

Update 1 of: C₂-Symmetric Chiral Bis(oxazoline) Ligands in Asymmetric Catalysis

Giovanni Desimoni,^{*,†} Giuseppe Faita,[†] and Karl Anker Jørgensen^{*,‡}

[†]Department of Organic Chemistry, University of Pavia, Viale Taramelli 10, 27100 Pavia, Italy

[‡]Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

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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.^{1–3} 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 C₂-symmetric chiral ligand.

C₂-symmetric bis(oxazolines) (boxes) 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^{4,5} and in asymmetric catalysis.⁶ These particular ligands have two oxazoline rings separated by a spacer, and C₂-symmetric bis(oxazolines) having a single carbon atom with two identical substituents—different from hydrogen—as the spacer are the **focus** of this review. The **aim** is to cover all aspects of these box ligands, **except** those immobilized on heterogeneous media since **they have been covered in some recent reviews**.^{7,8}

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In 1991 two back-to-back communications appeared in *The Journal of the American Chemical Society*: one by Evans et al. **dealt with the** asymmetric cyclopropanation of alkenes⁹ and a **second** one by Corey et al. **that covered** enantioselective Diels–Alder reactions.¹⁰ **They reported the use of** 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 as 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. These communications also anticipated the usual research protocol to be ultimately used 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 FeCl₂/I₂]; (c) test 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 using chiral Lewis acid–box complexes will be followed in this review. **In the original review** the literature from 1991 to the spring of 2005 (ca. 400 papers) **was covered**. **In this update, a further 250 papers will be included to cover the latest developments up to the beginning of 2010.** The frequency of publications up to 2009 is shown in Figure 1.

2. SYNTHESSES OF BOX LIGANDS

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

- 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). **This is** the method followed by Evans and Corey in their pioneering work;
- the substitution of two hydrogen atoms with two identical groups on the spacer of a preformed box. **This protocol is** followed when the spacer requires substituents other than methyls. **This method** is based on the acidity of the

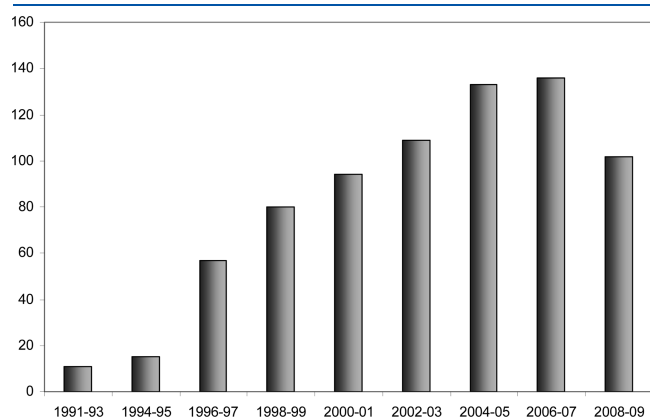
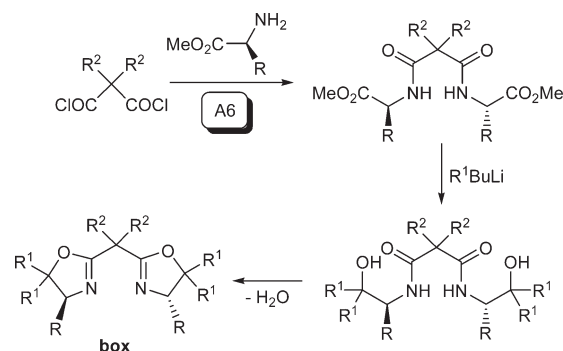
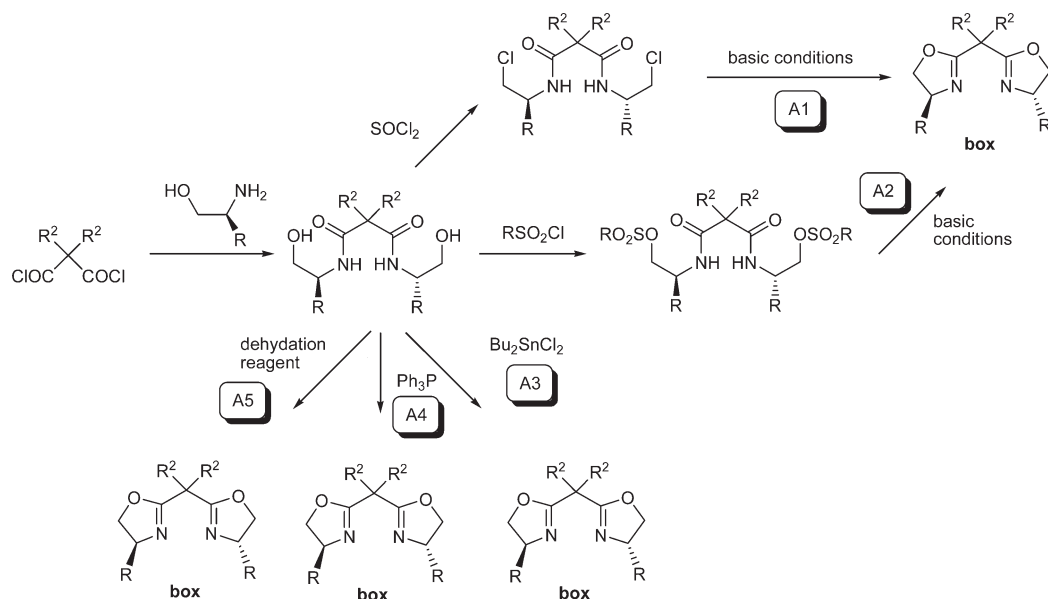


Figure 1. Number of papers dealing with C₂-symmetric chiral box ligands appearing in the literature **since 1991**.

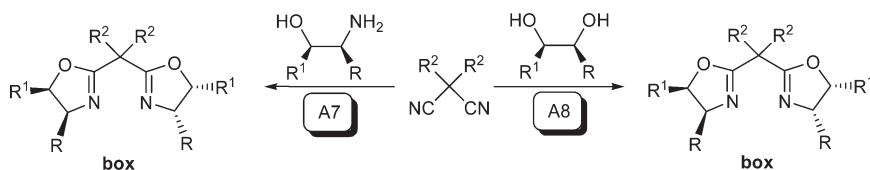
Scheme 2



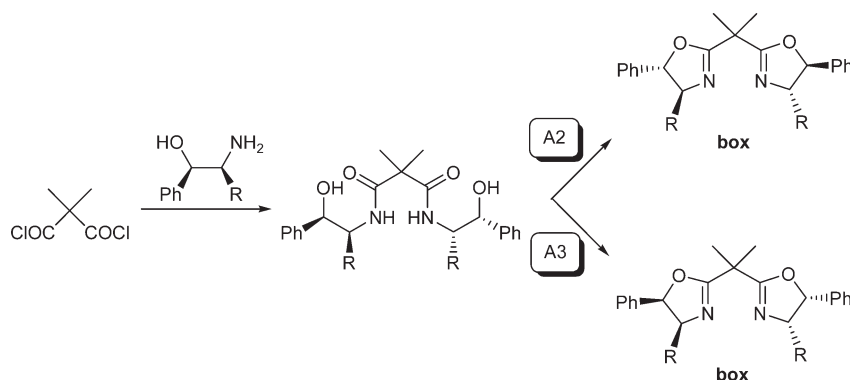
Scheme 1



Scheme 3



Scheme 4



methylene protons. This strategy consists of the formation of a dianion with 2 equiv of NaH or BuLi (rarely with Et₃N). There are three options for the dianion to react. It can lead to a nucleophilic substitution by reacting with 2 equiv of alkyl halide or can undergo a nucleophilic addition with suitable carbonyl compounds (B1). Alternatively the dianion can react with 1 equiv of alkyl dihalide to form a ring on the spacer (B2);

- (C) the modification of either the chiral groups on the oxazoline rings (C1) or the groups on the spacer (C2). The former is used to introduce heteroatoms sometimes useful as internal auxiliary ligands for increasing the standard bicoordination of the box ligand. In general, the latter is used to introduce functional groups suitable for grafting the box ligand to a solid surface.

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

Scheme 1 shows 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 in the classic approach to box synthesis, with several variants. Method A1 first used by Corey et al.¹⁰ consists of transformation with SOCl₂ into the bis-dichloride. Sometimes this occurs under more unusual conditions such as using undistilled acetyl chloride. By keeping it impure, the catalytic amount of hydrogen chloride necessary for the reaction is present.¹¹ Under different basic conditions, this is followed by cyclization to form the box. The hydroxy groups of the bis-amide can also be transformed using mesyl or tosyl chloride into good leaving groups suitable to give the box under basic conditions (method A2). The leaving group can also be a different halogen. In the synthesis of carbohydrate-based boxes, the anomeric thioethyl groups were activated with bromine or *N*-iodosuccinimide (NIS) and then cyclized either

under basic conditions or with a catalytic amount of trifluoromethanesulfonic acid.^{12,13}

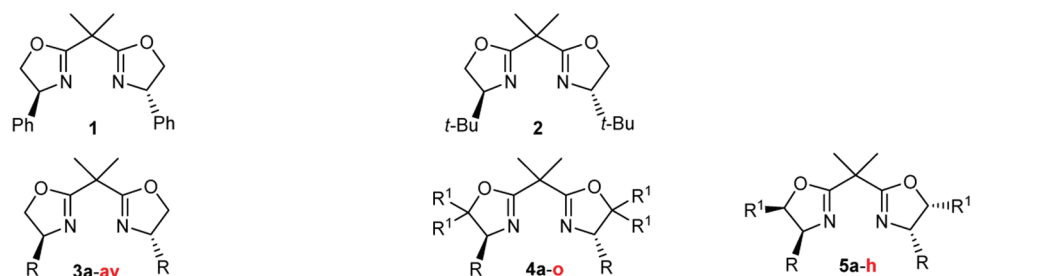
Sometimes other conditions can be used to cyclize the bis-amide (more or less easily), for example, with Bu₂SnCl₂ in refluxing xylene (the Masamune protocol)^{14,15} (method A3) or with Ph₃P/CCl₄/Et₃N (the conditions used by Evans et al.,^{9,16} method A4). The most direct method consists of the use of dehydration reagents (method A5): methanesulfonic acid in CH₂Cl₂, with CaH₂ or molecular sieves (MS) 4 Å, or SO₂Cl₂, or ZnCl₂, or Ti(OiPr)₄ in refluxing ClCH₂CH₂Cl or xylene, with continuous removal of H₂O. More sophisticated conditions using diethylaminosulfur trifluoride or methyl *N*-(triethylammonium sulfonyl)-carbamate (Burgess reagent), or with its poly(ethylene glycol) (PEG)-linked version, can also be used. Recently the ammonium salt (NH₄)₂MoO₄ was found to be an excellent cyclizing agent (as in method A5).^{17,18}

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 reacts with 4 equiv of an organolithium reagent and then under dehydrating conditions gives the expected box product (method A6, Scheme 2).

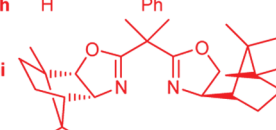
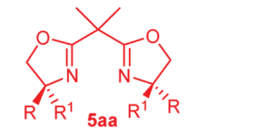
The second malonic acid derivative widely used in box synthesis is the symmetrically disubstituted malononitrile shown in Scheme 3. This can react with 2 equiv of an optically active β -amino alcohol (method A7) or a 1,2-diol (method A8). This approach is useful for making 4,5-disubstituted boxes. The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

The configuration of the substituents in a 4,5-disubstituted box is relevant and plays an important role in both the efficiency and the enantioselectivity induced in the catalyzed process. From this point of view methods A1 and A2 can be viewed as complementary to methods A3, A7, and A8. The bis-amides derived from dimethyl malondichloride and (1*S*,2*R*)-norephedrine (R = Me) or from

Chart 1

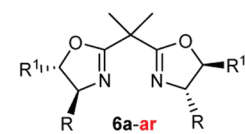


box	R	box	R	box	R	R ¹	box	R	R ¹
3a	Me	3y	2-Me-C ₆ H ₄	4a	<i>i</i> -Pr	Me	5a	Me	Ph
3b	Et	3z	2-OMe-C ₆ H ₄	4b	<i>i</i> -Pr	Ph	5b	Ph	Ph
3c	<i>i</i> -Pr	3aa	4-OMe-C ₆ H ₄	4c	<i>i</i> -Pr	4-tolyl	5c	Ph	Me
3d	CH ₂ Ph	3ab	4-Cl-C ₆ H ₄	4d	<i>i</i> -Pr	2-naphthyl	5d	Ph	CH ₂ OCHPh ₂
3e	CH ₂ CHMe ₂	3ac	2-OH-5- <i>t</i> -Bu-C ₆ H ₃	4e	<i>t</i> -Bu	Me	5e	4-Me-C ₆ H ₄	Me
3f	CH ₂ C ₆ H ₁₁	3ad	2-OMe-5- <i>t</i> -Bu-C ₆ H ₃	4f	<i>t</i> -Bu	4-tolyl	5f	4- <i>t</i> -Bu-C ₆ H ₄	Me
3g	(1-adamantyl)	3ae	2-(OCH ₂ CH ₂ Cl)-5- <i>t</i> -Bu-C ₆ H ₃	4g	Ph	Me	5g	2-naphthyl	2-naphthyl
3h	(1-naphthyl)	3af	2-OMe-5-Cl-C ₆ H ₃	4h	Ph	4-tolyl	5h	H	Ph
3i	(2-naphthyl)	3ag	CH ₂ -1-naphthyl	4i	CH ₂ Ph	4-tolyl			
3j	CH ₂ OH	3ah	CH ₂ -2-naphthyl	4j	CH ₂ Ph	2-naphthyl			
3k	CH ₂ OCOPh	3ai	9-anthryl	4k	CH ₂ OH	Me			
3l	CH ₂ OTBDPS	3aj	CH ₂ - <i>t</i> -Bu	4l	CH ₂ OCOPh	Me			
3m	CH(Me)OH ^{a,b}	3ak	CH(Me)Et ^a	4m	2-MeO-C ₆ H ₄	Me			
3n	CH(Me)OCOPh ^{a,b}	3al	CH(Me)Et ^a	4n	1-naphthyl	Me			
3o	CMe ₂ OSiMe ₃	3am	4-Br-C ₆ H ₄	4o	2-naphthyl	Me			
3p	CH ₂ SMe	3an	4-Ph-C ₆ H ₄						
3q	CH ₂ CH ₂ SMe	3ao	4- <i>t</i> -Bu-C ₆ H ₄						
3r	CMe ₂ SMe	3ap	4-CF ₃ -C ₆ H ₄						
3s	CH(Ph)OH ^a	3aq	3,4-(MeO) ₂ -C ₆ H ₃						
3t	CH(Ph)OMe ^a	3ar	2,4,6-(Me) ₃ -C ₆ H ₂						
3u	CH(Ph)OCH ₂ Ph ^a	3as	CH ₂ -NH-Ph						
3v	CH(Ph)OSiMe ₂ - <i>t</i> -Bu ^a	3at	CH ₂ -NH-(4-MeO-C ₆ H ₄)						
3w	CH(Ph)OCOMe ^a	3au	CH ₂ -NH-(3-CF ₃ -C ₆ H ₄)						
3x	CH(Ph)OCOPh ^a	3av	CH ₂ -P(O)Ph ₂						

box	R	R ¹
5aa	Ph	Me

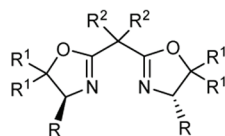
^a) Chiral substituent (S). ^b) Chiral substituent (R).



box	R	R ¹	box	R	R ¹
6a	Me	Ph	6z	Bn	Ph
6b	Ph	Ph	6aa	CH ₂ OTIPS	Ph
6c	Ph	CH ₂ OMe	6ab	4-(2-Me-C ₆ H ₄)C ₆ H ₄	CH ₂ OMe
6d	Ph	CH ₂ OCH ₂ Ph	6ac	4-Ph-C ₆ H ₄	CH ₂ OMe
6e	Ph	CH ₂ OCHPh ₂	6ad	4-Br-C ₆ H ₄	CH ₂ OMe
6f	Ph	CH ₂ OCPh ₃	6ae	4-(4-MeO-C ₆ H ₄)C ₆ H ₄	CH ₂ OMe
6g	Ph	CH ₂ OCH ₂ CH ₂ OMe	6af	4-(4-CF ₃ -C ₆ H ₄)C ₆ H ₄	CH ₂ OMe
6h	2,4,6-Me ₃ -C ₆ H ₂	CH ₂ OCHPh ₂	6ag	4-[2,6-(Me) ₂ -C ₆ H ₃]C ₆ H ₄	CH ₂ OMe
6i	1-naphthyl	CH ₂ OCHPh ₂	6ah	4-[2,6-(MeO) ₂ -C ₆ H ₃]C ₆ H ₄	CH ₂ OMe
6j	CH ₂ OCOAr ^a	Me	6ai	4-[3,5-(Me) ₂ -C ₆ H ₃]C ₆ H ₄	CH ₂ OMe
6k	CH ₂ OH	Ph	6aj	4-[3,5-(CF ₃) ₂ -C ₆ H ₃]C ₆ H ₄	CH ₂ OMe
6l	CH ₂ OMe	Ph	6ak	3,5-Ph ₂ -C ₆ H ₃	CH ₂ OMe
6m	CH ₂ OSiMe ₂ - <i>t</i> -Bu	Ph	6al	CO ₂ Me	Me
6n	CH ₂ OCOMe	Ph	6am	CH ₂ OH	Me
6o	CH ₂ OCOPh	Ph	6an	CH ₂ OMe	Me
6p	CH ₂ OCO-C ₆ H ₁₄ O ₃	Ph	6ao	CH ₂ OAc	Me
6q	CH ₂ OCODent1 ^b	Ph	6ap	CH ₂ OMs	Me
6r	CH ₂ OCODent2 ^b	Ph	6aq	CH ₂ NHMs	Me
6s	CH ₂ OCOCH(Me)NHAc ^c	Ph	6ar	CH ₂ NHTf	Me
6t	CH ₂ OCOCH(Me)NHBoc ^c	Ph			
6u	CH ₂ OCOCH(Me)NHTs ^c	Ph			
6v	CH ₂ OCOCH(<i>i</i> -Pr)NHCbz ^c	Ph			
6w	CH ₂ SMe	Ph			
6x	CH ₂ SPh	Ph			
6y	CH ₂ OH	4-SMe-C ₆ H ₄			

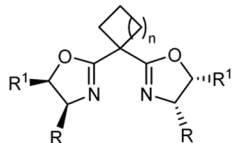
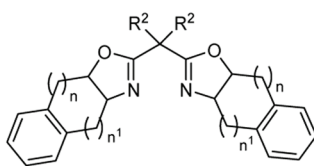
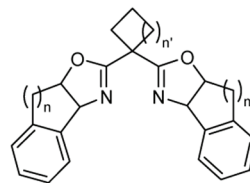
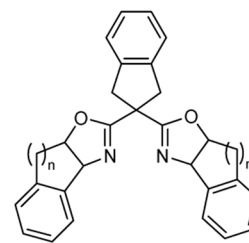
^a) Ar is 4-benzo-18-crown-6. ^b) Dent1 and Dent2 are dentritic substituents whose structure can be taken from the ref. ^c) Chiral substituent (S).

Chart 1. Continued

**7a-bc**

box	R	R ¹	R ²	box	R	R ¹	R ²
7a	<i>i</i> -Pr	H	Et	7ab	Ph	H	CH ₂ C ₆ H ₄ CH=CH ₂
7b	<i>i</i> -Bu	H	Et	7ac	<i>t</i> -Bu	H	CH ₂ C ₆ H ₄ CH=CH ₂
7c	<i>t</i> -Bu	H	Et	7ad	<i>t</i> -Bu	H	CH ₂ C ₆ H ₄ OH
7d	CH ₂ Ph	H	Et	7ae	<i>t</i> -Bu	H	CH ₂ C ₆ H ₄ OCH ₂ CH=CH ₂
7e	Ph	H	Et	7af	<i>t</i> -Bu	H	CH ₂ C ₆ H ₄ OCH ₂ Ar ^a
7f	C ₆ H ₄ -O(CH ₂) ₂ Br	H	Et	7ag	<i>i</i> -Pr	H	(CH ₂) ₃ C ₈ F ₁₇
7g	C ₆ H ₄ -O(CH ₂) ₃ Br	H	Et	7ah	<i>i</i> -Pr	H	(CH ₂) ₃ C ₁₀ F ₂₁
7h	C ₆ H ₄ -O(CH ₂) ₄ Br	H	Et	7ai	Ph	H	(CH ₂) ₃ C ₈ F ₁₇
7i	C ₆ H ₄ -O(CH ₂) ₅ Br	H	Et	7aj	Ph	H	(CH ₂) ₃ C ₁₀ F ₂₁
7j	C ₆ H ₄ -OCH ₂ Ph	H	Et	7ak	CH ₂ OH	H	(CH ₂) ₃ C ₈ F ₁₇
7k	CH ₂ C ₆ H ₄ -OCH ₂ Ph	H	Et	7al	CH ₂ OTBDMS	H	(CH ₂) ₃ C ₈ F ₁₇
7l	CMe ₂ Ph	H	Et	7am	<i>t</i> -Bu	H	CH ₂ C ₆ H ₄ O(CH ₂) ₃ C ₈ F ₁₇
7m	CMePh ₂	H	Et	7an	Ph	H	(CH ₂) ₆ OTBMS
7n	CPh ₃	H	Et	7ao	<i>i</i> -Pr	H	Ph
7o	<i>i</i> -Pr	Me	Et	7ap	<i>i</i> -Pr	H	CH ₂ -(2-naphthyl)
7p	<i>t</i> -Bu	H	<i>i</i> -Pr	7aq	<i>i</i> -Pr	H	CH ₂ -(2-pyridyl)
7q	<i>t</i> -Bu	H	<i>i</i> -Bu	7ar	<i>i</i> -Pr	H	CH ₂ -(3-pyridyl)
7r	CMePh ₂	H	<i>i</i> -Bu	7as	<i>i</i> -Pr	H	CH ₂ -(4-pyridyl)
7s	<i>i</i> -Pr	H	CH ₂ Ph	7at	Bn	H	Bn
7t	<i>t</i> -Bu	H	CH ₂ Ph	7au	<i>sec</i> -Bu	H	Et
7u	Ph	H	CH ₂ Ph	7av	<i>t</i> -Bu	H	Ph
7v	Ph	H	CH ₂ CH=CH ₂	7aw	<i>t</i> -Bu	H	CH ₂ OH
7w	<i>t</i> -Bu	H	CH ₂ CH=CH ₂	7ax	<i>t</i> -Bu	H	CH ₂ OCONH(CH ₂) ₃ -Si(OEt) ₃
7x	Bn	H	CH ₂ CH=CH ₂	7ay	<i>t</i> -Bu	H	(CH ₂) ₃ -C ₈ F ₁₇
7y	<i>t</i> -Bu	H	CH ₂ C(Me)=CH ₂	7az	CH ₂ (4-OAllyl)C ₆ H ₄	H	(CH ₂) ₃ -C ₈ F ₁₇
7z	<i>t</i> -Bu	H	CH ₂ C(CH ₂) ₂ Me	7ba	CH ₂ (4-OH)C ₆ H ₄	H	(CH ₂) ₃ -C ₈ F ₁₇
7aa	<i>i</i> -Pr	H	C ₁₁ H ₂₃	7bb	CH ₂ (4-OCH ₂ -C ₇ F ₁₅)C ₆ H ₄	H	(CH ₂) ₃ -C ₈ F ₁₇
				7bc	C ₆ H ₄ -O(CH ₂) ₄ -OPh	H	Et

^a) Ar = 3,5-(C₈F₁₇)₂-C₆H₃

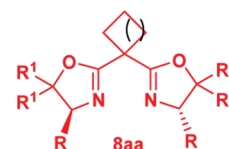
**8a-k****9a-i****10a-d****11a-b**

box	n	R	R ¹
8a	0	Ph	H
8b	0	<i>t</i> -Bu	H
8c	1	<i>t</i> -Bu	H
8d	2	<i>t</i> -Bu	H
8e	3	<i>t</i> -Bu	H
8f	0	Ph	Me
8g	0	Ph	Ph
8h	0	Bn	H
8i	1	Bn	H
8j	2	Bn	H
8k	3	Bn	H

box	R ²	n	n ¹
9a	Me	1	0
9b	Me	2	0
9c	CH ₂ Ph	1	0
9d	CH ₂ OH	1	0
9e	CH ₂ C ₆ H ₄ OH	1	0
9f	CH ₂ C ₆ H ₄ OCOt-Bu	1	0
9g	CH ₂ C ₆ H ₄ CH=CH ₂	1	0
9h	Me	0	1
9i	CH ₂ OCONH(CH ₂) ₃ Si(OEt) ₃	1	0

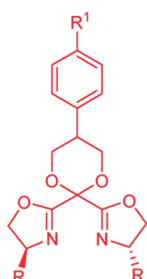
box	n	n ¹
10a	1	0
10b	1	1
10c	1	2
10d	1	3

box	n
11a	1
11b	2

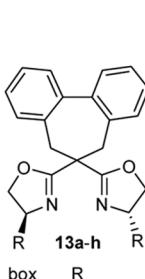


box	n	R	R ¹
8aa	0	(1-naphthyl)	H

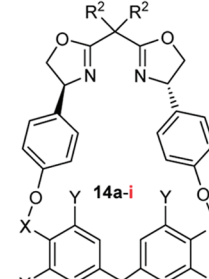
Chart 1. Continued



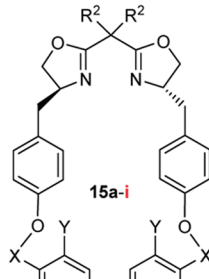
12aa-af



13a-h



14a-i



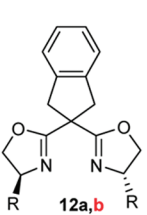
15a-i

box	R	R ¹
12aa	<i>i</i> -Pr	H
12ab	Bn	H
12ac	<i>t</i> -Bu	H
12ad	<i>t</i> -Bu	CH ₂ OTBDMS
12ae	<i>t</i> -Bu	CH ₂ OH
12af	<i>t</i> -Bu	CH ₂ OWang

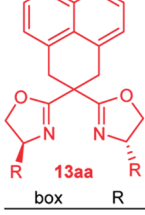
box	R
13a	Ph
13b	<i>i</i> -Pr
13c	CH ₂ CHMe ₂
13d	<i>t</i> -Bu
13e	CH ₂ Ph
13f	CO ₂ Me
13g	CMe ₂ OH
13h	CPh ₂ OH

box	R ²	X	Y	Z
14a	Et	(CH ₂) ₂ O	H	Me
14b	Et	(CH ₂) ₃ O	H	Me
14c	Et	(CH ₂) ₄ O	H	Me
14d	Et	(CH ₂) ₅ O	H	Me
14e	Et	CH ₂	H	H
14f	Et	(CH ₂) ₂ O	Me	Me
14g	Et	(CH ₂) ₃ O	Me	Me
14h	Et	(CH ₂) ₄ O	Me	Me
14i	Et	(CH ₂) ₅ O	Me	Me

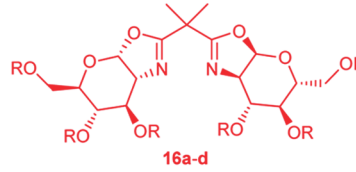
box	R ²	X	Y	Z
15a	Et	CH ₂	H	H
15b	Et	(CH ₂) ₂ O	H	Me
15c	Et	(CH ₂) ₃ O	H	Me
15d	Et	(CH ₂) ₂ O	Me	Me
15e	Et	(CH ₂) ₃ O	Me	Me
15f	Et	(CH ₂) ₄ O	H	Me
15g	Et	(CH ₂) ₅ O	H	Me
15h	Et	(CH ₂) ₄ O	Me	Me
15i	Et	(CH ₂) ₅ O	Me	Me



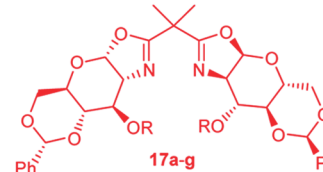
12a,b



13aa



16a-d



17a-g

box	R
12a	Ph
12b	Bn

box	R
13aa	Ph

box	R
16a	Ac
16b	H
16c	TMS
16d	Piv

box	R
17a	Bz
17b	Piv
17c	H
17d	Ac
17e	Me
17f	Bn
17g	TES

(1*S*,2*R*)-2-amino-1,2-diphenylethanol ($R = \text{Ph}$) (Scheme 4) can be stereodivergently cyclized, either under the Masamune conditions (method A3) with total retention of configuration giving *cis*-4,5-disubstituted boxes or through conversion into the mesylates and cyclization under basic conditions (method A2). The latter proceeds with complete inversion of configuration to give *trans*-4,5-disubstituted boxes.¹⁵

Using the methods A–C, more than 240 box ligands have been synthesized. Their attributes and their limitations are described in the Introduction. Their structures are listed in Chart 1 as well as the respective methods of preparation. Their resulting configurations are reported in Table 1.

3. STRUCTURE 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. This can spontaneously precipitate or be isolated by dilution with a less polar solvent. These chiral complexes are the precursors of the reacting intermediate involved in the catalytic cycle. Therefore, to try to understand the configuration of how the molecules involved in the reaction are arranged at the metal center, any information concerning

their structure is important. The reason is that this is the source of the chiral discrimination that produces the reaction stereoselectivity.

Isolation of these precursors is not essential for their success as enantioselective catalysts, and they can be efficiently prepared “in situ”. For this reason, it is not necessary to report their preparation protocol. Sometimes their structures can be investigated using spectroscopic methods, and depending on the metal involved in the complex, NMR spectroscopy might prove the best tool for these purposes. Furthermore, structures can be proposed on the basis of various types of calculations. In the following discussion, such data will be mentioned only in the specific sections when their contribution significantly contributes to 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 not only about the coordination number but also about the nature of any ligand(s), other than the box ligands, at the cation. The resulting data allow one to propose reasonable models for the reacting intermediate participating in the catalytic process.

Table 2 shows the X-ray crystal structures, as well as their most significant structural properties, of the box ligands reported in

Table 1. Syntheses of Box Ligands

<i>n</i>	box	conf. ^a	method	yield (%)	ref	<i>n</i>	box	conf. ^a	method	yield (%)	ref
1	1	S	A1	76	10	122	7j	R	A1	<i>b</i>	59a, 59b
2	2	S	A4	60	9, 16	123	7k	S	A1	<i>b</i>	59a, 59b
3	2	S	A2	72	19	124	7l	S	A2	62	40, 56
4	2	S	C2	43	22	125	7m	S	A2	83	40, 56
5	3a	S	A7	33	20	126	7n	S	A1	54	40, 56
6	3c	S	<i>b</i>	<i>b</i>	10	127	7o	S	A5	61	57
7	3d	R	A1	43	21	128	7p	S	B2	35	22
8	3e	S	A1	46	23	129	7q	S	A2	59	40, 56
9	3g	R	A1	70	24	130	7r	S	A2	35	60
10	3h	S	A2	60	25	131	7t	S	B1	76	60
11	3i	S	A1	39	26	132	7u	S	B1	88	60
12	3i	R	A1	39	26	133	7v	S	B1	85	60
13	3j	S	C1	97	27	134	7w	S	B1	79	60
14	3k	R	A1	65	27	135	7x	S	B1	87	60
15	3l	S	A2	64	28	136	7y	S	B1	<i>b</i>	22
16	3m	R	C1	88	27	137	7z	S	B1	80	22
17	3n	R	A1	78	27	138	7aa	S	B1	40	61
18	3o	R	A4	28	29	139	7ab	S	B1	<i>b</i>	60
19	3p	S	A7	38	30	140	7ac	S	B1	<i>b</i>	60
20	3p	S	A2	41	28	141	7ad	S	B1	<i>b</i>	62
21	3q	S	A7	74	30	142	7ae	S	C2	94	62
22	3q	R	A2	39	28	143	7af	S	B1	74	62
23	3r	S	A2	66	28	144	7ag	S	B1	37	61
24	3s	S	C1	76	31	145	7ah	S	B1	62	61
25	3t	S	C1	83	31	146	7ai	S	B1	49	61
26	3u	S	C1	72	31	147	7aj	S	B1	46	61
27	3v	S	C1	95	31	148	7ak	S	B1,C1	34	61
28	3w	S	A1	82	31	149	7al	R	B1	24	61
29	3x	S	A1	82	31	150	7am	S	C2	56	63
30	3z	S	A2	66	32	151	7an	S	B1	34	78
31	3ac	S	A2,C1	61	32	152	7ao	S	A5	96	64
32	3ad	S	A2	66	32	153	7ap	S	B1	55	65
33	3ae	S	A2	64	32	154	7aq	S	B1	69	65
34	3af	R	A2	65	32	155	7ar	S	B1	34	65
35	3ai	S	A5	93	33	156	7as	S	B1	48	65
36	3aj	S	<i>b</i>	<i>b</i>	34	157	7at	S	A2	75	66
37	3ak	S	<i>b</i>	<i>b</i>	34	158	7au	S	A2	78	66
38	3al	R	<i>b</i>	<i>b</i>	34	159	7av	S	A5	96	64
39	3am	S	A5	70	35a	160	7aw	S	B1	72	67
40	3an	S	C1	65	35a	161	7ax	S	C1	<i>b</i>	67
41	3ao	S	A3	<i>b</i>	36	162	7ay	S	B1	64	68
42	3ap	R	A3	<i>b</i>	36	163	7az	S	B1	57	69
43	3aq	R	A3	<i>b</i>	37	164	7ba	S	C1	72	69
44	3ar	S	A3	<i>b</i>	37	165	7bb	1S	C1	66	69
45	3as	R	A7	29	38	166	7bc	R	A1	55	70
46	3at	R	A7	59	38	167	8a	S	B2	48	45
47	3au	R	A7	51	38	168	8b	S	B2	25	22, 23
48	3av	S	A7	96	39	169	8b	S	A5	49	71a
49	4a	S	A5,A6	50	40	170	8c	S	B2	46	22
50	4c	S	A5	<i>b</i>	41	171	8d	S	B2	72	22
51	4d	S	A5	<i>b</i>	41	172	8e	S	B2	56	22
52	4f	S	A5	<i>b</i>	41	173	8f	S,R	B2	50	45
53	4g	S	A5	76	42	174	8g	R,S	B2	23	72
54	4h	S	A5	<i>b</i>	41	175	8h	S	A2	73	66
55	4i	S	A5	<i>b</i>	41	176	8i	S	A2	78	66
56	4j	S	A5	<i>b</i>	41	177	8j	S	A2	81	66
57	4k	R	C1	96	27	178	8k	S	A2	80	66
58	4l	R	A5	69	27	179	8aa	R	A5	72	71b
59	4m	R	A5	88	43	180	9a	S,R	A8	30	73
60	4n	R	A5	83	43	181	9a	S,R	B1	56	45, 74, 75
61	4o	R	A5	77	43	182	9b	S,R	B1	56–72	74
62	5a	R,S	A3	57	15	183	9c	S,R	B1	82	76
63	5b	R,S	B1	<i>b</i>	44	184	9d	R,S	B1	80	77
64	5b	R,S	A3	74	15	185	9e	S,R	C2	100	76
65	5c	S,R	B1	62	45	186	9f	S,R	B1	77	76
66	5e	S,R	C2	<i>b</i>	46	187	9g	S,R	B1	<i>b</i>	60
67	5f	S,R	C2	<i>b</i>	46	188	9h	R,S	A7	72	79
68	5g	S,R	A3	72	36	189	9i	S	C2	85	80

Table 1. Continued

<i>n</i>	box	conf. ^a	method	yield (%)	ref	<i>n</i>	box	conf. ^a	method	yield (%)	ref
69	5h	R	A7	83	47a	190	10a	S,R	B2	50–70	45, 81
70	5i	R,S	b	b	34	191	10b	S,R	B2	50–70	45, 81
71	5aa	S	A7	b	47b	192	10c	S,R	B2	50–70	45, 81
72	6a	R,R	A2	63	15	193	10d	S,R	B2	50–70	81
73	6b	R,R	A2	84	15	194	11a	S,R	B2	56–72	74
74	6c	R,S	A1	87	48	195	11b	S,R	B2	56–72	74
75	6d	R,S	A1	77	48	196	12a	S	B2	56–72	74
76	6e	R,S	A1	88	48	197	12b	S	A2	51	66
77	6f	R,S	A1	95	48	198	12aa	S	A5	90	82
78	6g	R,S	A1	72	48	199	12ab	S	A5	80	82
79	6h	R,S	A1	95	48	200	12ac	S	A5	95	82
80	6i	R,S	A1	93	48	201	12ad	S	A5	88	82
81	6j	R,R	C1	11	49	202	12ae	S	C2	91	82
82	6k	S,S	A7	51	30, 50	203	12af	S	C2	b	82
83	6m	S,S	b	b	51	204	13a	R	A2	59	83
84	6n	S,S	C1	98	50	205	13a	S	A2	55	83
85	6o	S,S	C1	100	52	206	13b	S	A2	50	83
86	6p	S,S	C1	63	52	207	13c	S	A2	55	83
87	6q	S,S	C1	44	52	208	13d	S	A2	60	84
88	6r	S,S	C1	24	52	209	13e	S	A2	50	83
89	6s	S,S	C1	78	50	210	13f	S	A5	63	84
90	6t	S,S	C1	96	50	211	13g	S	C1	75	84
91	6u	S,S	b	b	50, 53	212	13h	S	C1	71	84
92	6v	S,S	C1	86	50	213	13aa	R	B2	82	85
93	6w	R,S	C1	89	30	214	14a	R	A1,C1	29	59
94	6x	R,S	C1	47	30	215	14b	R	A1,C1	27	59
95	6z	S,S	A2	86	54	216	14c	R	A1,C1	49	59
96	6aa	S,S	C1	85	55	217	14d	R	A1,C1	25	59
97	6ab	R,S	C1	61	35a	218	14e	R	A1	73	70
98	6ac	R,S	C1	77	35a	219	14f	R	A1	14	70
99	6ad	R,S	A5	87	35a	220	14g	R	A1	32	70
100	6ae	R,S	C1	69	35a	221	14h	R	A1	40	70
101	6af	R,S	C1	52	35a	222	14i	R	A1	32	70
102	6ag	R,S	C1	67	35a	223	15a	S	A1	b	86
103	6ah	R,S	C1	94	35a	224	15b	S	A1	b	86
104	6ai	R,S	C1	71	35a	225	15c	S	A1	b	86
105	6aj	R,S	C1	76	35a	226	15d	S	A1	b	86
106	6ak	R,S	A2	48	35b	227	15e	S	A1	b	86
107	6al	R,R	A5	69	18a, 18b	228	15f	S	A1	50	70
108	6am	R,R	C1	65	18b	229	15g	S	A1	43	70
109	6an	R,R	C1	28	18b	230	15h	S	A1	37	70
110	6ao	R,R	C1	93	18b	231	15i	S	A1	41	70
111	6ap	R,R	C1	76	18b	232	16a	R,R	A1	94	11
112	6aq	R,R	C1	64	18b	233	16b	R,R	C1	quant.	13
113	6ar	R,R	C1	21	18b	234	16c	R,R	C1	74	13
114	7a	S	A2	83	40, 56, 57	235	16d	R,R	A2	60	13
115	7c	S	A2	74	40, 56, 57	236	17a	R,R	A2	84	13
116	7d	S	A2	76	40, 56, 57	237	17b	R,R	A2	82	13
117	7e	R	A1	b	58	238	17c	R,R	C1	80	13
118	7f	R	A1	b	59a	239	17d	R,R	A2	92	12
119	7g	R	A1	b	59a	240	17e	R,R	A2	85	12
120	7h	R	A1	b	59a	241	17f	R,R	A2	66	12
121	7i	R	A1	b	59a	242	17g	R,R	A2	71	12

^a Configuration refers to position 4 or to positions 4,5 of the oxazoline ring. ^b Not reported, as well as other physicochemical data of the box.

this review. For some of them, in particular those that may be useful models of the reacting intermediates in important enantioselective catalytic processes, we also report a homogeneous representation of the crystal structure based on the atomic coordinates. This information gives an immediate picture of the metal center coordination and the position of the chiral ligand in the complex or the anions. It also informs on the auxiliary ligands that can be replaced by at least one of the reagents to give rise to the reacting intermediate. For this reason, we always represent the cation and the box in the traditional color (oxygen as red; nitrogen as blue; the metal as violet). All the anion and auxiliary ligand atoms (except H₂O) are yellow. If an

organic molecule which is involved in the catalytic process is present in the crystal structure, then its carbon atoms will be represented by green. As far as possible, the other atoms are in their traditional colors. With few exceptions, a box with one carbon atom as the spacer generally behaves as a bidentate ligand through its nitrogen atoms.

Complexes with Box as a Monodentate Ligand

The crystal structures of {Ag[(S)-1]OTf(0.5 H₂O)} and {Ag[(S)-3d]OTf} (Table 2, entries 1 and 2, respectively) show both boxes behaving as monodentate ligands.⁸⁷ The silver cation coordinates to two nitrogen atoms from two different boxes.

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

entry	no.	metal	box	anion	further ligands	coord.	structure	ref
1		Ag(I)	(S)-1 ^a	OTf	0.5H ₂ O	single strand	zigzag conformation	87
2		Ag(I)	(S)-3d ^a	OTf		single strand	helical	87
3		Cu(I)	(S)-2 ^a	OTf		single strand	helical	16
4		Au(III)	(R)-3d	Cl	<i>b</i>	4	square-planar	88
5		Cu(II)	(S)-1	Cl		4	distorted square-planar	92
6	18	Cu(II)	(S)-1	Br		4	distorted square-planar	92
7	19	Cu(II)	(S)-1	SbF ₆	2H ₂ O	4	distorted square-planar	89–91
8	20	Cu(II)	(S)-2	SbF ₆	2H ₂ O	4	distorted square-planar	19, 89–91, 93, 94
9	21	Cu(II)	(S)-1	SbF ₆	BM ^c	4	distorted square-planar	96
10	22	Cu(II)	(S)-2	SbF ₆	BM ^c	4	distorted square-planar	95, 96
11		Cu(II)	(S)-2	SbF ₆	EM ^d	4	distorted square-planar	96
12		Cu(II)	(S)-2	Cl	-	4	distorted square-planar	92, 93
13	23	Cu(II)	(S)-2	Br		4	distorted square-planar	92
14		Cu(II)	(S)-2	OTf	2H ₂ O	5	distort square-pyramid	89–91
15	24	Cu(II)	(S)-2	OTf	DOBET ^e	5	distort square-pyramid	97
16		Cu(II)	(S)-3c	SbF ₆	2H ₂ O	4	distorted square-planar	89–91
17		Cu(II)	(S)-3h	Cl		4	distorted square-planar	33
18		Cu(II)	(S)-3i	Cl		4	distorted square-planar	33
19		Cu(II)	(S)-3af	Cl		4	distorted square-planar	98
20		Cu(II)	(S)-3an	Cl		4	distorted square-planar	35a
21		Cu(II)	(R,S)-5b	OTf	H ₂ O	6	octahedral	96
22	25	Cu(II)	(S,S)-6aa	OTf	H ₂ O	5	square-pyramid	55
23		Cu(II)	(S,S)-6aa	OTf ^f	53 (R = H), H ₂ O	5	square-pyramid	55
26		Cu(II)	(S)-7aq	OAc		6	distorted octahedral	65
27		Cu(II)	(R,S)-9a	OAc		4	distorted square-planar	100
28		Cu(II)	(S,R)-9a	Cl		4	distorted square-planar	92
29		Cu(II)	(S,R)-9a	Br		4	distorted square-planar	92
30		Cu(II)	(S)-3q	Cl		5	trigonal bipyramid	28
31		Cu(II)	(S)-3q	OTf		6	octahedral	28
32		Cu(II)	(S)-3r	OTf		5	trigonal bipyramid	28
33		Zn(II)	(S)-1	Cl		4	tetrahedral	92
34		Zn(II)	(S)-2	Cl		4	tetrahedral	92
35	26	Zn(II)	(S)-2	OTf	2H ₂ O	4	distort trigonal-bipyramid	101
36		Ni(II)	(S)-2	Cl		4	tetrahedral	102
37		Ni(II)	(S)-2	OTf	2H ₂ O	5	square-pyramid	102
38		Ni(II)	(S)-2	OTf		4	tetrahedral dimer	102
39		Fe(II)	(S)-2	Cl		4	distorted tetrahedral	103
40		Fe(II)	(S)-2	TMSCH ₂		4	distorted tetrahedral	103
41		W(0)	(S)-2		4CO	6	octahedral	104
42		W(0)	(S)-3c		4CO	6	octahedral	105
43		Rh(II)	(S)-3c	Cl	C ₅ Me ₅	4	distorted tetrahedral	106
44		Ru(II)	(S)-1	Cl	terpyridine	6	octahedral	107
45		Ru(II)	(R)-1	Cl	H ₂ O	4	distorted tetrahedral	108
46		Ru(II)	(R)-1	Cl	MeNH ₂	4	distorted tetrahedral	108
47		Ru(II)	(R)-1		Ph(CH ₂) ₃ O	4	distorted tetrahedral	109, 110
48		Ru(II)	(S)-3c	SbF ₆	mesityl, H ₂ O	4	distorted tetrahedral	111
49		Pd(II)	(S)-1	OTf		4	square-planar	36
50		Pd(II)	(S)-3c	Me, Cl		4	pseudosquare-planar	112
51		Pd(II)	(R)-3d	PF ₆	allyl	4	pseudosquare-planar	21, 51
52	27	Pd(II)	(R)-3d	PF ₆	1,3-diPhall ^g	4	pseudosquare-planar	21, 51
53		Pd(II)	(S)-3s	BF ₄	1,3-diPhall ^g	4	pseudosquare-planar	113
54		Pd(II)	(S)-3t	BF ₄	1,3-diPhall ^g	4	pseudosquare-planar	113
55		Pd(II)	(R)-7e	OTf		4	square-planar	36
56	28	Zn(II)	(S)-1 + (R)-1 ^h	ClO ₄		4	tetrahedral	114

^a Box as monodentate ligand. ^b SbF₆ as noncoordinating anion. ^c BM = benzylidene dimethylmalonate. ^d EM = ethylidene dimethylmalonate. ^e DOBET = 2,4-dioxobutanoic acid ethylester. ^f Noncoordinating anion. ^g 1,3-diPhall = 1,3-diphenylallyl. ^h Racemic complex with two box enantiomers.

This gives rise to single-stranded polymers. They have an infinite single-stranded helical coordination, 2-fold symmetry, left-handed helicity, and an infinite single strand with a zigzag conformation. A somewhat similar complex was obtained from (S)-2 and CuOTf·0.5C₆H₆ (Table 2, entry 3).¹⁶ The X-ray analysis shows a single-stranded helical polymeric structure with

3-fold symmetry and the box occupying a bridging position between two nearly linear bicoordinated Cu(I) ions.

In general, when boxes are involved in the formation of an optically active catalyst in which both nitrogen atoms coordinate to the same cation, it leads to rigid supramolecular devices that are capable of discriminating the diastereofaces of the coordinated

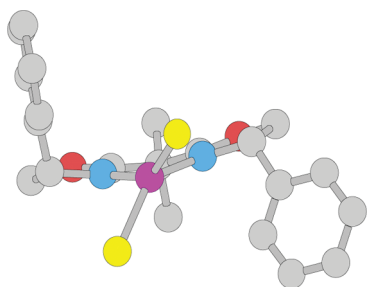


Figure 2. Molecular structure of [(S)-1·CuBr₂] (18) (ref 92).

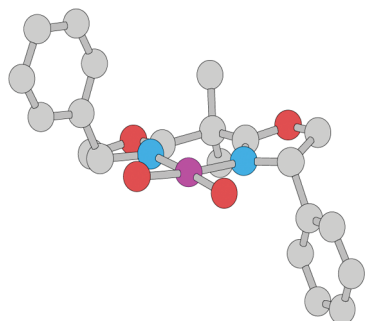


Figure 3. Molecular structure of [(S)-1·Cu(SbF₆)₂·2H₂O] (19) (refs 89–91).

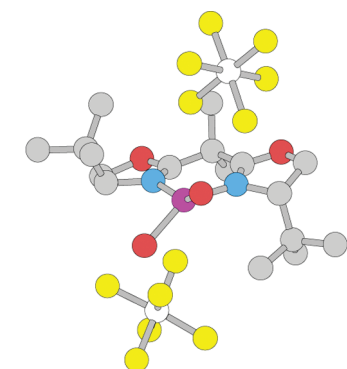


Figure 4. Molecular structure of [(S)-2·Cu(SbF₆)₂·2H₂O] (20) (refs 19, 89–91, 93, and 94).

reagent in an efficient manner. This discrimination is much more difficult to realize when the box behaves as a monodentate ligand. Compared to boxes acting as bidentate ligands attached to one metal center, these complexes have not proved 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 the N–H bonds of amines. In addition, the Cu(I) complex is an excellent enantioselective catalyst for the cyclopropanation of alkenes (vide infra).

Complexes with a Single Box as the Bidentate Ligand

This type of complex is by far the most popular in asymmetric catalysis. Several “new entries” have been reported in the recent literature. Among them of note is the [AuCl₃/(R)-3d] complex (Table 2, entry 4),⁸⁸ because this cation has recently assumed an important position among the new catalysts. Certainly Cu(II) is the leading cation in crystal structures involving box ligands

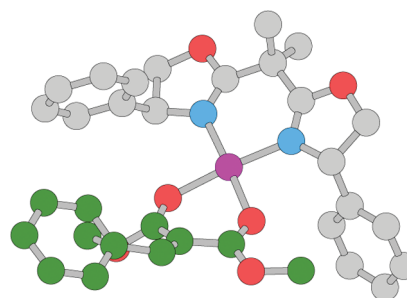


Figure 5. Molecular structure of [(S)-1·Cu(SbF₆)₂·PhCH=C(CO₂Me)₂] (21) (refs 95 and 96).

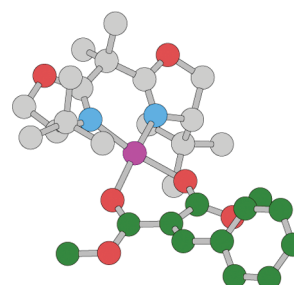


Figure 6. Molecular structure of [(S)-2·Cu(SbF₆)₂·PhCH=C(CO₂Me)₂] (22) (refs 95 and 96).

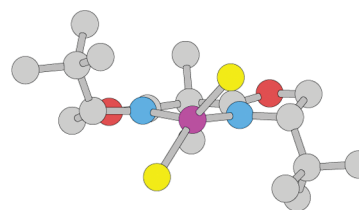


Figure 7. Molecular structure of [(S)-2·CuBr₂] (23) (ref 92).

(Table 2, entries 5–32). For boxes 1 and 2, the usual coordination number is four and is derived from a distorted square-planar coordination. However, this number may be expanded to five (the structure becomes a distorted square pyramid) when the counterion is triflate. This highlights the importance not only of the cation but also of the anion in the formation of the reacting intermediate, which is, of course, the chiral messenger in the reaction.

Cu(II) complexes with (S)-1 (Table 2, entries 5–7) are known to form with SbF₆, Cl, and Br. However, the ligands involved in the distorted square planar are two H₂O, Cl, and Br, respectively, since SbF₆ does not enter into the coordination sphere.^{89–92} 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 6, 18, Figure 2),⁹² the distortions from square planarity are large and nearly equal. The anions occupy the quadrants that are free from the substituents. The hydrated complex is more planar (Table 2, entry 7, 19, Figure 3).^{89–91} The O–Cu–N–C dihedral angles, which are -11.3° and -7.2° , are reversed due to the distortion of the H₂O molecules. This marks how far H₂O is from the oxazoline plane. The ligands are oriented toward the oxazoline phenyl substituents.

Cu(II) complexes with (S)-2 (Table 2, entries 8 and 10–15) have been studied in detail, and it was established that the counterion is of leading importance for the coordination number. The SbF₆ complex (Table 2, entry 8, 20, Figure 4) has a distorted

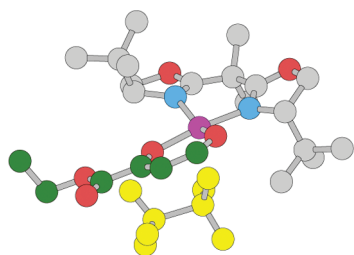


Figure 8. Molecular structure of $[(S)\text{-}2\cdot\text{Cu}(\text{OTf})_2\cdot\text{HCOCH}_2\text{CO}_2\text{Et}]$ (**24**) (ref 97).

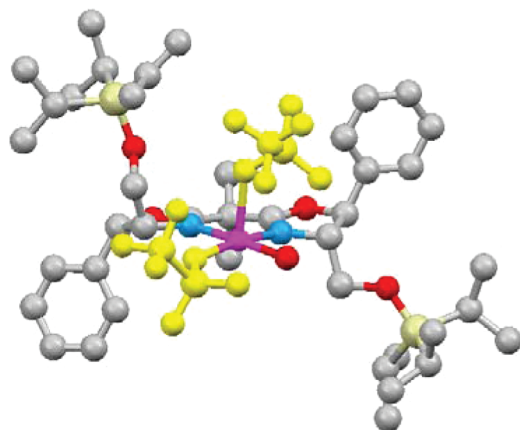


Figure 9. Molecular structure of $[(S)\text{-}6\text{aa}\cdot\text{Cu}(\text{OTf})_2\cdot\text{H}_2\text{O}]$ (**25**) (ref 55).

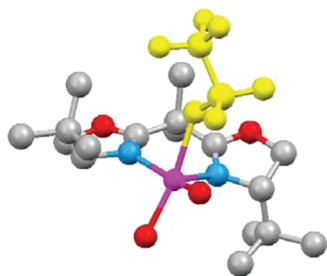


Figure 10. Molecular structure of $[(S)\text{-}2\cdot\text{Zn}(\text{OTf})_2\cdot 2\text{H}_2\text{O}]$ (**26**) (ref 101).

square-planar structure with two H_2O molecules in the coordination sphere (as in **19**). However, the distortion of the water molecules is large, with the ligands oriented far away from the *tert*-butyl groups. The $\text{O}-\text{Cu}-\text{N}-\text{C}$ dihedral angles are $+30.2^\circ$ and $+35.9^\circ$, respectively.^{19,89–91,93,94}

The importance of **19** and **20** can be understood if, after the coordination of the reagent, these complexes become the reacting intermediates in the many different reactions catalyzed by these complexes. If the reagent involved in ligation substitutes the H_2O molecules occupying their coordination sites, then the opposite distortions of the complexes may play a leading role in the development of the sense of enantioselection. Two of these reacting intermediates, the $\text{Cu}(\text{II})$ complexes with (*S*)-**1** and (*S*)-**2**, with benzylidene dimethylmalonate (Table 2, entries 9 and 10), were isolated, and their crystal structures were determined.^{95,96} The dicarbonyl ligand is coordinated to the positions formerly occupied by the H_2O molecules in the complexes **19** and **20**. Hence, in the (*S*)-**1** complex (Table 2, entry 9, **21**, Figure 5) the distortion remains small (1.4 and

Scheme 5

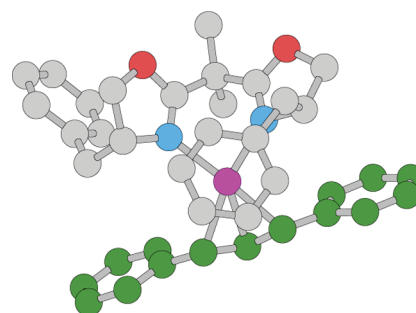
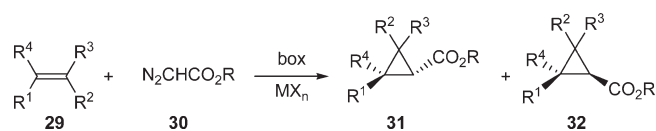


Figure 11. Molecular structure of $[(R)\text{-}3\text{d}\cdot\text{Pd}(1,3\text{-diphenylallyl})]^+$ (**27**) (refs 21 and 51).

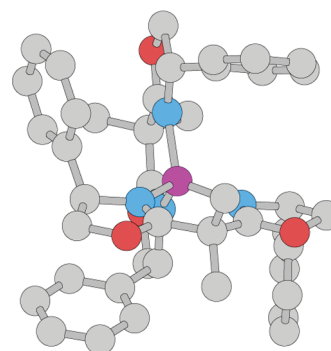


Figure 12. Molecular structure of $[(R)\text{-}1\cdot(S)\text{-}1\cdot\text{Zn}]$ (**28**) (ref 114).

2.3°), whereas the (*S*)-**2** complex (Table 2, entry 10, **22**, Figure 6) has the same strong distortion of the corresponding dehydrate, and the sense of the deviation from planarity is the same. Ethylidene dimethylmalonate can substitute the benzylidene analogue in the $[(S)\text{-}2/\text{Cu}(\text{II})]$ complex (entry 11),⁹⁶ and the resulting crystal structure is nearly superimposable with that of **22**.

The (*S*)-**2** complexes, with Cl and Br as the chelated anions (Table 2, entries 12 and 13, for Br, Figure 7),⁹² have distortions from square planarity that are large and nearly equal. The anions occupy the quadrants that are free from substituents with the same sense of distortion shown by (*S*)-**1** with analogous ligands.

When the copper anion is OTf, the complex has a distorted square-pyramidal structure with two H_2O molecules in the pseudoequatorial positions and one axial OTf (Table 2, entry 14).^{89,92,93} An interesting crystal structure with the H_2O molecules substituted by two carbonyl groups was found. The complex was obtained from a reaction catalyzed by $[(S)\text{-}2/\text{Cu}(\text{OTf})_2]$ involving (*E*)-2-oxo-4-ethoxybut-3-enoic acid ethyl ester as the 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, again in a distorted square-pyramidal structure (Table 2, entry 15, **24**, Figure 8).⁹⁷

Table 3. Asymmetric Cyclopropanation of Alkenes (29) with Diazoacetates (30) Catalyzed by Box Complexes

entry	R ¹	R ²	R ³	R ⁴	R	box	MX _n	yield (%)	31/32	31 ee (%) (conf.)	32 ee (%) (conf.)	ref
1	Ph	H	H	H	Et	(S)-2	CuOTf	77	73:27	99 (1R,2R)	97 (1R,2S)	9, 16, 59a, 115
2	Ph	H	H	H	Et	(S)-2	Cu(OTf) ₂	81	71:29	91 (1R,2R)	88 (1R,2S)	115
3	Ph	H	H	H	Et	(R)-1	Cu(I) ^a	77	70:30	65 (1S,2S)	54 (1S,2R)	59a
4	Ph	H	H	H	<i>t</i> -Bu	(S)-2	CuOTf	75	81:19	96 (1R,2R)	93 (1R,2S)	9
5	Ph	H	H	H	2,6-DMP ^b	(S)-2	CuOTf	68	86:14	97 (1R,2R)	96 (1R,2S)	9
6	Ph	H	H	H	2,6-BHT ^c	(S)-2	CuOTf	85	94:6	99 (1R,2R)		9
7	Ph	H	H	H	CH(C ₆ H ₁₁) ₂	(S)-2	CuOTf	83	88:12	97 (1R,2R)		116
8	Bn	H	H	H	2,6-BHT	(S)-2	CuOTf	<i>d</i>	99:1	99 (1R,2S)		9
9	H	Ph	Ph	H	Et	(S)-2	CuOTf	<i>d</i>		99 (1S)		9
11	H	Me	Me	H	Et	(S)-2	CuOTf	<i>d</i>		99 (1S)		9
12	C≡CMe ₂	Me	Me	H	<i>l</i> -menthyl	(R)-2	Cu(I)P ^e	60	84:16	24 (1R,2R)	20	8
13	CH ₂ OAc	Me	Me	H	Et	(S)-1	CuOTf	47	49:51	69 (1R,2R)	3	117
14	CH ₂ OAc	Me	Me	H	Et	(S)-2	CuOTf	50	80:20	95 (1R,2R)	47	117
15	CH ₂ OSiMe ₃	Me	Me	H	Et	(S)-1	CuOTf	52	64:36	66	<i>d</i>	117
16	CH ₂ OSiMe ₃	Me	Me	H	Et	(S)-2	CuOTf	33	76:24	87	<i>d</i>	117
17	CH ₂ OCH ₂ Ph	Me	Me	H	Et	(S)-2	CuOTf	74	88:12	93	<i>d</i>	117
18	CH ₂ OTrityl	Me	Me	H	Et	(S)-2	CuOTf	46	82:18	87	<i>d</i>	117
19	CH ₂ OCOPh	Me	Me	H	Et	(S)-2	CuOTf	82	82:18	92	<i>d</i>	117
20	CH ₂ OCOC ₆ H ₄ OMe	Me	Me	H	Et	(S)-2	CuOTf	61	91:9	92	12	117
21	Ph	H	H	F	Et	(S)-2	CuOTf	62	72:28	89 (1S,2S)	80	118, 119
22	Ph	H	H	F	<i>t</i> -Bu	(S)-2	CuOTf	56	81:19	93 (1S,2S)	89	118, 119
23	Ph	H	H	F	<i>l</i> -menthyl	(S)-2	CuOTf	28	81:19	92 (1S,2S)	>98	118, 119
24	<i>p</i> -ClPh	H	H	F	Et	(S)-2	CuOTf	64	81:19	93	91	118
25	Ph	Me	H	F	Et	(S)-2	CuOTf	62	82:18	65	<i>d</i>	118
26	C ₄ H ₉	H	H	F	Et	(S)-2	CuOTf	28	64:36	16	<i>d</i>	118

^a X not reported. ^b 2,6-DMP = 2,6-Dimethylphenyl. ^c 2,6-BHT = 2,6-Di-*t*-butyl-4-methylphenyl. ^d Not reported. ^e P = ClO₄(MeCN)₄.

