*)-**1**	$Cu(OTf)_2$	55		87 (*S*)		243

group gave hetero Diels−Alder as the sole reaction pathway (Table 50, entry 11).

Under catalysis with [box/$Cu(OTf)_2$] complexes, methyl and ethyl glyoxylate **85b** reacted with Danishefsky's diene **245** (R^2 = H) to give a mixture of the hetero Diels−Alder adduct **246** and the Mukaiyama−aldol product **247**, the latter converted to **246** with CF_3CO_2H (Scheme 88). The catalyst

Scheme 88

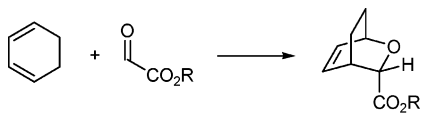


245 (R^2 = H) **85b** (R = Me, Et) **246** **247**

derived from (*S*)-**1** gave good enantioselectivity (44−47% ee) of (*S*)-**246** that derived from (*S*)-**2** poor enantioselectivity (17% ee) of the opposite enantiomer.[245]

An important contribution to the study of enantioselective catalyzed hetero Diels−Alder reactions has been done with 1,3-cyclohexadiene **248**, which gives the bicyclic *endo*-**249** adduct with **85b** (Scheme 89). A thorough study was done

Scheme 89



248 **85b** **249**

on box, cationic Lewis acid, counterion, and solvent, and some of the significant results are reported in Table 51.[59,225,243, 244,246,]

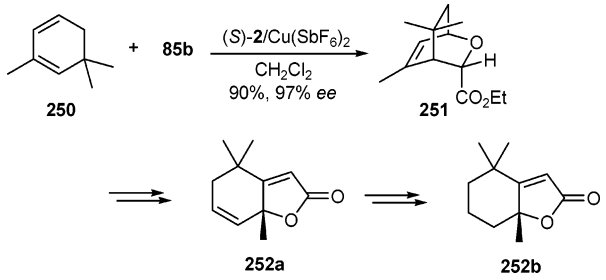
If the scope is to obtain the best enantioselectivity, then the best box is **2**, the best cation Cu(II), and the best counterion OTf (or SbF_6), while the solvent is relatively irrelevant (Table 51, entries 14−18).[59] Box **1** is sensitive to all parameters: $Zn(OTf)_2$ and $Cu(OTf)_2$ give opposite enantiomers in CH_2Cl_2 or $MeNO_2$ (Table 51, entries 1−4), and [(*S*)-**1**/$Cu(OTf)_2$] gives 79% (*S*)-**249** in $CHCl_3$ or 60% (*R*)-**249** in MeCN (Table 51, entry 5 vs 9), enantioselectivity being linearly related to the dielectric constant of the solvent.[59]

Table 51. Enantioselective Hetero Diels−Alder Reactions of 1,3-Cyclohexadiene 248 and Glyoxylate Esters 85b

entry	R	box	MgX_n	solvent	yield (%)	ee (%) (conf.)	ref
1	Et	(*R*)-**1**	$Zn(OTf)_2$	CH_2Cl_2	62	35 (*S*)	244
2	Et	(*R*)-**1**	$Zn(OTf)_2$	$MeNO_2$	84	27 (*R*)	244
3	Me	(*R*)-**1**	$Cu(OTf)_2$	CH_2Cl_2	63	47 (*S*)	246
4	Me	(*R*)-**1**	$Cu(OTf)_2$	$MeNO_2$	49	29 (*R*)	246
5	Et	(*S*)-**1**	$Cu(OTf)_2$	$CHCl_3$		78 (*R*)	59
6	Et	(*S*)-**1**	$Cu(OTf)_2$	THF		47 (*R*)	59
7	Et	(*S*)-**1**	$Cu(OTf)_2$	CH_2Cl_2	72	60 (*R*)	59, 243
8	Et	(*S*)-**1**	$Cu(OTf)_2$	$EtNO_2$		11 (*S*)	59
9	Et	(*S*)-**1**	$Cu(OTf)_2$	MeCN		60 (*S*)	59
10	Et	(*S*)-**2**	$Zn(OTf)_2$	CH_2Cl_2	57	23 (*S*)	244
11	Et	(*S*)-**2**	$Zn(OTf)_2$	$MeNO_2$	46	racemate	244
12	Me	(*S*)-**2**	$Cu(OTf)_2$	$MeNO_2$	63	92 (*S*)	246
13	Et	(*S*)-**2**	$Cu(SbF_6)_2$	$MeNO_2$	66	93 (*S*)	225
14	Et	(*S*)-**2**	$Cu(OTf)_2$	$MeNO_2$	99	≥97 (*S*)	59, 225
15	Et	(*S*)-**2**	$Cu(SbF_6)_2$	CH_2Cl_2	99	≥97 (*S*)	225
16	Et	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	99	≥97 (*S*)	59, 225
17	Et	(*S*)-**2**	$Cu(OTf)_2$	$CHCl_3$		97 (*S*)	59
18	Et	(*S*)-**2**	$Cu(OTf)_2$	THF		≥97 (*S*)	59

The hetero Diels−Alder reaction has useful applications in the synthesis of optically active natural products. The reaction between **85b** and 2,6,6-trimethyl-1,3-cyclohexadiene **250** to give (1*R*,3*S*,4*S*)-**251**, is the key step of the total syntheses of (*R*)-actinidiolide **252a** and (*R*)-dihydroactinidiolide **252b**, two flavor components of tobacco and tea plants (Scheme 90).[247] Analogously, the hetero Diels−Alder reac-

Scheme 90

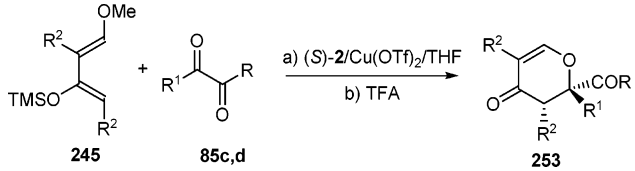


250 **251** **252a** **252b**

tion between Danishefsky's diene **245** and (benzyloxy)-acetaldehyde, catalyzed by [(*S*)-**1**/$Cu(OTf)_2$], gives an (*S*)-adduct in 76% yield and 51% ee, which is the starting product for the synthesis of the C_3-C_{14} segment of the antitumor macrolide laulimalide.[248]

A further step was to study the hetero Diels−Alder reaction of activated ketones (the analogues of pyruvate esters) **85c**,**d** with Danishefsky's dienes **245**, which, after trifluoroacetic acid (TFA) treatment of the reaction mixture, gives **253** (Scheme 91) with such an enantiomeric purity

Scheme 91



245 **85c,d** **253**

(Table 52) and derived from a process with such a low loading of chiral Lewis acid catalysts (down to 0.05% mol) that the process is comparable to a chemoenzymatic reaction.[249]

From the comparison of different box's (Table 52, entries 1 and 2 vs 3 and 4), different cations (Table 52, entries 8−12)

Table 52. Enantioselective Hetero Diels−Alder Reactions of Dienes 245 with α-Ketoesters and α-Diketones 85c,d

entry	R	R^1	R^2	box	MX_n	yield (%)	ee (%) (conf.)	ref
1[a]	OEt	Me	H	(*R*)-**1**	$Cu(SbF_6)_2$	24	23 (*S*)	249
2[a]	OEt	Me	H	(*R*)-**1**	$Cu(OTf)_2$	85	35 (*S*)	249
3[a]	OEt	Me	H	(*S*)-**2**	$Cu(SbF_6)_2$	37	89 (*S*)	249
4[a]	OEt	Me	H	(*S*)-**2**	$Cu(OTf)_2$	78	>99 (*S*)	249
5	OMe	Me	H	(*S*)-**2**	$Cu(OTf)_2$	96	>99 (*S*)	17, 249
6	OMe	Et	H	(*S*)-**2**	$Cu(OTf)_2$	80	94 (*S*)	249
7	OEt	*i*-Pr	H	(*S*)-**2**	$Cu(OTf)_2$	42	37 (*S*)	249, 250
8	OEt	Ph	H	(*S*)-**2**	$Cu(OTf)_2$	77	77 (*S*)	249, 250
9	OEt	Ph	H	(*S*)-**2**	$Sc(OTf)_3$	26	6	250
10	OEt	Ph	H	(*S*)-**2**	$Yb(OTf)_3$	70	4	250
11	OEt	Ph	H	(*S*)-**2**	$In(OTf)_3$	26	9	250
12	Me	Me	H	(*S*)-**2**	$Cu(OTf)_2$	90	94 (*S*)	249
13	Et	Me	H	(*S*)-**2**	$Cu(OTf)_2$	77	98 (*S*)	249
14	Et	Et	H	(*S*)-**2**	$Cu(OTf)_2$	84	90 (*S*)	249
15	Ph	Me	H	(*S*)-**2**	$Cu(OTf)_2$	95	94 (*S*)	249
16[a]	Et	$(CH_2)_8CH_3$	H	(*S*)-**2**	$Cu(OTf)_2$	77	47 (*S*)	251
17	OMe	Me	Me	(*S*)-**2**	$Cu(OTf)_2$	75	96 (*S*)	249
18	OEt	Ph	Me	(*S*)-**2**	$Cu(OTf)_2$	57	99 (*S*)	249
19	Me	Me	Me	(*S*)-**2**	$Cu(OTf)_2$	60	91 (*S*)	249

[a] Reaction run in CH_2Cl_2.

and counterions (Table 52, entry 3 vs 4), the best catalyst is [(*S*)-**2**/$Cu(OTf)_2$], which induces high enantioselectivity with a variety of α-ketoesters and α-diketones, with both Danishefsky's dienes **245** (R^2 = H or Me).

The absolute configuration of **253** (R = R^1 = Me, R^2 = H, Table 52, entry 5) was unambiguously determined to be (*S*), which is consistent with that of all other products. To form (*S*)-**253**, the diene has to approach the Si face of the bidentate-coordinated ketone to the copper center. The square-planar geometrical arrangement **254**, illustrated in Scheme 92, shows the carbonyl Re face of the carbonyl shielded by the *tert*-butyl group of the ligand.

Again, the hetero Diels−Alder reaction with α-ketoesters and α-diketones has been useful for several applications to the synthesis of optically active natural products (Scheme 93). Starting from (*S*)-**253** (R = Et, R^1 = $(CH_2)_8CH_3$, R^2 = H, Table 52, entry 16), the antibiotic (−)-malyngolide **255** was synthesized in enantiomerically enriched form.[251] (*S*)-**253** (R = Et, R^1 = Me, R^2 = H, Table 52, entry 4) was converted within seven steps into **256**, with the original (*S*)-configuration of the quaternary C_{10a} that induces the stereoselective formation of five additional stereocenters of a product that contains the correct stereochemical arrangements between functional groups necessary to gain access to phomactin A, a selective antagonist of platelet activating factor.[252]

Diethyl ketomalonate **257** is an interesting CO dienophile that may be regarded as a synthetic equivalent of CO_2; for this reason its enantioselective hetero Diels−Alder reaction with 1,3-cyclohexadiene **248**, which gives the tricyclic adduct **258** (Scheme 94), was the subject of much attention.[253] Box, cation, counterion, and solvent were accurately optimized, and some significant results are reported in Table 53.

(*S*)-**2** in combination with Cu(II) as the Lewis acid gave unsatisfactory results (Table 53, entries 1 and 2) when compared to catalysts derived from (*R*)-**1** and $Zn(OTf)_2$ or $Cu(OTf)_2$ (Table 53, entries 3−11). The solvent effect of these two catalysts was studied in detail, and the best solvents were those with the lower dielectric constants (toluene, Et_2O, and CH_2Cl_2; Table 53, entries 4−6, 9, and 10). Taking into account both yield and enantioselectivity, Et_2O was the best solvent for two comparable catalysts. The last point to mention is the absolute configuration found to be (1*R*,4*S*)-**258**, for catalysts derived from both (*S*)-**2** and (*R*)-**1** box's.

The hetero Diels−Alder reaction with C═N dienophiles is a topic not extensively studied; perhaps the modest results did not stimulate thorough investigations. Some isolated experiments are available, and the development of a catalytic enantioselective reaction can be considered "still in its infancy".[241] The imines derived from glyoxylates **81** react smoothly with Danishefsky's diene **245** (R^2 = H) to give **259** (Scheme 95). The reactions give excellent results with different catalysts, but with (*S*)-**2** and copper triflate[254] or iron trichloride,[255] the selectivity is satisfactory only with the last catalyst (Table 54).

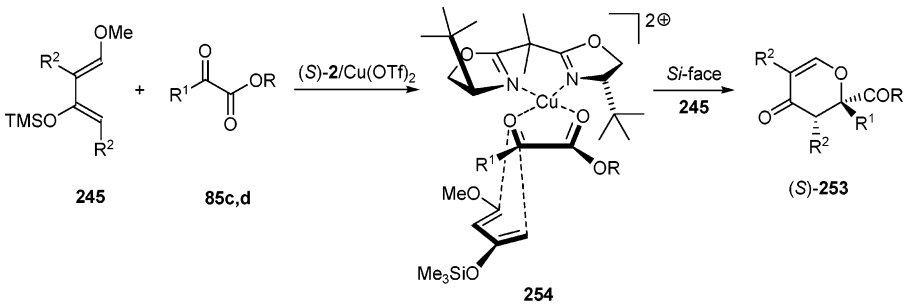
Unsatisfactory results have been obtained with the reaction of 2-benzyloxycarbonyl-1-azirine, as the azadienophile, and cyclopentadiene under catalysis with [(*S*)-**2**/$Mg(ClO_4)_2$] in the presence of 4 Å MS, because the yield was 25% and 52% ee.[256] Also the reaction between cyclopentadiene and [(2-oxo-1,3-oxazolidin-3yl)carbonyl]diazenyl formates **175** is unsatisfactorily catalyzed by [(*R*)-**1**/$Cu(OTf)_2$], because yields are excellent, but enantioselectivities do not exceed 22% ee.[257]

The asymmetric hetero Diels−Alder reactions of *N*-sulfinyl amides **260** with cyclohexadiene **248** close the discussion of heterodienophiles. If the catalyzed reactions are performed under stoichiometric conditions, then excellent results in terms of yields and selectivity are obtained; however, when performed under catalytic conditions (10 mol % of catalyst) the catalyst is less selective, but with 1 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf), it becomes strongly endo-selective affording **261** with good to excellent enantiomeric excess (Scheme 96 and Table 55).[258,259]

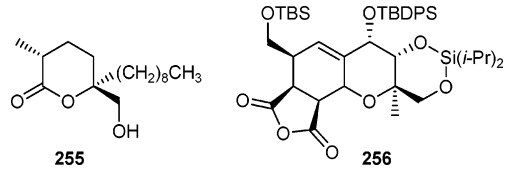
The hetero Diels−Alder reaction of α,β-unsaturated carbonyl compounds **262** as heterodienes with alkenes **263** to give dihydropyrans **264** (Scheme 97) is the best known example of cycloaddition with inverse electron demand, hence under $HOMO_{dienophile}/LUMO_{\alpha,\beta-unsaturated\ carbonyl}$ control.[241]

To minimize the frontier molecular orbital (FMO) separation, which will be further lowered with the coordination of the Lewis acid to the oxygen atom of the heterodiene, alkenes

Scheme 92



Scheme 93



Scheme 94

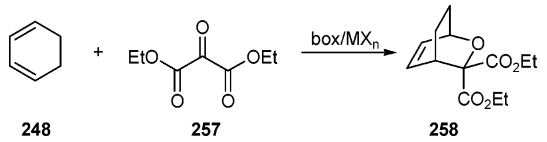


Table 53. Enantioselective Hetero Diels−Alder Reactions of Diethyl Ketomalonate 257 with 1,3-Cyclohexadiene 248[253]

entry	box	MX_n	solvent	yield (%)	ee (%) (conf.)
1	(*S*)-**2**	$Cu(SbF_6)_2$	CH_2Cl_2	11	64 (1*R*,4*S*)
2	(*S*)-**2**	$Cu(OTf)_2$	CH_2Cl_2	20	40 (1*R*,4*S*)
3	(*R*)-**1**	$Zn(SbF_6)_2$	CH_2Cl_2	65	27 (1*R*,4*S*)
4	(*R*)-**1**	$Zn(OTf)_2$	CH_2Cl_2	39	86 (1*R*,4*S*)
5	(*R*)-**1**	$Zn(OTf)_2$	Et_2O	94	91 (1*R*,4*S*)
6	(*R*)-**1**	$Zn(OTf)_2$	PhMe	68	90 (1*R*,4*S*)
7	(*R*)-**1**	$Zn(OTf)_2$	THF	15	86 (1*R*,4*S*)
8	(*R*)-**1**	$Zn(OTf)_2$	MeCN	17	23 (1*R*,4*S*)
9	(*R*)-**1**	$Cu(OTf)_2$	CH_2Cl_2	76	84 (1*R*,4*S*)
10	(*R*)-**1**	$Cu(OTf)_2$	Et_2O	64	93 (1*R*,4*S*)
11	(*R*)-**1**	$Cu(OTf)_2$	THF	70	72 (1*R*,4*S*)

Scheme 95

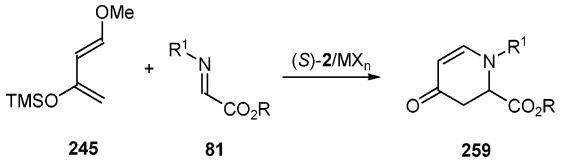


Table 54. Enantioselective Hetero Diels−Alder Reactions of Dienes 245 with Imines 81

entry	R	R^1	MX_n	solvent	additives	yield (%)	ee (%) (conf.)	ref
1	Et	tosyl	Cu(OTf)	THF		74	12 (*S*)	254
2	Et	tosyl	$Cu(OTf)_2$	THF		60	10 (*S*)	254
3	Me	*p*-MeOPh	$FeCl_3$	MeCN		n.r.	57	255
4	Me	*p*-MeOPh	$FeCl_3$	CH_2Cl_2	4 Å MS	67	92	255
5	Me	*p*-MeOPh	$FeCl_3$	CH_2Cl_2	2,6-lutidine	n.r	70	255

Scheme 96

are in general vinyl ethers or vinyl thioethers, and the α,*β*-unsaturated carbonyl compounds have in the α-position an electron-withdrawing group, an ester (**262a**)[260,261] or a phosphonic group (**262b**), having an oxygen atom that can also coordinate to the chiral catalyst.[57,58,262] The reactions are in general strongly endo-selective, and density functional theory (DFT) calculations on the model reaction between acrolein and methyl vinyl ether support the experimental results,[263] which for the cycloadditions in Scheme 97 are reported in Tables 56 and 57.

For these hetero Diels−Alder reactions the best Lewis acid is Cu(II); for **262a** when the anion of the catalyst is changed from OTf to PF_6 a small decrease of yield and enantioselectivity is observed (Table 56, entries 1 and 7 vs 2 and 8).

For the reactions of **262a** the best solvent is THF (Table 56, entries 1, 3, and 4), and whereas the substituent R does not significantly influence the selectivity, the vinyl ether gives excellent results when it is cyclic or X is an ethoxy group, but yield and selectivity drop for *tert*-butyl vinyl ether (Table 57, entry 9) probably due to a steric repulsion between the *t*-Bu group and the catalysts in the endo transition state of the reaction.

The catalysts derived from box (*S*)-**2** are better then those based on (*S*)-**1** (Table 57, entry 1 vs 5), but the outstanding result is that two catalysts derived from ligands with the same configuration at C(4) give opposite enantiomers of the endo product.

The hetero Diels−Alder reaction of α,*β*-unsaturated acyl phosphonates **262b** (E = $PO(OMe)_2$) was tested with an extended range of substituents either on the heterodiene or on the electron-rich alkenes **263**. Some results overlap those of the α,*β*-unsaturated carbonyl compounds **262a** (e.g., the effect of the substituent on the vinyl ether (Table 57, entries 3−5)); some are somewhat divergent: The results with both box ligands are quite similar (Table 57, entries 1 and 10−12 vs 2 and 13−15). Again, the attractive feature is the relationship between the configurations of the ligand and the product. Except the reactions with *tert*-butyl vinyl ether (Table 57, entries 5 and 8, because of the collapse of selectivity) and the reactions of α-TBSO-styrene (Table 57, entries 26 and 27), several couples of reactions, with either vinyl ethers or vinyl sulfides, run with catalysts derived from (*S*)-**2** or (*S*)-**1**, give opposite enantiomers (Table 57, entries 1, 3, 4, and 24 vs 2, 6, 7, and 25). If the bidentate coordination of **262** to catalysts derived from (*S*)-**2** or (*S*)-**1** occurs with the same opposite distortions resembling those observed in the X-ray structures and already illustrated in Figure 12 to rationalize the analogous opposite enantioselectivity of the Mukaiyama−Michael reaction, then the preferred approach to the opposite prochiral faces of **262** can be expected.

All reactions do not give side products, with two exceptions: **262a** and α-trimethylsilyloxy styrene with [(*S*)-**1**/$Cu(SbF_6)_2$] gives the Michael adduct as the main product (80% yield),[58] and the same phosphonate with cyclopentadiene affords a 34% yield of the Diels−Alder product (endo/exo ratio 7:1, endo 84% ee) besides a 66% yield of the hetero Diels−Alder adduct (endo/exo ratio 96:4, endo 95% ee).[58]

The reactivity of ketoester **262a** and acyl phosphonate **262b** was compared in a competition experiment, and the former was somewhat more reactive than the latter (*endo*-**264a**/*endo*-**264b** = 3.5:1).[58]

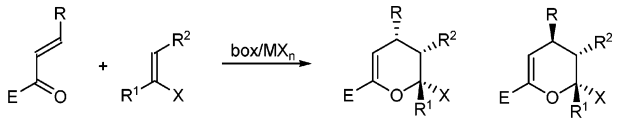
The intramolecular hetero Diels−Alder reaction occurring for **266**, developed by transetherification of methyl (*E*)-4-methoxy-2-oxo-3-butenoate **262a** and *δ*,*ϵ*-unsaturated alcohols **265**, catalyzed by [box/Cu(II)] complexes is an interesting approach to trans fused hydropyran−pyran derivatives **267** (Scheme 98).[264] The enantioselectivity is affected by both box and Cu(II) anion (Table 58), but the presence of MS (5 Å better than 4 Å, Table 58, entries 1, 3, and 5 vs 2, 4, and 6) as additives is determinant; otherwise racemic products are obtained.

Few examples of hetero Diels−Alder reactions with azadienes are known. A formal hetero Diels−Alder reaction of azoducarbonyl derivatives **175** to give the intermediate

Table 55. Enantioselective Hetero Diels−Alder Reactions of Cyclohexadiene with *N*-Sulfinyl Amides 260

entry	R	box	MX_n	additive	yield (%)	endo/exo	*endo*-**261** ee (%) (conf.)	ref
1	Cbz	(*R*)-**1**	$Cu(OTf)_2$		25	38:62	15 (1*R*,2*S*,4*S*)	258, 259
2	Cbz	(*S*)-**1**	$Cu(OTf)_2$	TMSOTf	85	>95:<5	96 (1*S*,2*R*,4*R*)	259
3	Cbz	(*R*)-**1**	$Zn(OTf)$		30	75:25	61 (1*R*,2*S*,4*S*)	258, 259
4	Cbz	(*S*)-**1**	$Zn(OTf)_2$	TMSOTf	70	92:8	86 (1*S*,2*R*,4*R*)	259
5	Tosyl	(*R*)-**1**	$Cu(OTf)$		93	82:18	36 (1*R*,2*S*,4*S*)	258, 259
6	Tosyl	(*S*)-**1**	$Cu(OTf)_2$	TMSOTf	56	92:8	80 (1*S*,2*R*,4*R*)	259
7	Tosyl	(*R*)-**1**	$Zn(OTf)_2$		39	92:8	78 (1*R*,2*S*,4*S*)	258, 259
8	Tosyl	(*S*)-**1**	$Zn(OTf)_2$	TMSOTf	86	>95:<5	97 (1*S*,2*R*,4*R*)	259

Scheme 97



262a: E = CO_2R **263**
262b: E = $PO(OMe)_2$

176 of the Mukaiyama−Michael reaction has been reported in Scheme 62.[178] An unequivocal example was reported by Ghosez for the reaction between azadienes **268** and 3-acryloyl- or 3-(*E*)-crotonoyl-2-oxazolidinones **163**, catalyzed by [(*S*)-**2**/$Cu(OTf)_2$] (Scheme 99).[265] The reaction is strongly exo-selective, and **269** is obtained with excellent yields and enantioselectivity (Table 59). The determined absolute configuration (3*S*,4*R*,5*S*,6*S*) of pyridone reported in Table 59 (entry 3) is consistent with the approach of the diene to the less hindered face of **163**, bicoordinated in a square-planar complex.

An intramolecular hetero Diels−Alder reaction involving a vinyl ether tethered to an 1-azadiene was attempted, but catalyst [(*S*)-**2**/$Cu(OTf)_2$] gave 60% yield of a nearly racemic product.[266]

4.9. 1,3-Dipolar Cycloaddition Reactions

After the enantioselective Diels−Alder reaction in all its variants, the second most important pericyclic reaction is probably the 1,3-dipolar cycloaddition reaction because of the possibility to construct, by this way, useful chiral heterocyclic synthons. The synthetic applications of isoxazolidines with three contiguous chiral centers, which may be obtained by the 1,3-dipolar cycloaddition reactions of nitrones with alkenes, led to the rapid development of a series of catalysts suitably designed for this scope,[267] and among the chiral ligands applied to this reaction, box had a relevant role in its success.

Three levels of control are required to develop stereospecificity in the 1,3-dipolar cycloaddition reaction: Taking the reaction between a nitrone **270** and 3-alkenoyl-2-oxazolidinones **163** as an example, a good optically active catalyst should control regioselectivity (4- vs 5-alkenoylisoxazolidines (**271** vs **272**)), diastereoselectivity (*endo*-**271** vs *exo*-**271**), and enantioselectivity ((4*S*,5*R*)-**271** vs (4*R*,5*S*)-**271** enantiomers) (Scheme 100).

The R^2 substituents on the nitrone play an important role in the reaction mechanism of the cycloaddition. If these substituents are alkyl or aryl groups, then nitrone prefers to react with an electron-deficient alkene (such as **163**), and the normal electron-demand cycloaddition is under $HOMO_{nitrone}-LUMO_{alkene}$ control. If R^2 is an electron-withdrawing group, then nitrone reacts with electron-rich alkenes (vinyl ethers), and the inverse electron-demand cycloaddition is under $HOMO_{alkene}-LUMO_{nitrone}$ control.

Table 56. Enantioselective Hetero Diels−Alder Reactions of α,β-Unsaturated Carbonyl Compounds 262a (E = CO_2R) with Electron-Rich Alkenes 263 (R^1 = H)'

entry	E	R	R^2	X	solvent	box	MX_n	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	CO_2Et	Me	H	OEt	CH_2Cl_2	(*S*)-**2**	$Cu(OTf)_2$	100[a]	98:2	98(4*R*,6*R*)	58,260
2	CO_2Et	Me	H	OEt	CH_2Cl_2	(*S*)-**2**	$Cu(SbF_6)_2$		57:43	95(4*R*,6*R*)	58
3	CO_2Et	Me	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$	89	n.r.	>99.5	260
4	CO_2Et	Me	H	OEt	$MeNO_2$	(*S*)-**2**	$Cu(OTf)_2$	100[a]	n.r.	76	260
5	CO_2Et	Me	H	OEt	CH_2Cl_2	(*S*)-**1**	$Cu(OTf)_2$	100[a]	95:5	64(4*S*,6*S*)	58,260
6	CO_2Me	Ph	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$	95	n.r.	99.5	260
7	CO_2Et	OEt	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$	93	n.r.	>99.5	260
8	CO_2Et	OEt	H	OEt	CH_2Cl_2	(*S*)-**2**	$Cu(PF_6)_2$	88	n.r.	97	260
9	CO_2Et	OEt	H	O*t*-Bu	THF	(*S*)-**2**	$Cu(OTf)_2$	61	80:20	90	260
10	CO_2Et	Me	OCH_2CH_2		THF	(*S*)-**2**	$Cu(OTf)_2$	51	n.r.	>99.5	260
11	CO_2Me	Ph	OCH_2CH_2		THF	(*S*)-**2**	$Cu(OTf)_2$	96	n.r.	99.5	260
12	CO_2Et	OEt	OCH_2CH_2		THF	(*S*)-**2**	$Cu(OTf)_2$	84	n.d.	97.5	260
13	CO_2Et	Ph	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$[b]	93	95:5	97(4*R*,6*R*)	261
14	CO_2Et	*i*-Pr	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$[b]	95	96:4	96(4*R*,6*S*)	261
15	CO_2Et	Me	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$[b]	87	96:4	97	261
16	CO_2Et	OMe	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$[b]	90	98:2	98	261
17	CO_2Et	OEt	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$[b]	98	98:2	98	261
18	CO_2Et	SBn	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$[b]	97	95:5	99	261
19	CO_2Et	*i*-Pr	OCH_2CH_2		THF	(*S*)-**2**	$Cu(OTf)_2$[b]	94	94:6	95	261
20	CO_2Et	Ph	OCH_2CH_2		THF	(*S*)-**2**	$Cu(OTf)_2$[b]	96	94:6	97	261
21	CO_2Et	Ph	H	SEt	THF	(*S*)-**2**	$Cu(OTf)_2$[b]	94	96:4	97	58
22	CO_2Et	Ph	H	SPh	THF	(*S*)-**2**	$Cu(OTf)_2$[b]	91	96:4	99	58

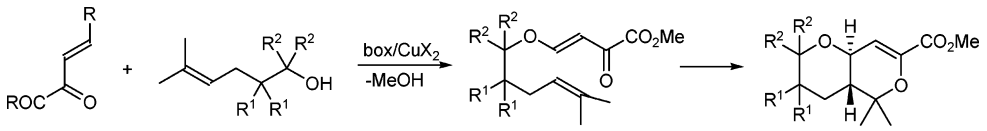
[a] Conversion. [b] Dihydrate salt.

Table 57. Enantioselective Hetero Diels−Alder Reactions of α,β-Unsaturated Acyl Phosphonates 262b (E = PO(OMe)$_2$) with Electron-Rich Alkenes 263 in CH_2Cl_2

entry	R	R^1	R^2	X	box	MX_n	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	Me	H	H	OEt	(*S*)-**2**	$Cu(OTf)_2$	89	99:1	99 (4*R*,6*R*)	57, 58, 261, 262
2	Me	H	H	OEt	(*S*)-**1**	$Cu(OTf)_2$	85	>99:1	94 (4*S*,6*S*)	57, 58, 261, 262
3	Me	H	H	OMe	(*S*)-**2**	$Cu(SbF_6)_2$		99:1	85 (4*R*,6*R*)	57, 58
4	Me	H	H	OEt	(*S*)-**2**	$Cu(SbF_6)_2$	84	99:1	85 (4*R*,6*R*)	57, 58, 262
5	Me	H	H	O*t*-Bu	(*S*)-**2**	$Cu(SbF_6)_2$	35	57:43	66 (4*R*,6*R*)	57, 58
6	Me	H	H	OMe	(*S*)-**1**	$Cu(SbF_6)_2$	95	>99:1	86 (4*S*,6*S*)	57, 58
7	Me	H	H	OEt	(*S*)-**1**	$Cu(SbF_6)_2$	100	>99:1	93 (4*S*,6*S*)	57, 58, 262
8	Me	H	H	O*t*-Bu	(*S*)-**1**	$Cu(SbF_6)_2$	100	91:9	2	57, 58
9	Me	H	H	OTBS[b]	(*S*)-**1**	$Cu(SbF_6)_2$		50:50	64	58
10	Ph	H	H	OEt	(*S*)-**2**	$Cu(SbF_6)_2$	88	97:3	94 (4*R*,6*R*)	58
11	*i*-Pr	H	H	OEt	(*S*)-**2**	$Cu(SbF_6)_2$	78	97:3	93 (4*R*,6*S*)	58
12	OEt	H	H	OEt	(*S*)-**2**	$Cu(SbF_6)_2$	96	>99:1	93 (4*R*,6*R*)[a]	58
13	Ph	H	H	OEt	(*S*)-**1**	$Cu(SbF_6)_2$	98	>99:1	98 (4*S*,6*S*)	58, 262
14	*i*-Pr	H	H	OEt	(*S*)-**1**	$Cu(SbF_6)_2$	99	>99:1	96 (4*S*,6*R*)	58, 262
15	OEt	H	H	OEt	(*S*)-**1**	$Cu(SbF_6)_2$	49	99:1	77 (4*S*,6*S*)[a]	58
16	Me	H	OCH_2CH_2		(*S*)-**2**	$Cu(OTf)_2$	91	>99:1	95 (4*R*,5*S*,6*R*)	58, 262
17	Ph	H	OCH_2CH_2		(*S*)-**2**	$Cu(SbF_6)_2$	99	>99:1	90 (4*S*,5*S*,6*R*)[a]	58
18	*i*-Pr	H	OCH_2CH_2		(*S*)-**2**	$Cu(SbF_6)_2$	79	98:2	90 (4*R*,5*S*,6*R*)[a]	58, 262
19	OEt	H	OCH_2CH_2		(*S*)-**2**	$Cu(SbF_6)_2$	98	>99:1	97 (4*S*,5*S*,6*R*)[a]	58, 262
20	Ph	H	OCH_2CH_2		(*S*)-**1**	$Cu(OTf)_2$	98	>99:1	94 (4*R*,5*R*,6*S*)[a]	58, 262
21	*i*-Pr	H	OCH_2CH_2		(*S*)-**1**	$Cu(SbF_6)_2$	94	>99:1	71 (4*S*,5*R*,6*S*)[a]	58
22	OEt	H	OCH_2CH_2		(*S*)-**1**	$Cu(OTf)_2$	100	>99:1	84 (4*R*,5*R*,6*S*)[a]	58
23	Me	H	$OCH_2CH_2CH_2$		(*S*)-**2**	$Cu(SbF_6)_2$	55	98:2	92 (4*R*,5*S*,6*S*)[a]	58, 262
24	Me	H	H	SEt	(*S*)-**2**	$Cu(SbF_6)_2$	31	95:5	76 (4*R*,6*S*)[a]	58
25	Me	H	H	SEt	(*S*)-**1**	$Cu(SbF_6)_2$	89	>99:1	95 (4*S*,6*R*)[a]	58
26	Me	Ph	H	OTBS[b]	(*S*)-**2**	$Cu(SbF_6)_2$		93:7	99 (4*R*,6*S*)[a]	58
27	Me	Ph	H	OTBS[b]	(*S*)-**1**	$Cu(SbF_6)_2$		60:40	96 (4*R*,6*S*)[a]	58

[a] Absolute configuration assigned by analogy. [b] OTBS is *t*-butyldimethylsilyloxy.

Scheme 98

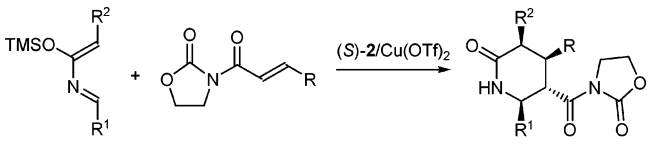


262a (R = OMe) **265** **266** **267**

Table 58. Intramolecular Hetero Diels−Alder Reactions of 266[264]

entry	R^1	R^2	box	CuX_2	additive	yield (%)	ee (%)
1	H	H	(*S*)-**1**	$Cu(SbF_6)_2$	4 Å MS	51	13
2	H	H	(*S*)-**1**	$Cu(SbF_6)_2$	5 Å MS	51	14
3	H	H	(*S*)-**2**	$Cu(SbF_6)_2$	4 Å MS	12	93
4	H	H	(*S*)-**2**	$Cu(SbF_6)_2$	5 Å MS	63	96
5	H	H	(*S*)-**2**	$Cu(OTf)_2$	4 Å MS	50	73
6	H	H	(*S*)-**2**	$Cu(OTf)_2$	5 Å MS	83	55
7	Me	H	(*S*)-**2**	$Cu(SbF_6)_2$	5 Å MS	83	98
8	H	Me	(*S*)-**2**	$Cu(SbF_6)_2$	5 Å MS	74	98

Scheme 99



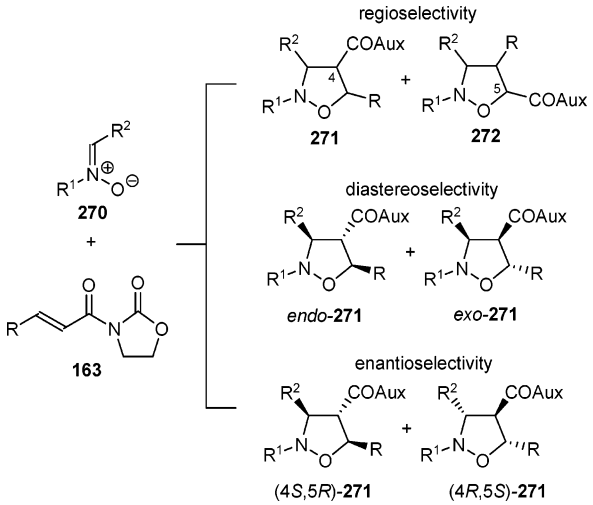
268 **163** **269**

The reaction between nitrone **270** (R^1 = Ph or Bn, R^2 = Ph) and **163** (R = Me or *n*-Pr) was the first box-based catalyzed 1,3-dipolar cycloaddition reaction. Yield, regioselectivity, and diastereoselectivity are controlled with the [(*S*)-**1**/MgI_2] catalyst for the reaction of diphenyl nitrone, the product is **271**, the reaction is strongly endo-selective, and the enantioselectivity is found to be dependent on the presence of 4 Å MS (Table 60, entries 16−20).[268] This unusual behavior was found also in the reaction between diphenyl nitrone **270** (R^1 = R^2 = Ph) and 3-acryloyl- or 3-(*E*)-crotonoyl-2-oxazolidinones **163** (Table 60, entries 12, 16, and 17), and having determined the absolute stereochemistry of the products, in the presence of MS (3*S*,4*R*,5*S*)-**271** is the preferred stereoisomer, whereas in the absence of MS the opposite enantiomer (3*R*,4*S*,5*R*)-**271** is obtained.[269] To understand the influence of MS on the different possible intermediates of the 1,3-dipolar cycloaddition reaction, the effects of several additives such as water or different drying agents were also tested (Table 60, entries 3−5 and 18). Taking the box constant, this behavior was observed changing the counterion of Mg(II) (ClO_4 or OTf) and changing the Lewis acid cation (Table 60, entries 6−15).[77,270,271] Few cations failed: $Mg(OTf)_2$ and $Zn(ClO_4)_2$ without MS;[77,271] $Yb(OTf)_3$ and $Sc(OTf)_3$,[272] which gave racemates.

Table 59. Enantioselective Hetero Diels−Alder Cycloaddition Reactions of Azadienes 268 with 163[265]

entry	R	R^1	R^2	yield (%)	exo/endo	exo ee (%) (conf.)
1	H	Ph	H	83	86:14	98 (*S*)
2	H	Ph	Me	96	>99:1	98 (*S*)
3	Me	Ph	Me	96	>99:1	94 (3*S*,4*R*,5*S*,6*S*)
4	Me	Ph	H	80	>99:1	93 (*R*)
5	Me	(*E*)-CMe=CHPh	Me	98	>99:1	90 (*S*)

Scheme 100



The same strong chiral amplification illustrated in Figure 15 for the Diels−Alder reaction was observed in the 1,3-dipolar cycloaddition reaction catalyzed by [(*R*)-**1**/Zn(ClO$_4$)$_2$/MS] (Table 60, entry 11),[77] both effects having the same origin from the reservoir effect induced by the thermodynamic stability of the racemic complex [(*R*)-**1**/(*S*)-**1**/Zn] **24** (Figure 10).

From data in Table 60 for the homogeneous series of the 1,3-dipolar cycloaddition reaction with acryloyl-oxazolidinone, it can be observed that, in the absence of MS, all reactions are highly endo-selective, whereas the use of MS as additives shifts the stereoselectivity toward the formation of the adduct *exo*-**272**. This effect is particularly evident for Co(II) and Zn(II) cations (Table 60, entries 10 and 11) that give exo-selective reactions; as it will be reported in a later section of this review, these data suggested the way to design exo-enantioselective catalysts for the nitrone cycloaddition.

A different approach to exo-enantioselective nitrone cycloadditions can be realized with 1-benzyl-2-crotonoyl-5,5-dimethylpyrazolidin-3-ones **167**, the interesting achiral template already mentioned in the aza-Michael reaction (section 4.4), which may relay and amplify the stereochemistry induced by the box. Its reaction with **270** (R^1 = Me, R^2 = Ph), catalyzed by [(*S*)-**2**/Cu(OTf)$_2$] that is not the best box catalyst for this scope, gives a low yield of exo/endo products in the ratio of 83:17 and the enantiomeric excess of **273** is 71% ee (Scheme 101).[273]

All reactions discussed above fall in the class of normal electron-demand cycloaddition; if nitrone **270** has R^2 = CO$_2$R, then it reacts with vinyl ethers **263** (X = OR) in accordance to an inverse electron-demand cycloaddition, and its enantioselective version has been developed employing chiral Cu(II)− and Zn(II)−box complexes as catalysts to give *exo*- and *endo*-**274** (Scheme 102).[274] The best catalyst is [(*S*)-**2**/Cu(OTf)$_2$], which gives excellent yields and high enantioselectivities of *exo*-**274** with ethyl vinyl ether and 2-methoxypropene (Table 61, entries 1 and 5).

On the basis of the absolute configuration of *exo*-**274** from entry 1 in Table 61, the pentacoordinated reaction intermediate **275** is proposed, in which both reagents are bound to the catalysts: Nitrone is equatorially bicoordinated, and ethyl vinyl ether is axial (Figure 16).

If the 1,3-dipolar cycloaddition reactions of nitrones have been the topic of extensive studies, few papers concern other 1,3-dipoles. Carbonyl ylide (from *o*-(methoxycarbonyl)-α-diazoacetophenone) reacts with *N*-phenylmaleimide, but [(*S*)-**2**/Cu(OTf)$_2$] gives a low yield of a 1:1 mixture of endo and exo products with enantiomeric excesses up to 20%.[275] Nitrile oxides react with **167**, and the best catalyst falling in this section is [(*S*)-**1**/MgI$_2$] that gives up to 44% ee,[276] whereas box **10a** affords excellent stereoselective catalysts, and for this reason the reaction will be discussed in a further section.

This section is closed with the fruitful enantioselective catalysis of the 1,3-dipolar cycloaddition reaction of azomethine ylides, derived from *N*-arylidene glycinates **276** and Et$_3$N, with electron-deficient alkenes **277** to afford **278** as a single diastereoisomer (Scheme 103).[277] After several solvents, box's, and triflates were tested, the best conditions were found to be THF and [(*S*)-**2**/Zn(OTf)$_2$], and the results are reported in Table 62.

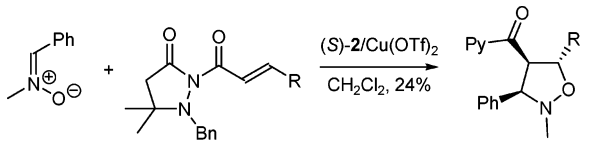
The absolute configuration of the product described in entry 7 was unambiguously determined to be (2*S*,3*S*,4*S*,5*R*).

Table 60. Enantioselective 1,3-Dipolar Cycloadditions of Nitrone 270 (R^2 = Ph) with 163

entry	R	R^1	box	MX$_n$	additive	yield (%)	exo/endo	endo ee (%) (conf.) [exo ee (%)]	ref
1	H	Ph	(*R*)-**1**	MgI$_2$		quant.[a]	100:0	48 (3*R*,4*S*)	269
2	H	Ph	(*R*)-**1**	MgI$_2$	4 Å MS	quant.[a]	73:23	82 (3*S*,4*R*)	269
3	H	Ph	(*R*)-**1**	MgI$_2$	H$_2$O		90:10	36 (3*R*,4*S*)	269
4	H	Ph	(*R*)-**1**	MgI$_2$	Mg(SO$_4$)$_2$		96:4	52 (3*R*,4*S*)	269
5	H	Ph	(*R*)-**1**	MgI$_2$	CaSO$_4$		80:20	41 (3*S*,4*R*)	269
6	H	Ph	(*R*)-**1**	Mg(ClO$_4$)$_2$		quant.[a]	95:5	48 (3*R*,4*S*)[b]	77, 270, 271
7	H	Ph	(*R*)-**1**	Mg(ClO$_4$)$_2$	4 Å MS	quant.[a]	70:30	70 (3*S*,4*R*)[b][70]	77, 270, 271
8	H	Ph	(*R*)-**1**	Mg(OTf)$_2$		quant.[a]	97:3	86 (3*R*,4*S*)[b]	77, 270, 271
9	H	Ph	(*R*)-**1**	Co(ClO$_4$)$_2$		quant.[a]	90:10	47 (3*R*,4*S*) [40]	271
10	H	Ph	(*R*)-**1**	Co(ClO$_4$)$_2$	4 Å MS	quant.[a]	24:76	42 (3*S*,4*R*) [84]	271
11	H	Ph	(*R*)-**1**	Zn(ClO$_4$)$_2$	4 Å MS	quant.[a]	27:73	31 (3*S*,4*R*) [84]	77, 271
12	H	Ph	(*R*)-**1**	Ni(ClO$_4$)$_2$		quant.[a]	98:2	74 (3*R*,4*S*)	271
13	H	Ph	(*R*)-**1**	Ni(ClO$_4$)$_2$	4 Å MS	quant.[c]	72:28	85 (3*S*,4*R*) [85]	271
14	H	Ph	(*R*)-**1**	Mn(ClO$_4$)$_2$		quant.[a]	93:7	52 (3*R*,4*S*) [racemate]	271
15	H	Ph	(*R*)-**1**	Mn(ClO$_4$)$_2$	4 Å MS	quant.[d]	48:52	14 (3*S*,4*R*) [26]	271
16	Me	Ph	(*R*)-**1**	MgI$_2$		73	97:3	46 (3*R*,4*S*,5*R*)	268, 269
17	Me	Ph	(*R*)-**1**	MgI$_2$	4 Å MS	72	96:4	79 (3*S*,4*R*,5*S*)	268, 269
18	Me	Ph	(*R*)-**1**	MgI$_2$	H$_2$O		97:3	50 (3*R*,4*S*,5*R*)	269
19	Me	Bn	(*S*)-**1**	MgI$_2$		82	89:11	racemate	268
20	*n*-Pr	Ph	(*S*)-**1**	MgI$_2$	4 Å MS	>95	53:47	82 [52]	268

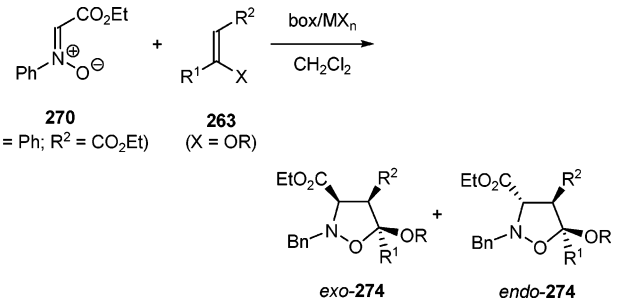
[a] Small amounts (<5%) of byproducts (regioisomers) determined by NMR. [b] The absolute configuration erroneously inverted in ref 270. [c] 12% of **272**. [d] 22% of **272**.

Scheme 101



270 (R¹ = Me; R² = Ph) **167** **273**

Scheme 102



270 (R¹ = Ph; R² = CO_2Et) **263** (X = OR)

exo-**274** *endo*-**274**

The reaction is extremely flexible, and the enantioselectivity drops only with the increase of the steric hindrance of the acrylate (Table 62, entries 2−4).

4.10. Ene and Hetero Ene Reactions

The hetero Diels−Alder reaction with C═O dienophiles, discussed in section 4.8, with dienes containing an allylic C−H bond affords, besides dihydropyrans deriving from the cycloaddition, unsaturated hydroxy esters from a hetero ene reaction.[243,244] The carbonyl−ene reaction is often the dominant reaction with ethyl glyoxylate, and hydroxy esters are the main reaction products (Table 50, entries 1, 4, 5, and 7−10). Under the same conditions, ethyl glyoxylate **85b** was found to react with a variety of 1,1-disubstituted alkenes **279**, all with at least an allylic hydrogen atom, to afford γ,δ-unsaturated α-hydroxy esters **280** (and sometimes **281**) in excellent yield and enantioselectivity (Scheme 104, Table 63).[278,279]

Some alkenes may give a single product (Table 63, entries 1, 2, and 11−17), some are asymmetrically disubstituted, and the reaction complex [catalysts−glyoxylate] must discriminate between two methylene groups (Table 63, entries 3−10). In these reactants the regioselective process favors the hydrogen abstraction from the alkyl versus the CH_2OR group. The attractive feature of the process is the enantioselectivity induced by the catalysts: [(*S*)-**2**/CuX_2] always gives products with the (*S*)-configuration; [(*S*)-**1**/CuX_2] always provides the opposite enantiomer. This is the same behavior already observed in the Mukayiama−Michael and hetero Diels−Alder reactions and again can be rationalized if **85b** coordinates to the catalysts giving rise to reacting complexes with opposite distortion, as illustrated in Figure 12.

Some alkenes give rise to products with two chiral centers (**282** and **283** in Scheme 105), usually both catalysts are anti-selective, again [(*S*)-**2**/CuX_2] gives (2*S*,3*S*)-products (Table 64, entries 1, 3, 7, and 9), [(*S*)-**1**/CuX_2] affords their (2*R*,3*R*)-enantiomers (Table 64, entries 2, 4, 8, and 10), and cycloheptene is nearly unreactive.[278,279,281] With 3-(cyclopentenyl)-trimethyl stannane **279** (R^1CH_2 = $SnMe_3$), the reaction is syn-selective, and this may be a simple synthetic procedure for the formation of the other diastereoisomer (Table 64, entries 5 and 6).[281]

This protocol has some useful applications. The carbonyl−ene reaction giving the product (2*R*,3*R*)-**282** described in Table 64 (entry 13) is the step inducing chirality in a novel synthesis of 3-branched uridine azido acid.[282] The reaction of methyl glyoxylate with methyl (2*S*)-*N*-Boc-4-(phenylthio)-allylglycinate **284**, catalyzed by [(*R*)-**1**/$Cu(OTf)_2$], gives (2*S*,6*S*)-**285** in 88% de (Scheme 106), which is a key intermediate in the synthesis of *meso*-diaminopimelic acid, an essential constituent of bacterial peptidoglycan.[283]

It is well-known that pyruvate esters **85c** are less reactive than glyoxylates; nevertheless they react with unactivated olefins **279** (methylene cyclopentane and cyclohexane, 2-methylpropene, and α-methylstyrene) with [(*S*)-**2**/$Cu(SbF_6)_2$] to give (*S*)-**286** with good yields (76−94%) and excellent enantioselectivities (98% ee) (Scheme 107).[279]

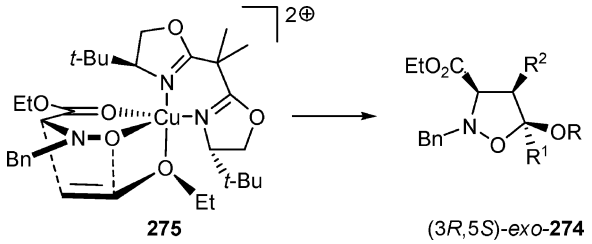
A carbonyl−ene reaction can be carried out between ethyl glyoxylate **85b** and (1-phenyl-vinyl)-carbamic acid benzyl ester **287**, which behaves as an aza-enophile. An unusual feature of the reaction is that both (*S*)-**1** and (*S*)-**2** complexes with $Cu(OTf)_2$ give the same product (*S*)-**288** with yields (and enantioselectivities) of 91% (31% ee) and 70% (73% ee), respectively (Scheme 108).[284]

The ene reaction is usually considered a [$4\pi + 2\sigma$]-pericyclic process, and the change of a carbon atom with the oxygen atom of glyoxylic ester **85b** allows the coordination with [box/Cu] to give the activated hetero ene of a carbonyl−ene reaction. As reported in Scheme 109 with propene as the enophile, the transition state leading to **280** has been suggested to be **289**. A recent DFT:PM3 calculation for this reaction gave a different result.[285] The carbonyl−ene reaction should proceed by a stepwise mechanism through the open zwitterionic intermediate **290**, and a 1,5-proton shift should lead to **280**.

The intramolecular ene reaction was tested early, in competition with an intramolecular hetero Diels−Alder reaction on (*E*)-1-acetyl-3-[2-(3-methyl-2-butenyloxy)benzylidene]-2-oxindole **291**.[286] The reaction affords three contiguous chiral centers, and the best catalyst in terms of chemo-, diastereo-, and enantioselectivity between (*R*)-**1** and (*S*)-**2** with $Mg(ClO_4)_2$ was the former, which gave (3*R*,3′*R*,4′*R*)-**292** in 67% yield and 30% ee (Scheme 110). These reaction conditions are not the most selective conditions, because [(4*R*,5*R*)-**6b**/$Mg(ClO_4)_2$] gives the same stereoisomer in 75% yield and 88% ee; unfortunately, all the catalysts are required in stoichiometric amounts due to the competition with the

Table 61. Enantioselective 1,3-Dipolar Cycloadditions of Nitrone 270 (R^2 = CO_2R) with Vinyl Ethers 263[274]

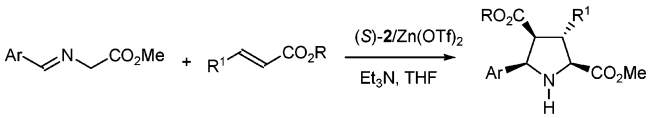
entry	R^1	R^2	OR	box	MX_n	yield (%)	exo/endo	exo ee (%) (conf.)	endo ee (%)
1	H	H	OEt	(*S*)-**2**	$Cu(OTf)_2$	93	84:16	89 (3*R*,5*S*)	35
2	H	H	OEt	(*S*)-**2**	$Zn(OTf)_2$	73	66:34	62 (3*R*,5*S*)	0
3	H	H	OEt	(*R*)-**1**	$Cu(OTf)_2$	86	43:57	44 (3*R*,5*S*)	0
4	H	H	OEt	(*R*)-**1**	$Zn(OTf)_2$	79	46:54	62 (3*S*,5*R*)	0
5	Me	H	OMe	(*S*)-**2**	$Cu(OTf)_2$	83	31:69	90	94
6	H	OCH_2CH_2		(*S*)-**2**	$Cu(OTf)_2$	43	50:50	12	0



275 (3*R*,5*S*)-*exo*-**274**

Figure 16. Proposed pentacoordinated reaction intermediate **275** of the reaction between *N*-benzyl-α-ethoxycarbonylmethanimine *N*-oxide **270** and ethyl vinyl ether, catalyzed by [(*S*)-**2**/Cu(OTf)$_2$].[274]

Scheme 103

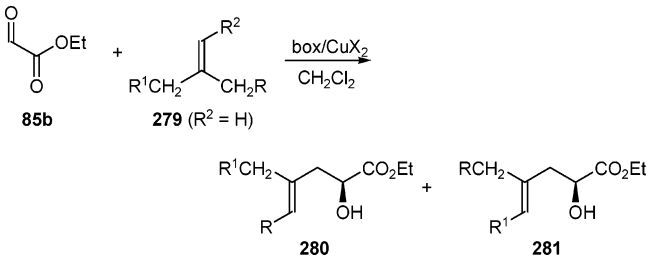


276 277 278

Table 62. Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides Derived from *N*-Arylidene Glycinates 276 with Alkenes 277[277]

entry	Ar	R^1	R	yield (%)	ee (%) (conf.)
1	Ph	H	Me	80	88
2	2-naphthyl	H	Me	84	91
3	2-naphthyl	H	Et	76	68
4	2-naphthyl	H	*t*-Bu	12	<5
5	*p*-BrC$_6$H$_4$	H	Me	89	94
6	Ph	CO_2Me	Me	78	76
7	2-naphthyl	CO_2Me	Me	84	90 (2*S*,3*S*,4*S*,5*R*)
8	*p*-BrC$_6$H$_4$	CO_2Me	Me	87	68

Scheme 104



85b 279 (R^2 = H) 280 281

CO groups of the products with those of the reagent to behave as bidentate ligands with the magnesium ion.

The same reaction conditions, with 2 equiv of [(*R*)-**1**/Mg(ClO$_4$)$_2$], allowed the intramolecular ene reaction of **293** to give a 72% yield of **294** (Scheme 111), which is a key intermediate in the synthesis of (−)-α-kainic acid.[287]

As pointed out, the two above examples required at least stoichiometric amounts of catalyst. However, the intramolecular carbonyl−ene reaction of unsaturated α-ketoesters **295**, due to the presence of the α-keto functionality that can coordinate in a bidentate fashion, proceedes under catalytic conditions in the presence of the Cu(OTf)$_2$ complex of **1** to give the optically active ene adduct **296** (Scheme 112, Table 65).[288]

It has been found that the ring closure reaction to cyclohexane versus cyclopentane occurs with better selectivity (Table 65, entry 1 vs 2), and double-induction experiments demonstrate that (*R*)-**295** matches well with [(*S*)-**1**/Cu(OTf)$_2$], because the enantiomeric catalyst lowers the enantioselectivity and much more diastereoselectivity (Table 65, entries 3 and 5 vs 4 and 6).

This section will be finisihed with an example of catalytic asymmetric domino-Claisen rearrangement. In this reaction, the chirality is induced in the first step but is usefully capitalized in the second step; hence it can be considered a paradigmatic bridge between this section and the next one. Starting from the achiral vinyl ether **297**, the catalysis with [(*S*)-**1**/Cu(OTf)$_2$] gives an excellent 98% yield of a mixture of two diastereoisomers in a ratio of 89:11, and the main product **299** (with three chiral centers) is obtained in an excellent 98% ee (Scheme 113).[289] This cyclohexane derivative is formed from a [box/Cu(II)]-catalyzed Claisen rearrangement, giving (*S*)-**298**, in which the role of the Cu(II) is to coordinate **298** through its C=O and O groups (the bidentate coordination of (benzyloxy)acetaldehyde in Scheme 23 has several points in common). Under the reaction conditions, the Claisen product **298** undergoes an intramolecular Claisen rearrangement, again catalyzed by the same catalysts, through a bidentate coordination involving the pair of carbonyls, with the enophile tethered to the oxy ene. The incomplete diastereoselectivity of the domino reaction is a consequence of an incomplete enantioselectivity of the Claisen rearrangement; the intramolecular Claisen rearrangement, in this case, proceeds with complete diastereoselectivity to produce (1*R*,2*R*,5*S*)-**299**.

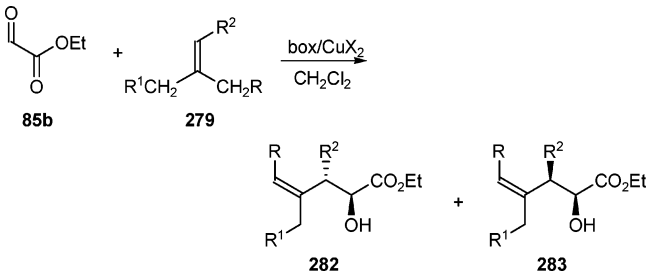
4.11. Other Pericyclic Reactions

Pericyclic reactions are characterized by an easy formation of new C−C (or X−Y) bonds and a predictable (from FMO theory) stereochemistry of the new centers formed. The major

Table 63. Enantioselective Carbonyl−Ene Reactions of Ethyl Glyoxylate 85b with 1,1-Disubstituted Alkenes 279

entry	R	CH_2R^1	box	CuX_2	yield (%)	**280**/**281**	**280** ee (%) (conf.)	ref
1	H	Me	(*S*)-**2**	Cu(SbF$_6$)$_2$2H$_2$O	83		96 (*S*)	278, 279
2	H	Me	(*S*)-**1**	Cu(OTf)$_2$	92		92 (*R*)	278, 279
3	H	Et	(*S*)-**2**	Cu(SbF$_6$)$_2$2H$_2$O	78	55:45	84 (*S*)	278, 279
4	H	Et	(*S*)-**1**	Cu(OTf)$_2$	91	67:33	90 (*R*)	278, 279
5	H	C_5H_{11}	(*S*)-**2**	Cu(SbF$_6$)$_2$2H$_2$O	89	74:26	96 (*S*)	278, 279
6	H	C_5H_{11}	(*S*)-**1**	Cu(OTf)$_2$	81	90:10	91 (*R*)	278, 279
7	H	$CH_2OTBDPS$	(*S*)-**2**	Cu(SbF$_6$)$_2$2H$_2$O	72	>99:1	96 (*S*)	278, 279
8	H	$CH_2OTBDPS$	(*S*)-**1**	Cu(OTf)$_2$	85	>99:1	91 (*R*)	278−280
9	H	CH_2OBn	(*S*)-**2**	Cu(SbF$_6$)$_2$2H$_2$O	62	>99:1	98 (*S*)	278, 279
10	H	CH_2OBn	(*S*)-**1**	Cu(OTf)$_2$	88	>99:1	92 (*R*)	278−280
11	H	Ph	(*S*)-**2**	Cu(SbF$_6$)$_2$2H$_2$O	97		93 (*S*)	278, 279
12	H	Ph	(*S*)-**1**	Cu(OTf)$_2$	99		89 (*R*)	278−280
13	C_3H_7	H	(*S*)-**2**	Cu(SbF$_6$)$_2$	96 (*E*)		92 (*S*)	278, 279
14	CH_2CH_2		(*S*)-**2**	Cu(SbF$_6$)$_2$2H$_2$O	95		96 (*S*)	278, 279
15	CH_2CH_2		(*S*)-**1**	Cu(OTf)$_2$	97		76 (*R*)	278, 279
16	$CH_2CH_2CH_2$		(*S*)-**2**	Cu(SbF$_6$)$_2$2H$_2$O	90		97 (*S*)	278, 279
17	$CH_2CH_2CH_2$		(*S*)-**1**	Cu(OTf)$_2$	99		87 (*R*)	278−280

Scheme 105



parts of papers dealing with this argument have already been discussed in previous sections discussing Diels−Alder, hetero Diels−Alder, 1,3-dipolar cycloaddition, ene, and hetero ene reactions, but some other important topics related to pericyclic reactions deserve attention.

The [2 + 2]-cycloaddition between ketenes and carbonyl compounds are discussed first, not only because these reactions satisfy the conditions to be classified as a pericyclic reaction but also because these reactions are a useful route to β-lactones. The [2 + 2]-cycloaddition between activated aldehydes or ketones **85b**−**d** and silylketenes **300**, catalyzed by Cu(II) complexes, is strongly diastereoselective (cis- and trans-silylated β-lactones **301** can be isolated (SiR_3 = $SiMe_2Ph$, Table 66, entry 6), the former is always the main product) and enantioselective, and desilylation with KF allows the isolation of **302** (Scheme 114, Table 66).[290]

As usual dealing with α-dicarbonyl derivatives, [(*S*)-**1**/$Cu(SbF_6)_2$] and [(*S*)-**2**/$Cu(SbF_6)_2$] give the opposite enantiomers of **302** (Table 66, entry 1 vs 2). The best catalyst is [(*S*)-**2**/$Cu(OTf)_2$] (Table 66, entries 1−5), which gives good yields and enantiomeric excesses with both ethyl glyoxylate **85b** (Table 66, entries 5 and 6) and different α-ketoesters **85c** (Table 66, entries 7−12). An extension to α-diketones **85d** not only gives excellent enantiomeric excess but the catalyst is able to discriminate between a methyl and an ethyl group (Table 66, entry 14).

Obviously an important target of any enantioselective [2 + 2]-cycloaddition is the β-lactam ring, and the reaction of aldimine **303** with the lithium ester enolates **304** could be an attractive route to **305** (Scheme 115). The enantioselective catalysis of the [2 + 2]-cycloaddition was tested with (*S*)-**1** and (*S*)-**2**, but to achieve acceptable enantioselectivity (75−80% ee) more than 2 equiv of box is required; the only box that gave the same result, but with 0.1−0.2 equiv, was (*S*)-**3a**.[291,292]

An unusual way to β-lactam is the reaction of diphenyl nitrone **270** ($R^1 = R^2 =$ Ph) with phenylacetylene, which is certainly not a pericyclic reaction but can be catalyzed by [(*S*)-**2**/CuI_2]. Unfortunately, to achieve a reasonable enantioselectivity (45% ee), a stoichiometric amount of catalyst is required.[293]

Methyl phenyl nitrone **270** (R^1 = Me, R^2 = Ph) reacts with dimethyl 1,1-cyclopropandicarboxylate, under Lewis acid catalysis, to give dimethyl 2-methyl-3-phenyl-tetrahydro-1,2-oxazine-4,4-dicarboxylate. To induce enantioselectivity [(*S*)-**2**/$Cu(OTf)_2$] was tested without any result, and the only active catalysts (47−75% yield, 34−37% ee) were obtained with **10a** and $Cu(OTf)_2$ or MgI_2.[294]

A nice example of enantioselective [4 + 3]-cycloaddition is the reaction of furan with 3-allenamide **306**, which must be epoxidized with dimethyldioxirane (DMDO) to achieve the nitrogen-stabilized oxyallyl cation **307**, the 2π-electron reagent that gives **308** (Scheme 116). The catalyst [(*R*)-**1**/$Cu(OTf)_2$] gives a 46% yield of the (*S*)-enantiomer with 74% ee, and [(*S*)-**2**/$Cu(OTf)_2$] gives a 46% yield of the (*R*)-enantiomer in only 10% ee; however, better results with different box's will be reported in the next section.[295]

The Nazarov cyclization is the cationic electrocyclic reaction of a divinyl ketone, which occurs, under acid (Lewis or protic) conditions, as a 4π conrotatory process. Therefore, asymmetric induction can be achieved if the direction of the conrotation process is controlled. A second carbonyl group (ester or amide) placed in the α-position of **309** to allow bidentate coordination to a [box/Cu(II)] catalyst gave the cationic intermediate **310**, which underwent the 4π conrotatory ring closure and shift to **311** (Scheme 117, Table 67).[296] When **309** has an ester group, the catalyst is required in stoichiometric amounts (Table 67, entries 1 and 2), the absolute stereochemistry of **311** was determined to be (*R*,*R*), and with an amide group the reaction can be carried out with substoichiometric amounts of catalyst (Table 67, entries 3−6).

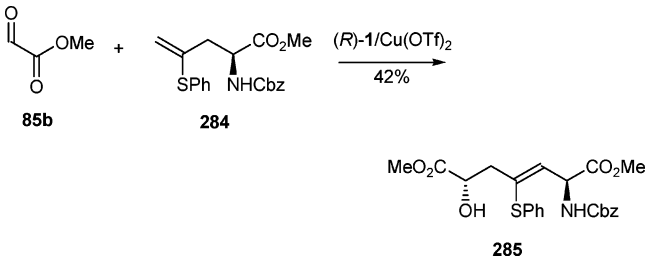
A classic electrocyclic reaction is the [3,3]-sigmatropic Claisen rearrangement performed with allyl vinyl ethers, which become substrates for enantioselective catalysis when 2-alkoxycarbonyl-substituted (**312**), and, with [box/CuX_2] catalysts, affords optically active **313** (Scheme 118, Table 68).[297−299]

The configuration of **313** depends on both the catalysts [(*S*)-**1**/$Cu(OTf)_2$] and [(*S*)-**2**/$Cu(OTf)_2$], which give opposite enantiomers (Table 68, entries 1 and 7 vs 2 and 8), and on the configurations (*Z*) or (*E*) of the double bond (Table 68, entries 2 vs 3). The importance of the ester group in promoting the formation of the reaction intermediate **314** and of the (*Z*)-double bond to induce enantioselectivity (in this case (*S*)-**313**, Table 68, entries 2 and 8) is illustrated in Scheme 118.

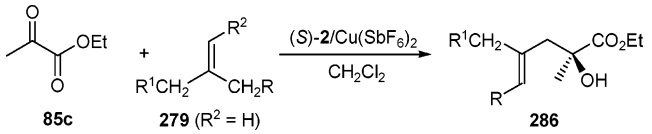
Table 64. Carbonyl−Ene Reactions of Ethyl Glyoxylate 85b with 1,2-Disubstituted Alkenes 279

entry	CH_2R^1	R	R^2	box	CuX_2	yield (%)	**282**/**283**	**282** ee (%) (conf.)	**283** ee (%) (conf.)	ref
1	H	H	Me	(*S*)-**2**	$Cu(SbF_6)_2$	54	40:60	98 (2*S*,3*S*)	n.d.	279
2	H	H	Me	(*S*)-**1**	$Cu(OTf)_2$	60	88:12	90 (2*R*,3*R*)	n.d.	279
3	H	CH_2CH_2		(*S*)-**2**	$Cu(SbF_6)_2$	83	66:33	96 (2*S*,3*S*)	n.d.	279
4	H	CH_2CH_2		(*S*)-**1**	$Cu(SbF_6)_2$	72	73:27	78 (2*R*,3*R*)	n.d.	279
5	H	CH_2CH_2		(*R*)-**1**	$Cu(OTf)_2$	56	88:12	92 (2*S*,3*S*)	87 (2*S*,3*R*)	281
6	$SnMe_3$	CH_2CH_2		(*R*)-**1**	$Cu(OTf)_2$	99	30:70	81 (2*S*,3*S*)	43 (2*S*,3*R*)	281
7	H	$CH_2CH_2CH_2$		(*S*)-**2**	$Cu(SbF_6)_2$	95	86:14	98 (2*S*,3*S*)	n.d.	278, 279
8	H	$CH_2CH_2CH_2$		(*S*)-**1**	$Cu(OTf)_2$	70	95:5	94 (2*R*,3*R*)	n.d.	278, 279
9	Me	$CH_2CH_2CH_2$		(*S*)-**2**	$Cu(SbF_6)_2 \cdot 2H_2O$	86	78:22	98 (2*S*,3*S*)	n.d.	279
10	Me	$CH_2CH_2CH_2$		(*S*)-**1**	$Cu(OTf)_2$	86	89:11	92 (2*R*,3*R*)	n.d.	279
11	H	$CH_2CH_2CH_2CH_2$		(*S*)-**2**	$Cu(SbF_6)_2$	<30				279
12	H	$CH_2CH_2CH_2CH_2$		(*S*)-**1**	$Cu(SbF_6)_2$	<30				279
13	H	$CH_2OTBDPS$	H	(*S*)-**1**	$Cu(SbF_6)_2$	70		90 (2*R*,3*R*)		282

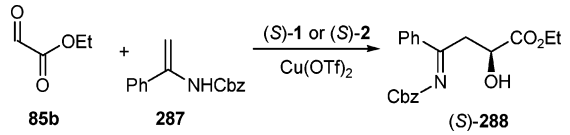
Scheme 106



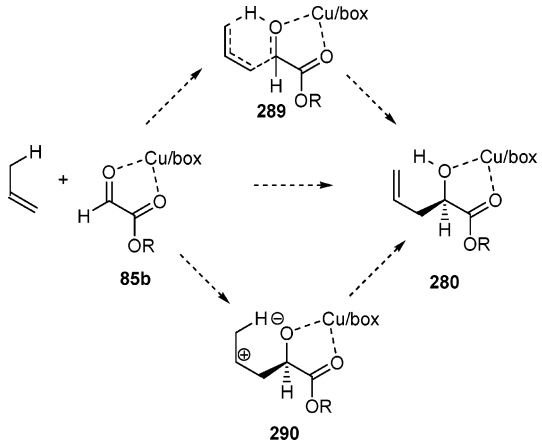
Scheme 107



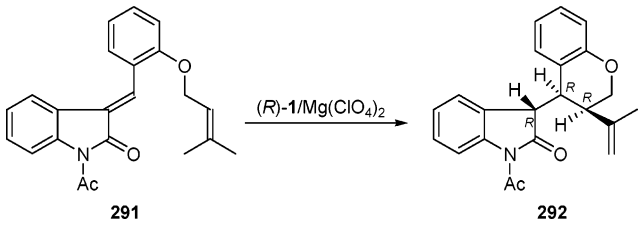
Scheme 108



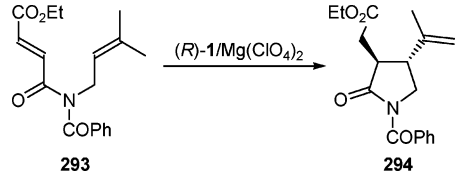
Scheme 109



Scheme 110



Scheme 111



A thorough study was undertaken to provide evidence of the relationship between the configuration of both double bonds of the starting vinyl allyl ether (**315**) and the configuration of the product (**316**), which is a couple of diastereoisomers (syn/anti), each being a couple of enantiomers (Scheme 119, Table 69).[297−299]

Scheme 112

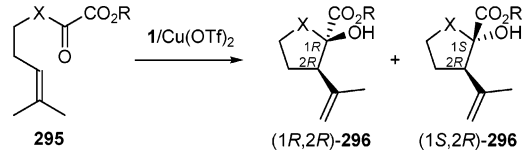


Table 65. Enantioselective Intramolecular Carbonyl−Ene Reactions of 295[288]

entry	R	X	**1** (conf.)	yield (%)	(*R*,*R*)-**296**/(*S*,*R*)-**296**	(*R*,*R*)-**296** ee (%)
1	Et	CH_2CH_2	(*S*)	81	>99:1	91
2	Et	CH_2	(*S*)	92	98:2	71
3	Me	(*R*)CHMe	(*S*)	95	96:4	97
4	Me	(*R*)CHMe	(*R*)	92	58:42	87
5	Bn	(*R*)CHMe	(*S*)	97	97:3	99
6	Bn	(*R*)CHMe	(*R*)	93	58:42	98

Two couples of four stereoisomers each (Table 69, entries 1−4 and 5−8) were submitted to [3,3]-Claisen rearrangement, each with the same catalyst (the choice in a wide range of examples was made to have two homogeneous comparable series), which was [(*S*)-**1**/$Cu(OTf)_2$] for the first series (Table 69, entries 1−4) and [(*S*)-**2**/$Cu(SbF_6)_2 \cdot 2H_2O$] for the second series (Table 69, entries 5−6). The result was a relationship between the configuration of **315**, syn/anti diastereoselectivity (except entry 7, Table 69), and enantioselectivity, which resulted in the formation of the opposite enantiomers for each couple of isomers (Table 69, entries 1 and 5, 2 and 6, 3 and 7, and 4 and 8). Hence, again, (*S*)-**1**− and (*S*)-**2**−copper catalysts afford opposite enantiomers.

When one double bond of the [3,3]-Claisen rearrangement is substituted with a heteroatom having a lone pair of electrons, the substrate is suitable to undergo a [2,3]-sigmatropic rearrangement. If an allyl ether, with a strong base (*t*-BuLi), gives an α-oxycarbanion, then its reaction is known as a [2,3]-Wittig rearrangement, which, to be enantioselectively catalyzed by box, requires the formation of an unusual complex between the ligands and Li(I). This unusual enantioselective catalyst has been usefully applied to the rearrangement of (*Z*)-cyclic furfuryl ether **317**, which gives diastereo- and enantioselectively *syn*-**318** with (*S*)-**2** and *t*-BuLi ((*S*)-**1** is inactive), although the chemical yield was very low (Scheme 120).[300]

A great variety of [2,3]-sigmatropic rearrangements is reported in the literature on iodonium, oxonium, and sulfur ylides, generated by catalytic diazo compound decomposition with a copper cation, which, in the enantioselective version, becomes the cation coordinating the box and the ylide in the reacting complex.

An example of a [2,3]-sigmatropic rearrangement of an iodonium ylide is exemplified by the [(*S*)-**2**/$Cu(MeCN)_4PF_6$]-catalyzed reaction between allyl iodides **319** and ethyl diazoacetate **26**, which, through the box-coordinated iodonium ylide **320**, affords **321** (R = H, 62%, 69% ee; R = Me, 67%, 37% ee) (Scheme 121).[301]

The same conceptual approach is at the base of the intramolecular reaction of **322** with [(*S*)-**2**/$Cu(MeCN)_4PF_6$], which induces decomposition of the diazogroup, generation of the ylide coordinated by the box complex, and enantioselective formation of the oxonium ylide that undergoes stereocontrolled internal [2,3]-sigmatropic rearrangement to form **323**, solely the cis stereoisomer, in 35% yield and 65% ee (Scheme 122).[301]

Scheme 113

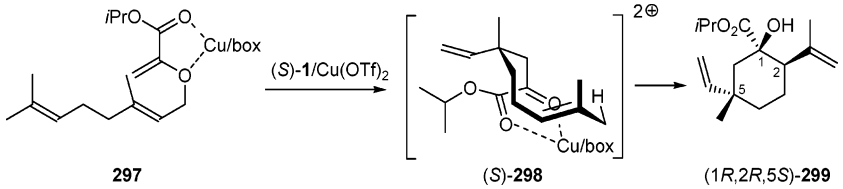
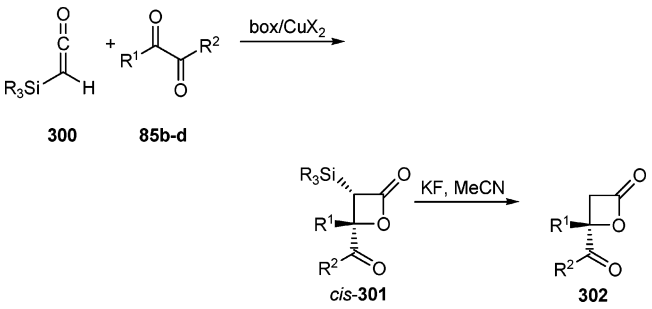


Table 66. Enantioselective Cycloaddition Reactions between 85b−d and Silylketenes 300[290]

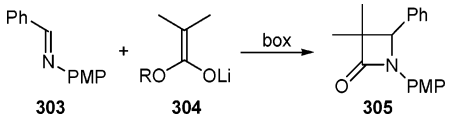
entry	R_3	R^1	R^2	solvent	box	CuX_2	yield (%)	*cis*-**301**/*trans*-**301**	**302** ee (%) (conf.)
1	Me_3	H	OEt	CH_2Cl_2	(*S*)-**1**	$Cu(SbF_6)_2$	>99	88:12	17 (*R*)
2	Me_3	H	OEt	CH_2Cl_2	(*S*)-**2**	$Cu(SbF_6)_2$	86	91:9	69 (*S*)
3	Me_3	H	OEt	CH_2Cl_2	(*S*)-**2**	$Cu(OTf)_2$	93	n.d.	77 (*S*)
4	Me_3	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$	>99	95:5	95 (*S*)
5	Me_3	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2 \cdot 2H_2O$	77	91:9	93 (*S*)
6	Ph,Me_2	H	OEt	THF	(*S*)-**2**	$Cu(OTf)_2$	>99	>95:5	92 (*S*)
7	Me_3	Me	OMe	CH_2Cl_2	(*S*)-**2**	$Cu(SbF_6)_2$	>99	n.r.	95 (*S*)
8	Me_3	Et	OMe	CH_2Cl_2	(*S*)-**2**	$Cu(SbF_6)_2$	92	n.r.	99 (*S*)
9	Me_3	*i*-Bu	OMe	CH_2Cl_2	(*S*)-**2**	$Cu(SbF_6)_2$	87	n.r.	83 (*S*)
10	Me_3	*i*-Pr	OEt	CH_2Cl_2	(*S*)-**2**	$Cu(SbF_6)_2$	86	n.r.	85 (*S*)
11	Me_3	Ph	OMe	CH_2Cl_2	(*S*)-**2**	$Cu(SbF_6)_2$	79	n.r.	87 (*S*)
12	Me_3	CH_2Br	OEt	CH_2Cl_2	(*S*)-**2**	$Cu(SbF_6)_2$	>99	n.r.	91 (*S*)
13	Me_3	Me	Me	CH_2Cl_2	(*S*)-**2**	$Cu(SbF_6)_2$	95	n.r.	>99 (*S*)
14	Me_3	Me	Et	CH_2Cl_2	(*S*)-**2**	$Cu(SbF_6)_2$	95[a]	n.r.	85 (*S*)

[a] Two regioisomers in the ratio 95:5.