The reason for the inversion of the distortion from square planarity, when going from (S)-1 to [(S)-2·Cu(SbF₆)₂·2H₂O] (20), is still an open question. However, it can be presumed that the strong effect observed in the latter structure is largely due to steric interactions, if the analogous complex [(S)-3c·Cu(SbF₆)₂·2H₂O] (Table 2, entry 16) 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)].^{89–91}

Several other box—Cu(II) crystal structures have been solved (Table 2, entries 17–32). When the counterion is Cl or Br, the majority of the complexes have a distorted square-planar structure (Table 2, entries 17–20, 25, 28, and 29).^{33,35a,64,92,98} As illustrated in Figures 2 and 7, the sense of the distortion is again the same with the anions far away from the indane groups of (R,S)-9a. This is independent of the box structure. The 1- and 2-naphthyls and the 2-methoxy-5-chlorophenyl of (S)-3h, (S)-3i, and (S)-3af all exhibit the same behavior as the phenyl box.

When the counterions are two acetate groups (Table 2, entries 26 and 27), a variable copper coordination number is observed. The complex with (S,R)-9a is square-planar because the acetates behave as monodentate anions. The resulting distortion from planarity is smaller than that occurring with halogens.¹⁰⁰ For the (S)-7aq box, the complex is octahedral with the acetates behaving as bicoordinating anions.⁶⁵

The [(S)-2/Cu(II)] complex with OTf as the anion has a square-pyramidal structure (Table 2, entry 14). The two H₂O molecules are in the pseudoequatorial positions, and the one OTf is axial. In Figure 9 the analogous complex 25 with the box (S,S)-6aa (Table 2, entry 22)⁵⁵ is shown. In this case, the pentacoordinated structure involves one H₂O and one OTf in the equatorial positions, and the second OTf is in the axial one. The importance of 25 will become evident in a later section, because it will be shown to be the starting product for the reacting intermediates in two catalytic processes (Table 2, entries 23 and 24).^{55,99}

Three Cu(II) complexes (Table 2, entries 30–32) have box ligands with substituents to some extent involved in the coordination.²⁸ (S)-3q has 2-methylthioethyl substituents. If the anions are Cl, then both participate in the 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 are in the equatorial plane of the box to give an octahedral coordination. (S)-3r has 1,1-dimethyl-1-methylthiomethyl substituents (Table 2, entry 32): One OTf, one sulfur atom, and one nitrogen atom are equatorial, the second nitrogen atom and the second sulfur atom are in the axial positions to form a trigonal-bipyramidal geometry. Despite the interesting structures generated, the coordination of the substituents appears to have a negative effect on their catalytic efficiency, given the poor enantioselectivity observed in several reactions tested.

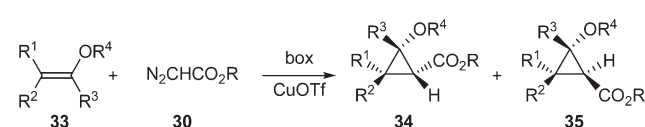
There is a difference between the crystal structures with composition [(S)-1/ZnCl₂] and [(S)-2/ZnCl₂] (Table 2, entries 33 and 34), which have a tetrahedral coordination,⁹² and the diaquo complex 26 with composition [(S)-2/Zn(OTf)₂·2H₂O] (Table 2, entry 35, Figure 10). The different coordination found in 26 derives from the presence of the two H₂O molecules, one axial and one equatorial. These lead to a hydrogen bond with the axial OTf.¹⁰¹

Three Ni(II) and two Fe(II) crystal structures, all with (S)-2 as the ligand, have been solved (Table 2, entries 36–40). All three [(S)-2/NiCl₂],¹⁰² [(S)-2/FeCl₂],¹⁰³ and [(S)-2·Fe(CH₂SiMe₃)₂] have slightly distorted tetrahedral structures.¹⁰³ Under different conditions, Ni(OTf)₂ gave either the dimeric anhydrous complex [(S)-2·Ni(OTf)₂]₂ with two OTfs bridging two nickel atoms or the hydrated complex [(S)-2·Ni(OTf)₂·(H₂O)₂] with one OTf coordinated in a square-pyramidal geometry.¹⁰²

The two different tungsten complexes (Table 2, entries 41 and 42), with (S)-2 and (S)-3c, have octahedral structures as a result of their four additional carbonyl ligands.^{104,105} The rhodium complex of (S)-3c (Table 2, entry 43) has a tetrahedral structure due to the presence of the [η-C₅Me₅·RhCl·(S)-3c] structure.¹⁰⁶ The ruthenium

Table 4. Asymmetric Cyclopropanation of Styrene (**29**, $R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$) with Ethyl Diazoacetate (**30**, $R = \text{Et}$) Catalyzed by Copper Box Complexes in Ionic Liquids

entry	box	CuX _n	ionic liquid	yield (%)	31/32 ^a	31 ee (%) (conf.)	32 ee (%) (conf.)	ref
1	(S)-1	CuCl ₂	CH ₂ Cl ₂	19	67:33	17 (1 <i>R</i> ,2 <i>R</i>)	13 (1 <i>R</i> ,2 <i>S</i>)	124
2	(S)-1	CuCl ₂	(EMIN)(NTf ₂)	34	67:33	55 (1 <i>R</i> ,2 <i>R</i>)	47 (1 <i>R</i> ,2 <i>S</i>)	124
3	(S)-1	CuCl ₂	(Oct ₃ NMe)(NTf ₂)	18	67:33	49 (1 <i>R</i> ,2 <i>R</i>)	41 (1 <i>R</i> ,2 <i>S</i>)	124
4	(S)-2	CuCl ₂	CH ₂ Cl ₂	24	70:30	2	7	124
5	(S)-2	CuCl ₂	(EMIN)(NTf ₂)	50	62:38	86 (1 <i>R</i> ,2 <i>R</i>)	85 (1 <i>R</i> ,2 <i>S</i>)	124
6	(S)-2	Cu(OTf) ₂	CH ₂ Cl ₂	61	71:29	91 (1 <i>R</i> ,2 <i>R</i>)	88 (1 <i>R</i> ,2 <i>S</i>)	124
7	(S)-2	Cu(OTf) ₂	(EMIN)(NTf ₂)	38	64:36	66 (1 <i>R</i> ,2 <i>R</i>)	64 (1 <i>R</i> ,2 <i>S</i>)	124
8	(S)-2	Cu(OTf) ₂	(EMIN)(BF ₄)	3	70:30	rac	rac	124
9	(S)-2	Cu(OTf) ₂	(Oct ₃ NMe)(NTf ₂)	18	63:37	23 (1 <i>R</i> ,2 <i>R</i>)	22 (1 <i>R</i> ,2 <i>S</i>)	124
10	(S)-2	CuOTf	CHCl ₃	59	73:27	89 (1 <i>R</i> ,2 <i>R</i>)	96 (1 <i>R</i> ,2 <i>S</i>)	125
11	(S)-2	CuOTf	(BMIM)Tf	53	76:24	97 (1 <i>R</i> ,2 <i>R</i>)	95 (1 <i>R</i> ,2 <i>S</i>)	125
12	(S)-2	CuOTf	(BMIM)(PF ₆)	47	75:25	95 (1 <i>R</i> ,2 <i>R</i>)	91 (1 <i>R</i> ,2 <i>S</i>)	125
13	(S)-2	CuOTf	(BMIM)(NTf ₂)	45	63:37	94 (1 <i>R</i> ,2 <i>R</i>)	93 (1 <i>R</i> ,2 <i>S</i>)	125
14	(S)-2	CuOTf	(BMIM)(BF ₄)	61	75:25	95 (1 <i>R</i> ,2 <i>R</i>)	89 (1 <i>R</i> ,2 <i>S</i>)	125

^a **31**, **32**: $R = \text{Et}$, $R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$.**Scheme 6**

complex has attracted much attention, and five structures (Table 2, entries 44–48) are reported. Only the (S)-1 complex with the tridentate ligand 2,2',6',2''-terpyridine (Table 2, entry 44) has an octahedral structure.¹⁰⁷ Four other tetrahedral structures are reported, with either (R)-1 or (S)-3c ligands (Table 2, entries 45–48) and a variety of anions or additional ligands.^{108–111}

Finally, to conclude this section, the structures of seven palladium complexes (Table 2, entries 49–55), all with a more or less distorted square-planar structure, are discussed.^{21,36,51,111–114} The use of [Pd(II)/box] complexes as catalysts in enantioselective allylic substitutions led to the isolation of four structures with either (R)-3d, (S)-3s, or (S)-3t (Table 2, entries 51–55). They all have pseudo-square-planar structures, and all have a bidentate allyl derivative as the ligand.^{21,51,113} Because, in principle, all these complexes can be considered as reacting intermediates in the enantioselective allylic substitution, the crystal structure of [(R)-3d·Pd(1,3-diphenylallyl)]⁺ (**27**, Table 2, entry 52) is shown in Figure 11.

Complexes with Two Boxes Coordinated to a Single Cation

When Zn(ClO₄)₂ was mixed with equimolar amounts of (R)-1 and (S)-1, an interesting complex separated out (Table 2, entry 56). The crystal structure date showed a tetrahedral arrangement of two box enantiomers at the Zn(II) cation (**28**, Figure 12).¹⁰¹ The remarkable nonlinear chiral amplification shown by reactions catalyzed by this chiral Zn(II)/box complex is due to the particular stability of this complex attributed to the nicely oriented phenyl groups, which 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 even became commercial products. Among these, **1**, available as both the (R)- and (S)-enantiomers, and

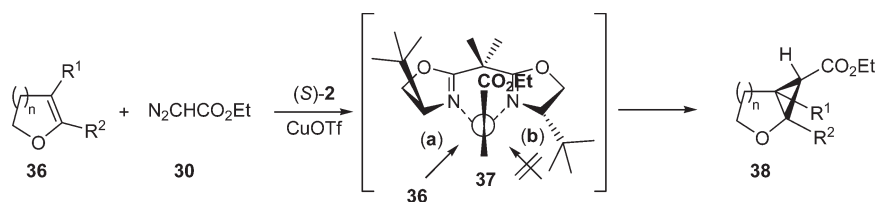
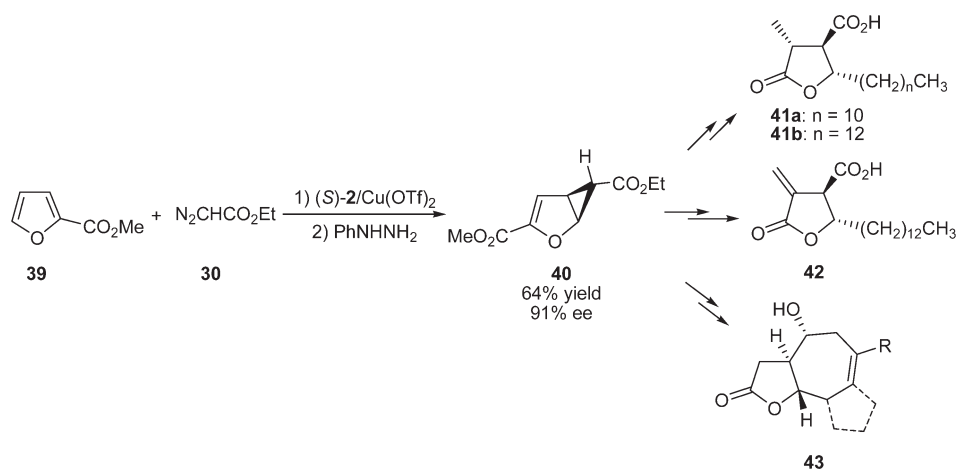
(S)-2 were reasonably priced and, hence, widely used to test the stereoselective properties of the catalysts derived from this class of ligands in a large number of reactions. These boxes, therefore, belong to the most widely reported ligands in the literature. Their behavior can provide a good representation of the efficiency of both 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. Subsequently, results are ameliorated with further progress in the field. It is only rarely that the first report already optimizes the stereoselectivity of the catalytic process. This is in fact what occurred with the first use of boxes as chiral ligands in the metal-catalyzed asymmetric cyclopropanation of alkenes.⁹ The reaction between alkenes **29** and diazoacetates **30** (Scheme 5) was catalyzed by (S)-2 and CuOTf with excellent yield, diastereoselectivity, and enantioselectivity (Table 3, entries 1 and 4–6). The reaction gave the *trans*- and *cis*-cyclopropanes, **31** and **32**, respectively. The cyclopropanation of styrene was finally achieved with a complex derived from box 2 and Cu(I) as the catalyst, since the results using either Cu(II) or box 1 (Table 3, entries 2 and 3) were less convincing.^{59a,115} Experiments have been performed to investigate the influence of the diazoester structure on the selectivity (Table 3, entries 4–7). It was found that increased steric demand determined increased *trans* selectivity. The ester was derived from 2,6-di-*tert*-butyl-4-methylphenol (BHT, Table 3, entry 6) giving a **31/32** ratio of 94:6. Excellent enantioselectivities were obtained using 3-phenylpropene, 1,1-diphenylethene, and 2-methylpropene (Table 3, entries 8–10). The symmetrically disubstituted alkenes gave a single enantiomer.⁹

To test the limitations of using boxes as ligands in Cu-catalyzed enantioselective cyclopropanation, several trisubstituted alkenes were tested (Table 3, entries 12–20).^{14,117} (S)-1 and (S)-2 gave the same absolute configuration as the optically active cyclopropanes (Table 3, entries 13 and 14), but enantioselectivity was much 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). The highest enantioselectivity (95% ee) obtained was for 3-methyl-2-butenoyl acetate (Table 3, entry 14), whereas several substrates gave unsatisfactory results. Vinyl fluorides were

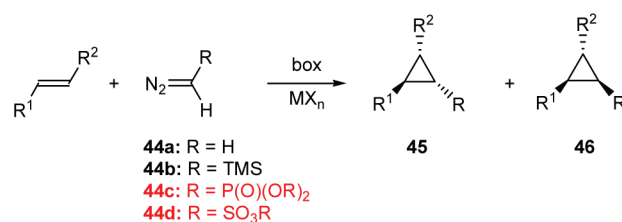
Table 5. Asymmetric Cyclopropanation of Enol Ethers (33) with Diazoacetates (30) Catalyzed by CuOTf

entry	R ¹	R ²	R ³	R ⁴	30 R	box	yield (%)	34/35	34 ee (%) (conf.)	35 ee (%) (conf.)	ref
1	Me	H	H	α -D-Glu	Me	(S)-2	74	3:97		60	126
2	Me	H	H	α -D-Glu	<i>t</i> -Bu	(S)-2	32	3:97		60	126
3	Me	H	H	α -D-Man	Me	(S)-2	54	12:88	14	65	126
4	Me	H	H	α -D-Man	<i>t</i> -Bu	(S)-2	71	<i>a</i>		63	126
5	H	H	Ph	TMS	Me	(S)-2	82	48:52	96	89	127
6	H	H	Ph	TMS	Et	(S)-2	77	44:56	95	90	127
7	H	(CH ₂) ₃		TMS	Me	(S)-2	56	73:27	92 (1 <i>S</i> ,5 <i>R</i> ,6 <i>R</i>)	87 (1 <i>R</i> ,5 <i>S</i> ,6 <i>R</i>)	127
8	H	(CH ₂) ₃		TMS	Et	(S)-2	46	75:25	85 (1 <i>S</i> ,5 <i>R</i> ,6 <i>R</i>)	40 (1 <i>R</i> ,5 <i>S</i> ,6 <i>R</i>)	127
9	H	(CH ₂) ₄		TMS	Me	(S)-2	7	27:73	11 (1 <i>S</i> ,5 <i>R</i> ,7 <i>R</i>)	<i>a</i>	127

^a Not determined.**Scheme 7****Scheme 8****Table 6. [CuOTf/(S)-2]-Catalyzed Asymmetric Cyclopropanation of Cyclic Enol Ethers (36) with Ethyl Diazoacetate (30)**¹²⁸

entry	<i>n</i>	R ¹	R ²	endo/exo	38 yield (%)	38 ee (%) (conf.)
1	1	Me	H	30:70	60	>95 (1 <i>R</i> ,5 <i>S</i> ,6 <i>S</i>)
2	1	CH ₂ Ph	H	21:79	77	96 (1 <i>R</i> ,5 <i>R</i> ,6 <i>S</i>)
3	2	H	H	13:87	77	Rac
4	2	Et	H	9:91	52	>95 (1 <i>R</i> ,6 <i>S</i> ,7 <i>S</i>)
5	2	<i>n</i> -Pr	H	6:94	54	>95 (1 <i>R</i> ,6 <i>S</i> ,7 <i>S</i>)
6	2	CH ₂ Ph	H	5:95	67	96 (1 <i>R</i> ,6 <i>R</i> ,7 <i>S</i>)
7	2	H	CH ₂ Ph	7:93	45	74 (1 <i>R</i> ,6 <i>R</i> ,7 <i>R</i>)

a further class of di- and trisubstituted alkenes quite intensively investigated.^{118,119} The best results were obtained for the reaction of diazoacetates and α -fluorostyrene, catalyzed by the Cu(I) complex of (S)-2 (Table 3, entries 21–23), since cyclopropanes

Scheme 9

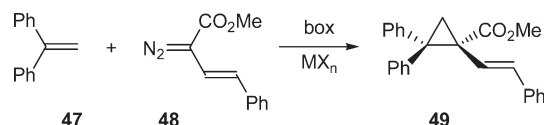
were obtained with more than 90% ee. The presence of a further substituent or an alkyl group instead of the aryl caused a significantly lower enantioselectivity (Table 3, entries 24–26).

Other experiments, mainly directed at comparing the efficiency of the catalysts derived from some new box-like ligands compared to box 1 or 2, were performed. The related references

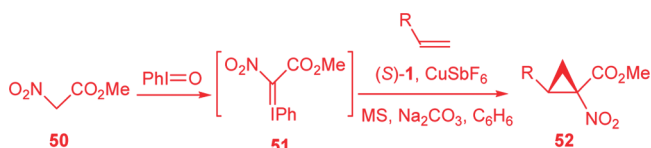
Table 7. Asymmetric Cyclopropanation of Alkenes with Diazomethane Derivatives **44a–d** (Scheme 9)

entry	R ¹	R ²	44R	box	MX _n ^a	yield (%)	45/46	45 ee (%)	46 ee (%)	ref
1	Ph	CO ₂ Me	H	(S)-1	CuOTf	80		72		132
2	Ph	CO ₂ Me	H	(S)-2	CuOTf	30		24		132
3	Ph	CO ₂ Et	H	(S)-1	CuOTf	80		73		132
4	Ph	CO ₂ <i>i</i> -Pr	H	(S)-1	CuOTf	43		69		132
5	Ph	CO ₂ CH ₂ Ph	H	(S)-1	CuOTf	79		75		132
6	Ph	CO ₂ Ph	H	(S)-1	CuOTf	49		74		132
7	<i>p</i> -NO ₂ Ph	CO ₂ Me	H	(S)-1	CuOTf	62		80		132
8	<i>p</i> -MePh	CO ₂ Me	H	(S)-1	CuOTf	79		60		132
9	<i>p</i> -MeOPh	CO ₂ Me	H	(S)-1	CuOTf	81		55		132
10	Ph	H	SiMe ₃	(S)-1	CuOTf	50	86:14	2	5	133
11	Ph	H	SiMe ₃	(S)-1	CuPF ₆	60	97:3	63	43	133
12	Ph	H	SiMe ₃	(S)-2	CuOTf	45	96:4	69	50	133
13	Ph	H	SiMe ₃	(S)-2	CuPF ₆	26	90:10	43	15	133
14	<i>p</i> -BrPh	H	SiMe ₃	(S)-1	CuPF ₆	86	100:0	66		133
15	<i>p</i> -MePh	H	SiMe ₃	(S)-1	CuPF ₆	54	96:4	58	38	133
16	<i>p</i> -MeOPh	H	SiMe ₃	(S)-1	CuPF ₆	80	95:5	49	61	133
17	Ph	H	P(O)(OMe) ₂	(S)-1	CuOTf	75	80:20	79	83	134
18	Ph	H	P(O)(OMe) ₂	(S)-2	CuOTf	74	86:14	93	99	134
19	Ph	H	P(O)(OEt) ₂	(S)-2	CuOTf	65	84:16	92	99	134
20	Ph	H	P(O)(O <i>i</i> -Pr) ₂	(S)-2	CuOTf	65	90:10	92	nd	134
21	Ph	H	P(O)(ONeopent) ₂	(S)-2	CuOTf	67	92:8	92		134
22	Ph	H	SO ₃ Neopent	(S)-2	CuOTf	90	86:14	92	79	135
23	<i>p</i> -MePh	H	SO ₃ Neopent	(S)-2	CuOTf	87	84:16	90	90	135
24	<i>p</i> -MeOPh	H	SO ₃ Neopent	(S)-2	CuOTf	92	80:20	89	85	135
25	<i>p</i> -ClPh	H	SO ₃ Neopent	(S)-2	CuOTf	85	86:14	90	88	135
26	<i>m</i> -NO ₂ Ph	H	SO ₃ Neopent	(S)-2	CuOTf	69	90:10	>99	97	135
27	<i>m</i> -NO ₂ Ph	H	SO ₃ CH(<i>i</i> -Pr) ₂	(S)-2	CuOTf	65	92:8	>99		135
28	Me ₃ CO	H	SO ₃ Neopent	(S)-2	CuOTf	81	76:24	77	91	135
29	MeCO ₂ CH ₂	H	SO ₃ Neopent	(S)-2	CuOTf	34	82:18	>99		135

Scheme 10



Scheme 11

Table 8. Asymmetric Cyclopropanation of 1,1-Diphenylethene **47** with Diazoacetate Derivative **48**¹³⁷

entry	box	MX _n	49 yield (%)	49 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

are reported here for the sake of completeness.^{64,120–122} Of even more interest is the existence of a positive nonlinear effect ((+)-NLE) in the asymmetric cyclopropanation of styrene with **30**. The reaction is catalyzed by a [(*R*)-**1**·Cu(I)] complex. A 70% ee of catalyst gave nearly the same ee of **31** obtained using an optically pure catalyst.¹²³ The most probable explanation is that a stable catalytic inactive heterochiral meso-complex is involved.

One interesting development led to the testing of 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 (ENIM), methyltri-*n*-octylammonium (Oct₃NMe),

Table 9. Asymmetric Cyclopropanation of Alkenes using Iodonium Ylide **51** Derived from Methyl Nitroacetate¹³⁷

entry	alkene	yield (%)	dr	52 ee (%)
1	Ph-CH=CH ₂	82	94:6	91
2	4-Cl-Ph-CH=CH ₂	45	92:8	91
3	4-MeO-Ph-CH=CH ₂	71	93:7	68
4	4-Me-Ph-CH=CH ₂	76	93:7	92
5	1-naphthyl-CH=CH ₂	53	93:7	91
6	2-naphthyl-CH=CH ₂	74	91:9	91
7	CH ₂ =CH-CH=CH ₂	84	82:18	90
8	2,3-dimethylbutadiene	54	95:5	85

and 1-butyl-3-methylimidazolium (BMIM) with different anions were all examined (Table 4).^{124,125} When the reactions were carried out with catalysts prepared from CuCl₂ and (*S*)-**1** or (*S*)-**2** in ionic liquids a significant improvement resulted compared to the disappointing result obtained in CH₂Cl₂ (Table 4, entries 1 and 4 vs 2, 3, and 5). Furthermore, the results from Cu(OTf)₂ and (*S*)-**2** actually lowered the performance (Table 4, entry 6 vs 7–9). The reactions using CuOTf and (*S*)-**2** significantly improved the

Scheme 12

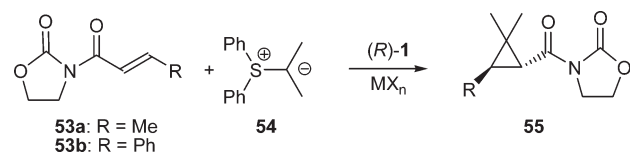


Table 10. Asymmetric Cyclopropanation of Acyldien-Oxazolidinones 53 with the Sulfur Ylide 54 Catalyzed by (R)-1/Lewis Acid Complexes¹³⁸

entry	R	MX _n ^a	55 yield (%)	55 ee (%)
1	Me	Zn(OTf) ₂	63	95
2	Me	Zn(OTf) ₂	65	82
3	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.

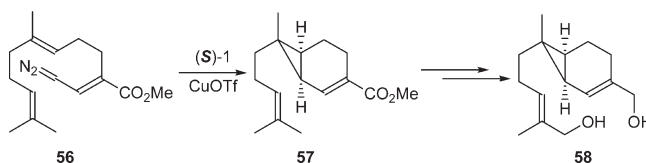
enantioselectivity of the reaction when it was run in CHCl₃, albeit mainly for the major trans product **31** (Table 4, entry 10 vs 11–14).

The diazoacetates **30** reacted with the enol ethers **33**, some of them with different chiral auxiliaries, to give the cyclopropanecarboxylates **34** and **35** (Scheme 6, Table 5).^{126,127} The glucose- and mannose-derived chiral auxiliaries (Table 5, entries 1–4) induced an excellent trans stereoselectivity with **35** being the main product. However, diastereoselectivity was found to be only moderate.¹²⁶ 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). The cyclohexene derivative (Table 5, entry 9) gave poor results under the reaction conditions studied.¹²⁷

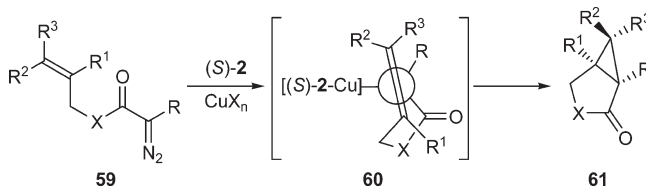
The cyclic enol ethers derived from 2,3-dihydrofuran and 2,3-dihydropyran (**36**, *n* = 1, 2) were useful substrates for enantioselective cyclopropanation with ethyl diazoacetate (**30**, R = Et). The reaction was catalyzed by the complex derived from (S)-2 and CuOTf (Scheme 7).¹²⁸ If unsubstituted dihydropyran is excluded, the exo/endo diastereoselectivity reached 95:5. The enantioselectivity was higher than 95% ee in nearly all cases (Table 6, entries 1–6). This selectivity can be easily rationalized if the intermediate **37** is assumed to be the reacting complex with the approach of **36** following pathway b disfavored by the strong repulsive steric interaction between the approaching enol ether and the *tert*-butyl group of the ligand.¹²⁸ The excellent stereoselectivity of the catalytic stereoselective cyclopropanation reaction leading to **38** (Table 6, entry 4, R¹ = Et, R² = H) was used as the key step in the asymmetric synthesis of (+)-quebrachamine, which is an indole alkaloid of the *Aspidosperma* family.¹²⁸

The product of the enantioselective cyclopropanation of furan-2-carboxylic methyl ester (**39**) with ethyl diazoacetate (**30**, Scheme 8) resulted in another useful synthon of natural γ -butyrolactone.

Scheme 13



Scheme 14



The catalyst was prepared from (S)-2, Cu(OTf)₂, and phenylhydrazine and lead to the formation of cyclopropane **40** with 91% ee (>99% ee after only a single crystallization). This key intermediate was successfully converted to (–)-nephrosteranic acid **41a**,¹²⁹ (–)-roccellaric acid **41b**,^{129,130} (–)-protolichesterinic acid **42**,⁸⁸ and the core nuclei (**43**) of xanthanolides, guaianolides, and eudesmanolides.¹³¹

The carbene source of the cyclopropanations previously reported were diazoacetate esters. The enantioselective cycloadditions with diazomethane **44a**, trimethylsilyldiazomethane **44b**, diazomethylphosphonates **44c**, and diazomethylsulfonates **44d** are, therefore, rather unusual (Scheme 9). The reaction of diazomethane **44a** with cinnamate esters was tested with both (S)-1 and (S)-2 in combination with CuOTf (Table 7, entries 1 and 2). The best result was obtained with the former ligand. Different ester groups (Table 7, entries 1 and 3–6) give comparable results. 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).¹³²

Trimethylsilyldiazomethane **44b** and styrene react with a remarkably high trans selectivity leading to **45** as the major product (Table 7, entries 10–13). It was found that substrates with phenyl groups having electron-withdrawing substituents led to an increase in both the trans selectivity and the enantioselectivity (Table 7, entries 11 and 14–16).¹³³

The reactions of diazomethylphosphonates **44c** and styrene, catalyzed by CuOTf, gave a better enantioselectivity with (S)-2 than with (S)-1 (Table 7, entries 17 and 18). The stereo- and enantioselectivity increased with the increase in steric hindrance of the phosphonate residue (Table 7, entries 18–21).¹³⁴

The best catalyst for the reaction between diazosulfonate esters **44d** and alkenes is [(S)-2 CuOTf] (Table 7, entries 22–29).¹³⁵ In general, the enantioselectivity with vinylbenzenes is excellent, sometimes >99% (Table 7, entries 22–27). With unsaturated ethers and allyl esters (Table 7, entries 28 and 29), on the other hand, the results were not always excellent. Again, the stereo- and enantioselectivity increased with the increase in size of the sulfonate residue (Table 7, entries 26 and 27).

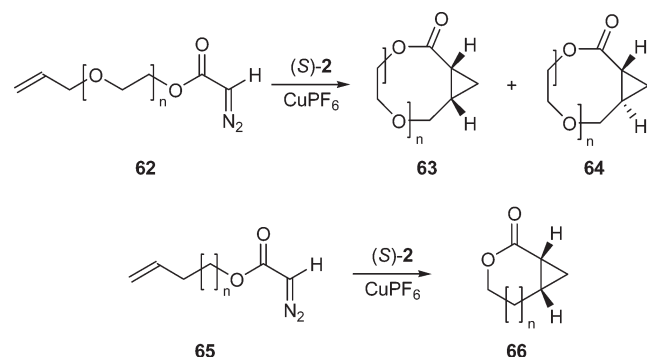
To summarize the results presented in this section, when the carbene sources are diazoalkanes the best catalysts are Cu(I)– or Cu(II)–box complexes, and OTf is a better counterion than PF₆.

Table 11. Asymmetric Intramolecular Cyclopropanation of Derivatives 59

entry	box	CuX _n	X	R ¹	R ²	R ³	R	61 yield (%)	61 ee (%) (conf.)	ref
1	(S)-2	CuPF ₆	O	H	H	H	H	61	20 (1R,5S)	140
2	(S)-2	CuPF ₆	O	H	Me	Me	H	80	13 (1R,5S)	140
3	(S)-2	CuPF ₆	O	H	H	Pr	H	74	29 (1S,5R)	140
4	(S)-2	CuPF ₆	O	H	Pr	H	H	82	37 (1S,5S)	140
5	(S)-2	CuPF ₆	O	Me	H	H	H	58	87 (1S,5R)	140
6	(S)-2	CuPF ₆	O	Bu	H	H	H	73	82 (1S,5R)	140
7	(S)-1	CuOTf	CH ₂	H	F	CO ₂ Et	H	79	65 (1S,5S,6S)	72
8	(S)-1	Cu(OTf) ₂	CH ₂	H	F	CO ₂ Et	H	80	61 (1S,5S,6S)	72
9	(S)-1	CuOTf	CH ₂ CH ₂	OTES	Me	Me	H	38	13 (1R,6S)	29
10	(S)-2	CuOTf	CH ₂ CH ₂	OTES	Me	Me	H	82	78 (1R,6S)	29
11	(S)-2	Cu(OTf) ₂	CH ₂	Ph	H	H	SO ₂ Mes	61	68 (1R)	141
12	(S)-2	Cu(OTf) ₂	CH ₂	MDOP ^a	H	H	SO ₂ Mes	77	20	141
13	(S)-2	Cu(OTf) ₂	CH ₂	TBSOP ^b	H	H	SO ₂ Mes	61	51	141
14	(S)-2	Cu(OTf) ₂	CH ₂	OBzP ^c	H	H	SO ₂ Mes	56	54	141
15	(S)-2	CuOTf	CH ₂	H	H	H	SO ₂ Nap ^d	59	45 (1R)	142
16	(S)-2	Cu(OTf) ₂	CH ₂	H	H	H	SO ₂ Xyl ^e	89	37 (1R)	142

^a MDOP is 3,4-methylenedioxyphenyl. ^b TBSOP is 3,4-di-*tert*-butyldimethylsilyloxyphenyl. ^c OBzP is 3,4-dibenzoyloxyphenyl. ^d Nap is 1-naphthyl. ^e Xyl is 2,4-dimethylphenyl.

Scheme 15



1,1-Diphenylethene (47) reacts with styryl-diazoacetate (48) to give cyclopropane 49 (Scheme 10). The best ligand with Cu(OTf)₂ is (R)-1 (Table 8, entry 2 vs 1). However, the best enantioselectivity, in spite of the very low yield, is obtained with (S)-2 and RuCl₂ or Sc(OTf)₃ (Table 8, entries 4 and 5).¹³⁶

The cyclopropanation of alkenes using iodonium ylides derived from methyl nitroacetate 50 furnished an interesting route to the chiral building blocks 52. These are useful precursors of the non-naturally occurring amino acid derivatives (Scheme 11). The one-pot reaction requires nitroester and PhIO to generate the ylide 51. Subsequent reaction with the alkene is catalyzed by [(S)-1 • CuSbF₆] in the presence of molecular sieves (MS), as the water scavenger, and Na₂CO₃ as the additive. The best solvent proved to be benzene.¹³⁷ The results are reported in Table 9 (entries 1–8). Excellent diastereomeric and enantiomeric excesses were obtained with aromatic-substituted alkenes (Table 9, entries 1–6) whereas somewhat intriguing results were obtained with dienes (Table 9, entries 7 and 8).

Dimethylsulfonium isopropylide (54) can be an interesting alternative to diazoderivatives as the source of carbene, because its reaction with 3-crotonoyl- and 3-cinnamoyl-2-oxazolidinones (53a, R = Me; 53b, R = Ph, Scheme 12) can be catalyzed by complexes of (R)-1 with several salts (Table 10, entries 1 and 4–10). The enantioselectivity with Zn(II) and Mg(II) complexes can be as high as 95% ee.¹³⁸ Unfortunately, the limit of this

Table 12. Asymmetric Intramolecular Cyclopropanation of Poly(ethyloxy)-Allyl Diazoacetates (62) Catalyzed by CuPF₆/(S)-2

entry	n	conv. (%)	cycloprop. (%)	63/64	63 ee (%) (conf.)	64 ee (%)	ref
1	0		61		20 (1R,5S)		144
2	1	61	3		71 (1S,8R)		144
3	2	58	58	86:14	79	85	144
4	3	73	61	40:60	88	80	144, 145

synthetic protocol is the stoichiometric amount of Lewis acid required. Namely, a significant loss of enantioselectivity is observed with less than 1 equiv of catalyst (Table 10, 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.¹³⁹ The starting product was the suitably substituted diazotriene 56. It was exposed to several known catalysts with a view to promoting an enantioselective [2 + 1]-cycloaddition (Scheme 13). Many failed, but Cu(I) catalysts in combination with (S)-1 or (S)-2 as ligands gave 57, which was easily converted in two steps to the target sirenin 58. The resulting 68% yield was promising, and it had 60% ee. These results stimulated the authors to develop a new class of more efficient box ligands that resulted in an increased enantioselectivity of 90% ee. However, the structures of this new class of ligands lie well outside the scope of this review.

This approach was largely applied to the cyclization of allylic diazoacetates 59 (X = O, R = H) that give cyclopropa[c]furans 61 (Scheme 14).¹⁴⁰ With [(S)-2/CuPF₆] as the catalyst, the enantioselectivity largely depends on the double bond substituents, and the best enantioselectivities are obtained with 2-substituted allyl groups (Table 11, entries 5 and 6). This is attributed to the steric hindrance of R¹ favoring conformation 60 of the substrate. It should be noted also that the absolute configuration of the product depends on the substituents, even if this cannot be easily rationalized. An important complementary result is obtained with dirhodium(II)tetrakis(methyl 2-oxopyrrolidine carboxylates). These are the catalysts of choice for

making the products described in Table 11, entries 1–4. 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 14 is also obtained from ethyl (2*Z*)-7-diazo-2-fluoro-6-oxohept-2-enoate (**59**, $R^1 = H$, $R^2 = F$, $R^3 = CO_2Et$, $X = CH_2$; Table 11, entries 7 and 8)⁷² and 1-diazo-7-methyl-6-triethylsilyloxy-6-octen-2-one (**59**, $R = H$, $R^1 = OTES$, $R^2 = R^3 = Me$, $X = CH_2CH_2$; Table 11, entries 9 and 10).²⁹ These compounds are useful starting products for the preparation of the enantiopure fluorobicycloketone and TMSO-bicyclohexanone (**61**), whose structure constitutes that of the CD-ring skeleton of phorbol.

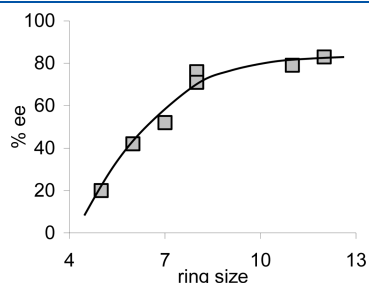
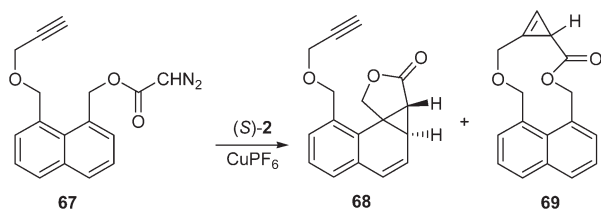


Figure 13. Enantiomeric excess (%) vs ring size of the cis-fused cyclopropanes for the intramolecular reaction of **62** and **65** (refs 144–147).

Scheme 16



Scheme 17

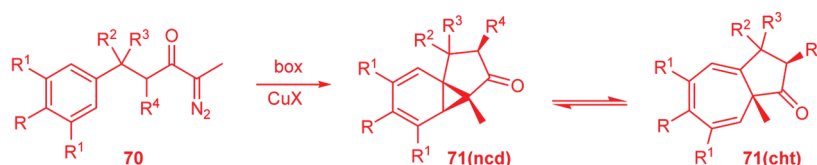


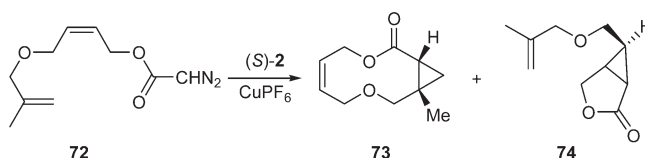
Table 13. Asymmetric Intramolecular Büchner Reaction of α -Diazoketones

entry	box	X_n	R	R^1	R^2	R^3	R^4	71 yield (%)	71 ee (%)	ref
1	(<i>R</i>)-1	PF ₆ ^a	H	H	Me	Me	H	97	78	149, 150
2	(<i>R</i>)-1	SbF ₆	H	H	Me	Me	H	72	80	149
3	(<i>R</i>)-1	BARF ^b	H	H	Me	Me	H	57	78	150
4	(<i>S</i>)-2	SbF ₆	H	H	Me	Me	H	60	4	149
5	(<i>R</i>)-1	PF ₆	Me	Me	Me	Me	H		95	149
6	(<i>R</i>)-1	SbF ₆	H	H	Ph	Me	H	60 ^c	72	149
7	(<i>S</i>)-2	SbF ₆	H	H	Ph	Me	H	43 ^d	20	149
8	(<i>R</i>)-1	PF ₆	H	H	H	H	Bn	78	82	149
9	(<i>S</i>)-2	PF ₆	H	H	H	H	Bn	57	20	149
10	(<i>R</i>)-1	PF ₆ ^a	Me	H	Me	Me	H	80	80	150
11	(<i>R</i>)-1	BARF	Me	H	Me	Me	H	46	80	150
12	(<i>R</i>)-1	PF ₆ ^a	Cl	H	Me	Me	H	63	62	150
13	(<i>R</i>)-1	BARF	Cl	H	Me	Me	H	54	78	150

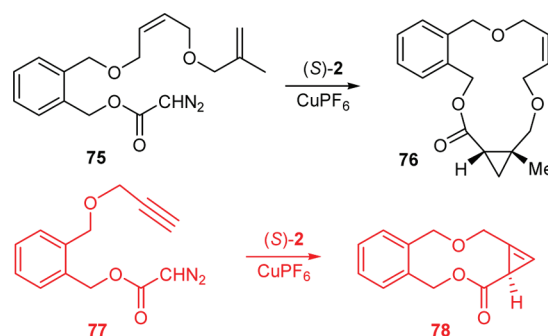
^a PF₆ is (MeCN)₄PF₆. ^b BARF is tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. ^c Diastereomeric ratio 94:6. ^d Diastereomeric ratio 88:12.

Recently the cyclopropanation illustrated in Scheme 14 was carried out using the more sterically hindered 5-aryl-1-diazo-1-mesitylsulfonyl-5-hexen-2-ones (**59**, $R^1 = Ar$, $R^2 = R^3 = H$, $X = CH_2$, $R = SO_2Mes$; Table 11, entries 11–13),¹⁴¹ 1-diazo-1-arylsulfonyl-5-hexen-2-ones (**59**, $R^1 = R^2 = R^3 = H$, $X = CH_2$, $R = SO_2Ar$; Table 11, entries 14 and 15),¹⁴² and 2-diazo-3-oxo-6-heptenoic acid esters (**59**, $R^1 = R^2 = R^3 = H$, $X = CH_2$, $R = CO_2R$).¹⁴³ Whereas the sulfonyl derivatives gave interesting results, the cyclopropanation of the carboxylic esters failed with (*S*)-**2** (an ee not over 11%). Only the use of different box ligands allowed a significant increase in the enantioselectivity of the reaction. Similar behavior was observed also for other derivatives with the general formula **59**, and this will be the topic of the next section.

Scheme 18



Scheme 19

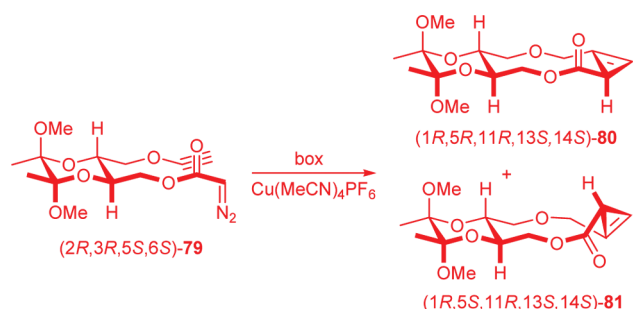


The intramolecular cyclopropanation works nicely for the construction of large rings. Diazoacetates tethered to the allyl group through 0–3 ethylene glycols units (Scheme 15, **62**) not only give products from the cyclopropanation (**63** and **64**) but also give side-products deriving from C–H insertion, intermediate oxonium ylides, and carbene dimerization. The interesting point is that the [(*S*)-**2**/CuPF₆] catalyst increases enantioselectivity as a function of the ring size (Table 12, entries 1–4).^{144,145}

If, in addition to the above data, the results of the catalyzed cyclopropanation of homoallylic diazoacetate (**65**, *n* = 1), the homologues with *n* = 3, 4, and 8¹⁴⁶ and 2-(propen-1-yloxy-methyl)benzyl diazoacetate,¹⁴⁷ are all considered and the enantioselectivities of the cis-fused cyclopropanes **63** and **66** are plotted versus the ring size, then the above observations appear to be a general trend (Figure 13).^{144,146,147} However, it has also been established that the preferred formation of the macrocycle has a negative effect on the reaction stereoselectivity (**63/64**).

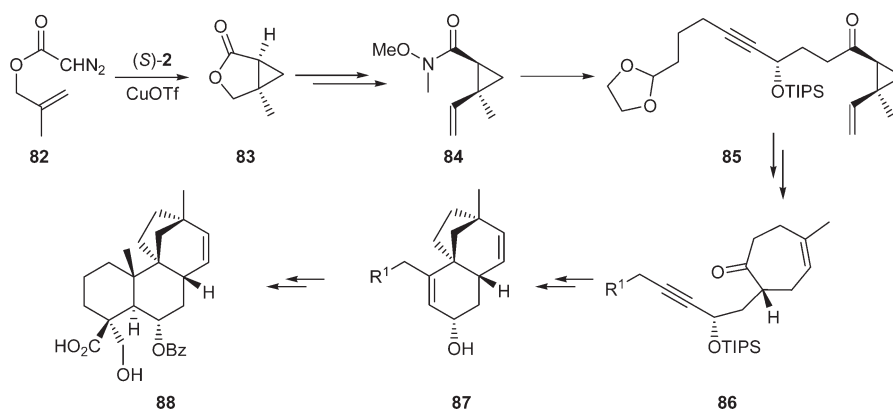
Catalytic intramolecular cycloadditions prefer a double versus a triple bond, even if the former belongs to an aromatic ring. A naphthalene-1,8-dimethanol derivative carrying a propargylic and a diazo acetate group (**67**, Scheme 16) was found to largely prefer the formation of the norcaradienic derivative **68** (62% yield, 59% ee)

Scheme 20

Table 14. Diastereoselectivity in Intramolecular Cyclopropanation of **79** Catalyzed by Copper(I) Catalysts¹⁵²

entry	catalyst	yield 80 + 81	d.r. (80/81)
1	Cu(MeCN) ₄ PF ₆	80	86:14
2	[(<i>R</i>)- 1 Cu(MeCN) ₄ PF ₆]	75	46:54
3	[(<i>S</i>)- 2 Cu(MeCN) ₄ PF ₆]	73	97:3
4	[(<i>S</i>)- 1 Cu(MeCN) ₄ PF ₆]	77	99:1

Scheme 21



rather than the macrocyclic cyclopropene **69** (10% yield, enantiomeric excess not determined).¹⁴⁸

To determine the effectiveness of a box–Lewis-acid-catalyzed cyclopropanation of the naphthalene system, compound **67** with no substituent in position 8 was used as a model system. [(*S*)-**2**/CuPF₆] was found to catalyze an aromatic cycloaddition with 83% yield and 42% ee.¹⁴⁸ This particular catalytic intramolecular cyclopropanation of an aromatic ring is known as the Büchner reaction. When **70** was used as the starting compound, the norcaradiene derivative **71(ncd)** was formed, which is in dynamic equilibrium with the cycloheptatriene **71(cht)** (Scheme 17 and Table 13).^{149,150} The reaction can also be carried out on substituted aromatic rings as long as the substrates are judiciously chosen. It is important that their symmetry does not allow the formation of regioisomers (Table 13, entries 5 and 10–13). Reaction is possible also using reagents with more than one aryl group, but only if they are equivalent (Table 13, entries 6–9). Box **1** gives a catalyst that performs better than that obtained from **2** (Table 13, entries 1, 6, and 8 vs 4, 7, and 9).¹⁴⁹ The sensitivity of their enantioselection response has been investigated using the reactions with CuSbF₆, [Cu(MeCN)₄]PF₆, and Cu-(BARF) (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) as a comparison.^{149,150}

When two or more double bonds are present in the substrate, the regioselectivity depends on both the catalyst and the specific structure of the reagent. In the intramolecular cyclopropanation of either 4-(2-methyl-2-propenyloxy)-(*Z*)-2-butenyl diazoacetate **72** or the homologous **75**, [(*S*)-**2**/CuPF₆] leads to the formation of the largest cycle as the major product.¹⁵¹ For **72** (Scheme 18), two competing products are formed; the largest bicyclic derivative (**73**) that predominates is obtained with the highest enantioselectivity (**73**, 43% yield, 87% ee; **74**, 19% yield, 41% ee). On the other hand, the reaction of **75** is highly regioselective and the macrocycle **76** is the only reaction product formed (regioisomeric ratio > 25:1, 61% yield, 90% ee) (Scheme 19).¹⁵¹ When the diazoacetate contains a triple bond as in **77** (Scheme 19), the [(*S*)-**2**/CuPF₆]-catalyzed intramolecular [2 + 1]-cycloaddition gives a macrocycle condensed to the cyclopropene (**78**) with 80% ee.¹⁵²

Scheme 22

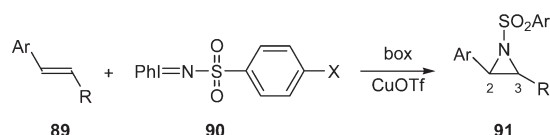


Table 15. Asymmetric Aziridination of Different Alkenes **89** with **90** (X = Me)

entry	Ar	R	box	solvent	91 yield (%)	91 ee (%) (2-conf.)	ref
1	Ph	H	(S)- 2	styrene	89	63 (R)	157
2	Ph	H	(S)- 2	benzene	<i>a</i>	57 (R)	157
3	Ph	H	(S)- 2	CH ₂ Cl ₂	<i>a</i>	36 (R)	157
4	Ph	H	(S)- 2	MeCN	<i>a</i>	6 (R)	157
5	Ph	Me	(S)- 2	MeCN	62	70 (S)	157
6	Ph	CO ₂ Me	(S)- 2	MeCN	16	19 (S)	157
7	Ph	CO ₂ Me	(S)- 1	MeCN	21	70 (S)	157
8	Ph	CO ₂ Me	(S)- 1	benzene	63	94 (S)	157
9	Ph	CO ₂ Ph	(S)- 1	benzene	64	97 (S)	157
10	Ph	CO ₂ <i>t</i> -Bu	(S)- 1	benzene	60	96 (S)	157
11	1-Naph	CO ₂ Me	(S)- 1	benzene	76	95 (S)	157
12	2-Naph	CO ₂ Me	(S)- 1	benzene	73	96 (S)	157
13	Ph	COPh	(S)- 1	CH ₂ Cl ₂	38	86 (S)	158, 159, 160
14	Ph	CO-4-MeC ₆ H ₄	(S)- 1	CH ₂ Cl ₂	24	85 (S)	161
15	Ph	CO-4-FC ₆ H ₄	(S)- 1	CH ₂ Cl ₂	10	86 (S)	161
16	Ph	CO-4-BrC ₆ H ₄	(S)- 1	CH ₂ Cl ₂	12	84 (S)	161
17	Ph	CO-4-CF ₃ C ₆ H ₄	(S)- 1	CH ₂ Cl ₂	4	65 (S)	161
18	Ph	CO-4- <i>t</i> -BuC ₆ H ₄	(S)- 1	CH ₂ Cl ₂	10	87 (S)	161
19	4-MeC ₆ H ₄	CO-4- <i>t</i> -BuC ₆ H ₄	(S)- 1	CH ₂ Cl ₂	7	81 (S)	161
20	Ph	COMe	(S)- 1	CH ₂ Cl ₂	15	85 (S)	161
21	Ph	CH=CH-COPh	(S)- 1	CH ₂ Cl ₂	28	80 (S)	162

^a Not reported.Table 16. Asymmetric Aziridination of Styrene (**89**, R = H) with **90** (X = Me): Effect of the Counterion¹⁶³

entry	box	Cu(I) counterion	yield (%)	benzene 91 ee (%) (conf.)	MeCN 91 ee (%) (conf.)
1	(R)- 1	OTf	<i>a</i>	1 (S)	28 (S)
2	(R)- 1	ClO ₄	<i>a</i>	5 (S)	28 (S)
3	(R)- 1	Cl	<i>a</i>	17 (S)	28 (S)
4	(R)- 1	PF ₆	<i>a</i>	33 (S)	28 (S)
5	(R)- 1	(S)-B(BN) ₂	75	22 (S)	
6	(R)- 1	(R)-B(BN) ₂	85	24 (S)	
7	(S)- 2	OTf	<i>a</i>	66 (R)	2 (R)
8	(S)- 2	ClO ₄	<i>a</i>	57 (R)	2 (R)
9	(S)- 2	Cl	<i>a</i>	26 (R)	2 (R)
10	(S)- 2	PF ₆	<i>a</i>	33 (R)	2 (R)
11	(S)- 2	(S)-B(BN) ₂	<i>a</i>	13 (R)	
12	(S)- 2	(R)-B(BN) ₂	<i>a</i>	12 (R)	

^a Not reported.

Several investigations of intramolecular cyclopropanations have been carried out on enantiomerically pure substrates to test their match/mismatch diastereoselectivity with enantiomeric box catalysts.^{152,153} Scheme 20 shows the results for diazoacetate **79** with the configuration (2*R*,3*R*,5*S*,6*S*), which is derived from D-tartaric acid. The [box/Cu(MeCN)₄PF₆]-catalyzed decomposition of **79** afforded the diastereomeric cyclopropenes **80** and **81**. The ratio depends on the catalyst used (Table 14). If the diastereomeric ratio in the absence of box (Table 14, entry 1) is taken as the reference, then the reduction in diastereoselectivity obtained by using [(*R*)-**1**/Cu(MeCN)₄PF₆] (Table 14, entry 2) indicates that this is a mismatched catalyst for the decomposition of **79**. Although both [(*S*)-**2**/Cu(MeCN)₄PF₆] and [(*S*)-**1**/Cu(MeCN)₄PF₆] (Table 14, entries 3 and 4)

exhibited a diastereocontrol higher than the reference, the best matched catalyst is undoubtedly the latter.¹⁵²

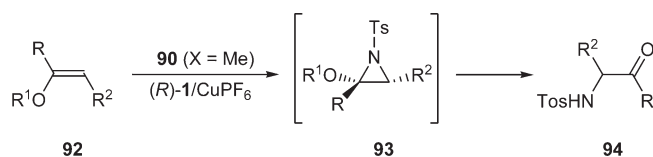
A nice application of the intramolecular cyclopropanation is demonstrated by Overman et al. in the enantiodivergent total syntheses of (+) and (–)-Scopadulcic acid **A** (Scheme 21). Even if the enantioselective [2 + 1]-cycloaddition is introduced at an early stage of the synthesis protocol, the chiral information is the messenger of half of the total chirality of the process.¹⁵⁴ The key synthon is (1*S*,5*R*)-5-methyl-2-oxo-3-oxabicyclo[3.1.0]hexane (**83**), prepared on a multigram scale with 80% yield and 88% ee (raised to 99% ee by crystallization) by the catalytic cyclopropanation of the diazoester **82** catalyzed by [(*R*)-**2**/CuOTf]. The bicyclic lactone was opened to give 1-(*N,O*-dimethylhydroxamido)-2-ethenyl-2-methylcyclopropane **84**. This is then coupled with the stereodivergence messenger to

Table 17. Asymmetric Aziridination of Substituted Styrene (89, R = H) with 90: Effect of the Substituents

entry	Ar	X	box	CuAn _n	solvent	yield (%)	91 ee (%) (conf.)	ref
1	Ph	Me	(S)-2	ClO ₄	CH ₂ Cl ₂	82	29 (S)	164
2	Ph	Me	(S)-2	ClO ₄	C ₆ H ₆	75	48 (S) ^a	164
3	Ph	NO ₂	(S)-2	ClO ₄	C ₆ H ₆	94	75 (S)	164
4	Ph	Cl	(S)-2	ClO ₄	C ₆ H ₆	90	52 (S)	164
5	Ph	H	(S)-2	ClO ₄	C ₆ H ₆	82	50 (S)	164
6	Ph	<i>t</i> -Bu	(S)-2	ClO ₄	C ₆ H ₆	75	44 (S)	164
7	Ph	MeO	(S)-2	ClO ₄	C ₆ H ₆	55	33 (S)	164
8	<i>p</i> -FC ₆ H ₄	NO ₂	(S)-2	ClO ₄	C ₆ H ₆	95	72 (S)	164
9	<i>p</i> -CF ₃ C ₆ H ₄	NO ₂	(S)-2	ClO ₄	C ₆ H ₆	64	51 (S)	164
10	<i>p</i> -MeC ₆ H ₄	NO ₂	(S)-2	ClO ₄	C ₆ H ₆	78	45 (S)	164
11	<i>o</i> -ClC ₆ H ₄	NO ₂	(S)-1	(OTf) ₂	MeCN	90	83 (S)	165
12	<i>m</i> -ClC ₆ H ₄	NO ₂	(S)-1	(OTf) ₂	MeCN	89	72 (S)	165
13	<i>p</i> -ClC ₆ H ₄	NO ₂	(S)-1	(OTf) ₂	MeCN	90	93 (S)	165
14	<i>o</i> -FC ₆ H ₄	NO ₂	(S)-1	(OTf) ₂	MeCN	85	71 (S)	165
15	<i>m</i> -FC ₆ H ₄	NO ₂	(S)-1	(OTf) ₂	MeCN	80	83 (S)	165
16	<i>p</i> -FC ₆ H ₄	NO ₂	(S)-1	(OTf) ₂	MeCN	85	41 (S)	165
17	<i>m</i> -BrC ₆ H ₄	NO ₂	(S)-1	(OTf) ₂	MeCN	79	83 (S)	165
18	<i>m</i> -MeC ₆ H ₄	NO ₂	(S)-1	(OTf) ₂	MeCN	78	80 (S)	165
19	<i>m</i> -NO ₂ C ₆ H ₄	NO ₂	(S)-1	(OTf) ₂	MeCN	48	68 (S)	165

^aThis result is in contrast with that in Table 16, entry 8.

Scheme 23



give **85** (or its diastereoisomer) after having been submitted first to a Cope rearrangement to give **86**. After a Heck cyclization that gives **87**, the key target tricyclic intermediate **88** known as (–)-Scopadulcic acid **A** is finally obtained.

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.^{155,156}

4.2. Aziridination Reactions

The first report dealing with the use of boxes as ligands in asymmetric reactions concerned the catalytic aziridination of styrene leading to optically active aziridines and appeared already in 1991. Good yields and promising enantioselectivities were reported.⁹ Two years later, another paper described the reaction of several alkenes (**89**) with *N*-(*p*-toluenesulfonylimino)phenyliodine (**90**, X = Me) as the nitrene source. Two catalysts were used, [(S)-**1**/CuOTf] and [(S)-**2**/CuOTf], to give the aziridines **91** (Scheme 22, Table 15).¹⁵⁷

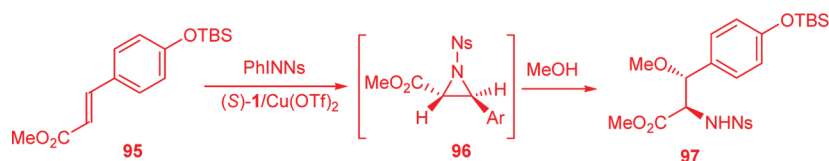
There are four points that deserve attention. (i) The best results are found for unsaturated esters that show enantioselectivities of up to 96% ee (Table 15, entries 6–12). Neither aryl nor ester substituents significantly influence the enantioselectivity. (ii) The best box is (S)-**1** (Table 15, entry 7 vs 6). (iii) A significant solvent effect is observed. For example, for the styrene and cinnamate esters it was found that better enantioselectivities were obtained in the less

polar solvents. (iv) With the same catalyst configuration, the absolute configuration of the chiral carbon atom in the aziridine obtained from styrene was found to be (*R*). This is the opposite to that found for trans-disubstituted alkenes (*S*). A similar result was reported for the aziridination of chalcone (**89**, Ar = Ph, R = COPh; Table 15, entry 13).^{158–160} The substituent effect on both groups of the α,β-unsaturated ketone **89** (R = COR¹) was studied in detail (Table 15, entries 13–20). However, given that in general the yields are rather low, the enantioselectivity was not greatly influenced by the nature of the substituent either at Ar (Table 15, entries 13–18) or at R¹ (Table 15, entry 19).¹⁶¹ The reaction for methyl styryl ketone (Table 15, entry 20) gave similar yields and enantioselectivity. All adducts obtained using the catalyst derived from (S)-**1** were found to be (2*S*)-**91**. An interesting result was found for 1,5-diphenyl-2,4-pentadien-1-one (**89**, Ar = Ph, R = CH=CH–COPh; Table 15, entry 21). It reacted chemoselectively to give (2*S*)-**91** with 80% ee.¹⁶²

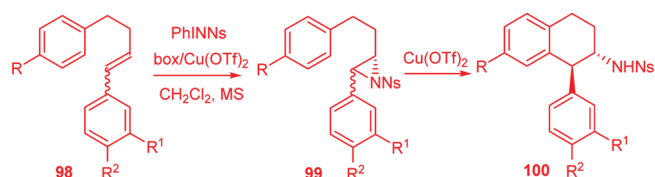
The data listed in Table 15 (entries 8–12) are among the best results reported in the literature for catalytic reactions run under homogeneous conditions. One of the reasons for the apparently limited interest in a field that gives access to important chiral building blocks is that better overall enantioselectivities are achievable with heterogeneous catalysts than under homogeneous conditions.⁷

A significant effect on the stereochemical outcome of the reaction was observed in the aziridination of styrene (**89**, R = H). The reaction was catalyzed by Cu(I) salts in combination with (R)-**1** and (S)-**2**. Various counterions, both achiral and chiral [(R)- or (S)-B(binaphthol)₂[–]–B(BN)₂[–]], in benzene and MeCN (Table 16), were all investigated.¹⁶³ In these studies a significant solvent effect was also observed. In benzene, the best box proved to be (S)-**2**. The enantioselectivity improved on changing the counterion from PF₆ to OTf (Table 16, entries 7–10). However, this order was inverted for (R)-**1** (Table 16, entries 1–4). Here, a change in enantioselectivity to more than 30% ee was observed. In the more polar solvent MeCN,

Scheme 24



Scheme 25

Table 18. Asymmetric Aziridination and Subsequent Friedel–Crafts Synthesis of *trans*-2-Amino-1-aryltetralins **100**¹⁷²

entry	box	R	R ¹	R ²	100 yield (%)	100 ee (%)
1	(R)-1	H	H	OMe	85	92
2	(S)-2	H	H	OMe	61	45 ^a
3	(R)-1	H	H	H	62	59
4	(R)-1	H	Me	H	77	86
5	(R)-1	OMe	Me	H	81	76
6	(R)-1	OMe	Cl	H	66	82
7	(R)-1	OMe	OMe	H	78	74
8	(R)-1	OMe	H	OMe	76	83
9	(R)-1	H	H	OMe	79	73
10	(R)-1	H	H	Br	58	66

^a The opposite enantiomer was predominantly formed.