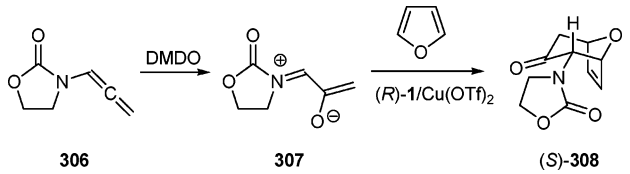
Scheme 114



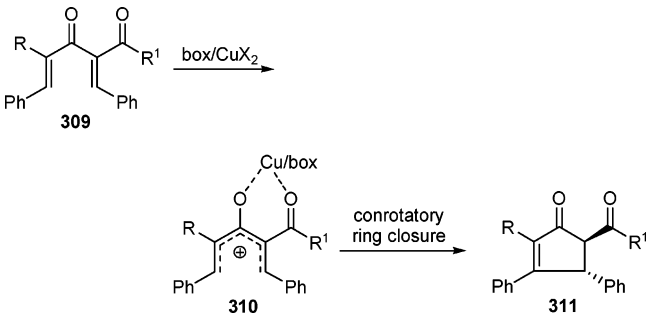
Scheme 115



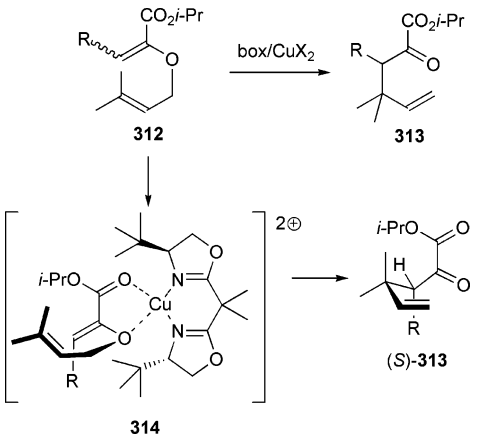
Scheme 116



Scheme 117



Scheme 118



The ylide **324** coordinated to box, obtained by copper-catalyzed decomposition of diazoesters **323**, reacts with allyl sulfides **325**, and the intermediate sulfur ylides undergo asymmetric [box/CuX]-catalyzed [2,3]-sigmatropic rearrangement to afford alkyl- and aryl-substituted allyl sulfides **326** (Scheme 123, Table 70).[302,303] The catalyst derived from (*S*)-**2** gives better enantioselectivity than that based on (*S*)-**1**, independently from the copper salt (Table 70, entries 3, 5, and 8 vs 4, 6, and 9), and moderately high enantioselectivities are obtained with aryldiazoacetate (Table 70, entries 7, 8, and 10), the best enantioselectivity being obtained with methyl 1-naphthyldiazoacetate (78% ee). The absolute configuration of the diphenyl-substituted methylester (Table 70, entry 7) is (*R*)-**326**.[303]

Applications of this reaction to more complicated structures (reaction of 2-thioindoles with substituted vinyl diazoacetates catalyzed by (*S*)-**2** and $CuPF_6$) gave low yields of the rearrangement products with negligible enantioselectivity.[304] A different result was realized when the reaction described above was run between diazoacetates **323** and aryl propargyl sulfides **327**, since the allenic derivatives **327**,

Table 67. Nazarov Cyclizations of 309[296]

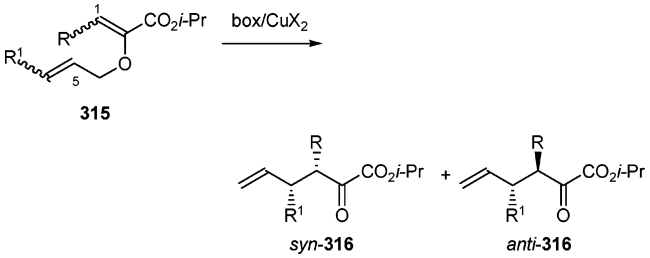
entry	R	R^1	box	CuX_2	catalyst	yield (%)	ee (%)
1	Me	OEt	(*S*)-**1**	$Cu(SbF_6)_2$	1 equiv	85	5
2	Me	OEt	(*S*)-**2**	$Cu(SbF_6)_2$	1 equiv	70	44
3	Ph	NEt_2	(*S*)-**1**	$Cu(SbF_6)_2$	0.5 equiv	56	86
4	Ph	NEt_2	(*S*)-**2**	$Cu(SbF_6)_2$	0.5 equiv	56	87
5	Me	NEt_2	(*S*)-**1**	$Cu(SbF_6)_2$	1 equiv	21	75
6	Me	NEt_2	(*S*)-**2**	$Cu(SbF_6)_2$	0.5 equiv	56	85

Table 68. Catalytic Enantioselective Claisen Rearrangements of (*Z*)- or (*E*)-312[297−299]

entry	R	configuration	box	CuX_2	yield (%)	ee (%) (conf.)
1	Me	*Z*/*E* 96:4	(*S*)-**1**	$Cu(OTf)_2$	100	82 (*R*)
2	Me	*Z*/*E* 96:4	(*S*)-**2**	$Cu(OTf)_2$	99[a]	88 (*S*)
3	Me	*Z*/*E* 4:96	(*S*)-**1**	$Cu(OTf)_2$	99	82 (*S*)
4	Et	*Z*/*E* 100:0	(*S*)-**1**	$Cu(OTf)_2$	99	84 (*R*)
5	2-propyl	*Z*/*E* 90:10	(*S*)-**1**	$Cu(OTf)_2$	98	78 (*R*)
6	2-propenyl	*Z*/*E*100:0	(*S*)-**1**	$Cu(OTf)_2$	100	86 (*R*)
7	Bn	*Z*/*E* 97:3	(*S*)-**1**	$Cu(OTf)_2$	100	76 (*R*)
8	Bn	*Z*/*E* 97:3	(*S*)-**2**	$Cu(OTf)_2$	94[a]	84 (*S*)
9	Bn	*Z*/*E* 97:3	(*S*)-**2**	$Cu(SbF_6)_2$ $2H_2O$	62	46 (*S*)
10	CH_2OTIPS	*E*	(*S*)-**2**	$Cu(SbF_6)_2$ $2H_2O$	98[a]	99 (*S*)

[a] MS 4 Å as an additive.

Scheme 119



formed through a [2,3]-sigmatropic rearrangement of the intermediate sulfur ylides (Scheme 124), were obtained under catalysis with both (*S*)-**1** or (*S*)-**2** and $CuPF_6$, and the enantioselectivity with the second catalyst was up to 81% ee.[305]

A [(*R*)-**1**/CuOTf]-catalyzed imidation of sulfides or selenides **329a**,**b** with [*N*-(*p*-tolylsulfonyl)imino]-phenyliodinane **330** affords intermediate chiral allylic sulfides or selenides (**331a,b**) with the nitrogen atom lone pair electrons suitably placed to be involved in the enantioselective [2,3]-sigmatropic rearrangement that gives allyl sulfonamides or, respectively, selenamides **332a**,**b** (Scheme 125).[306−308] The reaction with allyl sulfides **329a** (R = Me, Ph; R^1 = Ar) affords **332a** with yields of 30−80% and enantioselectivities in the range of 25−58% ee,[306,307] and with aryl cinnamyl selenides **329b**, the yields of **332b** were again in the range of 35−71%, but the enantiomeric excesses were poor (17−30% ee).[308]

4.12. Miscellaneous Reactions

This section for obvious reasons collects different types of reactions, some marginal in the economy of the review, some important from both the synthetic and the mechanistic point of view. Therefore, even if homogeneity is certainly not the major characteristic, future important developments of single parts cannot be excluded.

The last section was closed with the [(*R*)-**1**/CuOTf]-catalyzed imidation of sulfides or selenides with [*N*-(*p*-tolylsulfonyl)imino]-phenyliodinane **330** affording chiral allylic sulfides or selenides that give a [2,3]-sigmatropic rearrangement. If the prochiral thio- or selenoethers **333a**,**b** do not have suitably placed double bonds to undergo further reactions, the chiral sulfimides and selenimides **334a**,**b** are stable, isolable products (Scheme 126).[306−308] The variety of substituents tested is large, and the reaction is flexible. The best solvent was toluene, the best catalysts were again [(*R*)-**1**/CuOTf], yields were from satisfactory to good (up to 82%), and the best enantioselectivity for **334a** was 71% ee for R and R^1 being 1-naphthyl and benzyl, respectively,[306,307] and for **334b** 36% ee for R and R^1 being 2-naphthyl and benzyl, respectively.[308]

A lithium cyclopentadienide derivative can be obtained through enantioselective addition of 2-methylphenyllithium to 6-(dimethylamino)fulvene, and the yield with (*S*)-**2** as catalysts is 77%, but the enantiomeric excess of the (*R*)-product (20% ee) cannot be compared with the enantioselectivity obtained with sparteine.[309]

The target of several groups is the intramolecular C−H insertion of ylides. The reaction of phenyliodonium ylide **335** is catalyzed by [(*R*)-**1**/$Cu(OTf)_2$] and [(*S*)-**2**/$Cu(OTf)_2$], and after hydrolysis (*R*)-**336** is the product of both catalysts in about 50% yield and enantioselectivities of 13% and 23% ee, respectively (Scheme 127).[310]

The intramolecular C−H insertion of electron-poor carbenes into the Cp−H bond of the electron-rich cyclopentadienyl ring of ferrocene derivatives **337a**,**b** can be catalyzed by [(*S*)-**1**/CuOTf]. Both the formation of the cyclohexanone ring in **338a** and the dimethylcyclopentanone in **338b** occur with good yields and remarkable enantiomeric excesses (Scheme 128).[311]

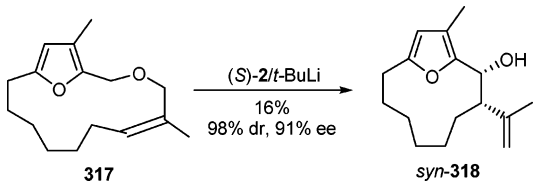
The key reaction for the asymmetric approach to 1,2-disubstituted mitosenes is based on the decomposition of the diazoester **339** and the subsequent intramolecular C−H insertion of metallo-carbene onto two sets of diastereotopic pyrrolidinic hydrogen atoms oriented endo and exo (Scheme 129). Different chiral catalysts have been tested, and that giving the best dr (4.4:1) of epimeric esters is [(*R*)-**1**/CuOTf], with the endo/anti isomer **340** obtained in 53% ee, which converges to **341** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation.[312−313]

An intermolecular variant of the above reactions is the Cu(I)−carbenoid− and the Ag(I)−Lewis acid−box-catalyzed

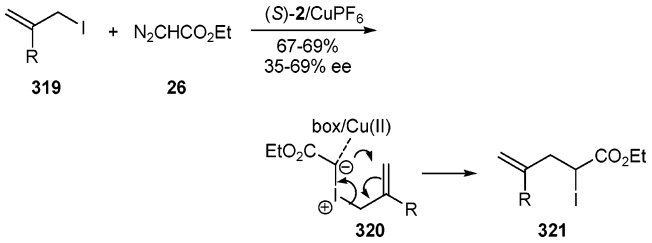
Table 69. Catalytic Enantioselective Claisen Rearrangements of Four Stereoisomers of 315[297,299]

entry	R	R^1	config.	box	CuX_2	yield (%)	syn/anti	syn ee (%) (conf.)	anti ee (%) (conf.)
1	Me	*n*-Pr	1*Z*,5*Z*	(*S*)-**1**	$Cu(OTf)_2$	98	99:1	84 (3*R*,4*S*)	
2	Me	*n*-Pr	1*E*,5*Z*	(*S*)-**1**	$Cu(OTf)_2$	99	3:97		88 (3*S*,4*S*)
3	Me	*n*-Pr	1*Z*,5*E*	(*S*)-**1**	$Cu(OTf)_2$	100	28:72		72 (3*R*,4*R*)
4	Me	*n*-Pr	1*E*,5*E*	(*S*)-**1**	$Cu(OTf)_2$	100	86:14	82 (3*S*,4*R*)	
5	CH_2OBn	CH_2OTIPS	1*Z*,5*Z*	(*S*)-**2**	$Cu(SbF_6)_2$ $2H_2O$	99	99:1	98 (3*R*,4*R*)	
6	CH_2OBn	CH_2OTIPS	1*E*,5*Z*	(*S*)-**2**	$Cu(SbF_6)_2$ $2H_2O$	97	14:86	98(3*S*,4*S*)	98 (3*S*,4*R*)
7	CH_2OBn	CH_2OTIPS	1*Z*,5*E*	(*S*)-**2**	$Cu(SbF_6)_2$ $2H_2O$	98	63:37	99(3*R*,4*R*)	95 (3*R*,4*S*)
8	CH_2OBn	CH_2OTIPS	1*E*,5*E*	(*S*)-**2**	$Cu(SbF_6)_2$ $2H_2O$	99	89:11	94 (3*S*,4*S*)	

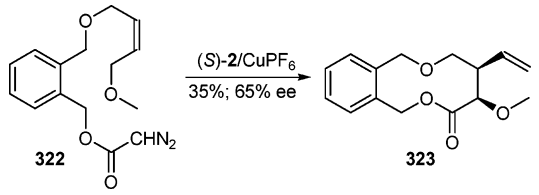
Scheme 120



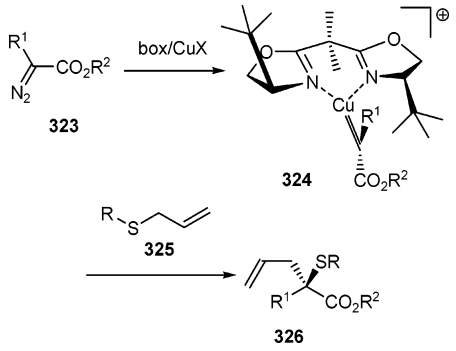
Scheme 121



Scheme 122



Scheme 123



insertion of α-diazocompounds **323** into the N−H bond of aniline derivatives **342** to give optically active secondary amine **343** (Scheme 130).[314] Several reagents have been tested, and some significant results are reported in Table 71. There are indications that for Cu(I) catalysts the carbene pathway is predominant, whereas for the Ag(I) systems an elimination reaction seems to predominate. Even if yields or enantioselectivites are sometimes low, the results are the highest asymmetric inductions obtained for an intramolecular N−H insertion via a chiral carbene complex or chiral Lewis acid catalysis.[314]

An enantiotopic differentiation of pro-R or pro-S chlorines in (dichloromethyl)borate **344** by BuLi, catalyzed by box's and metal triflates, allows the enantioselective intermolecular insertion into the C−Cl bond with the formation of (1-chloropentyl)boronate **345** in 86% yield (Scheme 131). First experiments with stoichiometric amounts of different catalysts suggest that [(*R*)-**1**/Yb(OTf)$_3$] is the catalyst of choice for the reaction (Table 72, entries 1−5), attempts to use catalytic amounts of this catalyst led to a lower enantiomeric excess (Table 72, entry 6), and the best compromise is catalytic amounts of triflate with large amounts of box (Table 72, entry 8).[315]

The catalytic enantioselective conversion of a C−H bond into a C−halogen bond (halogenation) only recently has been faced and solved for β-ketoesters and β-ketophosphonates **140b**,**c**, producing the corresponding α-halogenated compounds **346b**,**c**, using *N*-chloro- (NCS) and *N*-bromosuccinimide (NBS) as chlorine and bromine sources, *N*-fluorobenzenesulfonimide (NFSI) as a fluorinating agent, and (obviously) box complexes as catalysts (Scheme 132).[316−319]

As it can be seen from some significant results reported in Table 73, after the screening of box's, Cu(II) salts, solvents, and halogenation reagents (Table 73, entries 1−5), the best catalyst for chlorination and bromination of β-ketoesters **140b** is [(*S*)-**2**/Cu(OTf)$_2$], in Et$_2$O with NCS and dioxane with NBS (Table 73, entries 5−10).[316] The same holds, except with THF as the solvent, for β-ketophosphonates (Table 73, entries 20 and 21).[319] The formation of the (*S*)-enantiomer for the product described in entry 6 of Table 73 is in accordance with the coordination of the β-ketoesters to the Cu(II) catalysts in a bidentate fashion, with the plane of the β-ketoesters tilted from that of the box by approximately 45°. The ligand (*S*)-**2** in the reaction intermediate shields the Re face of the enolate leaving the Si face available for the attack.[316]

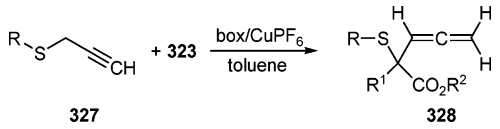
The fluorination of β-ketoesters differs from previous halogenations because first it gave the best enantioselectivites with [(*R*)-**1**/Cu(OTf)$_2$] (Table 73, entries 11−13, 18, and 19),[317] then [(*R*)-**1**/Ni(ClO$_4$)$_2$] was found to be a more selective catalyst (Table 73, entries 15−17).[318] The attractive feature of fluorination is that nickel and copper complexes give opposite enantiomers.

Three interesting reactions could be taken as examples of the flexibility and variety of box complexes as catalysts, but enantioselectivity is not comparable with that obtained with different chiral catalysts. α-Methoxyacetophenone can be reduced with [(*S*)-**1**/Zn(OTf)$_2$] as the catalyst and catecholborane as the reducing agent. The product is (*S*)-2-methoxy-1-phenylethanol in 62% yield and 42% ee.[320] Phenyl glyoxal undergoes an intramolecular Canizzaro reaction in the presence of 2-propanol and [(*S*)-**1**/Cu(OTf)$_2$] to give (*R*)-

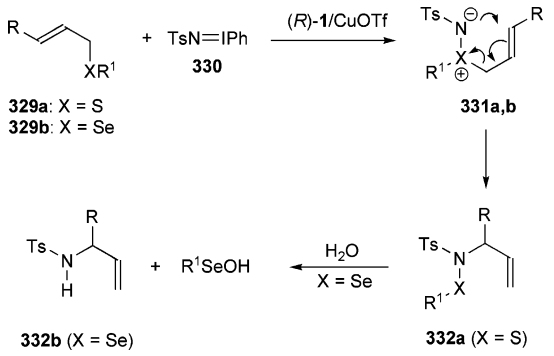
Table 70. Catalytic Enantioselective [2,3]-Sigmatropic Rearrangements of Allyl Sulfides

entry	R	R^1	R^2	solvent	box	CuX	yield (%)	ee (%) (conf.)	ref
1	Me	H	Et	$CHCl_3$	(*S*)-**2**	CuOTf	58	3	302
2	Ph	H	Et	$CHCl_3$	(*S*)-**2**	CuOTf	59	14	302
3	adamanthyl	H	Et	$CHCl_3$	(*S*)-**2**	CuOTf	62	26	302
4	adamanthyl	H	Et	$CHCl_3$	(*S*)-**1**	CuOTf	60	12	302
5	*o*-diMePh	H	Et	$CHCl_3$	(*S*)-**2**	CuOTf	62	52	302
6	*o*-diMePh	H	Et	$CHCl_3$	(*S*)-**1**	CuOTf	64	11	302
7	Ph	Ph	Me	benzene	(*S*)-**2**	$CuPF_6$	89	41 (*R*)	303
8	*o*-MePh	Ph	Me	benzene	(*S*)-**2**	$CuPF_6$	92	62	303
9	*o*-MePh	Ph	Me	benzene	(*S*)-**1**	$CuPF_6$	92	48	303
10	*o*-MePh	1-naphthyl	Me	benzene	(*S*)-**2**	$CuPF_6$	66	78	303

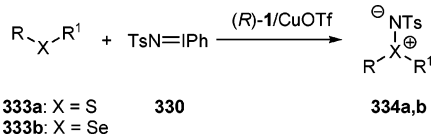
Scheme 124



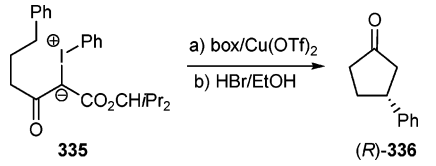
Scheme 125



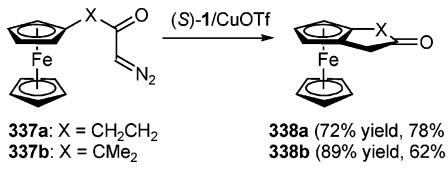
Scheme 126



Scheme 127



Scheme 128



isopropyl mandelate in 57% yield and 28% ee.[321] The Passerini three-component coupling reaction between benzoic acid, (benzyloxy)benzaldehyde, and *p*-methoxyphenyl isocyanide gives the amidoester **347** under catalysis with both [(*S*)-**1**/CuX_2] and [(*S*)-**2**/CuX_2] where X is OTf or SbF_6 (Scheme 133). Yields are excellent (up to 93%), and enantioselectivities are good (50−64% ee), but pybox-based catalysts give the same yield with 97% ee.[322]

To close this section and to demonstrate the unknown possibilities of the box-based catalysis an unusual reaction has been recently described. A racemic mixture of (*S*,*S*)- and (*R*,*R*)-hydroxybenzoin **348** is treated with 0.5 mol of PhCOCl and diisopropylethylamine (DIPEA) in the presence of 5 mol % [(*R*)-**1**/$CuCl_2$]: 48% of (*S*,*S*)-**348** is selectively monobenzoylated to give (*S*,*S*)-**349** in >99% ee, and (*R*,*R*)-**348** can be recovered as a pure enantiomer (Scheme 134).[323] The kinetic resolution of other 1,2-diols has been similarly performed. If the same method is applied to *meso*-**348**, but with 1.0 mol of PhCOCl, a 79% yield of monobenzoylated (*S*,*R*)-**350** is obtained in 94% ee, this being an excellent route to the desymmetrization of 1,2-diols (Scheme 134).[323]

5. Other Box Ligands: Effects of Substituents on the Catalytic Behavior

As seen in section 4, Ph- and *t*-Bu-box's allow the catalysis of a wide range of reactions, but other box ligands give catalysts that significantly improve efficiency and selectivity in the same or in new reactions. As seen in Chart 1, more than 150 box's have been synthesized; in the next sections these will be grouped in homogeneous classes whose behaviors will be discussed, making comparisons with those of **1** and **2**, considered as the prototypes of 4-aryl- and 4-alkyl-substituted box's. Only those ligands whose complexes significantly improve or modify the selectivity of the catalysts derived from prototypes will be discussed in detail.

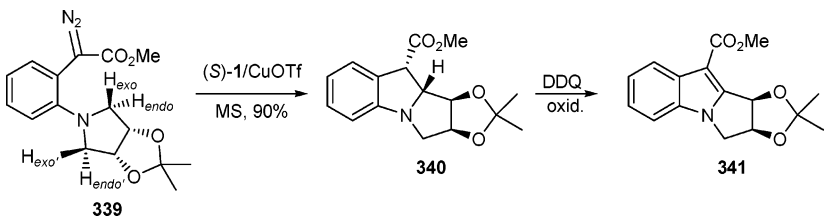
5.1. 4-Aryl-Substituted Box's

Two types of 4-aryl-substituted box's have been used with the aim to prepare more bulky or more rigid catalysts: those with one or more substituents on the phenyl group and those with a naphthyl group.

The success of 4-aryl-box was very limited (with one significant exception) since in general the enantioselectivity induced by catalysts based on these box's was comparable, and sometimes lower, than that obtained with **1**. The enantioselective mercuriocyclization of γ-hydroxy-*cis*-alkene to 2-substituted tetrahydrofuran with 4-(*o*-methoxyphenyl)-box (*S*)-**3z** gave enantioselectivities significantly lower than that with (*R*)-**1** (both were surpassed in selectivity by other types of ligands).[324] The hetero Diels−Alder reaction of α,β-unsaturated acyl phosphonates **262b** with ethyl vinyl ether **263** gives results nearly superimposable to that of (*S*)-**1** (Table 57, entry 2) when run with 4-OMe- or 4-chlorophenyl-box (*S*)-**3aa** and (*S*)-**3ab**.[58] The enantioselectivity of the intramolecular cyclopropanation in Scheme 12 does not change when *o*-tolyl-box (*S*)-**3y** is used instead of (*S*)-**1**;[95] both the diastereo- and the enantioselectivity of the intermolecular cyclopropanation catalyzed by [(*R*)-**1**/Cu(I)] described in Table 3 (entry 3) is improved (from 40% to 68−80% de and from 65% up to 80% ee) with catalysts derived from macrocyclic box (*R*)-**14a**,**b**.[39a]

The significant exception is given by a new class of box ligands with the 4-(2′,5′-disubstituted)-phenyl (Scheme 135), which has been usefully applied to the Mukaiyama−aldol reactions between α-ketoesters **85c** and silylketene acetal **97** to give dioxenones (S)-**98** (Scheme 27).[24] Table 74 reports

Scheme 129



Scheme 130

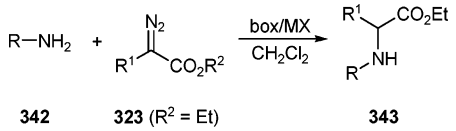


Table 71. Catalytic Enantioselective Insertions of α-Diazocompounds 323 into N−H Bonds[314]

entry	R	R^1	box	CuX	yield (%)	ee (%) (conf.)
1	Ph	Me	(*R*)-**1**	$CuPF_6$	62	20
2	Ph	Me	(*R*)-**2**	$CuPF_6$	54	28
3	Ph	Me	(*R*)-**2**	AgOTf	5	48
4	Ph	Me	(*R*)-**2**	$AgSbF_6$	8	25
5	Ph	Me	(*R*)-**2**	$AgClO_4$	5	48
6	Ph	Ph	(*R*)-**1**	$CuPF_6$	67	19
7	Ph	Ph	(*R*)-**2**	$CuPF_6$	82	13
8	2-naphthyl	Me	(*R*)-**2**	$CuPF_6$	27	24
9	Bn	Me	(*R*)-**2**	$CuPF_6$	27	10 (*R*)

Scheme 131

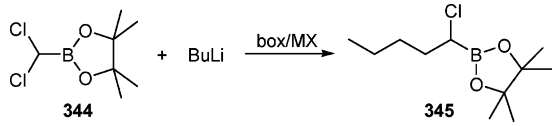
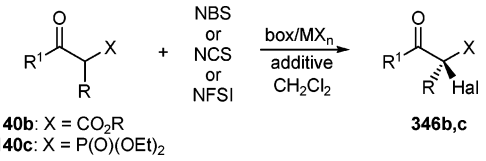


Table 72. Catalytic Enantioselective Insertions of BuLi into the C−Cl Bond of 344[315]

entry	box	$M(OTf)_n$	ratio (box/$M(OTf)_n$/**344**)	ee (%) (conf.)
1	(*R*)-**1**	$Zn(OTf)_2$	1:1:1	45 (*R*)
2	(*R*)-**1**	$Cu(OTf)_2$	1:1:1	45 (*R*)
3	(*S*)-**2**	$Cu(OTf)_2$	1:1:1	racemate
4	(*R*)-**1**	$Yb(OTf)_3$	1.1:0.9:1	71 (*R*)
5	(*R*)-**1**	$Lu(OTf)_3$	1:1:1	60 (*R*)
6	(*R*)-**1**	$Yb(OTf)_3$	0.5:0.4:1	62 (*R*)
7	(*R*)-**1**	$Yb(OTf)_3$	5:1:1	86 (*R*)
8	(*R*)-**1**	$Yb(OTf)_3$	5:0.3:1	88 (*R*)

Scheme 132



the comparison between (*S*)-**1** and **3z**,**ad**−**af** complexes of $Cu(OTf)_2$ and $CuCl_2$ in the reaction of methyl pyruvate.

The configuration of **98** is always (*S*), independent from box and copper counterion, and the effect of the ortho substituent is limited (Table 74, entry 2 vs 1) as in previous examples, but the presence of a chlorine atom or, even better, of a bulky *tert*-butyl group in position 5 of the aryl ring induces the highest level of asymmetric induction (Table 74, entries 3 and 4), which is strongly lowered by the modification of the OMe group in the ortho position (Table 74, entry 5). The catalyst [(*S*)-**3ad**/$CuCl_2$] was tested on the Mukaiyama−aldol reaction of **97** with 13 different α-ketoesters; the yields and the enantioselectivities of (*S*)-**98** are in the ranges of 70−91% and 79−98% ee, respectively.[24] From these results it seems resonable to predict a positive impact of this new class of aryl-box's on future research in the field.

The next interesting class of box's are those with 1- or 2-naphthyl groups **3h** and **3i** (Chart 2), which were used in different reactions, all in comparison with **1** (Table 75).

The majority of the reactions with naphthyl-box, mainly those in which the reaction center is relatively remote from the coordination site, show a significant improvement of the enantiomeric excess compared to those with phenyl-box (Table 75, entries 1−3 and 6−9). The Mukaiyama−Michael reaction is the most interesting reaction (Table 75, entry 7), because, on going from (*S*)-**1** to (*S*)-**3h**, not only the enantiomeric excess increases from 56% to 70% ee but a reversal of the stereochemistry also is observed.[17] In all other reactions **1** and **3h**,**i** induce the same enantioselectivity.

5.2. 4-Aryl-5-Substituted Box's

This section gives interesting information about the transfer of the chiral information from the optically active catalyst to the product. A substituent in position 5 of the box may be cis or trans to the 4-aryl group, and the first comparison of **1** with its 5-phenyl-substituted analogues **5b** and **6b** (Chart 3) can be done. To have the information on the effect of the 5-substituent on the selectivity induced by the 4-phenyl group, only homogeneous reactions will be compared, and the absolute configurations of the products (when available) will be referred to the box ligands with (4*R*)-configurations.

Some reactions have been catalyzed by (*R*)-**1** and *cis*-(4*R*,5*S*)-**5b** complexes, the Michael reaction[158] and the Mannich reaction in Scheme 44[152b] and the Claisen rearrangement in Scheme 118,[298] and give nearly identical results in terms of enantioselectivity and sense of the induction. The [4 + 3]-cycloaddition between furan and allenamides **306** (Scheme 116), on going from [(*R*)-**1**/$Cu(OTf)_2$] to [(4*R*,5*S*)-**5b**/$Cu(OTf)_2$], showed an increase in the enantioselectivity of (*S*)-**308** from 78% to 90% ee.[295]

Some reactions have been catalyzed by (*R*)-**1** and *trans*-(4*R*,5*R*)-**6b** complexes, and under both conditions, the hetero Diels−Alder reactions in Schemes 91, 94, and 95[249,253,254,260] do not change significantly. The Mukaiyama−Michael reaction in Scheme 61 does not change if the Lewis acid is $Mg(ClO_4)_2$, the enantioselectivity increases with the *trans*-box with $Co(ClO_4)_2$,[175] and the same increase is observed for the Mukaiyama−aldol reaction reported in Scheme 22.[17]

The most important series of data concerns reactions that have been run under the same catalytic conditions with (*R*)-**1**, *cis*-(4*R*,5*S*)-**5b**, and *trans*-(4*R*,5*R*)-**6b** complexes (Table 76). Both the allylic substitution reported in Scheme 64 and the allylic oxidation in Scheme 81 display higher enantioselectivities by using either **5b** or **6b** box, with the same sense of induction whatever the configuration at C-5 (Table 76, entries 1 and 2).[325]

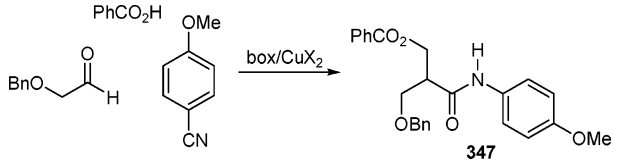
The Diels−Alder reaction between **163** and cyclopentadiene (Scheme 84) has been studied with the three box's and different conditions, and the results with $Mg(ClO_4)_2$, $Mg(ClO_4)_2$ + 2 equiv of H_2O, and $Mg(OTf)_2$ are reported in Table 76, entries 3−5. In Figure 14 the reaction complexes have been illustrated: tetrahedral with $Mg(ClO_4)_2$, octahedral with H_2O or OTf. If the reacting complex is tetrahedral, then the *cis*-box lowers the enantioselectivity, and the *trans*-box strongly increases both diastereo- and enantioselectivity, always with the same sense of induction. If the reaction complex is octahedral, then the *cis*-box increases enantioselectivity with the same sense of induction, and the *trans*-box not only lowers the enantiomeric excess but the absolute configuration also depends on the stereochemistry of the octahedron.[217,220]

An important effect of the substituent on C-5 is observed in the 1,3-dipolar cycloaddition reaction between nitrone **270**

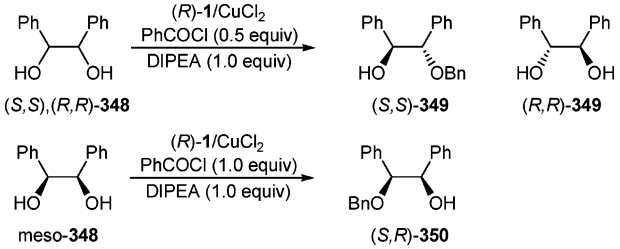
Table 73. Catalytic Enantioselective Halogenations of β-Ketoesters 140b and β-Ketophosphonates 140c

entry	R	R^1	X	halogen source	box	MX_n	additive	solvent	yield (%)	ee (%) (conf.)	ref
1	Me	Me	CO_2Et	NCS	(*R*)-**1**	$Cu(OTf)_2$		Et_2O	98	32	316
2	Me	Me	CO_2Et	NCS	(*S*)-**2**	$Cu(OTf)_2$		Et_2O	n.r.	77	316
3	Me	Me	CO_2Et	NCS	(*S*)-**2**	$Cu(OTf)_2$		dioxane	n.r.	62	316
4	Me	Me	CO_2Et	NCS	(*S*)-**2**	$Cu(SbF_6)_2$		Et_2O	n.r.	44	316
5	Me	Me	CO_2Et	NBS	(*S*)-**2**	$Cu(OTf)_2$		dioxane	98	80	316
6	Me	Ph	CO_2Et	NCS	(*S*)-**2**	$Cu(OTf)_2$		Et_2O	98	53 (*S*)	316
7	Me	Ph	CO_2Et	NBS	(*S*)-**2**	$Cu(OTf)_2$		dioxane	95	41 (*S*)	316
8	$(CH_2)_3$		CO_2Et	NCS	(*S*)-**2**	$Cu(OTf)_2$		Et_2O	96	72	316
9	$(CH_2)_4$		CO_2Et	NCS	(*S*)-**2**	$Cu(OTf)_2$		Et_2O	99	76	316
10	$(CH_2)_4$		CO_2Et	NBS	(*S*)-**2**	$Cu(OTf)_2$		dioxane	85	82	316
11	$(CH_2)_3$		CO_2t-Bu	NFSI	(*S*)-**2**	$Cu(OTf)_2$		Et_2O	91	20	317
12	$(CH_2)_3$		CO_2t-Bu	NFSI	(*R*)-**1**	$Cu(OTf)_2$		Et_2O	82	72 (*R*)	317
13	$(CH_2)_3$		CO_2t-Bu	NFSI	(*R*)-**1**	$Cu(OTf)_2$	HFIP	Et_2O	94	82 (*R*)	317
14	indanone		CO_2t-Bu	NFSI	(*S*)-**1**	$Cu(OTf)_2$		CH_2Cl_2	50	39 (*S*)	318
15	indanone		CO_2t-Bu	NFSI	(*S*)-**1**	$Ni(ClO_4)_2$		CH_2Cl_2	92	76 (*R*)	318
16	indanone		CO_2t-Bu	NFSI	(*S*)-**1**	$Ni(ClO_4)_2$	MS	CH_2Cl_2	87	93 (*R*)	318
17	indanone		CO_2(1-adamantyl)	NFSI	(*S*)-**1**	$Ni(ClO_4)_2$	MS	CH_2Cl_2	74	79	318
18	$(CH_2)_4$		CO_2t-Bu	NFSI	(*R*)-**1**	$Cu(OTf)_2$	HFIP	Et_2O	92	63	317
19	Me	Ph	CO_2t-Bu	NFSI	(*R*)-**1**	$Cu(OTf)_2$	HFIP	Et_2O	56	43 (*S*)	317
20	Me	Ph	$P(O)(OEt)_2$	NCS	(*S*)-**2**	$Cu(OTf)_2$		THF	>95	64	319
21	Me	Ph	$P(O)(OEt)_2$	NCS	(*S*)-**2**	$Zn(OTf)_2$		THF	>95	45	319

Scheme 133



Scheme 134

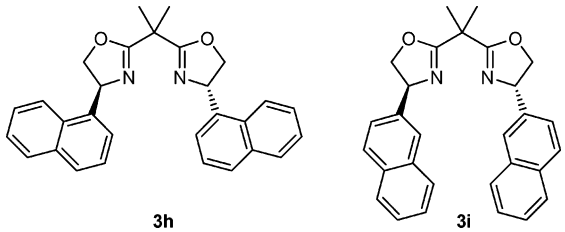


and **163**, with the three box's (**1**, *cis*-**5b**, and *trans*-**6b**) and Mg(II), Ni(II), Co(II), and Zn(II) perchlorates as Lewis acids (Table 76, entries 6−9). The complexes of (4*R*,5*S*)-**5b** largely give the same sense of induction (with a lower enantioselectivity) of the corresponding complex with (4*R*)-**1** as a ligand, which derives from a preferred attack to the Re face for all endo adducts and the exo adducts of magnesium and nickel and to the Si face for the exo adducts of cobalt and zinc. Interesting results have been obtained with *trans*-(4*R*,5*R*)-**6b** complexes, because magnesium, cobalt, and mainly nickel give exo-selective catalysts. This result allowed the isolation of an exo enantiomer with 99% ee, whose unknown absolute configuration was established to be

Table 74. Comparison between Different [Box/Cu(II)] Complexes in the Mukaiyama−Aldol Reactions between Methyl Pyruvate 85c (R = R^1 = Me) and Silylketene Acetal 97[24]

				$Cu(OTf)_2$		$CuCl_2$	
entry	Y	Y^1	box	yield (%)	ee (%) (conf.)	yield (%)	ee (%) (conf.)
1			(*S*)-**1**	70	11 (*S*)	35	40 (*S*)
2	Me	H	(*S*)-**3z**	80	39 (*S*)	75	20 (*S*)
3	Me	Cl	(*S*)-**3af**			80	86 (*S*)
4	Me	*t*-Bu	(*S*)-**3ad**	78	76 (*S*)	81	94 (*S*)
5	$(CH_2)_2Cl$	*t*-Bu	(*S*)-**3ae**	75	11 (*S*)	78	44 (*S*)

Chart 2



(3*R*,4*R*)-**271**, deriving from a preferred attack to the Re face of the tetrahedral reacting intermediate **351** (Scheme 136). In conclusion, if the result in Table 76 (entry 10) is added to the above data, from two box's with the same (4*R*)-configuration, all stereoisomers can be obtained in very good yields and enantioselectivities: the endo enantiomers from [(*R*)-**1**/$Ni(ClO_4)_2$] and [(4*R*,5*R*)-**6b**/$Zn(ClO_4)_2$] (Table 76, entries 7 and 9), the exo enantiomers from [(4*R*,5*R*)-**6b**/$Ni(ClO_4)_2$] and [(*R*)-**1**/$Co(ClO_4)_2$] (Table 76, entries 7 and 8).[271]

Scheme 135

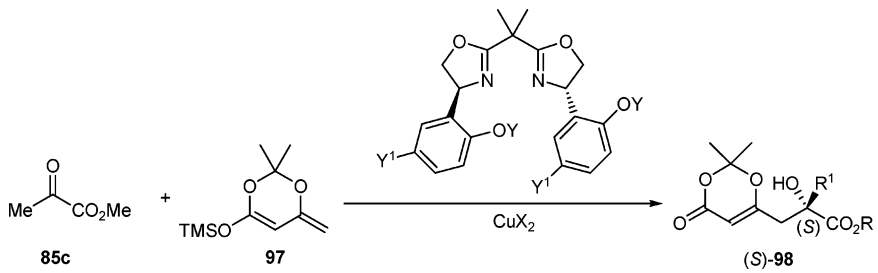
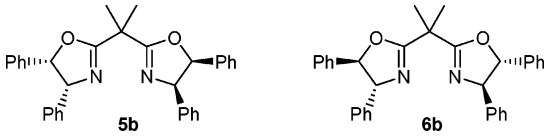


Table 75. Comparison of Phenyl-Box (1) and Naphthyl-Box (3h,i) Complexes as Enantioselective Catalysts for Different Reactions

				(*S*)-**1**		(*S*)-**3h**		(*S*)-**3i**		
entry	reaction[a]	reagents	Lewis acid	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)	ref
1	D.A.	**163** + Cy[b] (Scheme 84)	$Cu(OTf)_2$	92	30	92	44			60
2	D.A.	**163** + Cy[b] (Scheme 84)	$Mg(ClO_4)_2$	>98	70			>98	77	18, 217
3	D.A.	**163** + Cy[b] (Scheme 84)	$Mg(OTf)_2$	>98	88			>98	94	18, 220
4	H.D.A.	**85c** + **245** (Scheme 91)	$Cu(OTf)_2$	n.r.	13	n.r.	19			17
5	M.A.R.	**85c** + **86** (Scheme 22)	$Cu(OTf)_2$	73	24	n.r.	19			17
6	M.A.R.	**85c** + **97** (Scheme 27)	$Cu(OTf)_2$	99	16	73	51			17
7	M.Mi.R.	**153** + **86** (Scheme 59)	$Cu(SbF_6)_2$	67	56	55	70[c]			17
8	O.Mi.R.	**158** + **149** (Scheme 54)	$Mg(OTf)_2$	32	44	53	62			28
9	F.C.R.	**130** + **131** (Scheme 41)	$Zn(OTf)_2$	10	19	22	27			148

[a] D.A., Diels−Alder reaction; H.D.A., hetero Diels−Alder reaction; M.A.R., Muykaiyama−aldol reaction; M.Mi.R., Muykaiyama−Michael reaction; O.Mi.R., Oxa-Michael reaction; F.C.R., Friedel−Crafts reaction. [b] Cy is cyclopentadiene. [c] Reversal of stereochemistry on going from (*S*)-**3h** to (*S*)-**1**.

Chart 3



The C-5 position can have a methyl group, and *cis*-(4*S*,5*R*)-**5c** (Chart 4) has been tested on the radical reaction of 3-(3-phenyl-2-propenoyl)-2-oxazolidinone **163** (R = Ph) in Scheme 75, but the result, compared to that of (*S*)-**1**, was unsatisfactory since (*S*)-**207** is obtained with 31% and 47% ee, respectively.[29]

This reaction allows the introduction of **9a**, an indene box synthesized in 1996,[45] which seems formally to be a 4-aryl-5-alkyl-substituted box (Chart 4). This ligand, applied to the same radical reaction, gives the product in 89% ee, but even if the configuration at C-4 is the same as that of **5c**, a different shielding of the reagent must be involved in the reaction intermediate since (*R*)-**207** is the main enantiomer.[29]

If the catalytic effects of **9a** complexes are compared with those of prototype **1**, then sometimes the results are negative or nearly similar; hence the commercial box remains advantageous. This occurs with the aldol reaction of **108** and benzaldehyde in Scheme 31,[66] the Kharasch oxidations of cycloalkenes **221** or hexynes **225** with $PhCO_3t$-Bu in Schemes 81 and 82,[208,211] and the [4 + 3]-cycloaddition between **307** and furan in Scheme 116.[295]

An interesting test was made with the Diels−Alder reaction between **163** (R = H) and cyclopentadiene (Scheme 84) comparing the catalytic efficiency of the $Cu(OTf)_2$ complexes with (*S*)-**1**, (4*S*,5*R*)-**9a**, and (4*S*,5*R*)-**9b**.[46,326] All reactions are endo-selective, (*S*)-**229** is the major product, and the enantiomeric excesses reported in Table 77 (entries 1−3) show for the conformationally constrained box **9a** an enhanced level of stereoselectivity. When **163** has R = 4-$CF_3C_6H_4CO_2$ (Table 77, entries 4−6),[224] the enantiomeric excesses with (*S*)-**1** and (4*S*,5*R*)-**9a** are comparable, but the enantioselection is opposite, and the latter gives the same (*R*,*R*)-enantiomer obtained with (*S*)-**2**.

The hetero Diels−Alder reactions of α-carbalcoxy α,β-unsaturated carbonyl compounds **262a** with vinyl ether **263** (Scheme 137) were carried out with [(4*R*,5*S*)-**9a**/$Cu(OTf)_2$], both reactions were strongly endo-selective (endo/exo = 95:5), and compounds (4*S*,6*S*)-**264a** were obtained with 95% and 97% ee, respectively.[327]

The radical reaction performed on **163** with alkyl iodides in the presence of Et_3B/O_2 and Bu_3SnH, catalyzed by stoichiometric amounts of [box/MX_2] and already described in Scheme 75, was tested with the pyrazole template **235** (R = Ph), 2-iodopropane, and stoichiometric amounts of [(4*S*,5*R*)-**9a**/$Zn(OTf)_2$] (Scheme 138), and (*S*)-**352** was obtained in 72% yield and 43% ee. The same result was obtained with box **10** and different alkyl iodides.[328]

Table 76. Comparison between Complexes of 4-Phenyl-Box (1) and 4,5-Diphenyl-Box (5,6b) as Enantioselective Catalysts for Different Reactions

				(4*R*)-**1**			(4*R*,5*S*)-**5b**			(4*R*,5*R*)-**6b**			
entry	reaction[a]	reagents	Lewis acid	yield (%)	endo/exo (%)	ee (%) (conf.)[b]	yield (%)	endo/ exo	ee (%) (conf.)[b]	yield (%)	endo/ exo	ee (%) (conf.)[b]	ref
1	A.S.R.	**182** + Malon (Sc 64)	$PdCl_2$	23		95 (*R*)	90		98 (*R*)	70		97 (*R*)	30, 325
2	Rad.R.	**221** + *t*BP[g] (Sc 81)	CuOTf	84		71 (*R*)	70		80 (*R*)	80		84 (*R*)	205, 325
3	D.A.	**163** + **Cy** (Sc 84)	$Mg(ClO_4)_2$	>98	96:4	73 (*S*)[c]	>98	96:4	30 (*S*)[c]	>98	>99:1	97 (*S*)[c]	217
4	D.A.	**163** + **Cy** (Sc 84)	$Mg(ClO_4)_2$[d]	>98	95:5	73 (*R*)[c]	>98	96:4	89 (*R*)[c]	>98	98:2	78 (*S*)[c]	217
5	D.A.	**163** + **Cy** (Sc 84)	$Mg(OTf)_2$	>98	92:8	88 (*R*)[c]	>98	94:6	93 (*R*)[c]	>98	89:11	60 (*R*)[c]	220
6	1,3-D.C.	**163** + **270** (Sc 100)	$Mg(ClO_4)_2$[e]	>98	70:30	70 (*S*,*R*) 70 (*R*,*R*)	96	84:16	16 (*R*,*S*) 70 (*R*,*R*)	97	26: 74	50 (*S*,*R*) 94 (*R*,*R*)	271
7	1,3-D.C.	**163** + **270** (Sc 100)	$Ni(ClO_4)_2$[e]	88	72:28	85 (*S*,*R*) 85 (*R*,*R*)	88	56:44	77 (*S*,*R*) 52 (*R*,*R*)	>98	10: 90	75 (*S*,*R*) 99 (*R*,*R*)	271
8	1,3-D.C.	**163** + **270** (Sc 100)	$Co(ClO_4)_2$[e]	>98	24:76	42 (*S*,*R*) 84 (*S*,*S*)	91	44:56	68 (*S*,*R*) 33 (*S*,*S*)	>98	16:84	79 (*S*,*R*) 92 (*R*,*R*)	271
9	1,3-D.C.	**163** + **270** (Sc 100)	$Zn(ClO_4)_2$[e]	>98	27:73	31 (*S*,*R*) 84 (*S*,*S*)	95	39:61	59 (*S*,*R*) 56 (*S*,*S*)	>98	85:15	90 (*R*,*S*) 40 (*R*,*R*)	271
10	1,3-D.C.	**163** + **270** (Sc 100)	$Mg(OTf)_2$	>98	97:3	86 (*R*,*S*)							271
11	I.E.R.[f]	**291** (Sc 110)	$Mg(ClO_4)_2$	61		30 (*R*,*R*,*R*)	48		51 (*R*,*R*,*R*)	75		88 (*R*,*R*,*R*)	286

[a] A.S.R, allylic substitution reaction; D.A., Diels−Alder reaction; 1,3-D.C., 1,3-dipolar cycloaddition reaction; I.E.R., intramolecular ene reaction. [b] Absolute configuration of endo/exo isomers. [c] Absolute configuration of the endo isomer. [d] Plus 2 equiv of H_2O. [e] Molecular sieves. [f] Stoichiometric conditions. [g] *t*BP is *tert*-butyl perbenzoate.

Scheme 136

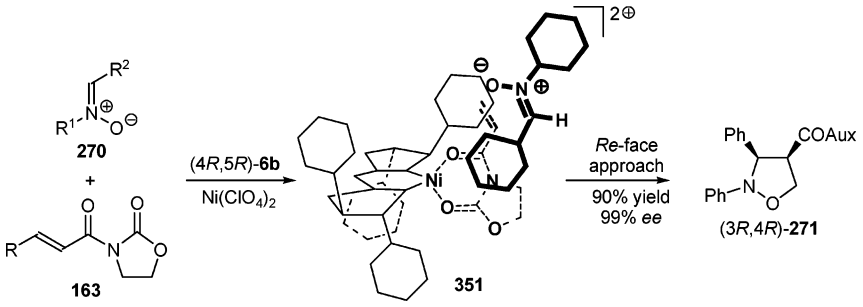


Chart 4

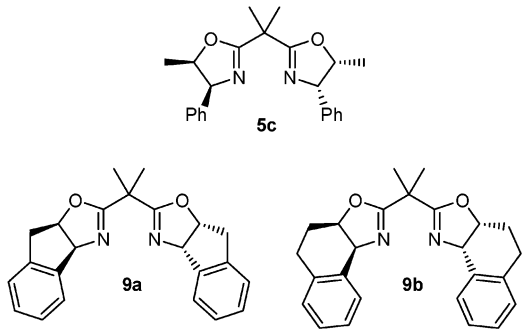
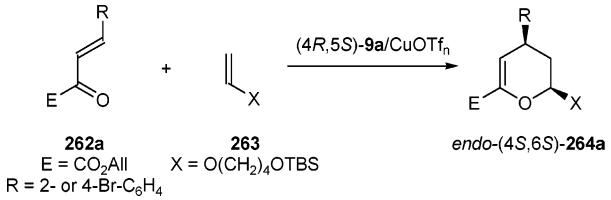


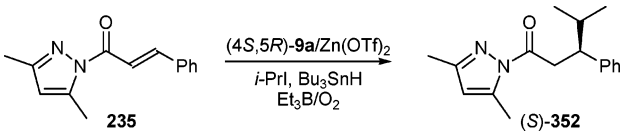
Table 77. Comparison between Cu(OTf)$_2$ Complexes of Box's 9a,b, 1, and 2 as Enantioselective Catalysts for the Diels−Alder Reactions between 163 and Cyclopentadiene

entry	R	box	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	H	(4*S*,5*R*)-**9a**	n.r.	98:2	83 (*S*)	46, 326
2	H	(*S*)-**1**	92	95:5	30 (*S*)	60
3	H	(4*S*,5*R*)-**9b**	n.r.	98:2	38 (*S*)	46
4	H	(*S*)-**2**	>98	98:2	>98 (*S*)	60
5	4-$CF_3C_6H_4CO_2$	(4*S*,5*R*)-**9a**	99	90:10	83 (*R*,*R*)	224
6	4-$CF_3C_6H_4CO_2$	(*S*)-**1**	99	94:6	89 (*S*,*S*)	224
7	4-$CF_3C_6H_4CO_2$	(*S*)-**2**	99	90:10	54 (*R*,*R*)	224

Scheme 137



Scheme 138



Box (4*R*,5*S*)-**9a** finds two applications to the Henry reaction: The first, with $Cu(OAc)_2$ as the Lewis acid, concerns the synthesis of protected 4-hydroxyornithine **354**, a key constituent of antibiotics clavalanine and biphenomycins, by diastereoselective addition of $MeNO_2$ to the homoserine-derived aldehyde **353** (Scheme 139).[329] The yield is 94%, and the diastereoselectivity is 94% de; a lowering of the diastereomeric excess to 84% with (4*S*,5*R*)-**9a** reflects a mismatched pairing.

The second Henry reaction has already been mentioned in Scheme 37 and concerns the addition of $MeNO_2$ to aldehydes. The catalyst of election for this reaction is

Scheme 139

Scheme 140

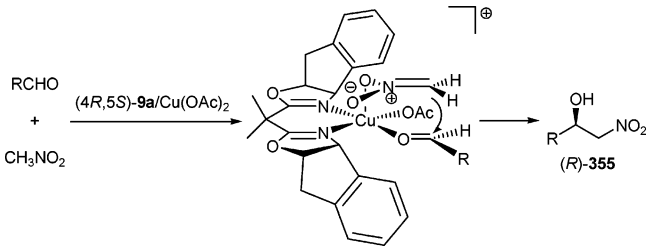


Table 78. Comparison between the Cu(OTf)$_2$ Complexes of Box's 9a, 1, and 2 as Enantioselective Catalysts for the Henry Reactions of Aldehydes and $MeNO_2$ in Scheme 140[65]

entry	R	box	yield (%)	ee (%) (conf.)
1	*p*-$NO_2C_6H_4$	(4*R*,5*S*)-**9a**	85	81 (*R*)
2	*p*-$NO_2C_6H_4$	(*R*)-**1**[a]	n.r.	43 (*R*)
3	*p*-$NO_2C_6H_4$	(*R*)-**2**[a]	n.r.	37 (*R*)
4	Ph	(4*R*,5*S*)-**9a**	76	94 (*R*)
5	*o*-$MeOC_6H_4$	(4*R*,5*S*)-**9a**	91	93 (*R*)
6	*o*-NOC_6H_4	(4*R*,5*S*)-**9a**	86	89 (*R*)
7	1-naphthyl	(4*R*,5*S*)-**9a**	66	87 (*R*)
8	*i*-Pr	(4*R*,5*S*)-**9a**	86	94 (*R*)
9	*n*-Bu	(4*R*,5*S*)-**9a**	87	93 (*R*)
10	*t*-Bu	(4*R*,5*S*)-**9a**	83	94 (*R*)

[a] (*S*)-**1** and (*S*)-**2** were used in the specific experiments yielding (*S*)-**355**.

[(4*R*,5*S*)-**9a**/$Cu(OAc)_2$], which reacts with a variety of aldehydes to give **355** in very good yields and with excellent enantiomeric excesses (Scheme 140, Table 78), and the absolute configuration of which can be compared to those obtained with (*S*)-**1** and (*S*)-**2**.[65] If the crystal structure of the catalyst (Table 2, entry 16) is taken into account, then a distorted square-pyramidal configuration can be proposed for the reaction intermediate **356**, with the nucleophile in the axial position and the electrophile in the ligand plane on the basis of both steric and electronic considerations, which accounts for the observed sense of asymmetric induction.[65]

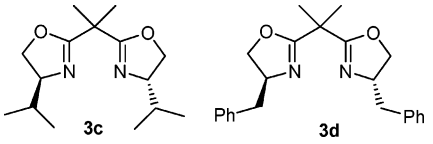
As a consequence of the results in this section, when Cu(II) complexes of **9a, 1**, and **2** have the same configuration at C-4, all give the same sense of enantioselection (Henry reaction in Table 78, Diels−Alder reaction with acryloyloxazolidinone **163** in Table 77, entries 1, 2, and 4). In other cases **1** gives enantioselection opposite to that of **9a** and **2** (Diels−Alder reaction with **163** (R = 4-$CF_3C_6H_4CO_2$) in

Table 77, entries 5−7), and the **1**-based complex becomes the best catalyst.

5.3. 4-Alkyl-Substituted Box's

This is by far the section with the largest number of references, not only for the variety of substituents but also because two of them (4-isopropyl-box **3c** and 4-benzyl-box **3d**, Chart 5) are among the most popular box's, used to

Chart 5



catalyze several reactions, often in the glorious early period. The benchmark of the box complexes in this section is the corresponding complex derived from **2**, and a simple mention will be made to those reactions where 4-alkyl-substituted box's do not significantly improve the efficiency of the benchmark. When the comparison of homogeneous reactions will result in significant improvements of the catalytic efficiency or will give a different result in terms of chirality transfer, the absolute configuration of the products (when available) will be referred to the box ligands with (4*R*)-configuration.

Ligands **3c** and **3d** have been used as chiral ligands for copper-catalyzed intermolecular cyclopropanation reactions between alkenes and diazoderivatives,[78,80−82,91,330,331] and an example of [**3e**/Cu(I)]-catalyzed intramolecular cyclopropanation is also reported.[21] The efficiency of these catalysts is, in general, lower than those derived from **1** or **2**, whose results have already been reported in section 4.1.

The comparison of the catalytic effect of [**2**/Cu(OTf)$_2$] versus [**3c**/Cu(OTf)$_2$] on the reaction of methyl 2-furancarboxylic acid **35** and diazoester **26** (R = Et) in Scheme 8 (91% vs 81% ee) again illustrates the better efficiency of the *t*-Bu box, but the best enantioselectivity is obtained when diazoester **26** has R = *t*-Bu and the catalyst is [**3c**/Cu(OTf)$_2$] (95% ee), and the importance of this result may be appreciated since adduct **36** was converted to nephrosteranic acid, roccellaric acid, and protolichesterinic acid.[88]

When phenyliodonium ylides are the source of the carbenoids involved in the intramolecular cyclopropanation, the Cu(I) catalysts derived from **3c** and **3f** may give somewhat better results than those based on **2**, but the values of the enantomeric excesses show that these catalysts are not suitable for this reaction.[332,333] The Cu(OTf)$_2$ complexes of the above two box's must be cited as catalysts for the intramolecular C−H insertion reaction of phenyliodonium ylide **335**, illustrated in Scheme 127. After hydrolysis, 3-phenylcyclopentanone **336** is obtained with a yield of about 50% and with the same stereoselectivity in each case, but the enantioselectivities are 42% and 38% ee, with **3c** and **3f**, respectively, versus 23% ee obtained with **2**.[310]

An important difference between various 4-alkyl-substituted box's on the enantioselectivity of the intramolecular cyclopropanation of α-diazo-*β*-ketosulfones **357** has been reported. The results of the catalysis with CuOTf complexes of (*S*)-**2**, (*S*)-**3c**, and (*S*)-**3d** to give the bicylic reaction products **358** (Scheme 141) are reported in Table 79. The catalysts derived from these box's induce the same enantioselection, and the most efficient ligand for all substrates is

Scheme 141

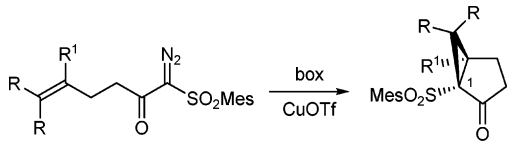


Table 79. Comparison between the CuOTf Complexes of Box's 2, 3c, and 3d as Enantioselective Catalysts for the Intramolecular Cyclopropanations of α-Diazo-*β*-Ketosulfones 357 in Scheme 141[334]

entry	R	R^1	box	yield (%)	ee (%) (conf.)
1	H	H	(*S*)-**2**	48	31 (1*R*)
2	H	H	(*S*)-**3c**	93	83 (1*R*)
3	H	H	(*S*)-**3d**	78	72 (1*R*)
4	H	Br	(*S*)-**3c**	68	92 (1*S*)
5	H	Br	(*S*)-**3d**	44	56 (1*S*)
6	H	CH_2OTr	(*S*)-**3c**	91	78 (1*R*)
7	H	CH_2OTr	(*S*)-**3d**	96	73 (1*R*)
8	Me	H	(*S*)-**3c**	74	74 (1*R*)
9	Me	H	(*S*)-**3d**	77	71 (1*R*)

Table 80. Enantioselective Catalysis of the Mukaiyama−Aldol Reactions between 85b and Trimethylsilylketene Acetals 86 with Sn(OTf)$_2$ Complexes of Box's 3c and 3d[122]

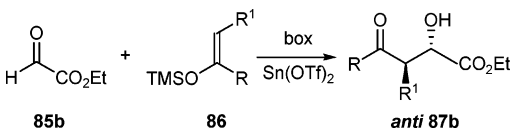
entry	R	R^1	box	yield (%)	anti/syn	**87b** ee (%) (conf.)
1	SPh	H	(*S*)-**3c**	*a*		93 (*S*)
2	SPh	H	(*S*)-**3d**	90		98 (*S*)
3	SPh	Me	(*S*)-**3d**	87	90:10	95 (2*R*,3*S*)
4	SPh	Et	(*S*)-**3d**	90	92:8	95 (2*R*,3*S*)
5	SPh	*i*-Pr	(*S*)-**3d**	72	93:7	95 (2*R*,3*S*)
6	SPh	*i*-Bu	(*S*)-**3d**	88	92:8	98 (2*R*,3*S*)
7	SEt	*i*-Bu	(*S*)-**3d**	83	92:8	92 (2*R*,3*S*)
8	S*t*-Bu	*i*-Bu	(*S*)-**3d**	83	96:4	96 (2*R*,3*S*)

[a] Not reported.

(*S*)-**3c**.[334] The absolute configuration of **358** is that reported in Scheme 141 except when R = Me (Table 79, entries 8 and 9).

The Mukaiyama−aldol reaction had several applications of 4-alkyl-substituted box-based catalysts.[121,124,127] Among them, the reaction mentioned in Scheme 22 (again reported for clarity in Scheme 142) between ethyl glyoxylate **85b**

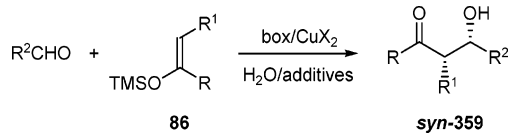
Scheme 142



and silylketene acetals **86**, strongly anti-selective, gives **87b** and serves to check the effect on enantioselectivity of the Sn(OTf)$_2$ complexes of (*S*)-**3c** and (*S*)-**3d** (Table 80), compared to the 91% ee obtained with [(*S*)-**1**/Sn(OTf)$_2$] (Table 15, entry 9).[122]

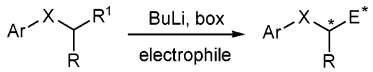
A test of the efficiency of [(*R*)-**3d**/Sn(OTf)$_2$] is its use as a catalyst for the Mukaiyama−aldol reaction between ethyl glyoxylate **85b** and silylketene acetals **86** [R = SPh; R^1 = (2*R*)-*sec*-butyl]. The adduct (2*S*,3*R*)-**87b**, obtained with the same enantioselection observed in the above examples in 99% yield, 98% de, and 99% ee, is the key intermediate in the total syntheses of the antitumor *β*-lactones Belactosin A and C.[335]

Scheme 143



86 ***syn*-359**

Scheme 144



111a: X = S
111b: X = Se

113a,b

A new catalytic technology for the Mukaiyama−aldol reaction was developed by the Kobayashi group, which consisted first in running the reaction in H_2O−EtOH solutions,[336,337] then organic solvents were completely avoided using a combined Lewis acid−surfactant catalyst system [box/Cu(II)dodecyl sulfate],[338] in accordance to the paradigms of green chemistry. The reaction between several monodentate aldehydes and silylketene acetals **86** is syn-selective and gives **359** (Scheme 143, Table 81).

The best box is (*S*)-**3c**, and the inversion of stereoselection on going from 4-alkyl-substituted box [(*S*)-**3c**,**d**,**ag**,**ah**] to (*S*)-**2**, which is also the worst ligand in terms of the enantioselectivity induced, seems rather unusual (Table 81, entries 1, 2, and 4−7). Through the use of [(*S*)-**3c**/Cu(II)-dodecyl sulfate] as a catalyst, the Lewis acid nature more influences yield than stereoselectivity (Table 81, entries 10, 11, 17, and 18).

The aldol reaction between 3-propionoyl-2-thiazolidinethione (**108**) and benzaldehyde can be catalyzed with [(*S*)-**3c**/$Ni(OTf)_2$], but the enantiomeric excess was lower than that resulting with the **2**-based complex.[66] This behavior cannot be generalized: The aldol reaction between methyl malonic acid half thioester **102** undergoes decarboxylative addition catalyzed by [(*S*)-**3c**/$Cu(OTf)_2$] with 3-phenylpropionaldehyde to afford *syn*-(2*R*,3*S*)-3-hydroxy-2-methylthiopentanoic acid (*S*)-phenyl esters **103** (R = CH_2CH_2Ph) with 87% ee (Scheme 29), with the more steric demanding (*S*)-**2**-based complex giving only traces of the product.[130]

The results of the reactions between α-thio- and α-seleno-carbanions with aldehydes or ketones acting as electrophiles have been reported in Table 20.[132−138a] The lithium cation is the Lewis acid that coordinates the carbanion with the chiral ligand, and the reaction of **111a**,**b** giving **113a**,**b** (Scheme 144) seldom gives better results with **3c**,**d** than that with **2**.[132−134] Table 82, which can be considered as a complement of Table 20, compares the results of 4-alkyl-substituted box's with those of the benchmark **2**.

If diastereoselectivity is unsatisfactory (Table 82, entries 8, 9, 15, 20, and 26−29), then the enantioselectivity is excellent, and the sense of the induction depends on the nature of Ar. When it is a phenyl group, the anion is monocoordinated to the lithium cation bound to box, and the less hindered transition state gives the (*S*)-enantiomer (Table 82, entries 1−8 and 21−23). When Ar is 2-pyridyl or 2-quinolyl, the anions behave as bidentate, the electrophile adds with the Re face, and (*R*) is the major enantiomer (Table 82, entries 10−14, 16−19, 24, and 25). Each diastereomer of the addition to 4-substituted cyclohexanones, obtained in high optical purity (Table 82, entries 27−29) afforded axially chiral benzylidenecyclohexanes with enantioselectivities up to 99% ee.[138a]

cis-Bicyclo[3.3.0]octane-3,7-dione monoethylene ketals **114** behave as electrophiles in the reaction with α-thio- or α-seleno-carbanions derived from 1-phenyl-1-(phenylthio)-1-(tributylstannyl)methane **111a** and bis(phenylseleno)phenylmethane **111b**, respectively, and the endo-selective aldol reaction can be catalyzed by BuLi and (*S*)-**3c** or (*S*)-**2** to afford (*S*)-**115** (Scheme 145).[138b] Table 83 compares the results of **3c** (entries 1, 3, 5, and 7) with those of the benchmark **2**, already reported in Table 20. Whereas **3c** is a better ligand to induce both diastereo- and enantioselectivity with the thio-carbanion, **2** still induces better stereoselectivity with the seleno-carbanion.

The (*S*)-**3c**-catalyzed organolithium addition to *o*-vinyl-imines **360** gives excellent yields of (*R*)-**361** with enantioselectivities in the range 50−73% ee; these adducts are interesting inasmuch as they can be cyclized to give optically active 1-substituted tetrahydroisoquinolines (*R*)-**362** (Scheme 146).[339]

Table 81. Enantioselective Catalysis of the Mukaiyama−Aldol Reactions between Aldehydes and Trimethylsilylketene Acetals 86 Run in Aqueous Media

entry	R	A	R^2 (conf.)[a]	box	X_2	solvent/additive	yield (%)	syn/anti	**359** ee (%) (conf.)	ref
1	Ph	Ph	Me (*Z*)	(*S*)-**2**	OTf	*b*	92	90:10	15 (2*R*,3*R*)	123, 336
2	Ph	Ph	Me (*Z*)	(*S*)-**3c**	OTf	*b*	74	76:24	67 (2*S*,3*S*)	123, 336
3	Ph	Ph	Me (*Z*)	(*S*)-**3c**	DS[c]	$C_{11}H_{23}CO_2H$	38	63:37	56 (2*S*,3*S*)	337
4	Ph	Ph	Me (*Z*)	(*S*)-**3d**	OTf	*b*	>99	67:33	61 (2*S*,3*S*)	123, 336
5	Ph	Ph	Me (*Z*)	(*S*)-**3e**	OTf	*b*	98	72:28	37 (2*S*,3*S*)	123
6	Ph	Ph	Me (*Z*)	(*S*)-**3ag**	OTf	*b*	63	58:42	31 (2*S*,3*S*)	123
7	Ph	Ph	Me (*Z*)	(*S*)-**3ah**	OTf	*b*	86	64:36	47 (2*S*,3*S*)	123
8	Ph	Et	Me (*E*)	(*S*)-**3c**	OTf	*b*	32	62:38	32	123, 336
9	Ph	Et	Me (*Z*)	(*S*)-**3c**	OTf	*b*	81	78:22	81	123, 336
10	Ph	Et	Me (*Z*)	(*S*)-**3c**	DS[c]		23	76:24	58	337, 338
11	Ph	Et	Me (*Z*)	(*S*)-**3c**	DS[c]	$C_{11}H_{23}CO_2H$	76	74:26	69	337, 338
12	Ph	*i*-Pr	Me (*Z*)	(*S*)-**3c**	OTf	*b*	17	80:20	67	123, 336
13	2-naphthyl	*i*-Pr	Me (*Z*)	(*S*)-**3c**	OTf	*b*	97	80:20	81	123, 336
14	2-furyl	Et	Me (*Z*)	(*S*)-**3c**	OTf	*b*	86	80:20	76	123, 336
15	2-thienyl	Et	Me (*Z*)	(*S*)-**3c**	OTf	*b*	78	85:15	75	123, 336
16	*c*-C_6H_{11}	Ph	Me (*Z*)	(*S*)-**3d**	OTf	*b*	77	82:18	42	123, 336
17	Ph	Et	Me (*Z*)	(*S*)-**3c**	DS[c]	HCl	31	73:27	61	337
18	Ph	Et	Me (*Z*)	(*S*)-**3c**	DS[c]	(+)-CSA[d]	34	75:25	63	337
19	2-naphthyl	Et	Me (*Z*)	(*S*)-**3c**	DS[c]	$C_{11}H_{23}CO_2H$	75	76:24	66	337

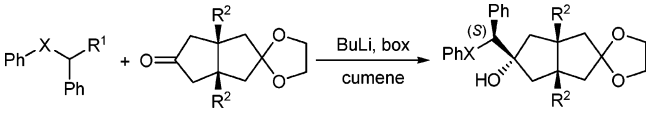
[a] Main configuration. [b] EtOH/H_2O 9:1. [c] Dodecyl sulfate. [d] (+)-Camphorsulfonic acid.

Table 82. Enantioselective Additions of α-Sulfenyl and α-Selenyl Carbanions from 111a,b to Various Carbonylic Electrophiles Catalyzed by LiBu and 4-Alkyl-Substituted Box's

entry	Ar	X	R	R^1	box	electrophile	yield (%)	anti/syn	ee (%) (conf.)	ref
1	Ph	S	Ph	$SnBu_3$	(*S*)-**3d**	Ph_2CO	17		59 (*S*)	132, 133
2	Ph	S	Ph	$SnBu_3$	(*S*)-**3c**	Ph_2CO	79		99 (*S*)	132, 133
3	Ph	S	Ph	H	(*S*)-**3c**	Ph_2CO	40		97 (*S*)	133
4	Ph	S	Ph	SePh	(*S*)-**3c**	Ph_2CO	93		93 (*S*)	133
5	Ph	S	Ph	$SnBu_3$	(*S*)-**3c**	Me_2CO	71		>99 (*S*)	132, 133
6	Ph	S	Ph	$SnBu_3$	(*S*)-**3c**	Cyhex[c]	100		98 (*S*)	132, 133
7	Ph	S	Ph	$SnBu_3$	(*S*)-**3c**	CO_2	87		74 (*S*)	133
8	Ph	S	Ph	$SnBu_3$	(*S*)-**3c**	PhCHO	100	40:60	87 (1*S*,2*S*)[a]	132, 133
9	Ph	S	Ph	$SnBu_3$	(*S*)-**3c**	EtCHO	51	62:38	96[b]	132, 133
10	2-Pyr	S	Ph	H	(*S*)-**2**	Ph_2CO	86		90 (*R*)	133
11	2-Pyr	S	Ph	H	(*S*)-**3d**	Ph_2CO	13		58 (*R*)	133
12	2-Pyr	S	Ph	H	(*S*)-**3c**	Ph_2CO	89		64 (*R*)	133
13	2-Pyr	S	Ph	H	(*S*)-**3c**	Me_2CO	67		54 (*R*)	133
14	2-Pyr	S	Ph	H	(*S*)-**3c**	CO_2	60		70 (*R*)	133
15	2-Pyr	S	Ph	H	(*S*)-**3c**	PhCHO	94	63:37	81[b]	133
16	2-Quin	S	Ph	H	(*S*)-**2**	Ph_2CO	99		71 (*R*)	134
17	2-Quin	S	Ph	H	(*S*)-**3c**	Ph_2CO	95		89 (*R*)	134
18	2-Quin	S	Ph	H	(*S*)-**3c**	Me_2CO	40		80 (*R*)	134
19	2-Quin	S	Ph	H	(*S*)-**3c**	CO_2	54		83 (*R*)	134
20	2-Quin	S	Ph	H	(*S*)-**3c**	PhCHO	55	55:45	93[b]	134
21	Ph	Se	Ph	Se-Ph	(*S*)-**2**	Ph_2CO	63		70 (*S*)	136
22	Ph	Se	Ph	Se-Ph	(*S*)-**3c**	Ph_2CO	60		85 (*S*)	136
23	Ph	Se	Ph	Se-Ph	(*S*)-**3d**	Ph_2CO	51		67 (*S*)	136
24	2-Pyr	Se	Ph	Se-Ph	(*S*)-**2**	Ph_2CO	51		41 (*R*)	136
25	2-Pyr	Se	Ph	Se-Ph	(*S*)-**3c**	Ph_2CO	50		56 (*R*)	136
26	Ph	S	Ph	$SnBu_3$	(*S*)-**2**	4-*t*-Bu-cyhex[c]	68	64:36[d]	92[e]	138a
27	Ph	S	Ph	$SnBu_3$	(*S*)-**3c**	4-*t*-Bu-cyhex[c]	65	63:37[d]	99[e]	138a
28	Ph	Se	Ph	$SnBu_3$	(*S*)-**3c**	4-Me-cyhex[c]	71	65:35[d]	99[e]	138a
29	Ph	Se	Ph	$SnBu_3$	(*S*)-**3c**	4-Ph-cyhex[c]	53	52:48[d]	99[e]	138a

[a] Configuration of the major syn isomer. [b] Configuration of the major anti isomer. [c] Cyhex is cyclohexanone. [d] The cis/trans ratio. [e] Configuration of the major cis isomer.

Scheme 145

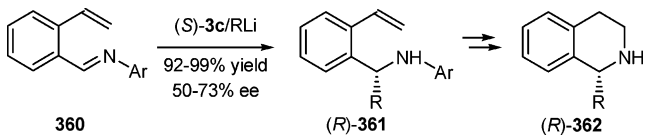


111a,b **114** ***endo*-(*S*)-115**

Table 83. Comparison between Box's (*S*)-3c and (*S*)-2 in the Enantioselective Additions of α-Sulfenyl and α-Selenyl Carbanions Derived from 111a,b[138b]

entry	X	R^1	R^2	box	yield (%)	endo/ exo	endo ee (%) (conf.)	exo ee (%) (conf.)
1	S	$SnBu_3$	H	(*S*)-**3c**	77	>98:2	99 (*S*)	
2	S	$SnBu_3$	H	(*S*)-**2**	80	>98:2	95 (*S*)	
3	S	$SnBu_3$	Me	(*S*)-**3c**	98	88:12	98 (*S*)	99 (*S*)
4	S	$SnBu_3$	Me	(*S*)-**2**	97	86:14	92 (*S*)	90 (*S*)
5	Se	SePh	H	(*S*)-**3c**	70	>98:2	56 (*S*)	
6	Se	SePh	H	(*S*)-**2**	80	>98:2	92 (*S*)	
7	Se	SePh	Me	(*S*)-**3c**	93	73:27	64 (*S*)	57 (*S*)
8	Se	SePh	Me	(*S*)-**2**	92	82:18	91 (*S*)	86 (*S*)

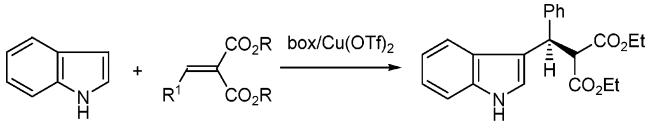
Scheme 146



360 **(*R*)-361** **(*R*)-362**

Several additions to a carbonyl group, the majority of them already mentioned in part 4, have taken advantage of catalysts based on 4-alkyl-substituted box's. The Henry reaction, run with $MeNO_2$ and *p*-nitrobenzaldehyde **121** in MeOH (Scheme 37),[65] is catalyzed by [box/$Cu(OAc)_2$], and (*S*)-**122** is obtained with 37%, 67%, and 45% ee, with (*S*)-**2**, (*S*)-**3c**, and (*S*)-**3d**, respectively. Again, the more steric demanding **2** is not the best ligand. Sometimes, the successful choice between two box's is a matter of the solvent: The Friedel−Crafts/Michael reaction of indole with diethyl benzylidene malonate **153** (Scheme 147) gives **154** and can

Scheme 147



153: R = Et, R^1 = Ph **154**

be catalyzed by [(*S*)-**2**/$Cu(OTf)_2$] or [(*S*)-**3c**/$Cu(OTf)_2$] complexes.[163] Table 84 shows the results of both catalysts in four different solvents and the reverse of the enantioselection of the **3c** complex in halogenated solvents (Table 84, entries 3 and 4).

Some aza-Michael reactions involving the addition of hydroxylamines to α,β-unsaturated carbonyl compounds were tested with **3c,d**-based complexes with different results. The addition of *O*-benzyl-hydroxylamine to 3-(*E*)-crotonoyl-

Table 84. Enantioselective Additions of 153 to Indole: Relationship between Solvent, Box, and Enantioselectivity[163]

		(*S*)-**2**/$Cu(OTf)_2$		(*S*)-**3c**/$Cu(OTf)_2$	
entry	solvent	yield (%)	ee (%) (conf.)	yield (%)	ee (%) (conf.)
1	THF	77	60 (*S*)	99	46 (*S*)
2	*i*-BuOH	95	40 (*S*)	99	83 (*S*)
3	CH_2Cl_2	71	57 (*S*)	88	67 (*R*)
4	$(CHCl_2)_2$	20	27 (*S*)	89	71 (*R*)

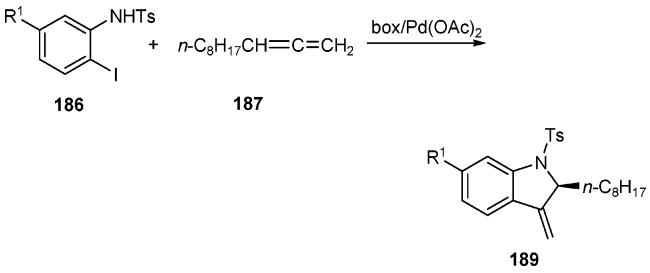
4,4-dimethyl-2-oxazolidinone **163** (R = R^1 = Me) gave racemates,[167] whereas the reaction between *N*,*O*-bis(trimethylsilyl)hydroxylamine and alkylidene malonates **153**, catalyzed by [(*S*)-**3c**/Cu(OTf)$_2$] or [(*S*)-**3d**/Cu(OTf)$_2$] complexes, leads to an enantioselective reaction, since the former complex gives the products in discrete yields and enantiomeric excesses, but the latter one gives yields in the range of 52−73% and up to 76% ee.[171,340] The reaction between 1-benzyl-2-crotonoyl-4,4-dimethylpyrazolidin-3-one **167** and *N*-(4-methoxybenzyl)-hydroxylamine in Scheme 58 offers a comparison between [(*S*)-**3c**/Zn(OTf)$_2$] and [(*S*)-**3d**/Zn(OTf)$_2$] with the benchmark [(*S*)-**2**/Zn(OTf)$_2$]. The yields of the chiral isoxazolidine (*S*)-**169** are comparable (73−84%), but the enantiomeric excesses are 70% (**3c**), 50% (**3d**), and 17% (**2**).[170]

The Mukaiyama−Michael reactions between an activated α,β-unsaturated carbonyl derivative and silylketene acetals have been catalyzed by 4-alkyl-box-based complexes with various results: **86** (A = S*t*-Bu, R^2 = H) and alkylidene malonates **153** lead to the formation of 3-substituted *tert*-butyl 4,4-dicarbomethoxy-butanethioate **170** (Scheme 59). The best enantioselectivities are always obtained with the benchmark [**2**/Cu(OTf)$_2$],[173] but the results with the Cu(SbF$_6$)$_2$ complexes of (*S*)-**2**, (*S*)-**3c**, and (*S*)-**3d** give an interesting relationship between the box substituents and the selectivity of the reaction.[63] The reaction between the same silylketene acetal **86** and 3-[(*E*)-3-(ethoxycarbonyl)propenyl]-2-oxazolidinone **163** (R = CO_2Et) (Scheme 60) has been catalyzed with [(*S*)-**3c**/Cu(SbF$_6$)$_2$] and the analogous complexes with (*S*)-**3d** and (*S*)-**2**.[61] Whereas the second complex gives a somewhat lower enantioselectivity (78% ee), the first catalyst gives a result superimposable with that of the benchmark: (*S*)-**172** is obtained in more than 80% yield and with 89% ee.