(R)-1 showed better enantioselection, but no counterion effect was observed (Table 16, entries 1–4 and 7–10). Hopefully, the current disappointing results for both enantiomers of the chiral counterion [B(BN)₂][−] (Table 16, entries 5, 6, 11, and 12) will not prevent further investigation of this original theme.

The aziridination of styrene derivatives was investigated in detail. The substituents both on the substrate (Ar group of **89**)^{164,165} and on the nitrene reagent (X group of **90**), prepared in situ from the commercially available PhI(OAc)₂ and sulfonamides X–C₆H₄–SO₂–NH₂, were varied. The results are summarized in Table 17.¹⁶⁴

Using (S)-2, Cu(ClO₄)(MeCN)₄, and benzene as solvent,¹⁶⁴ the enantioselectivity changed with the change of the substituent X on sulphonamide, and it regularly increased with the increasing electron-withdrawing character of the substituent (Table 17, entries 2–7). Therefore, the best results were obtained using *p*-nitrobenzenesulfonylnitrene. A comparison of the results for substituted styrene (Table 17, entries 8–10) with those obtained for [(S)-1/Cu(OTf)₂] in MeCN (Table 17, entries 11–19)¹⁶⁵ confirms the features shown by the data in Table 16: The phenyl-box is a better ligand than the *tert*-butyl one. For (S)-1, acetonitrile is the solvent of choice, whereas (S)-2 prefers benzene. Concerning the specific effect of the substituents on styrene, although the enantioselectivity does greatly change, there is no clear relationship with the electronic properties of the substituent.

Table 19. Asymmetric Intramolecular Aziridination of Alkyl Sulfamates **104**¹⁷⁶

entry	box	R	R ¹	R ²	n	105 yield (%)	105 ee (%)
1	(S)-2	H	H	H	1	81	52
2	(S)-2	H	H	H	2	72	47
3	(S)-1	H	Ph	H	1	40	20
4	(S)-2	H	Ph	H	1	86	84
5	(S)-2	H	Me	H	1	80	80
6	(S)-2	Me	H	H	1	24	36
7	(S)-2	H	Et	H	1	83	80
8	(S)-2	H	H	Et	1	86	72
9	(S)-2	H	CO ₂ Me	H	1	79	62

An even better preparation of the nitrene precursors **90** was realized in a “one-pot” reaction starting from sulfonamides and iodosylbenzene.¹⁶⁶ This protocol was tested for the reaction of styrene catalyzed by [(S)-2/Cu(OTf)₂].¹⁶⁶ Both yield and enantioselectivity were found to be comparable to those described previously. However, when the reaction was applied to the aziridination of *tert*-butyl-(R)-N-(9-phenyl-9H-fluoren-9-yl)allylglycinate, the resulting yield and diastereoselectivity were somewhat unsatisfactory.^{167,168}

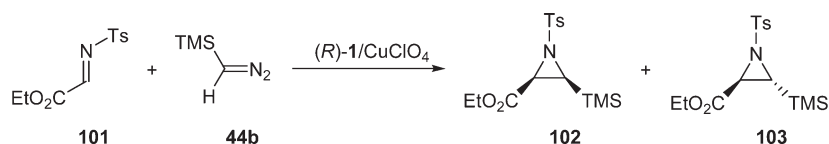
An interesting use of enantioselective aziridination to create chiral building blocks is the reaction of the enol ethers and esters **92** with **90** using [(R)-1/CuPF₆] as the catalyst (Scheme 23).¹⁶⁹ The resulting alkoxyaziridines **93** are unstable and spontaneously (or under mild hydrolysis) decompose to yield the optically active α-amino ketones **94**. When **92** is a vinyl ether with R = Ph and R² = Me, the major product is (S)-**94**. When **92** is 1-acetoxy-1-phenylpropene, (R)-**94** is obtained with 52% ee, which is the best enantiomeric excess of all these experiments. The mechanism was rationalized as occurring with a front-side attack of **92** on the coordinated nitrene, under conditions of minimal steric interactions.

It should be noted that the reactions listed under entries 11–19 in Table 17 produce benzaldehydes as the side-products. Also, the aziridination of styrene with [(S)-1/Cu(OTf)₂] may occur with an increase in enantioselectivity with the conversion due to further reaction of the product.¹⁷⁰

An alternative source of nitrene is PhINNs [N-(*p*-nitrophenyl-sulfonyl)iminophenylidiodane]. This was used in the preparation of the protected form of (2*R*,3*R*)-β-methoxytyrosine **97** (Scheme 24), a nonproteinogenic amino acid constituent of several cyclic depsipeptide natural products. The cycloaddition with **95** occurs with excellent enantioselectivity. In addition, the ring-opening of the intermediate aziridine **96** with methanol is very stereoselective as evidenced by the fact that **97** is obtained in 89% yield with a diastereomeric ratio (dr) greater than 90% and an ee of 94%.¹⁷¹

PhINNs was once more the nitrene source for the [box/Cu(OTf)₂]-catalyzed aziridination of 2-arylethylstyrenes **98** (an *E/Z*

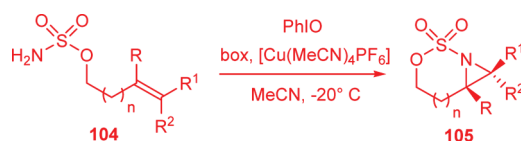
Scheme 26

Table 20. Catalyzed Enantioselective Mukaiyama–Aldol Reactions between Aldehydes (**106**, $\text{R}^1 = \text{H}$) and Trimethylsilylketene Acetals **107**

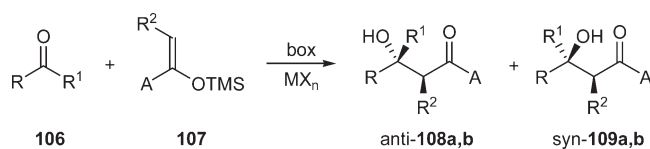
entry	R	A	R^2	box	MX_n	solvent	yield (%)	anti/syn	108 ee (%) (conf.)	109 ee (%) (conf.)	ref
1	CH_2OBn	<i>St</i> -Bu	H	(<i>S</i>)- 1	$\text{Zn}(\text{SbF}_6)_2$	CH_2Cl_2	<i>a</i>		85 (<i>S</i>)		178
2	CH_2OBn	<i>St</i> -Bu	H	(<i>S</i>)- 1	$\text{Cu}(\text{OTf})_2$	CH_2Cl_2	<i>a</i>		9 (<i>R</i>)		179
3	CH_2OBn	<i>St</i> -Bu	H	(<i>S</i>)- 2	$\text{Cu}(\text{OTf})_2$	CH_2Cl_2	<i>a</i>		91 (<i>R</i>)		177–179
4	CH_2OBn	<i>St</i> -Bu	H	(<i>S</i>)- 2	$\text{Cu}(\text{SbF}_6)_2$	CH_2Cl_2	<i>a</i>		≤64 (<i>S</i>)		179
5	CH_2OBn	OE <i>t</i>	H	(<i>S</i>)- 2	$\text{Cu}(\text{OTf})_2$	CH_2Cl_2	<i>a</i>		50 (<i>R</i>)		179
6	CH_2OBn	Me	H	(<i>S</i>)- 2	$\text{Cu}(\text{OTf})_2$	CH_2Cl_2	<i>a</i>		38 (<i>R</i>)		179
7	CH_2OBn	Ph	H	(<i>S</i>)- 2	$\text{Cu}(\text{OTf})_2$	CH_2Cl_2	<i>a</i>		51 (<i>R</i>)		179
8	CH_2OBn	<i>St</i> -Bu	Me	(<i>S</i>)- 2	$\text{Cu}(\text{OTf})_2$	CH_2Cl_2	50	81:19	84 (<i>R,S</i>)	<i>a</i>	179
9	CO_2Et	SPh	H	(<i>S</i>)- 1	$\text{Sn}(\text{OTf})_2$	CH_2Cl_2	<i>a</i>		91 (<i>S</i>)		180
10	Ph	Ph	Me	(<i>S</i>)- 2	$\text{Cu}(\text{OTf})_2$	H_2O	92	10:90	<i>a</i>	15	181

^a Not reported.

Scheme 27



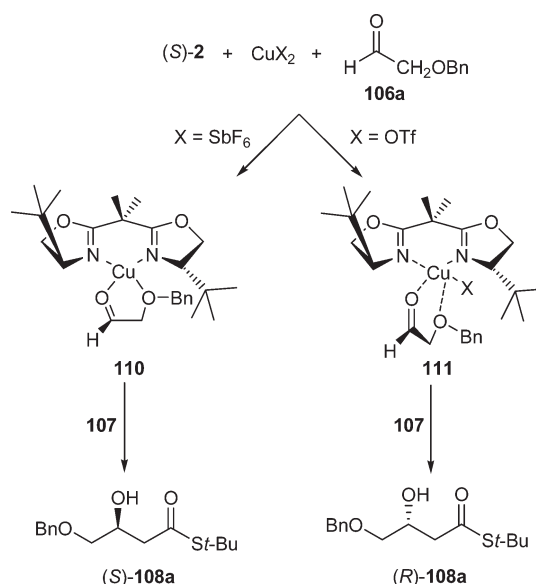
Scheme 28



mixture $\leq 85:15$) (Scheme 25).¹⁷² An intramolecular Friedel–Crafts alkylation of the tethered and in situ generated aziridines **99**, catalyzed by the same $\text{Cu}(\text{II})$ cation, provides a “one-pot” efficient method for the synthesis of trans-2-amino-1-aryltetralylns **100**. Excellent diastereo- ($\text{dr} > 99:1$) and enantioselectivity (up to 92% ee) (Table 18) were found. The best **box** again proved to be **1** (Table 18, entry 1 vs 2). Clearly the presence of electron donor substituents favors the reaction (Table 18, entry 3 and 4).

A completely different approach to making optically active aziridines is possible with a chiral catalyst-mediated transfer of carbenes to imines. An early approach, catalyzing the reaction between *N*-arylidene anilines and ethyl diazoacetate **30** with $[(S)\text{-1}]/\text{CuPF}_6$ ¹⁷³ or $[(R)\text{-1}]/\text{Zn}(\text{OTf})_2$,¹⁷⁴ gave low yields (only up to 37%) and interesting enantioselectivity (up to 67% ee). The formation of significant amounts of 1,2-diarylpyrrolidine 2,3,4-triethylcarboxylate (derived from the incorporation of the carbene dimer diethyl fumarate) severely limited the usefulness of this process. The same type of aziridination reaction, but using *N*-tosyl α-imino ester **101** and trimethyldiazomethane **44b**, was investigated with $[(R)\text{-1}]/\text{CuClO}_4$ as the

Scheme 29



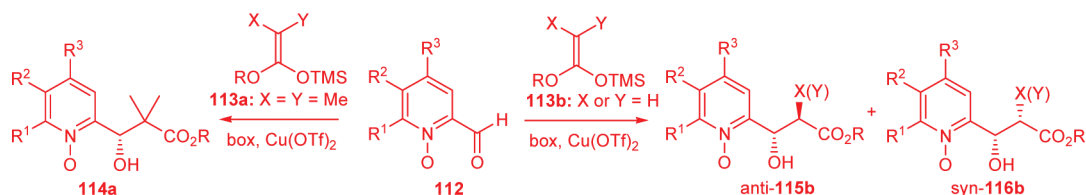
catalyst (Scheme 26).¹⁷⁵ The yield was very low (28%) with a **102/103** ratio of 2:1. However, the enantioselectivities obtained for both isomers (40 and 63% ee, respectively) were promising.

More recently, an example of an enantioselective $\text{Cu}(\text{I})$ -catalyzed intramolecular aziridination was performed on alkenyl sulfamates **104**. Iodosylbenzene proved a suitable reagent for generating the nitrene (Scheme 27), and unexpectedly the best **box** was (*S*)-**2** (Table 19, entry 3 vs 4).¹⁷⁶ The yields were in general good, and the enantioselectivity was up to 84% ee. Both of these were strongly lowered for the R substituent (Table 19, entry 6).

4.3. Aldol and Aldol-like Reactions

The aldol addition is one of the main topics of virtually every review dealing with asymmetric catalysis. This is because it is one

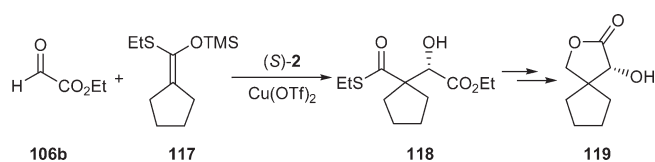
Scheme 30

Table 21. Catalytic Enantioselective Mukaiyama–Aldol Reaction between 1-Oxypyridine-2-carbaldehydes **112** and Silyl Ketene Acetals **113a,b**¹⁸²

entry	R ¹	R ²	R ³	OR	X	Y	box	yield (%)	114a ^d ee (%)	115b/116b	115b ^b ee (%)	116b ^c ee (%)
1	H	H	H	OMe	Me	Me	(S)-1	80	88			
2	H	H	H	OMe	Me	Me	(S)-2	79	93			
3	Me	H	H	OMe	Me	Me	(S)-2	78	81			
4	Br	H	H	OMe	Me	Me	(S)-2	92	96			
5	Ph	H	H	OMe	Me	Me	(S)-2	64	77			
6	H	Br	H	OMe	Me	Me	(S)-2	72	93			
7	H	Ph	H	OMe	Me	Me	(S)-2	84	>99			
8		benzene	H	OMe	Me	Me	(S)-2	90	35			
9	H		benzene	OMe	Me	Me	(S)-2	89	>99			
10	H	H	H	OPh	H	OBn	(S)-2	75		4:1	99	n.d.
11	H	Br	H	OPh	H	OBn	(S)-2	88		5:1	99	n.d.
12	H		benzene	OPh	H	OBn	(S)-2	91		12:1	99	n.d.
13	H		benzene	OMe	CH ₂ Ph	H	(S)-2	96		5:1	99	98
14	H		benzene	OMe	H	CH ₂ Ph	(S)-2	97		3:1	99	99
15	H		benzene	O <i>t</i> -Bu	Me	H	(S)-2	97		3:1	88	66

^a Absolute configuration of all products is (S) except for the product from entry 1, where it is (R). ^b Absolute configuration of products is (3S). ^c n.d. means not determined.

Scheme 31



of the most popular reactions for the construction of C–C bonds. In addition, because nearly all the chiral ligand families, and the optically active catalysts derived therefrom, have been tested on this reaction, it can be considered a benchmark for establishing the efficiency of a chiral catalyst. **The Diels–Alder is, of course, the other landmark reaction, in this context.**

One of the first investigations using box catalysts was the Mukaiyama–aldol variant of the aldol reaction. This is between aldehydes (**106a,b**, R¹ = H) or activated ketones (**106c**, R¹ ≠ H) and silylketene acetals (**107**, Scheme 28). Two reviews describe early applications in this field.^{6b,c} The pioneering work of Evans et al. on the use of box and pybox ligands for Mukaiyama–aldol reactions is a true foundation stone for the many applications using these ligands.

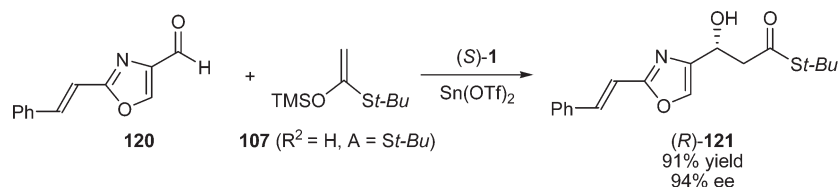
In general, the carbonyl derivative **106** has a substituent R or R¹ with an atom or a group suitable for inducing bidentate coordination to the chiral Lewis acid. Hence, (benzyloxy)acetaldehyde (**106a**,

R = CH₂OBn, R¹ = H) and ethyl glyoxylate (**106b**, R = CO₂Et, R¹ = H), were the early aldehydes tested.^{177,178} However, later, the catalyst of choice for the former was found to have pybox as the better ligand. Several silylketene acetals were tested in their reaction with aldehydes. In the case of **107** having R² ≠ H, two products, *anti*-**108a** and *syn*-**109a**, were obtained. The overall results with aldehydes are reported in Table 20.

Some significant results will be highlighted here. All the boxes tested have an (S)-configuration. However, the chiral information transferred to the adduct is dependent not only on the substituent but also on both the cation (Lewis acid, Table 20, entry 1 vs 2) and counterion (Table 20, 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 the change in the coordination number in the reaction intermediate. If the anion SbF₆ is not involved as an auxiliary ligand, then a square-planar-like coordination is preferred. This leads to an attack at the Si face of **110**, and (S)-**108a** 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 **111** leads to the opposite (R)-**108a** enantiomer being formed (Scheme 29).¹⁷⁹

The reaction between ethyl glyoxylate **106b** and **107**, in CH₂Cl₂ (Table 20, entry 9), gave an excellent 91% ee of the **108b**, but more interesting results were obtained with the box (S)-**3d** as the chiral ligand. This will be discussed in a later section.¹⁸⁰ It is notable that when benzaldehyde was reacted with **107** in H₂O (Table 20, entry

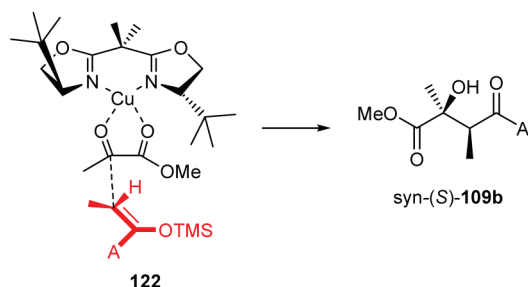
Scheme 32

Table 22. Catalyzed Asymmetric Mukaiyama–Aldol Reactions between α -Ketoesters 106c ($\text{R}^1 \neq \text{H}$) and Trimethylsilylketene Acetals 107

entry	106c		107			box	MX_n	solvent	yield (%)	syn/anti	109b ee (%) (conf.)	ref
	R	R^1	R^2	A	conf.							
1	CO_2Me	Me	H	St-Bu		(S)-1	Cu(OTf)_2	CH_2Cl_2	73		43(S)	25, 186
2	CO_2Me	Me	H	St-Bu		(S)-2	Cu(OTf)_2	CH_2Cl_2	96		99(S)	25, 185, 186
3	CO_2Me	Me	H	St-Bu		(S)-2	$\text{Cu(SbF}_6)_2$	CH_2Cl_2	<i>a</i>		75(S)	186
4	CO_2Me	Me	H	St-Bu		(S)-2	Cu(OTf)_2	Et_2O	94		99(S)	186
5	CO_2Me	Me	H	St-Bu		(S)-2	Cu(OTf)_2	THF	95		99(S)	186
6	CO_2Me	Me	H	St-Bu		(S)-2	Cu(OTf)_2	PhCH_3	91		96(S)	186
7	CO_2Me	Me	H	St-Bu		(S)-2	Cu(OTf)_2	hexane	42		96(S)	186
8	CO_2Me	Me	H	St-Bu		(S)-2	Cu(OTf)_2	PhCF_3	88		95(S)	186
9	CO_2Me	Me	H	St-Bu		(S)-2	Cu(OTf)_2	dioxane	84		92(S)	186
10	CO_2Me	Me	H	St-Bu		(S)-2	Cu(OTf)_2	MeNO_2	95		75(S)	186
11	CO_2Me	Me	H	St-Bu		(S)-2	Cu(OTf)_2	MeCN	<i>a</i>		23(S)	186
12	CO_2Bn	Me	H	St-Bu		(S)-2	Cu(OTf)_2	THF	95		99(S)	185, 186
13	$\text{CO}_2t\text{-Bu}$	Me	H	St-Bu		(S)-2	Cu(OTf)_2	THF	91		99(S)	185, 186
14	CO_2Me	Et	H	St-Bu		(S)-2	Cu(OTf)_2	THF	84		94(S)	185, 186
15	CO_2Me	<i>i</i> -Bu	H	St-Bu		(S)-2	Cu(OTf)_2	THF	94		94(S)	185, 186
16	CO_2Et	<i>i</i> -Pr	H	St-Bu		(S)-2	Cu(OTf)_2	THF	84		36(R)	185, 186
17	CO_2Me	Me	H	EtS		(S)-2	Cu(OTf)_2	THF	97		97(S)	186
18	CO_2Me	Me	H	Ph		(S)-2	Cu(OTf)_2	THF	77		99(S)	186
19	CO_2Me	Me	H	Me		(S)-2	Cu(OTf)_2	THF	76		93(S)	186
20	CO_2Me	Me	Me	St-Bu	(Z)	(S)-2	Cu(OTf)_2	CH_2Cl_2	96	94:6	96(S)	186
21	CO_2Me	Me	Me	St-Bu	(E)	(S)-2	Cu(OTf)_2	CH_2Cl_2	90	95:5	98(S)	186
22	CO_2Me	Me	Me	SEt	(Z)	(S)-2	Cu(OTf)_2	CH_2Cl_2	95	90:10	95(S)	186
23	CO_2Me	Me	Me	SEt	(E)	(S)-2	Cu(OTf)_2	CH_2Cl_2	78	98:2	98(S)	186
24	CO_2Me	Me	<i>i</i> -Pr	SEt	(Z)	(S)-2	Cu(OTf)_2	CH_2Cl_2	80	90:10	99(S)	186
25	CO_2Me	Me	<i>i</i> -Bu	SEt	(Z)	(S)-2	Cu(OTf)_2	CH_2Cl_2	88	90:10	93(S)	186
26	CO_2Et	Me	<i>i</i> -Bu	SEt	(Z)	(S)-2	Cu(OTf)_2	THF	85	90:10	>91(S)	187

^a Not reported.

Scheme 33

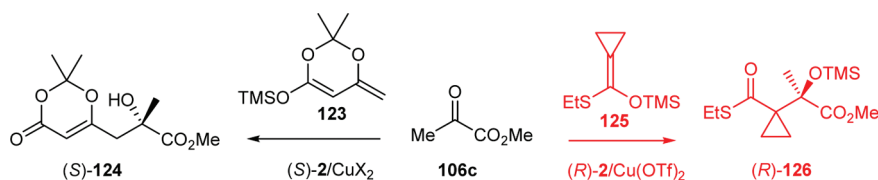


10)¹⁸¹ the reaction was syn-selective, but enantioselectivity with (S)-2 was much lower than that with other box systems.

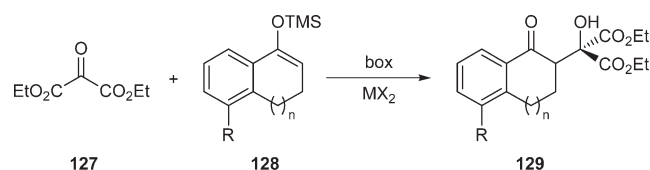
The catalytic and asymmetric Mukaiyama–aldol reaction between silylketene acetals and 1-oxypyridine-2-carbaldehyde 112 derivatives (Scheme 30), catalyzed by $\text{Cu(OTf)}_2/\text{box}$ complexes, with 113a gave methyl (S)-3-hydroxy-2-

2-dimethyl-3-(1-oxypyridin-2-yl)propionate derivatives (114a) in good yield and excellent ee (Table 21, entries 1–9). Not only did [(S)-2/ Cu(OTf)_2] show better catalytic properties than its (S)-1 analogue (Table 21, entry 1 vs 2), but the former gave (S)-114a, whereas the latter gave the (R) enantiomer. The enantioselectivity of the reaction with 5-phenyl-1-oxypyridine-2-carbaldehyde was better than that with the 6-phenyl analogue (Table 21, entry 5 vs 7). In addition, this reaction gave excellent results both with quinoline and isoquinoline aldehydes (Table 21, entries 8,9). The reaction was also performed using the 2-monosubstituted silylketene acetals 113b and different pyridine- or isoquinoline-N-oxide-carbaldehyde derivatives, under the same optimized conditions. The reaction led to 2-substituted (3S)-3-hydroxy-3-(1-oxypyridin-2-yl)propionates (*anti*-115b and *syn*-116b), with diastereoselectivity favoring the formation of the anti product and an enantioselectivity of up to 99% (Table 21, entries 10–15).¹⁸² This anti diastereoselectivity is in contrast with the syn selectivity found for the aldol reaction reported in Table 20, entry 10.¹⁸¹ However, it is in agreement with the reaction

Scheme 34



Scheme 35



reported in Table 20, entry 8;¹⁷⁹ both were catalyzed by [(S)-2/Cu(OTf)₂].

The diastereoselectivity of the Mukaiyama–aldol reaction with pyruvates as the reagents will be discussed in the following sections. The results discussed will also illustrate just how decisive is the contribution of the *N*-oxide group in the reagent to the enantioselectivity of the reaction.

These particular reactions with aldehydes have interesting applications in the synthesis of two natural products. The Mukaiyama–aldol reaction between ethyl glyoxylate 106b and silylketene acetal 117 can be catalyzed by [(S)-2/Cu(OTf)₂] to give (S)-118 in 61% yield and 98% ee. Subsequently, these can be easily converted into the optically active pantolactone derivative 119 (Scheme 31).¹⁸³

Phorboxazole B is a marine product with a complex macro-lactone (C₁–C₂₄) and lactol (C₃₃–C₃₇) ring system. Its total synthesis involved a sequence of aldol- and enolate-bond constructions.¹⁸⁴ The construction of the C₁₅-stereocenter was realized with a [(S)-1/Sn(OTf)₂]-catalyzed Mukaiyama–aldol reaction between the aldehyde 120 and 107 yielding (R)-121 in 91% yield and 94% ee (Scheme 32). Using 120 had the advantage that the oxazole ring became part of the final cyclic product.

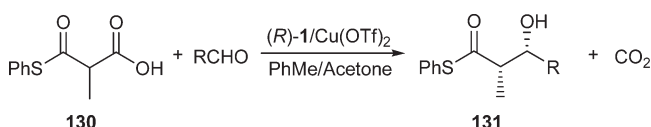
α-Ketoesters 106c (R¹ ≠ H) are the second most important class of reagents widely undergoing Mukaiyama–aldol reactions with silylketene acetals 107. The reason for this choice is that some of them are commercial products, even if only in solution, but also largely because, as is evidenced by the early papers,^{126,127} box ligands proved to be the best for this reaction. They gave high yields of the adducts as well as excellent enantioselectivities of the products. The overall results with α-ketoesters are shown in Table 22.

The results presented in Table 22 show that Mukaiyama–aldol reactions have been explored in great detail: this includes substrate, reagent, ligand, and solvent. With regard to the solvents, it appears that with the exception of MeNO₂ and MeCN all the other seven solvents investigated gave enantioselectivities > 90%. Also, taking into account the yields, tetrahydrofuran (THF), Et₂O, and CH₂Cl₂ can be classified as the best solvents for the reaction between methyl pyruvate and 1-*tert*-butylthio-1-trimethylsilyloxyethene (Table 22, entries 2 and 4–11). Different ester groups were tested (Table 22, entries 12–16), some homologous of pyruvic acid. It was observed that

Table 23. Catalyzed Enantioselective Mukaiyama–Aldol Reactions between Ketomalonate 127 and Cyclic Trimethylsilylketene Acetals 128¹⁸⁹

entry	<i>n</i>	R	box	MX ₂	solvent	<i>T</i> /°C	129 yield (%)	ee (%)
1	2	H	(S)-2	Cu(OTf) ₂	CH ₂ Cl ₂	rt	87	1
2	2	H	(R)-1	Zn(OTf) ₂	CH ₂ Cl ₂	rt	65	43
3	2	H	(R)-1	Cu(OTf) ₂	Et ₂ O	−78	88	93
4	2	H	(R)-1	Cu(OTf) ₂	Et ₂ O	−10	81	86
5	2	H	(R)-1	Cu(OTf) ₂	<i>t</i> -BuOMe	−10	77	83
6	2	H	(R)-1	Cu(OTf) ₂	CH ₂ Cl ₂	−10	80	78
7	2	H	(R)-1	Cu(SbF ₆) ₂	CH ₂ Cl 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 ₂ O	−10	81	77
10	1	H	(R)-1	Cu(OTf) ₂	Et ₂ O	−78	91	86
11	0	H	(R)-1	Zn(OTf) ₂	Et ₂ O	−10	91	45
12	0	H	(R)-1	Cu(OTf) ₂	Et ₂ O	−78	82	58
13	1	OMe	(R)-1	Cu(OTf) ₂	Et ₂ O	−78	90	85

Scheme 36



only the isopropyl group in entry 16 actually lowered the enantioselectivity. A wide range of silylketene acetals was also tested: the substituents at either the α- or β-position were changed as well as the double bond configuration. Excellent results were always obtained (Table 22, entries 17–25), which is clear confirmation of the flexibility of this reaction. Indeed, pyruvate esters undergo reaction with β-substituted silylketene acetals to provide aldol products with high *syn* diastereoselectivity (Table 22, entries 20–26). Both the (*Z*) and (*E*) isomers react in a stereoconvergent manner to provide the *syn*-aldol adduct with excellent diastereo- and enantioselectivity. The X-ray structure of [(S)-2/Cu(II)] complex seen in Figure 4 shows a distorted square-planar geometry. PM3 semiempirical calculations support this structure when dimethyl pyruvate coordinates at Cu(II) to give the reacting complex 122.¹⁸⁶ A simple inspection of this model shows that the Re face of the coordinated ketone is shielded by a *tert*-butyl group; hence, the (*S*)-products are easily predicted (Scheme 33). Furthermore, the attack on the carbonyl group is favored when the β-alkyl group is *gauche* to the methyl of the pyruvic acid because it minimizes destabilizing interactions. Hence, the preferred product is the *syn*-(*S*)-109b.

Scheme 37

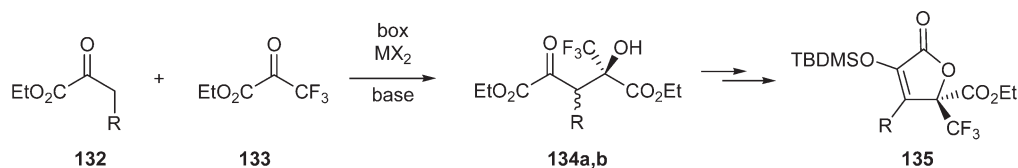


Table 24. Catalyzed Enantioselective Cross-Aldol Reactions between 132 and 133 and Homo-Aldol Reactions of 106c

entry	R	electrophile	amine	box	MX _n	solvent	conv. (%)	dr	ee (%) (conf.)	ref
1	H	133		(S)-2	Cu(OTf) ₂	Et ₂ O	40		47	198a
2	H	133	DMT	(S)-2	Cu(OTf) ₂	Et ₂ O	40		39	198a
3	H	133	DBT	(S)-2	Cu(OTf) ₂	Et ₂ O	40		39	198a
4	H	133	CyNMe ₂	(S)-2	Cu(OTf) ₂	Et ₂ O	40		42	198a
5	Me	133		(S)-2	Cu(OTf) ₂	Et ₂ O	>80	45:55	70/93	198a
6	Me	133	DMT	(S)-2	Cu(OTf) ₂	Et ₂ O	>80	58:42	82/95	198a
7	Me	133	DBT	(S)-2	Cu(OTf) ₂	Et ₂ O	>80	43:57	69/96	198a
8	Me	133	CyNMe ₂	(S)-2	Cu(OTf) ₂	Et ₂ O	>80	52:48	81/93	198a
9	CH ₂ Cy	133	DMT	(S)-2	Cu(OTf) ₂	Et ₂ O	32 ^a	45:55	68/84	198a
10	CH ₂ CH ₂ CH=CH ₂	133	DMT	(S)-2	Cu(OTf) ₂	Et ₂ O	52 ^a	42:58	85/96	198a
11	<i>n</i> -C ₅ H ₁₁	133	DMT	(S)-2	Cu(OTf) ₂	Et ₂ O	28 ^a	45:55	92/91	198a
12	<i>i</i> -Bu	133	DMT	(S)-2	Cu(OTf) ₂	Et ₂ O	66 ^a	45:55	62/75	198a
13 ^b	H	106c		(S)-2	Cu(OTf) ₂	Et ₂ O	>80		65 (S) ^c	198a, 198b
14 ^b	H	106c		(S)-2	Cu(SbF ₆) ₂	Et ₂ O	~80		50 (S) ^c	198a, 198b
15 ^b	H	106c	DMA	(S)-2	Zn(OTf) ₂	Et ₂ O	>80		16 (R) ^c	198b
16 ^b	H	106c	DMA	(R)-1	Cu(OTf) ₂	Et ₂ O	>80		28 (R) ^c	198b
17 ^b	H	106c	DMA	(S)-2	Cu(OTf) ₂	Et ₂ O	>80		96 (S) ^c	198a, 198b
18 ^b	H	106c	DBA	(S)-2	Cu(OTf) ₂	Et ₂ O	>80		93 (S) ^c	198a
19 ^b	H	106c	CyNMe ₂	(S)-2	Cu(OTf) ₂	Et ₂ O	>80		50 (S) ^c	198a
20 ^b	H	106c	DMA	(S)-2	Cu(OTf) ₂	toluene	~80		62 (S) ^c	198a
21 ^b	H	106c	DMA	(S)-2	Cu(OTf) ₂	CH ₂ Cl ₂	~80		21 (R) ^c	198a
22 ^b	H	106c	DMA	(S)-2	Cu(SbF ₆) ₂	CH ₂ Cl ₂	>80		63 (R) ^c	198a
23 ^b	H	106c	DBA	(S)-2	Cu(SbF ₆) ₂	CH ₂ Cl ₂	>80		75 (R) ^c	198a
24 ^b	H	106c	CyNMe ₂	(S)-2	Cu(SbF ₆) ₂	CH ₂ Cl ₂	>80		77 (R) ^c	198a, 198b

^a Isolated yields of corresponding isotetronic acid derivative 135. ^b Dimerization reaction of 106c. ^c ee of the corresponding isotetronic acid derivative 135.

Obviously this model does not account for the anti diastereoselectivity given by 1-oxypyridine-2-carbaldehyde **112** derivatives (Scheme 30). The involvement of the *N*-oxide group in the structure of a different reacting complex will be emphasized in a further section.

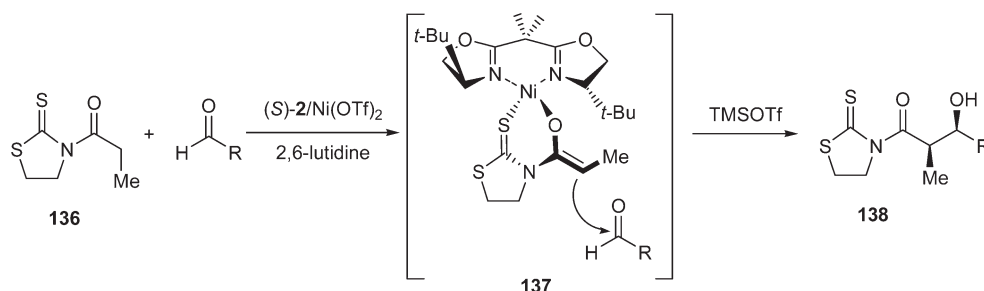
Methyl pyruvate **106c** can undergo the Mukaiyama–aldol reaction with the silylketene acetal **123** to give dioxenone (S)-**124** (Scheme 34). This polyfunctionalized building block is most useful for further transformations. The chiral ligand (S)-**2** is much better than the corresponding **1** (but less efficient than **3a**, **d**), and (rather unusually) the Cl counterion is much better than OTf (91% ee vs 74 ee).^{25,32} The reaction between the same ketoester and silylketene acetal **125** (Scheme 34), which is highly reactive because of the strain associated with the exocyclic double bond, was used in an early step in the synthesis of the antitumor agent (–)-irofulven.¹⁸⁸ The reaction gave **126** with the required (R)-configuration in 95% yield and 92% ee.

Among the activated ketones, diethyl ketomalonate **127** is particularly worth noting. Its reaction with several silylketene

acetals can be catalyzed by box-based complexes with different ligands, cations, and counterions and in different solvents.¹⁸⁹ The adducts **129** are obtained in high yields and excellent enantioselectivities when the trimethylsilylketene acetals **128** have a cyclic aromatic structure (Scheme 35, Table 23). Points worth noting are as follows: The double bond in the five-membered ring reduces the enantioselectivity compared to those of six- and seven-membered rings (Table 23, entries 11 and 12), (R)-**1** is much better than the *tert*-Bu-box (Table 23, entry 1 vs 6), Cu(OTf)₂ is better than Cu(SbF₆)₂ (Table 23, entry 7 vs 8), and furthermore, although Zn(II) can be used as the Lewis acid, the enantiomeric excess is lowered (Table 23, entries 2, 9, and 11). Among the other silylketene acetals tested, only (Z)-1-phenyl-1-trimethylsilyloxypropene gives an ee of 90%.

Other experiments, mainly directed at comparing the efficiency of the catalysts derived from some supported box or other new ligands versus box **1** or **2**, have been carried out. The relevant references are reported here mainly for the sake of completeness.^{33,98,190–193} More interesting, however, with possible future

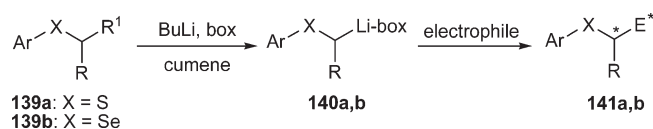
Scheme 38

Table 25. Enantioselective Aldol Additions of **136** to Various Aldehydes¹⁰²

entry	R	box	syn/anti	(<i>R,R</i>)- 138 ee (%)
1 ^a	Ph	(<i>S</i>)- 1	70:30	60
2	Ph	(<i>S</i>)- 2	94:6	97
3	<i>p</i> -MeC ₆ H ₄	(<i>S</i>)- 2	93:7	95
4	<i>p</i> -ClC ₆ H ₄	(<i>S</i>)- 2	90:10	91
5	1-naphthyl	(<i>S</i>)- 2	93:7	92
6	2-naphthyl	(<i>S</i>)- 2	92:8	93
7	2-furyl	(<i>S</i>)- 2	88:12	95
8	Me-CH=CH	(<i>S</i>)- 2	93:7	97
9	Ph-CH=CH	(<i>S</i>)- 2	88:12	93
10	Me	(<i>S</i>)- 2	97:3	93
11	Et	(<i>S</i>)- 2	97:3	90
12	<i>i</i> -Pr	(<i>S</i>)- 2	98:2	90

^a Reaction catalyzed by $\text{Ni}(\text{SbF}_6)_2$.

Scheme 39



developments of the protocol in mind, are some results concerning Mukaiyama–aldol reactions performed in aqueous media or in ionic liquids, catalyzed by zinc or copper(II) complexes of box **1** and **2**.^{194,195}

As an alternative to the Mukaiyama–aldol approach, the classic 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 uses the methyl malonic acid half thioester (**MAHT**) **130** as the enolate source catalyzed by $[(R)\text{-1}/\text{Cu}(\text{OTf})_2]$; this undergoes decarboxylative addition at ambient temperature with a variety of aldehydes to afford the *syn*-3-hydroxy-2-methylthiopropionic acid (*S*)-phenyl esters **131** (Scheme 36).¹⁹⁶ Yields are in general very good, and the enantioselectivity is always excellent (in the range 89–96% ee). However, the *syn*/*anti* diastereoselectivity is less satisfactory, since it is seldom $>9:1$. The absolute configuration of **131** for $\text{R} = \text{CH}_2\text{CH}_2\text{Ph}$ was determined to be (*2S,3R*).

A thorough investigation of the mechanism of this reaction was undertaken to determine whether or not the ester enolate is generated from **MAHT** by decarboxylation or deprotonation. Both kinetic studies and the use of labeled reagents allowed a mechanism to be formulated. This involved deprotonative enolization, addition to the aldehyde, decarboxylation, and finally protonation of the β -hydroxyenolate to give **131**.¹⁹⁷

α -Ketoesters can 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., **133**), while the precursor of the enolate **132** has at least one hydrogen atom in the α -position to the carbonyl group (Scheme 37). When $\text{R} = \text{H}$, two enantiomers are obtained; if $\text{R} \neq \text{H}$, two diastereoisomers **134a,b**, each constituting an enantiomeric couple, are formed. These can be converted into the isotetronic derivative **135**.¹⁹⁸ Table 24 reports the results.

Among the cross-aldol reactions, that between ethyl pyruvate and ethyl trifluoropyruvate and catalyzed by $[(S)\text{-2}/\text{Cu}(\text{OTf})_2]$ (Table 24, entries 1–4) was found to give a low enantiomeric excess independently of the presence or type of base. Better results in terms of enantioselectivity (up to 96% ee) were obtained with ethyl α -ketobutyrate and its homologues (Table 24, entries 5–12). The scope of the reaction is, however, limited by the poor 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.¹⁹⁸ With Et_2O as the solvent, the optimized conditions for box, cation, and counterion are those reported in Table 24 (entries 13–19). The crucial factor when $[(S)\text{-2}/\text{Cu}(\text{OTf})_2]$ is used as the catalyst becomes the choice of amine. This is because *N,N*-dimethylaniline (DMA) and *N,N*-dibenzylaniline (DBA) both give the analogous of (*S*)-**135** (with a methyl group instead of CF_3) in 96% and 93% ee, respectively, whereas using cyclohexyldimethylamine (CyNMe_2) and several others amine bases gives results that do not exceed the enantioselectivity obtained in the absence of base (Table 24, entry 13 vs 19). The reaction was studied in some detail in different solvents. The most significant feature, when the catalyst is $[(S)\text{-2}/\text{Cu}(\text{SbF}_6)_2]$, is the strong inversion of the enantioselectivity in CH_2Cl_2 and the reduced importance of the role of the amine (Table 24, entries 22–24).

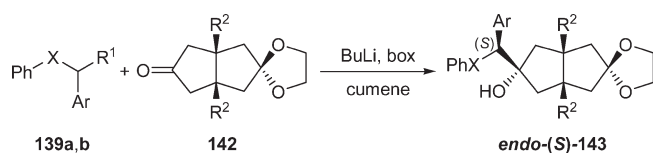
The important target of a catalyzed aldol reaction is to control diastereo- and enantioselectivity at the same time during the synthesis process. The rigid structure of the reacting intermediate, when the reagent coordinates in a bidentate fashion, may help to achieve this result. The complex $[(S)\text{-2}/\text{Ni}(\text{OTf})_2]$ was found to be the best catalyst for the addition of

Table 26. Enantioselective Addition of α -Sulfenyl and α -Selenyl Carbanions (140a,b) to Various Carbonyl Electrophiles

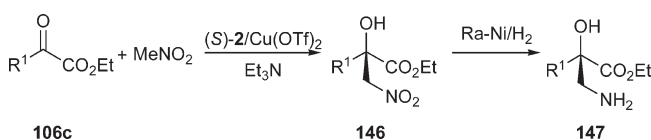
entry	Ar	X	R	R ¹	box	electrophile	yield (%)	anti/syn	ee (%) (conf.)	ref
1	Ph	S	Ph	SnBu ₃	(S)-1	Ph ₂ CO	60		66 (S)	199, 200
2	2-Pyr	S	Ph	H	(S)-1	Ph ₂ CO	49		51	200
3	2-Pyr	S	Ph	H	(S)-2	Ph ₂ CO	86		90 (R)	200
4	2-Quin	S	Ph	H	(S)-2	Ph ₂ CO	99		71 (R)	201
5	Ph	S	S-Ph	H	(S)-1	PhCHO	55		6	202
6	Ph	S	S-Ph	H	(S)-2	PhCHO	99		33	202
7	2-Pyr	S	<i>St</i> -Bu	H	(S)-1	Ph ₂ CO	86		61	202
8	2-Pyr	S	<i>St</i> -Bu	H	(S)-2	Ph ₂ CO	53		68	202
9	2-Pyr	S	<i>Si</i> -Pr	H	(S)-1	Ph ₂ CO	92		68	202
10	2-Pyr	S	S-Me	H	(S)-1	Ph ₂ CO	80		42	202
11	2-Pyr	S	S-Ph	H	(S)-1	Ph ₂ CO	75		18	202
12	2-Pyr	S	<i>St</i> -Bu	H	(R)-1	PhCHO	91	83:17	85 (1 <i>R</i> ,2 <i>S</i>) ^a	202
13	2-Pyr	S	<i>St</i> -Bu	H	(S)-1	MesCHO	83	90:10	85 (1 <i>R</i> ,2 <i>S</i>) ^a	202
14	2-Pyr	S	<i>St</i> -Bu	H	(S)-1	2-NaphCHO	92	80:20	83 (1 <i>R</i> ,2 <i>S</i>) ^a	202
15	Ph	Se	Ph	Se-Ph	(S)-1	Ph ₂ CO	62		81 (S)	203
16	Ph	Se	Ph	Se-Ph	(S)-2	Ph ₂ CO	78		78 (S)	203
17	Ph	Se	Ph	Se-Ph	(S)-2	cyclohexanone	83		95	203
18	2-Pyr	Se	Ph	Se-Ph	(S)-1	Ph ₂ CO	77		64 (R)	203
19	2-Pyr	Se	Ph	Se-Ph	(S)-2	Ph ₂ CO	73		77 (R)	203

^a ee of the anti product.

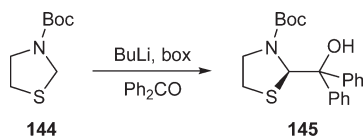
Scheme 40



Scheme 42



Scheme 41



3-propionoyl-2-thiazolidinethione (**136**) to various aldehydes (Table 25).¹⁰² It was found that 2,6-lutidine was the base most suitable for generating the bichelated enolate bound in the reacting intermediate **137**. If the coordination at 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 and *syn*-**138** is the main diastereoisomer (Scheme 38). The silylation and decomplexation of the coordinated product gives the substituted (2*R*,3*R*)-3-hydroxy-2-methyl-1-[2-thioxo(1,3-thiazolidin-3-yl)]propan-1-ones (**138**) with excellent diastereomeric ratio and enantioselectivity (Table 25).

The Toru group studied in detail the formation of α -thio- and α -seleno-carbanions (**140a,b**) from derivatives of phenyl or 2-pyridyl sulfide or selenide (**139a,b**), (eventually α -selenyl, or α -stannyl substituted) with BuLi, in the presence of box. Their enantioselective reactions with aldehydes or ketones acting as electrophiles give products **141a,b** (Scheme 39).^{199–204}

It should be pointed out that **1** and **2** are not always the best box ligands. This is probably because this particular reaction has such intrinsic diversity with the majority of the catalyses reported in this review. BuLi acts as a base for the generation of the carbanion, and its lithium cation behaves as a Lewis acid that coordinates the carbanion with the chiral ligand. This induces the enantioselectivity, and this small, hard cation prefers **3c** (instead of the more sterically demanding **2**) in the construction of the reactive intermediate involved in the catalytic cycle.²⁰⁰ Among the different reactions reported in Table 26, α -thio-carbanions **140a** give better enantioselectivity if the attached group is 2-pyridyl (Table 26, entries 2, 3, and 7–11 vs 1, 5, and 6). In this case, there is not a net choice between box **1** and **2**, and the reaction is anti-diastereoselective (Table 26, entries 12–14).^{200–202} The reaction can also be run with α -lithiated allyl aryl sulfides: Enantioselectivity is reasonable, and the chemoselectivity is unsatisfactory.²⁰⁴

Outstanding results for these reagents can be observed in the enantioselective reaction of the α -lithio-benzyl-2-pyridyl selenide **140b** (Ar = 2-pyridyl, R = Ph), which gives products with an absolute configuration of the chiral center opposite to that obtained in the reaction for the α -lithio-benzyl phenyl selenide **140b** (Ar = R = Ph) (Table 26, entries 15 and 16 vs 18 and 19).²⁰³ Furthermore, the reaction of this last anion with cyclohexanone (Table 26, 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 Et₃N) and the formation of the axially chiral benzylidenecyclohexanones with 90% ee.^{205a}

The recent **expansion of this reaction to using *cis*-bicyclo[3.3.0]octane-3,7-dione monoethylene ketals 142** as electrophiles is **that cyclohexanones are now used**. The aldol reaction is strongly endo-selective, and (*S*)-143a,b are the products. The reaction occurs frequently with a diastereomeric ratio > 98:2 and enantioselectivities > 90% ee (Scheme 40).^{205b} In contrast, it was found that the different substituents on 142 do not have a strong influence on the selectivity and box 2 rather than 1 is by far the better ligand (Table 22, entry 1 vs 2–7).

The lithiated α -thio-carbanion can derive from *N*-Boc-thiazolidine 144 (Scheme 41), and the enantioselectivity of the reaction with benzophenone depends on the box employed: (*S*)-1 gives (*R*)-145 (illustrated in the scheme) with 82% ee, whereas (*S*)-2 gives the (*S*)-enantiomer with 68% ee.²⁰⁶

The addition reaction between carbonyl compounds and nitroalkanes to yield nitroalcohols, in the presence of a base that deprotonates the nitroalkanes to give nitronates, is known as the Henry reaction. One report focused on the asymmetric version of this reaction.²⁰⁷ The first test of the capacity of a box to be a useful ligand in the field was the reaction between α -ketoesters 106c and MeNO₂ (Scheme 42).^{208,209} The optimization of the box [(*S*)-2], cation [Cu(II)] proved better because Zn(II) gave unsatisfactory enantioselectivity of the (*S*)-enantiomer, counterion (OTf although SbF₆ also gave comparable enantioselectivities), and base (Et₃N and *N*-methyl-morpholine were by far the best deprotonating agents) all made it possible to explore this reaction in some detail. Its importance lies in the fact that the product 146 opens up easy access to the β -amino- α -hydroxy

esters 147, which make it possible to assign the (*R*)-configuration to the chiral center.²⁰⁹

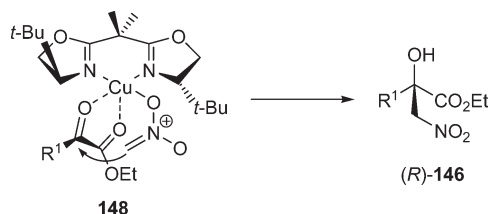
Some **relevant** effects of the R¹ substituents, which are reported in Table 28, should be pointed out: The presence of unsaturation in the γ,δ -position of 106c reduces the enantioselectivity (Table 28, entry 9 vs 7 and 8). Both yield and enantioselectivity are lowered with an increase in the electron-donating character of the aryl group (Table 28, entries 10–13).

The absolute (*R*)-configuration, which was unambiguously demonstrated for 147 (R¹ = *p*-C₆H₄-Cl),²⁰⁹ can be rationalized if both the α -ketoester and MeNO₂ are coordinated to the copper cation in the equatorial position. The ester carbonyl oxygen atom, on the other hand, is coordinated to the axial position (Scheme 43). After deprotonation of MeNO₂ to form the nitronate, the square-pyramidal configuration of 148 allows the attack of the nucleophilic carbon atom of the nitronate at the Re face of the keto group with subsequent formation of (*R*)-146.

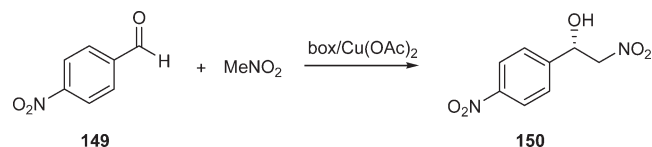
The Henry reaction was carried out using MeNO₂ and a range of aldehydes.^{66,100,210} The best cationic source was found to be Cu(OAc)₂ whereas both (*S*)-1 and (*S*)-2 gave unsatisfactory enantiomeric excesses of (*S*)-150 (ca. 40%). This is the product of the reaction with *p*-nitrobenzaldehyde 149 (Scheme 44). The boxes of choice for reaction **with a large variety of aldehydes are 7a and (*R,S*)-9a**.^{66,100} They gave excellent enantiomeric excesses of the products, but this will be discussed in a further section. We can anticipate that the reacting complex has a square-pyramidal configuration similar to 148, with the oxygen atom of the aldehyde and nitronate both coordinated to Cu(II) together with an acetoxy group.

A variant of the Henry reaction, similar to the Mukaiyama–aldol reaction, can also occur where silyl nitronates are used instead of nitroalkanes. Cu(OTf)₂ proved to be the best Lewis

Scheme 43



Scheme 44

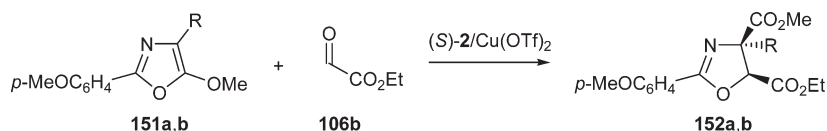
Table 28. Enantioselective Henry Reactions of α -Ketoesters 106c and MeNO₂, with Et₃N as Base; Catalyzed by (*S*)-2/ Cu(OTf)₂

entry	R ¹	yield (%)	(<i>R</i>)-146 ee (%)	ref
1	Me	>95	92	208, 209
2	Et	73	87	208, 209
3	PhCH ₂ CH ₂	47	77	208, 209
4	<i>n</i> -hexyl	91	93	209
5	<i>i</i> -Bu	99	92	209
6	Me ₂ CHCH ₂ CH ₂	90	94	209
7	CH ₂ =CHCH ₂ CH ₂	97	94	209
8	MeCH=CHCH ₂ CH ₂	92	94	209
9	MeCH=CH	>96	60	209
10	<i>p</i> -MeOC ₆ H ₄	68	57	209
11	Ph	81	86	208, 209
12	<i>p</i> -ClC ₆ H ₄	91	88	209
13	<i>p</i> -NO ₂ C ₆ H ₄	99	93	208, 209

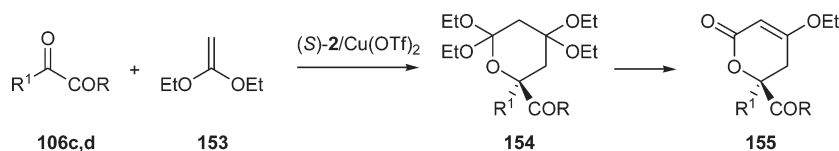
Table 27. Enantioselective Addition of α -Sulphenyl and α -Selenyl Carbanions from 139a,b to 142^{205b}

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

Scheme 45



Scheme 46

Table 29. Enantioselective Aldol Additions of 106c,d to Ketene Diethylacetal 153²¹³

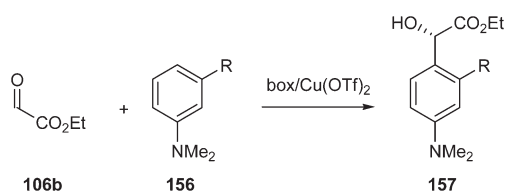
entry	R ¹	R	box	CuX ₂	solvent	yield (%)	(R)-154 ee (%)
1	Ph	OEt	(S)-2	OTf	Et ₂ O	80 ^a	93
2	Ph	OEt	(S)-2	SbF ₆	CH ₂ Cl ₂	<20	^b
3	Ph	OEt	(S)-2	OTf	THF	61 ^a	77
4	Ph	OEt	(R)-1	OTf	Et ₂ O	79 ^a	12
5	Me	OMe	(S)-2	OTf	Et ₂ O	74	83
6	Et	OMe	(S)-2	OTf	Et ₂ O	70	77
7	<i>i</i> -Pr	OEt	(S)-2	OTf	Et ₂ O	58	80
8	Me	Me	(S)-2	OTf	Et ₂ O	71	95
9	Me	Et	(S)-2	OTf	Et ₂ O	70	90
10	Me	Ph	(S)-2	OTf	Et ₂ O	58	90

^a 2-Hydroxy-2-phenylsuccinic acid as a side product (6–14% yield).^b Not determined.Table 30. Enantioselective Friedel–Crafts Reaction of Ethyl Glyoxylate 106b with *N,N*-Dimethylanilines 156²¹⁴

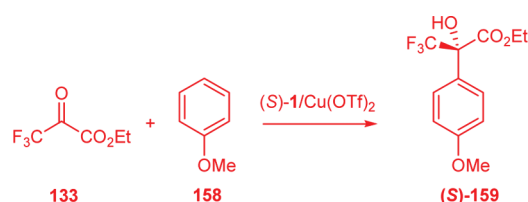
entry	R	box	solvent	yield (%)	ee (%) (conf.)
1	H	(R)-1	CH ₂ Cl ₂	70	54 (S)
2	H	(R)-1	Et ₂ O	76	42 (S)
3	H	(R)-1	THF	81	22 (S)
4	H	(S)-2	CH ₂ Cl ₂	81	80 (S)
5	H	(S)-2	Et ₂ O	78	89 (S)
6	H	(S)-2	THF	72	90 (S)
7	F	(S)-2	THF	58 (80) ^a	81 (85) ^a
8	Cl	(S)-2	THF	41 (84) ^a	95 (93) ^a
9	Br	(S)-2	THF	36 (68) ^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 excess in CH₂Cl₂.

Scheme 47



Scheme 48

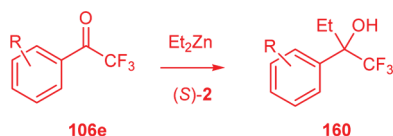


acid. However, (S)-1 and (S)-2 are not the best boxes, and benzaldehyde gave an ee of only 19%.²¹¹ The reactions are threo-selective and good stereoselectivity was in fact obtained using a different box, and this makes the reaction more promising.

Ethyl glyoxylate 106b (R¹ = CO₂Et) can undergo enantioselective aldol reactions with 5-alkoxyoxazoles 151a,b. The reaction is efficiently catalyzed by [(S)-2/Cu(OTf)₂·(H₂O)₂]. Assuming the analogue of 122 shown in Scheme 33 represents a suitable model reaction, the electrophilic 4-position of 151 attacks the Si face of the Lewis-acid-coordinated glyoxylate to give (4*R*,5*S*)-152a,b (Scheme 45). Excellent yields, diastereoselectivities, and enantioselectivities [**a** (R = H), >99%, *cis/trans* 95:5, 97% ee (*cis*); **b** (R = Me), 94%, *cis/trans* 94:6, 99% ee (*cis*)] were obtained.²¹²

The oxazole fragment –O–C₅(=C₄)–OMe is analogous to the ketene diethylacetal 153; hence its aldol reaction with either α-ketoesters or α-diketones 106c,d is not unexpected. However, the ratio (2:1) of the reactants leading to 154 and their subsequent hydrolysis to yield the optically active unsaturated lactones 155 makes this reaction both synthetically and mechanistically very attractive (Scheme 46).²¹³ Sometimes the monoaddition product of ethyl benzoylformate 106c (R¹ = Ph, R = OEt) (2-hydroxy-2-phenylsuccinic acid) is a side product of the reaction (6–30% yield, up to 99% ee). Again, its known absolute (*R*)-configuration allows the assumption that 122 is a valid reacting model, involving the attack of the ketene acetal to the Si face of the bound α-ketoesters. When optimized, the reaction, with [(S)-2/Cu(OTf)₂] and Et₂O as solvent

Scheme 49

Table 31. Enantioselective Addition of Diethylzinc to Trifluoromethyl Aryl Ketones 106e²¹⁷

entry	R	box	160 yield (%)	160 ee (%)
1	H	(S)-2	95	51
2	H	(R)-1	99	7
3	4-Br	(S)-2	99	38
4	4-Cl	(S)-2	74	41
5	4-OMe	(S)-2	83	56
6	4-SMe	(S)-2	99	52
7	4- <i>t</i> -Bu	(S)-2	75	60
8	4-CN	(S)-2	71	16
9	4-CO ₂ Et	(S)-2	92	25
10	3-Me	(S)-2	99	54
11	3-NO ₂	(S)-2	83	7
12	2-Cl	(S)-2	99	12

(Table 29, entries 1–4), is flexible and can be performed using different α -ketoesters **106c** (Table 29, entries 1 and 5–7) and α -diketones **106d** (Table 19, entries 8–10).

When the nucleophile is an aromatic or a heterocyclic compound, the addition to the activated carbonyl group of ethyl glyoxylate (**106b**, R = CO₂Et, R¹ = H) can be considered as an enantioselective *Friedel–Crafts reaction*. Clearly, the aromatic ring must be activated by suitable substituents (e.g., *N,N*-dimethylaniline and its substituted derivatives **156**) for the electrophilic substitution to occur. The products **157** (Scheme 47) are obtained in very good yields and excellent enantioselectivities but only with Cu(OTf)₂ and the solvents reported in Table 30.^{214,215} Three points deserve attention: A sharp regioselectivity, dictated by the dimethylamino group, is always observed; the box (S)-2 gives better enantioselectivity than (R)-1 (Table 30 entries 1–3 vs 4–6); and finally both catalysts derived from (R)-1 and (S)-2 give (S)-129 (R = H) as product.

This reaction can be successfully performed with *N,N*-(dimethylamino)-1-naphthalene, *N,N*-(dimethylamino)-1-anthracene, as well as several heterocycles such as *N*-methylindoline, *N*-methyl-tetrahydroquinoline, julolidine, and 2-methyl- or 2-TMS-furan. The best enantioselectivities were obtained with the first two heterocycles (83 and 93% ee, respectively). The regioselectivity in the carbocyclic ring recalls that of *N,N*-dimethylaniline.²¹⁴

Some interesting conditions that were tested for the *Friedel–Crafts reaction* between anisole **158** and ethyl trifluoropyruvate **133** have been reported. Under solvent-free conditions, the reaction catalyzed by [(S)-1 Cu(OTf)₂] gave (S)-159 in 85% yield and 79% ee (Scheme 48).²¹⁶ Rather unusually, box **2** proved to be inactive and the catalyst of choice for a large number of aromatic ethers was found to be [(*R,S*)-5b/Cu(OTf)₂]. This will be further discussed in section 5.2.