The prototype of the allylic substitution reaction between *rac*-3-acetoxy-1,3-diphenyl-1-propene **182** and dimethyl malonate affords the optically active methyl (*E*)-2-methoxycarbonyl-3,5-diphenylpent-4-enoate **183** reported in Scheme 64. Employing [(*R*)-**3d**/Pd(C$_3$H$_5$)Cl] in CH_2Cl_2 and KOAc with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as the base, (*R*)-**183** was obtained in 97% yield and 88% ee.[13,33,341] The same reaction was later used for a systematic comparison between a series of thiazoline and oxazoline ligands. The 4-alkyl-substituted box's (*R*)-**3b**, (*R*)-**3c**, (*R*)-**3d**, and (*R*)-**2** again give (*R*)-**183**, and its respective yields (and enantioselectivies) are 7% (4% ee), 8% (19% ee), 97% (88% ee), and 20% (33% ee).[180]

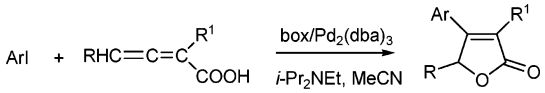
The allylic substitution reaction has several intramolecular versions with the reagent undergoing the cyclization derived from different routes. *N*-Tosyl-2-iodoaniline **186** (R^1 = H) reacts with 1,2-undecadiene **187** under a palladium-catalyzed coupling to give a palladium complex that undergoes the intramolecular allylic substitution reaction affording *N*-tosyl-2,3-dihydro-3-methylene-2-*n*-octylindole **189** (R^1 = H) (Scheme 148).[182,342] The yields (88% and 94%) and the enantioselectivities (67% and 82% ee) with (*S*)-**3c** and (*R*)-**3d**, respectively, suggested the latter as the optimal ligand for this reaction, which was run on **186** (R^1 = Br) allowing determination of the absolute (*S*)-configuration of **189** (R^1 = Br, 64% yield, and 67% ee) and inference of the catalytic mechanism of the intramolecular nucleophilic displacement. With the catalyst based on (*R*)-**3d**, several heterocycles, either monocyclic or bicyclic, have been obtained with enantioselectivities often >80% ee.[182,342]

Scheme 148



186 187 189

Scheme 149



363 364

A somewhat similar reaction occurs between 2,3-allenoic acids **363** and aryl iodides that, under conditions specific for the coupling cyclization, afford butenolides **364** (Scheme 149). The reaction with iodobenzene and undeca-2,3-dienoic acid gives a racemate with (*S*)-**1**, a negligible 13% ee with (*S*)-**3c**, but a satisfactory 52% ee with (*S*)-**3d**. With the same catalyst the enantiomeric excess is always around 50% ee with a series of aryl iodides and 2,3-allenoic acids.[343]

Not every intramolecular allylic substitution reaction is suitable for catalysis with the palladium complexes of **3c**,**d**, since several examples afford racemates or unsatisfactory enantioselectivities.[184,185,187,344]

The radical addition derived from alkyl iodides to alkylidene sulfones bound to pyridyl, or better to benzimidazolyl moiety **212a**,**b**, gives radical **213** that can be trapped either by allylation (with Bu$_2$Sn(allyl)$_2$) or by hydrogen (with Bu$_3$SnH) (Scheme 78). The best catalyst is [(*S*)-**1**/Zn(OTf)$_2$], and the screening of the analogous complexes with (*S*)-**2**, (*S*)-**3c**, and (*S*)-**3d** gives enantiomeric compositions not far from racemates.[200,201]

Several box-catalyzed radical processes involve N-acyl-substituted oxoheterocycles, which behave as bidentate reagents during the catalytic cycle. Among them, compounds **163** (R = Me or Ph, R^1 = H) react with the radical derived from the cleavage of R^2I to give **207**, which is formally the product of the conjugate addition of R^2H (Scheme 75). The best results with stoichiometric amounts of [(*S*)-**2**/MgBr$_2$] (Table 42) and [(*S*)-**3e**/MgI$_2$] were obtained with cinnamoyl-**163** (77% and 82% ee, respectively) and crotonoyl-**163** (82% and 74% ee, respectively). These results have been approached only by using catalytic amounts of the **3e**-based catalyst.[195]

1-Substituted 2-alkenoyl-4,4-dimethylpyrazolidin-3-one **167** was a fruitful reagent that allowed the application of the chiral relay strategy to the radical addition. If the process is a substrate-bound radical addition, then the chiral catalysts would convert the achiral template into a chiral nonracemic template that may relay and amplify the stereochemistry induced by the box. The reaction consists of the addition of the radical derived from the cleavage of R^1I promoted by Et$_3$B/O$_2$, and the formation of optically active **365** is catalyzed by Mg(II) and Cu(II) complexes of (*S*)-**3a** and (*S*)-**3c** (Scheme 150 and Table 85).[345] Different substituents on the template and different radicals always give excellent yields and enantioselectivities, and the larger the fluxional group in the template, the higher the selectivity (Table 85, entries 1−4). Taking constant the configuration of the box,

Scheme 150

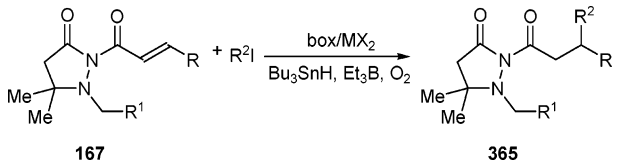
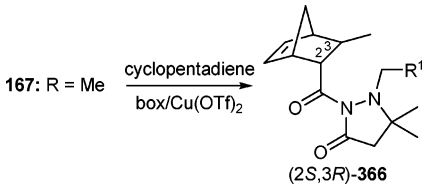


Table 85. Enantioselective Additions of a Radical to 167: Effect of Box and Lewis Acid on the Enantioselectivity[345]

entry	R	R^1	R^2	box	MX_2	yield (%)	ee (%) (conf.)
1	Ph	*n*-Pr	*i*-Pr	(*S*)-**3a**	$Cu(OTf)_2$	95	52 (*S*)
2	Ph	*i*-Pr	*i*-Pr	(*S*)-**3a**	$Cu(OTf)_2$	95	58 (*S*)
3	Ph	1-naphthyl	*i*-Pr	(*S*)-**3a**	$Cu(OTf)_2$	91	90 (*S*)
4	Ph	Ph	*i*-Pr	(*S*)-**3a**	$Cu(OTf)_2$	92	82 (*S*)
5	Ph	Ph	*i*-Pr	(*S*)-**3a**	$Co(ClO_4)_2$	87	58 (*R*)
6	Ph	Ph	*i*-Pr	(*S*)-**3c**	$Mg(NTf_2)_2$	90	62 (*R*)
7	Ph	Ph	*i*-Pr	(*S*)-**3c**	$Cu(OTf)_2$	94	98 (*S*)
8	Ph	Ph	Et	(*S*)-**3c**	$Cu(OTf)_2$	83	92
9	Ph	Ph	*t*-Bu	(*S*)-**3c**	$Cu(OTf)_2$	92	98
10	Me	Ph	*i*-Pr	(*S*)-**3c**	$Cu(OTf)_2$	80	95 (*S*)
11	Et	Ph	*i*-Pr	(*S*)-**3c**	$Cu(OTf)_2$	84	98 (*S*)
12	3-Furyl	Ph	*i*-Pr	(*S*)-**3c**	$Cu(OTf)_2$	60	95 (*S*)
13	CO_2Et	Ph	*i*-Pr	(*S*)-**3c**	$Cu(OTf)_2$	52	58 (*S*)

Scheme 151



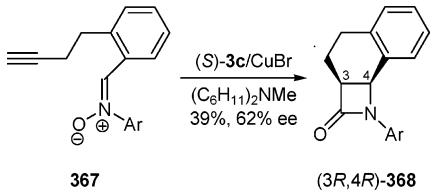
Co(II) and Mg(II) give enantioselection opposite to that induced by Cu(II) (Table 85, entries 5 and 6 vs 4 and 7). Finally, the amplification of the stereochemistry induced by the chiral relay strategy can be appreciated in entries 1−5 where the methyl of the weakly directing box (*S*)-**3a** is enough to induce enantioselectivity up to 90% ee. Comparable results can be obtained with the more strongly directing box (*S*)-**3c** and (*S*,*R*)-**9a**.

The asymmetric Kharasch reaction, the reaction mechanism of which has been illustrated in Scheme 81 and the results with (*S*)-**1** and (*S*)-**2** have been reported in Table 45, was also tested with Cu(I) complexes of (*S*)-**3c** and (*S*)-**3d**. The reactions of cycloalkenes with *tert*-butyl perbenzoate or *p*-nitroperbenzoate as oxidants give for these two box's results comparable with those obtained with (*S*)-**2**;[205,210] only the oxidation of cyclohexene with *t*-BuO_2H/AcOH gives better results with the [(*R*)-**3d**/Cu(I)] catalysts than with the benchmark.[212]

The Diels−Alder reaction between cyclopentadiene and different dienophiles (**163**, **233**, and methacrolein), catalyzed by complexes of (*S*)-**3c** or (*S*)-**3d** with Cu(II), Mg(II), Rh(II), or Zn(II), cannot compete in terms of enantioselectivity with the corresponding benchmark.[12,70,214,218] As just seen above for the radical reactions, if the chiral relay strategy promoted by **167** (R = Me) is applied to the Diels−Alder reaction with cyclopentadiene (Scheme 151, Table 86), then the $Cu(OTf)_2$ complexes of (*S*)-**3a**, (*S*)-**3c**, and (*S*)-**3d** give enantiomeric excesses of (2*S*,3*R*)-**366** comparable with the best values reported in the literature.[12] The larger fluxional group in the template (R^1 = 1-naphthyl) gives the best enantiomeric excess (Table 86, entries 3), and the difference between these values and the enantiomeric excess obtained under the same conditions with **163** (R = Me) (Table 86, entries 4) allows evaluation of the contribution of this template.

β-Lactams can be synthesized with the Kinugasa reaction between alkynes and nitrones. An enantioselective intramolecular example is reported in Scheme 152 where alkyne

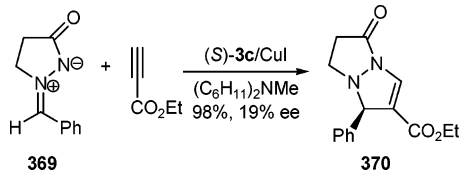
Scheme 152



nitrone **367** (Ar = *p*-carboethoxyphenyl) produces the tricyclic β-lactam (3*R*,4*R*)-**368** in 39% yield and 62% ee when the cyclization is catalyzed by the [(*S*)-**3c**/CuBr] complex.[346]

1,3-Dipolar cycloaddition reactions have been reported in section 4.9, and with the exception of nitrones, very few examples involving other 1,3-dipoles are known; hence any new box-catalyzed example deserves attention even if enantioselectivity is at the moment unsatisfactory. This is the case for the reaction catalyzed by [(*S*)-**3c**/CuI] between azomethine imine **369** and ethyl propynoate to give the bicyclic product **370** in excellent yield (98%) but with an enantioselectivity of only 19% ee (Scheme 153).[347]

Scheme 153



Among the pericyclic reactions, complex [(*R*)-**3d**/$Cu(OTf)_2$] was one of the catalysts tested in the [4 + 3]-cycloaddition reported in Scheme 116, but the enantiomeric excess of (*S*)-**308** was unsatisfactory.[295] Analogously, only racemic products have been obtained both in the intramolecular ene reaction catalyzed by [(*R*)-**3d**/$Fe(acac)_3$/3 Et_3Al][348] and in the aza-Claisen rearrangement of allyl imidates catalyzed by [(*S*)-**3d**/$PdCl_2(MeCN)_2/AgBF_4$].[349]

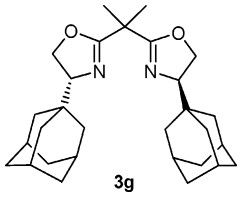
This section is based on the comparison between the results obtained from catalysts with 4-alkyl-substituted box as ligands and the benchmark that is the corresponding complex

Table 86. Enantioselective Diels−Alder Reactions between Cyclopentadiene and 167: Effect of Box on the Enantioselectivity[12]

		[(*S*)-**3a**/$Cu(OTf)_2$]		[(*S*)-**3c**/$Cu(OTf)_2$]		[(*S*)-**3d**/$Cu(OTf)_2$]	
entry	R^1	endo/exo	ee (%)	endo/exo	ee (%)	endo/exo	ee (%)
1	Me	91:9	64	96:4	56	88:12	55
2	Ph	93:7	71	93:7	71	91:9	71
3	1-naphthyl	94:6	96	80:20	99	81:19	96
4	**163**, R = Me	88:12	38	87:13	23	86:14	17

derived from **2**. A box that reproduces the results of the benchmark is 2,2′-isopropylidenebis[(*R*)-(1-adamantyl)-2-oxazoline] **3g** (Chart 6).[16] Four reactions have been tested

Chart 6



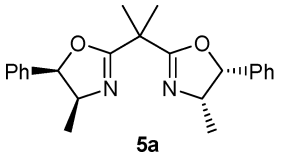
3g

following the protocols reported in the literature for (*S*)-**2**, the cyclopropanations of styrene and 1,1-diphenylethylene with ethyl diazoacetate (Scheme 5, Table 3, entries 1 and 9), the Kharasch reaction between cyclopentene and *tert*-butylperbenzoate (Scheme 81, Table 45, entry 1), and the Diels−Alder reaction between **167** and cyclopentadiene (Scheme 84, Table 46, entry 7), and for each reaction the result was the same as that obtained with the benchmark.

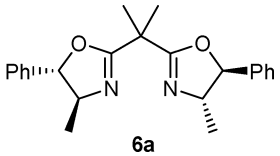
5.4. 4-Alkyl-5-Substituted Box's

Very few examples are known of box's with an alkyl group in position 4 and a further group in position 5. If box's having heteroatoms in the substituents are excluded (since these will be considered in the next section) only ligands **5a** and **6a**, prepared from norepherine (Chart 7),[9] have found

Chart 7



5a



6a

rare applications in catalysis. Since the methyl group in position 4 alone gives a weakly directing box, a strong influence of the phenyl group in position 5 on the sense of the induction could be expected, but the results were disappointing.

[(4*S*,5*R*)-**5a**/Cu(OTf)$_2$] was tested as a catalyst for the enantiotopic differentiation of pro-R or pro-S chlorines in (dichloromethyl)borate **344** by BuLi (Scheme 131): The resulting (1-chloropentyl)boronate **345** was a racemate.[315] [(4*S*,5*S*)-**6a**/Mg(ClO$_4$)$_2$] catalyzed the intramolecular ene reaction of (*E*)-1-acetyl-3-[2-(3-methyl-2-butenyloxy)benzylidene]-2-oxindole **291** (Scheme 110), and (3*S*,3′*S*,4′*S*)-**292** was obtained in 63% yield and 47% ee. This is not a bad result, first because the reaction that usually requires stechiometric amounts of catalysts can be run under catalytic conditions (ratio reagent/catalyst = 3:1), and second because this is one of the most chemoselective catalysts since the ratio of hetero Diels−Alder/intramolecular ene reaction is 91:9.[286]

5.5. 4-Aryl- and 4-Alkyl-5,5-Disubstituted Box's

Box's **4a**−**j** in Chart 1 have in position 4 either an aryl or an alkyl group and two substituents in position 5. Their easy access, from an α-aminoester and an excess Grignard reagent, led to their syntheses and use in the early years of this research. In 1993, just after the very first two papers,[6,7] Corey and Ishihara reported the synthesis of (*S*)-**4g**, and its complexes with Fe(III) and Mg(II) were tested on the Diels−Alder reaction between **163** (R = R^1 = H) and cyclopentadiene in Scheme 84.[27] The results with [(*S*)-**4g**/FeI$_3$/I$_2$] (yield 87%, endo/exo 95:5, and 85% ee of (*R*)-**229**) are slightly higher than those for the parallel experiments for the complex with (*S*)-**1** (Table 46, entry 1), but the most interesting result is obtained with [(*S*)-**4g**/MgI$_2$/I$_2$]: yield 82%, endo/exo 97:3, and 91% ee of (*R*)-**229**. For the first time the reaction intermediate of a box-catalyzed reaction has only one arrangement of the box and dienophile with a well-defined tetrahedral geometry (Figure 17), and this was

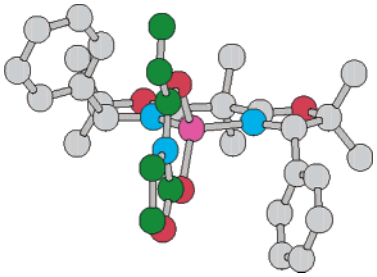


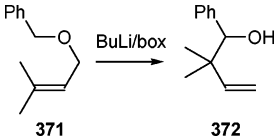
Figure 17. Tetrahedral magnesium complex of **163** and (*S*)-**4g**.[27]

the key to interpret the transmission of the chiral information from the ligand to the product.

The addition of two substituents in position 5 seldom has a beneficial effect on selectivity, since the enantiomeric excesses induced by complexes of **4**, compared to those of complexes derived from the corresponding 5-unsubstituted box, are in general lower. This occurs in the intramolecular cyclopropanation giving sirenin where **4g** gives a racemate,[95] in the cyclopropanation of styrene with ethyl diazoacetate **26** (R = Et) (Scheme 5) where **4c**,**d**,**f**,**h**−**j** complexes with Cu(OTf)$_2$ give both diastereo- and enantioselectivities lower than those of the corresponding copper complexes of 4-alkyl- and 4-aryl-5-unsubstituted box's (Table 3),[26] in the intramolecular allylic substitution carboannulation of allenes,[182] and in the enantioselective mercuriocyclization of γ-hydroxy-*cis*-alkenes.[324] If the enantiomeric excesses of the Kharasch reaction on cyclopentene, cyclohexene, and cyclooctene (Scheme 81) catalyzed by [(*S*)-**2**/Cu(OTf)$_2$] (Table 45, entries 1, 7, and 15) are compared to those with [(*S*)-**4e**/Cu(OTf)$_2$], the result is an unavailing effect of the 5-substituents, but [(*S*)-**4g**/Cu(OTf)$_2$], which fails with cyclohexene and cyclooctene, is the best catalyst for cyclopentene (49% yield and 81% ee of (*S*)-**222** (Ar = Ph, *n* = 1)).[206,207]

The most interesting effect of 5-substituents is observed in the [2,3]-Wittig rearrangement of benzyl prenyl ether **371** enantioselectively giving **372** with BuLi and box (Scheme 154).[350] The reaction with (*S*)-**3c** affords a good enantiomeric

Scheme 154



371 **372**

excess of (*S*)-**372** (Table 87, entry 1), the 5,5-dimethyl-box (*S*)-**4a** gives a lower enantiomeric excess, and the 5,5-

Table 87. Effect of 5-Substituents on the [2,3]-Wittig Rearrangements of 371[350]

entry	box	yield (%)	ee (%) (conf.)
1	(*S*)-**3c**	31	62 (*S*)
2	(*S*)-**4a**	11	25 (*R*)
3	(*S*)-**4b**	39	66 (*R*)

diphenyl-box (*S*)-**4b** gives a slightly higher enantiomeric excess, but the interesting result is that the sense of the asymmetric induction has now reversed and (*R*)-**372** is obtained (Table 87, entries 2 and 3).

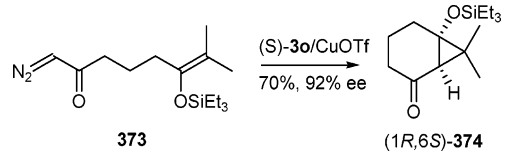
5.6. Heteroatoms in 4- or 5-Substituents

The design of box's with heteroatoms in one of the oxazoline substituents is always moved by the remote hope that either the new ligand allows two simultaneous binding interactions, one with the heterocycle's nitrogen that is standard for box and one with the heteroatoms in the chains. The bifunctional ligand, in addition to the standard formation of the reaction intermediate with the Lewis acid and one reagent, may be involved in a second interaction, which either increases the catalyst selectivity in molecular recognition or may be involved with an interaction between the second reagent and the side chain that may assist the reaction and promote a specific stereochemical outcome.

This explains the variety of box's that fall in this section, **3j**−**x**, **4k**,**l**, and **6c**−**x**, several with a hydroxy group in the chains, which is the most promising substituent since its hydrogen bonds may realize the scope of the design.

Unfortunately, the majority of these box's do not satisfy any of the expectations, and the substituent carrying the heteroatom behaves only as a more or less sterically congested substituent. This is the role of CMe_2OSiMe_3 in the complex [(*S*)-**3o**/CuOTf]; the catalyst is by far better than those based on **1** and **2** (Table 10, entries 9 and 10) used for the intramolecular cyclopropanation of **373**, which gives 92% ee of (1*R*,6*S*)-**374** (Scheme 155).[21] The same role of

Scheme 155

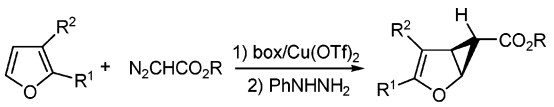


373 (1*R*,6*S*)-**374**

CH_2OSiMe_2t-Bu in the complex [(*S*,*S*)-**6m**/Pd(OAc)$_2$], which catalyzes the reaction of *N*-tosyl-2-iodoaniline **186** (R^1 = H) with 1,2-undecadiene **187**, affords *N*-tosyl-2,3-dihydro-3-methylene-2-*n*-octylindole **189** (R^1 = H) (Scheme 148) in an excellent (for the reaction) 87% yield and 78% ee.[182]

Several cyclopropanations have been tested. The reaction between styrene and methyl or ethyl diazoacetate (Scheme 5), when catalyzed by CuOTf complexes of **3s**−**3x**[23] or by Cu(I) complexes of **6k**, **6n**, or **6t**,[32] cannot compete with the enantiomeric excesses induced by [**2**/CuOTf] (Table 3). The enantioselective cyclopropanation of furan and methyl furan carboxylates (**35**) with methyl or ethyl diazoacetate (**26**), already mentioned in Scheme 8 and now again illustrated in Scheme 156, is more fruitful because of their

Scheme 156



35 **26** **36**

use as synthons of natural products. The catalysts have been prepared from several box's, Cu(OTf)$_2$, and phenylhydrazine leading to the formation of cyclopropanes (1*S*,5*S*,6*S*)-**36**, with the results reported in Table 88. Furan-2- and -3-carboxylates are the best substrates (Table 88, entry 1 vs 2 and 3), **6k**

Table 88. Enantioselective Cyclopropanations of Furan Carboxylates 35 with Diazoacetates 26

entry	R^1	R^2	R	box	yield (%)	ee (%)	ref
1	H	H	Me	(4*S*,5S)-**6k**	7	51	88
2	H	CO_2Me	Et	(4*S*,5S)-**6k**	27	74	88
3	CO_2Me	H	Me	(4*S*,5S)-**6k**	45	69	32, 88
4	CO_2Me	H	Me	(4*S*,5S)-**6n**	46	45	32
5	CO_2Me	H	Et	(4*S*,5S)-**6s**	33	85	32
6	CO_2Me	H	Et	(4*S*,5S)-**6t**	42	83	32
7	CO_2Me	H	Et	(4*S*,5S)-**6u**	36	91	32
8	CO_2Me	H	Me	(4*S*,5S)-**6u**	39	88	32, 35
9	CO_2Me	H	Me	(4*S*,5S)-**6v**	41	62	32

and **6n** are not the ligands of choice for the reaction (Table 88, entries 2−4), and therefore it is difficult for **6k** to imagine an active participation of the hydroxy group to the catalytic cycle, whereas, among **6s**−**6v**, three of them (Table 88, entries 5−7) induce excellent enantioselections.[32]

The reaction of *rac*-3-acetoxy-1,3-diphenyl-1-propene **182** with dimethyl malonate to give optically active **183** (Scheme 64), a benchmark for the asymmetric allylic alkylation, has again to be discussed because several palladium complexes of box's with heteroatoms in the 4- or 5-substituents (Chart 8) have been used as catalysts, and their results are listed in Table 89.

An early investigation compared the palladium complexes of (*R*)-**3d** and (4*S*,5*S*)-**6m**, the base being BSA and KOAc (Table 89, entries 1 and 2). The latter catalysts gave excellent yields and enantioselectivities, the enantioselection being driven by the 4-substituents, and if CH_2OSiMe_2t-Bu can be considered a substituent more sterically congested than the benzyl group, then the increased enantioselectivity can be rationalized.[33] Some results cast doubt on this simple interpretation: The palladium complexes of (4*S*,5*S*)-**6k** and (4*S*,5*S*)-**6l** give the same enantioselection (Table 89, entries 3 and 4), but the best substituent is the smallest hydroxymethyl group of **6k**.[351] The investigation of the pairs of complexes with (*S*)-**3j**, (*R*)-**3k**, (*R*)-**4k**, and (*R*)-**4l** (which despite their descriptors have the same absolute configuration depicted in Chart 8) always gives (*S*)-**183** (Table 89, entries 5−8).[19] When the analogous series of (*S*)-box's with two chiral centers (one at 4, one (always *S*) in the 4-substituent) (*S*,*S*)-**3s**, (*S*,*S*)-**3t**, (*S*,*S*)-**3u** (*S*,*S*)-**3w**, and (*S*,*S*)-**3x** were tested, **3u** gave no reaction, three led to (*R*)-selectivity, and the hydroxymethyl derivative **3s** led to (*S*)-selectivity with 92% ee (Table 89, entries 10, 12, and 13 vs 9).[76] This inversion of enantioselection requires the presence of a second chiral center in the substituent (see the already discussed results in entries 5−8). To infer the conditions required to invert the enantioselection, the Pd complexes of two copies of diastereoisomers were tested: (*R*,*R*)-**3m** and (*R*,*R*)-**3n** inverted, and (*R*,*S*)-**3m** and (*R*,*S*)-**3n** did not invert the enantioselection (Table 89, entries 14 and 15 vs 16 and 17).[19]

The results in Table 89, entries 5−17, are obtained when the base is NaH, and the nucleophile attacking the palladium π-allyl complex **375** is the Na salt of dimethylmalonate (Figure 18). When box has a hydroxy group [(*S*,*S*)-**3s**], the interaction of the hydroxy group with the nucleophile assists the attack and governs the regioselectivity affording (*S*)-**183**, assistance impossible when the hydroxy group is protected (Table 89, entries 10, 12, and 13 vs 9). The base BSA/KOAc affords different results, the most intriguing being the opposite enantioselection obtained with (*S*,*S*)-**3s** (Table 89,

Chart 8

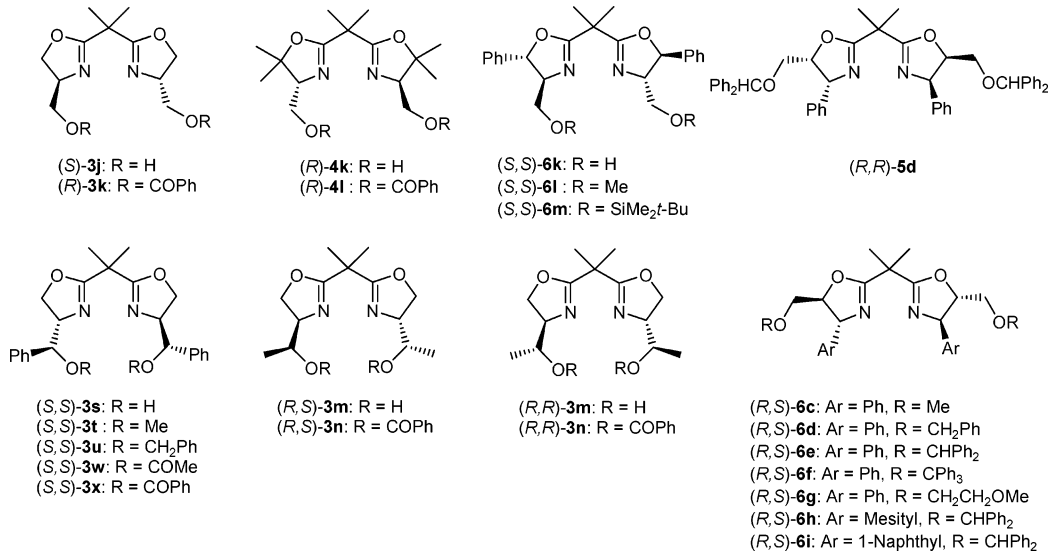


Table 89. Enantioselective Allylic Alkylations of 1,3-Diphenyl-2-Propenyl Acetate 182 with Dimethyl Malonate

entry	box	base	yield (%)	ee (%) (conf.)	ref
1	(*R*)-**3d**	BSA,[a] KOAc	97	88 (*R*)	33
2	(4*S*,5*S*)-**6m**	BSA,[a] KOAc	97	97 (*S*)	33
3	(4*S*,5*S*)-**6k**	BSA,[a] KOAc	b	96 (*S*)	351
4	(4*S*,5*S*)-**6l**	BSA,[a] KOAc	b	89 (*S*)	351
5	(*S*)-**3j**	NaH	100	80 (*S*)	19
6	(*R*)-**3k**	NaH	100	80 (*S*)	19
7	(*R*)-**4k**	NaH	88	77 (*S*)	19
8	(*R*)-**4l**	NaH	80	85 (*S*)	19
9	(*S*,*S*)-**3s**	NaH	98	92 (*S*)	19, 76
10	(*S*,*S*)-**3t**	NaH	65	85 (*R*)	76
11	(*S*,*S*)-**3u**	NaH	0		76
12	(*S*,*S*)-**3w**	NaH	99	77 (*R*)	76
13	(*S*,*S*)-**3x**	NaH	98	90 (*R*)	19, 23, 76
14	(*R*,*S*)-**3m**	NaH	90	72 (*S*)	19
15	(*R*,*S*)-**3n**	NaH	95	97 (*S*)	19
16	(*R*,*R*)-**3m**	NaH	90	63 (*R*)	19
17	(*R*,*R*)-**3n**	NaH	90	68 (*S*)	19
18	(*S*,*S*)-**3s**	BSA,[a] KOAc	70	91 (*R*)	19
19	(*S*,*S*)-**3s**	BSA,[a] NBu_4F	75	52 (*S*)	19
20	(4*R*,5*S*)-**6c**	BSA,[a] KOAc	26	94 (*R*)	30
21	(4*R*,5*S*)-**6d**	BSA,[a] KOAc	16	95 (*R*)	30
22	(4*R*,5*S*)-**6e**	BSA,[a] KOAc	60	96 (*R*)	30
23	(4*R*,5*S*)-**6f**	BSA,[a] KOAc	94	96 (*R*)	30
24	(4*R*,5*S*)-**6g**	BSA,[a] KOAc	81	93 (*R*)	30
25	(4*R*,5*S*)-**6h**	BSA,[a] KOAc	8	50 (*R*)	30
26	(4*R*,5*S*)-**6i**	BSA,[a] KOAc	100	96 (*R*)	30
27	(4*R*,5*R*)-**5d**	BSA,[a] KOAc	0		30

[a] *N*,*O*-Bis(trimethylsilyl)acetamide. [b] Not reported.

entry 18 vs 9). If BSA acts as a silylating agent, then the nucleophile becomes the silyl ketene acetal of malonate, the hydroxy group cannot assist the attack on **375**, and (*R*)-**183** is the product. To confirm this hypothesis, the reaction carried out with an equimolar amount of tetrabutylammonium fluoride, in which the fluorine traps the TMS group, affords again (*S*)-**183** (Table 89, entry 18 vs 19). These experiments, together with DFT calculations of **375** both before and after the nucleophilic attack,[351] demonstrate that sometimes a heteroatom in the box substituents may be involved with an interaction that assists the reaction and promotes a specific enantioselectivity.

To close the argument, a series of palladium complexes with a homogeneous set of 4,5-disubstituted box's must be mentioned since the substituent carrying the heteroatom is now in position 5 (Table 89, entries 20−27).[30] Except the cis-disubstituted box (4*R*,5*R*)-**5d** that affords no reaction and (4*R*,5*S*)-**6h** where the 4-mesityl could be a too sterically demanding group, all catalysts afford excellent yields and enantiomeric excesses. The comparison of the catalysts deriving from (4*R*,5*S*)-**6c** and (4*S*,5*S*)-**6l** where the Ph and the CH_2OMe groups are interchanged and the absolute configuration of the substituents is opposite (Table 89, entry 20 vs 4) suggests that perhaps only the hydroxy group group may interfere, assisting the catalytic reaction; otherwise the overall steric hindrance may play a fundamental role in determing the stereoselectivity.

The attempts to introduce in the substituents more sophisticated residues containing a second binding site with a crown ether moiety,[31] substituents with pendant sulfides suitable to assist a carbenic reagent in the addition to a carbonyl and promote enantioselective epoxidation,[22] or the addition of MeLi to aromatic aldimines[20] did not afford remarkable selectivity, in any case not superior to the catalysts with the corresponding naked scaffold.

Is it therefore possible to postulate that a bifunctional box may be involved in a second interaction, which may assist the reaction and promote a specific enantioselectivity? The

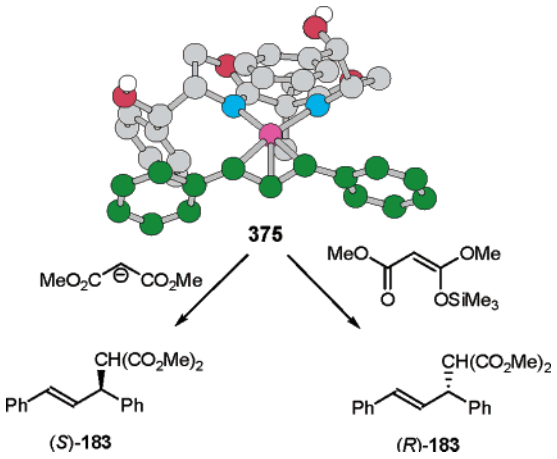
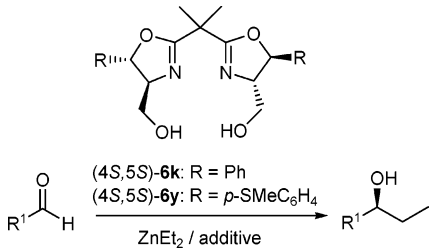


Figure 18. Different enantioselective attacks of the palladium π-allyl complex **375** by the Na salt of dimethylmalonate and by the silyl ketene acetal of malonate.

Scheme 157



answer for specific reactions can be positive in the presence of a hydroxy-containing pendant. The enantioselective addition of ZnR_2 to aldehydes can be catalyzed by (4*S*,5*S*)-**6k** and (4*S*,5*S*)-**6y** to give optically active 1-phenylpropanol (Scheme 157), and Table 90 compares these results with those obtained with (*S*)-**2**.[352]

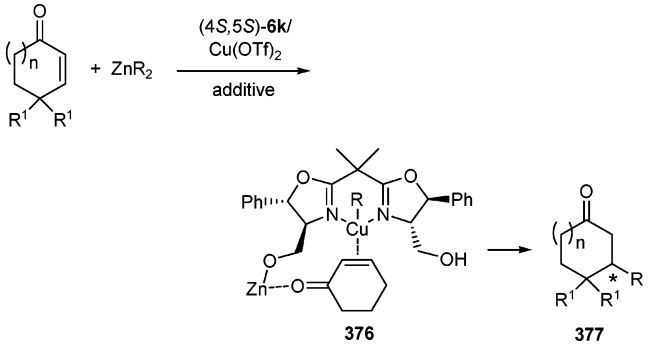
Table 90. Enantioselective Additions of $ZnEt_2$ to Aldehydes[352]

entry	R^1	box	additive (mol %)	yield (%)	ee (%) (conf.)
1	Ph	(*S*)-**2**		60	20 (*S*)
2	Ph	(4*S*,5*S*)-**6k**		96	93 (*S*)
3	Ph	(4*S*,5*S*)-**6y**		56	83 (*S*)
4	*p*-$OMeC_6H_4$	(4*S*,5*S*)-**6k**		99	95 (*S*)
5	*p*-ClC_6H_4	(4*S*,5*S*)-**6k**		76	83 (*S*)
6	*p*-FC_6H_4	(4*S*,5*S*)-**6k**		74	88 (*S*)
7	*n*-C_6H_{13}	(4*S*,5*S*)-**6k**		31	36 (*S*)
8	*n*- C_6H_{13}	(4*S*,5*S*)-**6k**	*n*-BuLi (2)	60	66 (*S*)
9	*n*- C_6H_{13}	(4*S*,5*S*)-**6k**	*n*-BuLi (6)	68	47 (*S*)

The hydroxy-substituted box gives better catalysts than *t*-Bu-box; therefore a second coordination site is involved in the addition. Whereas aromatic aldehydes with (4*S*,5*S*)-**6k** give excellent enantiomeric excesses without any additive (Table 90, entries 2−6), with heptanal yield and enantioselectivity can be increased by addition of catalytic amounts of BuLi with an optimum of 2 mol % (Table 90, entries 7−9), with the most probable effect on the deprotonation of the alcohol functionality of the box.

The further test of the hydroxy-functionalized box was the Michael addition of ZnR_2 to cycloalkenones to afford 4-substituted cycloalkanones **377** (Scheme 158 and Table

Scheme 158



91).[352] Again the importance of the hydroxy pendant is evident from the excellent results obtained with [(4*S*,5*S*)-**6k**/$Cu(OTf)_2$] and [(4*S*,5*S*)-**6y**/$Cu(OTf)_2$] vs [(*S*)-**2**/$Cu(OTf)_2$] as catalysts (Table 91, entries 2 and 3 vs 1). The efficiency of the catalyst allowed the first enantioselective 1,4-asymmetric phenyl transfer to enone with diphenylzinc as a regent (Table 91, entry 6). The stringent requirement of two

Table 91. Enantioselective [Box/$Cu(OTf)_2$]-Catalyzed Michael Additions of ZnR_2 to Cycloalkenones[352]

entry	R^1	*n*	R	box	yield (%)	ee (%) (conf.)
1	H	1	Et	(*S*)-**2**	65	0
2	H	1	Et	(4*S*,5*S*)-**6k**	93	94 (*S*)
3	H	1	Et	(4*S*,5*S*)-**6y**	81	90 (*S*)
4	H	2	Et	(4*S*,5*S*)-**6k**	71	41
5	Me	1	Et	(4*S*,5*S*)-**6k**	42	8
6	H	1	Ph	(4*S*,5*S*)-**6k**[a]	53	69 (*S*)

[a] In the presence of 1 equiv of Et_2Zn as an additive.

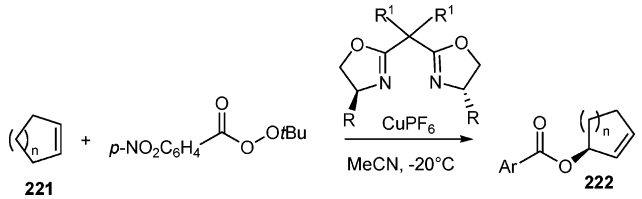
coordinating sites for two different metals allows the postulation of **376** as the reaction intermediate in the catalytic cycle.

5.7. Substituents Other Than Methyls on the Methylene Bridge

In the above sections only box's with an isopropylidene bridge have been discussed, but several different substituents have been placed at the carbon connecting the oxazoline rings, and Chart 1 reports box's **7**, **9**, and **13**−**15** that still retain the C_2-symmetry. In addition to these box's with substituents other than methyls on the methylene bridge, there is a class of spirocyclic box's in which the substituents, which are obviously different than methyls, induce strain in the ligand, changing the angle Φ between the heterocycles and the bridge ($C_2-C-C_{2'}$), but this will be the topic of the next section, and therefore **8** and **10**−**12** will not be discussed in this section.

To evaluate the effect of the bridge substituent, the efficiencies and selectivities promoted by the catalysts derived from these box's will be compared to the selectivities exerted by the catalysts derived from the corresponding isopropylidene box's taken as the benchmarks. Obviously, the more selective the new catalyst, the more promising for the development of new box ligands the substituent. Unfortunately, many of these box's behave as the benchmark, but some intriguing results have been reported. One of these is the Kharasch reaction of cycloalkenes **221** with *tert*-butyl *p*-nitroperbenzoate, catalyzed by $CuPF_6$ complexes of eight box's: (*S*)-**1**, (*S*)-**2**, (*S*)-**3c**, and (*S*)-**3d**, taken as the benchmark, and the corresponding *gem*-diethyl-box's (*S*)-**7a**, (*S*)-**7c**, (*S*)-**7d**, and (*S*)-**7e** (Scheme 159, Table 92).[210]

Scheme 159



All eigtht Cu(I) box complexes give the same (*S*)-enantiomer, but yields and enantioselectivities change significantly (Table 92). The reaction with cyclohexene **221** ($n = 2$) gives better enantiomeric excesses with the methyl-substituted box, whereas cyclopentene **221** ($n = 1$) gives better enantiomeric excesses with (*S*)-**7a**,**d**,**e** than with the corresponding benchmarks. Few reactions of cycloheptene **221** ($n = 3$) and 1,5-cyclooctadiene **221** ($n = 4$) have been compared, but (*S*)-**7e** for the former substrate and (*S*)-**7a** for the latter give better enantioselection than the corresponding

Table 92. Enantioselective [Box/$CuPF_6$]-Catalyzed Kharasch Reactions of Cycloalkenes 221 Yielding (*S*)-222[210]

				$n=1$		$n=2$		$n=3$		$n=4$[a]	
entry	box	R	R^1	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)
1	(*S*)-**1**	Ph	Me	49	82	44	96	23	56	46	74
2	(*S*)-**7e**	Ph	Et	41	99	50	75	12	86	34	59
3	(*S*)-**3c**	*i*-Pr	Me	42	51	40	82	14	99	25	36
4	(*S*)-**7a**	*i*-Pr	Et	36	83	26	78			27	78
5	(*S*)-**3d**	Bn	Me	25	75	30	71				
6	(*S*)-**7d**	Bn	Et	28	80	50	53				
7	(*S*)-**2**	*t*-Bu	Me	52	79	61	84	3	95	13	94
8	(*S*)-**7c**	*t*-Bu	Et	31	38	25	16				

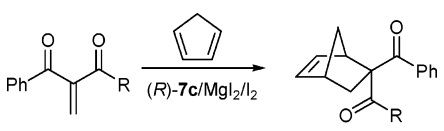
[a] 1,5-Cyclooctadiene.

benchmarks. Again, it is difficult to draw general conclusions for reactions where each of them have a specific tailor-made box, but to test box's with different substituents on the methylene bridge may give pleasant surprises.