The addition of more traditional nucleophiles to carbonyl groups is not often performed with the type of catalysts derived from the boxes discussed in this section because suitably

substituted ligands are required. However, an interesting result has recently been achieved with the first report of an asymmetric variant of the nucleophilic addition of diethylzinc to trifluoromethyl aryl ketones **106e**. The reaction was run in the presence of (S)-2 and gave 2-aryl-1,1,1-trifluorobutan-2-ols **160** with up to 61% ee (Scheme 49, Table 31). However, the enantioselectivity was found to fall in the presence of electron-attracting substituents and using (R)-1 as the chiral ligand.²¹⁷

The general synthesis of enantiomerically enriched amines and amino acids in organic chemistry using catalytic processes has attracted the interest of several groups. Many strategies have been developed, but at least two deserve particular 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 potentially suggestive strategy, because of its analogy to a well-known enzymatic reaction, whose potentiality has not yet been fully explored. The reaction of ethyl pyruvate and pyridoxamine, catalyzed by [(S)-1/Zn(OTf)₂], gives a 66% yield of the Boc-protected alaninate. The enantiomeric excess cannot be determined for technical reasons. On changing to methyl 3-indole pyruvate **161** and 4-picolyamine **162**, the reaction, catalyzed by both Zn(OTf)₂ or CuPF₆ complexes of (R)-1 (Scheme 50), affords **163** in moderate yield and low enantioselectivity (20% ee).²¹⁸

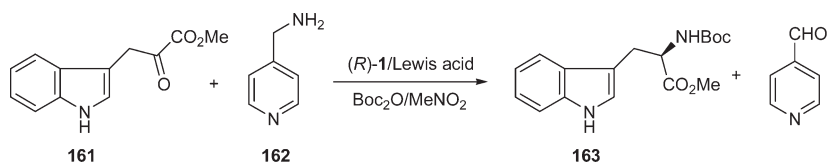
Within the context of the *addition of organometallic reagents to imines*, the effect of the box structure in the asymmetric addition of MeLi has been studied in detail by taking (S)-2 as the reference; for this reason the results of the addition of organolithium to **164** to give the amine **165** (Scheme 51 and Table 32) are considered in this section.^{22,219,220} However, the comparison with other box ligands will be discussed 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 asymmetric synthesis of (R)-desmethyisibutramine. This is a pharmacologically active metabolite of the antiobesity drug sibutramine. It is important to note, as reported in Table 32 (entries 1 and 5 vs 2 and 6), that (S)-2 gave an excellent yield of the amine with a satisfactory enantioselectivity (95% yield and 40% ee). On the other hand, (S)-1 did not catalyze the reaction.²²¹

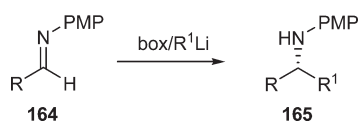
The enantioselective nucleophilic addition of Grignard reagents to *N*-(2-pyridylsulfonyl)imines **166**, in the presence of box catalysts, affords the products (S)-167 with good yield and ee (Scheme 52, Table 33).^{222,223} The results presented in Table 33 raise some interesting points: (i) Phenyl box is better than the corresponding *tert*-butyl one (Table 33, entries 1 vs 2). (ii) The enantioselectivity depends on the Grignard reagent R¹MgX. By changing X, ee increases in the order Cl > Br > I (Table 33, entries 3–5). The steric hindrance of R¹ has a negative effect (Table 33, entries 11–15). (iii) The structure of the amine residue influences the yield more than the enantioselectivity (Table 33, entries 6–10). The same reaction catalyzed by (S)-1 with **166** (R = Ph) and MeLi gives (R)-167 in 35% yield and 35% ee.²²² This result is much better than those obtained in previous experiments.²²⁴

When the nucleophile that adds to the imino group is a CN anion, then the reaction is known as the named *Strecker reaction*. In its enantioselective form, it is one of the most important synthetic methods for obtaining optically active α -amino acids. Of the different *N*-aryl- and *N*-alkyl-substituted imines investigated, only the *N*-(2-pyridylsulfonyl)imines **166**, mentioned previously, were activated by the complex that formed between (S)-1

Scheme 50



Scheme 51



Scheme 52

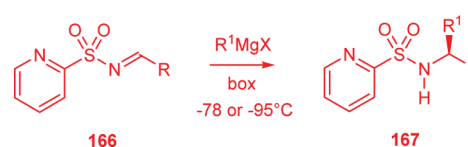


Table 32. Asymmetric Addition of Organolithiums to Imine 164

entry	R	R ¹	box	solvent	yield (%)	ee (%) (conf.)	ref
1	Ph	Me	(S)-2	toluene	90	67 (R)	22, 220
2	Ph	Me	(S)-1	toluene	93	44 (R)	219
3	(E)-PhCH=CH	Me	(S)-2	toluene	73	94 (R)	22, 220
4	PhCH ₂ CH ₂	Me	(S)-2	toluene	81	93 (R)	22, 220
5	Ph	<i>n</i> -Bu	(S)-2	toluene	96	29 (R)	219
6	Ph	<i>n</i> -Bu	(S)-1	toluene	74	3 (R)	219

and either Cu(OTf)₂ or Mg(OTf)₂ to give (R)-**168** (Scheme 53, Table 34).^{223,225} The best compromise between yield and enantioselectivity is reached when Mg(OTf)₂ is the Lewis acid (Table 34, entries 1, 2, 7, and 8 vs 4–6). This result can be safely attributed to the dual role played by the 2-pyridylsulfonyl group. It acts as both an activator and a controller of the induced stereoselectivity. This is possible because one of the sulfonyl oxygens and the heteroaryl nitrogen are involved in the coordination of **166** to the catalyst.

The *N*-(2-pyridylsulfonyl)imines **166** can also undergo a Mannich-type reaction with the silyl ketene acetal **113a** to give β-amino acid derivatives **169** (Scheme 54). After a careful screening of the different ligands and Lewis acids, the best catalyst was found to be the complex formed between (S)-**1** and Cu(OTf)₂ (Table 35). The absolute configuration of the product was found to be (R)-**169**. This results from its approach to the Si face of **166**, which forms a square-planar complex with the Cu(II) through one of the sulfonyl oxygens and the heteroaryl nitrogen.²²⁶

Several Mannich reactions were found to be catalyzed by box complexes. For example, the reaction of the α-iminoester **101** with enol nucleophiles derived from the α-ketoesters **132** (Scheme 55) gives **170** with excellent syn-diastereo- and enantioselectivity (Table 36).^{227a}

The [box/Cu(II)] complexes have some specific properties: first they promote the keto to enol tautomerization of the β-ketoester, then they catalyze the diastereo- and enantioselective C–C bond formation. This versatile methodology has been further extended to the reaction of α-ketoesters **132** with azodicarboxylic esters **171**. Here, there is formation of a C–N bond, which is the core of the synthetically important products **172** (Scheme 56).^{227b} The acidity of the proton next to the keto group makes this product unstable. Hence, a stereoselective reduction with L-Selectride, cyclization, and esterification with

TMS-diazomethane gave the final product *N*-amino oxazolidinones **173**. Table 37 reports yields and enantioselectivities of these reactions. The results show that the best catalyst is [(R)-1/Cu(OTf)₂] (Table 37, entry 1 vs 2), and the configuration of the products in entries 1–3 was shown to be (4*S*,5*R*)-**173**.

The Mannich reaction with *N*-tosyl-α-iminoester **101** can also be performed for malonates **174a**,^{228a} β-ketoesters **174b**,^{228a} and β-ketophosphonates **174c**,^{228b} to give **175a–c** (Scheme 57). Reactions involving the malonates **174a** (R¹ = OR, X = CO₂R) can 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 to assist the catalytic turnover (Table 38, entries 1 vs 2–6). On the other hand, the latter gives better yields and enantioselectivities without the need for an additive (Table 38, entries 7 vs 8–12). The same absolute configuration (R) was found for the Mannich adducts of diethyl malonate (Table 38, entries 1, 2, 8, and 9) prepared using [(R)-1/Cu(OTf)₂] and [(S)-2/Cu(OTf)₂], although the ligands have opposite configurations. In the reaction of β-ketoesters **174b** (X = CO₂R), there is a good correlation between the size of the ester moiety and the selectivity (Table 38, entries 13–19). β-Ketoesters derived from primary alcohols (Table 38, entries 13 and 14) gave products with good yields and diastereoselectivities but low enantioselectivities. However, β-ketoesters derived from tertiary alcohols (Table 38, entries 15–19) proved to be the best substrates. In spite of the fact that the yields were moderate, the diastereo- and enantioselectivities were good. More bulky substituents on the ester moiety caused inversion of the absolute configuration of the products (Table 38, entries 15 and 16).^{228a} After extensive screening of different boxes, 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 **101** and β-ketophosphonates **174c** [X = P(O)(OEt)₂].^{228b} The absolute configuration of **175c** (R = R¹ = Me) (Table 38, entry 27) was found to be (2*R*,3*R*) and is a result of the attack on the Re face of the coordinated enolized **174c**.

The box-based catalytic enantioselective α-amination via the enolate form of the β-ketoesters **174b**^{229a} and β-ketophosphonates **174c**^{229b} with azodicarboxylates **171** can be achieved without the necessity of a base as is sometimes required in reactions with *N*-tosyl-α-iminoesters. The aminated products **176b,c** (Scheme 58) are obtained with excellent yields and enantioselectivities as reported in Table 39. The best box is (S)-**1** in combination with Cu(OTf)₂ for the β-ketoesters, whereas Zn(OTf)₂ turned out to be

Table 33. Asymmetric Addition of Grignard Reagents to *N*-(2-Pyridylsulfonyl)imines **166**

entry	R	Grignard reagent	box	167 yield (%)	167 ee (%) (conf.)	ref
1	Ph ^a	MeMgI	(<i>S</i>)- 1	75	59 (<i>S</i>)	222, 223
2	Ph ^a	MeMgI	(<i>S</i>)- 2	56	40 (<i>S</i>)	222, 223
3	Ph ^b	MeMgI	(<i>S</i>)- 1	27	72 (<i>S</i>)	222, 223
4	Ph ^b	MeMgBr	(<i>S</i>)- 1	79	83 (<i>S</i>)	222
5	Ph ^b	MeMgCl	(<i>S</i>)- 1	53	86 (<i>S</i>)	222, 223
6	<i>p</i> -Tolyl ^b	MeMgBr	(<i>S</i>)- 1	67	83	222, 223
7	<i>p</i> -ClC ₆ H ₄ ^b	MeMgBr	(<i>S</i>)- 1	77	76	222
8	1-naphthyl ^b	MeMgBr	(<i>S</i>)- 1	74	76	222
9	(<i>E</i>)-PhCH=CH ^b	MeMgBr	(<i>S</i>)- 1	98	82	222
10	2-furyl ^b	MeMgBr	(<i>S</i>)- 1	38	87	222
11	Ph ^b	EtMgBr	(<i>S</i>)- 1	74	50	222
12	Ph ^b	BuMgBr	(<i>S</i>)- 1	69	51	222
13	Ph ^b	<i>i</i> PrMgBr	(<i>S</i>)- 1	87	6	222
14	Ph ^a	<i>t</i> -BuMgBr	(<i>S</i>)- 1	15	6	222
15	Ph ^b	PhMgBr	(<i>S</i>)- 1	72	61	222

^a Temperature -78°C . ^b Temperature -95°C .

Table 34. Strecker-type Reaction of TMSCN with *N*-(2-Pyridylsulfonyl)imines **166**

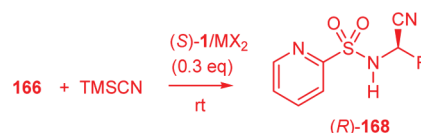
entry	R	MX ₂	solvent	168 yield (%)	168 ee (%) (conf.)	ref
1	Ph	Mg(OTf) ₂	CH ₂ Cl ₂	81	75 (<i>R</i>)	223, 225
2	Ph	Mg(ClO ₄) ₂	CH ₂ Cl ₂	91	49 (<i>R</i>)	223, 225
3	Ph	MgBr ₂	CH ₂ Cl ₂	92	21 (<i>R</i>)	223, 225
4	Ph	Cu(OTf) ₂	CH ₂ Cl ₂	27	71 (<i>R</i>)	223, 225
5	Ph	Cu(SbF ₆) ₂	CH ₂ Cl ₂	28	73 (<i>R</i>)	225
6	Ph ^a	Cu(OTf) ₂	CH ₂ Cl ₂	10	94 (<i>R</i>)	223, 225
7	Ph	Mg(OTf) ₂	ClCH ₂ CH ₂ Cl	99	72 (<i>R</i>)	225
8	Ph ^b	Mg(OTf) ₂	ClCH ₂ CH ₂ Cl	99	75 (<i>R</i>)	225
9	<i>p</i> -MeC ₆ H ₄ ^b	Mg(OTf) ₂	ClCH ₂ CH ₂ Cl	99	72	225
10	<i>p</i> -ClC ₆ H ₄ ^b	Mg(OTf) ₂	ClCH ₂ CH ₂ Cl	99	72	225
11	<i>p</i> -MeOC ₆ H ₄ ^b	Mg(OTf) ₂	ClCH ₂ CH ₂ Cl	99	84	225
12	1-naphthyl ^b	Mg(OTf) ₂	ClCH ₂ CH ₂ Cl	99	75	225
13	2-naphthyl ^b	Mg(OTf) ₂	ClCH ₂ CH ₂ Cl	99	73	225

^a MS4 Å added. ^b Catalyst loading 10 mol %.

the best Lewis acid for the β -ketophosphonates. The absolute configurations were determined using X-ray crystal structure analysis. Using the oxazolidinone derivatives analogous to **173**, they were found to be (*R*)-**176b** (Table 39, entry 1) and (*S*)-**176c** (Table 39, entry 12), respectively.

Excellent results were also obtained for the Mannich reaction of benzyl azodicarboxylate **171** ($R^2 = \text{Bn}$) with the 2-acylcycloalkanones **174d** (Scheme 59).²³¹ The enantioselective amination is achieved using the [(*R*)-**1**/Cu(OTf)₂] complex. The best solvent proved to be CH₂Cl₂. The results reported in Table 40 emphasize the flexibility of the reaction, which has excellent enantioselectivity, independent of the size of the cycle and the steric demands of the acyl group. The absolute configuration of **176d** as reported in the scheme can be rationalized by the presence of a reacting complex derived from the bidentate coordination of the β -diketone to the Cu(II) complex of (*R*)-**1**.

An attempt at performing a Mannich reaction between *N*-tosyl- α -iminoester **170** and benzophenone imine glycine methyl ester was also tried. However, when using [(*S*)-**2**/CuClO₄] as the catalyst, the product obtained was found to be a racemate.²³²

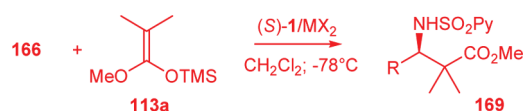
Scheme 53

The reaction between the α -iminoester **164a** ($R = \text{CO}_2\text{Et}$, $R^1 = \text{H}$) and the nitronates **177** (either derived from nitroalkanes in the presence of a base or as TMS-derivatives)—known as the *aza-Henry reaction*—is an interesting approach to obtaining the optically active β -nitro- α -amino acid derivatives **178a** (Scheme 60).²³³ The reaction is catalyzed by Cu(I)- or Cu(II)-based box complexes, and it is strongly *anti*-selective. The solvent of choice is CH₂Cl₂ if the reaction is performed using nitroalkanes and Et₃N ($R^2 = \text{H}$). With trimethylsilyl nitronates ($R^2 = \text{TMS}$), THF proved to be the best. The results of the diastereo- and enantioselective *aza-Henry* reactions are reported in Table 41 (entries 1–16).

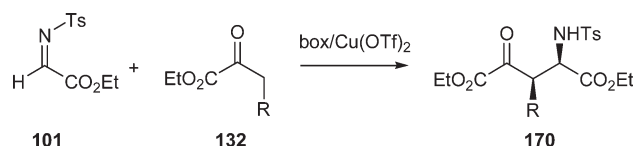
The aza-Henry reaction gives optically active **ethyl 2-(4-methoxyphenyl)amino-3-nitroalkanoates 178a** with good yields and excellent diastereo- and enantioselectivities either with nitroalkanes and Et₃N or with preformed trimethylsilyl nitronates (Table 41, entry 4 vs 14). Among the chiral ligands, **1** is better than **2**. Results for **2** show lower yields, diastereoselectivities, or enantioselectivities (Table 41, entries 3, 10, and 11). The reaction is flexible, and excellent selectivities are found for several nitroalkanes (Table 41, entries 1, 2, 4, and 6–8, the exception is R³ = Ph, entry 9). Scheme 61 shows the proposed intermediate for the aza-Henry reaction. The α -iminoester **164a** coordinates in a bidentate fashion, with the nitrogen atom in the equatorial position, to the catalyst derived from [(S)-1/Cu(OTf)₂]. This accounts for both the diastereo- and enantioselectivities of the aza-Henry reaction. It cannot be ignored that the similarity of **179** to the reactive intermediate **148** accounts for the stereoselectivity observed in the Henry reaction.

Later, the reaction of **177** (R² = TMS, R³ = Et) was carried out using **164b** (R = alkyl, aryl, or heteroaryl group) to give the *N*-[1-aryl (or alkyl)-2-nitrobutyl]-4-methoxybenzenamines (**178b**) (Scheme 60).²³⁴ The best catalyst is the complex between (S)-2

Scheme 54

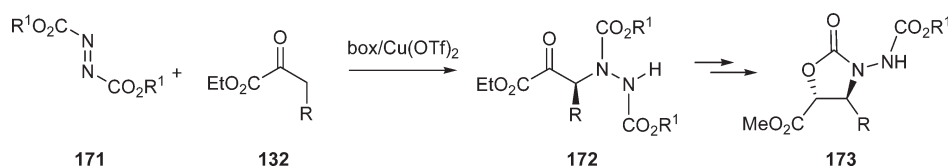


Scheme 55

Table 35. Enantioselective Mannich-type Reaction of *N*-(2-Pyridylsulfonyl)imines **166**²²⁶

entry	R	MX ₂	169 yield (%)	169 ee (%) (conf.)
1	Ph	Cu(OTf) ₂	80	86 (R)
2	Ph	CuOTf	32	38 (R)
3	Ph	Mg(OTf) ₂	37	29 (R)
4	Ph	Zn(OTf) ₂	16	62 (R)
5	Ph	Sc(OTf) ₃	42	62 (R)
6	<i>p</i> -MeC ₆ H ₄	Cu(OTf) ₂	40	70 (R)
7	<i>p</i> -ClC ₆ H ₄	Cu(OTf) ₂	52	75
8	<i>p</i> -MeOC ₆ H ₄	Cu(OTf) ₂	58	83
9	1-naphthyl	Cu(OTf) ₂	76	73
10	2-naphthyl	Cu(OTf) ₂	97	67
11	2-furyl	Cu(OTf) ₂	86	81
12	(<i>E</i>)-PhCH=CH	Cu(OTf) ₂	89	83

Scheme 56



and Cu(OTf)₂ (Table 41, entry 17 vs 18). In general, again the reaction is anti-selective but here the yield and diastereo- and enantioselectivities are a function of the substituents. The steric hindrance induced by the substituents on the aryl group plays a key role (Table 41, see entries 19, 20, and 21). It was furthermore found that, as reported in Table 41, entry 25, the reaction gives negligible yields with imines derived from the ketones **164b** (R, R¹ = Me or Ph).

The development of the catalytic aza-Henry reaction opened up the formation of optically active quaternary centers such as found in **181** through the reaction of (*p*-methoxyphenylimino)acetic acid ethyl ester **164a** with the esters of 2-nitro propanoic acid **180** (Scheme 62). In addition, this versatile reaction made it also possible to combine a box-based Lewis acid and chiral base catalysis (the former to coordinate the **164a**, the latter to form the nitronate from **180**) into a chiral molecular recognition approach to synthesis.^{233c} The data in Table 42 confirm the increasing selectivity with bulky ester groups (Table 42, entry 1 vs 2) as well as the great improvement in both the diastereomeric ratio and enantiomeric excess with cinchona alkaloids (Table 42, entries 3–6). The best chiral bases proved to be quinidine and quinine, and these were tested with both (R)- and (S)-1 (Table 42, entries 5 and 6 vs 7 and 8). The selectivity with both bases decreases with (S)-1; hence the enantioselectivity is governed by the chiral Lewis acid ligand.

4.4. Michael and Mukaiyama–Michael reactions

The *Michael reaction* involves the addition of active methylene compounds to electrophilic π -systems. It is one of the most useful C–C bond-forming reactions known. The catalytic enantioselective version has been extensively studied with the aim of constructing quaternary stereocenters.²³⁵ 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.^{78,236,237} However, the reaction with these catalysts gave more or less racemic products, whereas other boxes, which will be

Table 36. Catalytic Diastereo- and Enantioselective Mannich Reactions between α -Ketoesters **132** and the *N*-Tosyl- α -Iminoester **101**^{227a}

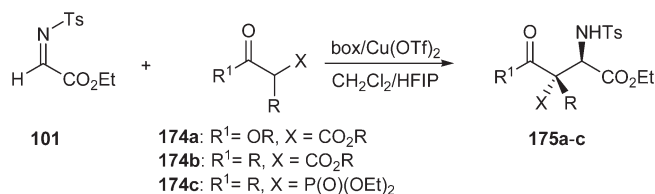
entry	R	box	solvent	yield (%)	syn/anti	syn ee (%) (conf.)	anti ee (%)
1	H	(S)-2	CH ₂ Cl ₂	76		33 (R)	
2	H	(R)-1	CH ₂ Cl ₂	70		89 (R)	
3	H	(R)-1	THF	45		76 (R)	
4	H	(R)-1	Et ₂ O	<5			
5	Me	(R)-1	CH ₂ Cl ₂	89	>98:2	>98 (R)	>90
6	Bn	(R)-1	CH ₂ Cl ₂	94	>98:2	97 (R)	
7	Br	(R)-1	CH ₂ Cl ₂	79	75:25	78	

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.

Table 37. Catalytic Asymmetric Mannich Reactions between α -Ketoesters 132 and Azodicarboxylic Esters 171^{227b}

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

Scheme 57



Together with the reaction of pyrones, phenalen-2-one, 1,4-naphthoquinone, and various enamines of the cyclic 1,3-diketones, it was the topic of a Michael reaction study between a series of different 4-hydroxycoumarins **182** with various 2-oxo-3-butenate esters **183** (Scheme 63).²³⁸ To achieve a high enantiomeric excess of the Michael adduct **184**, Et₂O was found to be the best solvent. The Lewis acids Cu(SbF₆)₂, Zn(OTf)₂, and Ni(ClO₄)₂ all proved to be inferior to Cu(OTf)₂. The results using (R)-1 and (S)-2 as the chiral ligands and carried out under optimized reaction conditions are reported in Table 43.

The most noteworthy results are: (i) the product configuration is (R), which suggests **183** coordinates in a bidentate fashion to the copper leaving the SI face shielded by the *tert*-butyl group of (S)-2; hence coumarin attacks the Re face; (ii) box **1** promotes

Scheme 58

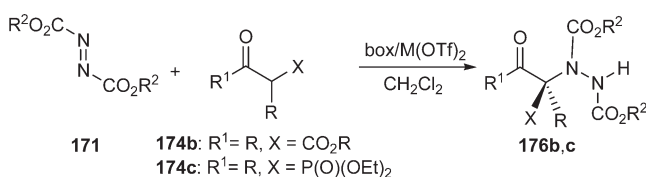


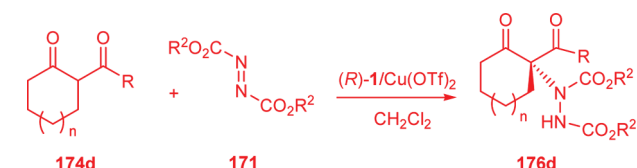
Table 38. Catalytic Asymmetric Mannich Reactions of N-Tosyl- α -Iminoester 101 with Malonates 174a, β -Ketoesters 174b, and β -Ketophosphonates 174c

entry	R ¹	R	X	box	additive	yield (%)	dr	ee (%) (conf.) ^a	ref
1	OEt	H	CO ₂ Et	(R)-1		95		39 (R)	228a
2	OEt	H	CO ₂ Et	(R)-1	HFIP	63		80 (R)	228a
3	OEt	Me	CO ₂ Et	(R)-1	HFIP	71		79	228a
4	OEt	<i>n</i> -Bu	CO ₂ Et	(R)-1	HFIP	80		82	228a
5	OEt	<i>i</i> -Bu	CO ₂ Et	(R)-1	HFIP	60		79	228a
6	OEt	CH ₂ Ph	CO ₂ Et	(R)-1	HFIP	65		79	228a
7	OEt	H	CO ₂ Et	(S)-2	HFIP	80		45 (R)	228a
8	OEt	H	CO ₂ Et	(S)-2		80		74 (R)	228a
9	OEt	Me	CO ₂ Et	(S)-2		99		85	228a
10	OEt	<i>n</i> -Bu	CO ₂ Et	(S)-2		63		91	228a
11	OEt	<i>i</i> -Bu	CO ₂ Et	(S)-2		64		96	228a
12	OEt	CH ₂ Ph	CO ₂ Et	(S)-2		54		94	228a
13	Me	Me	CO ₂ Et	(R)-1		90	90:10	42	228a
14	Et	Me	CO ₂ Et	(R)-1		76	84:16	23 (2R,3R)	228a
15	Et	Me	CO ₂ -1-Adamantyl	(R)-1		43	>95:<5	66 (2S,3S)	228a
16	Et	Me	CO ₂ <i>t</i> -Bu	(R)-1		33	>95:<5	68 (2S,3S)	228a
17	Me	Me	CO ₂ <i>t</i> -Bu	(S)-2		87	93:7	88 (2R,3R)	228a
18	Et	Me	CO ₂ <i>t</i> -Bu	(S)-2		80	98:2	92 (2R,3R)	228a
19	<i>i</i> -Pr	Me	CO ₂ <i>t</i> -Bu	(S)-2		55	84:16	91 (2R,3R)	228a
20	Ph	Me	P(O)(OEt) ₂	(R)-1		70	60:40	50	228b
21	Ph	Me	P(O)(OEt) ₂	(R)-1	Et ₃ N	>98	79:21	56	228b
22	Ph	Me	P(O)(OEt) ₂	(S)-2		32	67:33	55	228b
23	Ph	Me	P(O)(OEt) ₂	(S)-2	Et ₃ N	>98	71:29	84	228b
24	Ph	Me	P(O)(OEt) ₂	(S)-2	DMA ^b	>98	66:34	64	228b
25	Ph	Me	P(O)(OEt) ₂	(S)-2	2,6-Lutidine	78	84:16	72	228b
26	2-Naphthyl	Me	P(O)(OEt) ₂	(S)-2	Et ₃ N	88	91:9	51	228b
27	Me	Me	P(O)(OEt) ₂	(S)-2	Et ₃ N	61	63:37	43 (2R,3R)	228b
28	Pr	Me	P(O)(OEt) ₂	(S)-2	Et ₃ N	87	62:38	70	228b
29	<i>t</i> -Bu	Me	P(O)(OEt) ₂	(S)-2	Et ₃ N	44	86:14	67	228b
30	EtO	Me	P(O)(OEt) ₂	(S)-2	Et ₃ N	72	82:18	79	228b

^a Enantiomeric excess of the major diastereoisomer. ^b *N,N*-dimethylaniline.

Table 39. Catalytic Enantioselective Mannich Reactions of Azodicarboxylates 171 with β -Ketoesters 174b and β -Ketophosphonates 174c

entry	R	R ¹	X	R ²	box	M	yield (%)	ee (%) (conf.)	ref
1	Me	Me	CO ₂ Et	Bn	(S)-1	Cu	98	98 (R)	229a
2	Me	Me	CO ₂ Et	Bn	(R)-1	Cu	93	98 (S)	210, 230
3	Me	Me	CO ₂ Et	Et	(S)-1	Cu	87	>95	229a
4	Me	Et	CO ₂ Et	Bn	(S)-1	Cu	94	98	229a
5	Me	Ph	CO ₂ Et	Bn	(S)-1	Cu	85	95	229a
6	Me	<i>i</i> -Pr	CO ₂ <i>t</i> Bu	Bn	(S)-1	Cu	96	98	229a
7	Me	Bn	CO ₂ <i>t</i> Bu	Bn	(S)-1	Cu	84	98	229a
8	allyl	Me	CO ₂ <i>t</i> Bu	Bn	(S)-1	Cu	80	98	229a
9	Me	Me	CO ₂ <i>t</i> Bu	Bn	(S)-1	Cu	86	98	229a
10	Me	Ph	P(O)(OEt) ₂	Et	(S)-2	Zn	20	12	229b
11	Me	Ph	P(O)(OEt) ₂	Et	(S)-1	Zn	80	92	229b
12	Me	Ph	P(O)(OEt) ₂	Bn	(S)-1	Zn	85	92 (S)	229b
13	Me	2-naphthyl	P(O)(OEt) ₂	Bn	(S)-1	Zn	93	92	229b
14	Me	Bn	P(O)(OEt) ₂	Bn	(S)-1	Zn	60	95	229b
15	Me	Me	P(O)(OEt) ₂	Bn	(S)-1	Zn	75	85	229b
16	Allyl	Ph	P(O)(OEt) ₂	Bn	(S)-1	Zn	85	98	229b
17	Me	Ph	P(O)(OMe) ₂	Bn	(S)-1	Zn	97	94	229b

Scheme 59

the same enantioselection with Cu(OTf)₂ but not with Zn(OTf)₂ (Table 43, entries 1 and 2); (iii) aryl groups on 183 always induce (R)-enantioselectivity.

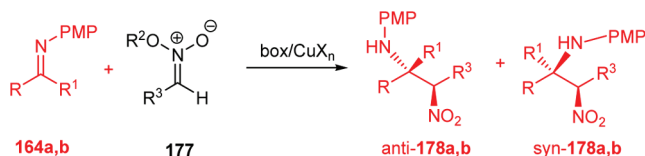
In addition to hydroxycoumarins, a variety of nucleophiles have also been added to α,β -unsaturated carbonyl compounds. The conjugate addition of allyltrimethylsilane to cyclic unsaturated ketoesters 185 to give allylated ketoesters 186 (Scheme 64) was performed with various [box/Cu(OTf)₂] complexes. The best of these was derived from (S)-1 (Table 44, entry 1 vs 2).²³⁹ This catalyst gave methyl 2-allyl-6-oxocyclohexanecarboxylate 186 (*n* = 1) with the (2*R*) configuration. The reaction was tested for rings of different size (*n* = 0, 1, and 3), and with different sterically hindered substrates because both parameters were found to influence the yield and diastereoselectivity.

Another Michael addition catalyzed by the [(S)-2/Zn(OTf)₂] complex involves 1-methylenaminepyrrolidine (187) as the nucleophile and substituted 4-hydroxy-4-methylpent-1-en-3-one (188) (Scheme 65).¹⁰¹ The selectivity observed in this nucleophilic addition (Table 45) can be rationalized if the complex 26, with the composition [(S)-2/Zn(OTf)₂ · 2H₂O] (Figure 10), is taken as the reacting complex template. Its distorted trigonal-bipyramidal geometry is retained after complexation with hydroxyenone 188, which replaces the two water molecules and whose orientation is fixed by a stabilizing OH—OTf hydrogen bond. Thus, the attack onto the Si face of the enone is favored.

One rather unusual case is the multicomponent reaction in which the first step is the catalyzed generation of the nucleophile,

Table 40. Enantioselective Catalyzed Mannich Additions of 3-Acylcycloalkanones 174d to Dibenzyl Azodicarboxylate 171 (R² = Bn)²³¹

entry	R	<i>n</i>	yield (%)	ee (%)
1	Ph	1	87	91
2	Me	1	82	84
3	Et	1	83	94
4	<i>i</i> -Pr	1	86	94
5	<i>s</i> -Bu	1	76	95
6	<i>s</i> -Bu	0	60	89
7	<i>s</i> -Bu	2	90	83

Scheme 60

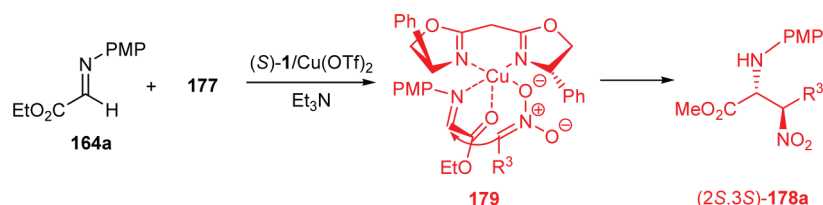
which is followed by the second step, the enantioselective catalyzed Michael reaction. An example is the reaction between the methyl aryldiazoacetate 190, water, and α,β -unsaturated 2-acylimidazole 191. It is catalyzed by [Rh₂(OAc)₄] and the [box/Zn(OTf)₂] complex (Scheme 66).²⁴⁰ The first catalyst generates the highly nucleophilic oxonium ylide 192, which is enantioselectively trapped by 191 to give, with excellent diastereo- and enantioselectivity, the α -hydroxy- δ -ketoester 193. After careful screening and optimization of catalysts, the best box was found to be (S)-2 (Table 46, entry 1 vs 2). Subsequently, this was usefully applied to a wide range of substrates. The configuration of the major brominated product, reported in entry 3 of Table 46, was found to be 2*S*,3*S*.

Table 41. Catalytic Aza-Henry Reactions between *N*-(*p*-Methoxyphenyl)- α -Iminoester 164 and Nitronates 177

entry ^a	R	R ¹	R ²	R ³	box	CuX _n	yield (%)	anti/syn	anti ee (%) (conf.)	syn ee (%)	ref
1	CO ₂ Et	H	H	H	(<i>R</i>)-1	Cu(OTf) ₂	38		87 (2 <i>R</i> ,3 <i>R</i>)		233a
2	CO ₂ Et	H	H	Me	(<i>R</i>)-1	Cu(OTf) ₂	61	70:30	97 (2 <i>R</i> ,3 <i>R</i>)	95	233a
3	CO ₂ Et	H	H	Et	(<i>S</i>)-2	Cu(OTf) ₂	8	95:5	89 (2 <i>R</i> ,3 <i>R</i>)	70	233a
4	CO ₂ Et	H	H	Et	(<i>R</i>)-1	Cu(OTf) ₂	81	95:5	97 (2 <i>R</i> ,3 <i>R</i>)	87	233a
5	CO ₂ Et	H	H	Et	(<i>R</i>)-1	Cu(SbF ₆) ₂	85	60:40	26 (2 <i>R</i> ,3 <i>R</i>)	21	233a
6	CO ₂ Et	H	H	Et	(<i>R</i>)-1	CuBr ₂	69	95:5	93 (2 <i>R</i> ,3 <i>R</i>)	86	233a
7	CO ₂ Et	H	H	pentyl	(<i>R</i>)-1	Cu(OTf) ₂	52	93:7	97 (2 <i>R</i> ,3 <i>R</i>)	89	233a
8	CO ₂ Et	H	H	PhCH ₂	(<i>R</i>)-1	Cu(OTf) ₂	80	95:5	95 (2 <i>R</i> ,3 <i>R</i>)	88	233a
9	CO ₂ Et	H	H	Ph	(<i>R</i>)-1	Cu(OTf) ₂	59	55:45	74 (2 <i>R</i> ,3 <i>R</i>)	77	233a
10	CO ₂ Et	H	TMS	Et	(<i>S</i>)-2	CuClO ₄	99	92:8	12 (2 <i>S</i> ,3 <i>S</i>)		233b
11	CO ₂ Et	H	TMS	Et	(<i>S</i>)-2	Cu(OTf) ₂	58	88:12	56 (2 <i>R</i> ,3 <i>R</i>)		233b
12	CO ₂ Et	H	TMS	Et	(<i>S</i>)-1	CuClO ₄	90	75:25	90 (2 <i>S</i> ,3 <i>S</i>)		233b
13	CO ₂ Et	H	TMS	Et	(<i>S</i>)-1	CuPF ₆	63	83:17	56 (2 <i>S</i> ,3 <i>S</i>)		233b
14	CO ₂ Et	H	TMS	Et	(<i>S</i>)-1	Cu(OTf) ₂	67	95:5	89 (2 <i>S</i> ,3 <i>S</i>)		233b
15	CO ₂ Et	H	TMS	Et	(<i>S</i>)-1	Cu(SbF ₆) ₂	92	86:14	70 (2 <i>S</i> ,3 <i>S</i>)		233b
16	CO ₂ Et	H	TMS	Me	(<i>S</i>)-1	CuClO ₄	67	83:17	>98 (2 <i>S</i> ,3 <i>S</i>)		233b
17	Ph	H	TMS	Et	(<i>S</i>)-2	Cu(OTf) ₂	84	>98:2	94 (1 <i>S</i> ,2 <i>S</i>)		234
18	Ph	H	TMS	Et	(<i>S</i>)-1	Cu(OTf) ₂	n.d.	90:10	51		234
19	4-Cl-C ₆ H ₄	H	TMS	Et	(<i>S</i>)-2	Cu(OTf) ₂	84	>98:2	92		234
20	2-Cl-C ₆ H ₄	H	TMS	Et	(<i>S</i>)-2	Cu(OTf) ₂	79	89:11	73		234
21	2,6-diCl-C ₆ H ₃	H	TMS	Et	(<i>S</i>)-2	Cu(OTf) ₂	<5	n.d.	n.d.		234
22	2-furyl	H	TMS	Et	(<i>S</i>)-2	Cu(OTf) ₂	89	92:8	94 (1 <i>S</i> ,2 <i>S</i>)		234
23	cyclohexyl	H	TMS	Et	(<i>S</i>)-2	Cu(OTf) ₂	88	>98:2	87		234
24	<i>n</i> -pentyl	H	TMS	Et	(<i>S</i>)-2	Cu(OTf) ₂	88	50:50	86		234
25	Ph	Ph	TMS	Et	(<i>S</i>)-2	Cu(OTf) ₂	<5	n.d.	n.d.		234

^a From entry 1 to entry 16, the products **178** are ethyl 2-(4-methoxyphenyl)amino-3-nitroalkanoates; from entry 17 to entry 24, the products are *N*-(1-aryl (or alkyl)-2-nitrobutyl)-4-methoxybenzeneamines.

Scheme 61



Scheme 62



The first example of a box-catalyzed intramolecular Michael reaction, which serves nicely as a bridge to the next topic on Friedel–Crafts addition, was performed on a pyrrole *N*-tethered to 3-alkenoyl-2-oxazolidinone **194**. The reaction with [(*R*)-1/Cu(OTf)₂] gave (*S*)-**195** with a yield of 95% and an ee of 88% (Scheme 67).²⁴¹

The enantioselective catalytic Friedel–Crafts-type addition of aromatic and heteroaromatic C–H bonds to 4-substituted 2-oxo-3-butenolate **183** was tested with 1,3-dimethoxybenzene and 2-methylfuran. In addition, it was also tested in detail with indoles of the type **196** and was found to give 4-substituted-4-(3-indolyl)-2-oxobutanoates **197** (Scheme 68).^{215,242}

Table 42. Catalytic Aza-Henry Reactions between α -Iminoester 164a and Nitroesters 180^{233c}

entry	R	box	base	yield (%)	dr ^a	ee 181 (%)
1	Et	(<i>R</i>)-1	Et ₃ N	95	50:50	
2	<i>t</i> -Bu	(<i>R</i>)-1	Et ₃ N	>90	67:33	80
3	<i>t</i> -Bu	(<i>R</i>)-1	cinchonine	76	88:12	94
4	<i>t</i> -Bu	(<i>R</i>)-1	hydroquinine	90	91:9	95
5	<i>t</i> -Bu	(<i>R</i>)-1	quinidine	80	90:10	96
6	<i>t</i> -Bu	(<i>R</i>)-1	quinine	90	93:7	98
7	<i>t</i> -Bu	(<i>S</i>)-1	quinidine	90	89:11	–91
8	<i>t</i> -Bu	(<i>S</i>)-1	quinine	76	90:10	–93

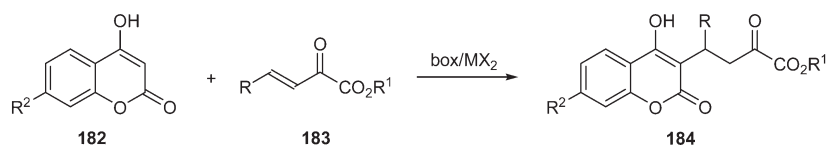
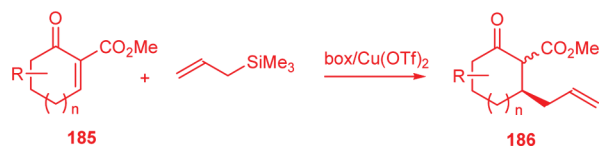
^a Diastereomeric ratio.

In Table 47 are found the results of a Michael reaction that is analogous to the reaction of activated carbonyl compounds acting as electrophiles with electron-rich aromatic compounds as shown in Scheme 47. The reactions reported in Table 47 also can be regarded as Friedel–Crafts alkylation/Michael reactions

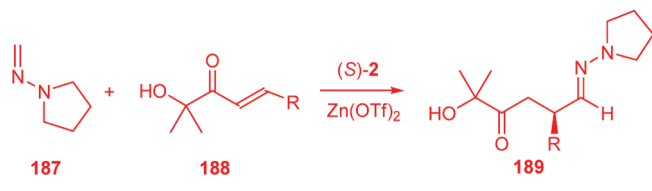
Table 43. Enantioselective Catalyzed Michael Additions of 4-Hydroxycoumarin 182 and 2-Oxo-3-Butenoate Esters 183²³⁸

entry	R	R ¹	R ²	box	MX ₂	solvent	yield (%)	ee (%) (conf.)
1	Ph	Me	H	(S)-1	Zn(OTf) ₂	CH ₂ Cl ₂	98	25 (S)
2	Ph	Me	H	(R)-1	Cu(OTf) ₂	Et ₂ O	85	77 (S)
3	Ph	Me	H	(S)-2	Cu(OTf) ₂	CH ₂ Cl 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 ₂ O	98	86 (R)
6	<i>p</i> -ClC ₆ H ₄	Me	H	(S)-2	Cu(OTf) ₂	Et ₂ O	98	73 (>99.5) (R) ^a
7	<i>p</i> -MeC ₆ H ₄	Me	H	(S)-2	Cu(OTf) ₂	Et ₂ O	95	78 (R)
8	<i>p</i> -MeOC ₆ H ₄	Me	H	(S)-2	Cu(OTf) ₂	Et ₂ O	98	64 (R)
9	2-Furyl	Et	H	(S)-2	Cu(OTf) ₂	Et ₂ O	95	81 (S)
10	Ph	Me	OMe	(S)-2	Cu(OTf) ₂	Et ₂ O	47	91 (R)
11	Ph	Me	F	(S)-2	Cu(OTf) ₂	Et ₂ O	45	91 (R)

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

Scheme 63**Scheme 64****Table 44. Enantioselective Catalyzed Michael Additions of Allyltrimethylsilane and Cyclic Unsaturated Ketoesters 185²³⁹**

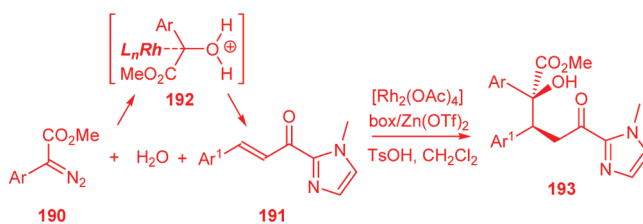
entry	<i>n</i>	substituent R on 185	box	186 yield (%)	186 ee (%) (conf.)
1	1		(S)-2	78	90 (2R)
2	1		(S)-1	>95	10
3	1	3,3-diMe	(S)-2	77	64
4	1	4,4-diMe	(S)-2	51	55
5	1	5,5-diMe	(S)-2	65	97
6	0		(S)-2	69	70 (1R,2R)
7	3		(S)-2	65	>98

Scheme 65

of the indole with the α,β-unsaturated carbonyl compounds. The best enantioselectivities are obtained with Et₂O as the solvent (Table 47, entries 2–4), although CH₂Cl₂ gives somewhat comparable results. The enantioselectivities are always as reported in Scheme 68 [(R)-197 for R = Ph] except with [(S)-1/Cu(OTf)₂] (Table 47, entry 1). Excellent enantiomeric excesses are also obtained with [(S)-2/Cu(OTf)₂] irrespective of the

Table 45. Michael Additions of 187 to α-Hydroxy Enones 188¹⁰¹

entry	R	yield (%)	ee (%) (conf.)
1	Me	93	66 (S)
2	<i>i</i> -Pr	75	82 (R)
3	<i>i</i> -Bu	95	80 (S)
4	<i>t</i> -Bu	50	82 (R)
5	CH ₂ CH ₂ Ph	78	72 (S)
6	<i>n</i> -pentyl	85	84 (S)
7	cyclohexyl	73	82 (R)

Scheme 66

nature of the substituents either in the indole ring (either electron-withdrawing or electron-donating substituents, Table 47, entries 7–11) or in the α,β-unsaturated carbonyl compounds (Table 47, entries 6 and 10–12).

The Friedel–Crafts alkylation/Michael reaction of the indoles 196 can also be performed with the arylidene malonates 198 (Scheme 69). Decarboxylation of the products 199 to give the monoesters allows the formal transformation of the reaction into a Friedel–Crafts alkylation of indoles using cinnamates.^{215,243,244} The most significant results are obtained with THF as the solvent and [(S)-2/Cu(OTf)₂] as the catalyst. However, the enantiomeric excesses are somewhat lower than those for the 2-oxo-3-butenates reported in Table 47. On the other hand, negligible enantioselectivities

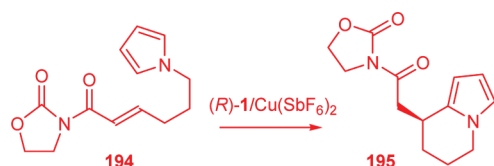
were obtained when the reaction was run with 2-methylfuran and pyrrole instead of **196**.

Interesting enantioselectivities were obtained in the reaction involving acyl-substituted methylenemalonates, that is, when **198** has a ketone, an ester, or an amide as the R^1 group.^{245,246} The reaction with the indoles **196** was studied in detail by changing the substituents wherever possible on the reagents, and the best conditions are those reported in Scheme 69. The authors suggested that the (*R*) configuration of **199** can be explained by a secondary orbital interaction where **196** approaches the less-hindered side of the reacting complex.²⁴⁵

Table 46. Enantioselective Multicomponent Reactions of Diazocompounds **190, Water, and α,β -Unsaturated 2-Acylimidazole **191****²⁴⁰

entry	Ar	Ar ¹	box	yield (%)	d.r.	ee (%) (conf.)
1	Ph	Ph	(<i>S</i>)- 2	75	90:10	91
2	Ph	Ph	(<i>S</i>)- 1	40	83:17	29
3	Ph	4-BrC ₆ H ₄	(<i>S</i>)- 2	78	97:3	96 (2 <i>S</i> ,3 <i>S</i>)
4	Ph	4-NO ₂ C ₆ H ₄	(<i>S</i>)- 2	86	95:5	90
5	Ph	4-MeOC ₆ H ₄	(<i>S</i>)- 2	60	92:8	99
6	Ph	2-BrC ₆ H ₄	(<i>S</i>)- 2	73	99:1	97
7	Ph	3-BrC ₆ H ₄	(<i>S</i>)- 2	81	99:1	96
8	4-MeOC ₆ H ₄	Ph	(<i>S</i>)- 2	80	99:1	93
9	3-ClC ₆ H ₄	Ph	(<i>S</i>)- 2	72	99:1	85

Scheme 67



Scheme 68



Table 47. Enantioselective Catalyzed Michael Additions of Indoles **196 and 2-Oxo-3-Butenoate Esters **183****

entry	R	R ¹	R ²	R ³	box	MX ₂	solvent	yield (%)	ee (%) (conf.)	ref
1	Ph	Me	H	H	(<i>S</i>)- 1	Cu(OTf) ₂	Et ₂ O	100	42 (<i>S</i>)	242
2	Ph	Me	H	H	(<i>S</i>)- 2	Cu(OTf) ₂	Et ₂ O	100	99.5 (<i>R</i>)	215, 242
3	Ph	Me	H	H	(<i>S</i>)- 2	Cu(OTf) ₂	CH ₂ Cl ₂ ^a	99	89 (<i>R</i>)	242
4	Ph	Me	H	H	(<i>S</i>)- 2	Cu(OTf) ₂	THF	100	74 (<i>R</i>)	242
5	Ph	Me	H	H	(<i>S</i>)- 2	Zn(OTf) ₂	Et ₂ O	100	87 (<i>R</i>)	242
6	Me	Et	H	H	(<i>S</i>)- 2	Cu(OTf) ₂	Et ₂ O	96	95 (<i>S</i>)	215, 242
7	Ph	Me	OMe	H	(<i>S</i>)- 2	Cu(OTf) ₂	Et ₂ O	95	>99.5 (<i>R</i>)	215, 242
8	Ph	Me	H	Cl	(<i>S</i>)- 2	Cu(OTf) ₂	Et ₂ O	69	97 (<i>R</i>)	215, 242
9	Ph	Me	H	CO ₂ Me	(<i>S</i>)- 2	Cu(OTf) ₂	Et ₂ O	82	94 (<i>R</i>)	242
10	Me	Et	OMe	H	(<i>S</i>)- 2	Cu(OTf) ₂	Et ₂ O	95	>99.5 (<i>S</i>)	215, 242
11	CH ₂ OBn	Et	OMe	H	(<i>S</i>)- 2	Cu(OTf) ₂	Et ₂ O	98	95 (<i>S</i>)	215, 242
12	CH ₂ OBn	Et	H	Cl	(<i>S</i>)- 2	Cu(OTf) ₂	Et ₂ O	70	80 (<i>S</i>)	242

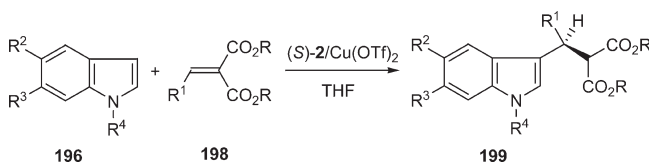
^a CH₂Cl₂ and pentane (1:2).

Acyl-substituted methylenemalonates **198** give a [(*S*)-**2**/Cu(OTf)₂]-catalyzed Friedel–Crafts reaction with substituted pyrroles and furans (Scheme 70, **200**, X = NR or O). Both substrates react in the 2-position with good yields but sometimes unsatisfactory enantioselectivities (ee in the range 16–72%). The absolute configuration of the furan product **201** (X = O, R = Et, R¹ = CO₂-*tert*-Bu, R² = *n*-Bu, R³ = H; yield about 90%, 62% ee) was shown to be (*R*).²⁴⁶

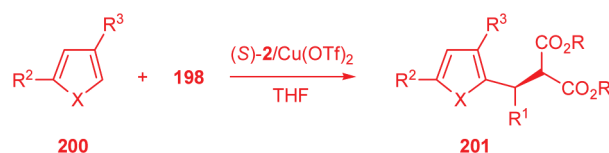
The same authors investigated the intramolecular version of the reaction with **198** tethered to dimethoxybenzene through either an alkyl or an ether pendant (Scheme 71). However, although the conversion of **202** (X = CH₂ or O) into **203** occurred in good yields, ee's of only 14% and 20%, respectively, were obtained.²⁴⁶

The Friedel–Crafts alkylation/Henry reaction of the indoles **196** was performed with β -nitrostyrene derivatives. When the nitro-olefin only had the aryl substituent **204** (R¹ = H), the reaction catalyzed by the [(*S*)-**1**/Zn(OTf)₂] complex gave excellent yields and high enantioselectivities of (*S*)-**205** (R¹ = H) (up to 90% ee) (Scheme 72).²⁴⁷ An experiment carried out

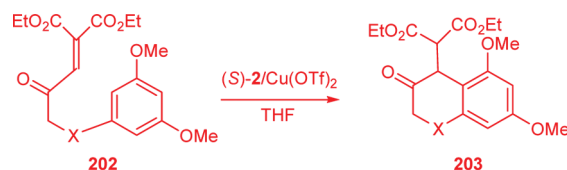
Scheme 69



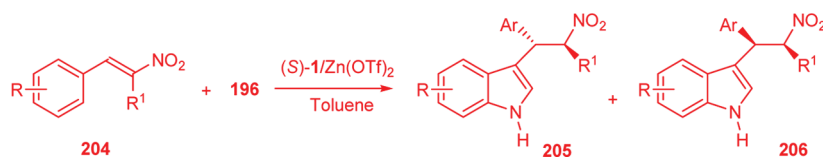
Scheme 70



Scheme 71



Scheme 72



Scheme 73

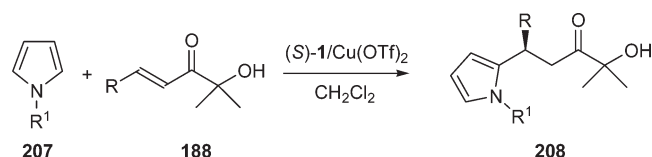


Table 48. Enantioselective Catalyzed Friedel–Crafts Reactions of Indoles 196 and Acyl-Substituted Methylenemalonates 198²⁴⁵

entry	R	R ¹	R ²	R ³	R ⁴	yield (%)	ee (%) (conf.)
1	Me	CO ₂ - <i>t</i> -Bu	H	H	H	59	68
2	Et	CO ₂ - <i>t</i> -Bu	H	H	H	75	73
3	<i>i</i> -Pr	CO ₂ - <i>t</i> -Bu	H	H	H	43	44
4	Et	CO ₂ CH ₂ Ph	H	H	H	81	84
5	Et	CO ₂ CH ₂ C ₆ H ₄ -4-Br	H	H	H	90	82
6	Et	COMe	H	H	H	86	38
7	Et	COPh	H	H	H	92	69
8	Et	CON(CH ₂) ₅	H	H	H	92	53
9	Et	CO ₂ - <i>t</i> -Bu	OMe	H	H	96	86
10	Et	CO ₂ CH ₂ Ph	H	H	Me	87	95
11	Et	CO ₂ CH ₂ Ph	Br	H	H	84	56 (R)
12	Et	CON(CH ₂) ₅	Br	H	H	59	56 (R)

with ethyl 1-nitro-2-*p*-tolylacrylate (204, R¹ = CO₂Et) gave nearly equimolecular amounts of the *anti*-205 and *syn*-206; ee's were 6 and 61%, respectively.²⁴⁸

The α'-hydroxy enones 188 proved to be excellent electrophiles for the enantioselective Friedel–Crafts alkylation/Michael reaction of the pyrroles 207. They give a bidentate coordination, through their oxygen atoms, to [(S)-2/Cu(OTf)₂] and easily afford 208 (Scheme 73).²⁴⁹ Table 49 presents some results showing the great flexibility of a reaction that, as well as pyrroles, can also be applied to a variety of indoles. They always give excellent yields and enantioselectivities (>90% ee). The absolute configuration of 208 (R = *i*-Pr, R¹ = Me; Table 49, entry 5) was determined to be (R).

If the nucleophile is localized on a heteroatom, then two important variants of the Michael reaction lead to the formation of either C–O or C–N bonds. An example of an *oxa*-Michael reaction is the first step in the tandem reaction of 2-oxo-3-butenate esters 183 with phenol 209 (R = OMe). The adducts 210 then undergo an intramolecular Friedel–Crafts alkylation to give the optically active chromans 211 (Scheme 74).^{33,44} Other box-based catalysts that give enantioselectivities up to 74% ee will be discussed in section 5.1; [(S)-1/Mg(OTf)₂] and [(S)-2/Mg(OTf)₂] give (2*R*,4*S*)-211 (Ar = 4-ClC₆H₄) with ee's of 65 and 18%, respectively.

The *aza*-Michael reaction, catalyzed with [(S)-2/Zn(OTf)₂], was tested for the addition of aromatic amines to 3-alkenoyl-1,3-oxazolidin-2-one as a possible route to forming β-amino acid derivatives and gave good yields but disappointing enantioselectivities.²⁵⁰

Table 49. Enantioselective Catalyzed Friedel–Crafts Alkylations of Pyrroles 207 with α-Hydroxy Enones 188²⁴⁹

entry	R	R ¹	yield (%)	ee (%) (conf.)
1	PhCH ₂ CH ₂	H	83	90
2	PhCH ₂ CH ₂	Me	86	92
3	CH ₃ (CH ₂) ₅	H	87	91
4	CH ₃ (CH ₂) ₅	Me	82	96
5	<i>i</i> -Pr	Me	86	95 (R)
6	cyclohexyl	Me	84	97
7	Et	Me	88	94
8	(CH ₃) ₂ CHCH ₂	Me	86	94

More appreciable results, in terms of yield and enantioselectivity, were obtained in the addition of α'-hydroxy enones 188 to carbamates 212 to give the β-amino-protected hydroxyketones 213 (Scheme 75). These then can be easily oxidized to form *N*-protected β-amino acids.²⁵¹ The reaction proceeds for a variety of enones and carbamates, and Table 50 reports a representative selection of the results. The catalyst of choice was [(S)-2/Cu(OTf)₂] (Table 50, entries 1 and 2). The optically active 213 was obtained with excellent enantioselectivities (generally >90% ee). The corresponding Mg(II)- and Zn(II)-based catalysts proved to be ineffective.

Alkoxy carbonyl-substituted methylenemalonates 198 react with methylanilines 214 to give the *aza*-Michael products 215. After optimizing the conditions, with [(S)-2/Cu(OTf)₂] as the catalyst and THF as the solvent (Scheme 76),²⁵² five reactions were explored. The yields were good (58–91%), and enantioselectivities were in the 41–87% ee range.

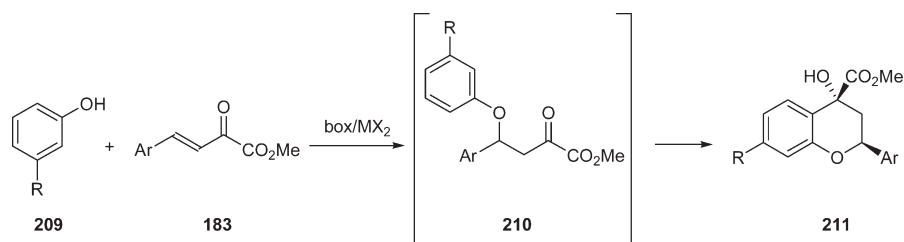
Among the different activated double bonds that have been the topic of extensive research in enantioselective box-catalyzed additions and cycloadditions, special attention has been devoted to substituted *N*-alkenoyl-oxazolidinones. These substrates are characterized by a β-dicarbonyl functionality that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

3-(*E*)-Crotonoyl-4,4-dimethyl-2-oxazolidinone 216 undergoes a conjugate addition of *O*-benzyl-hydroxylamine (Scheme 77). Even if (S)-1 and (S)-2 do not represent the best catalysts for this reaction, (S)-217 is still obtained in excellent yield; unfortunately, the enantioselectivities are only 14 and 47% ee, respectively.²⁵³

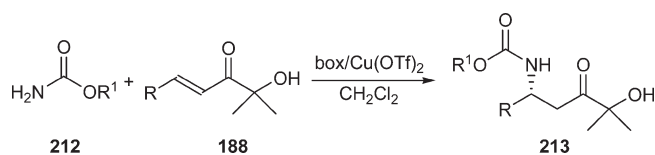
The reaction of 1-(*E*)-crotonoyl-3-phenyl-2-imidazolidinone 218 and 2-furancarbaldehyde oxime gives an addition product with a nitrone structure (219, Scheme 78). Again the yields with the catalysts [(R)-1/Cu(OTf)₂] and [(S)-2/Cu(OTf)₂] are very good, but the enantioselectivities are only 15 and 29% ee, respectively.²⁵⁴

The 1-substituted 2-alkenoyl-4,4-dimethylpyrazolidin-3-ones 220 are interesting substrates and hence will be considered

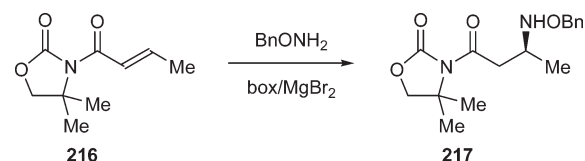
Scheme 74



Scheme 75

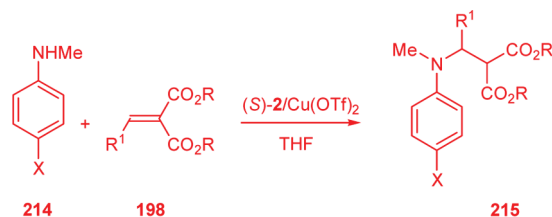


Scheme 77

Table 50. Enantioselective Catalyzed Aza-Michael Additions of Enones 188 to Carbamates 212²⁵¹

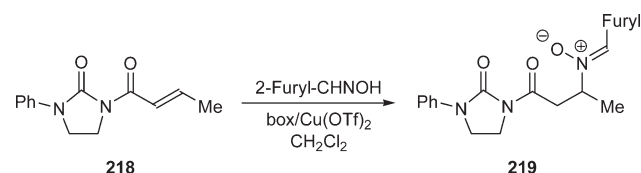
entry	R	R ¹	box	yield (%)	ee (%) (conf.)
1	PhCH ₂ CH ₂	PhCH ₂	(S)-1	49	83 (S)
2	PhCH ₂ CH ₂	PhCH ₂	(S)-2	86	96 (S)
3	PhCH ₂ CH ₂	Me	(S)-2	51	99
4	PhCH ₂ CH ₂	Et	(S)-2	74	96
5	PhCH ₂ CH ₂	<i>t</i> -Bu	(S)-2	92	88
6	Et	PhCH ₂	(S)-2	83	96
7	<i>i</i> -Pr	PhCH ₂	(S)-2	53	98
8	<i>i</i> -Bu	PhCH ₂	(S)-2	71	96 (S)
9	<i>t</i> -Bu	PhCH ₂	(S)-2	65	94
10	<i>n</i> -Hex	<i>t</i> -Bu	(S)-2	76	96
11	<i>c</i> -C ₆ H ₁₁	<i>t</i> -Bu	(S)-2	85	91
12	<i>c</i> -C ₆ H ₁₁	PhCH ₂	(S)-2	57	94

Scheme 76



several times during the course of this review. They were developed by Sibi et al. for a novel protocol termed “chiral relay”. This strategy focuses on the design of achiral templates that can relay and amplify the stereochemistry induced by the box. The essence of this strategy is that the chiral catalysts are capable of converting an achiral template such as **220** into a chiral nonracemic template.²⁵⁵ The chiral relay methodology was applied to the enantioselective aza-Michael reaction involving

Scheme 78



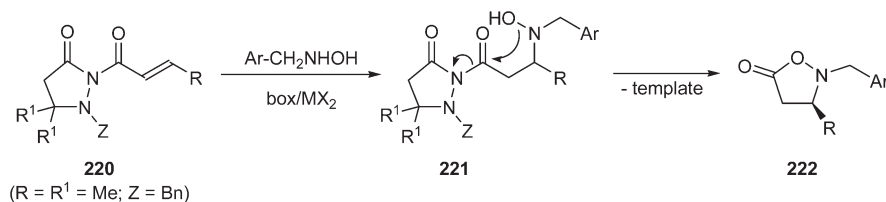
the addition of *N*-(4-methoxybenzyl)-hydroxylamine to **220**. The results, in terms of enantioselectivity with (S)-**1** or (S)-**2** and Mg(ClO₄)₂ or Zn(OTf)₂, cannot be compared to those obtained with (S)-**3c** and (4*S*,5*R*)-**10a**, but the addition product **221**, which undergoes elimination of the template to give the chiral isoxazolidine (S)-**222** with enantioselectivities of up to 41% ee (Scheme 79), is a good illustration of this elegant process.²⁵⁶

The aza-Michael reaction of *N*,*O*-bis(trimethylsilyl)hydroxylamine with arylidene malonates **198** is catalyzed by several box-based catalysts, and some of them give enantioselectivities up to 76% ee. However, the catalyst [(S)-**1**/Cu(OTf)₂] cannot be counted among them because both the yield and enantioselectivity afforded by this complex are unsatisfactory.²⁵⁷

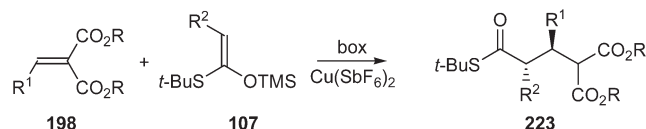
The Mukaiyama–Michael reaction is probably the most important variant of the Michael reaction. It occurs between an activated α,β-unsaturated carbonyl derivative (the electrophilic π-systems) and silylketene acetals (**107**). The first applications of catalysis by box-based complexes of these reactions are found in two publication highlights.^{6c,89}

The first example of a 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(SbF₆)₂ as the catalyst to give the syn and anti adducts in ratios of 9:1 and 60:1 and enantioselectivities of 66% and 60% ee, respectively.²⁵⁸ Detailed and important developments were made by Evans et al., who focused on the Mukaiyama–Michael reaction of **107** with the arylidene malonates **198**. These lead to the formation of 3-substituted *tert*-butyl 4,4-dicarbomethoxy-butanethioate **223** (Scheme 80).⁹⁵

Scheme 79



Scheme 80



Several parameters were investigated, and Table S1 reports the most significant results for each variable. Catalysts derived from the box ligands (S)-1 or (S)-2 gave adducts with opposite configurations (Table S1, entries 1 and 14 vs 2 and 15), with the latter providing the highest enantiomeric excess. For R² ≠ H in **107**, the diastereoselectivity was found to depend on the enolsilane geometry (Table S1, entries 16–19). Arylidene and heteroarylidene malonates gave excellent enantiomeric excesses (Table S1, entries 2 and 6–8), whereas alkylidene malonates with branched alkyl substituents gave adducts with high enantioselectivities; the stereochemistries are reported in Scheme 80 (Table S1, entries 9–11). Unbranched alkyl substituents in the malonate proved to be far less effective, and the configuration of ethylidene (Table S1, entry 14) is the result of an opposite facial attack, as is probably the case for other unbranched alkyl groups (Table S1, 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 corresponds to an opposite facial attack of the nucleophile. Substituents larger than methyl appear to provide an intermediate selectivity.

The crystal structures of [(S)-1·Cu(SbF₆)₂·PhCH=C(CO₂Me)₂] (**21**) and [(S)-2·Cu(SbF₆)₂·PhCH=C(CO₂Me)₂] (**22**) as shown in Figures 5 and 6, respectively, have been proposed as the reacting intermediates in the catalytic cycles of **198** with these boxes as ligands. On the basis of these structures, Figure 14 reports a simple rationale to explain the opposite configuration obtained in these reactions. The attack of the nucleophiles to coordinated benzylidene malonate occurs on the Re face in **21** and on the Si face of **22**.⁹⁶

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-enamidomalones **198** (R¹ = ROCHN) and **107**.²⁵⁹

3-Alkenoyl-2-oxazolidinones **53** are also excellent substrates for the Mukaiyama–Michael reaction since they easily undergo a conjugate addition of enolsilanes **107** (Scheme 81). Monitoring the reaction in situ using IR spectroscopy showed that the reaction occurs through the dihydropyran intermediate **224**. This then converts to the Michael products *anti*-**225** (plus the syn diastereoisomer) in the presence of small amounts of protic

additives (the best is HFIP) that serve to facilitate the catalyst turnover.^{94,260} This reaction is discussed in this section for traditional reasons, although clearly the formation of dihydropyran **224** can also be regarded as an example of a hetero Diels–Alder reaction between **53**, acting as a heterodiene, and **107**, behaving as an electron-rich dienophile.

The most significant results are reported in Table S2. The best catalyst proved to be [(S)-2/Cu(OTf)₂] (Table S2, entries 1 vs 2); hence, this complex was widely used in a range of different experiments. Excellent enantioselectivities were obtained with the 2-unsubstituted enolsilanes **107** when reacted with **53** (Table S2, entries 2–4 and 17–19). If the 2-substituted enolsilane **107** has the (Z)-configuration, then the product is largely syn and the diastereoselectivity increases concomitantly with the size of A. However, if the configuration is (E), then although the product is largely anti the diastereoselectivity decreases with the increasing size of A (Table S2, entries 5–7 and 8–10). Different substituents in the β-position of enolsilane did not change the enantioselectivity, which is always >90% ee (Table S2, entries 10–13). For 1-phenyl- or 1-(1-pyrrolyl)-enolsilanes, as well as other substituents in the reactants, excellent diastereo- and enantioselectivities are always obtained (Table S2, entries 14–16 and 20–22). Finally it should be noted that the dihydropyran intermediate **224** is isolable (even if in only 6% yield) in experiment 20, Table S2. Its (4S,5S,6S) configuration is consistent with that of **225** obtained under the same conditions.

The 3-alkenoyl-2-oxazolidinones **53** also give excellent results in the Mukaiyama–Michael reaction with 2-(trimethylsilyloxy)furan **173**, again catalyzed by box–metal complexes (Scheme 82).^{261,262} Table S3 presents some interesting results; one in particular is noteworthy of 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 the opposite configuration, all lead to the same chiral induction (Table S3, entries 2 and 3 vs 4–6).

These optically active adducts of the Michael reaction can be useful synthons for a range of natural products: One example is the *anti*-(S,S)-**227** (entry 2, Table S3) that is converted in five steps to *trans*-whisky lactone.²⁶³

2-(Trimethylsilyloxy)furan **226** also proved to be an excellent partner for the Mukaiyama–Michael reaction of α'-phosphoric enone **228a** but in particular the α'-phenylsulfonyl enones **228b** (Scheme 83).⁹⁶ A careful screening of suitable boxes, Lewis acids, and solvents led to the development of [(R)-1/Cu(OTf)₂] in CHCl₃, which is an excellent catalytic system (Table S4). Results are comparable to those obtained with (4R,5S)-**5b**. The reactions are also highly anti selective, suggesting a strong analogy with the reaction reported in Scheme 82.

The Mukaiyama–Michael reaction of enolsilanes **107** was performed with [(2-oxo-1,3-oxazolidin-3-yl)carbonyl]diazonyl formates **230** (Scheme 84).²⁶⁴ A survey of [box/Cu(II)] complexes revealed that [(S)-2/Cu(OTf)₂] is the catalyst of choice.

Scheme 81

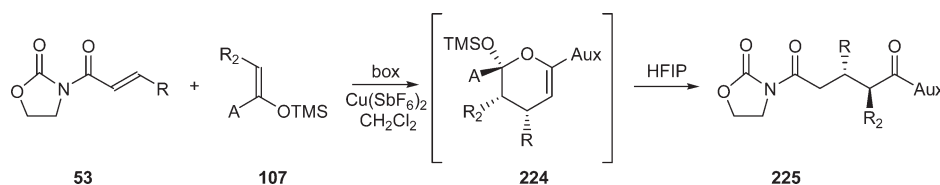


Table 51. Diastereo and Enantioselectivity in the Catalyzed Mukaiyama–Michael Reactions of Enolsilanes 107 and Alkylidene Malonates 198

entry	R ¹	R	R ² (conf.)	box	yield (%)	anti/syn	anti-223 ee (%) (conf.)	syn ee (%)	ref
1	Ph	Me	H	(S)-1	99		52 (S)		33, 95b
2	Ph	Me	H	(S)-2	>98		93 (R)		33, 95
3	Ph	Et	H	(S)-2	>98		88 (R)		95b
4	Ph	<i>i</i> -Pr	H	(S)-2	80		58 (R)		95b
5	Ph	<i>t</i> -Bu	H	(S)-2					95b
6	2-Furyl	Me	H	(S)-2	88		94		95a
7	3-Ts-indolyl	Me	H	(S)-2	99		86		95a
8	<i>o</i> -MeOPh	Me	H	(S)-2	92		99 (R)		95a
9	<i>t</i> -Bu	Me	H	(S)-2	89		90 (R)		95
10	cyclohexyl	Me	H	(S)-2	95		95 (S)		95
11	<i>i</i> -Pr	Me	H	(S)-2	93		93 (S)		95
12	<i>n</i> -Pr	Me	H	(S)-2	87		27		95b
13	Et	Me	H	(S)-2	82		22		95b
14	Me	Me	H	(S)-1	91		40 (R)		95b
15	Me	Me	H	(S)-2	91		44 (S)		95
16	Ph	Me	Me (<i>E</i>)	(S)-2		55:45	<5	<5	95b
17	Ph	Me	Me (<i>Z</i>)	(S)-2		92:8	80	70	95b
18	Me	Me	Me (<i>E</i>)	(S)-2		95:5	68	30	95b
19	Me	Me	Me (<i>Z</i>)	(S)-2		29:71	10	62	95b

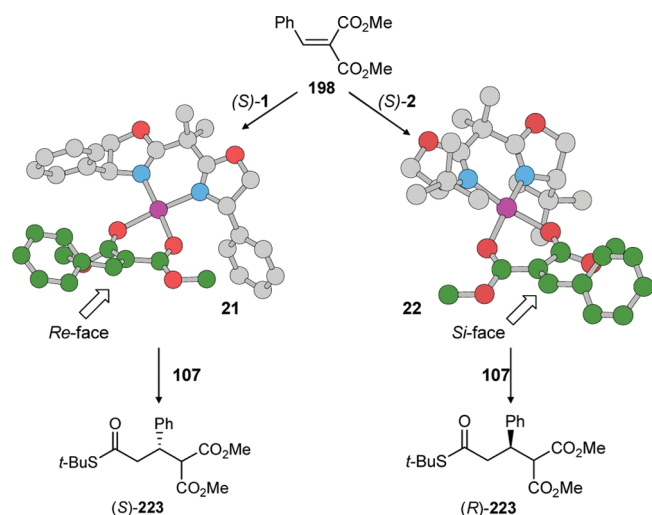


Figure 14. Different reacting complexes of 198 with (S)-1 and (S)-2 and their influence on the configuration of the Mukaiyama–Michael adducts with 107.

It afforded (*R*)-hydrazino adducts 232 in excellent yields and enantioselectivities as shown in Table 55.

The use of trifluoroethanol as an additive is critical to achieving a good catalyst turnover (Table 55, entry 1 vs 2). Enolsilanes afford the (*R*)-hydrazino products independently of the nature of the substituents (Table 55, entries 2–6 and 8). However, the (*E*)- and (*Z*)-thioester silylketene acetals give the

opposite enantiomers (Table 55, entry 6 vs 7). The investigation was extended to the silylketene acetals of acylpyrroles, and here the nature of the β -substituent proved crucial. The steric hindrance of the *tert*-butyl-substituted 107 impedes the β -attack (easy for R¹ = Me). Hence, amination occurs exclusively on the pyrrole ring (Table 55, entry 9 vs 8). Monitoring the reaction by in situ IR spectroscopy led to the discovery that the reaction occurs through an intermediate. This is proposed to be the dihydropyran 231, which is analogous with the Mukaiyama–Michael reaction illustrated in Scheme 81.

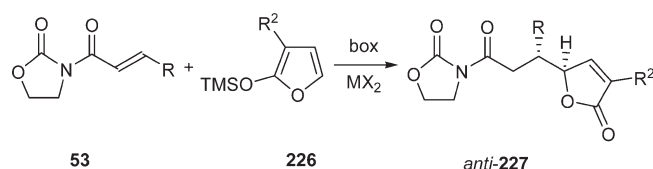
4.5. Allylic Substitution Reactions

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 were considered as starting compounds for the construction of the catalysts. Boxes with different substituents, sometimes even quite sophisticated ones, were mainly studied.^{21,265} The generally accepted mechanism, in the simplest intermolecular version, is outlined in Scheme 85. The first step involves the complexation of the racemic X-allyl-substituted reagent 233 to the box–palladium complex 234 to give, after ionization, two diastereomeric palladium complexes 235a,b. These in turn react with a nucleophile to give, after decomplexation, the optically active allyl-substituted products 236.

This reaction differs from other box-catalyzed reactions in the facile preparation, isolation, and characterization, frequently using X-ray crystal structures (Table 2, entries 50–53, and Figure 11), of the reactive intermediate(s) 235a,b. This in turn allows the inference of the enantiodiscrimination mechanism.

Table 52. Diastereo and Enantioselective Catalyzed Mukaiyama–Michael Reactions of Enolsilanes **107** and 3-Alkenoyl-2-Oxazolidinones **53**

entry	R	A	R ² (conf.)	box	yield (%)	anti/syn	anti ee (%) (conf.)	syn ee (%) (conf.)	ref
1	CO ₂ Et	<i>S</i> -Bu	H	(<i>S</i>)-1	n.d.		57 (3 <i>S</i>)		94
2	CO ₂ Et	<i>S</i> -Bu	H	(<i>S</i>)-2	86		89 (3 <i>S</i>)		94
3	CO ₂ Et	Ph	H	(<i>S</i>)-2	54		98		94
4	CO ₂ Et	Cyhex	H	(<i>S</i>)-2	31		99		94
5	CO ₂ Et	<i>S</i> -Bu	Me (<i>Z</i>)	(<i>S</i>)-2	94	1:>99		99 (3 <i>S</i> ,4 <i>R</i>)	94, 260
6	CO ₂ Et	SEt	Me (<i>Z</i>)	(<i>S</i>)-2	91	25:75		92 (3 <i>S</i> ,4 <i>R</i>)	94
7	CO ₂ Et	SMe	Me (<i>Z</i>)	(<i>S</i>)-2	90	34:66		90 (3 <i>S</i> ,4 <i>R</i>)	94, 260
8	CO ₂ Et	<i>S</i> -Bu	Me (<i>E</i>)	(<i>S</i>)-2	65	78:22	96 (3 <i>S</i> ,4 <i>S</i>)		94, 260
9	CO ₂ Et	SEt	Me (<i>E</i>)	(<i>S</i>)-2	77	86:14	91 (3 <i>S</i> ,4 <i>S</i>)		94
10	CO ₂ Et	SMe	Me (<i>E</i>)	(<i>S</i>)-2	90	95:5	90 (3 <i>S</i> ,4 <i>S</i>)		94, 260
11	CO ₂ Et	SMe	Et (<i>E</i>)	(<i>S</i>)-2	89	95:5	90 (2 <i>S</i> ,3 <i>S</i>)		94, 260
12	CO ₂ Et	SMe	<i>i</i> -Pr (<i>E</i>)	(<i>S</i>)-2	93	>99:1	98 (3 <i>S</i> ,4 <i>S</i>)		94, 260
13	CO ₂ Et	SMe	CH ₂ Cy ^a (<i>E</i>)	(<i>S</i>)-2	84	96:4	97 (3 <i>S</i> ,4 <i>S</i>)		94
14	CO ₂ Et	Ph	Me (<i>Z</i>)	(<i>S</i>)-2	99	95:5	92 (3 <i>S</i> ,4 <i>S</i>)		94, 260
15	CO ₂ Et	Ph	Et (<i>Z</i>)	(<i>S</i>)-2	99	99:1	94 (2 <i>S</i> ,3 <i>S</i>)		94, 260
16	CO ₂ Et	Ph	<i>i</i> -Pr (<i>Z</i>)	(<i>S</i>)-2	99	99:1	94 (2 <i>S</i> ,3 <i>S</i>)		94, 260
17	Me	1-pyr ^b		(<i>S</i>)-2	90		91 (3 <i>R</i>)		94
18	CO ₂ Et	1-pyr ^b		(<i>S</i>)-2	92		95 (2 <i>R</i>)		94
19	Ph	1-pyr ^b		(<i>S</i>)-2	94		90 (3 <i>R</i>)		94
20	Me	1-pyr ^b	Me (<i>Z</i>)	(<i>S</i>)-2	88	99:1	98 (2 <i>S</i> , 3 <i>S</i>)		94, 260
21	CO ₂ Et	1-pyr ^b	Me (<i>Z</i>)	(<i>S</i>)-2	91	97:3	94 (2 <i>S</i> , 3 <i>S</i>)		94, 260
22	Ph	1-pyr ^b	Me (<i>Z</i>)	(<i>S</i>)-2	97	99:1	98 (2 <i>S</i> , 3 <i>S</i>)		94

^a Cy is cyclopentyl. ^b 1-Pyr is 1-pyrrolyl.**Scheme 82**

In this section, the discussion will be limited to Ph- and *tert*-Bu-box; other important boxes will be discussed later.

The asymmetric allylic alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene **237** with dimethyl malonate, catalyzed by [(*R*)-**1**/Pd(PF₆)₂], gives (*R*)-**238** with 95% ee (Scheme 86).^{33,48} In addition to this particular result, the use of new 4,5-disubstituted boxes (whose behavior as ligands for catalysts of the above reaction will be discussed later) and the isolation of their palladium complexes have also been reported. In spite of the fact that none of these complexes proved to be suitable for X-ray analysis, their structures were successfully solved using ¹H NMR spectroscopy. The complex [(*R*)-**1**/Pd(PF₆)₂·(CH₂CHCH₂)] deserves specific mention because 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 86 can be also catalyzed by [(*S*)-**2**/Pd(PF₆)₂], and (*S*)-**238** is obtained with 33% ee.²⁶⁶

The enantioselective substitution of the methoxy group in 1-substituted 3,4-didehydro-2-methoxypiperidines (**239**, R = Ar and OR) was inferred. The mechanism of elimination/addition occurs through the cation **240** as intermediate. This undergoes the

enantioselective addition of malonate to position 2 to give the 1-acyl-3,4-didehydro-2-piperidyl malonates **241** (Scheme 87).^{267–270} Depending on the reaction conditions and substituents, some side-products, derived from the attack at position 4 of **240**, are also formed. The yields are in the range 36–86%, and the enantioselectivities are in the 21–95% ee range. The best results are obtained with aryl-substituted malonates as the reagents and [(*S*)-**1**/Cu(OTf)₂] as the catalyst. When (*S*)-**2**/Cu(OTf)₂ is the catalyst, a lower enantiomeric excess is found.^{267a,270} The involvement of a square-planar reactive intermediate involving box and malonate, which then undergoes attack of the iminium ion **240**, can be used to rationalize the enantioselective formation of (*R*)-**241**.²⁷⁰

The allylic substitution reaction also has an intramolecular version. The reagent undergoing the cyclization can be derived from different routes. When the aryl compound **242** (or vinylic iodides) with a nucleophilic substituent in the ortho (or, respectively, in the allylic) position reacts with the allenes **243** under a palladium-catalyzed coupling, it gives the palladium complex **244**. This in turn undergoes the intramolecular allylic substitution reaction to give the heterocyclic product **245** (Scheme 88).²⁷¹ The result of a thorough screening of several ligands revealed that (*R*)-**3d** was the optimal ligand for this reaction. Using this catalyst, several heterocycles, either monocyclic or bicyclic such as **245**, were obtained with enantioselectivities often >80% ee. For example, **245** was obtained in 94% yield and 82% ee. Their configurations were found to be (*S*), which can be explained by the backside nucleophilic displacement of **244**.

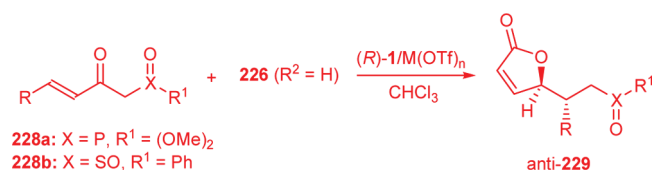
The reaction of allene-β-ketoester **246** with dibenzyl azodicarboxylate **171** is an alternative pathway to introducing the nucleophile via a [(*S*)-**1**/Cu(OTf)₂]-catalyzed enantioselective

Table 53. Diastereo- and Enantioselective Catalyzed Mukaiyama–Michael Reactions of 3-Alkenoyl-2-oxazolidinones 53 and 2-TMSO-furans 226

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)	262b
2	Me	H	(S)-2	Cu(OTf) ₂	HFIP, MS	89	89:11	95 (S,S)	262
3	Me	H	(S)-2	Cu(OTf) ₂	MS	37	91:9	92 (S,S)	262b
4	Me	H	(R)-1	Mg(ClO ₄) ₂	MS	94	85:15	20 (S,S)	261
5	Me	H	(R)-1	Ni(ClO ₄) ₂	MS	91	82:18	32 (S,S)	261
6	Me	H	(R)-1	Zn(ClO ₄) ₂	MS	90	>99:1	31 (S,S)	261
7	Me	Me	(S)-2	Cu(OTf) ₂	HFIP, MS	95	96:4	91 (S,S)	262

^a HFIP is hexafluoroisopropanol and MS are 4 Å MS.

Scheme 83



amination. The carbopalladiation reaction of the allene with an aryl (or vinyl or heteroaryl) iodide (RI) affords the π -allyl palladium intermediate **247**. This in turn can be trapped by the NH in the diastereoselective step to give the pyrazoline derivatives (3*R*,5*R*)- and (3*R*,5*S*)-**248** (Scheme 89).^{272,273} The solvent plays a very important role in both steps; CH₂Cl₂ is required with copper complexes and THF with palladium complexes. The reaction can be run in a “one-pot” reaction by diluting the first solvent with 1,4-dioxane to allow the reaction to be run at 100 °C. The reaction suffers from one important limitation; although with each R group the enantioselectivity of both pyrazolidines is very high (97–99% ee), the diastereoselectivity is disappointing, within the range 1:1–1:2.

In an intramolecular allylic substitution reaction, the nucleophile can be accessed from a triple bond. Here 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, which has AcO as the leaving group.^{274–276} The sequence reported in Scheme 90 starting from (*Z*)-4'-acetoxy-2'-butenyl-2-alkynoates **249** (X = O) affords, with the catalyst [(*R*)-1/Pd(OAc)₂] in AcOH, the α -(*Z*)-acetoxyalkylidene- β -vinyl- γ -butyrolactones **250**. The results for different R groups are reported in Table 56. The same reaction was applied to the cyclization of (*Z*)-*N*-allylic 2-alkynamides to afford the α -(*Z*)-acetoxyalkylidene- γ -butyrolactams (**250**, X = N–Bn or N–Ts). Reaction with [(*R*)-1/Pd(OAc)₂] gave good yields but with only moderate enantioselectivities (Table 56, entries 6 and 7).²⁷⁷

From our point of view, the most interesting Pd-catalyzed reaction is the asymmetric cyclization/carbonylation that occurs with the incorporation of CO into the final structure. Two variants are reported: one in which carbon monoxide becomes part of a carboxylate substituent and the second in which CO becomes part of a ring.

An example of the first variant is the cyclization of 1-*p*-tolylbut-3-en-1-one with CO and MeOH. It is catalyzed by [(*R*)-1 or (*R*)-2/PdCl₂] and gives the methyl 2-(3'-*p*-tolyl- Δ^2 -isoxazolin-5'-yl)-acetates in 67 and 73% yield with 34 and 15% ee, respectively.²⁷⁸ Another example is the oxidative cyclization carbonylation with CO and the alcohols of 2-methyl-2-propargyl-cyclohexan-1,3-dione

(**251**), to give the hemiacetal **252a** (Scheme 91). The stereoselective step involves an intramolecular nucleophilic attack of the –OH group at the triple bond coordinated to [(*S*)-1/Pd(CF₃CO₂)₂]. The resulting organo-palladium **252b** is then carbonylated and esterified to give **253**. The effect of ROH is critical since the use of bulky alcohols increases the enantiomeric excess, going from 8% ee of (*R*)-**253** with MeOH to 43% ee (*S*)-**253** with *i*-BuOH.^{37,279}

If the same reaction is performed in methanol on 2-methyl-2-propargyl-1,3-diol **254** with [(*S*)-1/Pd(OCOCF₃)₂] as the catalyst, the bicyclic- β -alkoxyacrylates (*S*)-**255** are obtained in 98% yield and with 65% ee (Scheme 92).^{36,280} These products can be converted into useful intermediates suitable for the synthesis of natural products.

An example of a reaction in which CO is incorporated into a ring is the oxidative carbonylation of racemic *N*-tosyl-1-amino-pent-4-ene-3-ol **256**. It gives a bicyclization catalyzed by [(*S*)-1/Pd(OAc)₂] with CO and *p*-benzoquinone, to furnish (*R,R*)-**257** in 40% ee. In addition, the optically active (*S*)-**256** (Scheme 93) is recoverable.²⁸¹ The same reaction was performed on the analogous diol.²⁸²

4.6. Radical Reactions

Enantioselective radical processes were covered in a strongly recommended review by authors deeply engaged in box chemistry.²⁸³

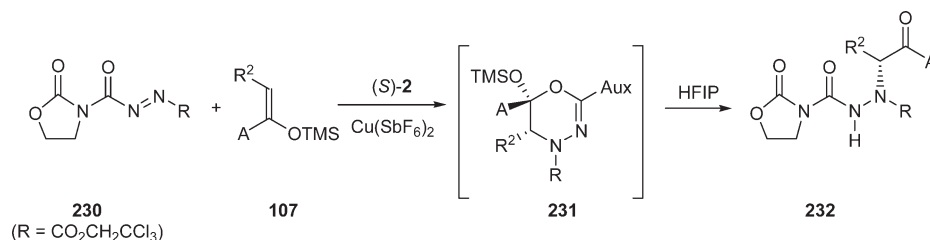
As is the case for all the catalytic enantioselective processes covered previously, a box-complexed Lewis acid gives either a substrate-bound or a radical-bound species. This then determines the approach of the second reagent in the enantioselectivity-determining step. Due to its specific effect as a Lewis acid, it also determines the increase in rate of the chiral pathway versus the background reaction. Since the majority of 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 **258** has an α -iodine atom in the chain (R = Me, X = I), then homolysis of the C–X bond gives two radicals, one of which is bound and can be transferred, in a reagent-bound process, to the unsaturated group of 1-octene. The result is two diastereomers **259a** (X = I), which can be dehalogenated with Zn/AcOH to finally give a pair of enantiomers **259b** (X = H) (Scheme 94).²⁸⁴ The optimized conditions with [(*S*)-1/Zn(OTf)₂] give (*S*)-**259b** in 40% ee.

The pair of radicals derived from bromo derivatives **258** with Et₃B (an efficient initiator at low temperatures) can be trapped with either allylsilanes or allylstannanes in the presence of box-based Lewis acids. This is a reagent-bound process and gives β -bromo silane (or stannane) **260**, which then undergoes elimination of ZBr to give **261**; this is formally the result of an allyl

Table 54. Diastereo- and Enantioselective Catalyzed Mukaiyama–Michael Reactions of TMSO-furan 226 with Enones 228⁹⁶

entry	R	X	R ¹	M(OTf) _n	yield (%)	anti/syn (%)	anti ee (%) (conf.)
1	Me	P	(OMe) ₂	Cu(OTf) ₂	92	97:3	82
2	H	SO	Ph	Cu(OTf) ₂	85		91 (S)
3	Me	SO	Ph	Sc(OTf) ₃	35	96:4	10 (S,S)
4	Me	SO	Ph	Zn(OTf) ₂	99	99:1	88 (S,S)
5	Me	SO	Ph	Cu(OTf) ₂	99	98:2	98 (S,S)
6	Et	SO	Ph	Cu(OTf) ₂	80	>99:1	99
7	Pr	SO	Ph	Cu(OTf) ₂	99	83:17	99
8	CH ₂ CH ₂ Ph	SO	Ph	Cu(OTf) ₂	92	95:5	>99
9	Ph	SO	Ph	Cu(OTf) ₂	95	>99:1	97

Scheme 84**Table 55. Enantioselective Catalyzed Mukaiyama–Michael Reactions of Enolsilanes 107 and Azodicarbonyl Derivatives 230²⁶⁴**

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>i</i> -Bu	Ph	(S)-2	TFE ^b	92	98 (R)
5	Ph	4'-MeOPh	(S)-2	TFE ^b	94	97 (R)
6	Me (<i>E</i>)	<i>S</i> <i>t</i> -Bu	(S)-2	TFE ^b	85	96 (R)
7	Me (<i>Z</i>)	<i>S</i> <i>t</i> -Bu	(S)-2	TFE ^b	89	84 (S)
8	Me	1-pyrrole	(S)-2	TFE ^b	96	99 (R)
9	<i>t</i> -Bu	1-pyrrole	(S)-2	TFE ^b	<i>a</i>	

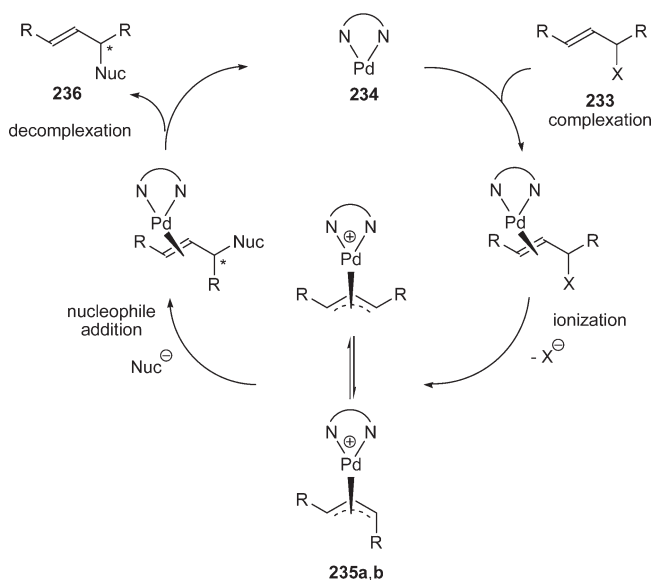
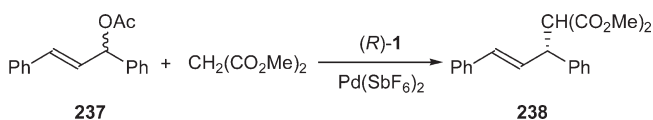
^a 80% yield of amination in position 2 of the pyrrole ring. ^b TFE is trifluoroethanol.

transfer (Scheme 95).²³ Some appreciable results are reported in Table 57; among them are Zn(OTf)₂ (which gives the best enantiomeric excess) and MgI₂. Interestingly, under identical conditions these give opposite enantiomers (Table 57, entries 4 and 5).

The same reaction can be performed using allyltrimethylsilane with 3-bromo-1-(2-pyridyl)-2-pyrrolidone **262**, which behaves as a bidentate ligand with [(*S*)-**1**/Zn(OTf)₂]. Again this is a reagent-bound process, and it gives (*S*)-**263** in 59% ee (Scheme 96).²⁸⁵

In the absence of a radical trap, under oxidative conditions, the radical derived from **258** (R = Ph, X = H) dimerizes to give **264** (Scheme 97). The *D,L*/meso ratio is ~1:1, and it is noteworthy that both (*R*)-**1** and (*S*)-**2** give the same (*S,S*)-**264** enantiomer despite their opposite configurations.²⁸⁶

Porter et al. reported one of the earliest examples of a substrate-bound process activated by a [box/Lewis acid] complex.²⁸⁷ Their process involves the addition of a radical generated from alkyl iodides to 3-acryloyl-2-oxazolidinone **53**. The resulting new radical is then trapped by allyltributylstannane, with an intermediate (as reported in Scheme 95) that loses Bu₃SnBr to give **265**. Under the

Scheme 85**Scheme 86**

stoichiometric conditions reported and shown in Scheme 98, for R² = cyclohexyl and *tert*-butyl, the yields of (*S*)-**265** are 61% and 78%, and the enantiomeric excesses are 80% and 88% ee, respectively, whereas [(*S*)-**2**/Zn(OTf)₂] gives racemic products.²⁸⁷

The stereochemical efficiency of the reactions in Scheme 98 can be compared: the substrate-bound addition/trapping process from **53** to **265** versus the reagent-bound process involving fragmentation of **266** and addition of allyl stannate to the resulting radical.²⁸⁸ In both cases the selectivity increases with an increase in Lewis acid equivalents. The substrate-bound addition/trapping sequence gives a higher enantiomeric excess than the corresponding reagent-bound fragmentation reaction. Both processes give higher enantioselectivity with an increase in the steric hindrance of R (74 and 90% ee, respectively, for R = *t*-Bu). 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 **53** reacts with the radical derived from the cleavage of R^2I promoted by Et_3B/O_2 . But the new radical was quenched by Bu_3SnH to give **267**, which is formally the product of the conjugate addition of R^2H (Scheme 99).^{45,289} The results for this reaction are reported in Table 58. These are obtained by using stoichiometric amounts of [box/ MX_2], except for 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 58, entries 3 and 7–9), (*S*)-**2** the best enantioselectivity with $MgBr_2$ (Table 58, entries 5 and 10). From the data in Table 58 it can also be seen that box ligands having identical absolute configurations give opposite enantiomers.

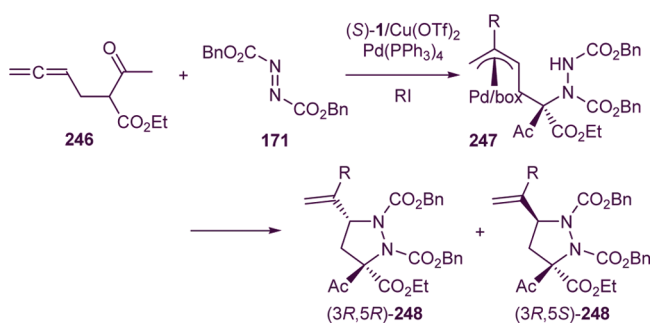
An attempt was made to use optically active Lewis acids derived from metal triflamides under catalytic conditions; the complexes were tested in the reaction shown in Scheme 99 between **53** (R = Ph) and *i*-PrI.²⁹⁰ (*S*)-**2** gives interesting results (94% yield and 80% ee) only with $Fe(NTf_2)_2$. However, it could not compete with box **10a** and MgI_2 ,⁴⁵ which (together with **9a**, **10b,c**, and MgI_2 , $Mg(NTf_2)_2$, and $Fe(NTf_2)_2$)²⁹⁰ give **267** (R = Ph, $R^2 = i$ -Pr) in yields between 82% and 99% and enantioselectivities up to 98% ee, under substoichiometric conditions.⁴⁵

Substrate-bound conjugate radical additions can be carried out using several substrates. The reaction of R^2I and 3-(β -acyloxy)-acryloyl-2-oxazolidinones (**53**, R = acyloxy) 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, and this suggests either a slow turnover of the catalyst or a competition with the uncatalyzed process.²⁹¹ The absolute stereochemistry was determined for two products (Table 59, entries 2 and 9) and is consistent with a Si face radical

addition to *s*-cis conformer of the substrate. This is the same sense of selectivity as that obtained with cinnamate and crotonate oxazolidinones (see Table 58) and suggests the presence of similar reacting intermediates. The success, or not, of the catalytic version probably depends on the stability of the reactive intermediate that influences the turnover rate. For the reactions with 3-(β -acyloxy)-acryloyl-2-oxazolidinones the presence of an additional donor atom in the substrate must be considered.

The factor required for a substrate to undergo a fruitful radical addition is its ability to coordinate the catalyst in a bidentate fashion. As seen above, this can be achieved with a β -dicarbonyl derivative. On the other hand, α' -hydroxy enones **188** can participate in such a coordination through the carbonyl and the hydroxy group. The reaction occurs nicely with alkyl iodides in the presence of *n*- Bu_3SnH as the source of the hydrogen radical. After careful screening of both the boxes and Lewis acids, the best catalyst for obtaining enantioselectively the adducts **268** was found to be [(*R*)-**1**/ $Mg(NTf_2)_2$] (Scheme 100, Table 60).

Scheme 89



Scheme 90

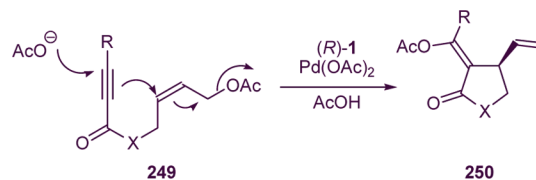
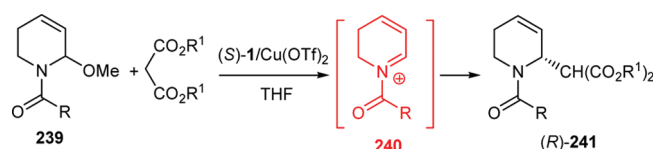


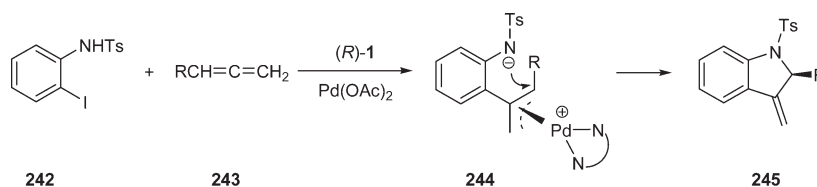
Table 56. Asymmetric Cyclization of 249

entry	R	X	yield (%)	ee (%) (conf.)	ref
1	Me	O	78	92 (R)	274, 275
2	<i>n</i> -Pr	O	80	80 (R)	274, 275
3	Ph	O	58	79 (R)	274, 275
4	<i>i</i> -C ₇ H ₁₅	O	77	85 (R)	274, 275
5	MeOCH ₂	O	67	87 (R)	274, 275
6	Me	N-Bn	96	35	277
7	Me	N-Ts	81	65	277

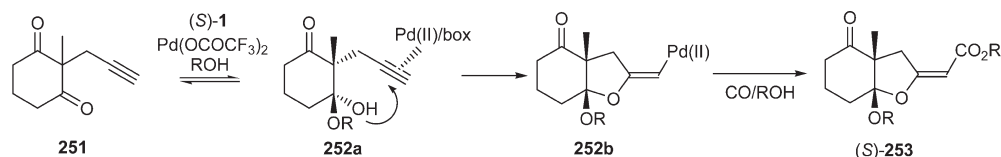
Scheme 87



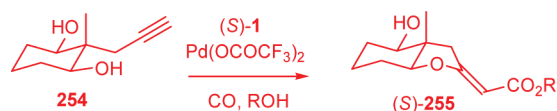
Scheme 88



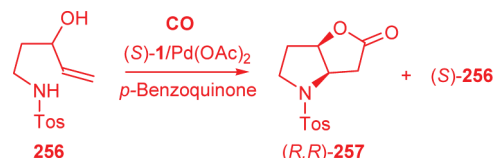
Scheme 91



Scheme 92



Scheme 93



Among the different substituents, only $R^1 = \text{Ph}$ had a dramatic effect on the enantioselectivity (Table 60, entry 9).²⁹²

Other bidentate substrates suitable for enantioselective radical additions are α,β -unsaturated-2-pyridyl ketones **269**, which give **270** enantioselectively with $[(S)\text{-}1/\text{Zn}(\text{OTf})_2]$ as the catalyst (Scheme 101).²⁹³ The reaction is compatible with different alkyl radicals, but enantioselectivity is better when there are aryl rather than alkyl groups on the double bond (Table 61). The absolute configuration determined for the product reported in entry 1 of Table 61 is in agreement with an octahedral reacting intermediate.

Substrate-bound radical additions can also take place on the C=N bond of glyoxylic oxime methyl ester **271** with *i*-PrI in the presence of chiral Lewis acids derived from (R)-**1**. $\text{Mg}(\text{OTf})_2$, $\text{Zn}(\text{OTf})_2$, $\text{Yb}(\text{OTf})_3$, and MgBr_2 all were tested. Their enantiomeric excesses for (R)-**272** were 2%, 10%, 24%, and 52% ee, respectively (Scheme 102).²⁹⁴ Only a limited stoichiometric amount of chiral Lewis acid is required for this potentially useful asymmetric synthesis of α -amino acids. This is probably due to the difficult substitution of product **272** by **271** in the reacting complex 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-iminoarylidene-2-piperidinone **273** gives **274** (Scheme 103): Yields are in the range 44–88%, and the enantiomeric excess is ~90%, but stoichiometric conditions are required.²⁹⁵ The reaction with 1-iminobenzylidene derivative and *i*-PrI was optimized with $[(S)\text{-}2/\text{Cu}(\text{OTf})_2]$ in benzene/ CH_2Cl_2 as the solvent and gave (R)-**274** with an excellent yield and 95% ee.

Alkylidene sulfones bound to pyridyl, or even better to the benzimidazolyl moiety **275a,b**, can achieve a bidentate chelation with the $[\text{box}/\text{Zn}(\text{OTf})_2]$ complexes. A substrate-bound radical addition derived from R^2I (in the presence of Et_3B as the initiator) gives a bound radical **276** ($\text{R} = \text{H}$ or Me from **275a,b**, respectively) (Scheme 104).^{296,297} This intermediate can be trapped either by allylation (with $\text{Bu}_3\text{Sn}(\text{allyl})_2$) or by hydrogen (with Bu_3SnH). Surprisingly diallylbutyltin approaches the Si face of the carbon radical to give 84% ee of (S)-**277a**, whereas the tin hydride approaches the Re face of the radical center to achieve 38% ee of (S)-**277b**. All reactions occur under stoichiometric conditions. With suitable substituents, products with up to 91% ee can be obtained. On the other hand, with **275b** as the starting reagent, the Lewis acids derived from (S)-**2** give only negligible enantioselectivity (5% ee).

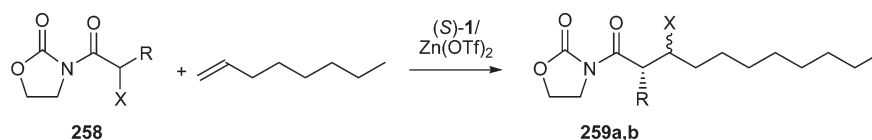
If both the radical source and the radical trap are in the same molecule, then the resulting intramolecular reaction promotes a cyclization. This is an interesting reaction as multiple stereocenters are formed. When the radical is created by cleavage of the C–Br bond of **278**, which incorporates a C=C bond, the intramolecular version of the reaction already reported in Scheme 86 gives **279** (Scheme 105).^{298,299} In the catalytic version with $[(S)\text{-}2/\text{Mg}(\text{ClO}_4)_2]$ and 4 Å MS, the yields and enantiomeric excesses of **279** are reported in Table 62. The presence of another double bond (Scheme 79,²⁸⁰ ($n = 1$)) promotes a radical cyclization cascade with formation of (2R,3S,4S,5S)-**281** (24% yield and 33% ee).³⁰⁰ The homologous **281** ($n = 2$) is obtained in 16% yield and 84% ee, but its absolute configuration is unknown.

An enantioselective PhSe-group transfer was realized by Se–C bond cleavage, radical cyclization, and selenium radical trapping. In this way, **282** was treated with $\text{Et}_3\text{B}/\text{O}_2$ as the radical initiator, in the presence of the $[(S)\text{-}2/\text{Mg}(\text{ClO}_4)_2]$ complex (0.3 equiv), which coordinates with the β -dicarbonyl fragment. Excellent configuration control gives the same (2R,3S,11R)-**283** (Scheme 106), starting either from (Z)-**282** ($\text{R} = \text{Et}$, $\text{R}^1 = \text{H}$, 81% yield, 84% ee) or from its stereoisomer (E)-**282** ($\text{R} = \text{H}$, $\text{R}^1 = \text{Et}$, 66% yield, 87% ee).³⁰¹ The product was a single stereoisomer, in contrast to the results obtained from the previously mentioned bromine atom transfer reaction, in which two diastereomeric products were obtained in about equimolecular amounts. Other substrates were tested, and again the enantioselectivities were excellent.

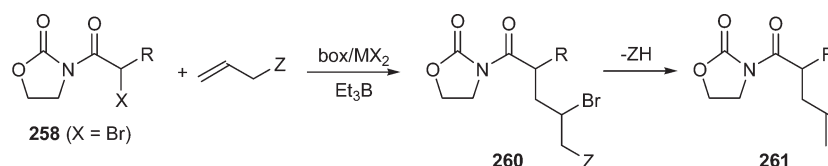
If α,β -unsaturated sulfones, bound to the benzimidazolyl moiety, are tethered to a potential radical source, the C–I bond in **284**, then its cleavage promotes a radical cyclization that can be accomplished by a hydrogen atom donor to give **285** (Scheme 107). The reaction is run under stoichiometric conditions, and the coordination of one of the sulfonyl oxygen atoms and the unsubstituted benzimidazole nitrogen atom by $[(S)\text{-}1/\text{Zn}(\text{OTf})_2]$ gives (R)-**285** in 93% yield and 70% ee. The same reaction with (S)-**2**, however, gives a racemate.³⁰²

The participating radical can be generated on atoms other than carbon (e.g., nitrogen), and intramolecular carboamination of alkenes becomes a direct method for (nitrogen) heterocycle syntheses. The reaction involves Cu(II), which facilitates the oxidative cyclization process. Hence, it was tested with the $[(R)\text{-}1/\text{Cu}(\text{OTf})_2]$ complex as the potential catalyst to make the

Scheme 94

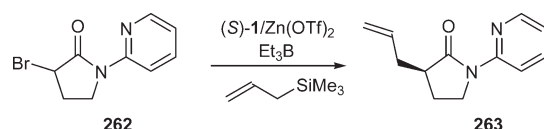


Scheme 95

Table S7. Reactions of 3-(α -Bromoacyl)-2-oxazolidinone **258** with Allylsilanes and -stannanes²³

entry	R	Z	box	MX_2	yield (%)	ee (%) (conf.)
1	Et	SnBu_3	(R)-1	$\text{Zn}(\text{OTf})_2$	84	42 (S)
2	Et	$\text{Si}(\text{OEt})_3$	(R)-1	$\text{Zn}(\text{OTf})_2$	65	60 (S)
3	$\text{CH}_2t\text{-But}$	SnBu_3	(R)-1	$\text{Zn}(\text{OTf})_2$	63	74 (R)
4	$\text{CH}_2t\text{-But}$	SiMe_3	(R)-1	$\text{Zn}(\text{OTf})_2$	88	90 (R)
5	$\text{CH}_2t\text{-But}$	SiMe_3	(R)-1	MgI_2	86	68 (S)
6	$\text{CH}_2t\text{-But}$	SiMe_3	(S)-2	MgI_2	61	78 (R)

Scheme 96

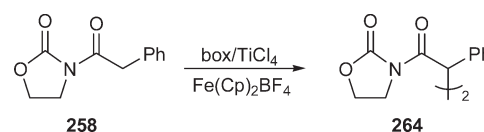


reaction enantioselective. *N*-alkenyl benzenesulfonamides **286**, with catalyst and oxidant, at 120 °C give **287** with good yields and excellent ee's (Scheme 108, Table 63). From *N*-(1-allyl cyclohexylmethyl)-4-methyl benzenesulfonamide (Table 63, entry 7), 7-methyl-2,2-cyclohexyl-2,3,9,9a-tetrahydro-1*H*-4-thia-3a-aza-(*S*)-cyclopenta[*b*]naphthalene 4,4-dioxide was obtained. The same (*S*) absolute configuration was achieved for an *N*-alkenyl thiophene-2-sulfonamide, confirming the excellent flexibility of this process.³⁰³

The mechanism of the enantioselective intramolecular carbamination was investigated by carrying out the reaction of **288** with [(*S*)-1/ $\text{Cu}(\text{OTf})_2$] and the tetramethylaminopyridyl radical. Under these conditions, the optically active primary carbon radical species is trapped by 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), before cyclizing on the phenyl group, to give (*R*)-**289** in 97% yield and 83% ee (Scheme 109).³⁰⁴

The above reactions involve carbon or nitrogen radicals adding to a carbon–carbon double bond. An earlier study, undertaken on the enantioselective intermolecular addition of ethyl radicals to the endocyclic carbon–nitrogen double bond of 5-hydroxy-3-methyl-2*H*-benzo[*b*][1,4]oxazin-2-one, was catalyzed by [(*R*)-1/ $\text{Zn}(\text{OTf})_2$]. The addition product with an absolute (*R*) configuration was obtained.³⁰⁵

Scheme 97

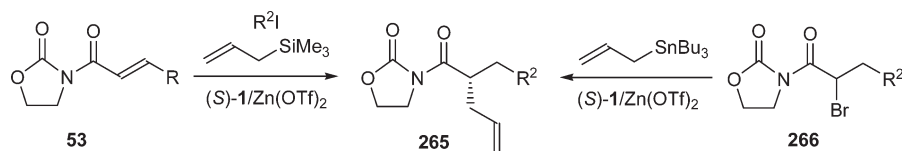
Table S8. Enantioselective Radical Additions to 3-Alkenoyl-2-Oxazolidinone **53** of R^2 ²⁸⁹

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

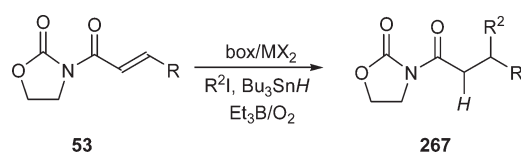
^a Under catalytic conditions (0.2 equiv of Lewis acid).

If susceptible positions of organic compounds (e.g., the allylic position) can be acyloxylated by *t*-butyl peresters in the presence of a trace of Cu(I) in accordance to the Kharasch reaction, why not experiment with the enantioselective variant running the reaction in the presence of chiral ligands such as box? In fact, this has been done using either cyclopentene or cyclohexene **290** ($n = 1, 2$), *tert*-butyl perbenzoate, (*S*)-1 or (*S*)-2, and CuOTf , to give cycloalkenyl-2-benzoate **291**. The mechanism starts with the cleavage of the peroxy bond, which gives the [box/ $\text{Cu}(\text{II})$ benzoate] **292** and a *tert*-butoxy radical that abstracts an allylic hydrogen atom to give *t*-BuOH and the allyl radical. The addition of this radical to **292** generates the Cu(III) species **293**, which subsequently undergoes fragmentation to give **291** and [Cu(I)/box] (Scheme 110).³⁰⁶ Because, with cyclopentene and cyclohexene, [(*S*)-1/ CuOTf] gave 84% and 77% yields of **291** with 71% and 67% ee's, respectively, these early results were good enough to stimulate the interest of several groups. The same

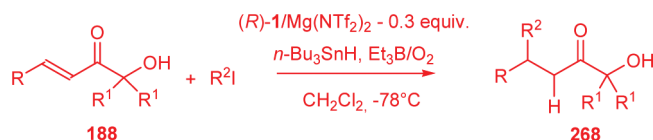
Scheme 98



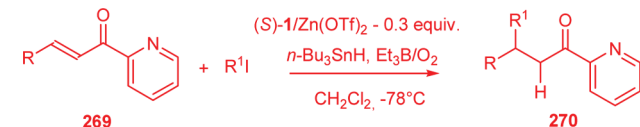
Scheme 99



Scheme 100



Scheme 101

Table 59. Enantioselective Radical Additions of 3-(β-Acyloxy)acryloyl-2-oxazolidinones 53 with R^2I in the Presence of 1 equiv of Lewis Acid $[(S)\text{-2}/\text{MgI}_2]$ ²⁹¹

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

reactions performed with $[(S)\text{-2}/\text{CuOTf}]$ gave 61% and 64% yields and 84% and 77% ee's, respectively.

The asymmetric Kharasch reaction was tested on several alkenes, using different aromatic perester oxidants, box ligands, copper salts, and solvents. A selection of the most significant results is reported in Table 64. The best solvent is MeCN,

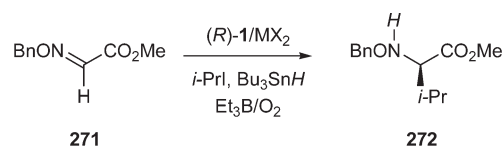
Table 60. Enantioselective Radical Additions of R^2I on α'-Hydroxy Enones 188 with $[(R)\text{-1}/\text{Mg}(\text{NTf}_2)_2]$ as Catalyst²⁹²

entry	R	R^1	R^2	yield (%)	ee (%) (conf.)
1	Ph	Me	Et	82	80
2	Ph	Me	<i>i</i> -Pr	78	78 (<i>R</i>)
3	Ph	Me	<i>t</i> -Bu	90	78
4	Ph	Me	<i>c</i> -Hex	77	67
5	CH ₂ CH ₂ Ph	Me	Et	87	72
6	CH ₂ CH ₂ Ph	Me	<i>t</i> -Bu	66	75
7	Ph	H	<i>t</i> -Bu	91	73
8	Ph	(CH ₂) ₄	<i>t</i> -Bu	75	71
9	Ph	Ph	<i>t</i> -Bu	72	2

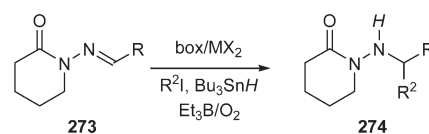
Table 61. Enantioselective Radical Additions between α,β-Unsaturated 2-Pyridyl Ketones 269 and R^1I with $[(S)\text{-1}/\text{Zn}(\text{OTf})_2]$ as Catalyst²⁹³

entry	R	R^1	yield (%)	ee (%) (conf.)
1	Ph	<i>i</i> -Pr	97	64 (<i>S</i>)
2	<i>p</i> -ClC ₆ H ₄	<i>i</i> -Pr	99	66
3	<i>p</i> -MeOC ₆ H ₄	Et	50	69
4	<i>p</i> -MeOC ₆ H ₄	<i>i</i> -Pr	97	66
5	<i>p</i> -MeOC ₆ H ₄	<i>t</i> -Bu	88	43
6	<i>p</i> -MeOC ₆ H ₄	<i>c</i> -Pent	79	59
7	<i>p</i> -MeOC ₆ H ₄	<i>c</i> -Hex	59	54
8	Me	<i>c</i> -Pent	92	17
9	Me	<i>c</i> -Hex	91	33

Scheme 102



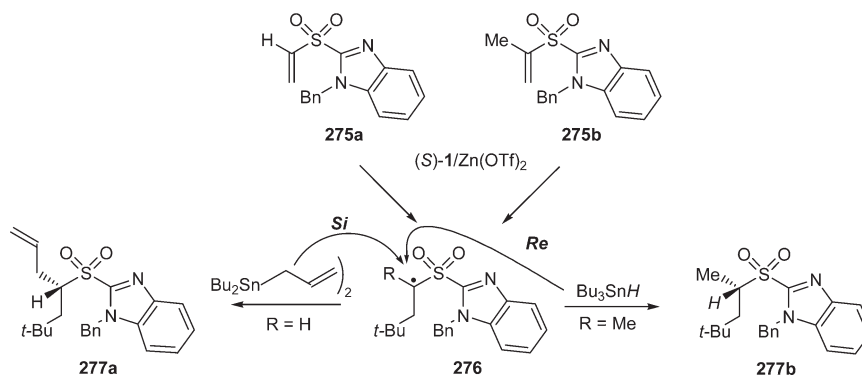
Scheme 103



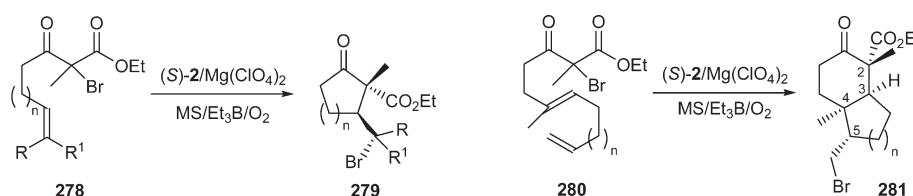
tert-butyl *p*-nitroperbenzoate is the best oxidant, and both (*S*)-1 and (*S*)-2 give the same enantiomer. The best enantiomeric excess is obtained with the (*S*)-2 box (Table 64, entries 1, 10, 13, and 16 vs 4, 12, 14, and 17). In addition, the three Cu(I) salts give comparable results although the most frequently used is CuPF_6 .

The Kharasch oxidation can be performed on acetylenes having a propargylic hydrogen atom (294). The benzoyl esters

Scheme 104



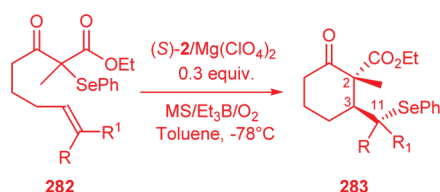
Scheme 105

Table 62. Enantioselective Radical Cyclizations of 278 in Toluene²⁹⁸

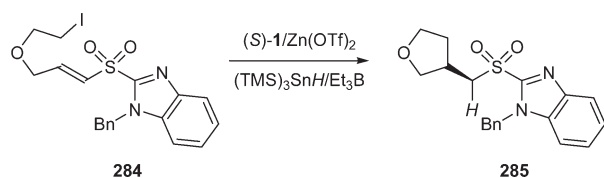
entry	<i>n</i>	R	R ¹	yield (%)	dr	ee (%) (conf.)
1	1	Me	Me	68		92 (2 <i>R</i> ,3 <i>S</i>)
2	2	Me	Me	53		94 (2 <i>R</i> ,3 <i>S</i>)
3	2	Et	H	81	1:1.4	74 (2 <i>R</i> ,3 <i>S</i>), 95 (2 <i>R</i> ,3 <i>S</i>) ^a
4	2	H	Et	58	1:1	74 (2 <i>R</i> ,3 <i>S</i>), 87 (2 <i>R</i> ,3 <i>S</i>) ^a

^a The enantiomeric excess of the diastereomers and the absolute configuration of the ring stereocenters.

Scheme 106

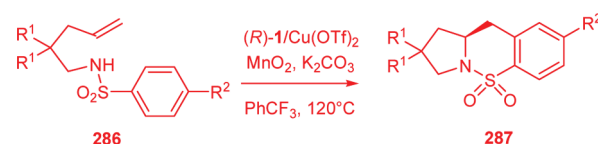


Scheme 107



of the corresponding propargylic alcohols **295** are obtained in high yields and reasonable levels of induction (Scheme 111).³¹²

Scheme 108

Table 63. Enantioselective Intramolecular Carboaminations of *N*-Alkenylsulfonamides **286** Catalyzed by [(*R*)-1/Cu(OTf)₂]³⁰³

entry	R ¹	R ²	287 yield (%)	ee (%) (conf.)
1	H	H	77	82
2	H	Me	68	80
3 ^a	Me	Me	85	92
4	Me	Cl	45	92
5	Me	OMe	75	94
6	–CH ₂ (CH ₂) ₂ CH ₂ –	Me	83	92
7	–CH ₂ (CH ₂) ₃ CH ₂ –	Me	68	92 (<i>S</i>)

^a The same reaction catalyzed by [(*S*)-2/Cu(OTf)₂] gives the opposite enantiomer (hence **1** and **2** with the same configuration give the same sense of induction), but with 50% yield and 24% ee.

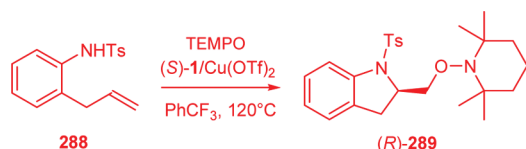
[(*S*)-1/CuPF₆] gives better enantioselectivities than the corresponding catalysts derived from (*S*)-2. Enantioselectivities of about 50% ee are obtained only using 1-trimethylsilyl- and 1-phenyl-2-hexyne.