Among the less significant applications of box's **7**, their nontraditional use in asymmetric anionic polymerization of maleimides[353] and the low enantiomeric excesses obtained in the allylic substitution/allene cycloannulation reaction,[182] in the cyclopropanation of α,β-unsaturated carbonyl compounds with diazomethane,[37] and in the radical addition to pyrazole template **235** (R = Ph) (Scheme 138) can be mentioned.[328]

Useful applications of **7** have been found in some Diels−Alder reactions and [2,3]-sigmatropic rearrangements. The reaction of cyclopentadiene and ethyl α-phenylthioacrylate **232** (R = Et, R^1 = Ph), catalyzed by [(*S*)-**1**/$Cu(SbF_6)_2$], has been reported in Table 49, entry 6, to give an endo/exo ratio of 94:6 and >95% ee of the (*R*)-adduct. This excellent performance can be replicated with [(*S*)-**12a**/$Cu(SbF_6)_2$] (endo/exo ratio 92:8 and enantioselectivity >95% ee).[231] The Diels−Alder reaction between **163** (R = H) and cyclopentadiene (Scheme 84) has been catalyzed with $Cu(OTf)_2$ complexes of (*S*)-**12a**, (*S*,*R*)-**11b**, and (*S*,*R*)-**11a**. All catalysts are endo-selective, but enantioselectivity is disappointing except with the last catalyst (97% de and 96% ee of (*S*)-**229**), this result being better than that obtained with the corresponding benchmark derived from (4*S*,5*R*)-**9a** (Table 77, entry 1).[46] The third Diels−Alder reaction, between 1,1-dicarbonylethenes **378a**,**b** and cyclopentadiene, when catalyzed by [(*R*)-**7e**/MgI_2/I_2], is very selective both for R = OEt (**378a**) (since (*R*)-**379a** is obtained in 81% yield, diastereomeric excess >99:1, and 85% ee) and for R = Me (**378b**) ((*S*)-**379b**, 77% yield, diastereomeric excess 98:2, and 78% ee) (Scheme 160).[354]

Scheme 160

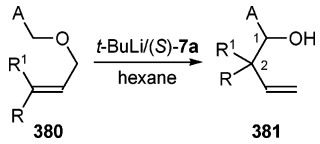


378a: R = OEt
b: R = Me

(*R*)-**379a**
(*S*)-**379b**

[(*S*)-**7a**/*t*-BuLi] is an unsatisfactory enantioselective catalyst (18% ee) of the [2,3]-sigmatropic rearrangement that transforms (*Z*)-cyclic furfuryl ether **317** into *syn*-**318** (Scheme 120), but when [(*S*)-**7c**/*t*-BuLi] is used as the catalyst for the same reaction, the 93% ee overcomes that obtained with the benchmark ([(*S*)-**2**/*t*-BuLi], 91% ee).[300]

Scheme 161



380 **381**

Table 93. [2,3]-Sigmatropic Rearrangements of 380 Catalyzed by [(*S*)-7a/*t*-BuLi]

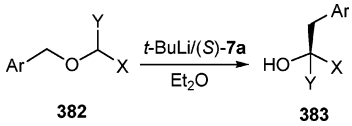
entry	A	R	R^1	yield (%)	erythro/ threo	ee (%) (conf.)[a]	ref
1	Ph	Me	Me	74		33 (*S*)	350
2	Ph	H	Me	*b*	89:11	40 (1*R*,2*S*)	355, 356
3[c]	Ph	H	Me	*b*	89:11	23 (1*R*,2*S*)	356
4	Me-C≡C	Me	H	*b*	<5:>95	89 (1*S*,2*S*)	355, 356
5	Me-C≡C	H	Me	*b*	94:6	39 (1*S*,2*R*)	355, 356
6	TMS−C≡C	Me	H	*b*	80:20	32 (1*S*,2*R*)	355, 356
7	TMS−C≡C	H	Me	*b*	95:5	45 (1*S*,2*R*)	355, 356
8	TMS−C≡C	H	Ph	48	45[d]:55	73 (1*S*,2*R*)	356

[a] Of the major diastereoisomer. [b] Yield >90%. [c] Catalytic version with 0.2 equiv of [box/*t*-BuLi]. [d] Enantiomeric excess of 12% (1*S*,2*S*).

The [2,3]-sigmatropic rearrangement of allyl ethers **380** (Scheme 161) with (*E*)- or (*Z*)-configuration of the double bond, and with A being either phenyl, 1-propynyl, or TMS-ethynyl, have been extensively studied with [(*S*)-**7a**/*t*-BuLi], and both the erythro/threo ratio of **381** and the enantiomeric excess of the major diastereoisomer are reported in Table 93.[350,355,356]

Even if stoichiometric amounts of [box/*t*-BuLi] are required, the rearrangement of propynyl ether occurs with very good diasteromeric and enantiomeric excesses (Table 93, entry 4), and the configuration of the double bond strongly changes the erythro/threo ratio (Table 93, entries 4 and 5). The reaction run under catalytic conditions lowers the enantiomeric excess (Table 93, entry 3), but it demonstrates that selectivity is promoted by the reacting complex [(*S*)-**7a**/Li(I)/**380**] involved in the catalytic cycle. If the same experimental conditions are applied to deprotonable ethers **382**, the enantioselective version of the [1,2]-Wittig rearrangement gives **383** (Scheme 162), and the results of some

Scheme 162



382 **383**

Table 94. [1,2]-Wittig Rearrangements of 382 Catalyzed by [(*S*)-7a/*t*-BuLi][357]

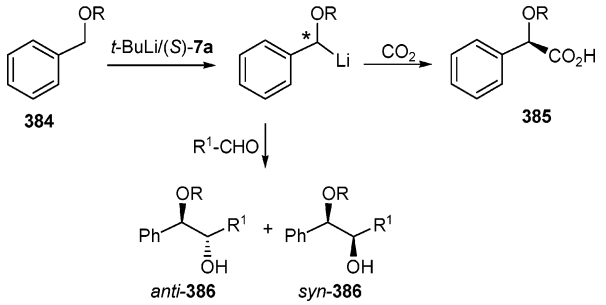
entry[a]	Ar	X	Y	yield (%)	ee (%) (conf.)
1	Ph	Ph	H	86	60 (*S*)
2	*m*-diMeC_6H_3	3,5-diMeC_6H_3	H	65	56
3	Ph	TMS−C≡C	Ph	55	54 (*R*)
4	Ph	TIPS−C≡C	Ph	65	65 (*R*)

[a] *t*-BuLi, 2 equiv; (*S*)-**7a**, 0.1 equiv.

selected examples are reported in Table 94 where the benzyl-type group migrates and the enantioselectivity might be determined in the radical recombination step involving the [box/Li(I)]-bound radical anion.[357]

The same group that studied [1,2]- and [2,3]-sigmatropic rearrangements used the same catalyst [(*S*)-**7a**/*t*-BuLi] to

Scheme 163



achieve enantioselective lithiation at the benzyl carbon atom of benzyl ethers **384**, which reacted with either CO_2 or aldehydes as electrophiles to give phenylacetic acids **385**[358] or the anti and syn adducts **386** (Scheme 163).[359] The results are reported in Table 95, and it is worthwhile to note that the effect of the solvent not only influences the enantioselectivity but also changes the sense of the induction (entries 1−3).

Instead of benzyl ethers, the reaction may be run over phthalan or isochroman **387** (n = 1 or 2, respectively), the cyclic analogues of benzyl ether, with alkyl halides or carbonyl derivatives as electrophiles, and the results are reported in Table 96. Scheme 164 reports the reaction with methyl bromoacetate to give (*R*)-**388**, which, upon reduction with $LiAlH_4$, mesylation with $MsCl/Et_3N$, and reaction with 4-(piperazin-1-yl)benzenesulfonamide, furnishes the (*R*)-enantiomer of dopamine D_4 antagonist U-101387.[360]

The lithiation of 1′,2,2′,3′,4′,5,5′-heptamethylazaferrocene **389** may be run with [(*S*)-**7a**/*sec*-BuLi], and the subsequent enantioselective reaction with electrophiles affords the methyl-functionalized product **390** in excellent enantiomeric excess, the only limit being the amount of catalyst required (Scheme 165, Table 97).[361]

Not all substituents have been placed at the carbon atom connecting the oxazoline rings box with the aim to synthesize a ligand to put in competition with the benchmark. Sometimes the substituents will become the linkers of solid-supported or polymer-immobilized box's, and their use in the cyclopropanation reaction of styrene with diazoacetates esters (Scheme 5) becomes tests of the homogeneous versus the heterogeneous catalysis. Since the benchmark of these homogeneous catalysts is [(*S*)-**2**/CuOTf] (Table 3, entry 1, 99% ee), the enantioselectivity promototed by Cu(I) or Cu(II) complexes of **7j,k**,[331] **7t,u**,[40a,b,362] **7v**−**x**,[40b] **7af**,[42] **13a**−**c**,**e**,[52] and **14a**−**d**[39a] must be taken as the results of model catalysts. The cyclopropanation of methyl cinnamate with diazomethane was catalyzed by [(*S*)-**7u**/CuOTf], but the enantioselectivity (60% ee) is worse than that obtained with the (*S*)-**1**-based catalyst (Table 7, entry 1).[91] In view of the application of supported box's to the catalysis of the carbonyl−ene reaction between α-methylstyrene and the Mukaiyama−aldol reaction between **86**, both with **85b**, the $Cu(OTf)_2$ complexes with **7af** and **7am** were tested, and their selectivities were taken as the results of model catalysts.[42,43] The comparison between diastereomeric excess and enantiomeric excess obtained in the catalysis of the aza-Henry reaction, between **133** (R = CO_2Et) and nitroalkanes $R^2CH_2NO_2$ with [**7an**/$Cu(OTf)_2$] (R^2 = H, 51% ee; Me, 60: 40 de, 91% ee; Et, 90:10 de, 94% ee; pentyl, 92:8 de, 94% ee)[50] and those obtained with [**1**/$Cu(OTf)_2$] (Table 30, entries 1, 2, and 4) encouraged the application of this ligand in solid-supported catalysts.

The allylic substitution reaction of *rac*-3-acetoxy-1,3-diphenyl-1-propene **182** with dimethyl malonate to give optically active **183** (Scheme 64) was catalyzed (in the presence of BSA and KOAc) by several palladium complexes of box with substituents on the spacer. Box's **7d**,**e**,**j**,**k**, **14a**, and (*S*)-**15a**−**e** induce good enantioselectivities (80−92% ee), and taking constant their configurations as (*S*), all ligands afford (*S*)-**183**.[54] The only exception could be (*S*)-**7d** (86% ee of (*R*)-**183**), since the enantioselection induced by (*R*)-**3d** (88% ee of (*R*)-**183**) is opposite.[33] Certainly the influence of the substituent on the spacer cannot be underestimated: The same reaction catalyzed by the palladium complexes of (*S*)-**13a**, (*S*)-**13b**, (*S*)-**13c**, and (*S*)-**13e** (in the presence of BSA and KOAc) gives 73−86% ee of (*R*)-**183**.[363]

The literature that reports a homogeneous series of reactions differing only by the substituent on the spacer is important for a clean evaluation of this factor. One of the few examples is the intramolecular cyclopropanation already discussed in Scheme 141 of α-diazo-β-ketosulfones **391** to bicyclic ketosulfones **392** (Scheme 166)**,** catalyzed by CuOTf complexes of (*S*)-**3c**, (*S*)-**7a**, and (*S*)-**7s**, all *i*-Pr-substituted box's, with methyl (the benchmark), ethyl, and benzyl groups on the bridge (Table 98).[334,364]

A clear effect of the different substituents on the spacer emerges. In most cases the yield is better with the benchmark, but enantioselectivity always increases on going from methyl to ethyl, and the best enantiomeric excesses are obtained with (*S*)-**7s**. The reaction was also run with 2,5-cyclohexadien-α-diazo-β-ketosulfones, and tricyclic products were obtained with the same excellent enantioselectivities.[334,364]

Important applications of the box's discussed in this section are found in the additions of organometallic reagents to aldehydes and imines. The addition of organolithium (R^1Li) to R−CH═N−PMP (**133**) to give amine **134** has been already discussed (Scheme 42); the results with the spacer-substituted box's and the comparison with (*S*)-**2** as a

Table 95. Reactions of Benzyl Ethers 384 with Electrophiles Catalyzed by [(*S*)-7a/*t*-BuLi]

entry	R	electrophiles CO_2 or $R^1(CHO)$	solvent	yield (%)	anti/syn	anti ee (%) (conf.)	syn ee (%) (conf.)	ref
1	Me	CO_2	hexane	>95		95 (*R*)		358
2	Me	CO_2	THF	85		17 (*S*)		358
3	Me	CO_2	ether	>95		racemate		358
4[a]	CH_2OMe	CO_2	hexane	46		30 (*R*)		358
5	Me	Ph	hexane	>95	88:12	90 (1*R*,2*S*)	60 (1*R*,2*R*)	359
6	Me	*n*-C_8H_{17}	hexane	77	71:29	61	47	359
7	Me	cyclohexyl	hexane	68	58:42	78	61	359
8	Me	(*E*)-PHCH═CH	hexane	17	64:36	37	15	359
9	Me	Ph-C≡C	hexane	>95	90:10	>98 (1*R*,2*S*)	84 (1*R*,2*R*)	359
10	Me	*t*-$BuPh_2Si$−C≡C	hexane	>95	91:9	>98 (1*R*,2*S*)	86 (1*R*,2*R*)	359

[a] *sec*-BuLi.

Table 96. Reactions of Phthalan and Isochroman (387) with Electrophiles Catalyzed by [(*S*)-7a/*t*-BuLi] in Hexane[360]

entry	*n*	electrophiles	yield (%)	ee (%) (conf.)
1	1	MeI	68	36 (*R*)
2	1	$PhCH_2Br$	37	30
3	1	CO_2	84	62 (*S*)
4	1	PhCHO	79[a]	83[b]
5	2	MeI	92	36 (*R*)
6	2	$PhCH_2Br$	37	30
7	2	$CH_2{=}CHCH_2Cl$	63	34
8	2	CO_2	75	89 (*S*)
9	2	PhCHO	94[c]	97[b]

[a] A 76:24 mixture of diastereoisomers. [b] Enantiomeric excess of the major diastereoisomer. [c] A 60:40 mixture of diastereoisomers.

benchmark are reported in Table 99.[14,36] In the reaction between iminobenzaldehyde **133** (R = Ph) and MeLi, run under stoichiometric conditions and without changing the substituent (Table 99, entries 1−3 and 5−11), the benchmark is not the best catalyst (entry 1 vs 3) since the best results are obtained with (*S*)-**7p**, (*S*)-**7q**, and (*S*)-**7z**, whereas (*S*)-**7n** is inactive. The reactions of different aldimines with various organolithiums can also be run under catalytic conditions (Table 99, entries 4 and 12−16) with appreciable enantioselectivities.

The addition of diethylzinc to aldehydes affording chiral secondary alcohols (Scheme 157) was studied in the presence of four spiro-box's bearing dibenzo[*a*,*c*]cycloheptadiene as spacers: (*S*)-**13d**, (*S*)-**13f**, (*S*)-**13g**, and (*S*)-**13h**. The best result with benzaldehyde is obtained with (*S*)-**13g** (Table 100, entries 3 vs 1, 2, and 4), and the interesting results of this box with some aldehydes are reported in entries 5−10.[53]

At the beginning of this section dedicated to the substituents at the box spacer, the efficiency and selectivity promoted by the catalyst compared to the selectivity exerted by the catalyst derived from the corresponding isopropylidene box taken as the benchmark were chosen as the most important parameters to evaluate the effects of the bridge substituents. We close this section with six box's ((*S*)-**7ag**, (*S*)-**7ah**, (*S*)-**7ak**, (*S*)-**7ai,** (*S*)-**7aj**, and (*R*)-**7al**) (Chart 9) bearing two fluorous ponytails on the spacer, substituents which influence the behavior of the ligand.[41,365]

The complexes of these ligands have been tested as catalysts of two reactions. The palladium complexes are the catalysts of the allylic substitution reaction of *rac*-3-acetoxy-1,3-diphenyl-1-propene **182** with dimethyl malonate (in the presence of BSA and KOAc) to afford **183** (Scheme 64). The conversions are in the range of 89−100%, and the enantioselectivity in the range of 89−96% ee. The enantioselection with the six box's, which have all the same absolute configuration, affords (*S*)-**183** with the 4-Ph- and 4-*i*-Pr-box ((*S*)-**7ai**, (*S*)-**7aj**, (*S*)-**7ag**, and (*S*)-**7ah**) and the enantiomer (*R*)-**183** with box containing the oxygen atom in the oxazolinic substituents ((*S*)-**7ak** and (*R*)-**7al**). The Cu(I) complexes (exept that of (*S*)-**7ak**, which is inactive) are the catalysts for the Kharasch reaction of cyclohexene **221** (*n* = 2) with *tert*-butyl perbenzoate to give always (*S*)-cyclohexenyl-2-benzoate **222** (Scheme 81) with yields in the range of 37−67% and 60−73% ee. The above results are in the range of box catalysts discussed in previous sections. The peculiar character, which is transmitted from the spacer fluorous substituents to the box, is that these ligands can be easily recovered from the reaction mixtures by liquid−liquid extraction using FC72 as the fluorous solvent and reused without purification, with the same enantioselectivities.[41,365]

5.8. Effect of Strained Cyclic Substituents on the Box Geometry

This section is dedicated to spiro-box's **8** and **10** in which the substituents induce strain in the ligand, changing the angle Φ between the heterocycles and the bridge ($C_2-C-C_{2'}$).

A few years after the discovery of box's, Davies et al. synthesized four box's (*S*,*R*)-**10a**−**d** (Chart 10) with cyclopropylidene, cyclobutylidene, cyclopentylidene, and cyclohexylidene groups as spacers,[51] with the declared scope to prepare a series of ligands having different bridge angles Φ and to compare their Cu(II) catalysts with those derived from isopropylidene-box **9a**[45] to establish the influence on diastereo- and enantioselectivity of the bite angle θ in the complex.

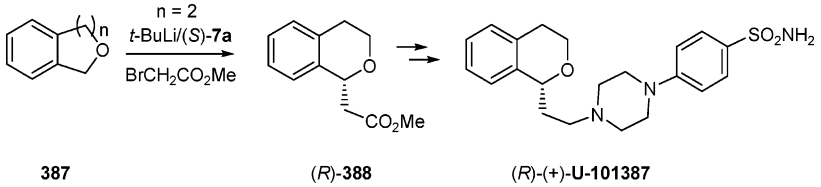
Computational methods were used to determine the value of Φ for the uncomplexed spiro-box and the bite angles θ of the Cu(II) complexes. Theses values were cheeked with the data of the corresponding crystal structures, and the agreement between theory and experiment was found to be good.[366] Table 101 reports the calculated values of Φ and θ and the diastereomeric and enantiomeric excesses of the Diels−Alder reaction between acryloyloxazolidinone **163** and cyclopentadiene at −50 °C reported in Scheme 84. The diastereomeric excess lowers from **10a** to **10d**, but this is due to the steric hindrance of the residue on the spacer. What is important is that the larger the bite angle θ, the higher the enantioselectivity (and the same for Φ), *at least for Cu(II) catalysts*.

The influence of the spiro group on enantioselectivity of the Diels−Alder reaction was further investigated, and correctly assuming that chirality is a property of the whole molecule, the parameter "computed chirality content" (CCM) was determined for **10a**−**d** catalysts. A linear relationship was found between CCM and the enantioselectivty of the Diels−Alder reaction, and since the deformation of these catalysts led to changes in the CCM, the influence of the spiro-box distortions on enantioselectivity was found to be a function of the angles of twist, pucker, and bite with the effect increasing in that order.[367]

The above-described excellent behavior of the [(*S*,*R*)-**10a**/Cu(II)] complex as catalysts raised chemist's hope to test it as well as other box ligands with a cyclopropylidene as spacer, and the results of the investigations are discussed below.

The attempts to catalyze intramolecular cyclopropanation of both phenyliodonium ylides with [(*R*,*S*)-**10a**/Cu(I)][333] and

Scheme 164



387 (*R*)-**388** (*R*)-(+)-**U-101387**

Scheme 165

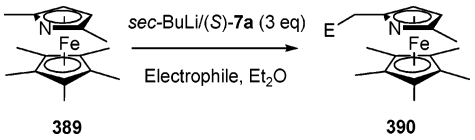
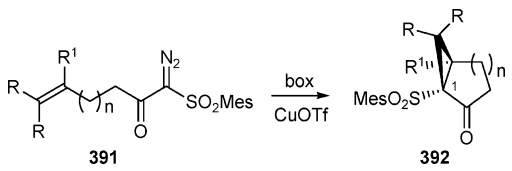


Table 97. Reactions of 1′,2,2′,3′,4′,5,5′-Heptamethylazaferrocene 389 with Electrophiles Catalyzed by [(*S*)-7a/*sec*-BuLi] in Ether[361]

entry	electrophiles	E	yield (%)	ee (%) (conf.)
1	Ph_2CO	$C(OH)Ph_2$	57	99
2	$(TMSO)_2$	OH	17	99 (R_p)
3	$(PhS)_2$	SPh	46	99
4	$TMSCH_2N_3$	NH_2	46	96

Scheme 166



diazoketones with the Cu(II) complexes of (*S*)-**8a**, (*S*)-**8b**, and (*S*)-**8g**[44] gave enantioselectivities lower than those obtained with the benchmark. Even worse results were obtained for the intramolecular C−H insertion of phenyliodonium ylides[310] and the intermolecular insertion of methyl diazo acetate into the N−H bond of aniline.[314] The cyclopropanation of methyl cinnamate with diazomethane catalyzed by [(*S*)-**8a**/Cu(I)] gave a positive result, since the enantioselectivity (77% ee) was better than that obtained with the complex of (*S*)-**1** (Table 7, entry 1).[91] As a whole, carbenoids are not the best reagents for [cyclopropylidene-box/Cu] catalysts.

During the extensive experiments to check the best catalysts for the addition of organometallic reagents to imines, **10a** was tested with the formation of racemates.[150] The Mannich reaction between *N*-tosyl-α-iminoester **135** and *β*-ketophosphonates **140c**[153b] to afford **141c** (Scheme 45) was tested with $Cu(OTf)_2$ complexes of (*R*,*S*)-**10a** and (*S*)-**8b**. The former catalyst gave racemates, and the latter gave a good selectivity (2.2:1 dr, 74% ee) but lower than that obtained with the corresponding benchmark (*S*)-**2** (Table 28, entry 23).[153b]

The enantioselective Friedel−Crafts alkylation/Michael reaction of indole **151** ($R^2 = R^3 = H$) with α′-hydroxy enones **156** occurs at position 3 and affords **393** (Scheme 53).[164] Table 102 reports the selectivity induced by [(*S*)-**8b**/$Cu(OTf)_2$] as catalysts, compared with the results obtained by the benchmark [(*S*)-**2**/$Cu(OTf)_2$], and the effect of cyclopropylidene as a spacer in box **8b** is to increase both yields and enantioselectivities (Table 102, entries 1 and 3 vs 2 and 4).

α′-Hydroxy enone **156** ($R = CH_2CH_2Ph$) adds benzylcarbamate **161**, in accordance to an aza-Michael reaction, to give the *β*-amino-protected carbonyl adduct **162** (Scheme 55).[166] The $Cu(OTf)_2$ complex of (*S*)-**2** is an excellent catalyst (Table 35, entry 2, yield 86%, 96% ee (*S*)), but the strained analogue (*S*)-**8b** is not inferior since the yield is 90% and the enantiomeric excess of (*S*)-**162** is 98%.

N-Substituted alkenoyls, characterized by a *β*-dicarbonyl fragment, one carbonyl belonging to the unsaturated chain and one to the heterocycle, behave as bidentate reagents during the catalytic cycle and some of them have been employed in box-catalyzed reactions. The [box/$MgBr_2$]-catalyzed conjugate addition of *O*-benzyl-hydroxylamine to 3-(*E*)-crotonoyl-4,4-dimethyl-2-oxazolidinone **163** ($R = R^1 = Me$) (Scheme 56), with (*S*)-**1** and (*S*)-**2**, gives low enantiomeric excesses of **395**, which can be easily converted into protected *β*-amino acids. Since the best catalysts are [(*S*,*R*)-**10a**/$MgBr_2$], Table 103 reports the results with different *β*-substituted templates (**394**, Scheme 168).[167]

Not only the reaction gives good enantiomeric excesses of **395** with different enones, but the face selectivity in these additions is temperature-dependent and shows an unusual reversal of enantioselection between 0 and −60 °C.

When the [(*S*,*R*)-**10a**/MgX_2]-catalyzed conjugate addition to enones **396** is performed with N-substituted hydroxylamine (Scheme 169), the addition product **397** undergoes elimination of the template and gives chiral isoxazolidinones **169** with yields and enantioselectivities reported in Table 104.[170,368]

Several enones **396** give excellent enantiomeric excesses with complexes of (*S*,*R*)-**10a**, which seems to be the tailor-made ligand for the reaction (Table 104, entries 1, 3, and 6−9). Among them, 1-substituted 2-alkenoyl-4,4-dimethylpyrazolidin-3-ones **167** ($Z = CH_2$, $R^1 = Me$, $Y = NBn$) and the analogues in Table 104 (entries 11−13) are achiral templates that relay and amplify the stereochemistry induced by (*S*,*R*)-**10a**. Hence, a great deal of effort has been focused on the development of systems having the same behavior.

In the field of α,*β*-unsaturated enones, a significant success was obtained with 2-substituted *N*-acyl-2-enimides **398**, for the easy preparation of the cheap template and the flexibility of the reaction (Table 105), which allows the preparation of chiral 3,4-disubstituted isoxazolones **399** in high diastereo- and enantioselectivities. The isoxazolones, by hydrogenation, can be converted to α,*β*-disubstituted *β*-amino acids **400** (Scheme 170).[369] The best catalysts have $Mg(NTf_2)_2$ as the Lewis acid (Table 105, entry 4 vs 3), which gives high

Table 98. Intramolecular Cyclopropanations of α-Diazo-*β*-Ketosulfones 391 Catalyzed by CuOTf Complexes of Box's (*S*)-3c, (*S*)-7a, and (*S*)-7s

				(*S*)-**7s**		(*S*)-**7a**		(*S*)-**3c**		
entry	R	R^1	*n*	yield (%)	ee (%) (conf.)	yield (%)	ee (%) (conf.)	yield (%)	ee (%) (conf.)	ref
1	H	H	1	87	93 (1*R*)	89	90 (1*R*)	93	83 (1*R*)	334
2	H	Me	1	90	98 (1*R*)	94	87 (1*R*)	96	81 (1*R*)	334
3	H	Br	1	63	98 (1*S*)	43	95 (1*S*)	68	92 (1*S*)	334
4	Me	H	1	84	92 (1*R*)	54	76 (1*R*)	74	74 (1*R*)	334
5	H	CH_2OTr	1	98	91 (1*R*)	75	84 (1*R*)	91	78 (1*R*)	334
6	H	H	2	31[a]	98 (1*R*)	23[a]	94 (1*R*)	36[a]	90 (1*R*)	364
7	H	Me	2	43[a]	98 (1*R*)	26[a]	94 (1*R*)	41[a]	90 (1*R*)	364

[a] C−H insertion byproduct.

Table 99. Asymmetric Additions of Organolithiums to Imines 133 (Scheme 42)

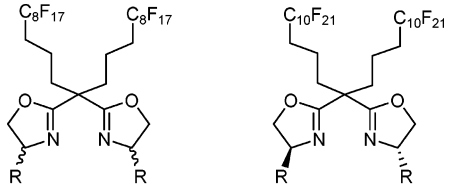
entry	R	R^1	box	yield (%)	ee (%) (conf.)	ref
1[a]	Ph	Me	(*S*)-**2**	90	67 (*R*)	14
2[a]	Ph	Me	(*S*)-**7a**	90	70 (*R*)	36
3[a]	Ph	Me	(*S*)-**7c**	95	75 (*R*)	14,36
4[b]	Ph	Me	(*S*)-**7c**	98	68 (*R*)	36
5[a]	Ph	Me	(*S*)-**7d**	91	34 (*R*)	36
6[a]	Ph	Me	(*S*)-**7l**	75	64 (*R*)	36
7[a]	Ph	Me	(*S*)-**7m**	99	81 (*R*)	36
8[a]	Ph	Me	(*S*)-**7n**	0		36
9[a]	Ph	Me	(*S*)-**7p**	87	89 (*R*)	14
10[a]	Ph	Me	(*S*)-**7q**	95	85 (*R*)	14, 36
11[a]	Ph	Me	(*S*)-**7z**	85	85 (*R*)	14
12[b]	1-naphthyl	Me	(*S*)-**7c**	97	60 (*R*)	36
13[b]	(*E*)-PhCH=CH	Me	(*S*)-**7c**	92	68 (*R*)	36
12[b]	$PhCH_2CH_2$	Me	(*S*)-**7c**	81	82 (*R*)	36
15[b]	$PhCH_2CH_2$	*n*-Bu	(*S*)-**7c**	92	51 (*R*)	36
16[b]	$PhCH_2CH_2$	CH_2=CH	(*S*)-**7c**	82	82	36

[a] Stoichiometric amounts of catalyst. [b] Catalytic amounts of catalyst.

Table 100. Asymmetric Additions of Diethylzinc to Aldehydes in Toluene/Hexane 1:1 at 0 °C (Scheme 157)[53]

entry	RCHO	box	yield (%)	ee (%) (conf.)
1	Ph	(*S*)-**13d**	28	18 (*R*)
2	Ph	(*S*)-**13f**	81	racemate
3	Ph	(*S*)-**13g**	86	87 (*R*)
4	Ph	(*S*)-**13h**	38	50 (*R*)
5	*p*-$Me_2NC_6H_4$	(*S*)-**13g**	86	74 (*R*)
6	*p*-$MeOC_6H_4$	(*S*)-**13g**	91	95 (*R*)
7	*p*-ClC_6H_4	(*S*)-**13g**	90	96 (*R*)
8	*p*-$NO_2C_6H_4$	(*S*)-**13g**	84	75 (*R*)
9	1-naphthyl	(*S*)-**13g**	90	90 (*R*)
10	(*E*)-Ph-CH=CH	(*S*)-**13g**	86	61 (*R*)

Chart 9



diastereomeric and enantiomeric excesses and allows the preparation of enantiopure disubstituted β-amino acids.

The chiral relay methodology can be applied to templates without the carbonyl group, if the framework allows a bidentate coordination to the catalyst. These characteristics can be found in 1-alkenoyl-3,5-dimethylpyrazoles **235** (where its N(2) is the second binding site of the reagent), which adds *O*-benzylhydroxylamine to give **401** (Scheme 171). The limit of the reaction lies in the amount of catalyst [(*S*,*R*)-**10a**/$MgBr_2$] required (30 mol %), and at lower catalytic loading selectivity decreases; for this reason Table 106 reports the results run under these conditions.

The Michael reaction of active methylene compounds to α,β-nitroalkenes **402** gave nearly racemic products with (*S*)-**1** or (*S*)-**2** and several Cu, Ni, Fe, or Mg salts. What failed with the classic box was successfully carried out with 1,3-dicarbonyl compounds **140a**,**b** by using [(*S*,*R*)-**10a**/$Mg(OTf)_2$] (Scheme 172, Table 107).[158,371]

Two points deserve attention: the comparison of catalysts [(*S*,*R*)-**10a**/$Mg(OTf)_2$] and [(*S*,*R*)-**9a**/$Mg(OTf)_2$] (Table 107, entry 1 vs 2), which focuses the positive effect of the strain induced by cyclopropylidene, and the excellent selectivity for each substrate except those with *tert*-butyl esters (Table 107, entries 4 and 8).

The above protocol was followed for the enantioselective synthesis of two biologically active molecules. Endothelin A is the receptor of the potent vasoconstrictive endothelin-1, and its antagonist ABT-546 (**409**) is used in the treatment of cancer and congestive heart failure. The asymmetric conjugate addition of ketoester **140b** (R = Et, R^1 = $CH_2C(Me)_2n$-Pr) to nitroolefin **404**, catalyzed by [(*S*,*R*)-**10a**/

Chart 10

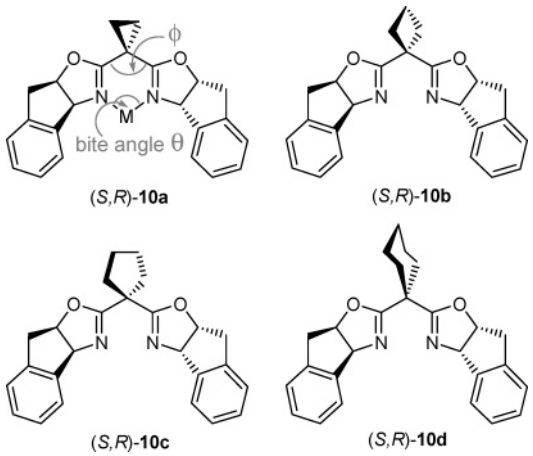


Table 101. Calculated Values of Φ and θ of (*S*,*R*)-10a−d and (*S*,*R*)-9a Cu(II) Complexes and Observed Selectivity of the Diels−Alder Reactions between 163 and Cyclopentadiene (Scheme 84)[51,366]

entry	box	Φ (deg)	θ (deg)	de (endo) (%)	ee (*S*) (%)
1	(*S*,*R*)-**10a**	120.6	97.7	96	96.3
2	(*S*,*R*)-**10b**	115.8	96.3	95	92.0
3	(*S*,*R*)-**10c**	113.2	95.7	95	89.5
4	(*S*,*R*)-**10d**	111.5	94.9	93	83.3
5	(*S*,*R*)-**9a**	112.8	95.4	96	82.5

Table 102. Enantioselective Friedel−Crafts Alkylations of Indole with α-Hydroxy Enones 156[164]

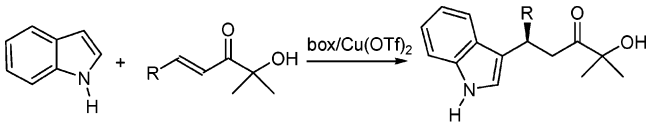
entry	R	box	yield (%)	ee (*R*) (%)
1	*i*-Pr	(*S*)-**8b**	68	93
2	*i*-Pr	(*S*)-**2**	44	85
3	cyclohexyl	(*S*)-**8b**	80	96
4	cyclohexyl	(*S*)-**2**	32	85
5	4-ClC_6H_4	(*S*)-**8b**	95	83

Table 103. Additions of *O*-Benzyhydroxylamine to 394 Catalyzed by [(*S*,*R*)-10a/$MgBr_2$][167]

entry	R	Z	R^1	*T* (°C)	yield (%)	ee (%) (conf.)
1	Me	O	Me	0	85	50 (*R*)
2	Me	O	Me	−60	80	43 (*S*)
3	Pr	O	Me	0	76	31 (−)[a]
4	Pr	O	Me	−60	66	81 (+)[a]
5	$CH_2C_5H_{11}$	O	Me	0	89	29 (−)[a]
6	$CH_2C_5H_{11}$	O	Me	−60	79	68 (+)[a]
7	Me	O	Ph	0	85	37 (*R*)
8	Me	O	Ph	−60	87	44 (*S*)
9	Me	CH_2	Me	0	62	30 (*R*)
10	Me	CH_2	Me	−60	49	25 (*S*)

[a] Absolute configuration not established.

Scheme 167



151 156 393

Scheme 168

394: Z = O, R^1 = Me (**163**), Z = NPh, R^1 = H (**165**) **395**

Table 105. Additions of *N*-Benzylhydroxyamines to 398 Catalyzed by [(*S*,*R*)-10a/MgX_2][369]

entry	R	R^1	R^2	X	yield (%)	de (%)	ee (%) (conf.)
1	Ph	Me	Me	ClO_4	47	94	75 (2*R*,3*R*)
2	*t*-Bu	Me	Me	ClO_4	45	92	57 (2*R*,3*R*)
3	cyclohexyl	Me	Me	ClO_4	76	92	88 (2*R*,3*R*)
4	cyclohexyl	Me	Me	NTf_2	66	90	96 (2*R*,3*R*)
5	*i*-Pr	Me	Me	NTf_2	72	96	96 (2*R*,3*R*)
6	*i*-Pr	Ph	Me	NTf_2	90	95	90
7	*i*-Pr	Me	Ph	NTf_2	38	95	76 (2*R*,3*S*)
8	*i*-Pr	Ph	Ph	NTf_2	49	93	84

$Mg(OTf)_2$], gives adduct **405** in 82% yield and 88% selectivity (Scheme 173). The reduction of the nitroketone, first with H_2−Raney/Ni, then with $NaBH(OAc)_3$, which delivers the hydride syn to the 3-carboxylate, provides the enantiomerically enriched *trans*,*trans*-pyrrolidine **406**. The pure (2*S*,3*R*,4*S*)-enantiomer **407** was obtained as the tartrate salt, which was transformed with standard reactions, through **408**, into the target **409**.[371]

Rolipram **412** is an inhibitor of a phosphodiesterase employed in the treatment of depression. To pursue the asymmetric synthesis of its (*R*)-enantiomer, the [(*R*,*S*)-**10a**/$Mg(OTf)_2$]-catalyzed Michael reaction between diethyl malonate **140a** and nitrostyrene derivative **410** was achieved following the above-described protocol, the adduct **411** was reduced with H_2−Raney/Ni in the presence of a catalytic amount of H_3PO_4 to the corresponding pyrrolidone, which was saponified and decarboxylated to (*R*)-**415** with an excellent overall yield and selectivity (Scheme 174).[371]

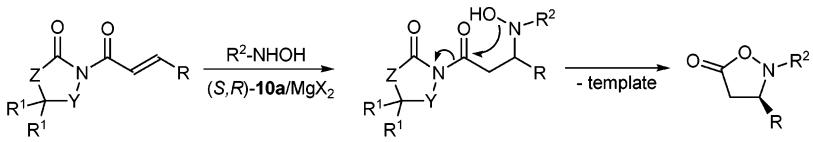
The enantioselective Mukaiyama−Michael reaction of silylketene acetals **86** with β-enamidomalonates **153** (R^1 = ROCHN) (Scheme 59), which fails with complexes based on **1** and **2** ($\leq$60% ee), can be usefully catalyzed by [(*S*,*R*)-**10a**/$Cu(OTf)_2$], and Table 108 reports some significant results changing either the substituent in the α position to the OTMS group of **86** or the R^1 group of **153**.[173]

The radical reactions were the most fertile field to test spirocyclic box's in which the substituents induce strain in the ligand.

An early example concerns the fragmentation, promoted by Et_3B, of *N*-(2-bromo-4,4-dimethylpentanoyl)-2-oxazolidinone **198**, which loses bromine giving a radical that is trapped by trimethylallylsilane (Scheme 71).[15] The effect of the cyclopropylidene as a spacer of the box is shown by the comparison of the catalytic properties of [(*R*)-**8b**/MgI_2] and [(*S*)-**2**/MgI_2]: The yield (83% vs 65%) is better with the latter complex, but the best enantioselectivity of (*R*)-**201** (82% vs 88% ee) is obtained with the **8b** complex.

The most important application in the field of radical reactions concerns the addition of the radical derived from the cleavage of R^2I promoted by Et_3B/O_2 to the alkenoyl derivative of an heterocyclic template (**413**) that, through a carbonyl group or a lone pair, behaves as a bicoordinating reagent. The new box-bound radical is trapped by Bu_3SnH to give **414**, which is formally the product of the conjugate addition of R^2H and can be a useful source of optically active carboxylic acids **415** (Scheme 175). The results with different heterocyclic templates and the effects of different parameters that influence the selectivity of the reaction are reported in Table 109.