An interesting variant of the Kharasch reaction was performed using peroxycarbamates **296**, which decompose in the presence of [(*R*)-1/Cu(MeCN)₄PF₆], and cycloalkenes **290** to give the Cu(II)–carbamate complex **297**. Depending on the substitution of the aromatic ring, **297** is either stabilized (and therefore reacts

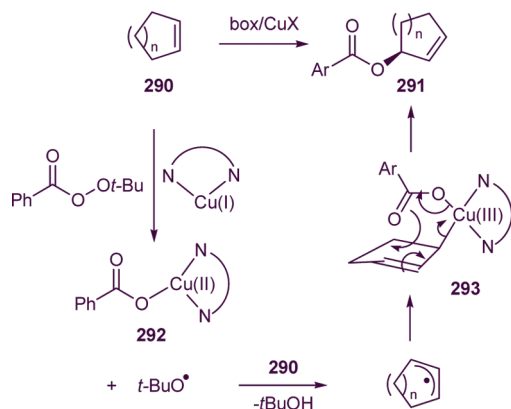
to give the oxidation product **298**) or decarboxylated to give the Cu(II) amino complex **299** that in turn reacts with cycloalkenyl radicals to produce the final amination products **300** (Scheme 112, Table 65).³¹³ The tendency of the peroxy-carbamates to decarboxylate correlates with the stability of the resulting anions and, hence, the pK_a of the corresponding sulfonamide or aniline.

tert-Butyl hydroperoxide, box, and CuOTf are the conditions for the asymmetric peroxidation of the cycloalkenes **290**; the peroxides **301** are obtained in good yields, but the enantioselectivities are in the range 4–20% ee. An interesting result is obtained with *t*-BuO₂H/AcOH. Here the cyclohexene **290** ($n = 2$) gives both the peroxide **301** and the acetate **302** (Scheme 113). While (*S*)-**2** gives both products in good yields

Scheme 109



Scheme 110



but in nearly racemic form, (*S*)-**1** again gives the peroxide as a racemate. On the other hand, (*S*)-**302** is obtained in 47% ee.³¹⁴

The Baeyer–Villiger reaction of 3-phenylcyclobutanone, catalyzed by [(*S*)-**2**/Pd],³¹⁵ is the only other example of a box-catalyzed oxidation reported in the literature. Strictly speaking it should not be considered in this section because it does not involve radicals, but clearly the modest 15% ee does not justify dedicating a specific section 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 boxes as ligands for the preparation of optically active catalysts. The one by Corey et al.¹⁰ described the enantioselective Diels–Alder reaction of 3-acryloyl-2-oxazolidinone **216** ($R = R^1 = H$) with cyclopentadiene, catalyzed by [(*S*)-**1**/Fe(III)X₃] ($X = \text{halogens}$) complexes. The reaction (Scheme 114) was found to be endo-selective [**303**/**304** = 96:4], and (1*R*,2*R*,4*R*)-**303**, whose configuration from now on will be simplified as (2*R*), was obtained in 82% ee. This was the beginning of a long, groundbreaking story: Box complexes were found to be capable of functioning as asymmetric Diels–Alder catalysts with alkenyl imide dienophiles.⁸⁹ In particular, the 3-acryloyl- and 3-crotonyl-oxazolidinones were used as the benchmark for comparing the efficiency of different catalysts in asymmetric Diels–Alder reactions. A summary of this extraordinary story will now be presented. Table 66 summarizes some of the results obtained during these years. The many reactions investigating the cycloaddition between 3-acryloyl-2-oxazolidinone and cyclopentadiene with different catalysts (changing the cations and their counterions with phenyl- and *tert*-butyl-boxes), different solvents, and the effects of

Scheme 111

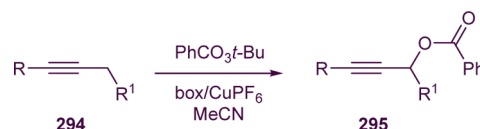


Table 64. Asymmetric Allylic Oxidations of Alkenes

entry	alkene	Ar	box	CuX _n	solvent	yield (%)	ee (%) (conf.)	ref
1	cyclopentene	Ph	(<i>S</i>)- 2	CuOTf	MeCN	44	70 (<i>S</i>)	307
2	cyclopentene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 2	CuBr	MeCN	52	53 (<i>S</i>)	308
3	cyclopentene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 2	CuPF ₆	MeCN	52	79 (<i>S</i>)	311
4	cyclopentene	Ph	(<i>S</i>)- 1	CuPF ₆	MeCN	72	69 (<i>S</i>)	309
5	cyclopentene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 1	CuBr	MeCN	37	54 (<i>S</i>)	308
6	cyclopentene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 1	CuPF ₆	MeCN	49	82 (<i>S</i>)	311
7	cyclohexene	Ph	(<i>S</i>)- 2	CuOTf	MeCN	43	80 (<i>S</i>)	307, 308
8	cyclohexene	Ph	(<i>S</i>)- 2	CuPF ₆	MeCN	74	40 (<i>S</i>)	309
9	cyclohexene	Ph	(<i>S</i>)- 1	CuPF ₆	MeCN	71	59 (<i>S</i>)	309
10	cyclohexene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 2	CuPF ₆	MeCN	61	84 (<i>S</i>)	311
11	cyclohexene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 2	CuBr	MeCN	53	63 (<i>S</i>)	308
12	cyclohexene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 1	CuPF ₆	MeCN	44	96 (<i>S</i>)	308, 311
13	cycloheptene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 2	CuPF ₆	MeCN	3	95 (<i>S</i>)	311
14	cycloheptene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 1	CuPF ₆	MeCN	23	56 (<i>S</i>)	311
15	cyclooctene	Ph	(<i>S</i>)- 2	CuOTf	MeCN	44	13 (<i>S</i>)	308
16	1,5-cyclooctadiene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 2	CuPF ₆	MeCN	13	94 (<i>S</i>)	311
17	1,5-cyclooctadiene	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 1	CuPF ₆	MeCN	46	74 (<i>S</i>)	311
18	allylbenzene	Ph	(<i>S</i>)- 2	CuOTf	PhH	34	36 (<i>R</i>)	307
19	bicyclopentadiene	Ph	(<i>S</i>)- 2	Cu(OTf) ₂	MeCN	14	87 ^a	310

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

several additives that sometimes have a dramatic effect on the enantioselectivities are presented.

From the research studies carried out by Evans et al., it appears that the best combination is box **2** and Cu(II),^{74,93,178,316,317,324} and the best counterions are OTf and SbF₆ (Table 66, entries 3–8). Among the tests with different cations (Table 66, entries 9–16), only cobalt and manganese gave discrete enantiomeric excesses, although still not comparable to copper. The sense of asymmetric induction [(*S*)-**2** gives (*S*)-**303** as the main product] can be rationalized by involving a square-planar rather than a tetrahedral reacting intermediate (Figure 15).³¹⁶ Double stereo-differentiating experiments using dienophiles with a second chiral center on the oxazolidinone ring support this model. The results show that the catalysis with [(*S*)-**2**/Cu(OTf)₂] gives a matched pair if **216** has R¹ = (*R*)-benzyl and a mismatched pair for the (*S*)-enantiomer (Table 66, entries 17 and 18). The solvent effect (Table 66, entries 3–6) suggests that not only protic solvents but also MeCN, which significantly reduces enantioselectivity, are unsuitable.

Although the best Lewis acid for **1** is Zn(SbF₆)₂ (Table 66, entry 34),^{93,178} the most interesting cation is Mg(II).^{318,319,322} With (*R*)-**1**, the enantioselectivity is dependent on both the counterion and additives that behave as auxiliary ligands. When the counterion is perchlorate, the product is (*S*)-**303**, but if 2 equiv of H₂O, 1 equiv of ethylene glycol, or 2 equiv of tetramethylurea (TMU) are added, then (*R*)-**303** is obtained (Table 66, entries 19, 20, 24, and 25). When the counterion is OTf, the reaction product is (*R*)-**303** and the enantioselectivity does not change if H₂O or TMU are added (Table 66, entries 27–29). To summarize this unusual behavior: the same chiral box with the same cation and the same counterion can give opposite enantiomers if an achiral component is added. This behavior can be rationalized by assuming that H₂O, TMU, or (CH₂OH)₂ behave as ligands and 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 in coordination is supported by ¹H NMR spectroscopy data and the position of the auxiliary ligands by results from a diethylene glycol study. With the more coordinating OTf anions, the reactive intermediate always has an octahedral coordination (with two OTf's in the axial positions), and this complex does not change on the addition of either H₂O or TMU. Figure 16 represents the three reacting intermediates; the tetrahedral one makes the Re face of the dienophile available to the attack by the cyclopentadiene; those with the octahedral structures allow attack at the Si face.

The three reacting intermediates represented in Figure 16 involve a ratio (*R*)-**1**/**216** of 1:1; hence, using catalysts with different enantiomeric purities, a linear relationship between the

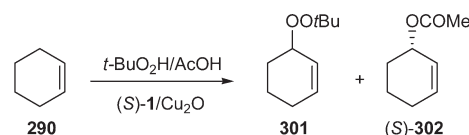
enantiomeric excess of **303** and that of the catalysts is expected. This was tested and actually observed.^{319,322} When the same experiment was carried out in the [(*R*)-**1**/Zn(ClO₄)₂/MS]-catalyzed reaction (Table 66, entry 33), a strong chiral amplification was observed.¹¹⁴ Figure 17 illustrates the relationships between the enantiomeric excess of (*R*)-**1** and the enantiomeric excess of (*S*)-**303** for the reactions in Table 66 entries 19 (linear) and 33 (curve). The rationale for the observed positive nonlinear effect is derived from the thermodynamic stability of the racemic complex [(*R*)-**1**/(*S*)-**1**/Zn(II)] **28**. This complex was isolated, and its X-ray structure was determined (Figure 12). It proved to be much more stable and insoluble than the corresponding chiral complex [2(*R*)-**1**/Zn(II)]. This behavior, known as the

Table 65. Allylic Oxidations and Aminations with Peroxy-carbamates **296 and Cycloalkenes **290**, Catalyzed by [(*R*)-**1**/Cu(MeCN)₄PF₆]³¹³**

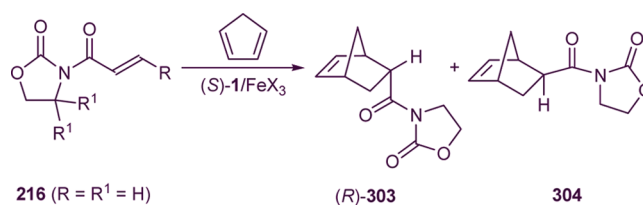
entry	Ar	solvent	<i>n</i>	298 yield (%)	300 yield (%)	ee (%) (conf.)
1	Ph	AcOEt	1	34		76
2	<i>p</i> -BrC ₆ H ₄	AcOEt	1	26		70
3	<i>m</i> -NO ₂ C ₆ H ₄	AcOEt	1	40		81
4	<i>p</i> -NO ₂ C ₆ H ₄	AcOEt	1	48		85
5	Ph	AcOEt	2	37		61 (<i>R</i>)
6 ^a	<i>p</i> -BrC ₆ H ₄	AcOEt	2	29		67
7	<i>m</i> -NO ₂ C ₆ H ₄	AcOEt	2	57		65
8	<i>p</i> -NO ₂ C ₆ H ₄	AcOEt	2	65		72
9	<i>p</i> -MeC ₆ H ₄ SO ₂	CH ₂ Cl ₂	1		30	46 (<i>S</i>)
10	<i>p</i> -MeC ₆ H ₄ SO ₂	CH ₂ Cl ₂	2		44	51 (<i>S</i>)
11 ^a	<i>p</i> -MeC ₆ H ₄ SO ₂	MeCN	2		20	31 (<i>R</i>)
12 ^a	<i>p</i> -MeC ₆ H ₄ SO ₂	Me ₂ CO	2		14	70 (<i>R</i>)
13 ^a	<i>p</i> -MeC ₆ H ₄ SO ₂	AcOEt	2		26	51 (<i>R</i>)

^a Reaction performed with (*S*)-**1**.

Scheme 113



Scheme 114



Scheme 112

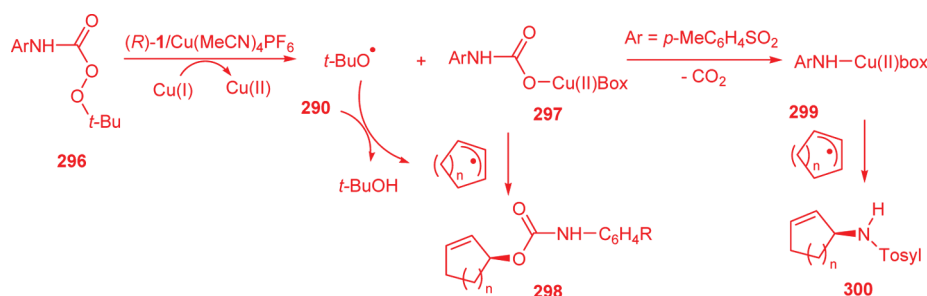
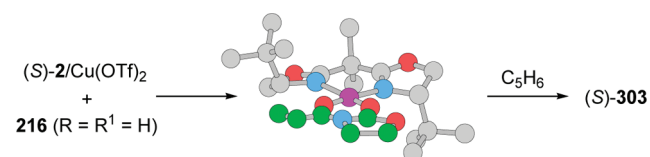


Table 66. Enantioselective Diels–Alder Reactions between Cyclopentadiene and 3-Acryloyl-2-oxazolidinone **216** ($R = H$) Catalyzed by $[\text{Box}/\text{MX}_n]$

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)	10
2	H,H	(S)-1	$\text{Cu}(\text{OTf})_2$		CH_2Cl_2	92	95:5	30 (S)	93, 316
3	H,H	(S)-2	$\text{Cu}(\text{OTf})_2$		CH_2Cl_2	86	98:2	>98 (S)	93, 316, 320, 324
4	H,H	(S)-2	$\text{Cu}(\text{OTf})_2$		THF	>98	97:3	98 (S)	93
5	H,H	(S)-2	$\text{Cu}(\text{OTf})_2$		MeNO_2	>98	92:8	84 (S)	93
6	H,H	(S)-2	$\text{Cu}(\text{OTf})_2$		MeCN	87	92:8	58 (S)	93
7	H,H	(S)-2	$\text{Cu}(\text{SbF}_6)_2$		CH_2Cl_2	>95	96:4	>98 (S)	93, 178
8	H,H	(S)-2	$\text{Cu}(\text{ClO}_4)_2^a$		CH_2Cl_2	85	97:3	6 (S)	323
9	H,H	(S)-2	$\text{Co}(\text{OTf})_2$		CH_2Cl_2	85	90:10	50 (S)	93
10	H,H	(S)-2	$\text{Mn}(\text{OTf})_2$		CH_2Cl_2	80	85:15	50 (S)	93
11	H,H	(S)-2	$\text{Ni}(\text{OTf})_2$		CH_2Cl_2	75	90:10	40 (S)	93
12	H,H	(S)-2	$\text{Zn}(\text{OTf})_2$		CH_2Cl_2	85	95:5	38 (S)	93
13	H,H	(S)-2	LiOTf		CH_2Cl_2	89	85:15	14 (S)	93
14	H,H	(S)-2	$\text{Cd}(\text{OTf})_2$		CH_2Cl_2	80	90:10	10 (S)	93
15	H,H	(S)-2	$\text{Sm}(\text{OTf})_3$		CH_2Cl_2	78	80:20	racem.	93
16	H,H	(S)-2	$\text{Lu}(\text{OTf})_3$		CH_2Cl_2	75	75:25	racem.	93
17	(R)-Bn	(S)-2	$\text{Cu}(\text{OTf})_2$		CH_2Cl_2	100	99:1	>98 (S) ^b	93, 316
18	(S)-Bn	(S)-2	$\text{Cu}(\text{OTf})_2$		CH_2Cl_2	20	>95:5	36 (S) ^b	93, 316
19	H,H	(R)-1	$\text{Mg}(\text{ClO}_4)_2$		CH_2Cl_2	>98	93:7	73 (S)	318, 319, 322
20	H,H	(R)-1	$\text{Mg}(\text{ClO}_4)_2$	$2\text{H}_2\text{O}$	CH_2Cl_2	>98	95:5	73 (R)	318, 319, 322
21	H,H	(R)-1	$\text{Mg}(\text{ClO}_4)_2$	2MeOH	CH_2Cl_2	>98	91:9	42 (R)	319
22	H,H	(R)-1	$\text{Mg}(\text{ClO}_4)_2$	2EtOH	CH_2Cl_2	>98	91:9	16 (R)	319
23	H,H	(R)-1	$\text{Mg}(\text{ClO}_4)_2$	$2t\text{-BuOH}$	CH_2Cl_2	>98	92:8	33 (S)	319
24	H,H	(R)-1	$\text{Mg}(\text{ClO}_4)_2$	$(\text{CH}_2\text{OH})_2$	CH_2Cl_2	>98	91:9	58 (R)	319
25	H,H	(R)-1	$\text{Mg}(\text{ClO}_4)_2$	TMU ^c	CH_2Cl_2	>98	96:4	51 (R)	322
26	H,H	(R)-1	$\text{Mg}(\text{ClO}_4)_2$	Py or Et_3N	CH_2Cl_2	0	0	0	322
27	H,H	(R)-1	$\text{Mg}(\text{OTf})_2$		CH_2Cl_2	>98	92:8	88 (R)	320, 322
28	H,H	(R)-1	$\text{Mg}(\text{OTf})_2$	$2\text{H}_2\text{O}$	CH_2Cl_2	>98	92:8	86 (R)	322
29	H,H	(R)-1	$\text{Mg}(\text{OTf})_2$	TMU ^c	CH_2Cl_2	>98	93:7	88 (R)	322
30	H,H	(S)-1	MgI_2/I_2		CH_2Cl_2	>98	94:6	76 (R)	93
31	H,H	(R)-1	$\text{Zn}(\text{OTf})_2$		CH_2Cl_2	>98	90:10	32 (R)	320
32	H,H	(R)-1	$\text{Zn}(\text{ClO}_4)_2^a$		CH_2Cl_2	>98	92:8	20 (R)	114
33	H,H	(R)-1	$\text{Zn}(\text{ClO}_4)_2$	MS^d	CH_2Cl_2	>98	92:8	73 (S)	114
34	H,H	(S)-1	$\text{Zn}(\text{SbF}_6)_2$		CH_2Cl_2	>90	98:2	92 (R)	93, 178
35	H,H	(R)-1	$\text{Ni}(\text{ClO}_4)_2^a$		CH_2Cl_2	97	88:12	52 (R)	221
36	H,H	(S)-1	$\text{Cu}(\text{ClO}_4)_2^a$		CH_2Cl_2	84	97:3	41 (S)	323

^a Hexahydrate salt. ^b Major endo diastereoisomer. ^c TMU is tetramethylurea. ^d MS are 4 Å MS.

**Figure 15.** Square-planar intermediate complex of the Diels–Alder reaction catalyzed by $[(S)\text{-}2/\text{Cu}(\text{OTf})_2]$ between **216** ($R = R^1 = H$) and cyclopentadiene.

“reservoir effect”, is one of the possible reasons for the observed chiral amplification.

The enantioselectivity of the reaction between the acryloyl-oxazolidinone **216** ($R = R^1 = H$) and cyclopentadiene, a benchmark for enantioselective catalysts, is influenced by a number of factors: the ligand, the Lewis acid, or the addition of additives

capable of changing the coordination number at the cation in the reacting complex. Recently, a new class of fluxional additives (**A–C**) was tested. Their ability to modify the coordination number through the effect of groups suitably placed to be involved in coordination was examined. In addition, the capacity of chiral Lewis acids to influence the configuration of the fluxional centers and transform the achiral additive into a chiral auxiliary that could amplify the enantioselectivity was also tested.³²⁵ Table 67 shows the results for the same reaction performed both with $[(S)\text{-}1/\text{M}(\text{ClO}_4)_n]$ with or without **A–C**. The results clearly demonstrate that: (a) Even if it has a β -dicarbonyl framework, **A** does not increase the enantioselectivity. (b) **B** and **C** significantly increase both the diastereo- and enantioselectivity for $\text{Mg}(\text{II})$, $\text{Ni}(\text{II})$, $\text{Zn}(\text{II})$, $\text{Co}(\text{II})$, and $\text{Fe}(\text{II})$ (sometimes with quite significant improvements). (c) What is excellent for $\text{Fe}(\text{II})$ is useless for $\text{Fe}(\text{III})$. (d) $\text{Cu}(\text{ClO}_4)_2$ is

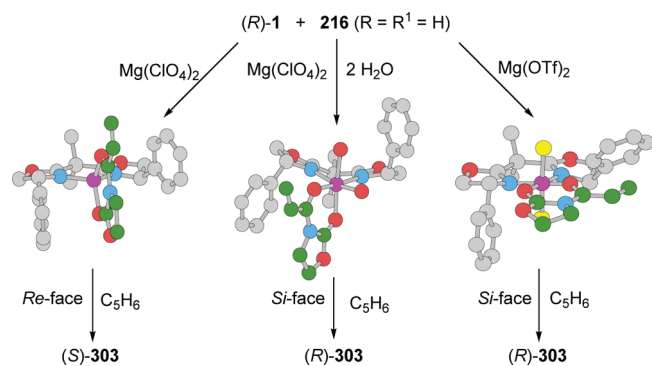


Figure 16. Tetrahedral or octahedral intermediate complexes of the Diels–Alder reactions catalyzed by [(*R*)-1]/Mg(ClO₄)₂ or [(*R*)-1]/Mg(OTf)₂ between **216** (*R* = *R*¹ = H) and cyclopentadiene, with or without H₂O.

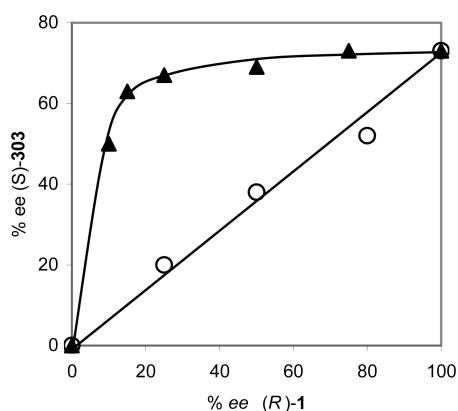


Figure 17. Relationships between the enantiomeric excess of (*R*)-1 and the enantiomeric excess of (*S*)-303 for entries 19 (○) and 33 (▲) in Table 66.

unsuitable for the intended purpose either with or without additives.

1-Substituted 2-alkenyl-4,4-dimethylpyrazolidin-3-ones **220** were developed by Sibi et al. as achiral templates that may prove to be capable of relaying and amplifying the stereochemistry induced by box-based catalysts (Scheme 115). When they are coordinated to the reacting complex, they are converted from being achiral templates into a chiral nonracemic template. The data in Table 68 show that this results in amplified enantioselectivities. If the fluxional template includes a double bond (as does **220**), it can undergo a Diels–Alder reaction. The results for cyclopentadiene and [(*S*)-2/Cu(OTf)₂] as the catalyst are reported in Table 68.^{20,326} The absolute configuration of the (*endo*)-**305** adduct as reported in entry 3 (Table 68) is (1*S*,2*S*,3*R*,4*R*). This is identical to that obtained from **216** (*R* = Me, *R*¹ = H) (Table 69, entry 7),⁹³ using the same catalyst. These results suggest that the reacting intermediate is not too far structurally from that reported in Figure 15. More extensive, even better results for different boxes will be discussed in the following sections.

Several examples of enantioselective, [box/MX_n]-catalyzed Diels–Alder reactions between cyclopentadiene and β-substituted 3-acryloyl-2-oxazolidinone **216** (*R*¹ = H) have been reported. Some significant results are listed in Table 69. The reaction of the crotonoyl derivative (*R* = Me) is best catalyzed by

Table 67. Enantioselective Diels–Alder Reactions between Cyclopentadiene and 3-Acryloyl-2-oxazolidinone **216** (*R* = *R*¹ = H) in the Presence of Different Fluxional Additives³²⁵

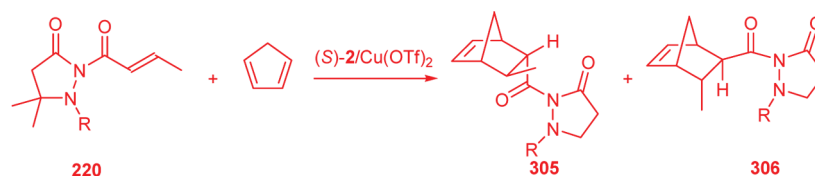
entry ^a	M(ClO ₄) _n	additives	<i>R</i>	<i>R</i> ¹	<i>R</i> ²	endo/exo	endo ee (%) (conf.)
1	Mg(ClO ₄) ₂					83:17	56 (<i>R</i>)
2	Mg(ClO ₄) ₂	A				83:17	56 (<i>R</i>)
3	Mg(ClO ₄) ₂	B	Ph	Me	Ph	88:12	84 (<i>R</i>)
4	Mg(ClO ₄) ₂	B	2-Naph	Ph	Me	90:10	89 (<i>R</i>)
5	Mg(ClO ₄) ₂	C	Ph			92:8	88 (<i>R</i>)
6	Ni(ClO ₄) ₂					83:17	66 (<i>R</i>)
7	Ni(ClO ₄) ₂	A				86:14	66 (<i>R</i>)
8	Ni(ClO ₄) ₂	B	Ph	Me	Ph	93:7	92 (<i>R</i>)
9	Zn(ClO ₄) ₂					88:12	3
10	Zn(ClO ₄) ₂	B	Ph	Me	Ph	91:9	71 (<i>R</i>)
11	Co(ClO ₄) ₂					83:17	69 (<i>R</i>)
12	Co(ClO ₄) ₂	B	Ph	Me	Ph	91:9	95 (<i>R</i>)
13	Co(ClO ₄) ₂	C	Ph			92:8	98 (<i>R</i>)
14	Co(ClO ₄) ₂	C	2-Naph			95:5	97 (<i>R</i>)
15	Fe(ClO ₄) ₂					86:14	60 (<i>R</i>)
16	Fe(ClO ₄) ₂	B	Ph	Me	Ph	86:14	85 (<i>R</i>)
17	Fe(ClO ₄) ₂	C	Ph			92:8	91 (<i>R</i>)
18	Fe(ClO ₄) ₃					88:12	1
19	Fe(ClO ₄) ₃	B	Ph	Me	Ph	92:8	1
20	Cu(ClO ₄) ₂					75:25	12 (<i>S</i>)
21	Cu(ClO ₄) ₂	B	Ph	Me	Ph	90:10	16 (<i>S</i>)

^a Isolated yields were >85%.

[(*S*)-2/Cu(OTf)₂] or [(*S*)-2/Cu(SbF₆)₂] (Table 69, entries 7 and 9).^{93,316} In addition, it tolerates ionic liquids (Table 69, entry 8).³²⁷ With (*R*)-1 and Mg(II) as the catalyst, the enantioselectivity is again found to be a function of the counterion, eventually coupled with TMU as the auxiliary ligand (Table 69, entries 1–4).³²² The enantioselectivity of the reaction with 3-(acyloxy)acrylates (Table 69, entries 12 and 13) is found to invert by changing the substituent of the box ligands (**1** or **2**), taking constant their (*S*)-configuration.³²⁸

Several examples have been reported of enantioselective Diels–Alder reactions between various dienes and 3-acryloyl-2-oxazolidinone **216** (*R* = *R*¹ = H). Table 70 shows the most significant results. The majority of them report (*S*)-**2** and CuX₂ (*X* = OTf or SbF₆) as the catalysts. These have been isolated as either the anhydrous or aquo complexes, and their X-ray structures were determined (Table 2, entries 7 and 13). Cu-(SbF₆)₂ gives the most efficient catalysts with 1,3-pentadiene [either anhydrous or hydrated (the bis-aquo complex formed from OTf proved to be inactive)] (Table 70, entries 8 and 9 vs 5 and 6). The addition of MS regenerates the aquo-triflate catalyst, while suppressing the activity of the aquo-hexafluoroantimonate one (Table 70, entries 6, 7, 10, and 11).^{93,317,332} Although the Diels–Alder reaction with furan equilibrates rapidly at –20 °C, the enantiomerically pure *endo* product can be successfully isolated at –78 °C (Table 70, entry 21).^{330,332} Recently, the reactions between the silylated dienes **J** and **K** (Table 70, entries 22–24) and acryloyl- or crotonoyl-oxazolidinones **216** (*R* = H or Me, *R*¹ = H) were carried out using [(*S*)-2/Cu(OTf)₂]. The reactions were strongly *exo*-selective, and the adducts proved to

Scheme 115



be useful starting products for the synthesis of enantioenriched fluorinated carbocycles.³³³

Other experiments using β -dicarbonyl dienophiles were mainly directed at comparing the efficiency of some supported boxes or various new ligands suitable for carrying out Diels–Alder reactions in ionic liquids. The relevant references are reported here mainly for sake of completeness.^{334–336}

Efficient bidentate dienophiles can have one carbonyl group and a lone pair donor as ligands. An example is the arylsulfonyl enones 307. They behave as bidentate dienophiles because of the presence of the carbonyl and S=O groups. Hence, they react with cyclopentadiene, and after careful screening, [(S)-1/Cu(OTf)₂] was found to be the catalyst of choice (Table 71, entries 1–4). Scheme 116 shows the results of the reaction that gives (*endo*)-(1*R*,2*S*,3*S*,4*S*)-308 and (*exo*)-309. Some general conclusions can be reached: Varying the arylsulfonyl group had little effect (Table 71, entries 4–6); high enantioselectivities and good diastereoselectivities were obtained using β -aryl-substituted compounds regardless of their electronic nature (Table 71, entries 7–9); the nature of R possibly influences the yield and the diastereoselectivity but not the enantioselectivity (Table 71, entries 10–12); and finally, when R¹ = Me, then the reaction gives a 1:1 diastereomeric mixture (Table 71, entries 13 and 14).³³⁷

The comparison between 2-alkenyl pyridines 310a (Y = N) and their N-oxides 310b (Y = N–O) as bidentate dienophiles is interesting because the former can bind to the catalyst through the carbonyl and the pyridine nitrogen, and the latter can bind with the carbonyl and the N–O oxygen. Enantioselective Diels–Alder reactions with cyclopentadiene are catalyzed by [(S)-box/Cu(OTf)₂] complexes to give *endo*-311a,b and *exo*-312a,b (Scheme 117). The results are reported in Table 72.³³⁸

The above results are clear evidence of the inefficiency of the pyridine nitrogen as a ligand (Table 72, entries 1 and 2 vs 3 and 4), the reaction tolerance for using different R groups, and the inversion of the enantioselectivity promoted by (S)-2 vs (S)-1 (Table 72, entry 5 vs 4). Excellent enantioselectivities were obtained using N-oxides with different dienes.³³⁸ Some questions that still remain are as follows: what is the type of coordination involving the N-oxide and what is the absolute configuration of 311? These will be discussed in detail in a later section.

Several dienophiles were tested in these enantioselective Diels–Alder reactions, the majority with cyclopentadiene as the diene. The most significant results are given in Table 73.

It is not unexpected that the majority of dienophiles have either a β -dicarbonyl system (313, 316, 318, and 319) or a suitable group β to the carbonyl. Because of its lone pairs, this group makes the dienophile suitable as a bicoordinating reagent. In some cases the new group ameliorates the binding properties of the carbonyl: e.g., 315 (Table 73, entries 9–11) is 20–30 times more reactive than the corresponding oxazolidinone.⁹³ The α -thioacrylates 314 display higher enantioselectivities with

Table 68. Enantioselective Diels–Alder Reactions between Cyclopentadiene and 1-Substituted 2-Alkenyl-4,4-Dimethylpyrazolidin-3-ones 220 Catalyzed by [(S)-2/Cu(OTf)₂]³²⁶

entry ^a	R	endo/exo	endo ee (%) (conf.)
1	Et	93:7	77
2	Bn	92:8	97
3	CH ₂ (1-Naph)	90:10	99 (1 <i>S</i> ,2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i>)
4	CH ₂ (2-Naph)	93:7	99

^a Isolated yields averaged around 85–90%.

phenylthio groups compared to the corresponding methylthio-derivatives or those with small or moderately sized ester substituents (Me \approx Et \approx *i*-Pr \gg *t*-Bu) (Table 73, entries 3 and 8 vs 4–7). The effect of the phenyl group is attributed to the coordination, which involves only one of the two enantiotopic lone pairs of sulfur. The result is that it becomes asymmetric and the subsequent orientation forces the phenyl below the plane of the reacting complex 320. This in turn induces shielding of the Si face of the dienophile and leads to the *endo* product (S)-321 (Scheme 118).^{340,341} This is another example of the strategy developed by Sibi et al. and termed “chiral relay”.²⁵⁵ In essence it involves the chiral catalysts converting an achiral template such as 314 into a chiral nonracemic template.

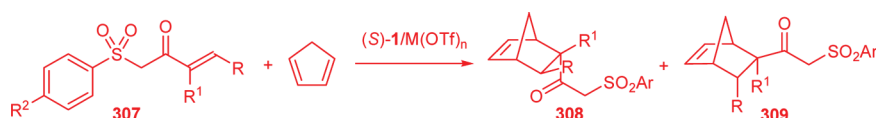
A similar effect that results in controlled enantioselectivity is that induced by R in 316. Since, under chelation control with the [(R)-1/Mg(II)] complex, the acryloyl group cannot adopt a coplanar position with the aromatic ring (dihedral angle Φ CN–CO \neq 0°), the result is that the template becomes chiral. If the counterion (ClO₄) favors a tetrahedral reacting intermediate, then (R)-1 box intrinsically shields the Si face. However, the different twisting induced when R = H or = Me [$\Phi_{(AM1)}$ = 14° and 43°, respectively] favors the Si (H) or the Re face (Me), which results in the opposite enantiomers (Table 73, entries 12 and 14). If the counterion (Br) favors an octahedral complex, then the enantioselectivity correlates with the increase in 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 efficient chelation of the metal ion (Table 73, entries 13 and 15–18).³⁴² An excellent efficiency is obtained with a variety of α' -hydroxy enones such as 188 because, in addition to the Diels–Alder reactions with cyclopentadiene (Table 73, entries 20–22), there are several other dienes that give products with enantioselectivity in the range 90–99% ee. The compounds 318 and 319 are, at the moment, considered promising dienophiles, 319 because it is a unique example of an acetylenic dienophile and 318 because the *exo* adducts (*exo* selectivity with 2,4-disubstituted butadienes is >99:1 and enantioselectivities in the range 97–98% ee, even larger than the

Table 69. Enantioselective Diels–Alder Reactions between Cyclopentadiene and β -Substituted 3-Acryloyl-2-oxazolidinone **216** ($R^1 = H$) 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 (4S,5R)	322
2	Me	(R)-1	Mg(ClO ₄) ₂	TMU ^b	93	84:16	87 (4R,5S)	322
3	Me	(R)-1	Mg(OTf) ₂		94	81:19	84 (4R,5S)	322
4	Me	(R)-1	Mg(OTf) ₂	TMU ^b	88	81:19	84 (4R,5S)	322
5	Me	(S)-1	Zn(SbF ₆) ₂		>98	86:14	64 (4R,5S)	93
6	Me	(S)-1	FeI ₃ /I ₂		>98	76:24	32 (4R,5S)	93
7	Me	(S)-2	Cu(OTf) ₂		85	96:4	97 (4S,5R)	93, 316
8 ^a	Me	(S)-2	Cu(OTf) ₂		65	93:7	92 (4S,5R)	327
9	Me	(S)-2	Cu(SbF ₆) ₂		99	85:15	99 (4S,5R)	93
10	Ph	(S)-2	Cu(OTf) ₂		85	90:10	90 (4R,5R)	93, 316, 317
11	Ph	(S)-2	Cu(SbF ₆) ₂		96	81:19	96 (4R,5R)	93, 317
12	<i>p</i> -CF ₃ C ₆ H ₄ CO ₂	(S)-1	Cu(OTf) ₂		99	94:6	89 (4S,5S)	328
13	<i>p</i> -CF ₃ C ₆ H ₄ CO ₂	(S)-2	Cu(OTf) ₂		99	90:10	54 (4R,5R)	328
14	CO ₂ Et	(S)-2	Cu(OTf) ₂		92	94:6	95 (4R,5R)	93, 316
15	CO ₂ Et	(S)-2	Cu(SbF ₆) ₂		88	82:18	87 (4R,5R)	93
16	Cl	(S)-2	Cu(OTf) ₂		96	93:7	53 (3S,4R)	93, 317
17	Cl	(S)-2	Cu(SbF ₆) ₂		96	86:14	95 (3S,4R)	93, 317

^a Reaction run in 1,3-dibutylimidazolium tetrafluoroborate (DiBuIm). ^b TMU is tetramethylurea.

Scheme 116



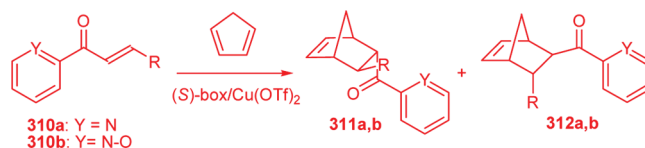
Diels–Alder reaction with cyclopentadiene) have potential to be useful synthons for marine natural toxins.³⁴⁵

One such synthon for the enantioselective synthesis of the spirocyclic imine of the marine toxin (–)-gymnodimine is the adduct **324**. It is the product of the Diels–Alder reaction between the dienophile **322** and the diene **323** (Scheme 119). It is catalyzed by [(S)-2/Cu(SbF₆)₂], and the synthon product is obtained in 85% yield with dr > 19:1 and 95% ee.³⁴⁶

The intramolecular enantioselective Diels–Alder reaction depicted in Scheme 120 is based on the structure **325**. It has a diene tethered to the β -position of acryloyl-oxazolidinone.^{332,347,348} If the catalyst is [(S)-2/Cu(SbF₆)₂], then the square-planar bicoordination of the carbonyl groups to copper allows the occurrence of the concept previously illustrated in Figure 13 to this intramolecular variant. The resulting absolute configuration (4′R,5′R,6′S)-**326a** of the bicyclo[4.3.0]non-1′-ene-4′-carbonyl-2-oxazolidinone is consistent with the proposed reacting intermediate. This illustrates the excellent potential of the above reaction: diastereo- and enantioselectivities up to >99:1 and 96%, respectively, and with as many as four contiguous stereogenic centers created in a single step. Overall, **326c** was transformed in only a few steps and an overall yield of 62% into the marine toxin (–)-isopulopone.^{332,347}

To conclude this section, it should be mentioned that computational studies related to the Diels–Alder reactions of acryloyl-oxazolidinone and cyclopentadiene have also been carried out. These mainly focused on the reaction catalyzed by box and copper and appear with increasing frequency in the literature.^{349–352} To emphasize possible future developments in the field, research tends either to identify the smallest fragment of the reactive intermediate that carries the molecular chirality³⁴⁹ information or to attempt to understand the geometric and energetic consequences of the box substituents (in particular

Scheme 117



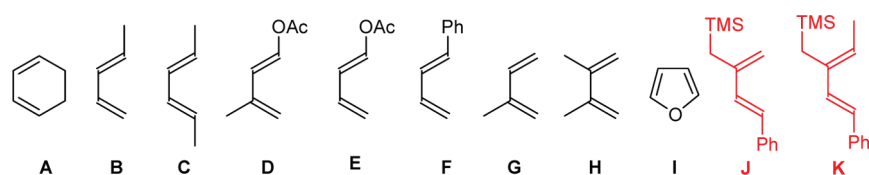
tert-butyl group) in creating a steric barrier. The latter is suggestively christened the “axial gateway”, in that it maintains the electrophilicity of the catalyst by shielding the copper center from nucleophilic attack.³⁵¹

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 six-membered rings. Its variant using heteroatoms either on the diene or on the dienophile, the hetero Diels–Alder reaction, is the parallel pathway to synthesizing chiral heterocycles.

Where cycloadditions of dienes to carbonyls and those of α,β -unsaturated carbonyl compounds to olefins are concerned, great progress has been achieved in developing box-based catalysts that allow enantioselective reactions for both unactivated and activated carbonyl compounds. This field has been the topic of two specific reviews.^{6b,353}

The first C=O dienophile to be tested was the glyoxylate ester **106b**. It was chosen because of its high reactivity in catalyzed hetero Diels–Alder reactions with dienes such as **327**. It proved reactive even with unactivated ones.³⁵⁴ The expected product of the reaction is dihydropyran **328**, but when the diene contains an

Table 70. Enantioselective Diels–Alder Reactions in CH₂Cl₂ between Various Dienes and 3-Acryloyl- or Crotonoyl-2-oxazolidinones 216 (R = H or Me, R¹ = H) Catalyzed by [(*S*)-2/MX_n]

entry	diene	R	MX _n	add.	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	A	H	Cu(OTf) ₂		90	98:2	82 (2 <i>S</i>)	317, 329, 332
2	A	H	Cu(SbF ₆) ₂		90	95:5	93 (2 <i>S</i>)	317, 329, 332
3 ^a	A	H	Cu(OTf) ₂		90		92 (2 <i>S</i>)	329
4 ^a	A	H	Cu(SbF ₆) ₂		87		96 (2 <i>S</i>)	329
5	B	H	Cu(OTf) ₂		72	75:25	86	93, 317, 332
6	B	H	Cu(OTf) ₂ · 2H ₂ O		<10	n.d.	n.d.	93
7	B	H	Cu(OTf) ₂ · 2H ₂ O	MS	95	74:26	85	93
8	B	H	Cu(SbF ₆) ₂		89	83:17	94	93, 317, 332
9	B	H	Cu(SbF ₆) ₂ · 2H ₂ O		100	83:17	94	93
10	B	H	Cu(SbF ₆) ₂ · 2H ₂ O	MS	10	n.d.	n.d.	93
11	C	H	Cu(OTf) ₂		66	78:22 ^b	84	317, 332
12	C	H	Cu(SbF ₆) ₂		59	77:23 ^b	93	317, 332
13	D	H	Cu(SbF ₆) ₂		57	27:73	98 (3 <i>S</i> ,4 <i>S</i>) ^c	331
14	E	H	Cu(SbF ₆) ₂		75	85:15 ^b	96 (3 <i>R</i> ,4 <i>S</i>)	332
15	F	H	Cu(OTf) ₂		89	67:33 ^b	84 (3 <i>R</i> ,4 <i>S</i>)	332
16	F	H	Cu(SbF ₆) ₂		95	85:15 ^b	97 (3 <i>R</i> ,4 <i>S</i>)	332
17	G	H	Cu(OTf) ₂		95	97:3 ^d	60 (4 <i>S</i>)	332
18	G	H	Cu(SbF ₆) ₂		81	96:4 ^d	59 (4 <i>S</i>)	332
19	H	H	Cu(OTf) ₂		95		60	332
20	H	H	Cu(SbF ₆) ₂		78		65	332
21	I	H	Cu(SbF ₆) ₂		97	80:20	97 (3 <i>S</i>)	330, 332
22	J	Me	Cu(OTf) ₂	MS	79	10:90	90 ^c	333
23	K	H	Cu(OTf) ₂	MS	78	25:75	89 ^c	333
24	K	Me	Cu(OTf) ₂	MS	45	<5:95	94 ^c	333

^a Reaction performed in MeNO₂. ^b Cis/trans ratio. ^c Enantiomeric excess of exo product. ^d (1,4):(1,3) regioisomer ratio.

Table 71. Enantioselective Diels–Alder Reactions between Arylsulfonyl Enones 307 and Cyclopentadiene Catalyzed by [(*S*)-1/*M*(OTf)_n]³³⁷

entry	R	R ¹	R ²	MX _n	yield (%)	endo/exo	endo ee (%) (conf.)	exo ee (%)
1	Ph	H	Me	Mg(OTf) ₂	64	80:20	73	nd
2	Ph	H	Me	Zn(OTf) ₂	quant.	87:13	93	nd
3	Ph	H	Me	Cu(SbF ₆) ₂	quant.	86:14	56	nd
4	Ph	H	Me	Cu(OTf) ₂	97	93:7	95	nd
5	Ph	H	OMe	Cu(OTf) ₂	92	93:76	95	nd
6	Ph	H	Cl	Cu(OTf) ₂	89	93:7	97	98
7	4-MeOC ₆ H ₄	H	Me	Cu(OTf) ₂	95	96:4	95 (2 <i>S</i> ,3 <i>S</i>)	nd
8	4-BrC ₆ H ₄	H	Me	Cu(OTf) ₂	93	92:8	95	94
9	4-NO ₂ C ₆ H ₄	H	Me	Cu(OTf) ₂	90	90:10	95	95
10	H	H	Me	Cu(OTf) ₂	50	92:8	96	nd
11	Me	H	Me	Cu(OTf) ₂	93	92:8	92	nd
12	<i>t</i> -Bu	H	Me	Cu(OTf) ₂	99	43:57	90	83
13	H	Me	Me	Cu(OTf) ₂	65	49:51	94	90
14	Me	Me	Me	Cu(OTf) ₂	93	50:50	96	88

allylic C–H bond, both hetero Diels–Alder and hetero ene reactions can take place, the latter with formation of **329** (Scheme 121).

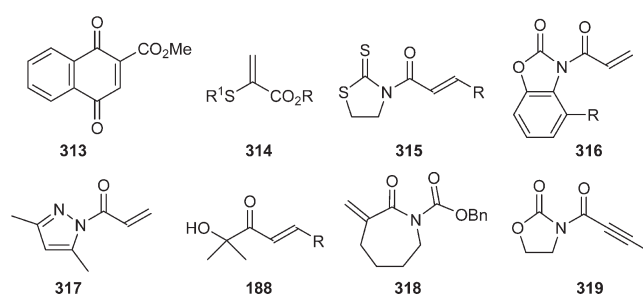
The first paper reporting box-catalyzed reactions of dienes with glyoxylate esters illustrates the particular behavior that forces the discussion in this section of the formation of some products that strictly speaking should be discussed later (Table 74).^{355,356} After carrying out a series of experiments using different solvents (CH₂Cl₂ proved the best) and Lewis acids

(Table 74, entries 1–3), [(*S*)-2/Cu(OTf)₂] was found to be the best catalyst (Table 74, entries 4–6 vs 7–9) and the methyl ester was the best glyoxylate. Clearly, the absence of any methyl group meant that the hetero Diels–Alder was the sole reaction pathway (Table 74, entry 11).

Under catalysis with [box/Cu(OTf)₂] complexes, methyl and ethyl glyoxylate **106b** reacted with Danishefsky's diene **330** (R² = H) to give a mixture of the hetero Diels–Alder adduct **331** and the Mukaiyama–aldol product **332**. The latter is converted to

Table 72. Enantioselective Diels–Alder Reactions between 2-Alkenoyl Pyridines 310a (Y=N) and Their N-Oxides 310b (Y=N–O) and Cyclopentadiene³³⁸

entry	Y	R	(S)-box/M(OTf) ₂	yield (%)	endo/exo	endo ee (%)	exo ee (%)
1	N	Ph	(S)-1/Zn(OTf) ₂	quant	82:18	23	41
2	N	Ph	(S)-1/Cu(OTf) ₂	quant.	86:14	19	11
3	N–O	Ph	(S)-1/Zn(OTf) ₂	quant.	96:4	91	35
4	N–O	Ph	(S)-1/Cu(OTf) ₂	98	98:2	96	81
5	N–O	Ph	(S)-2/Cu(OTf) ₂	quant.	97:3	–96 ^a	–94 ^a
6	N–O	4-MeOC ₆ H ₄	(S)-1/Cu(OTf) ₂	95	97:3	95	
7	N–O	4-NO ₂ C ₆ H ₄	(S)-1/Cu(OTf) ₂	93	95:5	96	
8	N–O	<i>t</i> -Bu	(S)-1/Cu(OTf) ₂	92	78:22	93	

^a The opposite enantiomers to those in entries 1–4 were obtained.**Table 73. Enantioselective Diels–Alder Reactions in CH₂Cl₂ using a Range of Dienophiles and Cyclopentadiene, Catalyzed by [Box/MX_n]**

entry	dienophiles	box	MX _n	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	313	(R)-1	Cu(OTf) ₂	60		18	339
2	313	(S)-2	Cu(OTf) ₂	51		14	339
3	314 R = Et, R ¹ = Me	(S)-1	Cu(OTf) ₂	53	71:29	40 (R)	340, 341
4	314 R = Me, R ¹ = Ph	(S)-1	Cu(OTf) ₂	44	79:21	84 (R)	340, 341
5	314 R = Et, R ¹ = Ph	(S)-1	Cu(OTf) ₂	76	88:12	>95 (R)	340, 341
6	314 R = Et, R ¹ = Ph	(S)-1	Cu(SbF ₆) ₂ ^a	92	94:6	>95 (R)	340, 341
7	314 R = <i>i</i> -Pr, R ¹ = Ph	(S)-1	Cu(OTf) ₂	70	70:30	85 (R)	340, 341
8	314 R = <i>t</i> -Bu, R ¹ = Ph	(S)-1	Cu(OTf) ₂	91	71:29	26 (R)	340, 341
9	315 R = Me	(S)-2	Cu(OTf) ₂	82	96:4	94 (4S,5R)	93, 316
10	315 R = Ph	(S)-2	Cu(OTf) ₂	86	92:8	97 (4R,5R)	93, 316
11	315 R = CO ₂ Et	(S)-2	Cu(OTf) ₂	88	84:16	96 (4R,5R)	93, 316
12	316 R = H	(R)-1	Mg(ClO ₄) ₂ ^b	97	92:8	70 (R)	342
13	316 R = H	(R)-1	MgBr ₂	98	96:4	14 (S)	342
14	316 R = Me	(R)-1	Mg(ClO ₄) ₂ ^b	98	97:3	86 (S)	342
15	316 R = Me	(R)-1	MgBr ₂	97	97:3	74 (S)	342
16	316 R = Et	(R)-1	MgBr ₂	97	97:3	76 (S)	342
17	316 R = Bn	(R)-1	MgBr ₂	97	92:8	86 (S)	342
18	316 R = CH ₂ <i>t</i> -Bu	(R)-1	MgBr ₂	98	95:5	10 (S)	342
19	317 R = H	(S)-1	Mg(ClO ₄) ₂	80	86:14	60	343
20	188 R = H	(S)-2	Cu(OTf) ₂	99	>99:1	>99	344
21	188 R = Et	(S)-2	Cu(SbF ₆) ₂	90	>98:2	>99	344
22	188 R = Ph	(S)-2	Cu(SbF ₆) ₂	86	94:6	>99	344
23	318	(S)-2	Cu(OTf) ₂	66	38:62	94 ^c	345
24	319	(S)-2	Cu(SbF ₆) ₂	65		52	93

^a From CuBr₂ and AgSbF₆. ^b Freshly dried. ^c exo enantiomeric excess, endo 93% ee.

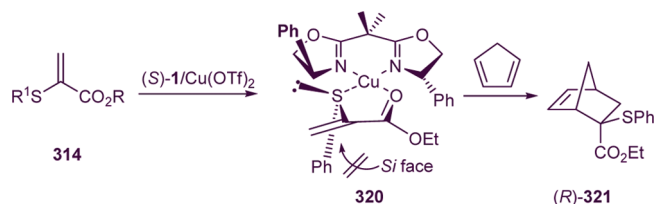
331 with CF₃CO₂H (Scheme 122). The catalyst derived from (S)-1 gave good enantioselectivity (44–47% ee) of (S)-331 that derived from (S)-2 poor enantioselectivity (17% ee) of the opposite enantiomer.³⁵⁷

An important contribution to the study of enantioselective catalyzed hetero Diels–Alder reactions involved using 1,3-cyclohexadiene 333. It gives the bicyclic *endo*-334 adduct with 106b (Scheme 123). A thorough study was carried out on **optimizing the box**, the cationic Lewis acid, the counterion, and the

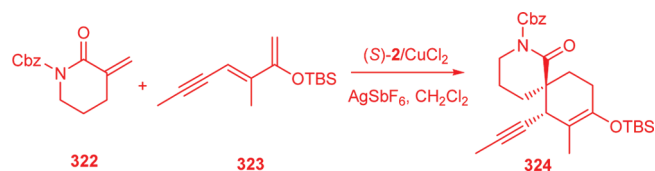
solvent. Some of the significant results are reported in Table 75.^{92,329,355,356,358}

If the **ultimate aim** is to obtain the best enantioselectivity, then the best box is 2, the best cation Cu(II), and the best counterion either OTf or SbF₆. The solvent, on the other hand, appears to be relatively irrelevant (Table 75, entries 14–18).⁹² Box 1 is sensitive to all the experimental parameters: Zn(OTf)₂ and Cu(OTf)₂ give opposite enantiomers in CH₂Cl₂ or MeNO₂ (Table 75, entries 1–4), and [(S)-1/Cu(OTf)₂]₂ gives 79% (S)-334 in CHCl₃ or 60%

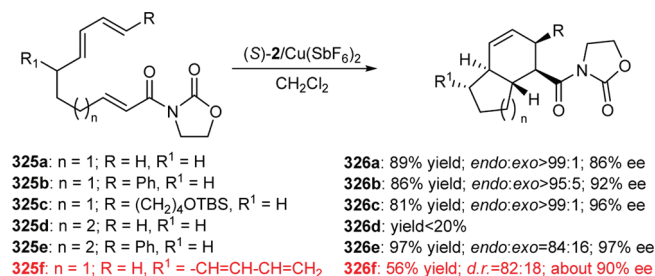
Scheme 118



Scheme 119



Scheme 120



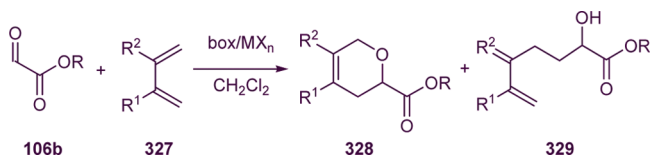
$(R)\text{-334}$ in MeCN (Table 75, entry 5 vs 9). The enantioselectivity appears to be linearly related to the dielectric constant of the solvent.⁹²

Hetero Diels–Alder reactions have useful applications in the synthesis of optically active natural products. For example, the reaction between **106b** and 2,6,6-trimethyl-1,3-cyclohexadiene **335** to give $(1R,3S,4S)\text{-336}$, is the key step in the total syntheses of (R) -actinidiolide **337a** and (R) -dihydroactinidiolide **337b**, two flavor components of tobacco and tea plants (Scheme 124).³⁵⁹ Analogously, the hetero Diels–Alder reaction between Danishefsky's diene **330** and (benzyloxy)acetaldehyde, catalyzed by $[(S)\text{-1}]/\text{Cu}(\text{OTf})_2$, gives an (S) -adduct in 76% yield and 51% ee. This is the starting product for the synthesis of the C_3 – C_{14} segment of the antitumor macrolide laulimalide.³⁶⁰

The next step in this synthesis story was to study the hetero Diels–Alder reaction of activated ketones (the analogues of pyruvate esters) **106c,d** with Danishefsky's dienes **330**. Treatment of the reaction mixture with trifluoroacetic acid (TFA) gives **338** (Scheme 125) with such an excellent enantiomeric purity (Table 76) and employing a process with such a low loading of chiral Lewis acid catalysts (down to 0.05% mol) that the process can be safely compared to a chemoenzymatic reaction.³⁶¹

From a comparison of the data in this table for the different boxes (Table 76, entries 1–3 vs 4 and 5), different cations (Table 76, entries 9–13), and different counterions (Table 76, entry 4 vs 5), it can be concluded that the best catalyst is $[(S)\text{-2}]/\text{Cu}(\text{OTf})_2$.

Scheme 121



With both Danishefsky's dienes **330** ($R^2 = \text{H}$ or Me), it is capable of inducing high enantioselectivities with a variety of α -ketoesters and α -diketones.

The absolute configuration of **338** ($R = R^1 = \text{Me}$, $R^2 = \text{H}$, Table 76, entry 6) was unambiguously determined to be (S) . This is consistent with that of all the other products. To form $(S)\text{-338}$, the diene has to approach the Si face of the bidentate-coordinated ketone copper center. The square-planar geometrical arrangement **339**, illustrated in Scheme 126, shows the 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 proven useful in several applications for the synthesis of optically active natural products (Scheme 127). Starting from $(S)\text{-338}$ ($R = \text{Et}$, $R^1 = (\text{CH}_2)_8\text{CH}_3$, $R^2 = \text{H}$; Table 76, entry 17), the antibiotic $(-)$ -malynogolide **340** was synthesized in an enantiomerically enriched form.³⁶³ $(S)\text{-338}$ ($R = \text{Et}$, $R^1 = \text{Me}$, $R^2 = \text{H}$; Table 76, entry 5) was converted in seven steps into **341**. The original (S) -configuration of the quaternary C_{10a} induced the stereoselective formation of the five additional stereocenters of the product that contains the correct stereochemical arrangement necessary to gain access to phomactin A, a selective antagonist of platelet activating factor.³⁶⁴

Diethyl ketomalonate **342** is an interesting CO dienophile that can be regarded as a synthetic equivalent of CO_2 . For this reason its enantioselective hetero Diels–Alder reaction with 1,3-cyclohexadiene **333**, which gives the tricyclic adduct **343** (Scheme 128), has been the subject of much attention.³⁶⁵ Box, cation, counterion, and solvent were accurately optimized, and some significant results are reported in Table 77.

On the other hand, $(S)\text{-2}$ in combination with $\text{Cu}(\text{II})$ as the Lewis acid gave unsatisfactory results (Table 77, entries 1 and 2) when compared to catalysts derived from $(R)\text{-1}$ and $\text{Zn}(\text{OTf})_2$ or $\text{Cu}(\text{OTf})_2$ (Table 77, entries 3–11). The solvent effect on these two catalysts was studied in detail. The best solvents were those with the lower dielectric constants (toluene, Et_2O , and CH_2Cl_2 ; Table 77, entries 4–6, 9, and 10). Taking into account both yield and enantioselectivity, Et_2O was the best solvent for the two comparable catalysts. Finally it should be mentioned that the absolute configuration was found to be $(1R,4S)\text{-343}$, for catalysts derived from both $(S)\text{-2}$ and $(R)\text{-1}$ boxes.

The carbonyl group of 5-bromo-*N*-oxyppyridine-2-carbaldehyde **112**, which was the site of an asymmetric Mukaiyama–aldol reaction with silylketene acetals (Scheme 30), has proven to be a useful heterodienophile with Danishefsky's diene **330**. The hetero Diels–Alder reaction can be catalyzed by box complexes (Scheme 129, Table 78).³⁶⁶ With $(S)\text{-2}$, after careful screening of a range of Lewis acids and solvents, $(S)\text{-344}$ was obtained with 80% ee. On the other hand, $[(S)\text{-1}]/\text{Cu}(\text{OTf})_2$ gave the opposite (R) enantiomer with 87% ee. These are clearly not the optimum reaction conditions for inducing enantioselectivity because the $\text{Cu}(\text{OTf})_2$ complex with box $(S,S)\text{-5b}$ with different *N*-oxyppyridine-2-aldehydes and ketones gave (S) products with ee's up to 99%.

Table 74. Enantioselective Hetero Diels–Alder and Hetero Ene Reactions between Dienes 327 and Glyoxylate Esters 106b

entry	R	R ¹	R ²	box	MX _n	yield (%)	328/329	328 ee (%) (conf.)	329 ee (%)	ref
1	Et	Me	Me	(S)-2	MgI ₂	30	33:67	5 (S)	10	355
2	Et	Me	Me	(S)-2	Zn(OTf) ₂	66	63:37	23 (S)	31	356
3	Et	Me	Me	(R)-1	Zn(OTf) ₂	67	63:37	81 (S)	68	356
4	Me	Me	Me	(S)-2	Cu(OTf) ₂	64	39:61	90 (S)	85	355
5	Et	Me	Me	(S)-2	Cu(OTf) ₂	56	36:64	85 (S)	83	355
6	<i>i</i> -Pr	Me	Me	(S)-2	Cu(OTf) ₂	24	50:50	77 (S)	83	355
7	Me	Me	Me	(R)-1	Cu(OTf) ₂	86	42:58	81 (S)	85	355
8	Et	Me	Me	(R)-1	Cu(OTf) ₂	81	39:61	83 (S)	88	355
9	<i>i</i> -Pr	Me	Me	(R)-1	Cu(OTf) ₂	71	43:57	87 (S)	90	355
10	Et	Me	H	(R)-1	Cu(OTf) ₂	67	50:50	80	91	355
11	<i>i</i> -Pr	H	H	(R)-1	Cu(OTf) ₂	55		87 (S)		355

Hetero Diels–Alder reactions with C=N dienophiles is a topic that has not been extensively studied. Possibly the modest results did not stimulate further, more thorough investigation. Some isolated experiments are reported, and the development of a catalytic enantioselective reaction can be considered “still in its infancy”.³⁵³ The imines derived from glyoxylates **101** react smoothly with Danishefsky’s diene **330** (R² = H) to give **345** (Scheme 130). The reactions give excellent results with different catalysts, but with (S)-2 and copper triflate³⁶⁷ or iron trichloride,³⁶⁸ the selectivity is satisfactory only with the latter catalyst (Table 79).

With yields of only 25% and 52% ee, results for the reaction of 2-benzoyloxycarbonyl-1-azirine, as the azadienophile, and cyclopentadiene, which was catalyzed by [(S)-2/Mg(ClO₄)₂] in the presence of 4 Å MS, can be considered most unsatisfactory.³⁶⁹ In addition, the reaction between cyclopentadiene and [(2-oxo-1,3-oxazolidin-3-yl)carbonyl]diazanyl formates **230** is also unsatisfactorily catalyzed by [(R)-1/Cu(OTf)₂], because although the yields are excellent, the enantioselectivities do not exceed 22% ee.³⁷⁰

The asymmetric hetero Diels–Alder reactions of *N*-sulfinyl amides **346** with cyclohexadiene **333** will 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 using 10 mol % of catalyst, then it is less selective, but with 1 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf), it becomes strongly endoselective affording **347** with good to excellent enantiomeric excess (see Scheme 131 and Table 80).^{371–373} The reaction is applicable to unusual *N*-substituents, and excellent enantioselectivities are obtained for both zinc(II) and copper(II) triflates.³⁷⁴

When the same *N*-sulfinyl amides **346** and acyclic dienes **348** are reacted with the Cu(OTf)₂ complex of box **1** as the catalyst in the presence of 1 equiv of TMSOTf, highly diastereoselective hetero Diels–Alder reactions with *cis*-**349** as the major isomer (Scheme 132) are the result.³⁷³ To give an idea of the stereoselectivity of this reaction and the absolute configuration of the products, some selected examples are reported in Table 81.

The hetero Diels–Alder reaction of the α,β -unsaturated carbonyl compounds **350** as the heterodienes with alkenes **351** to give the dihydropyrans **352** (Scheme 133) is the best known example of a cycloaddition with inverse electron demand. Namely, this reaction occurs under HOMO_{dienophile}/LUMO _{α,β -unsaturated carbonyl} control.³⁵³

To minimize the frontier molecular orbital (FMO) separation, which will be even further lowered with the coordination of the Lewis acid to the oxygen atom of the heterodiene, the alkenes of choice are generally vinyl ethers or vinyl thioethers. The α,β -unsaturated carbonyl compounds have an electron-withdrawing group in the α -position, either an ester (**350a**)^{375,376} or a phosphonic group (**350b**), with an oxygen atom that can also coordinate to the chiral catalyst.^{90,91,377} The reactions are, in general, strongly endo-selective, and density functional theory (DFT) calculations for the model reaction between acrolein and methyl vinyl ether support the experimental results.³⁷⁸ These are reported in Tables 82 and 83 for the cycloadditions in Scheme 133.

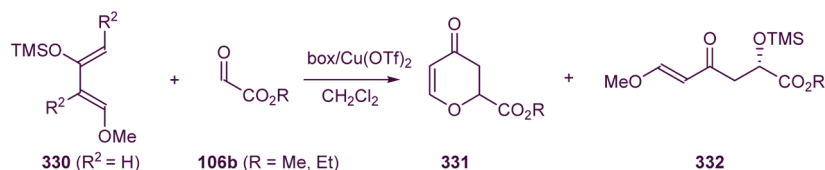
For these hetero Diels–Alder reactions the best Lewis acid is Cu(II); for **350a** when the anion of the catalyst is changed from OTf to PF₆, a small decrease in both the yield and enantioselectivity is observed (Table 82, entries 1 and 7 vs 2 and 8).

For the reactions of **350a**, the best solvent is THF (Table 82, entries 1, 3, and 4). 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 both the yield and selectivity drop for *tert*-butyl vinyl ether (Table 83, entry 9). This is probably due to steric repulsion between the *t*-Bu group and the catalysts in the endo transition state of the reaction.

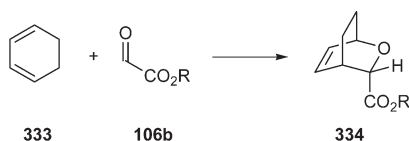
The catalysts derived from box (S)-2 are better than those based on (S)-1 (Table 83, entry 1 vs 5). However, the most outstanding result is for the two catalysts derived from ligands with the same configuration at C(4), which give opposite enantiomers of the endo product.

The hetero Diels–Alder reaction of α,β -unsaturated acyl phosphonates **350b** [E = PO(OMe)₂] was tested for an extended range of substituents either on the heterodiene or on the electron-rich alkenes **351**. Although some results overlap with those of the α,β -unsaturated carbonyl compounds **350a** [e.g., the effect of the substituent on the vinyl ether (Table 83, entries 3–5)], others are somewhat divergent: The results for both box ligands are quite similar (Table 83, 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. Some exceptions are the reactions with *tert*-butyl vinyl ether (Table 83, entries 5 and 8, because of the collapse of selectivity) and the reactions of α -TBSO styrene (Table 83, entries 26 and 27). Also, several couples of reactions, with either vinyl ethers or vinyl sulfides, when run with catalysts derived from (S)-2 or (S)-1, give

Scheme 122



Scheme 123



Scheme 124

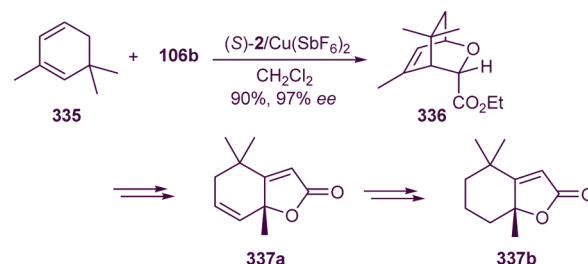


Table 75. Enantioselective Hetero Diels–Alder Reactions of 1,3-Cyclohexadiene 333 and Glyoxylate Esters 106b

entry	R	box	MgX _n	solvent	yield (%)	ee (%) (conf.)	ref
1	Et	(R)-1	Zn(OTf) ₂	CH ₂ Cl ₂	62	35 (S)	356
2	Et	(R)-1	Zn(OTf) ₂	MeNO ₂	84	27 (R)	356
3	Me	(R)-1	Cu(OTf) ₂	CH ₂ Cl ₂	63	47 (S)	358
4	Me	(R)-1	Cu(OTf) ₂	MeNO ₂	49	29 (R)	358
5	Et	(S)-1	Cu(OTf) ₂	CHCl ₃		78 (R)	92
6	Et	(S)-1	Cu(OTf) ₂	THF		47 (R)	92
7	Et	(S)-1	Cu(OTf) ₂	CH ₂ Cl ₂	72	60 (R)	92, 355
8	Et	(S)-1	Cu(OTf) ₂	EtNO ₂		11 (S)	92
9	Et	(S)-1	Cu(OTf) ₂	MeCN		60 (S)	92
10	Et	(S)-2	Zn(OTf) ₂	CH ₂ Cl ₂	57	23 (S)	356
11	Et	(S)-2	Zn(OTf) ₂	MeNO ₂	46	racemate	356
12	Me	(S)-2	Cu(OTf) ₂	MeNO ₂	63	92 (S)	358
13	Et	(S)-2	Cu(SbF ₆) ₂	MeNO ₂	66	93 (S)	329
14	Et	(S)-2	Cu(OTf) ₂	MeNO ₂	99	≥97 (S)	92, 329
15	Et	(S)-2	Cu(SbF ₆) ₂	CH ₂ Cl ₂	99	≥97 (S)	329
16	Et	(S)-2	Cu(OTf) ₂	CH ₂ Cl ₂	99	≥97 (S)	92, 329
17	Et	(S)-2	Cu(OTf) ₂	CHCl ₃		97 (S)	92
18	Et	(S)-2	Cu(OTf) ₂	THF		≥97 (S)	92

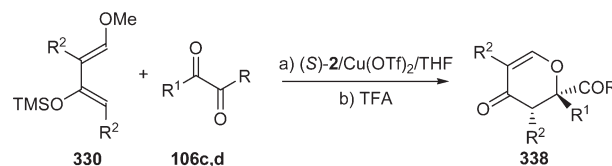
opposite enantiomers (Table 83, entries 1, 3, 4, and 24 vs 2, 6, 7, and 25). If the bidentate coordination of 350 to catalysts derived from $(S)\text{-}2$ or $(S)\text{-}1$ occurs with the same opposite distortion resembling those observed in the X-ray structures (already illustrated in Figure 14 to rationalize the analogous opposite enantioselectivity of the Mukaiyama–Michael reaction), then the preferred approach to the opposite prochiral faces of 350 can be expected.

All reactions do not give side products. There are two exceptions: 350a and α -trimethylsilyloxy styrene with $[(S)\text{-}1/Cu(SbF_6)_2]$ give the Michael adduct as the main product (80% yield).⁹¹ The same phosphonate with cyclopentadiene affords a yield of 34% 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).⁹¹

The reactivities of the ketoester 350a and acyl phosphonate 350b were compared in a competition experiment. The former proved somewhat more reactive than the latter (endo-350a/endo-350b = 3.5:1).⁹¹

Recently the reaction of the ketoester 350a and the acyl phosphonate 350b with a series of vinyl ethers and thioethers,

Scheme 125



catalyzed by the $[(S)\text{-}2/Cu(OTf)_2]$ complex, was performed in hydrophobic ionic liquids. Both reactivities and stereoselectivities were found to be comparable to those of the corresponding homogeneous reactions.³⁷⁹

In Scheme 117 are shown the Diels–Alder reactions in which 2-alkenyl pyridines 310a ($Y = N$) and their N -oxides 310b ($Y = N\text{-}O$) behaved as dienophiles with cyclopentadiene. With the electron-rich alkenes 351, they gave an inverse-electron demand hetero Diels–Alder reaction. The products were *endo*-353a,b and *exo*-354a,b (Scheme 134). The enantioselective reactions were catalyzed by $[(S)\text{-}box/Cu(OTf)_2]$ complexes, and the results are reported in Table 84. The absence of N -oxide had a dramatic effect on the enantioselectivity (Table 84, entry 1 vs 2). $(S)\text{-}1$ gives the enantiomer opposite to that obtained with $(S)\text{-}2$ (Table 84, entry 2 vs 3). The reaction can tolerate different R groups, and both the yield and stereoselectivity are excellent even with less traditional electron-rich alkenes (Table 84, entry 9).³⁸⁰

An interesting approach to obtaining the trans fused hydropyran–pyran derivatives 357 is found in the intramolecular hetero Diels–Alder reaction using 356. It is developed from the transesterification of methyl (*E*)-4-methoxy-2-oxo-3-butenate 350a and δ,ϵ -unsaturated alcohols 355 and is catalyzed by $[box/Cu(II)]$ complexes (Scheme 135).³⁸¹ The enantioselectivity is affected by both the choice of box and the Cu(II) anion (Table 85). The presence of MS (5 Å better than 4 Å, Table 85, entries 1, 3, and 5 vs 2, 4, and 6) as additives is essential; otherwise racemic products are obtained.

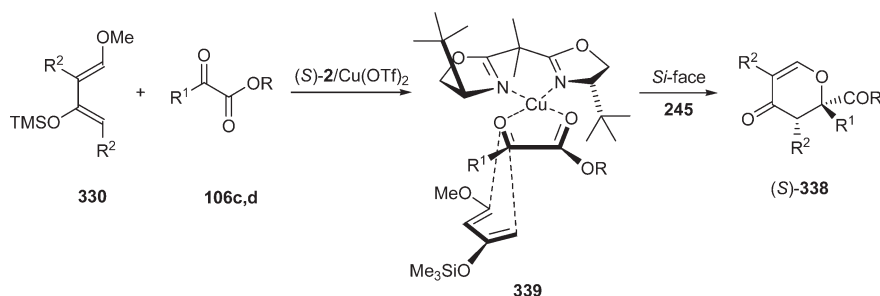
Only a few examples of hetero Diels–Alder reactions with azadienes are known. Scheme 84 shows a Mukaiyama–Michael

Table 76. Enantioselective Hetero Diels–Alder Reactions of Dienes 330 with α -Ketoesters and α -Diketones 106c,d

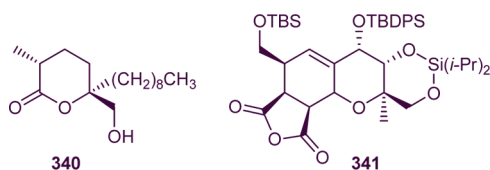
entry	R	R ¹	R ²	box	MX _n	yield (%)	ee (%) (conf.)	ref
1	OMe	Me	H	(S)-1	Cu(OTf) ₂	99	35 (R)	33
2 ^a	OEt	Me	H	(R)-1	Cu(SbF ₆) ₂	24	23 (S)	361
3 ^a	OEt	Me	H	(R)-1	Cu(OTf) ₂	85	35 (S)	361
4 ^a	OEt	Me	H	(S)-2	Cu(SbF ₆) ₂	37	89 (S)	361
5 ^a	OEt	Me	H	(S)-2	Cu(OTf) ₂	78	>99 (S)	361
6	OMe	Me	H	(S)-2	Cu(OTf) ₂	96	>99 (S)	25, 33, 361
7	OMe	Et	H	(S)-2	Cu(OTf) ₂	80	94 (S)	361
8	OEt	<i>i</i> -Pr	H	(S)-2	Cu(OTf) ₂	42	37 (S)	361, 362
9	OEt	Ph	H	(S)-2	Cu(OTf) ₂	77	77 (S)	361, 362
10	OEt	Ph	H	(S)-2	Sc(OTf) ₃	26	6	362
11	OEt	Ph	H	(S)-2	Yb(OTf) ₃	70	4	362
12	OEt	Ph	H	(S)-2	In(OTf) ₃	26	9	362
13	Me	Me	H	(S)-2	Cu(OTf) ₂	90	94 (S)	361
14	Et	Me	H	(S)-2	Cu(OTf) ₂	77	98 (S)	361
15	Et	Et	H	(S)-2	Cu(OTf) ₂	84	90 (S)	361
16	Ph	Me	H	(S)-2	Cu(OTf) ₂	95	94 (S)	361
17 ^a	Et	(CH ₂) ₈ CH ₃	H	(S)-2	Cu(OTf) ₂	77	47 (S)	363
18	OMe	Me	Me	(S)-2	Cu(OTf) ₂	75	96 (S)	361
19	OEt	Ph	Me	(S)-2	Cu(OTf) ₂	57	99 (S)	361
20	Me	Me	Me	(S)-2	Cu(OTf) ₂	60	91 (S)	361

^a Reaction performed in CH₂Cl₂.

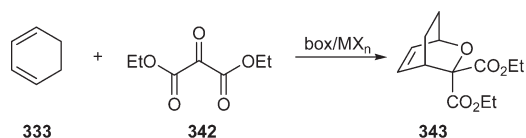
Scheme 126



Scheme 127



Scheme 128



reaction, a formal hetero Diels–Alder reaction, of the azodicarbonyl derivatives 230 to give the intermediate 231.²⁶⁴ An unequivocal example was reported by Ghosez for the reaction between the azadienes 358 and either the 3-acryloyl or 3-(*E*)-crotonoyl-2-oxazolidinones 53. As shown in Scheme 136, the reaction was catalyzed by [(S)-2/Cu(OTf)₂].³⁸² The reaction is

Table 77. Enantioselective Hetero Diels–Alder Reactions of Diethyl Ketomalonate 342 with 1,3-Cyclohexadiene 333³⁶⁵

entry	box	MX _n	solvent	yield (%)	ee (%) (conf.)
1	(S)-2	Cu(SbF ₆) ₂	CH ₂ Cl ₂	11	64 (1R,4S)
2	(S)-2	Cu(OTf) ₂	CH ₂ Cl ₂	20	40 (1R,4S)
3	(R)-1	Zn(SbF ₆) ₂	CH ₂ Cl ₂	65	27 (1R,4S)
4	(R)-1	Zn(OTf) ₂	CH ₂ Cl ₂	39	86 (1R,4S)
5	(R)-1	Zn(OTf) ₂	Et ₂ O	94	91 (1R,4S)
6	(R)-1	Zn(OTf) ₂	PhMe	68	90 (1R,4S)
7	(R)-1	Zn(OTf) ₂	THF	15	86 (1R,4S)
8	(R)-1	Zn(OTf) ₂	MeCN	17	23 (1R,4S)
9	(R)-1	Cu(OTf) ₂	CH ₂ Cl ₂	76	84 (1R,4S)
10	(R)-1	Cu(OTf) ₂	Et ₂ O	64	93 (1R,4S)
11	(R)-1	Cu(OTf) ₂	THF	70	72 (1R,4S)

strongly exo-selective, and 359 was obtained with excellent yield and enantioselectivity (Table 86). The determined absolute configuration of the pyridone as reported in Table 86 (entry 3), (3*S*,4*R*,5*S*,6*S*), is consistent with the diene approaching the less hindered face of 53, which is bicoordinated in a square-planar complex.

The azadienes 358 react with electron-poor dienophiles. This can probably be attributed to the presence and nature of the substituents. The *N*-tosyl-1-azadienes 360 prefer to react with the ethyl vinyl ether 351 (R¹, R² = H, X = OEt) according to an

Scheme 129

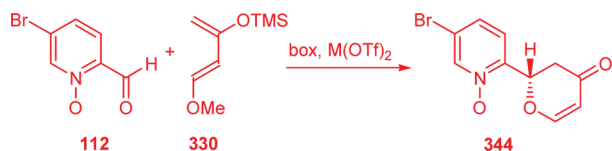
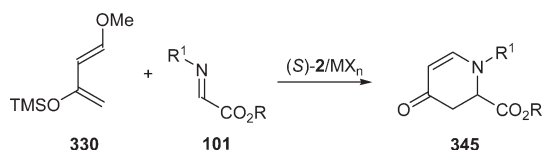


Table 78. Enantioselective Hetero Diels–Alder Reactions of 5-Bromo-*N*-oxypyridine-2-carbaldehyde 112 with Danishefsky's Diene 330³⁶⁶

entry	box	MX _n	solvent	344 yield (%)	344 ee (%) (conf.)
1	(<i>S</i>)-2	Zn(OTf) ₂	CH ₂ Cl ₂	35	7
2	(<i>S</i>)-2	Mg(OTf) ₂	CH ₂ Cl ₂	44	10
3	(<i>S</i>)-2	Cu(OTf) ₂	CH ₂ Cl ₂	30	80 (<i>S</i>)
4	(<i>S</i>)-2	Cu(OTf) ₂	PhMe	49	76 (<i>S</i>)
5	(<i>S</i>)-2	Cu(OTf) ₂	THF	41	79 (<i>S</i>)
6	(<i>S</i>)-1	Cu(OTf) ₂	CH ₂ Cl ₂	30	78 (<i>R</i>)

Scheme 130



inverse-electron demand hetero Diels–Alder mechanism (Scheme 137). Optimization of the catalyst showed preference for a bisoxazoline ligand. However, these lie outside the limits of this review. Among the boxes, the best catalyst proved to be [(*S*)-1/Cu(OTf)₂], which gave (2*R*,4*S*)-361 (Table 87). A reacting intermediate that certainly involves the participation of the 2-pyridylsulfonyl group of azadiene has been proposed.³⁸³

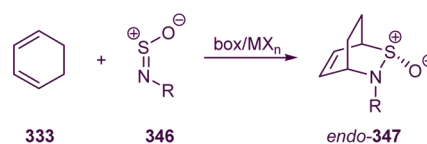
An intramolecular hetero Diels–Alder reaction involving a vinyl ether tethered to an 1-azadiene was attempted, but catalyst [(*S*)-2/Cu(OTf)₂] gave 60% yield of a nearly racemic product.³⁸⁴

4.9. 1,3-Dipolar Cycloaddition Reactions

After enantioselective Diels–Alder reactions, and variations thereof, the second most important class of pericyclic reactions is probably 1,3-dipolar cycloaddition reactions. This is because of their usefulness in constructing chiral heterocyclic synthons. For example, the synthetic applications of isoxazolidines with three contiguous chiral centers, which can be obtained from the 1,3-dipolar cycloaddition reaction of nitrones to alkenes, led to the rapid development of a series of catalysts specifically designed for this purpose.^{385,386} Among the chiral ligands used for these reactions, box examples played a relevant role in its success.

Three levels of control are required to develop stereospecificity in a 1,3-dipolar cycloaddition reaction. Taking the reaction between a nitrone 362 and 3-alkenyl-2-oxazolidinones 53 as an example, a good optically active catalyst should control the regioselectivity [4- vs 5-alkenylisoxazolidines (363 vs 364)], the diastereoselectivity (*endo*-363 vs *exo*-363), and the enantioselectivity [(4*S*,*SR*)-363 vs (4*R*,*SS*)-363 enantiomers] (Scheme 138).

Scheme 131



The R²-substituents on the nitrone play an important role in the cycloaddition reaction mechanism. If these substituents are alkyl or aryl groups, then the nitrone prefers to react with an electron-deficient alkene such as 53. In this case the normal electron-demand cycloaddition is under HOMO_{nitrone}–LUMO_{alkene} control. If R² is an electron-withdrawing group, then the nitrone reacts with electron-rich alkenes (vinyl ethers), and the inverse electron-demand cycloaddition is under HOMO_{alkene}–LUMO_{nitrone} control.

The reaction between the nitrone 362 (R¹ = Ph or Bn, R² = Ph) and 53 (R = Me or *n*-Pr) was the first box-based catalyzed 1,3-dipolar cycloaddition reaction reported. The yield, regioselectivity, and diastereoselectivity are all controlled by using the [(*S*)-1/MgI₂] catalyst for the reaction of the diphenyl nitrone. The product is 363, and the reaction is strongly *endo*-selective. In addition, the enantioselectivity is dependent on the presence of 4 Å MS (Table 88, entries 16–19 and 24).³⁸⁷ This unusual behavior was also found for the reaction between diphenyl nitrone 362 (R¹ = R² = Ph) and 3-acryloyl- or 3-(*E*)-crotonoyl-2-oxazolidinones 53 (Table 88, entries 12, 16, and 17). Having determined the absolute stereochemistry of the products, it was concluded that in the presence of MS (3*S*,4*R*,5*S*)-363 is the preferred stereoisomer, whereas in the absence of MS the opposite enantiomer (3*R*,4*S*,5*R*)-363 is obtained.³⁸⁸ 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 various drying agents were also tested (Table 88, entries 3–5 and 18). Keeping the box constant, the reaction behavior was observed on changing the counterion of Mg(II) (ClO₄ or OTf) or changing the Lewis acid cation (Table 88, entries 6–15).^{114,389,390} Few cations failed: namely, Mg(OTf)₂ with MS and Zn(ClO₄)₂ without MS,^{114,390} and Yb(OTf)₃ and Sc(OTf)₃,³⁹¹ which gave racemates.

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(ClO₄)₂/MS] (Table 88, entry 11).¹¹⁴ In both cases, the effects have the same origin, namely, from the reservoir effect induced by the thermodynamic stability of the racemic complex [(*R*)-1/(*S*)-1/Zn] 24 (Figure 12).

From the data presented in Table 88 for the homogeneous series of 1,3-dipolar cycloaddition reactions with acryloyl-oxazolidinone, it can be seen that, in the absence of MS, all the reactions are highly *endo*-selective. On the other hand, when MS is used as an additive, this shifts the stereoselectivity toward the formation of the *exo*-364 adduct. This effect is particularly evident for the Co(II) and Zn(II) cations (Table 88, entries 10 and 11). These give *exo*-selective reactions, and this finding, as will be discussed in a later section of this review, led to the design of *exo*-enantioselective catalysts for nitrone cycloadditions.

A new class of achiral additives, capable of amplifying the enantioselectivity through suitably placed groups that allow their involvement in coordination was developed. These made it possible to bias the configuration of the fluxional centers of the additive and transform it into a chiral auxiliary through the effect

Table 79. Enantioselective Hetero Diels–Alder Reactions of Dienes 330 with Imines 101

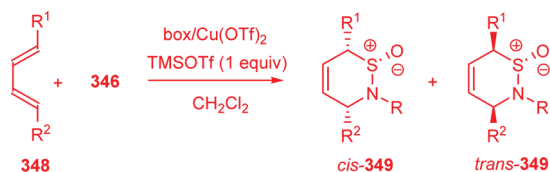
entry	R	R ¹	MX _n	solvent	additives	yield (%)	ee (%) (conf.)	ref
1	Et	tosyl	Cu(OTf)	THF		74	12 (S)	367
2	Et	tosyl	Cu(OTf) ₂	THF		60	10 (S)	367
3	Me	<i>p</i> -MeOPh	FeCl ₃	MeCN		n.r.	57	368
4	Me	<i>p</i> -MeOPh	FeCl ₃	CH ₂ Cl ₂	4 Å MS	67	92	368
5	Me	<i>p</i> -MeOPh	FeCl ₃	CH ₂ Cl ₂	2,6-lutidine	n.r.	70	368

Table 80. Enantioselective Hetero Diels–Alder Reactions of Cyclohexadiene with *N*-Sulfinyl Amides 346

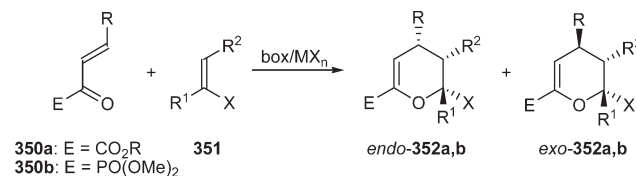
entry	R	box	MX _n	additive	yield (%)	endo/exo	endo-261 ee (%) (conf.)	ref
1	Cbz	(<i>R</i>)-1	Cu(OTf) ₂		25	38:62	15 (1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i>)	371, 372, 373
2	Cbz	(<i>S</i>)-1	Cu(OTf) ₂	TMSOTf	85	>95:<5	98 (1 <i>S</i> ,2 <i>R</i> ,4 <i>R</i>)	372, 373
3	Cbz	(<i>R</i>)-1	Zn(OTf) ₂		30	75:25	61 (1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i>)	371, 372, 373
4	Cbz	(<i>S</i>)-1	Zn(OTf) ₂	TMSOTf	70	92:8	86 (1 <i>S</i> ,2 <i>R</i> ,4 <i>R</i>)	372, 373
5	tosyl	(<i>R</i>)-1	Cu(OTf)		93	82:18	36 (1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i>)	371, 372
6	tosyl	(<i>S</i>)-1	Cu(OTf) ₂	TMSOTf	56	92:8	80 (1 <i>S</i> ,2 <i>R</i> ,4 <i>R</i>)	372, 373
7	tosyl	(<i>R</i>)-1	Zn(OTf) ₂		39	92:8	78 (1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i>)	371, 372, 373
8	tosyl	(<i>S</i>)-1	Zn(OTf) ₂	TMSOTf	86	>95:<5	97 (1 <i>S</i> ,2 <i>R</i> ,4 <i>R</i>)	372, 373
9	PO(OPh) ₂	(<i>S</i>)-1	Zn(OTf) ₂	TMSOTf	73	>95:<5	95 (1 <i>S</i> ,2 <i>R</i> ,4 <i>R</i>)	374
10	PO(OPh) ₂	(<i>S</i>)-1	Cu(OTf) ₂	TMSOTf	51	>95:<5	97 (1 <i>S</i> ,2 <i>R</i> ,4 <i>R</i>)	374
11	5-Me-3-Is ^a	(<i>S</i>)-1	Zn(OTf) ₂	TMSOTf	57	>95:<5	68	374

^a 5-Me-3-Is is 5-methyl-3-isoxazolyl.

Scheme 132



Scheme 133

Table 81. Enantioselective Hetero Diels–Alder Reactions of Acyclic Dienes 348 with *N*-Sulfinyl Amides 346³⁷³

entry	R	R	R ¹	box	yield (%)	<i>cis</i> /trans	<i>cis</i> -349 ee (%) (conf.)
1	Cbz	Me	Me	(<i>S</i>)-1	72	>95:<5	70 (1 <i>R</i> ,3 <i>S</i> ,3 <i>R</i>)
2	Cbz	H	Me	(<i>R</i>)-1	60	>95:<5	77 (1 <i>S</i> ,3 <i>R</i>)
3	Cbz	H	Ph	(<i>R</i>)-1	43	83:17	40
4	Cbz	Me	Ph	(<i>S</i>)-1	31	>95:<5	42
5	tosyl	Me	Me	(<i>R</i>)-1	68	>95:<5	97 (1 <i>S</i> ,3 <i>R</i> ,6 <i>S</i>)
6	tosyl	H	Me	(<i>R</i>)-1	68	73:27	87 (1 <i>S</i> ,3 <i>R</i>)
7	tosyl	H	Ph	(<i>S</i>)-1	68	>95:<5	92 (1 <i>R</i> ,2 <i>R</i>)
8	tosyl	Me	Ph	(<i>S</i>)-1	50	>95:<5	71

of the chiral Lewis acids. A similar use has previously been reported in the section on Diels–Alder reactions. These were also tested for the 1,3-dipolar cycloaddition of diphenylnitrone 362 (R¹ = R² = Ph) and 3-crotonoyloxazolidinone 53 (R = Me).³²⁵ The results for 2-benzoyl-5,5-dimethyl-1-naphthalen-2-ylmethyl-pyrazolidin-3-one (fluxional additive **B** reported in Table 67) catalyzed with Mg(II) and Co(II) perchlorate complexes of (*S*)-1 are reported, and the data are shown in entries 20–23 of Table 88. A strong beneficial effect on both the diastereoselectivity and enantioselectivity for the nitrone cycloadditions is evident from this data.

A different approach to *exo*-enantioselective nitrone cycloadditions was realized by employing 1-benzyl-2-crotonoyl-5,5-dimethylpyrazolidin-3-ones 220. This interesting achiral template has already been mentioned in the aza-Michael reaction

(section 4.4) as one which can relay and amplify the stereochemistry induced by the box. Its reaction with the nitrone 362 (R¹ = Me, R² = Ph) was catalyzed by [(*S*)-2/Cu(OTf)₂]. In fact this is not the best box catalyst for this application because it gives a low yield of *exo*/*endo* products in the ratio 83:17. The enantiomeric excess of 365 is 71% ee (Scheme 139).³⁹²

An excellent dipolarophile for nitrone cycloadditions was found to be 4-hydroxy-4-methylpent-1-en-3-one (188, R = H). As shown in section 4.4, it is capable of a bidentate coordination, through its oxygen atoms, to [(*S*)-2/Cu(OTf)₂]. This dipolarophile reacts easily with the nitrone 362 affording the regioisomers 366 and 367. The former is formed in large excess, with a strong *endo* preference, and excellent enantioselectivity (Scheme 140, Table 89). The absolute configuration of 366 was determined as being (3*S*,4*R*).³⁹³

All the reactions discussed above fall into the class of normal electron-demand cycloadditions; if the nitrone 362 has R² = CO₂R, then it reacts with vinyl ethers 351 (X = OR) in accordance with an inverse electron-demand cycloaddition. The enantioselective version of this reaction has been developed and employs chiral Cu(II)- and Zn(II)-box complexes as the catalysts to give *exo*- and *endo*-368 (Scheme 141).³⁹⁴ The best catalyst proved to be [(*S*)-2/Cu(OTf)₂]. It gives excellent yields and a high enantioselectivity of *exo*-368 with ethyl vinyl ether and 2-methoxypropene (Table 90, entries 1 and 5).

On the basis of the absolute configuration of *exo*-368 as seen in entry 1 Table 90, the pentacoordinated reaction intermediate 369 has been proposed. Here both reagents are bound to the

Table 82. Enantioselective Hetero Diels–Alder Reactions of α,β -Unsaturated Carbonyl Compounds 350a (E = CO₂R) with Electron-Rich Alkenes 351 (R¹ = H)

entry	E	R	R ²	X	solvent	box	MX _n	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	CO ₂ Et	Me	H	OEt	CH ₂ Cl ₂	(S)-2	Cu(OTf) ₂	100 ^a	98:2	98(4R,6R)	91, 373
2	CO ₂ Et	Me	H	OEt	CH ₂ Cl ₂	(S)-2	Cu(SbF ₆) ₂		57:43	95(4R,6R)	91
3	CO ₂ Et	Me	H	OEt	THF	(S)-2	Cu(OTf) ₂	89	n.r.	>99.5	373
4	CO ₂ Et	Me	H	OEt	MeNO ₂	(S)-2	Cu(OTf) ₂	100 ^a	n.r.	76	373
5	CO ₂ Et	Me	H	OEt	CH ₂ Cl ₂	(S)-1	Cu(OTf) ₂	100 ^a	95:5	64(4S,6S)	91, 373
6	CO ₂ Me	Ph	H	OEt	THF	(S)-2	Cu(OTf) ₂	95	n.r.	99.5	373
7	CO ₂ Et	OEt	H	OEt	THF	(S)-2	Cu(OTf) ₂	93	n.r.	>99.5	373
8	CO ₂ Et	OEt	H	OEt	CH ₂ Cl ₂	(S)-2	Cu(PF ₆) ₂	88	n.r.	97	373
9	CO ₂ Et	OEt	H	OT-Bu	THF	(S)-2	Cu(OTf) ₂	61	80:20	90	373
10	CO ₂ Et	Me		OCH ₂ CH ₂	THF	(S)-2	Cu(OTf) ₂	51	n.r.	>99.5	373
11	CO ₂ Me	Ph		OCH ₂ CH ₂	THF	(S)-2	Cu(OTf) ₂	96	n.r.	99.5	373
12	CO ₂ Et	OEt		OCH ₂ CH ₂	THF	(S)-2	Cu(OTf) ₂	84	n.d.	97.5	373
13	CO ₂ Et	Ph	H	OEt	THF	(S)-2	Cu(OTf) ₂ ^b	93	95:5	97(4R,6R)	376
14	CO ₂ Et	<i>i</i> -Pr	H	OEt	THF	(S)-2	Cu(OTf) ₂ ^b	95	96:4	96(4R,6S)	376
15	CO ₂ Et	Me	H	OEt	THF	(S)-2	Cu(OTf) ₂ ^b	87	96:4	97	376
16	CO ₂ Et	OMe	H	OEt	THF	(S)-2	Cu(OTf) ₂ ^b	90	98:2	98	376
17	CO ₂ Et	OEt	H	OEt	THF	(S)-2	Cu(OTf) ₂ ^b	98	98:2	98	376
18	CO ₂ Et	SBN	H	OEt	THF	(S)-2	Cu(OTf) ₂ ^b	97	95:5	99	376
19	CO ₂ Et	<i>i</i> -Pr		OCH ₂ CH ₂	THF	(S)-2	Cu(OTf) ₂ ^b	94	94:6	95	376
20	CO ₂ Et	Ph		OCH ₂ CH ₂	THF	(S)-2	Cu(OTf) ₂ ^b	96	94:6	97	376
21	CO ₂ Et	Ph	H	SEt	THF	(S)-2	Cu(OTf) ₂ ^b	94	96:4	97	91
22	CO ₂ Et	Ph	H	SPh	THF	(S)-2	Cu(OTf) ₂ ^b	91	96:4	99	91

^a Conversion. ^b Dihydrate salt.**Table 83. Enantioselective Hetero Diels–Alder Reactions of α,β -Unsaturated Acyl Phosphonates 350b [E = PO(OMe)₂] with Electron-Rich Alkenes 351 in CH₂Cl₂**

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 (4R,6R)	90, 261, 377
2	Me	H	H	OEt	(S)-1	Cu(OTf) ₂	85	>99:1	94 (4S,6S)	90, 91, 376, 377
3	Me	H	H	OMe	(S)-2	Cu(SbF ₆) ₂		99:1	85 (4R,6R)	90, 91
4	Me	H	H	OEt	(S)-2	Cu(SbF ₆) ₂	84	99:1	85 (4R,6R)	90, 91, 377
5	Me	H	H	OT-Bu	(S)-2	Cu(SbF ₆) ₂	35	57:43	66 (4R,6R)	90, 91
6	Me	H	H	OMe	(S)-1	Cu(SbF ₆) ₂	95	>99:1	86 (4S,6S)	90, 91
7	Me	H	H	OEt	(S)-1	Cu(SbF ₆) ₂	100	>99:1	93 (4S,6S)	90, 91, 377
8	Me	H	H	OT-Bu	(S)-1	Cu(SbF ₆) ₂	100	91:9	2	90, 91
9	Me	H	H	OTBS	(S)-1	Cu(SbF ₆) ₂		50:50	64	91
10	Ph	H	H	OEt	(S)-2	Cu(SbF ₆) ₂	88	97:3	94 (4R,6R)	91
11	<i>i</i> -Pr	H	H	OEt	(S)-2	Cu(SbF ₆) ₂	78	97:3	93 (4R,6S)	91
12	OEt	H	H	OEt	(S)-2	Cu(SbF ₆) ₂	96	>99:1	93 (4R,6R) ^a	91
13	Ph	H	H	OEt	(S)-1	Cu(SbF ₆) ₂	98	>99:1	98 (4S,6S)	91, 377
14	<i>i</i> -Pr	H	H	OEt	(S)-1	Cu(SbF ₆) ₂	99	>99:1	96 (4S,6R)	91, 377
15	OEt	H	H	OEt	(S)-1	Cu(SbF ₆) ₂	49	99:1	77 (4S,6S) ^a	91
16	Me	H		OCH ₂ CH ₂	(S)-2	Cu(OTf) ₂	91	>99:1	95 (4R,5S,6R)	91,377
17	Ph	H		OCH ₂ CH ₂	(S)-2	Cu(SbF ₆) ₂	99	>99:1	90 (4S,5S,6R) ^a	91
18	<i>i</i> -Pr	H		OCH ₂ CH ₂	(S)-2	Cu(SbF ₆) ₂	79	98:2	90 (4R,5S,6R) ^a	91,377
19	OEt	H		OCH ₂ CH ₂	(S)-2	Cu(SbF ₆) ₂	98	>99:1	97 (4S,5S,6R) ^a	58,262
20	Ph	H		OCH ₂ CH ₂	(S)-1	Cu(OTf) ₂	98	>99:1	94 (4R,5R,6S) ^a	58,262
21	<i>i</i> -Pr	H		OCH ₂ CH ₂	(S)-1	Cu(SbF ₆) ₂	94	>99:1	71 (4S,5R,6S) ^a	58
22	OEt	H		OCH ₂ CH ₂	(S)-1	Cu(OTf) ₂	100	>99:1	84 (4R,5R,6S) ^a	58
23	Me	H		OCH ₂ CH ₂ CH ₂	(S)-2	Cu(SbF ₆) ₂	55	98:2	92 (4R,5S,6S) ^a	58,262
24	Me	H	H	SEt	(S)-2	Cu(SbF ₆) ₂	31	95:5	76 (4R,6S) ^a	58
25	Me	H	H	SEt	(S)-1	Cu(SbF ₆) ₂	89	>99:1	95 (4S,6R) ^a	58
26	Me	Ph	H	OTBS	(S)-2	Cu(SbF ₆) ₂		93:7	99 (4R,6S) ^a	58
27	Me	Ph	H	OTBS	(S)-1	Cu(SbF ₆) ₂		60:40	96 (4R,6S) ^a	58

^a Absolute configuration assigned by analogy.

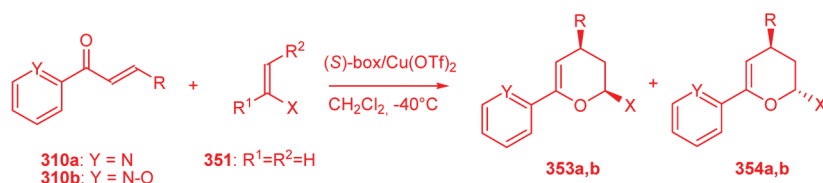
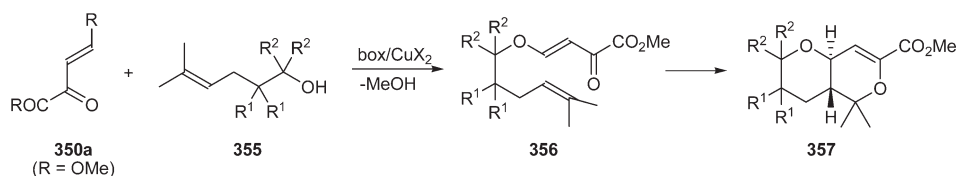
catalyst: Nitron is equatorially bicoordinated, and the ethyl vinyl ether is axial (Figure 18).

Although the 1,3-dipolar cycloaddition reactions of nitrones have been the topic of extensive studies, few papers concerning other 1,3-dipoles have appeared. A carbonyl ylide [from *o*-(methoxycarbonyl)- α -diazoacetophenone] reacts with *N*-phenylmaleimide, but with [(S)-2/Cu(OTf)₂] gives a low yield of a 1:1 mixture of endo and

exo products with ee up to 20%.³⁹⁵ Nitrile oxides react with **167**, and the best catalyst in this context is [(S)-1/MgI₂]. It gives up to 44% ee,³⁹⁶ whereas the box **10a** affords excellent stereoselective catalysts. For this reason this particular reaction will be discussed in a later section. Finally, the nitrile ylides give a cycloaddition with crotonyl oxazolidinone **216**, catalyzed by the [(S)-2/Mg(OTf)₂] complex. However, the ee is a disappointing 14%.³⁹⁷

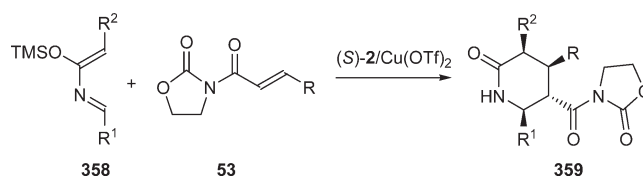
Table 84. Enantioselective Hetero Diels–Alder Reactions of 2-Alkenoyl Pyridines 310a (Y=N) and Their N-Oxides 310b (Y=N–O) with Electron-Rich Alkenes 351³⁸⁰

entry	Y	R	X	(S)-box	yield (%)	endo/exo	endo-353 ee (%) (conf.)	exo-354 ee (%)
1	N	Ph	OEt	(S)-1	n.r.	85:15	16	15
2	N–O	Ph	OEt	(S)-1	99	>99:1	96	
3	N–O	Ph	OEt	(S)-2	n.r.	94:6	–75 ^a	
4	N–O	4-MeOC ₆ H ₄	OEt	(S)-1	80	>99:1	94	
5	N–O	4-BrC ₆ H ₄	OEt	(S)-1	99	>99:1	96	
6	N–O	4-NO ₂ C ₆ H ₄	OEt	(S)-1	85	>99:1	96	
7	N–O	2-furyl	OEt	(S)-1	99	99:1	96	
8	N–O	<i>t</i> -Bu	OEt	(S)-1	99	95:5	96	37
9	N–O	Ph	1-pyrrolidone	(S)-1	93	>99:1	>99	
10	N–O	Ph	SEt	(S)-1	98	>99:1	96	
11	N–O	4-BrC ₆ H ₄	SEt	(S)-1	99	98:2	97 (4S,6R)	
12	N–O	Ph	4-MeOC ₆ H ₄	(S)-1	99	>97:3	77	

^a The opposite enantiomer to that of entry 1 was obtained.**Scheme 134****Scheme 135****Table 85. Intramolecular Hetero Diels–Alder Reactions of 356³⁸¹**

entry	R ¹	R ²	box	CuX ₂	additives	yield (%)	ee (%)
1	H	H	(S)-1	Cu(SbF ₆) ₂	4 Å	51	13
2	H	H	(S)-1	Cu(SbF ₆) ₂	5 Å	51	14
3	H	H	(S)-2	Cu(SbF ₆) ₂	4 Å	12	93
4	H	H	(S)-2	Cu(SbF ₆) ₂	5 Å	63	96
5	H	H	(S)-2	Cu(OTf) ₂	4 Å	50	73
6	H	H	(S)-2	Cu(OTf) ₂	5 Å	83	55
7	Me	H	(S)-2	Cu(SbF ₆) ₂	5 Å	83	98
8	H	Me	(S)-2	Cu(SbF ₆) ₂	5 Å	74	98

This section will be concluded by describing the fruitful enantioselective catalysis of the 1,3-dipolar cycloaddition reaction of azomethine ylides. These are derived from the *N*-arylidene glycines 370 and Et₃N, with the electron-deficient alkenes 371 to afford 372 as a single diastereoisomer (Scheme 142).³⁹⁸ After testing several solvents, boxes, and triflates, the best conditions were found to be THF and [(*S*)-2/Zn(OTf)₂], and these results are reported in Table 91. The absolute configuration of the product described in entry 7 was unambiguously determined to be (2*S*,3*S*,4*S*,5*R*). The reaction is

Scheme 136

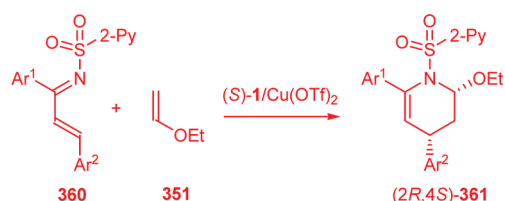
extremely flexible, and the enantioselectivity drops only with increasing steric hindrance of the acrylate (Table 91, entries 2–4).

4.10. Ene and Hetero Ene Reactions

Hetero Diels–Alder reactions with C=O dienophiles, discussed previously in section 4.8, with dienes containing an allylic C–H bond afford, besides dihydropyrans from the cycloaddition, unsaturated hydroxy esters from an hetero ene reaction.^{355,356} The carbonyl–ene reaction is often the dominant reaction with ethyl glyoxylate, and hydroxy esters are the main reaction products (Table 74, entries 1, 4, 5, and 7–10). Under the same conditions, ethyl glyoxylate 106b was found to react with a variety of 1,1-disubstituted alkenes 373. All of these had at

Table 86. Enantioselective Hetero Diels–Alder Cycloaddition Reactions of Azadienes 358 with 53³⁸²

entry	R	R ¹	R ²	yield (%)	exo/endo	exo-359 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(3S,4R,5S,6S)
4	Me	Ph	H	80	>99:1	93 (R)
5	Me	(E)-CMe=CHPh	Me	98	>99:1	90 (S)

Scheme 137

least one allylic hydrogen atom, and they afforded γ,δ -unsaturated α -hydroxy esters 374 (and sometimes 375) in excellent yields and enantioselectivities (Scheme 143, Table 92).^{399,400}

Some alkenes give only a single product (Table 92, entries 1, 2, and 11–17), some are asymmetrically disubstituted, and the reacting complex [catalyst-glyoxylate] must discriminate between two methylene groups (Table 92, entries 3–10). In these reactants the regioselective process favors hydrogen abstraction from the alkyl rather than the CH₂OR group. The attractive feature of the process is the enantioselectivity induced by the catalyst: [(S)-2/CuX₂] always gives the (S)-configuration products; [(S)-1/CuX₂] always provides the opposite enantiomer. This is the same behavior as already observed in Mukaiyama–Michael and hetero Diels–Alder reactions. Again, as illustrated in Figure 14, it can be rationalized by assuming that 106b coordinates to the catalyst giving rise to reacting complexes with the opposite distortion.

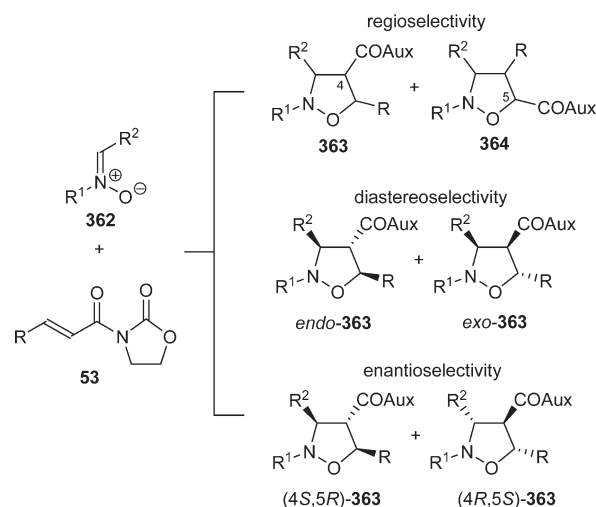
Some alkenes give rise to products with two chiral centers (376 and 377 in Scheme 144). In these cases usually both catalysts are anti-selective. Again [(S)-2/CuX₂] gives the (2S,3S)-products (Table 93, entries 1, 3, 7, and 9), and [(S)-1/CuX₂] affords their (2R,3R)-enantiomers (Table 93, entries 2, 4, 8, and 10). Cycloheptene, however, proves virtually unreactive.^{399,400,403} With 3-(cyclopentenyl)-trimethyl stannane 373 (R¹CH₂ = SnMe₃), the reaction is syn-selective, and this could prove to be a simple synthetic procedure for the formation of the other diastereoisomer (Table 93, entries 5 and 6).⁴⁰³

This protocol has some useful applications. The carbonyl–ene reaction that gives the product (2R,3R)-376 as described in Table 93 (entry 13) is the critical step which induces chirality in a novel synthesis of 3-branched uridine azido acid.⁴⁰⁴ The reaction of methyl glyoxylate with methyl (2S)-N-Boc-4-(phenylthio)allylglycinate 378, catalyzed by [(R)-1/Cu(OTf)₂], gives (2S,6S)-379 in 88% de (Scheme 145). This in turn is a key intermediate in the synthesis of *meso*-diaminopimelic acid, which is an essential constituent of the bacterial peptidoglycan.⁴⁰⁵

It is well-known that pyruvate esters 106c are less reactive than glyoxylates; nevertheless they react with the unactivated olefins

Table 87. Enantioselective Hetero Diels–Alder Reactions of Azadienes 360 with Ethyl Vinyl Ether³⁸³

entry	Ar ¹	Ar ²	yield (%)	endo/exo	endo ee (%) (conf.)
1	Ph	Ph	62	98:2	65 (2R,4S)
2	Ph	2-naphthyl	55	98:2	59 (2R,4S)
3	Ph	4-F-C ₆ H ₄	71	98:2	60 (2R,4S)
4	2-naphthyl	Ph	59	98:2	60 (2R,4S)
5	4-Cl-C ₆ H ₄	Ph	80	98:2	62 (2R,4S)
6	4-CF ₃ -C ₆ H ₄	Ph	87	98:2	65 (2R,4S)

Scheme 138

373 (methylene cyclopentane and -cyclohexane, 2-methylpropene, and α -methylstyrene). With [(S)-2/Cu(SbF₆)₂] they give (S)-380 in good yields (76–94%) and excellent enantioselectivities (98% ee) (Scheme 146).⁴⁰⁰

A carbonyl–ene reaction can be carried out between ethyl glyoxylate 106b and the (1-phenyl-vinyl)-carbamic acid benzyl ester 381, which behaves as an aza-enophile. An unusual feature of the reaction is that both the (S)-1 and (S)-2 complexes with Cu(OTf)₂ give the same product. (S)-382 is formed with good yields and enantioselectivities: 91% (31% ee) and 70% (73% ee), respectively (Scheme 147).⁴⁰⁶

The ene reaction is usually considered a [4 π + 2 σ]-pericyclic process. By changing the carbon atom for an oxygen atom of the glyoxylic ester 106b, this allows coordination with the [Cu/box] to give the activated hetero ene of a carbonyl ene reaction. As seen in Scheme 148, when the alkene is propene, it has been suggested that the transition state that leads to 374 is 383. DFT-PM3 calculations for this reaction, however, gave a different result.⁴⁰⁷ According to calculations the carbonyl–ene reaction should proceed by a stepwise mechanism through the open zwitterionic intermediate 384 and a 1,5-proton shift, which would lead to 374.

The intramolecular ene reaction was tested quite early using (E)-1-acetyl-3-[2-(3-methyl-2-butenyloxy)benzylidene]-2-oxindole 385 in a competition reaction in an intramolecular hetero Diels–Alder cycloaddition.⁴⁰⁸ The reaction afforded three contiguous chiral centers. Comparing (R)-1 and (S)-2 with Mg(ClO₄)₂ in terms of chemo-, diastereo-, and enantioselectivity, the best catalyst proved to

Table 88. Enantioselective 1,3-Dipolar Cycloadditions of Nitrone 362 ($R^2 = \text{Ph}$) with 53

entry	R	R^1	box	MX_n	additives	yield (%)	endo/exo	endo ee (%) (conf.) [exo ee %]	ref
1	H	Ph	(R)-1	MgI_2		quant. ^a	100:0	48 (3R,4S)	388
2	H	Ph	(R)-1	MgI_2	4 Å MS	quant. ^a	73:23	82 (3S,4R)	388
3	H	Ph	(R)-1	MgI_2	H_2O		90:10	36 (3R,4S)	388
4	H	Ph	(R)-1	MgI_2	$\text{Mg}(\text{SO}_4)_2$		96:4	52 (3R,4S)	388
5	H	Ph	(R)-1	MgI_2	CaSO_4		80:20	41 (3S,4R)	388
6	H	Ph	(R)-1	$\text{Mg}(\text{ClO}_4)_2$		quant. ^a	95:5	48 (3R,4S) ^b	114, 389, 390
7	H	Ph	(R)-1	$\text{Mg}(\text{ClO}_4)_2$	4 Å MS	quant. ^a	70:30	70 (3S,4R) ^b [70]	114, 389, 390
8	H	Ph	(R)-1	$\text{Mg}(\text{OTf})_2$		quant. ^a	97:3	86 (3R,4S) ^b	114, 389, 390
9	H	Ph	(R)-1	$\text{Co}(\text{ClO}_4)_2$		quant. ^a	90:10	47 (3R,4S) [40]	390
10	H	Ph	(R)-1	$\text{Co}(\text{ClO}_4)_2$	4 Å MS	quant. ^a	24:76	42 (3S,4R) [84]	390
11	H	Ph	(R)-1	$\text{Zn}(\text{ClO}_4)_2$	4 Å MS	quant. ^a	27:73	31 (3S,4R) [84]	114, 390
12	H	Ph	(R)-1	$\text{Ni}(\text{ClO}_4)_2$		quant. ^a	98:2	74 (3R,4S)	390
13	H	Ph	(R)-1	$\text{Ni}(\text{ClO}_4)_2$	4 Å MS	quant. ^c	72:28	85 (3S,4R) [85]	390
14	H	Ph	(R)-1	$\text{Mn}(\text{ClO}_4)_2$		quant. ^a	93:7	52 (3R,4S) [rac]	390
15	H	Ph	(R)-1	$\text{Mn}(\text{ClO}_4)_2$	4 Å MS	quant. ^d	48:52	14 (3S,4R) [26]	390
16	Me	Ph	(R)-1	MgI_2		73	97:3	46 (3R,4S,5R)	387, 388
17	Me	Ph	(R)-1	MgI_2	4 Å MS	72	96:4	79 (3S,4R,5S)	387, 388
18	Me	Ph	(R)-1	MgI_2	H_2O		97:3	50 (3R,4S,5R)	388
19	Me	Bn	(S)-1	MgI_2		82	89:11	racemate	387
20	Me	Ph	(S)-1	$\text{Mg}(\text{ClO}_4)_2$		>85	83:17	71 (3R,4S,5R)	325
21	Me	Ph	(S)-1	$\text{Mg}(\text{ClO}_4)_2$	flux ^e	>85	91:9	90 (3R,4S,5R)	325
22	Me	Ph	(S)-1	$\text{Co}(\text{ClO}_4)_2$		>85	75:25	53 (3R,4S,5R)	325
23	Me	Ph	(S)-1	$\text{Co}(\text{ClO}_4)_2$	flux ^e	>85	91:9	88 (3R,4S,5R)	325
24	n-Pr	Ph	(S)-1	MgI_2	4 Å MS	>95	53:47	82 [52]	387

^a Small amounts (>5%) of byproduct (regioisomers) determined by NMR. ^b The absolute configuration erroneously inverted in ref 389. ^c 12% of 272.

^d 22% of 272. ^e Flux is fluxional additive 2-benzoyl-5,5-dimethyl-1-naphthalen-2-ylmethyl-pyrazolidin-3-one.

be the former. It gave (3R,3'R,4'R)-386 in 67% yield and 30% ee (Scheme 149). These reaction conditions are not the most selective conditions, because [(4R,5R)-6b/Mg(ClO₄)₂] gives the same stereoisomer in 75% yield and 88% ee. Unfortunately, all the catalysts are required in stoichiometric amounts due to competition of the CO groups of the products with those of the reagent to behave as bidentate ligands with the magnesium ion.

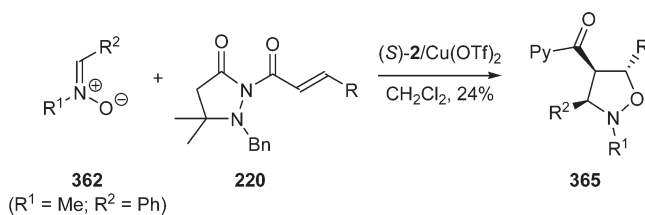
The same reaction conditions, using 2 equiv of [(R)-1/Mg-(ClO₄)₂], allowed the intramolecular ene reaction of 387, which gave 388 in 72% yield (Scheme 150). This is a key intermediate in the synthesis of (–)-α-kainic acid.⁴⁰⁹

As pointed out earlier, the two examples above required at least stoichiometric amounts of catalyst. However, the intramolecular carbonyl–ene reaction of the unsaturated α-ketoesters 389 proceeds under catalytic conditions in the presence of the Cu(OTf)₂ complex of 1 to give the optically active ene adduct 390 (Scheme 151, Table 94).⁴¹⁰ This is due to the presence of the α-keto functionality that can coordinate in a bidentate fashion.

It has been found that the ring closure reaction to form cyclohexane versus cyclopentane occurs with better selectivity (Table 94, entry 1 vs 2). Double-induction experiments demonstrated that (R)-389 is well-matched with [(S)-1/Cu(OTf)₂], because the enantiomeric catalyst lowers the enantioselectivity and leads to greater decrease in the diastereoselectivity (Table 94, entries 3 and 5 vs 4 and 6).

This section will conclude with an example of a catalytic asymmetric domino-Claisen rearrangement. In this reaction, although the chirality is induced in the first step, subsequently

Scheme 139



it is also usefully capitalized in the second step. Hence this reaction can be considered a paradigmatic bridge between this section and the following one. Starting from the achiral vinyl ether 391, catalysis with [(S)-1/Cu(OTf)₂] gives an excellent 98% yield of a mixture of two diastereoisomers in the ratio 89:11. The main product 393, which has three chiral centers, is obtained with an excellent 98% ee (Scheme 152).⁴¹¹ This cyclohexane derivative is formed as a result of a [box/Cu(II)]-catalyzed Claisen rearrangement, which gives (S)-392. Here the role of the Cu(II) is to coordinate 391 through its C=O and O groups. This has several points in common with the bidentate coordination of (benzyloxy)acetaldehyde shown in Scheme 29. Under the reaction conditions, the Claisen product 392 undergoes an intramolecular carbonyl–ene reaction, again catalyzed by the same catalyst, 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

Scheme 140

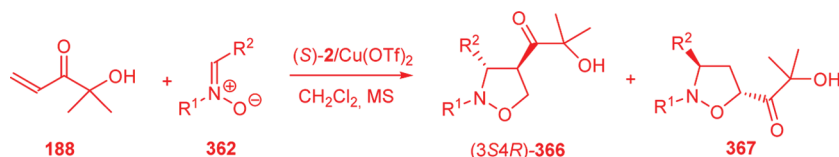


Table 89. Enantioselective 1,3-Dipolar Cycloadditions of Nitrones 362 with 4-Hydroxy-4-methylpent-1-en-3-one (188) Catalyzed by [(S)-2/Cu(OTf)₂]³⁹³

entry	R ¹	R ²	yield (%)	366/367	366 endo/exo	endo-366 ee (%) (conf.)
1	PhCH ₂	Ph	85	93:7	>98:2	94 (3S,4R)
2	PhCH ₂	4-MeOC ₆ H ₄	99	92:8	>98:2	92 (3S,4R)
3	PhCH ₂	4-MeC ₆ H ₄	81	92:8	>98:2	92 (3S,4R)
4	PhCH ₂	H	94	>98:2	>98:2	90 (3S,4R)
5	Me	Ph	55	90:10	>98:2	96 (3S,4R)
6	Ph	Ph	98	>98:2	76:24	>99 (3S,4R)

rearrangement. The intramolecular **carbonyl–ene reaction**, in this case, proceeds with complete diastereoselectivity to produce (1R,2R,5S)-393.

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 contributions of the papers dealing with this argument have already been discussed in previous sections: Diels–Alder, hetero Diels–Alder, 1,3-dipolar cycloaddition, ene, and hetero ene reactions. However, some other important topics related to pericyclic reactions deserve attention and hence will now be discussed.

[2 + 2]-Cycloadditions between ketenes and carbonyl compounds are discussed first. This is not only because these reactions satisfy the necessary conditions to be classified as pericyclic reactions but also because they are a useful route to the β-lactones. The [2 + 2]-cycloaddition between activated aldehydes or ketones **106b–d** and silylketenes **394**, catalyzed by Cu(II) complexes, is strongly diastereoselective, and **cis-395** are formed with up to >99% ee. The subsequent desilylation with KF allows the isolation of the final product **396** (Scheme 153, Table 95).⁴¹²

As is usual when dealing with α-dicarbonyl derivatives, [(S)-1/Cu(SbF₆)₂] and [(S)-2/Cu(SbF₆)₂] give the opposite enantiomers of **396** (Table 95, entry 1 vs 2). The best catalyst is [(S)-2/Cu(II)], which gives good yields and enantiomeric excesses with both ethyl glyoxylate **106b** (Table 95, entries 2–6) and different α-ketoesters **106c** (Table 95, entries 7–12). When this reaction is extended to α-diketones, **106d** not only gives excellent enantiomeric excess but the catalyst is able to discriminate between a methyl and an ethyl group (Table 95, entry 14).