Scheme 169

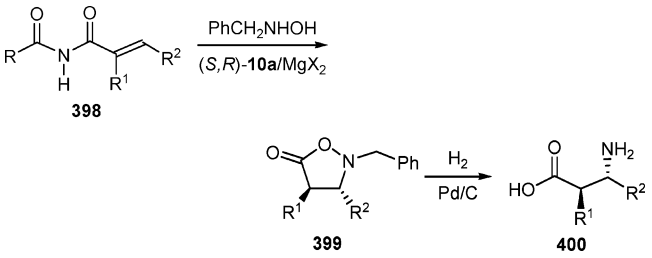


396: Z = O, R^1 = H, Y = CMe_2 (**163**), Z = NPh, R^1 = H, Y = CH_2 (**165**), Z = CH_2, R^1 = Me; Y = N-Bn (**167**) **397** **169**

Table 104. Additions of *N*-Benzylhydroxyamines to 396 Catalyzed by [(*S*,*R*)-10a/MgX_2]

entry	R	Z	Y	R^1	R^2	X	yield (%)	ee (%) (conf.)	ref
1	Me	O	CH_2	H	CH_2Ph	Br	74	92 (*R*)	368
2	Me	CH_2	CH_2	H	CH_2Ph	Br	80	86 (*R*)	368
3	Me	CMe_2	CH_2	H	CH_2Ph	Br	55	89 (*R*)	368
4	Me	CH_2	CH_2	H	$CHPh_2$	Br	90	85	368
5	Me	CH_2	CH_2	H	*p*-$MeOC_6H_4CH_2$	Br	78	86 (*R*)	368
6	Ph	CH_2	CH_2	H	CH_2Ph	ClO_4	80	96 (*S*)	368
7	*p*-$NO_2C_6H_4$	CH_2	CH_2	H	CH_2Ph	ClO_4	60	91	368
8	*p*-ClC_6H_4	CH_2	CH_2	H	CH_2Ph	ClO_4	87	96	368
9	3-furyl	CH_2	CH_2	H	CH_2Ph	I	80	91	368
10	Me	CH_2	NH	Me	*p*-$MeOC_6H_4CH_2$	ClO_4	75	76 (*R*)	170
11	Me	CH_2	NCH_2Ph	H	*p*-$MeOC_6H_4CH_2$	ClO_4	67	78 (*R*)	170
12	Me	CH_2	$NCHPh_2$	H	*p*-$MeOC_6H_4CH_2$	ClO_4	77	96 (*R*)	170
13	Me	CH_2	NCH_2-1-naphthyl	Me	*p*-$MeOC_6H_4CH_2$	ClO_4	76	96 (*R*)	170

Scheme 170



Scheme 171

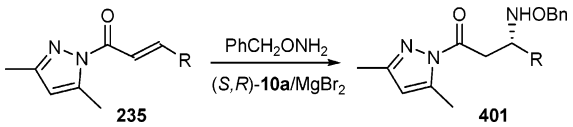


Table 106. Additions of *O*-Benzylhydroxyamines to 235 Catalyzed by 0.3 Equiv of [(*S*,*R*)-10a/MgBr$_2$][370]

entry	R	yield (%)	ee (%) (conf.)
1	Me	80	92 (*R*)
2	Et	74	92
3	$CH_2C_6H_{11}$	53	90
4	CH_2Ph	80	95
5	*i*-Pr	76	87
6	Ph	24	83

Scheme 172

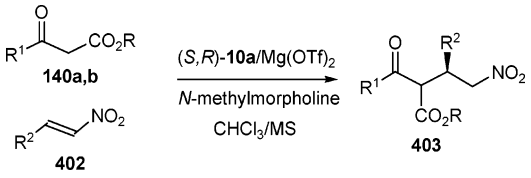


Table 107. Michael Reactions between 1,3-Dicarbonyl Compounds 140a,b and Nitroalkenes 402 Catalyzed by [(*S*,*R*)-10a/Mg(OTf)$_2$][158,371]

entry	R	R^1	R^2	yield (%)	ee[a] (%)
1	Et	Me	Ph	95	90
2[b]	Et	Me	Ph	44	77
3	*i*-Bu	Me	Ph	92	88
4	*t*-Bu	Me	Ph	94	29
5	Et	*i*-Pr	Ph	90	94
6	Me	OMe	Ph	96	93
7	Et	OEt	Ph	92	95 (*S*)
8	*t*-Bu	O*t*-Bu	Ph	88	33
9	Et	OEt	*n*-C_5H_{11}	93	89 (*R*)
10	Et	OEt	*i*-Bu	88	90

[a] The adducts of **140b** with nitrostyrenes are formed as 1:1 mixtures of diastereomeric compounds due to equilibration under the reaction conditions. [b] Reaction catalyzed by [(*S*,*R*)-**9a**/Mg(OTf)$_2$].

The important factors that influence the enantioselectivity of the radical reaction are:

(a) the strain induced in the box by cyclopropylidene is not enough to have excellent catalysis (Table 109, entries 2 and 4 vs 1 and 3); the substituent of the box is more important;

(b) the ligands belonging to the family of the so-called inda-box's (**9**,**10**) (entries 5−8) give very good enantiomeric excesses, and among them the best is **10a**;

(c) this is true for Mg(II) complexes, not for those with Zn(II) (Table 109, entries 26−29);

(d) Mg(II) and Fe(II) are the best cations with (*S*,*R*)-**10c**, and triflimide is the best counterion (Table 109, entries 10 and 11);

(e) the heterocyclic templates in **413** (het. = **A**−**I**) (Table 109, entries 12−19) strongly influence the enantioselectivity;

(f) the templates with a carbonyl group (**A**−**D**) and those with a nitrogen lone pair (**E**−**G**) promote the opposite sense of induction;

(g) radical R^2 (COMe excluded, entry 23) has a small effect on enantioselectivity.

With the different possibilities illustrated in Table 109, if the right template and the opportune catalyst are chosen, then these radical reactions have a large spectrum of applicability.

The above radical addition is the key step in the synthesis of (+)-Ricciocarpin A, a furanosesquiterpene lactone active against schistosomiasis. The reaction between 4-bromo-1-chloro-4-methylpentane and **413** (Scheme 176), catalyzed by [(*S*,*R*)-**10a**/MgI$_2$], gives (*R*)-**416** in excellent yield and enantioselectivity, which is converted, through **417**, into substituted methyl (1*S*,2*R*)-cyclohexanecarboxylate **418**. The deprotection and oxidation to aldehyde **419** and the introduction of the furyl substituent under specifically controlled conditions to optimize yield and diastereomeric excess gave the desired natural ricciocarpin **420**.[373]

When the reaction in Scheme 175 is run with allyltributyltin, the radical formed by the addition of R^2 to **413** adds an allyl group, and the addition occurs anti to R^2 to afford **421** (Scheme 177). The box of election is (*S*,*R*)-**10a**, and the best Lewis acids, after testing several cations and counterions, are MgI$_2$ and Cu(OTf)$_2$. These catalysts not only give good enantiomeric excesses but also have an important property: MgI$_2$ and Cu(OTf)$_2$ are able to afford opposite senses of induction (Table 110).[374]

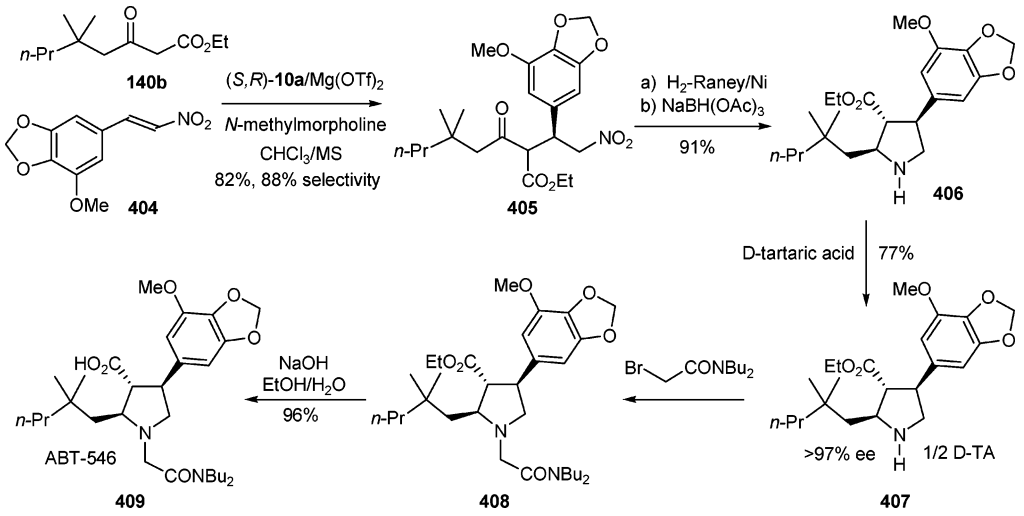
The radical addition to α,*β*-unsaturated carbonyl compounds may occur on the alkenoyl derivatives of amides **398**; therefore with a non-heterocyclic template, the catalyst being a Mg(II) complex of (*S*,*R*)-**10a**, and excellent results (with the exclusion of the example in Table 111, entry 6) have been obtained both in terms of diastereoselectivity, which favors the anti isomer **422** and enantioselectivity (Scheme 178).[375]

This protocol had several useful applications in the field of organic synthesis: In addition to the preparation of optically active carboxylic acids, it was demonstrated that the products provided a convenient route to unusual α- and *β*-amino acids and *β*-hydroxy acids. α-Acylamido acrylates **423** first add R^2 to the *β*-position, then the radical is trapped by Bu$_3$SnH to give **424**, which is the protected form of chiral α-amino acids (Scheme 179). The best catalyst is [(*S*,*R*)-**10a**/Mg(ClO$_4$)$_2$] (Table 112), the only limit being the stoichiometric amount of complex required.[376]

β-Acylamido acrylates **425**, by radical addition followed by hydrogen atom transfer, become the source of the protected form of chiral *β*-amino acids **426** (Scheme 180, Table 113). The effect of R and the configuration of the product suggest that the tetrahedral reaction intermediate **427** with the Mg cation coordinates box and **425**, this as an eight-membered chelate. After the R^2 radical addition, the hydrogen atom transfer on **428** depends on the steric hindrance of box and R that determines the face selectivity. This reaction works with a substoichiometric amount of catalyst.[377]

The radical addition to α-hydroxymethyl acrylates **429** is an interesting route to *β*-hydroxy esters **430** (Scheme 181).

Scheme 173



Scheme 174

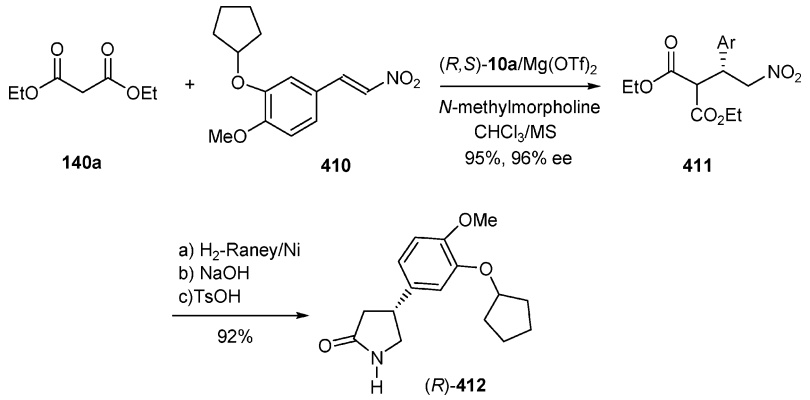
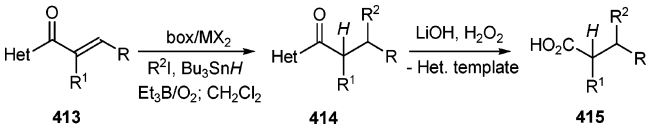


Table 108. Mukaiyama−Michael Reactions between Silylketene Acetals 86 and β-Enamidomalonates 153 (Scheme 59) Catalyzed by [(*S*,*R*)-10a/Cu(OTf)$_2$][173]

entry[a]	A	R^1	yield (%)	ee (%) (conf.)
1	*t*-BuS	Ph	96	89 (*R*)
2	Ph	Ph	97	64
3	*t*-Bu	Ph	39	40
4	*t*-BuS	*t*-Bu	97	83
5	Ph	*t*-Bu	74	73
6	*t*-BuS	CF_3	74	54
7	Ph	CF_3	95	67

[a] Reactions run in the presence of hexafluoro-2-propanol.

Scheme 175



A detailed investigation of ligand, Lewis acid, and substrate led to the choice of [(*R*,*S*)-**10a**/MgI_2] as the catalyst and demonstrated the importance of the size of the ester substituent (Table 114).[378] The addition of secondary and tertiary R^2 groups gave better enantiomeric excesses than ethyl radical, methyl ester gave the best enantioselectivity (Table 114, entries 1, 4, 6, and 8), the medium-sized benzyl ester was inferior, and the bulky *tert*-butyl group gave the opposite sense of induction (Table 114, entries 3, 5, 7, and 9).

This deeply discussed radical reaction, catalyzed by complexes of **10a**, was tested on vinyl sulfones but gave nearly racemic products.[200,201]

The Kharasch reaction between *tert*-butyl perbenzoate and cyclohexene (Scheme 81), catalyzed by $CuPF_6$ and (*R*,*S*)-**10a** gave the same routine results (yield 65%, 74% ee) obtained with (*R*,*S*)-**9a**.[208]

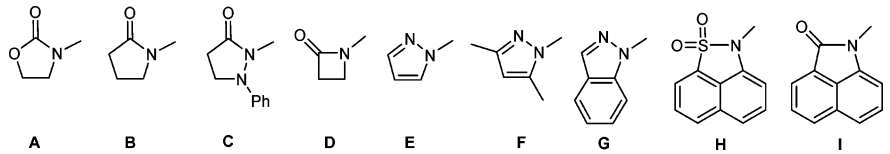
Box's with cyclopropylidene as spacers found useful applications in 1,3-dipolar cycloadditions. The reaction between nitrones **270** and 1-benzyl-2-alkenoyl-5,5-dimethylpyrazolidin-3-ones **167**, the achiral template already mentioned in Scheme 101, was performed with [(*S*,*R*)-**10a**/$Cu(OTf)_2$] as the catalyst (Scheme 182), and the results, good in terms of diastereoselectivity and always excellent in terms of enantioselectivity, are reported in Table 115.[273]

The same catalysts were later tested on the reaction between nitrones **270** and α,β-disubstituted acrylimides **425** (Scheme 183), a non-heterocyclic template already used in radical reactions. The exo-selective reaction gives **431,** and some significant results are collected in Table 116.[379]

Few examples are known of 1,3-dipolar cycloadditions with nitrile oxides, and for these examples, the catalysts of choice are the complexes of (*S*,*R*)-**10a**. Several nitrile oxides **432** have been tested, with different acrylamides **433** carrying the templates **Z1**−**Z7**, and two different regioisomers have been obtained, **434** and **435** (Scheme 184).[276,379] The excellent results are reported in Table 117.

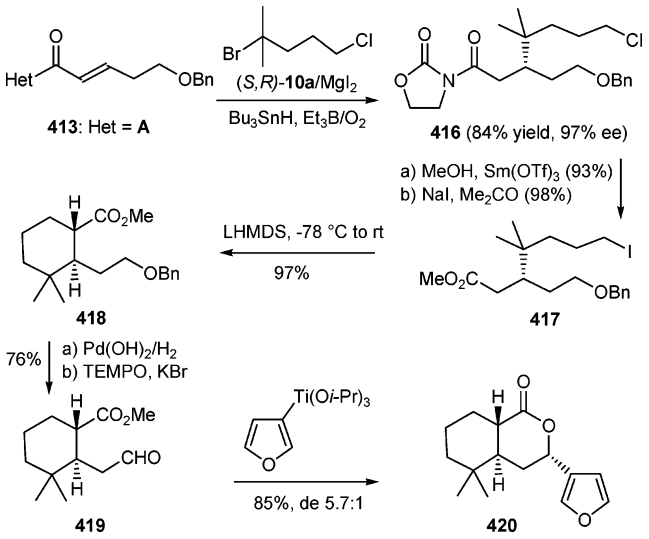
The selectivity largely depends on the nature of Z; good results are obtained with **Z3**, **Z6**, and **Z7**. Among them, **Z3**

Table 109. Enantioselective Radical Additions of R^2I to Alkenoyl-Heterocycles 413



entry	R	R^1	het.	R^2	box	MX_2	yield (%)	ee (%) (conf.)	ref
1	Ph	H	**A**	*i*-Pr	(*S*)-**1**	MgI_2	88	47 (*S*)	29
2	Ph	H	**A**	*i*-Pr	(*S*)-**8a**	MgI_2	87	37 (*S*)	29
3	Ph	H	**A**	*i*-Pr	(*S*,*R*)-**5c**	MgI_2	79	31 (*S*)	29
4	Ph	H	**A**	*i*-Pr	(*S*,*R*)-**8f**	MgI_2	88	36 (*S*)	29
5	Ph	H	**A**	*i*-Pr	(*S*,*R*)-**9a**	MgI_2	88	89 (*R*)	29
6	Ph	H	**A**	*i*-Pr	(*S*,*R*)-**10c**	MgI_2	92	82 (*R*)	29
7	Ph	H	**A**	*i*-Pr	(*S*,*R*)-**10b**	MgI_2	90	82 (*R*)	29
8	Ph	H	**A**	*i*-Pr	(*S*,*R*)-**10a**	MgI_2	95	96 (*R*)	29
9	Ph	H	**A**	*i*-Pr	(*S*,*R*)-**10a**	$Mg(ClO_4)_2$	91	94 (*R*)	196
10	Ph	H	**A**	*i*-Pr	(*S*,*R*)-**10a**	$Mg(NTf_2)_2$	99	98 (*R*)	196
11	Ph	H	**A**	*i*-Pr	(*S*,*R*)-**10a**	$Fe(NTf_2)_2$	95	98 (*R*)	196
12	H	Me	**A**	*i*-Pr	(*S*,*R*)-**10a**	$MgBr_2$	80	65 (*S*)	372
13	H	Me	**B**	*i*-Pr	(*S*,*R*)-**10a**	$MgBr_2$	76	42 (*S*)	372
14	H	Me	**C**	*i*-Pr	(*S*,*R*)-**10a**	$MgBr_2$	67	28 (*S*)	372
15	H	Me	**D**	*i*-Pr	(*S*,*R*)-**10a**	$MgBr_2$	54	15 (*S*)	372
16	H	Me	**E**	*i*-Pr	(*S*,*R*)-**10a**	$MgBr_2$	52	15 (*R*)	372
17	H	Me	**F**	*i*-Pr	(*S*,*R*)-**10a**	$MgBr_2$	54	38 (*R*)	372
18	H	Me	**G**	*i*-Pr	(*S*,*R*)-**10a**	$MgBr_2$	66	15 (*R*)	372
19	H	Me	**H**	*i*-Pr	(*S*,*R*)-**10a**	$MgBr_2$	59	88	372
20	H	Me	**H**	*t*-Bu	(*S*,*R*)-**10a**	$MgBr_2$	84	89	372
21	H	Me	**H**	Cyhex	(*S*,*R*)-**10a**	$MgBr_2$	96	89	372
22	H	Me	**H**	CH_2OMe	(*S*,*R*)-**10a**	$MgBr_2$	89	90	372
23	H	Me	**H**	COMe	(*S*,*R*)-**10a**	$MgBr_2$	<25	18	372
24	H	Me	**I**	CH_2OMe	(*S*,*R*)-**10a**	$MgBr_2$	61	6	372
26	Ph	H	**F**	*i*-Pr	(*S*,*R*)-**9a**	$Zn(OTf)_2$	72	43 (*S*)	328
27	Ph	H	**F**	*i*-Pr	(*S*,*R*)-**10c**	$Zn(OTf)_2$	90	50 (*S*)	328
28	Ph	H	**F**	*i*-Pr	(*S*,*R*)-**10b**	$Zn(OTf)_2$	81	44 (*S*)	328
29	Ph	H	**F**	*i*-Pr	(*S*,*R*)-**10a**	$Zn(OTf)_2$	76	51 (*S*)	328

Scheme 176



Scheme 177

deserves attention for its easy preparation, but the template of choice with all kinds of nitriloxides, those stable (R^2 = mesityl and *p*-Cl−C_6H_4) and those unstable (Table 117, entries 10−12), for excellent regio- and enantioselectivity

Table 110. Enantioselective Tandem Radical Additions of R^2 and Allyl Groups to Alkenoyl-Heterocycles 413 Catalyzed by Complexes of (*S*,*R*)-10a[374]

entry	R	het.	R^2	MX_2	yield (%)	dr (anti/syn)	ee (%)
1	Ph	A	*i*-Pr	MgI_2	93	97:3	93
2	Ph	A	*i*-Pr	$Zn(OTf)_2$	69	97:3	−43
3[a]	Ph	A	*i*-Pr	$Cu(OTf)_2$	93	97:3	−79
4	Ph	A	*t*-Bu	MgI_2	84	99:1	97
5[a]	Ph	A	*t*-Bu	$Cu(OTf)_2$	90	99:1	−96
6	Ph	A	Et	MgI_2	79	97:3	77
7	Ph	A	Cyhex	MgI_2	80	98:2	92
8	Me	A	Cyhex	$Mg(ClO_4)_2$	83	80:20	62
9	Me	B	*t*-Bu	$Mg(ClO_4)_2$	85	95:5	92
10[a]	Me	B	*t*-Bu	$Cu(OTf)_2$	66	98:2	−83

[a] Allyltriphenyltin was used.

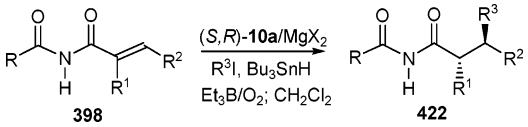
is **Z6**. The absolute stereochemistry of the product in Table 117 (entry 8) was determined to be (*S*,*S*)-**434**, and this can be rationalized by assuming the octahedral reaction intermediate in Figure 19 that allows the attack of **432** to the C_α Si face of the coordinated dipolarophile.

The first example of 1,3-dipolar cycloaddition of nitrile imines has been recently reported with the reaction between **163** and **437**, prepared in situ from hydrazonyl halides **436** in the presence of base (Scheme 185, Table 118). The best catalyst is [(*R*,*S*)-**10a**/$Mg(NTf_2)_2$] (Table 118, entries 1−3), and the base also has a relevant role in the success of the reaction (Table 118, entries 3−5). The cycloaddition is completely regioselective and gives **438** with excellent enantioselectivity, and the adducts are easily reduced to **439**.[380]

Table 111. Enantioselective Radical Additions of R^3I to Diamides 398 Catalyzed by Mg(II) Complexes of (*S*,*R*)-10a[375]

entry	R	R^1	R^2	R^3	MgX_2	yield (%)	dr (anti/syn)	anti ee (%)
1	*i*-Pr	Me	Me	*t*-Bu	$Mg(NTf_2)_2$	69	97:3	69
2	Cyhex	Me	Me	*t*-Bu	$Mg(NTf_2)_2$	67	98:2	65
3	Ph	Me	Me	*t*-Bu	$Mg(NTf_2)_2$	78	98:2	74
4	*t*-Bu	Me	Me	*t*-Bu	MgI_2	83	99:1	94
5	*t*-Bu	Me	Me	Cyhex	MgI_2	62	98:2	79
6	*t*-Bu	Me	Me	CH_2OMe	MgI_2	59	75:25	56
7	*t*-Bu	Me	Et	*i*-Pr	MgI_2	37	95:5	80
8	*t*-Bu	Me	Ph	*i*-Pr	MgI_2	71	99:1	93
9	*t*-Bu	Et	Me	*i*-Pr	MgI_2	50	87:13	74

Scheme 178



Scheme 179

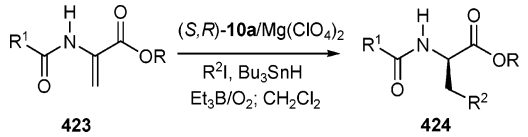
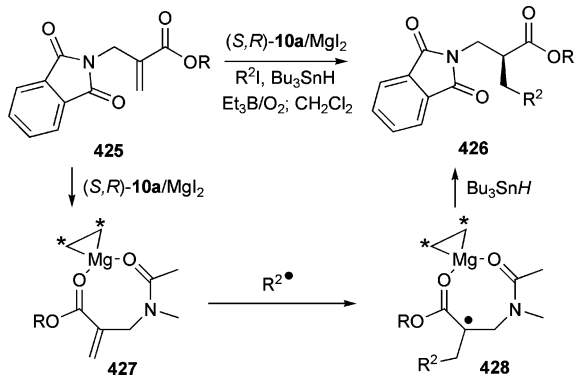


Table 112. Enantioselective Radical Additions of R^2I to Amidoesters 423 Catalyzed by [(*S*,*R*)-10a/$Mg(ClO_4)_2$][376]

entry	R	R^1	R^2	yield (%)	ee (%) (conf.)
1	Me	OBn	Et	61	22
2	Bn	2-naphthyl	Et	57	68
3	*t*-Bu	2-naphthyl	Et	56	71
4	Me	2-naphthyl	Et	72	85 (*R*)
5	Me	2-naphthyl	*i*-Pr	62	83 (*R*)
6	Me	2-naphthyl	Cyhex	62	55 (*R*)
7	Me	2-naphthyl	*t*-Bu	54	27 (*R*)

Scheme 180



The absolute stereochemistry of the product in Table 118 (entry 10) was determined to be (4*S*,5*S*)-**438**, and this can be rationalized by assuming the same octahedral reaction intermediate, allowing the attack of **437** to the C_α Si face of coordinated **163**, already reported in Figure 19 for the 1,3-dipolar cycloaddition with nitrile oxide.

At the end of this fruitful section two fundamental questions have to be faced. Do indanyl substituents induce box's to behave as alkyl- or as aryl-substituted ligands? Furthermore, is the trend illustrated in Table 101 for Cu(II) catalysts "the larger the bridge angle Φ, the higher the enantioselectivity induced in the reaction" a general effect valid for each cation involved with reagents and box's in the reacting intermediate?

Table 113. Enantioselective Radical Additions of R^2I to *β*-Acylamido Acrylates 425 Catalyzed by [(*S*,*R*)-10a/MgI_2][377]

entry	R	R^2	yield (%)	ee (%) (conf.)
1	Me	*i*-Pr	91	40 (*S*)
2	*t*-Bu	*i*-Pr	95	84 (*S*)
3	Me	*t*-Bu	81	20
4	*t*-Bu	*t*-Bu	88	71
5	*t*-Bu	Et	83	62
6	*t*-Bu	cyclohexyl	86	90
7	*t*-Bu	1-adamantyl	72	61

Scheme 181

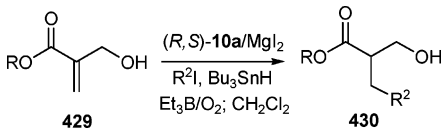


Table 114. Enantioselective Radical Additions of R^2I to α-Hydroxymethyl Acrylates 429 Catalyzed by [(*R*,*S*)-10a/MgI_2][378]

entry	R	R^2	yield (%)	ee (%) (conf.)
1	Me	Et	51	75
2	Bn	Et	85	40
3	*t*-Bu	Et	58	−62
4	Me	*i*-Pr	69	88 (*S*)
5	*t*-Bu	*i*-Pr	53	55 (*R*)
6	Me	cyclohexyl	52	78 (*S*)
7	*t*-Bu	cyclohexyl	75	71 (*R*)
8	Me	*t*-Bu	77	92
9	*t*-Bu	*t*-Bu	80	−53

Scheme 182

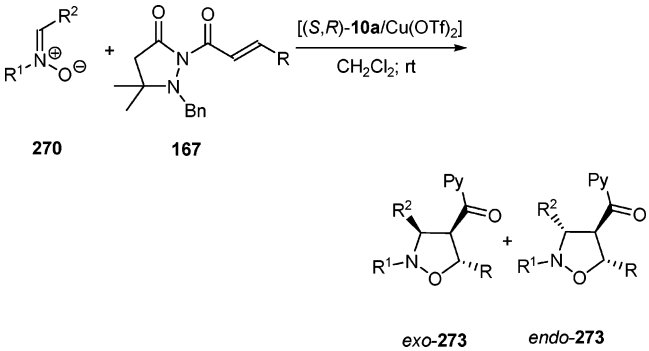


Table 115. Enantioselective 1,3-Dipolar Cycloadditions between Nitrones 270 and 167 Catalyzed by [(*S*,*R*)-10a/$Cu(OTf)_2$][273]

entry	R	R^1	R^2	yield (%)	exo/endo	exo ee (%)
1	H	Me	Ph	85	66:34	99
2	Me	Me	Ph	94	96:4	98
3	Et	Me	Ph	88	94:6	99
4	CO_2Et	Me	Ph	44	67:33	85
5	Me	Bn	Ph	92	93:7	99
6	Me	Bn	*p*-Cl-C_6H_4	52	85:15	98
7	Me	Bn	*p*-MeO-C_6H_4	45	95:5	98
8	Me	Ph	Ph	85	52:48	99

The Diels−Alder reaction between cyclopentadiene and **163** (R = 4-$CF_3C_6H_4CO_2$) gives *endo*-**440** as main adduct (Scheme 186), and both the enantioselectivity and the face selectivity of the reaction are a function of several factors (Table 119).[224]

When the copper counterion is OTf, the presence of 4 Å MS is strongly negative for enantioselectivity (Table

Scheme 183

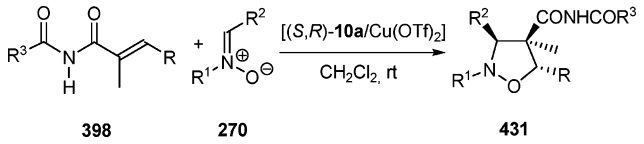
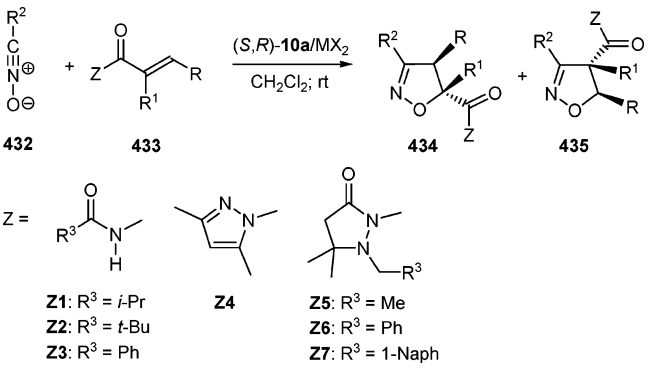


Table 116. Enantioselective 1,3-Dipolar Cycloadditions between Nitrones 270 and α,β-Disubstituted Acrylimides 398 Catalyzed by [(*S*,*R*)-10a/Cu(OTf)$_2$][379]

entry	R	R^3	R^1	R^2	yield (%)	exo/endo	exo ee (%)
1	H	*t*-Bu	Me	Ph	57	81:19	89
2	Me	*t*-Bu	Me	Ph	60	99:1	94
3	Et	*t*-Bu	Me	Ph	63	99:1	91
4	Me	*t*-Bu	Me	*p*-Br-C_6H_4	62	99:1	98
5	Me	*t*-Bu	Ph	Ph	50	85:15	86

Scheme 184



119, entry 1 vs 2), whereas this additive has no effect with $Cu(SbF_6)_2$. If the presence of cyclopropylidene as a spacer promotes a better enantioselection (Table 119, entry 1 vs 5), then the comparison of two box's with the same configuration at the C(4) center, (*S*,*R*)-**10a** and (*S*)-**1** (Table 119, entry 1 vs 7) affords the most important result since the enantiomeric excess values are the same, but the resulting face selectivity is opposite. This suggests that 4,5-indanyl mimics a 4-alkyl substituent more than a 4-aryl substituent in the behavior of the box.

The addition of MeLi to imines **133** to give amines **134** (Scheme 187), whose results have been already mentioned in Table 25, was studied in detail in the presence of

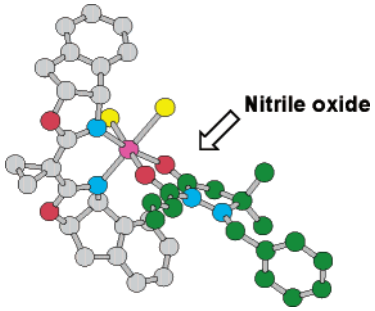


Figure 19. Stereochemical model of the 1,3-dipolar cycloaddition reaction of nitrile oxide with crotonoyl-amide in Table 117, entry 8.

(*S*)-**8b**−**e**, the four 4-*t*-Bu-substituted box's that have cycloalkylidenes as spacers (Chart 11). The enantioselectivity of three reactions with different R groups is compared with the variation of the bridge angle Φ of the corresponding [box/MeLi] complex resulting from molecular mechanics (MM2) calculations (Table 120).[14]

The common result in each of the three examples is that the enantiomeric excess is lower for the most strained box (*S*)-**8b**, and this is in sharp contrast with the enantioselectivity reported previously for the Cu(II) complexes of (*S*,*R*)-**10a**−**d** used as catalysts of the Diels−Alder reaction (Table 101). If on the same graph both the enantiomeric excesses of the MeLi addition to imine **133** (R = Ph), catalyzed by [(*S*)-**8b**−**e**/MeLi] and [(*S*)-**2**/MeLi], and the enantiomeric excesses of the Diels−Alder reaction between **163** and cyclopentadiene, catalyzed by [(*S*,*R*)-**10a**−**d**/Cu(OTf)$_2$] and [(*S*)-**9a**/Cu(OTf)$_2$], are plotted versus the bridge angle Φ, then the correlations in Figure 20 are obtained. This figure perhaps suggests that strongly strained cyclopropylidene box's with large bridge angles prefer cations with large radii, whereas cations with small radii do not fit these kinds of box's.

6. Complexes of Phenyl- and *tert*-Butyl-Box's with Different Inorganic Salts and Their Behaviors as Efficient Asymmetric Catalysts

Two families of catalysts, based on phenyl- and *tert*-butyl-box's, are the core of this review, and the knowledge of their

Table 117. Enantioselective 1,3-Dipolar Cycloadditions between Nitrile Oxides 432 and α,β-Disubstituted Acrylimides 433 Catalyzed by [(*S*,*R*)-10a/MX$_2$]

entry	R	R^1	Z	R^3	MX_2	yield (%)	**434**/**435**	**434** ee (%) (conf.)	ref
1	Me	H	**Z4**	mesityl	MgI_2	61	17:83	37	276
2	Me	H	**Z5**	mesityl	MgI_2	88	99:1	95	276
3	Me	H	**Z6**	mesityl	MgI_2	84	99:1	99	276
4	Me	H	**Z7**	mesityl	MgI_2	98	99:1	99	276
5	Et	H	**Z6**	mesityl	MgI_2	86	99:1	95	276
6	Ph	H	**Z6**	mesityl	MgI_2	85	99:1	99	276
7	CO_2Et	H	**Z6**	mesityl	MgI_2	75	99:1	99	276
8	Me	H	**Z6**	Ph	MgI_2	75	99:1	99 (*S*,*S*)	276
9	Me	H	**Z6**	*p*-Cl-C_6H_4	MgI_2	70	99:1	96	276
10	Me	H	**Z6**	*p*-MeO-C_6H_4	MgI_2	61	91:9	99	276
11	Me	H	**Z6**	*i*-Bu	MgI_2	63	97:3	79	276
12	Me	H	**Z6**	*t*-Bu	MgI_2	44	99:1	92	276
13	Me	Me	**Z1**	mesityl	$Mg(ClO_4)_2$	56	>99:<1	83	379
14	Me	Me	**Z2**	mesityl	$Mg(ClO_4)_2$	0			379
15	Me	Me	**Z3**	mesityl	$Mg(ClO_4)_2$	79	>99:<1	81	379
16	Me	Me	**Z3**	mesityl	$Mg(NTf_2)_2$	51	>99:<1	82	379
17	Me	Me	**Z3**	mesityl	$Ni(ClO_4)_2$	99	>99:<1	77	379
18	Me	Me	**Z7**	mesityl	$Mg(ClO_4)_2$	12	>99:<1	95	379

Scheme 185

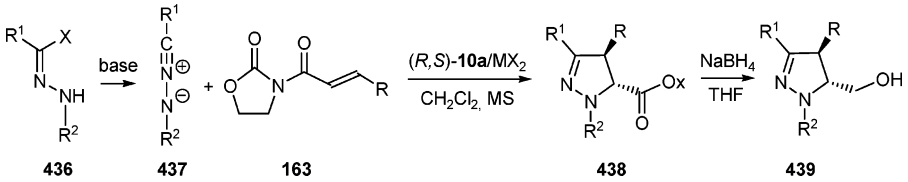


Table 118. Enantioselective 1,3-Dipolar Cycloadditions between Nitrile Imines 432 and 163 Catalyzed by [(*R*,*S*)-10a/MX_2][380]

entry	R	R^1	R^2	X	base	MX_2	yield (%)	ee (%) (conf.)
1	Me	Ph	*p*-BrC_6H_4	Br	*i*-Pr_2NEt	$Ni(ClO_4)_2$	61	28
2	Me	Ph	*p*-BrC_6H_4	Br	*i*-Pr_2NEt	$Mg(ClO_4)_2$	92	96
3	Me	Ph	*p*-BrC_6H_4	Br	*i*-Pr_2NEt	$Mg(NTf_2)_2$	93	99
4	Me	Ph	*p*-BrC_6H_4	Br	Et_3N	$Mg(NTf_2)_2$	99	95
5	Me	Ph	*p*-BrC_6H_4	Br	DABCO	$Mg(NTf_2)_2$	51	98
6	Ph	Ph	*p*-BrC_6H_4	Br	*i*-Pr_2NEt	$Mg(NTf_2)_2$	95	97
7	2-furyl	Ph	*p*-BrC_6H_4	Br	*i*-Pr_2NEt	$Mg(NTf_2)_2$	94	99
8	CO_2t-Bu	Ph	*p*-BrC_6H_4	Br	*i*-Pr_2NEt	$Mg(NTf_2)_2$	92	91
9	Me	*i*-Pr	*p*-BrC_6H_4	Br	*i*-Pr_2NEt	$Mg(NTf_2)_2$	98	99
10	Me	*p*-BrC_6H_4	*p*-BrC_6H_4	Br	*i*-Pr_2NEt	$Mg(NTf_2)_2$	95	95 (4*S*,5*S*)
11	Me	Ph	Ph	Cl	*i*-Pr_2NEt	$Mg(NTf_2)_2$	92	95
12	*p*-BrC_6H_4	Ph	Ph	Cl	*i*-Pr_2NEt	$Mg(NTf_2)_2$	97	97

Scheme 186

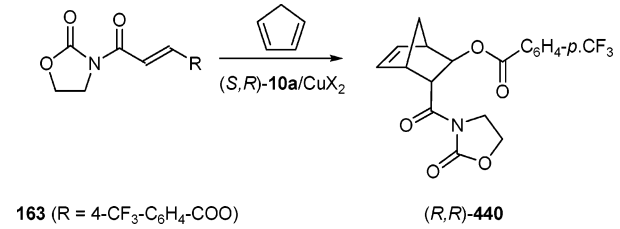
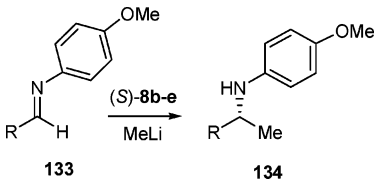


Table 119. Enantioselective Diels−Alder Reactions between 163 (R = 4-$CF_3C_6H_4CO_2$) and Cyclopentadiene[224]

entry	box	CuX_2	additive	yield (%)	endo/exo (%)	endo ee (%) (conf.)
1	(*S*,*R*)-**10a**	$Cu(OTf)_2$		99	90:10	90 (*R*,*R*)
2	(*S*,*R*)-**10a**	$Cu(OTf)_2$	4 Å MS	99	92:8	50 (*R*,*R*)
3	(*S*,*R*)-**10a**	$Cu(SbF_6)_2$		99	88:12	91 (*R*,*R*)
4	(*S*,*R*)-**10a**	$Cu(SbF_6)_2$	4 Å MS	99	91:9	90 (*R*,*R*)
5	(*S*,*R*)-**9a**	$Cu(OTf)_2$		99	90:10	83 (*R*,*R*)
6	(*S*)-**2**	$Cu(OTf)_2$		99	90:10	54 (*R*,*R*)
7	(*S*)-**1**	$Cu(OTf)_2$		99	94:6	89 (*S*,*S*)

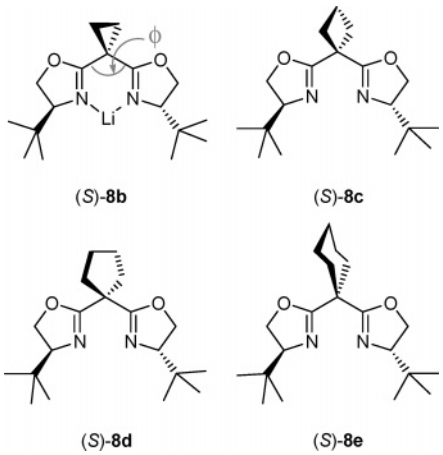
Scheme 187



behavior versus the different reactions may help the reader either to find a well-tested [box/cation] combination already successful in a certain class of reactions or to discover unusual catalysts whose potentialities are not yet fully explored. Among the many hundreds of results, the choice was limited to the complexes with **1** and **2** as ligands able to induce at least 50% enantiomeric excesses in the catalyzed reaction. The cluster of reactions satisfying this limit includes a total of 352 examples, and its composition is reported in Figure 21.

The result of this simple analysis is that phenyl- and *tert*-butyl-box's gave nearly the same contribution to the world of box catalysts.

Chart 11



The above cluster of 352 selected examples was analyzed, and the types of reactions catalyzed by complexes of **1** and **2** are reported in Figure 22. The most developed applications concern aldol, Diels−Alder, and cyclopropanation reactions. Some reactions prefer to be catalyzed by complexes of **1**: allylic substitutions (80%), 1,3-dipolar cycloadditions (65%), aziridinations (61%), and radical reactions (59%). Some other reactions prefer complexes involving **2** as the chiral ligand: cyclopropanation (72%), hetero Diels−Alder (60%), and Michael reactions (62%). The remaining reactions (and in particular the aldol reactions) can be usefully catalyzed by complexes involving both ligands.

To demonstrate the best fit between cation and box, the next step was the analysis of the data obtained with the different cations giving catalysts with **1** and **2** in terms of

Table 120. Calculated Bridge Angle (Φ) of [Box/LiMe] Complexes and Enantiomeric Excesses of MeLi Additions to Imines 133[14]

box	(*S*)-**8b**	(*S*)-**8c**	(*S*)-**8d**	(*S*)-**8e**	(*S*)-**2**
bridge angle Φ (deg)	122.7	110.0	111.8	106.8	109.7
ee for R = Ph	51	73	71	70	67
ee for R = (*E*)-PhCH=CH	2	84	90	91	94
ee for R = $PhCH_2CH_2$	44	90	91	75	93

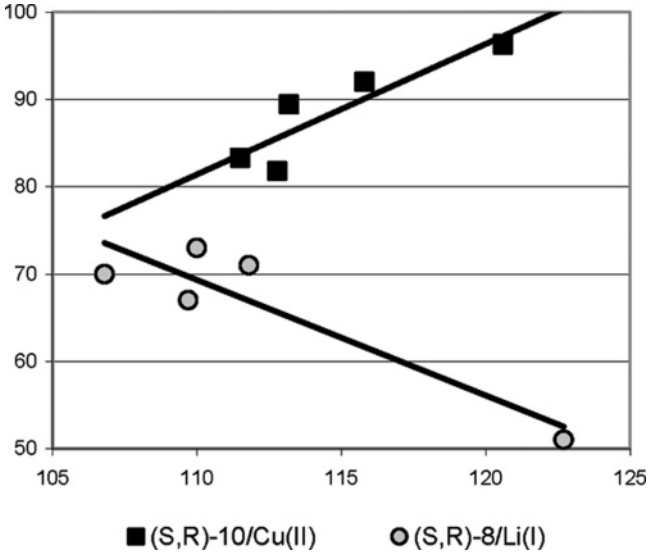


Figure 20. Relationships between the bridge angle Φ of the box complex and the enantiomeric excess of both the MeLi addition to imine **133** (R = Ph) (Table 120) and the Diels−Alder reaction between **163** and cyclopentadiene (Table 101).

Figure 21. Composition of the cluster of reactions catalyzed by complexes of phenyl- and *tert*-butyl-box (**1** and **2**) inducing at least 50% enantiomeric excesses in the catalyzed reaction.

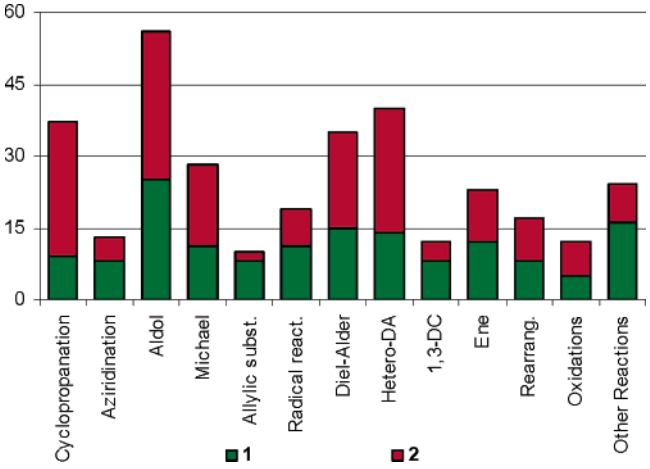


Figure 22. Types of reactions, catalyzed by complexes of **1** and **2**, occurring with at least 50% enantiomeric excesses.

relative composition of their corresponding clusters (Figure 23).

The graph in Figure 23 clearly suggests that *tert*-butyl-box has a specific affinity with copper, since about the 80% of catalysts with this ligand involve the copper cation. The importance of other cations in the **2**-based catalyst is marginal since the second relevant cation is lithium (7% of frequency) that has only a limited use in reactions involving the generation of carbanions by BuLi. The main difference with the cation distribution in phenyl-box-based catalysts (where copper takes again the position of most diffused cation (56%)) is the not negligible presence of catalysts derived

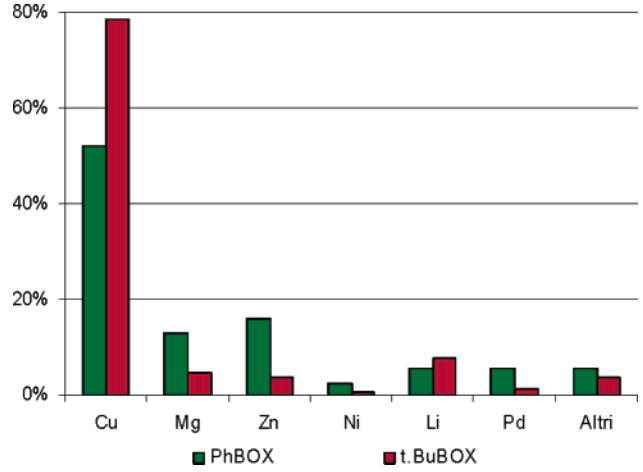


Figure 23. Most important cations giving complexes with **1** and **2** catalyzing reactions with at least 50% enantiomeric excesses.

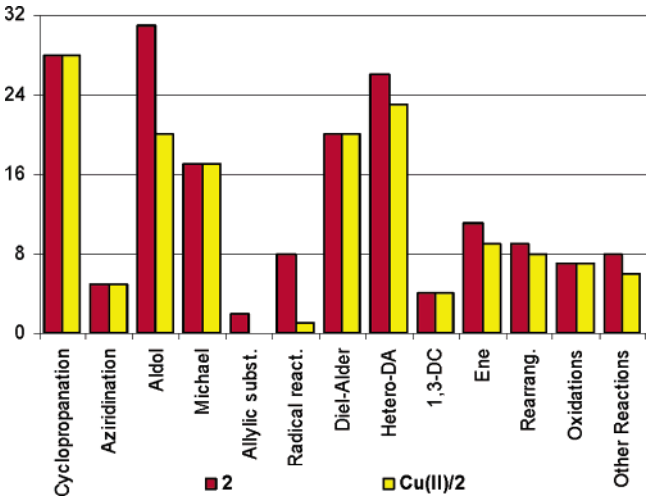


Figure 24. Types of enantioselective reactions catalyzed by complexes of **2** with copper.

from Zn(II) (18%) and Mg(II) (13%) cations. This diffusion (a total of 31% with **1** vs 7% with **2**) is important because it makes phenyl-box a more flexible ligand compatible with different cations, allowing a more extended use of the box-based catalysis. A clear example is given by the relative diffusion of palladium-based catalysts (6% with **1** vs 1% with **2**) that suggests phenyl-box as the ligand of choice for asymmetric allylic substitutions.

A further step is to look inside the different applications of the most frequently used [box/cation] couples in enantioselective catalysis. Given the specificity of **2** with copper, these complexes have been analyzed first (Figure 24). To the present state of the art, to run cyclopropanation, aziridination, and oxidation reactions, the use of the copper complexes is strictly required. The same is strongly recommended with Michael, Diels−Alder, hetero Diels−Alder, ene, and rearrangement reactions. The 1,3-dipolar cycloadditions as well as the aldol and radical reactions tolerate the use of complexes with other cations; obviously the very few examples of allylic substitution catalyzed by *tert*-butyl-box complexes strictly require palladium cation.

The same type of analysis was applied to the cluster of reactions catalyzed by complexes of **1** with copper (Figure 25). Again, to run cyclopropanation, aziridination, Michael, hetero Diels−Alder, ene, oxidation, and rearrangement reactions, the use of copper complexes is strongly recom-

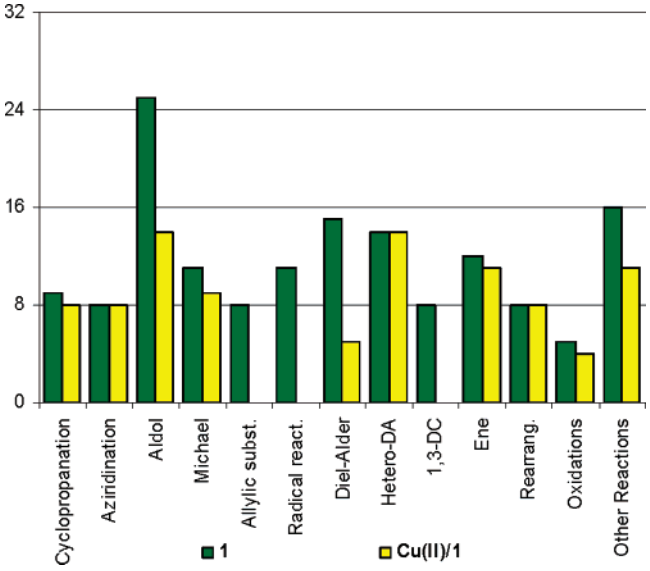


Figure 25. Types of enantioselective reactions catalyzed by complexes of **1** with copper.

mended. The main difference with the reaction distribution observed with **2** is that in some reactions the contribution of catalysts based on other cations (69% of Diels−Alder and 46% of aldol or aldol-like reactions) may become predominant. The importance of other cations is particularly evident in allylic substitution, 1,3-dipolar cycloadditions, and radical reactions, since all these processes have been run with cations other than copper.

Given the important contribution of cations other than copper to the preparation of efficient enantioselective catalysts with phenyl-box as the ligand (44% of the cluster), the contribution of the most diffused ones (Zn(II), Mg(II), and Pd(II)) to the different reaction was analyzed (Figure 26).

If Pd(II) is the obvious cation of choice for allylic substitutions, then Zn(II) is employed in hetero Diels−Alder, aldol, and aldol-like reactions, whereas Mg(II) and Zn(II) frequently participate in the development of enantioselective catalysts for Diels−Alder reactions, radical reactions, and 1,3-dipolar cycloadditions.

7. Relation between the Different Reagents Coordinated to Phenyl- and *tert*-Butyl-Box Metal Catalysts and the Stereochemical Outcome

The reader of this review has probably noted that some reagents have been used and discussed several times along the text since they successfully have been applied as the substrate in several reactions. An important the question that has attracted much attention in relation to the reaction course of these reactions is whether the enantioselectivity of the products is always the result of the same facial approach in the different reacting complexes. If the investigation could be limited to the simple generation of the complex between box, cation, and reagent, then a simple analysis of the different results could perhaps offer the answer. However, the question is complicated by the many different experimental conditions that can heavily influence the enantioselectivity of the reaction (solvent, counterion, additive, temperature, etc.). Therefore, this investigation will be limited to few ordinary reagents that may give a bidentate coordination with phenyl- and *tert*-butyl-box metal catalysts: α-oxoesters **85b**,**c**, β-oxoesters **140a-c** and **153**, and 3-alkenoyl-2-oxazolidinones **163**. A few assumptions will be made: e.g., the cisoid conformation of **163** and the reaction complexes being only formed from the [box/metal] catalysts and reagents described above. This is not always true (see, for example, the reacting intermediates illustrated in refs 131a and 156b and in the 1,3-dipolar cycloadditions), but the answer of interest in this section is simply on which face of the above coordinated reagents the attack preferentially occurs. With these limits, the face selectivity with (*S*)-**1** and (*S*)-**2** in different reactions with different cations and different counterions will be discussed.

One further limit has been considered: Among the hundreds of results, as much as possible, only those with dichloromethane as the solvent will be considered. The reason for this choice in reactions with α-oxoesters **85b,c** can be shared if the results of the hetero Diels−Alder reaction between ethyl glyoxylate **85b** (R = Et) and 1,3-cyclohexadiene **248** to give **249** (Scheme 89) are considered.[59] The enantioselectivity, in different modes with the different catalysts, strongly depends on the solvent, and Table 121 recalls these results.

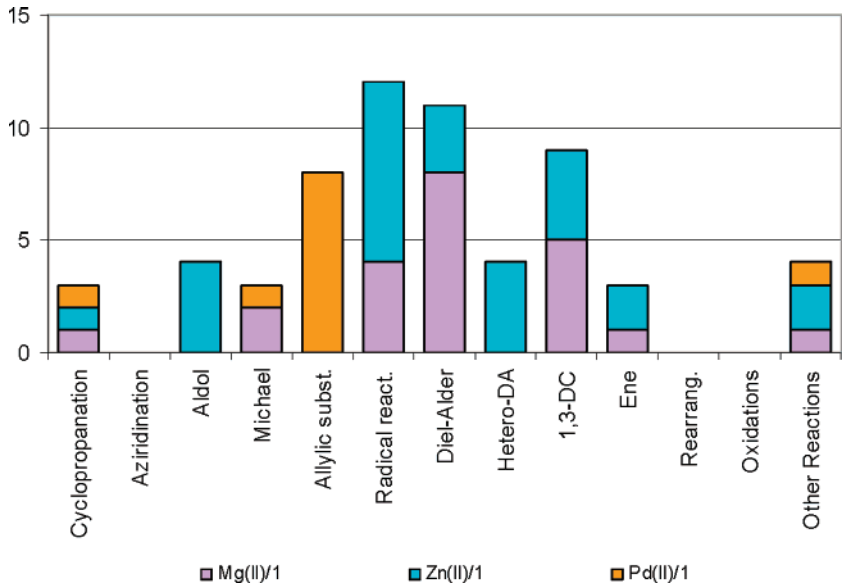


Figure 26. Types of enantioselective reactions catalyzed by complexes of **1** with Zn(II), Mg(II), and Pd(II).

Table 121. Effect of the Solvent on the Enantioselectivity of the Hetero Diels−Alder Reactions between 1,3-Cyclohexadiene and Ethyl Glyoxylate 85b[59]

	249 ee (%) and configuration	
solvent	[(*S*)-**1**/Cu(OTf)$_2$]	[(*S*)-**2**/Cu(OTf)$_2$]
$CHCl_3$	78 (*R*)	97 (*S*)
CH_2Cl_2	59 (*R*)	97 (*S*)
THF	47 (*R*)	99 (*S*)
$EtNO_2$	11 (*S*)	97 (*S*)
MeCN	60 (*S*)	

Whereas the reaction in $CHCl_3$, CH_2Cl_2, and THF shows opposite face selectivity when catalyzed by [(*S*)-**1**/Cu(OTf)$_2$] or [(*S*)-**2**/Cu(OTf)$_2$], in CH_3NO_2 the attack of the uncomplexed diene to the complexed α-oxoester occurs on the same face.

Under the above assumptions (with the exception of nine reactions run in Et_2O or THF and taken to broad the variety of reactions considered), all of the references dealing with reactions run with **85b,c** have been analyzed, and one significant example for each reaction and for each catalyst is reported in Table 122, together with the cations and anions used, the typical enantiomeric excesses obtained, and (the most important information) the face of attack under the previous assumptions.

About 50 reactions have been considered, and some specific results have been obtained:

•36 reactions have been catalyzed with (*S*)-**1** complexes, 42 with (*S*)-**2** complexes, of these 27 reactions have been catalyzed with both (*S*)-**1** and (*S*)-**2** complexes, which allows the derivation of a significant comparison between these two classes of catalysts;

•49 reactions have been run with Cu(II) as the Lewis acid, and two with Zn(II); hence the former seems to be the cation of choice for α-oxoesters;

Table 122. Face Selectivity of the Reactions with Glyoxylates 85b,c by (*S*)-1 and (*S*)-2 Box Complexes

				(*S*)-**1**		(*S*)-**2**		
entry	reaction	cation	anion	ee (%)	face	ee (%)	face	ref
1	aldol	Cu(II)	OTf	12	Re	90	Si	145
2[b]	aldol	Cu(II)	OTf			99	Si	144
3	Mukaiyama−aldol	Cu(II)	OTf	16	Re	49	Si	17
4	Mukaiyama−aldol	Cu(II)	OTf			98	Si	122
5	Mukaiyama−aldol	Cu(II)	OTf			98	Si	124
6	Mukaiyama−aldol	Cu(II)	OTf			97	Si	126
7	Mukaiyama−aldol	Cu(II)	OTf	43	Si	98	Si	127
8	Mukaiyama−aldol	Cu(II)	OTf	88	Re			283
9	Mukaiyama−aldol	Sn(II)	OTf	91	Si			122
10[a]	Friedel−Crafts	Cu(II)	OTf	42	Re	97	Si	161
11	Friedel−Crafts	Cu(II)	OTf	54	Re	80	Si	146
12	Friedel−Crafts	Cu(II)	OTf			93	Si	147
13	Mannich	Cu(II)	OTf	89	Si	33	Re	152a
14	Mannich	Cu(II)	OTf	56	Re	84	Si	153b
15[a]	Michael	Cu(II)	OTf			99	Si	147
16[a]	Michael	Cu(II)	OTf	77	Si	84	Si	160
17[b]	Michael	Cu(II)	Cl	40	Re	91	Re	24
18	hetero Diels−Alder	Cu(II)	OTf	94	Re	99	Si	58
19	hetero Diels−Alder	Cu(II)	OTf	59	Re	97	Si	59
20	hetero Diels−Alder	Cu(II)	OTf			97	Si	225
21	hetero Diels−Alder	Cu(II)	OTf	83	Re	85	Si	242
22	hetero Diels−Alder	Cu(II)	OTf	83	Re	85	Si	243
23	hetero Diels−Alder	Cu(II)	OTf	44	Si	17	Re	245
24	hetero Diels−Alder	Cu(II)	OTf	47	Re	85	Si	246
25	hetero Diels−Alder	Cu(II)	OTf	26	Re	92	Si	249
26	hetero Diels−Alder	Cu(II)	OTf			91	Si	250
27	hetero Diels−Alder	Cu(II)	OTf			99	Si	251
28	hetero Diels−Alder	Cu(II)	OTf	64	Re	96	Si	260
29	hetero Diels−Alder	Cu(II)	OTf	93	Re	99	Si	262
30	hetero Diels−Alder	Cu(II)	OTf	94	Re	99	Si	279
31[b]	hetero Diels−Alder	Cu(II)	OTf			99	Si	252
32[b]	hetero Diels−Alder	Cu(II)	OTf	94	Re	99	Si	261
33[a]	hetero Diels−Alder	Cu(II)	OTf	12	Re	99	Si	64
34	hetero Diels−Alder	Cu(II)	SbF_6	93	Re	93	Si	57
35	hetero Diels−Alder	Cu(II)	SbF_6			97	Si	247
36	hetero ene	Cu(II)	OTf	94	Re			56
37	hetero ene	Cu(II)	OTf	87	Re			57
38	hetero ene	Cu(II)	OTf	87	Re			278
39	hetero ene	Cu(II)	OTf	92	Re			280
40	hetero ene	Cu(II)	OTf	92	Re			281
41	hetero ene	Cu(II)	SbF_6			98	Si	56
42	hetero ene	Cu(II)	SbF_6			97	Si	57
43	hetero ene	Cu(II)	SbF_6			97	Si	278
44	hetero ene	Cu(II)	SbF_6	70	Re	96	Si	279
45	hetero ene	Cu(II)	SbF_6			98	Si	281
46	hetero ene	Cu(II)	SbF_6	90	Re			282
47	intramolecular hetero ene	Cu(II)	OTf	91	Re			288
48	aza-ene	Cu(II)	OTf	31	Si	73	Si	284
49	[2 + 2]-cycloaddition	Cu(II)	OTf	17	Re	69	Si	290
50	hetero Diels−Alder	Zn(II)	OTf	81	Re	23	Si	242
51	hetero Diels−Alder	Zn(II)	OTf	81	Re	23	Si	244

[a] Et_2O as the solvent. [b] THF as the solvent.

Table 123. Face Selectivity of the Reactions with β-Oxoesters Catalyzed by (*S*)-1 and (*S*)-2 Box Complexes

				(*S*)-**1**		(*S*)-**2**		
entry	reaction (β-oxoester)	cation	anion	ee (%)	face	ee (%)	face	ref
1	Mukaiyama−Michael(**153**)	Cu(II)	OTf	32	Si[a]	60	Si[a]	173
2	Mukaiyama−Michael (**153**)	Cu(II)	SbF_6			91	Si	62
3[b]	Mukaiyama−Michael (**153**)	Cu(II)	SbF_6	52	Re	93	Si	63
4	Friedel−Crafts(**153**)	Cu(II)	OTf			57	Re	163
5	Nazarov (**309**)	Cu(II)	SbF_6	86	Si	87	Si	296
6	Mannich (**140b**)	Cu(II)	OTf	68	Re	92	Re	153a
7	Mannich (**140b**)	Cu(II)	OTf	98	Re			154a
8[c]	chlorination (**140b**)	Cu(II)	OTf	32	Re	77	Si	316
9[c]	fluorination (**140b**)	Cu(II)	OTf	72	Re	20	Si	317
10	fluorination (**140b**)	Cu(II)	OTf	39	Si			318
11	fluorination (**140b**)	Ni(II)	ClO_4	71	Re			318
12	Mannich(**140c**)	Zn(II)	OTf	92	Re	12	Re	154b
13	intramolecular radical (**215**)	Mg(II)	ClO_4			71	Re	202
14	intramolecular radical (**217**)	Mg(II)	ClO_4			33	Re	203

[a] The face should be Re for priority reasons. [b] Toluene/CH_2Cl_2 3:1 as solvent. [c] Et_2O as solvent.

•several types of reactions (aldol, Mukaiyama−aldol, Friedel−Crafts, Mannich, Michael, hetero Diels−Alder, and hetero ene are the most significant ones) have been successfully performed.

The analysis of this large set of data gives some important information:

•in 37 of the 40 reactions catalyzed by [(*S*)-**2**/CuX_2] the nucleophile approaches the Si face of the complexed α-oxoester, independently of the reaction, the counterion, and the type of reagent;

•28 of the 34 reactions catalyzed by [(*S*)-**1**/CuX_2] occur with the attack on the Re face of the complexed α-oxoester, and three of the six exceptions were not run in CH_2Cl_2;

•20 of the 25 reactions catalyzed by both [(*S*)-**1**/CuX_2] and [(*S*)-**2**/CuX_2] give the attack of the nucleophile on opposite faces of **85b,c**; hence these catalysts with chiral ligands having the same configurations give opposite stereochemical outcomes;

•the few examples of hetero Diels−Alder reactions catalyzed by both [(*S*)-**1**/$Zn(OTf)_2$] and [(*S*)-**2**/$Zn(OTf)_2$] give the same opposite sense of induction observed for Cu(II) complexes, Re for the former complex, Si for the later one, the main difference between zinc and copper being the better enantiomeric excesses obtained with (*S*)-**1** when Zn(II) is the cation.

The second class of potentially bidentate reagents concerns β-oxoesters **140** and **153** (also in their variant allowing intramolecular reaction, e.g., **215** and **217**) as well as the corresponding β-ketophosphonates. Obviously, malonates were excluded from this investigation when these reagents are not involved in the coordination to the box catalyst but behave as attackers to the second coordinated reagent (e.g., the palladium-catalyzed allylic substitutions, Scheme 64). Again CH_2Cl_2 was the solvent of choice (with the exception of three reactions run either in diethyl ether or in toluene/CH_2Cl_2 in a ratio of 3:1). Fifteen reactions have been considered, and one significant example for each of them is reported in Table 123 with cations and anions, typical enantiomeric excesses obtained with the catalysts, and the faces of attack.

Of the 14 reactions considered:

•10 reactions have been catalyzed with (*S*)-**1** complexes, and 11 with (*S*)-**2** complexes, of these 7 reactions have been catalyzed with both (*S*)-**1** and (*S*)-**2** complexes;

•10 reactions have been run with Cu(II) as the Lewis acid, 2 with Mg(II) and 1 each with Ni(II) and Zn(II); again copper is the cation of choice for β-oxoesters;

•several types of reactions (chlorination, fluorination, Friedel−Crafts, Mannich, Mukaiyama−Michael, Nazarov, and intramolecular radical reactions) have been successfully performed.

The most relevant information deriving from this analysis is that:

•5 of the 8 reactions catalyzed by [(*S*)-**1**/CuX_2] occur with the attack on the Re face of the complexed β-oxoester, independent of the reaction and the type of reagent;

•6 of the 8 reactions catalyzed by [(*S*)-**2**/CuX_2] occur with the attack on the Si face of the complexed β-oxoester;

•in 3 of the 6 reactions catalyzed by both [(*S*)-**1**/CuX_2] and [(*S*)-**2**/CuX_2], the attack induces an opposite sense of induction (Re with the former catalyst, Si with the latter one);

•Mg(II), Ni(II), and Zn(II) complexes always give the same sense of induction, and the face of the attack is Re, independent of the type of box involved in the formation of the catalyst.

Even if the data in Table 123 do not allow an unambiguous prediction of the face selectivity, an interesting consideration can be derived from entries 2−3 of Table 123 (the reactions involving **153** as the β-oxoester). A rationalization of the Mukaiyama−Michael reaction between **153** and **86** has been reported on the basis of the crystal structure of the reaction complexes with [(*S*)-**1**/$Cu(SbF_6)_2$] (**19**) and [(*S*)-**2**/$Cu(SbF_6)_2$] (**20**) (Figure 12).[62,63] This favored the attack to the Re face of the former catalyst and to the Si face of the latter one (Figure 27). The above analysis rationalizes the sense of stereoinduction observed in the Mukaiyama−Michael reaction of the enamidomalonate in entries 1−3 but does not explain the stereoinduction observed in the Friedel−Crafts reaction with indole reported in entry 4.

The reader of this review became acquainted with the fact that 3-alkenoyl-2-oxazolidinones **163** are by far the most popular reagents tested with box catalysts in a variety of reactions. These reagents as well as the analogous 3-alkanoyl-derivatives **198** adopt a bidentate coordination; therefore an analysis of the enantioselective reactions catalyzed by the (*S*)-**1** and (*S*)-**2** complexes was undertaken. The reaction of **163** in the cisoid conformation was assumed, and again the exclusion of solvents other than CH_2Cl_2, even if, at least with (*S*)-**2** complexes with $Cu(OTf)_2$ or $Cu(SbF_6)_2$, the enantioselectivity of the reactions involving these reagents seems to be slightly affected by solvent.[60] The reactions involving **163** may occur either on its α,β-positions (Diels−Alder reactions and 1,3-dipolar cycloadditions), or in the

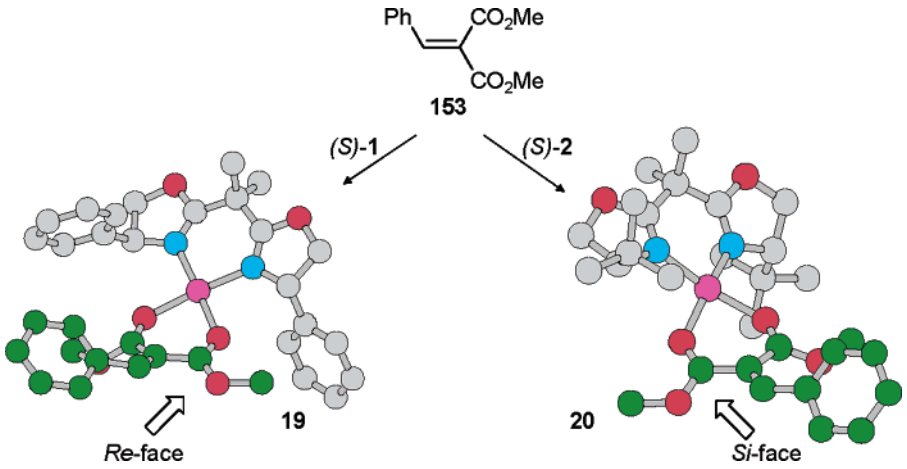
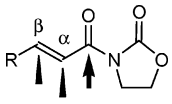


Figure 27. Reaction complexes between **153** and the Cu(II) complexes of (*S*)-**1** and (*S*)-**2** promoting opposite sense stereoinductions.

β-position (Mukaiyama−Michael and radical reactions) or even in the α-position of saturated **163** (radical additions). To have a homogeneus comparison between the stereochemical results of these substrates and those of the previously discussed ones, the preferred approached face is referred to the alkenoyl carbonyl group of complexed **163** (Scheme 188).

Scheme 188



163

If the Diels−Alder reaction with **163** is the benchmark of all catalysts, and therefore it is not unexpected that 35 different reactions have been found in the literature, 1,3-dipolar nitrone cycloadditions, Michael reactions in their different variants, and radical reactions led to a total of 68 different examples catalyzed by (*S*)-**1**- and (*S*)-**2**-based catalysts. In this large number of reactions three clusters can be detected, homogeneous with respect to the cation acting as the Lewis acid, Cu(II), Mg(II), Zn(II), and other divalent cations.

The cluster of 22 reactions characterized by Cu(II) is reported in Table 124 and consists of Diels−Alder cycloadditions and Mukaiyama−Michael reactions with three different counterions of Cu(II): ClO_4, SbF_6, and OTf. Twenty-one reactions are run with complexes of (*S*)-**2**, and the exception is to obtain an enantioselectivity lower than 95%. This is the clear demonstration that Cu(II), when coupled with (*S*)-**2,** gives a tailor-made catalyst for 3-alkenoyl-2-oxazolidinones **163**. This complex works nicely for Diels−Alder and Mukaiyama−Michael reactions, while its behavior in other reactions was rarely tested and is at the moment unknown. The reaction in entry 8 occurs with 6% ee, and the catalyst is [(*S*)-**2**/$Cu(ClO_4)_2$] prepared from hexahydrate salt; hence the anomalous result can be due to water that competes in the formation of the reaction intermediate. Molecular sieves do not influence enantioselectivity of the Mukaiyama−Michael reactions (Table 124, entries 19−21). Seven reactions are run with complexes of (*S*)-**1**, and the enantioselectivity is in general poor, except for the Diels−Alder reaction in entry 10, the only example where the favored approach is on the Re face instead the Si one.

The prominent feature derived from Table 124 is the sense of the stereoinduction. All reactions (21 reactions) catalyzed

Table 124. Face Selectivity of the Reactions with 3-Acyl-2-Oxazolidinones Catalyzed by (*S*)-1 and (*S*)-2 Cu(II) Complexes

					(*S*)-**1**		(*S*)-**2**		
entry	reaction	cation	anion	additive	ee (%)	face	ee (%)	face	ref
1	Diels−Alder	Cu(II)	OTf		30	Si			46
2	Diels−Alder	Cu(II)	OTf		30	Si	98	Si	60
3	Diels−Alder	Cu(II)	SbF_6				98	Si	60
4	Diels−Alder	Cu(II)	SbF_6				98	Si	120
5	Diels−Alder	Cu(II)	OTf		30	Si	98	Si	214
6	Diels−Alder	Cu(II)	SbF_6				93	Si	215
7	Diels−Alder	Cu(II)	OTf		22	Si	76	Si	218
8	Diels−Alder	Cu(II)	ClO_4	$6H_2O$	41	Si	6	Si	221
9	Diels−Alder	Cu(II)	OTf				99	Si	222
10	Diels−Alder	Cu(II)	OTf		89	Re	54	Si	224
11	Diels−Alder	Cu(II)	SbF_6				96	Si	225
12	Diels−Alder	Cu(II)	SbF_6				97	Si	226
13	Diels−Alder	Cu(II)	SbF_6				98	Si	227
14	Diels−Alder	Cu(II)	SbF_6				96	Si	228
15	intramolecular Diels−Alder	Cu(II)	SbF_6				92	Si	236
16	aza-Diels−Alder	Cu(II)	OTf				98	Si	265
17	Mukaiyama−Michael	Cu(II)	SbF_6		57	Si	89	Si	61
18	Mukaiyama−Michael	Cu(II)	SbF_6				97	Si	174
19	Mukaiyama−Michael	Cu(II)	OTf	HFIP, MS			95	Si	176a
20	Mukaiyama−Michael	Cu(II)	OTf	HFIP, MS			95	Si	176b
21	Mukaiyama−Michael	Cu(II)	OTf	HFIP, MS			95	Si	177

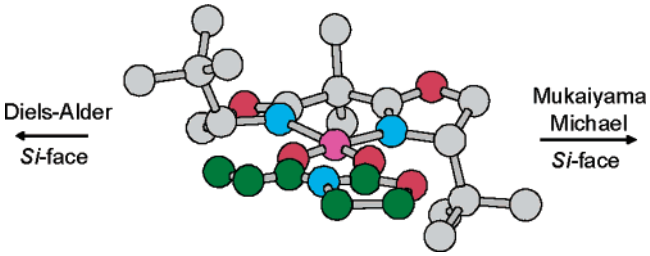


Figure 28. Reaction complexes of **163** and [(*S*)-**2**/CuX_2] promoting the Si sense of stereoinduction.

[(*S*)-**2**/CuX_2], independent of the counterion X, occur with the attack to the Si face. Six of the seven reactions catalyzed by [(*S*)-**1**/CuX_2] occur with the same sense of stereoinduction. If the Cu(II) complexes with box's have a distorted square-planar geometry, then the results with [(*S*)-**2**/CuX_2] can be rationalized assuming for both reactions the reaction intermediate illustrated in Figure 28. The stereoinduction given by [(*S*)-**1**/CuX_2] would not be supported by a reaction intermediate with the opposite tilt.[224]

The second cluster of 17 reactions, characterized by Mg(II) as the Lewis acid, is reported in Table 125 and consists of nitrone 1,3-dipolar cycloadditions, Diels−Alder reactions, and radical reactions with four different counterions: Br, I, ClO_4, and OTf. The main difference with Cu(II) is that 16 of the 17 reactions are run with complexes involving (*S*)-**1** and only 5 with those of (*S*)-**2**, which is an interesting ligand only in radical reaction catalysis**.** The sense of the stereoinduction is not constant (and this is the second difference with Cu(II)) and depends on two factors: type of anion and presence of additives. The effect of these variables is further complicated by the potential coordination ability of nitrone in 1,3-dipolar cycloadditions.

The nitrone 1,3-dipolar cycloadditions occur with attack to the Si face of the coordinated dipolarophile, independent of the anions (I, ClO_4, or OTf, Table 125, entries 1, 4, and 7). In the case of catalysts having iodide or perchlorate as counterions, the addition of water does not change this sense of induction (Table 125, entries 3 and 6), but the presence of MS reverses the stereochemical outcome (Table 125, entries 2 and 5). In the case of the catalyst having triflate as the counterion, the addition of either H_2O or MS determines the loss of any catalytic activity.[270]

The behavior of the Diels−Alder reaction is not the same. The use of different magnesium salts can deeply influence the stereochemical outcome since OTf and ClO_4 (without

Table 125. Face Selectivity of the Reactions with 3-Acyl-2-Oxazolidinones Catalyzed by (*S*)-1 and (*S*)-2 Mg(II) Complexes

				(*S*)-**1**		(*S*)-**2**		
entry	reaction	anion	additive	ee (%)	face	ee (%)	face	ref
1	nitrone 1,3-DC	I		46	Si			268, 269
2	nitrone 1,3-DC	I	MS	79	Re			268, 269
3	nitrone 1,3-DC	I	H_2O	50	Si			269
4	nitrone 1,3-DC	ClO_4		48	Si			270
5	nitrone 1,3-DC	ClO_4	MS	70	Re			270
6	nitrone 1,3-DC	ClO_4	H_2O	45	Si			270
7	nitrone 1,3-DC	OTf		86	Si			270
8	aza-Michael	Br		47	Si	14	Si	167
9	Diels−Alder	ClO_4		72	Re			77
10	Diels−Alder	ClO_4	MS	70	Re			77, 216, 217
11	Diels−Alder	ClO_4	H_2O	73	Si			216, 217
12	Diels−Alder	OTf		73	Si	racemate		218
13	Diels−Alder	OTf		88	Si			220
14	radical	I		68	Si	78	Si	15
15	radical	I		47	Si			29
16	radical	I		47	Si	61	Re	195
17	radical	I				93	Re	197

Table 126. Face Selectivity of the Reactions with 3-Acyl-2-Oxazolidinones Catalyzed by (*S*)-1 and (*S*)-2 Complexes of Zn(II) and Other Different Cations

					(*S*)-**1**		(*S*)-**2**		
entry	reaction	cation	anion	additive	ee (%)	face[a]	ee (%)	face	ref
1	nitrone 1,3-DC	Ni(II)	ClO_4[b]		74	Si			271
2	nitrone 1,3-DC	Ni(II)	ClO_4[b]	MS	85	Re			271
3	nitrone 1,3-DC	Mn(II)	ClO_4[b]		52	Si			271
4	nitrone 1,3-DC	Mn(II)	ClO_4[b]	MS	14[c]	Re			271
5	nitrone 1,3-DC	Co(II)	ClO_4[b]		47	Si			271
6	nitrone 1,3-DC	Co(II)	ClO_4[b]	MS	42[c]	Re			271
7	nitrone 1,3-DC	Zn(II)	ClO_4[b]	MS[d]	31	Re			77
8	Mukaiyama−Michael	Zn(II)	ClO_4	MS	31	Re			175
9	radical	Zn(II)	OTf		90	Re			15
10	radical	Zn(II)	OTf		50	Re	0		193
11	radical	Zn(II)	OTf		84	Re			194
12	radical	Zn(II)	OTf		61	Si	37	Re	195
13	Diels−Alder	Zn(II)	ClO_4[b]		20	Si			77
14	Diels−Alder	Zn(II)	ClO_4[b]	MS	73	Re			77
15	Diels−Alder	Zn(II)	SbF_6		92	Re			120
16	Diels−Alder	Fe(II)	Cl		80	Re			7
17	Diels−Alder	Ni(II)	ClO_4		52	Si			219

[a] Referred to the endo isomer. [b] The perchlorates were hexahydrates. [c] Enantiomeric excess of the endo isomer, the minor product. [d] Without MS only decomposition products were observed.

additives) give opposite senses of induction (Si the former, Re the latter, Table 125, entries 12 and 13 vs 9). The induction observed by using $Mg(ClO_4)_2$ does not depend on MS (Table 125, entries 9 and 10), whereas the addition of water reverses the sense of induction from Re to Si (Table 125, entry 11). The addition of water or MS to the $Mg(OTf)_2$-based catalyst does not influence either the catalytic activity or the stereochemical induction.

The rationalization of the different enantioselections induced by the counterion and by water in Diels−Alder reactions has already been illustrated in Figure 14 and can be assigned to the formation of different reaction complexes with tetrahedral or octahedral geometry.[216−218] A different mechanism could be responsible for the influence of MS on the absolute stereoselectivity of the 1,3-dipolar cycloaddition and could involve the participation of MS in the catalytic system, with the reaction intermediate bound to their surface.[268,269]

The last cluster of 17 reactions, characterized by Zn(II) and other bivalent cations acting as Lewis acids and with ClO_4, SbF_6, OTf, and Cl as counterions, is reported in Table 126. This cluster consists of nitrone 1,3-dipolar cycloadditions, Mukaiyama−Michael, radical, and Diels−Alder reactions, all run with (*S*)-**1** complexes, while (*S*)-**2** has only a very marginal use.

The most significant effect is shown in nitrone 1,3-dipolar cycloadditions where MS induce the change of the Si face selectivity into the opposite Re one with three different cations (Ni(II), Mn(II), and Co(II), as already evidenced for Mg(II) cation) (Table 126, entries 1−6). In general, Zn(II) favors the Re face selectivity, independent of the reaction and the counterion (Table 126, entries 7−15), and the best results are obtained in radical and Diels−Alder reactions (Table 126, entries 9, 11, and 15). For historical reasons the Re face selectivity induced by [(*S*)-**1**/$FeCl_2$] must be mentioned.

At least with 3-alkenoyl-2-oxazolidinones **163**, [(*S*)-**2**/CuX_2] is the steady catalyst that gives products in high enantiomeric excesses but with very few possibilities to change the canonical face selectivity deriving from the predictable distorted square-planar geometry. On the contrary, [(*S*)-**1**/MgX_2] is the sophisticated catalyst that gives products, perhaps in lower enantiomeric excesses, but with wide possibilities to influence the sense of the stereoinduction through a change of the anion or the addition of an achiral additive. The possibility to change the structure of the intermediate complex from tetrahedral to different octahedral geometries allows the opposite enantiomers to be obtained by using the same chirality source.

8. Conclusion

This review reports the history of box's since their invention in 1991 by Corey and Evans. The capacity of box's to behave as chiral ligands in the formation first of complexes with inorganic salts and then of reaction complexes makes these heterocyclic derivatives a precious source of catalysts whose versatility has been demonstrated in numerous catalytic asymmetric syntheses. A further reason for their success certainly derives from their simple preparation that has made available about 150 different structures, each of them tested in the enantioselective catalysis of organic reactions, and that will make new derivatives easily realizable.

Some questions concerning the mechanism of the chirality transfer from the catalyst to the product have been discussed and, hopefully, rationalized in the above sections, and this makes the box-based catalysts not only efficient but also clever *molecular robots*,[381] whose behavior can also be predicted.

In enantioselective catalysis with box complexes there are still unanswered questions, but given the spectacular development of the field, the authors are confident that these will be solved in the near future.

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