Clearly, one important target of any enantioselective [2 + 2]-cycloaddition is the formation of the β-lactam ring. The reaction of aldimine **397** with the lithium ester enolates **398** could be an attractive route to forming **399** (Scheme 154). Enantioselective catalysis of the [2 + 2]-cycloaddition was tested with (S)-1 and (S)-2. However, it was found that, to achieve acceptable

enantioselectivities (75–80% ee), more than 2 equiv of box are required; the only box that gave the same result, but with 0.1–0.2 equiv, was (S)-3a.^{413,414}

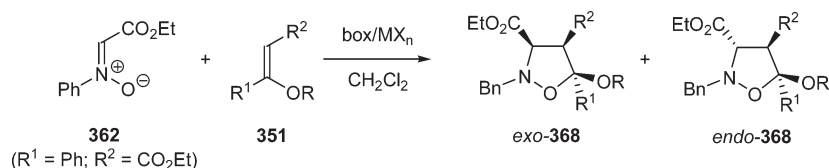
An unusual way to β-lactams is the reaction of diphenyl nitrone **362** (R¹ = R² = Ph) with phenylacetylene **400** (R = Ph). Although it is certainly not a pericyclic reaction (it has been christened the **Kinugasa reaction**), it can be catalyzed by [(S)-2/CuI₂]. In this case, to achieve a reasonable enantioselectivity (45% ee), a stoichiometric amount of the catalyst is required.⁴¹⁵ However, with the (R)-1 or (S)-2 complexes of Cu(ClO₄)₂, and in the presence of dicyclohexylamine, substoichiometric amounts of catalyst allow an enantioselective reaction. In spite of the fact that yields are low (~30%), it seems interesting to emphasize that two boxes with opposite configurations, (R)-1 and (S)-2, give 54% and 60% ee, respectively, of the same enantiomer (Scheme 155).⁴¹⁶

Methyl phenyl nitrone **362** (R¹ = Me, R² = Ph) reacts with dimethyl 1,1-cyclopropanedicarboxylate, under Lewis acid catalysis, to give dimethyl 2-methyl-3-phenyl-tetrahydro-1,2-oxazine-4,4-dicarboxylate. In an attempt to induce enantioselectivity, [(S)-2/Cu(OTf)₂] was tested. It failed to give a positive result, and the only active catalysts (47–75% yield, 34–37% ee) were obtained with **10a** and Cu(OTf)₂ or MgI₂.⁴¹⁷

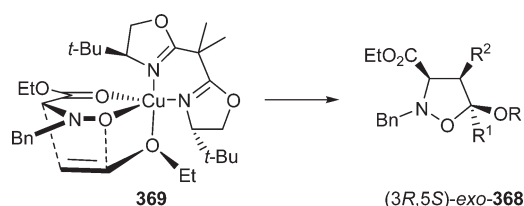
When [2 + 2]-cycloadditions involve a double and a triple carbon–carbon bond, these reactions hardly satisfy the necessary conditions to be classified as pericyclic reactions. Thus, 2-methoxycarbonyl-2-cyclopenten-1-one (**185**, R = H, n = 0) and phenylthioacetylene **400** (R = SPh) give 1-methylcarbonyl-2-oxo-7-(phenylthio)-bicyclo[3.2.0]hept-6-ene under catalysis with the [(S)-2/Cu(SbF₆)₂] complex, but the yield is only 20% and the ee is 32%.⁴¹⁸

A nice example of an enantioselective [4 + 3]-cycloaddition is the reaction of furan with 3-allenamide **402**. It must be epoxidized with dimethyldioxirane (DMDO) to achieve the nitrogen-stabilized oxyallyl cation **403**, the 2-π electron reagent that gives **404** (Scheme 156). 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 but with only 10% ee. However, better results using different boxes will be reported in the next section.⁴¹⁹

Scheme 141

Table 90. Enantioselective 1,3-Dipolar Cycloadditions of Nitrone 362 (R² = CO₂R) with Vinyl Ethers 351³⁹⁴

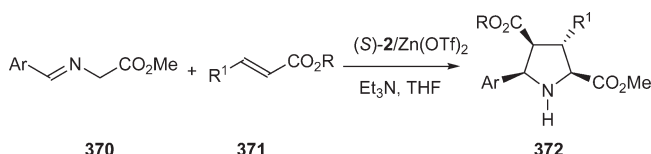
entry	R ¹	R ²	OR	box	MX _n	yield (%)	exo/endo	exo ee (%) (conf.)	endo ee (%)
1	H	H	OEt	(S)-2	Cu(OTf) ₂	93	84:16	89 (3R,5S)	35
2	H	H	OEt	(S)-2	Zn(OTf) ₂	73	66:34	62 (3R,5S)	0
3	H	H	OEt	(R)-1	Cu(OTf) ₂	86	43:57	44 (3R,5S)	0
4	H	H	OEt	(R)-1	Zn(OTf) ₂	79	46:54	62 (3S,5R)	0
5	Me	H	OMe	(S)-2	Cu(OTf) ₂	83	31:69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

Figure 18. Proposed pentacoordinated reactive intermediate **369** for the reaction between *N*-benzyl- α -ethoxycarbonylmethanimine *N*-oxide **362** and ethyl vinyl ether, catalyzed by [(*S*)-2/Cu(OTf)₂].³⁹⁴

The Nazarov cyclization is a cationic electrocyclic reaction of a divinyl ketone, which occurs, under acid (Lewis or protic) conditions, as a 4 π conrotatory process. Therefore, asymmetric induction can be achieved if the direction of the conrotation process is controlled. A second carbonyl group (ester or amide) in the α -position of **405** allows bidentate coordination to a [box/Cu(II)] catalyst to give the cationic intermediate **406**. Subsequently, this underwent the 4 π conrotatory ring closure and shift to form **407** (Scheme 157, Table 96).⁴²⁰ When **405** has an ester group, the catalyst is required in stoichiometric amounts (Table 96, entries 1 and 2). The absolute stereochemistry of **407** was determined as (*R,R*). With an amide group present, the reaction can be carried out with substoichiometric amounts of catalyst (Table 96, entries 3–6).

Recently an enantioselective tandem transformation via a Nazarov cyclization/electrophilic fluorination was accomplished. It employed **408**, which is the benzo-condensed analogue of the substrate shown in Scheme 117. The sequence, reported in Scheme 158, is a [(*R*)-1/Cu(OTf)₂]-catalyzed Nazarov conrotatory ring closure, which gives **410**. This in turn undergoes an electrophilic attack by a fluoro cation, furnished by *N*-fluorobenzenesulfonimide **409**, to give the enantiomerically enriched (2*S**,3*R**)-methyl 2-fluoro-2,3-dihydro-1-oxo-3-aryl-1*H*-indene-2-carboxylate **411**.⁴²¹ As seen from the few examples given in Table 97, the possible limit of this reaction is that it needs electron-donor substituents to favor the last electrophilic step, which in spite of this occurs with excellent diastereoselectivities and sometimes with excellent enantioselectivity. This is one of the few box-catalyzed tandem reactions; this is a field that might undergo further development in the future.

Scheme 142

Table 91. Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides Derived from *N*-Arylidene Glycinates **370** with Alkenes **371**³⁹⁸

entry	Ar	R ¹	R	yield (%)	ee (%) (conf.)
1	Ph	H	Me	80	88
2	2-Naph	H	Me	84	91
3	2-Naph	H	Et	76	68
4	2-Naph	H	<i>t</i> -Bu	12	<5
5	<i>p</i> -BrC ₆ H ₄	H	Me	89	94
6	Ph	CO ₂ Me	Me	78	76
7	2-Naph	CO ₂ Me	Me	84	90 (2 <i>S</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)
8	<i>p</i> -BrC ₆ H ₄	CO ₂ Me	Me	87	68

A classic electrocyclic reaction is the [3,3]-sigmatropic Claisen rearrangement performed with allyl vinyl ethers. These become substrates for enantioselective catalysis when they are 2-alkoxycarbonyl-substituted (**412**) and reacted with [box/CuX₂] catalysts. They afford optically active **413** compounds (Scheme 159, Table 98).^{422–424}

The configuration of **413** depends on both the nature of the catalyst—[(*S*)-1/Cu(OTf)₂] and [(*S*)-2/Cu(OTf)₂] give opposite enantiomers (Table 98, entries 1 and 7 vs 2 and 8)—and on the configuration (*Z*) or (*E*) of the double bond (Table 98, entry 2 vs 3). The importance of the ester group in promoting the formation of the reacting intermediate **414** and of the (*Z*)-double bond to induce enantioselectivity (in this case (*S*)-**413**, Table 98, entries 2 and 8) is illustrated in Scheme 159.

A thorough study was undertaken to provide evidence of the relationship between the configuration of both double bonds of

Scheme 143

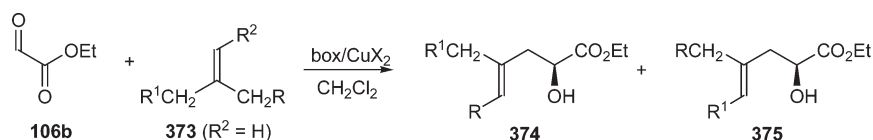


Table 92. Enantioselective Carbonyl–Ene Reactions of Ethyl Glyoxylate 106b with 1,1-Disubstituted Alkenes 373

entry	R	CH ₂ R ¹	box	CuX ₂	yield (%)	374/375	374 ee (%) (conf.)	ref
1	H	Me	(S)-2	Cu(SbF ₆) ₂ ·2H ₂ O	83		96 (S)	399, 400
2	H	Me	(S)-1	Cu(OTf) ₂	92		92 (R)	399, 400
3	H	Et	(S)-2	Cu(SbF ₆) ₂ ·2H ₂ O	78	55:45	84 (S)	399, 400
4	H	Et	(S)-1	Cu(OTf) ₂	91	67:33	90 (R)	399, 400
5	H	C ₅ H ₁₁	(S)-2	Cu(SbF ₆) ₂ ·2H ₂ O	89	74:26	96 (S)	399, 400
6	H	C ₅ H ₁₁	(S)-1	Cu(OTf) ₂	81	90:10	91 (R)	399, 400
7	H	CH ₂ OTBDPS	(S)-2	Cu(SbF ₆) ₂ ·2H ₂ O	72	>99:1	96 (S)	399, 400
8	H	CH ₂ OTBDPS	(S)-1	Cu(OTf) ₂	85	>99:1	91 (R)	399–401
9	H	CH ₂ OBn	(S)-2	Cu(SbF ₆) ₂ ·2H ₂ O	62	>99:1	98 (S)	399, 400
10	H	CH ₂ OBn	(S)-1	Cu(OTf) ₂	88	>99:1	92 (R)	399–402
11	H	Ph	(S)-2	Cu(SbF ₆) ₂ ·2H ₂ O	97		93 (S)	399, 400
12	H	Ph	(S)-1	Cu(OTf) ₂	99		89 (R)	399–401
13	C ₃ H ₇	H	(S)-2	Cu(SbF ₆) ₂	96 (E)		92 (S)	399, 400
14		CH ₂ CH ₂	(S)-2	Cu(SbF ₆) ₂ ·2H ₂ O	95		96 (S)	399, 400
15		CH ₂ CH ₂	(S)-1	Cu(OTf) ₂	97		76 (R)	399, 400
16		CH ₂ CH ₂ CH ₂	(S)-2	Cu(SbF ₆) ₂ ·2H ₂ O	90		97 (S)	399, 400
17		CH ₂ CH ₂ CH ₂	(S)-1	Cu(OTf) ₂	99		87 (R)	399–401

Scheme 144

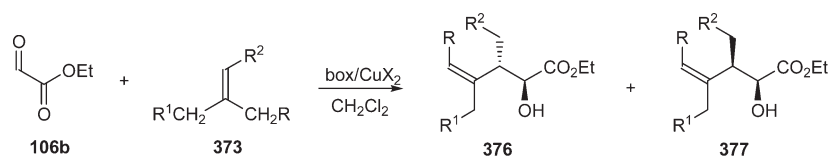


Table 93. Carbonyl–Ene Reactions of Ethyl Glyoxylate 106b with 1,1,2-Trisubstituted Alkenes 373

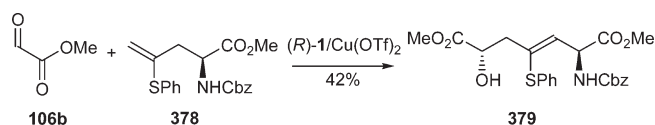
entry	CH ₂ R ¹	R	R ²	box	CuX ₂	yield (%)	376/377	376 ee (%) (conf.)	377 ee (%) (conf.)	ref
1	H	H	Me	(S)-2	Cu(SbF ₆) ₂	54	40:60	98 (2S,3S)	n.d.	400
2	H	H	Me	(S)-1	Cu(OTf) ₂	60	88:12	90 (2R,3R)	n.d.	400
3	H	CH ₂ CH ₂		(S)-2	Cu(SbF ₆) ₂	83	66:33	96 (2S,3S)	n.d.	400
4	H	CH ₂ CH ₂		(S)-1	Cu(SbF ₆) ₂	72	73:27	78 (2R,3R)	n.d.	400
5	H	CH ₂ CH ₂		(R)-1	Cu(OTf) ₂	56	88:12	92 (2S,3S)	87 (2S,3R)	403
6	SnMe ₃	CH ₂ CH ₂		(R)-1	Cu(OTf) ₂	99	30:70	81 (2S,3S)	43 (2S,3R)	403
7	H	CH ₂ CH ₂ CH ₂		(S)-2	Cu(SbF ₆) ₂	95	86:14	98 (2S,3S)	n.d.	399,400
8	H	CH ₂ CH ₂ CH ₂		(S)-1	Cu(OTf) ₂	70	95:5	94 (2R,3R)	n.d.	399,400
9	Me	CH ₂ CH ₂ CH ₂		(S)-2	Cu(SbF ₆) ₂ ·2H ₂ O	86	78:22	98 (2S,3S)	n.d.	400
10	Me	CH ₂ CH ₂ CH ₂		(S)-1	Cu(OTf) ₂	86	89:11	92 (2R,3R)	n.d.	400
11	H	CH ₂ CH ₂ CH ₂ CH ₂		(S)-2	Cu(SbF ₆) ₂	<30				400
12	H	CH ₂ CH ₂ CH ₂ CH ₂		(S)-1	Cu(SbF ₆) ₂	<30				400
13	H	CH ₂ OTBDPS	H	(S)-1	Cu(SbF ₆) ₂	70		90 (2R,3R)		404

the starting vinyl allyl ether (415) and the configuration of the product (416). The latter is a pair of diastereoisomers (syn/anti), and each of these is also a pair of enantiomers (Scheme 160, Table 99).^{422–424}

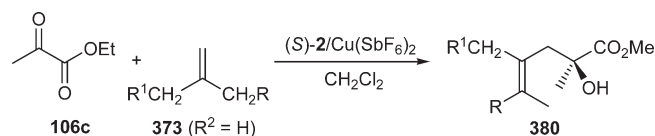
Two pairs of four stereoisomers each (Table 99, entries 1–4 and 5–8) were subjected to a [3,3]-Claisen rearrangement. The same catalyst was used in each case. The choice was made from a wide range to have two homogeneous comparable series. For the

first series, [(S)-1/Cu(OTf)₂] was used (Table 99, entries 1–4), and in the case of the second series, [(S)-2/Cu(SbF₆)₂·2H₂O] was used as seen in Table 99 (entries 5–6). The result was a relationship between the configuration of 415, syn/anti diastereoselectivity (except entry 7, Table 99), and the enantioselectivity, which resulted in the formation of the opposite enantiomers for each pair of isomers (Table 99, entries 1 and 5, 2 and 6, 3 and 7, and 4 and 8). Thus, it is found

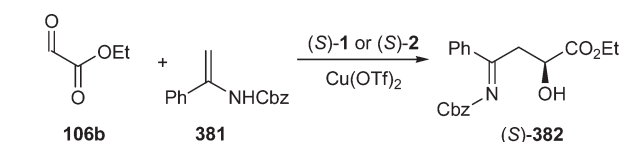
Scheme 145



Scheme 146



Scheme 147



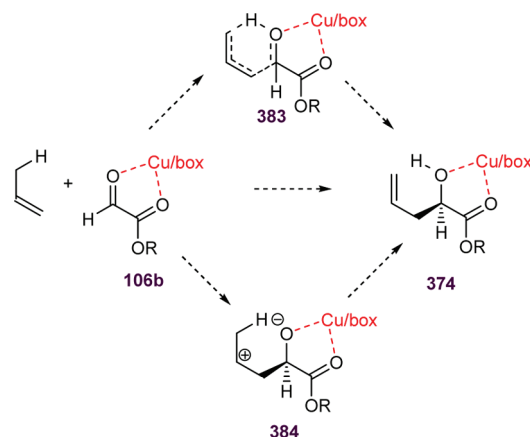
that once again the (S)-1- and (S)-2-copper catalysts afford opposite enantiomers.

A catalytic asymmetric Claisen rearrangement was the key starting step of the enantioselective synthesis of the C8–C20 fragment of curvicolide C, which is an antifungal polyketide isolated from the fermentation mixture of *Podospira curvicolli*. The [(S)-2/Cu(SbF₆)₂]-catalyzed rearrangement of (Z,Z)-417 (in 4.5 g scale) gives (3S,4R)-methyl 4-[(benzyloxy)methyl]-3-methyl-2-oxohex-5-enoate 418 in 98% yield, >90% de, and 99% ee (Scheme 161).⁴²⁵

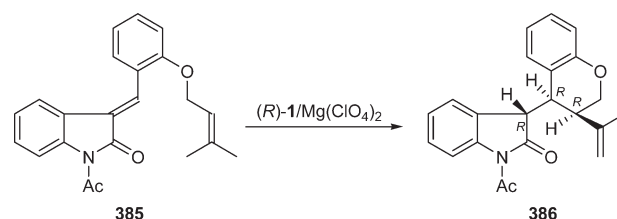
When one double bond of the [3,3]-Claisen rearrangement is substituted with a heteroatom having a lone pair of electrons, the substrate is rendered suitable for undergoing a [2,3]-sigmatropic rearrangement. If an allyl ether reacts with a strong base (*t*-BuLi) to give an α -oxycarbanion, then the reaction is known as a [2,3]-Wittig rearrangement. If this is to be enantioselectively catalyzed by a box catalyst, then it 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 419, which gives diastereo- and enantioselectively *syn*-420 with (S)-2 and *t*-BuLi ((S)-1 is inactive). It should be noted, however, that the chemical yield was very low (Scheme 162).⁴²⁶

One strong limitation of the enantioselective [2,3]-Wittig rearrangement as performed on substituted benzyl butenyl ethers 421 to lead to the synthesis of (1R,2S)-5-substituted-2-methyl-3-methylene-1-arylpentan-1-ol 422 (Scheme 163) is the amount of (S)-2 box required. Five equiv of box and 10 equiv of *t*-BuLi are needed.^{427,428} Despite the intrinsic high cost of the process, the reaction is interesting. Table 100 shows the many options related to changes in R, and the optimization of the solvent (Table 100, entries 1–8). Concerning the nature of Ar, an unsubstituted phenyl (entry 5) was found to give excellent results, but the enantioselectivity suffered as a result of the presence of a 2-methoxy substituent on the aryl group (Table 100, entries 10, 13, and 14).

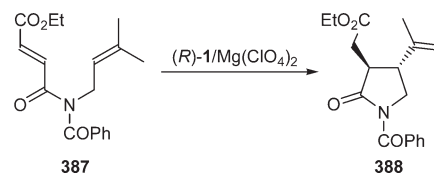
Scheme 148



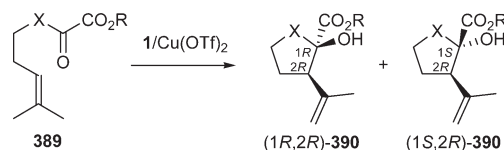
Scheme 149



Scheme 150



Scheme 151

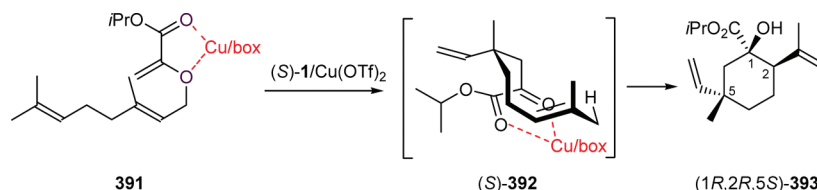


A great variety of [2,3]-sigmatropic rearrangements involving iodonium, oxonium, and sulfur ylides are reported in the literature. These are generated by the catalytic decomposition of a diazo compound with a copper cation. In the case of the enantioselective version, this becomes the cation coordinating 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)₄PF₆]-catalyzed reaction between allyl iodides 423 and ethyl diazoacetate 30. This involves the box-coordinated iodonium ylide 424, which affords 425 (R = H, 62% yield, 69% ee; R = Me, 67% yield, 37% ee) (Scheme 164).⁴²⁹

Table 94. Enantioselective Intramolecular Carbonyl–Ene Reaction of 389⁴¹⁰

entry	R	X	1 (conf)	yield (%)	(<i>R,R</i>)-390/(<i>S,R</i>)-390	(<i>R,R</i>)-390 ee (%)
1	Et	CH ₂ CH ₂	(<i>S</i>)	81	>99:1	91
2	Et	CH ₂	(<i>S</i>)	92	98:2	71
3	Me	(<i>R</i>)-CHMe	(<i>S</i>)	95	96:4	97
4	Me	(<i>R</i>)-CHMe	(<i>R</i>)	92	58:42	87
5	Bn	(<i>R</i>)-CHMe	(<i>S</i>)	97	97:3	99
6	Bn	(<i>R</i>)-CHMe	(<i>R</i>)	93	58:42	98

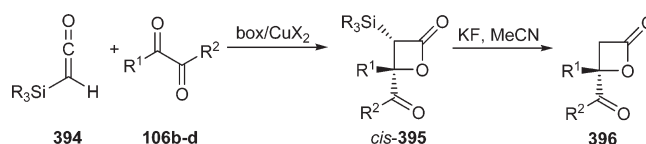
Scheme 152

The same conceptual approach is the basis of the intramolecular reaction of **426** with [(*S*)-2/Cu(MeCN)₄PF₆]. In this case decomposition of the diazogroup is induced, which leads to generation of the ylide that is coordinated by the box complex. Subsequently there is enantioselective formation of the oxonium ylide, which then undergoes a stereocontrolled internal [2,3]-sigmatropic rearrangement to form **427**. This is found to be cis-stereoisomer only and is formed in 35% yield with 65% ee (Scheme 165).⁴²⁹

The ylide **429** coordinated to the box is obtained by the copper-catalyzed decomposition of the diazoesters **428** (R² = OMe or OEt) and reacts with the allyl sulfides **430**. The intermediate sulfur ylides undergo an asymmetric [box/CuX]-catalyzed [2,3]-sigmatropic rearrangement to afford the alkyl- and aryl-substituted allyl sulfides **431** (Scheme 166, Table 101).^{430,431}

The catalyst derived from (*S*)-2 gives a better enantioselectivity than that based on (*S*)-1. Results show that this is independent of the nature of the copper salt (Table 101, entries 3, 5, and 8 vs 4, 6, and 9). Moderately high enantioselectivities are obtained with aryldiazoacetate (Table 101, entries 7, 8, and 10), but the best enantioselectivity was obtained with methyl 1-naphthyl diazoacetate (78% ee). The absolute configuration of the diphenyl-substituted methylester (Table 101, entry 7) is (*R*)-**431**.⁴³¹ The same reaction was accomplished using the diazoamides **428** (R¹ = Ph, R² = (1*S*)-camphorsultam) and **430** (R = 2-Cl-C₆H₄) with the (*S*)-1 and (*S*)-2 complexes of Cu(MeCN)(PF₆).⁴³² Although the best reaction catalyst does not actually fall within the limits of this review, the results for the boxes are reported in Table 101 (entries 11 and 12) because (*R*)-**431** is obtained in such good yield and with ee >85%.

Applications of this reaction to more complicated structures such as the reaction of 2-thioindoles with substituted vinyl diazoacetates catalyzed by (*S*)-2 and CuPF₆ gave low yields of the rearrangement products with negligible enantioselectivity.⁴³³ A different result was realized when the reaction described above was carried out between the diazoacetates **428** and the aryl propargyl sulfides **432**. Here, using both catalysts (*S*)-1 or (*S*)-2 and CuPF₆, the allenic derivatives **433** were formed as a result of a [2,3]-sigmatropic rearrangement of the intermediate sulfur

Scheme 153

ylides (Scheme 167). The enantioselectivity with the second catalyst was as high as 81% ee.⁴³⁴

A [(*R*)-1/CuOTf]-catalyzed imidation of the sulfides or selenides **434a,b** with [*N*-(*p*-tolylsulfonfyl)imino]-phenyliodine **435** affords the intermediate chiral allylic sulfides or selenides (**436a,b**). Here the nitrogen atom lone pair electrons are suitably placed for involvement in the enantioselective [2,3]-sigmatropic rearrangement that gives rise to either allyl sulfonamides or selenamides **437a,b**, respectively (Scheme 168).^{435–437} The reaction with the allyl sulfides **434a** (R = Me, Ph; R¹ = Ar) affords **437a** with yields of 30–80% and enantioselectivities in the range of 25–58% ee.^{435,436} In the case of the aryl cinnamyl selenides **434b**, the yields of **437b** were again in the range of 35–71%, but the enantiomeric excesses were poor (17–30% ee).⁴³⁷

4.12. Desymmetrization of meso-Derivatives and Kinetic Resolution of Racemates

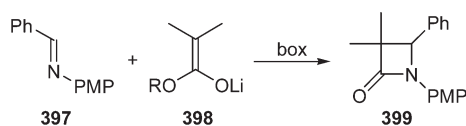
In the previous 2006 review, this section did not exist. However, the first part of that review that concerned Ph and *t*-Bu-box concluded with the following paragraph. “To finish this section and to evidence the unknown possibilities of the box-based catalysis, an unusual reaction has been recently described. A racemic mixture of (*S,S*)- and (*R,R*)-hydroxybenzoin **438** is treated with 0.5 mol PhCOCl and diisopropylethylamine (DIPEA) in the presence of 5% mol [(*R*)-1/CuCl₂]: 48% of (*S,S*)-**438** is selectively monobenzoylelated to give (*S,S*)-**439** in >99% ee and the (*R,R*)-**438** can be recovered as pure enantiomer (Scheme 169).⁴³⁸ The kinetic resolution of other 1,2-diols has been similarly performed.” In the intervening years this is no longer an unusual reaction, and several examples demonstrate the real potential of box complexes in kinetic resolutions.

Table 95. Enantioselective Cycloaddition Reactions between 106b–d and Silylketenes 394⁴¹²

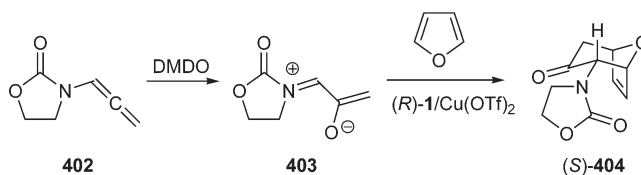
entry	R ₃	R ¹	R ²	solvent	box	CuX ₂	yield (%)	cis-395/trans-395	396 ee (%) (conf.)
1	Me ₃	H	OEt	CH ₂ Cl ₂	(S)-1	Cu(SbF ₆) ₂	>99	88:12	17 (R)
2	Me ₃	H	OEt	CH ₂ Cl ₂	(S)-2	Cu(SbF ₆) ₂	86	91:9	69 (S)
3	Me ₃	H	OEt	CH ₂ Cl ₂	(S)-2	Cu(OTf) ₂	93	n.d.	77 (S)
4	Me ₃	H	OEt	THF	(S)-2	Cu(OTf) ₂	>99	95:5	95 (S)
5	Me ₃	H	OEt	THF	(S)-2	Cu(OTf) ₂ · 2H ₂ O	77	91:9	93 (S)
6	Ph ₃ Me ₂	H	OEt	THF	(S)-2	Cu(OTf) ₂	>99	>95:5	92 (S)
7	Me ₃	Me	OMe	CH ₂ Cl ₂	(S)-2	Cu(SbF ₆) ₂	>99	n.r.	95 (S)
8	Me ₃	Et	OMe	CH ₂ Cl ₂	(S)-2	Cu(SbF ₆) ₂	92	n.r.	99 (S)
9	Me ₃	<i>i</i> -Bu	OMe	CH ₂ Cl ₂	(S)-2	Cu(SbF ₆) ₂	87	n.r.	83 (S)
10	Me ₃	<i>i</i> -Pr	OEt	CH ₂ Cl ₂	(S)-2	Cu(SbF ₆) ₂	86	n.r.	85 (S)
11	Me ₃	Ph	OMe	CH ₂ Cl ₂	(S)-2	Cu(SbF ₆) ₂	79	n.r.	87 (S)
12	Me ₃	CH ₂ Br	OEt	CH ₂ Cl ₂	(S)-2	Cu(SbF ₆) ₂	>99	n.r.	91 (S)
13	Me ₃	Me	Me	CH ₂ Cl ₂	(S)-2	Cu(SbF ₆) ₂	95	n.r.	>99 (S)
14	Me ₃	Me	Et	CH ₂ Cl ₂	(S)-2	Cu(SbF ₆) ₂	95 ^a	n.r.	85 (S)

^aTwo regioisomers in the ratio 95:5.

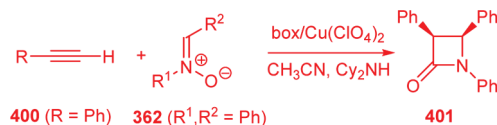
Scheme 154



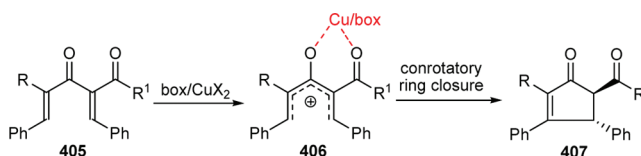
Scheme 156



Scheme 155



Scheme 157



The same kinetic resolution, performed with 1 mol % [(S)-1/CuCl₂], gave (*R,R*)-439 in 96% ee and (*S,S*)-438 in 95% ee.⁴³⁹

If the same method using [(*R*)-1/CuCl₂] as catalyst is applied to cyclic and acyclic *meso*-438, but with 1.0 mol of PhCOCl, up to quantitative yields of monobenzoylated (1*R*,2*S*)-440 products are obtained, with ee's in the range 58–97%. Hence, this is an excellent route for the desymmetrization of 1,2-diols with the exception of the five-membered ring derivatives (Table 102, entries 4, 8, and 9) (Scheme 170).^{438,440}

Asymmetric desymmetrization of *meso*-*vic*-diols 438 can be achieved by carbamoylation with 1 equiv of isocyanate and catalyzed by [(S)-1/Cu(OTf)₂] without the use of base. The resulting enantioselectivities of 441 (Scheme 170) were found to be up to 93% ee with acyclic and cyclic diols.⁴⁴¹ The method was successfully applied and gave the same results using tosylation. In this case [(*R*)-1/Cu(OTf)₂] was the catalyst, and enantioselectivities of up to >99% ee were obtained.⁴⁴² Some outstanding results, which were obtained using the methods illustrated in Scheme 170, are reported in Table 102.

To a certain extent the asymmetric desymmetrization of *meso*-*vic*-diols can also be realized by oxidation. Hence, *meso*-438 (R, R¹ = Ph) with *N*-bromosuccinimide (NBS), under the conditions reported in Scheme 170, gives the α-ketoalcohol (*R*)-443 in 83% yield and 72% ee together with a 17% yield of diketone 444.⁴⁴³

Enantioselective desymmetrization of 2,2-disubstituted *meso*-1,3-diols 445 with [box/Cu(II)] complexes, benzoyl chloride,

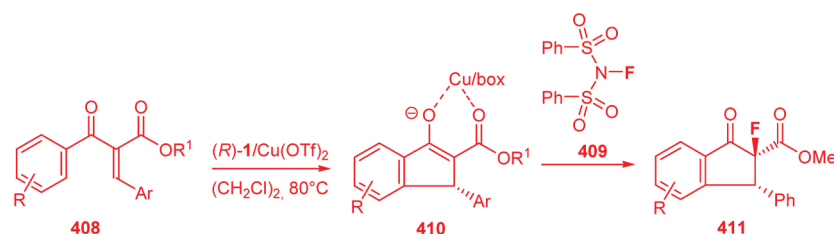
Table 96. Nazarov Cyclizations of 405⁴²⁰

entry	R	R ¹	box	CuX ₂	cat.	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

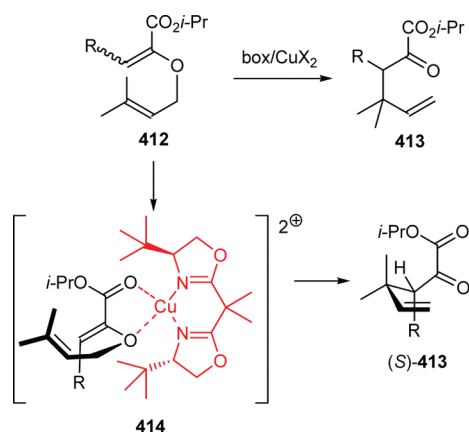
and triethylamine can also be accomplished. The results for some significant substituents are reported in Table 103. From the data shown it is seen that, even if 1 did not prove the best box, nevertheless it was by far better than box 2 (Table 103, entries 1 and 7 vs 2 and 8).^{444–446}

The above results are clear evidence that within a period of only five years what was “an unusual reaction” catalyzed by [box/Cu(II)] complexes became an important tool for solving the transformation of prochiral compounds into useful synthons having a stereogenic center. It is also true that the early resolution of the racemic 1,2-diols reported in Scheme 169 heralded a new chapter in resolution, and several racemates have been kinetically

Scheme 158



Scheme 159



resolved using only 1/2 equiv of a functionalizing reagent and a [box/Cu(II)] catalyst.

Methyl 2-hydroxy-2-phenylacetate does not react with *p*-tosyl chloride (*p*-TsCl) in the presence of [(*R*)-1/Cu(OTf)₂].⁴⁴⁷ On the contrary, the analogous 2-phenyl-2-hydroxyamides **447** (*R* = Ph, *n* = 0) and the homologous 3-hydroxyalkanamides **447** (*R* = alkyl, *n* = 1) undergo kinetic resolution to give (*S*)-**448** with yields close to the theoretical 50% and good or excellent enantioselectivities. In addition, excellent yields of recovered (*R*)-**447** are obtained (Scheme 172). After optimization of reagent, solvent, and base, the use of *p*-tosyl chloride, acetonitrile, and K₂CO₃ proved the best conditions for the former, whereas the latter resolution required benzoyl chloride, ethyl acetate, and K₂CO₃. The outstanding results reported in Table 104 illustrate the variety of either acyl or at the amino residue substituents conceivable using this protocol.^{447,448}

Other racemic molecules have also been kinetically resolved using [(*R*)-1/Cu(OTf)₂] as the catalyst: (DL)- α -hydroxyalkanephosphonates **449** give benzoylated (*R*)-**450** and (*S*)-**449**,⁴⁴⁹ and (DL)-aminoaldehydes **451** that undergo an interesting kinetic resolution involving oxidation with *N*-iodosuccinimide (NIS) in methanol, to give the (*R*)-aminoester **452** and the aldehyde dimethylacetal (*S*)-**453** (Scheme 173).⁴⁵⁰

An interesting exception is the use of [(*S*)-2/Cu(OTf)₂] instead of the box 1-based complex in the selective carbamoylation of racemic α -hydroxy- γ -lactones **454** with 1/2 equiv of *n*-propyl isocyanate. This particular enantiomeric differentiation is extremely efficient. It results in a stereoselectivity factor ($s = k_{\text{fast}}/k_{\text{slow}}$) of up to 209 that gives the (*R*)-**454** and the carbamoyl derivative (*S*)-**455**.

Table 97. Tandem Nazarov Cyclization/Electrophilic Fluorinations of **408**⁴²¹

entry	R	Ar	R ¹	yield (%)	trans/cis	411 ee (%)
1	3,4-OCH ₂ O	2-MeO-C ₆ H ₄	Me	69	95:5	44
2	3,4-OCH ₂ O	2,4,6-(MeO) ₃ -C ₆ H ₂	Me	80	>98:2	96
3	2,3(OMe) ₂	2,4,6-(MeO) ₃ -C ₆ H ₂	Et	60	>98:2	71

The substrate/catalyst molar ratio is 2000–3000 (Scheme 174, Table 105). The nature and position of the substituents *R* play a fundamentally important role in the enantioselectivity of the reaction (Table 105, entries 4–7).⁴⁵¹

Although an attempt at performing the desymmetrization of prochiral compounds leading to the kinetic resolution of racemates using electrochemical methods and [box/Cu(II)] complexes as catalysts has been reported, from the results it appears that any advantage of this protocol is at the moment questionable.^{452,453}

4.13. Polymerizations

A recently, rather unexpected, use of boxes is their application as ligands in asymmetric polymerization reactions. A range of processes have been reported for the syntheses of optically active polymers: Among them is an example of a reaction where an organolithium initiator in the presence of a chiral ligand has been shown to induce an asymmetric anionic polymerization. This protocol has been recently applied to the polymerization of 7-cyano-7-ethoxycarbonyl-1,4-benzoquinone methide **456** initiated by [(*S*)-1/*i*-PrPhOLi] at –78 °C and terminated by the addition of acetic anhydride (Scheme 175).⁴⁵⁴ The polymer **457**, obtained under these conditions, has the largest specific rotation ([α]₄₃₅ = +90.4) of any of those obtained using other chiral ligands.

The asymmetric oxidative coupling polymerization (AOCP) of 2,3-dihydroxynaphthalene **458** (DHN) with [box/Lewis acid] complexes, under an O₂ atmosphere, has been shown to yield **459** [poly(DHN)] which has a continuous acylated 1,1'-bi-2,2'-naphthol main chain structure derived from 10–70 monomers (Scheme 176, Table 106).^{455,456} The final product was obtained after quenching with acetyl chloride and pyridine. The values of [α]_D that are reported in Table 106 give a rough indication of the degree of asymmetry induced in the polymer. These suggest not only that the best catalyst is [(*S*)-1/VOSO₄] but also that the enantioselectivities induced by this catalyst are much higher than those observed for any of the previously reported catalysts.⁴⁵⁷

With a view to estimating the stereoselectivity during the polymerization, model AOCP reactions were performed on three different 3-substituted 2-naphthols **458** (*R* = Bn, Me,

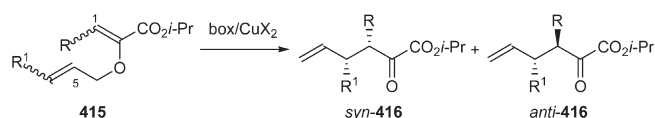
Table 98. Catalytic Enantioselective Claisen Rearrangements of (Z) or (E)-412^{422–424}

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 ₂ O	62	46 (S)
10	CH ₂ OTPS	E	(S)-2	Cu(SbF ₆) ₂ 2H ₂ O	98 ^a	99 (S)

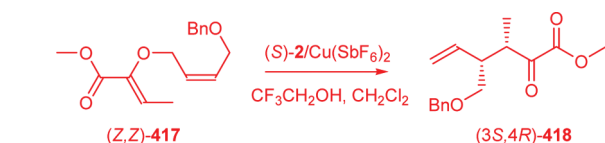
^a 4 Å MS as additive.Table 99. Catalytic Enantioselective Claisen Rearrangements of the Four Stereoisomers of 415^{422–424}

entry	R	R ¹	config.	box	CuX ₂	yield (%)	syn/anti	syn ee (%) (conf.)	anti ee (%) (conf.)
1	Me	<i>n</i> -Pr	1Z,5Z	(S)-1	Cu(OTf) ₂	98	99:1	84 (3R,4S)	
2	Me	<i>n</i> -Pr	1E,5Z	(S)-1	Cu(OTf) ₂	99	3:97		88 (3S,4S)
3	Me	<i>n</i> -Pr	1Z,5E	(S)-1	Cu(OTf) ₂	100	28:72		72 (3R,4R)
4	Me	<i>n</i> -Pr	1E,5E	(S)-1	Cu(OTf) ₂	100	86:14	82 (3S,4R)	
5	CH ₂ OBn	CH ₂ OTPS	1Z,5Z	(S)-2	Cu(SbF ₆) ₂ 2H ₂ O	99	99:1	98 (3R,4R)	
6	CH ₂ OBn	CH ₂ OTPS	1E,5Z	(S)-2	Cu(SbF ₆) ₂ 2H ₂ O	97	14:86	98 (3S,4S)	98 (3S,4R)
7	CH ₂ OBn	CH ₂ OTPS	1Z,5E	(S)-2	Cu(SbF ₆) ₂ 2H ₂ O	98	63:37	99 (3R,4R)	95 (3R,4S)
8	CH ₂ OBn	CH ₂ OTPS	1E,5E	(S)-2	Cu(SbF ₆) ₂ 2H ₂ O	99	89:11	94 (3S,4S)	

Scheme 160



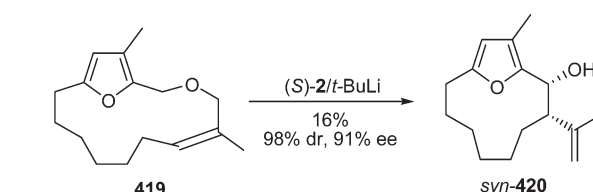
Scheme 161



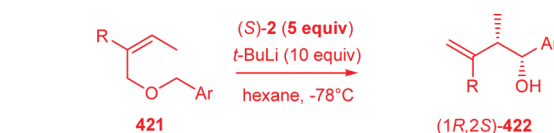
CH₂OCH₃). Using [(S)-1/CuCl] as the catalyst, (S)-3,3'-alkoxy-1,1'-binaphthalene-2,2'-diols **460** were always obtained (Scheme 177) with ees in the range 43–71% (Table 106, entries 7–9).⁴⁵⁷

The AOCPP reaction was subsequently performed on either the racemic or (S)-2,2'-methoxymethyl-1,1'-binaphthalene-3,3'-diols **461** (R = CH₂OCH₃). Using [(S)-1 or (R)-1/CuCl] complexes, under an O₂ atmosphere, the polymers **462** (R = CH₂OCH₃), with a number-average molecular weight of about 3 × 10³, were obtained (Scheme 178). From the enantioselectivities induced in the reaction as reported in Table 106 (entry 9), the polymers described in Table 107 (entries 2 and 3) consist of optically pure binaphthol units connected by a bond with the preferential (S)-configuration.

Scheme 162



Scheme 163



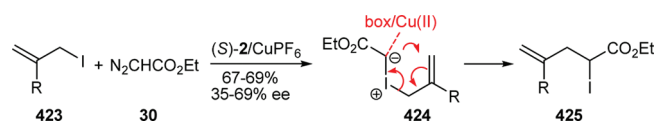
The higher stereoselectivity was obtained with the catalyst derived from (S)-1.⁴⁵⁷

An analogous and more detailed result was obtained by studying the AOCPP reactions of *rac*-(S)- and *rac*-(R)-2,2'-methoxy-1,1'-binaphthalene-3,3'-diols (**461**, R = Me). They were catalyzed by [(S)-1/CuCl] or [(R)-1/CuCl] complexes (Scheme 178), and both the estimated stereochemistry of the newly formed C–C bond (*S*:*R*) in the polymers **462** and the [α]_D values reported in Table 107 (entries 4–8) suggest that the reactions of (R)- and (S)-**461** with [(S)-1/CuCl] afford polymers with preferential (...SSSS...) and (...RSRS...) chain structures, respectively (Table 107, entries 5 and 6).^{458,459}

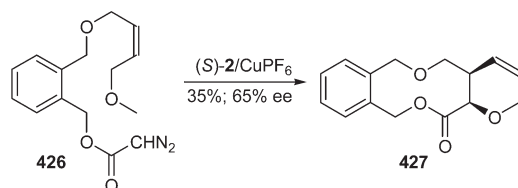
Table 100. Enantioselective [2,3]-Wittig Rearrangements of Aryl Butenyl Ethers 421

entry	Ar	R	solvent	yield (%)	ee (%) (conf.)	ref
1	Ph	H	hexane	63	38	428
2	Ph	Me	hexane	76	63	428
3	Ph	CH ₂ OMe	hexane	11	29	428
4	Ph	CH ₂ OTBS	hexane	18	91	428
5	Ph	CH ₂ OTIPS	hexane	65	98 (1 <i>R</i> ,2 <i>S</i>)	427, 428
6	4-MeO-C ₆ H ₄	CH ₂ OTIPS	THF	35	racemate	428
7	4-MeO-C ₆ H ₄	CH ₂ OTIPS	toluene	34	96 (1 <i>R</i> ,2 <i>S</i>)	428
8	4-MeO-C ₆ H ₄	CH ₂ OTIPS	hexane	34	98 (1 <i>R</i> ,2 <i>S</i>)	427, 428
9	3-MeO-C ₆ H ₄	CH ₂ OTIPS	hexane	75	95 (1 <i>R</i> ,2 <i>S</i>)	427, 428
10	2-MeO-C ₆ H ₄	CH ₂ OTIPS	hexane	73	8 (1 <i>R</i> ,2 <i>S</i>)	427, 428
11	3,4-(MeO) ₂ -C ₆ H ₃	CH ₂ OTIPS	hexane	32	87 (1 <i>R</i> ,2 <i>S</i>)	427, 428
12	3,5-(MeO) ₂ -C ₆ H ₃	CH ₂ OTIPS	hexane	72	85 (1 <i>R</i> ,2 <i>S</i>)	427, 428
13	2,3-(MeO) ₂ -C ₆ H ₃	CH ₂ OTIPS	hexane	58	17 (1 <i>R</i> ,2 <i>S</i>)	427, 428
14	2,5-(MeO) ₂ -C ₆ H ₃	CH ₂ OTIPS	hexane	58	22 (1 <i>R</i> ,2 <i>S</i>)	427, 428
15	3,4,5-(MeO) ₃ -C ₆ H ₂	CH ₂ OTIPS	hexane	76	85 (1 <i>R</i> ,2 <i>S</i>)	427, 428

Scheme 164



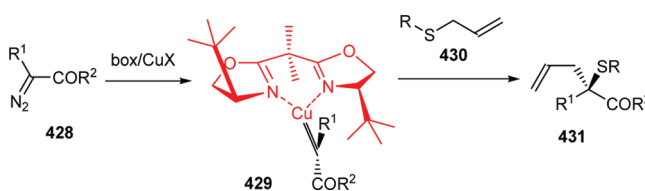
Scheme 165



When investigating polymerizations of this kind, an obvious extension of the research is to test the same conditions for copolymerization. Therefore, the next stage of AOCP was the study of the asymmetric oxidative cross-coupling (AOCC) of 2-naphthols. The reaction between **463** and **464** as reported in Scheme 179 was investigated. It gave three different dimers: one of these was the heterodimer (the target **465**), and two homodimers, **466** and **467**, the obvious side-products of the cross-coupling. The AOCC reaction, catalyzed by the [(*S*)-1/CuCl] complex, was performed at ambient temperature in THF. Sc(OTf)₃ proved an interesting cocatalyst capable of increasing the heterodimer selectivity. The most interesting data, which allow evaluation of both the substituent effects and that of the additives, are reported in Table 108.^{460–463}

The most useful substituents of **463** are the 2- and 7-benzyloxy (Table 108, entries 4 and 9) and 6-acetoxy groups (Table 108, entry 6). Bromine, on the other hand, transmits a negative effect (Table 108, entry 5). The phenyl carboxylate-substituted **464** is better by far than the methyl analogue (Table 108, entries 2 and 7 vs 1 and 6). Everyone will appreciate the importance of this reaction, particularly when run with Sc(OTf)₃ as the cocatalyst, for the synthesis of 1,1'-bi-2-naphthols **465**. Because of their axial

Scheme 166



dissymmetry they have widespread use as ligands in asymmetric catalysis and in chiral resolution.

A natural extension of the above reactions was the asymmetric oxidative cross-coupling polymerization of differently substituted binaphthols and 2,2'-binaphthalendiols. The copolymers involve the formation of C–C bonds at the 1,1'-positions, and the use of [box/CuCl] catalysts induces high cross-coupling selectivity (up to 96%) and appreciable enantioselectivities.^{464,465}

4.14. Miscellaneous Reactions

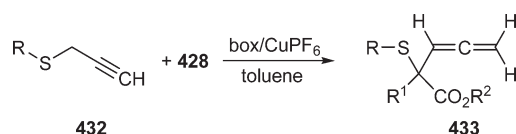
For obvious reasons, this section brings together different types of reactions ranging from some that are really of marginal relevance to this review to some more important ones from both the synthetic and the mechanistic point of view. Therefore, even if homogeneity is by no means the dominant theme, the future important developments of many of the reactions discussed here cannot be excluded.

Section 4.11 closed with a discussion of the [(*R*)-1/CuOTf]-catalyzed imidation of sulfides or selenides with [*N*-(*p*-tolylsulfonyl)imino]-phenyliodinane **435** affording chiral allylic sulfides or selenides that give a [2,3]-sigmatropic rearrangement. If the prochiral thio- or seleno-ethers **468a,b** lack suitably placed double bonds to undergo further reactions, the chiral sulfimides and selenides **469a,b** are rendered stable, isolable products (Scheme 180).^{435–437} The variety of substituents that has been tested is large, and the reaction has been shown to be flexible. However, one clear outcome is the fact that the sulfimides **469a** are obtained in better yields and higher enantioselectivities than the corresponding selenides **469b** (Table 109, entries 1, 6, and 8 vs 4, 7, and 9). The best solvent was toluene, and the best catalyst was again [(*R*)-1/CuOTf] (Table 109, entries 1–3).

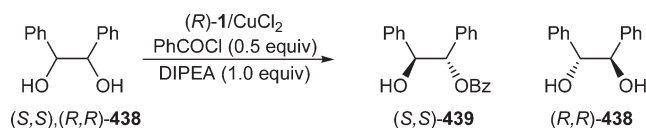
Table 101. Catalytic Enantioselective [2,3]-Sigmatropic Rearrangements of Allyl Sulfides

entry	R	R ¹	R ²	solvent	box	CuX	yield (%)	ee 431 (%) (conf.)	ref
1	Me	H	OEt	CHCl ₃	(S)-2	CuOTf	58	3	430
2	Ph	H	OEt	CHCl ₃	(S)-2	CuOTf	59	14	430
3	adamanthyl	H	OEt	CHCl ₃	(S)-2	CuOTf	62	26	430
4	adamanthyl	H	OEt	CHCl ₃	(S)-1	CuOTf	60	12	430
5	<i>o</i> -diMePh	H	OEt	CHCl ₃	(S)-2	CuOTf	62	52	430
6	<i>o</i> -diMePh	H	OEt	CHCl ₃	(S)-1	CuOTf	64	11	430
7	Ph	Ph	OMe	benzene	(S)-2	CuPF ₆	89	41 (<i>R</i>)	431
8	<i>o</i> -MePh	Ph	OMe	benzene	(S)-2	CuPF ₆	92	62	431
9	<i>o</i> -MePh	Ph	OMe	benzene	(S)-1	CuPF ₆	92	48	431
10	<i>o</i> -MePh	1-Naphth	OMe	benzene	(S)-2	CuPF ₆	66	78	431
11	<i>o</i> -ClPh	Ph	(1 <i>S</i>)-camphorsultam	CH ₂ Cl ₂	(S)-1	CuPF ₆	84	86 (<i>R</i>)	432
12	<i>o</i> -ClPh	Ph	(1 <i>S</i>)-camphorsultam	CH ₂ Cl ₂	(S)-2	CuPF ₆	79	87 (<i>R</i>)	432

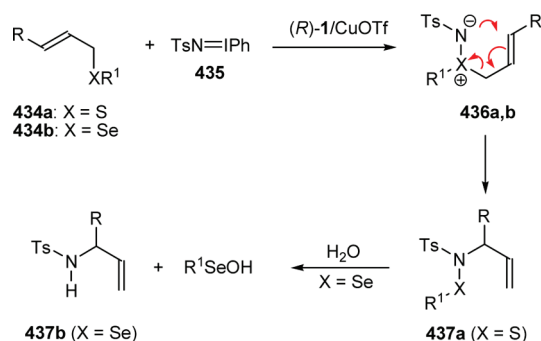
Scheme 167



Scheme 169



Scheme 168



Yields ranged from satisfactory to good (up to 82%). The best enantioselectivity for **469a** was 71% ee for R and R¹ being 1-naphthyl and benzyl, respectively,^{435,436} and for **469b** was 36% ee for R and R¹ being 2-naphthyl and benzyl, respectively.⁴³⁷

Recently, detailed research has been directed to test the asymmetric sulfamidation reaction of **468a** with [Cu(II)/box] catalysts. These are immobilized through microencapsulation with polystyrene [Cu(acac)₂-MC],⁴⁶⁶ immobilized in ionic liquids [Cu(acac)₂-IL],⁴⁶⁶ and supported with poly(vinylpyrrolidone) [Cu(OAc)₂-PVP].⁴⁶⁷ The results for the reaction of methyl tolyl sulfide are reported in Table 109, together with the corresponding reaction run under homogeneous conditions (Table 109, entries 11–17). Yields are excellent and the result with [(S)-2/Cu(OAc)₂-PVP] deserves particular attention because the enantioselectivity is far better than that obtained with the Ph-box-based catalysts (Table 109, entries 16 and 17).

A lithium cyclopentadienide derivative can be obtained by the enantioselective addition of 2-methylphenyllithium to 6-(dimethylamino)fulvene. The yield with (S)-2 as the catalyst is 77%, but the

enantiomeric excess of the (*R*)-product (20% ee) cannot be compared with the enantioselectivity obtained with sparteine.⁴⁶⁸

The target of several research groups is the intramolecular C–H insertion of ylides. The reaction of phenyliodonium ylide **470** is catalyzed by [(*R*)-1/Cu(OTf)₂] and [(*S*)-2/Cu(OTf)₂]. After hydrolysis (*R*)-**471** is obtained as the product of both catalysts in about 50% yield and enantioselectivities of 13% and 23% ee, respectively (Scheme 181).⁴⁶⁹

The intramolecular C–H insertion of electron-poor carbenes into the Cp–H bond of the electron-rich cyclopentadienyl ring of ferrocene derivatives **472a,b** can be catalyzed by [(*S*)-1/CuOTf]. The formation of both the cyclohexanone ring in **473a** and the dimethylcyclopentanone in **473b** occur with good yields and remarkable enantiomeric excesses (Scheme 182).⁴⁷⁰

The carbene derived from phenyldiazoacetate **428** (R¹ = Ph, R² = OMe) inserts into the C–H bond of THF, and the enantioselective reaction catalyzed with [(*S*)-1/Cu(OTf)₂], run under homogeneous conditions, gives a 49% yield of syn and anti products **474** with a ratio of 64:36 and 59% and 40% ee, respectively (Scheme 183). When the reaction is performed with the same catalyst supported on laponite, the yield is 66% with a syn/anti ratio of 75:25, but interestingly the enantioselectivity of (*2R,αS*)-**syn-474** is 84% and that of *anti-474* is 39% ee.⁴⁷¹

The key reaction for an asymmetric approach to obtaining the 1,2-disubstituted mitosenes is based on the decomposition of the diazoester **475**. This is followed by the intramolecular C–H insertion of the metallo-carbene into two sets of diastereotopic pyrrolidinic hydrogen atoms oriented endo and exo (Scheme 184). Different chiral catalysts have been tested. The one giving the best dr (4.4:1) of epimeric esters was found to be [(*R*)-1/CuOTf], with the endo/anti isomer **476** obtained in 53% ee, which converges to **477** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation.^{472,473}

An intermolecular variant of the above reactions is the Cu(I)–carbenoid– and the Ag(I)–Lewis acid–box-catalyzed insertion of α-diazocompounds **428** into the N–H bond of the

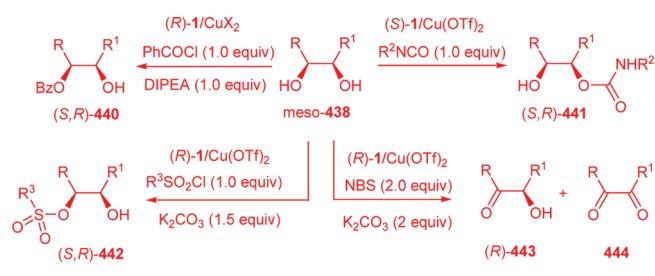
Table 102. Asymmetric Benzoylation, Carbamoylation and Tosylation Reactions of *meso*-1,2-Diols 438 with [(*R*)-1/Cu(OTf)₂]

entry	R	R ¹	440 yield %	ee (%) (conf.)	441 (R ² = Ph) yield %	ee (%) (conf.)	442 (R ³ = Ph) yield (%)	ee (%) (conf.)	ref
1	Me	Me	78	97 (1 <i>R</i> ,2 <i>S</i>)	94	70 (1 <i>R</i> ,2 <i>S</i>)	88	>99	440 ^a , 442
2	Ph	Ph	79	94					438, 442
3	CH ₂ OBn	CH ₂ OBn	36	96	91	82	71	93	442
4	(CH ₂) ₃		47	3	82	86 (1 <i>R</i> ,2 <i>S</i>)	91	95	440 ^a , 441, 442
5	(CH ₂) ₄		quant	95 (1 <i>R</i> ,2 <i>S</i>)	92	76 (1 <i>R</i> ,2 <i>S</i>)	quant	97 (1 <i>S</i> ,2 <i>R</i>)	441, 442
6	(CH ₂) ₅		88	58	83	91	81	99	441, 442
7	(CH ₂) ₆		85	65	96	86	96	98	441, 442
8	CH ₂ OCH ₂		81	racemate	99	64	80	95	442
9	CH ₂ SCH ₂		63	8	90	52	93	94	442
10	CH ₂ CH=CHCH ₂		68	93	96	59	>99	97	442

^a [(*S*)-1/CuCl₂] was used in this case as catalyst, and therefore, a product of opposite configuration was obtained.

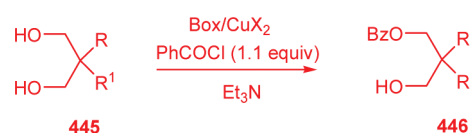
Table 103. Desymmetrizing Monobenzoylation of 445

entry	R	R ¹	Box/CuX ₂	yield (%)	446 ee (%) (conf.)	ref
1	OH	CH ₂ CH ₂ Ph	(<i>R</i>)-1/CuCl ₂	97	90 (<i>R</i>)	444
2	OH	CH ₂ CH ₂ Ph	(<i>S</i>)-2/CuCl ₂	53	14 (<i>S</i>)	444
3	NHCbz	CH ₂ CH ₂ Ph	(<i>R</i>)-1/CuCl ₂	74	53	445
4	NHSO ₂ Ph	CH ₂ CH ₂ Ph	(<i>R</i>)-1/CuCl ₂	38	58	445
5	NHPOPh ₂	CH ₂ CH ₂ Ph	(<i>R</i>)-1/CuCl ₂	55	55	445
6	NHCOCF ₃	CH ₂ CH ₂ Ph	(<i>R</i>)-1/CuCl ₂	13	57	445
7	NHCOPh	CH ₂ CH ₂ Ph	(<i>R</i>)-1/CuCl ₂	66	80 (<i>R</i>)	445
8	NHCOPh	CH ₂ CH ₂ Ph	(<i>S</i>)-2/CuCl ₂	31	15 (<i>S</i>)	445
9	NHCOPh	Me	(<i>R</i>)-1/Cu(OTf) ₂	97	95	446
10		[(CH ₂) ₃ N]-COPh	(<i>R</i>)-1/Cu(OTf) ₂	88	94	446

Scheme 170

aniline derivatives **478** to give the optically active secondary amine **479** (Scheme 185).⁴⁷⁴ Several reagents have been tested, and some significant results are reported in Table 110. 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 enantioselectivities are sometimes low, the results are to date the highest asymmetric inductions obtained for an intramolecular N–H insertion via a chiral carbene complex or chiral Lewis acid catalysis.⁴⁷⁴

Remarkable advances have been made with respect to the carbenoid asymmetric insertion into bonds other than C–H. Among the new entries presented is the [(*S*)-1/CuCl]-catalyzed O–H insertion of phenol by the carbenoid derived from ethyl α -diazopropionate **428** (R¹ = Me, R² = OEt). The reaction gives a 51% yield of (*R*)-ethyl 2-phenoxypionate, and the 32% ee obtained with this catalyst is significantly lower than the enantioselectivity obtained by using the much more complex

Scheme 171

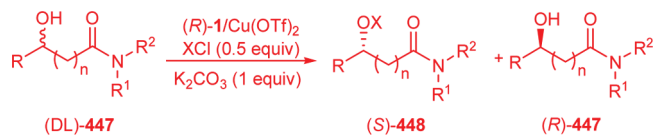
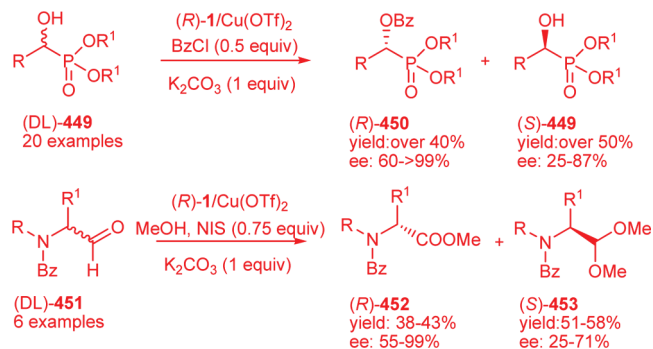
bisoxazoline ligands that lie well outside the topic of this review.⁴⁷⁵

A recent enantiotopic differentiation of pro-*R* and pro-*S* chlorines involved CH₂Cl₂ with ethyl diazoacetate (**30**) and [(*S*)-1/AgOTf] as the catalyst. The yield was 50% and the ee was 14%, and it found a useful synthetic application in the reaction between (dichloromethyl)borate **480** and BuLi.⁴⁷⁶ This reaction, catalyzed by boxes and metal triflates, allows enantioselective intermolecular insertion into the C–Cl bond with the formation of (1-chloropentyl)boronate **481** in 86% yield (Scheme 186). Initial experiments with stoichiometric amounts of different catalysts suggest that [(*R*)-1/Yb(OTf)₃] is the catalyst of choice for the reaction (Table 111, entries 1–5). Attempts to use catalytic amounts of this catalyst led to a lower enantiomeric excess (Table 111, entry 6), and the best compromise appears to use catalytic amounts of triflate with large amounts of box (Table 111, entry 8).⁴⁷⁷

The catalytic enantioselective conversion of a C–H bond into a C–halogen bond (halogenation) has only recently been confronted and solved for β -ketoesters and β -ketophosphonates **174b,c**. It produced the corresponding α -halogenated compounds **482b,c**, using *N*-chloro- (NCS) and *N*-bromosuccinimide (NBS) as the chlorine and bromine sources, *N*-fluorobenzenesulfonimide (NFSI)

Table 104. Kinetic Resolution of Racemic 447 with [(*R*)-1/Cu(OTf)₂]

entry	R	R ¹	R ²	n	XCl	(<i>S</i>)-448 yield %	ee (%)	(<i>R</i>)-447 yield (%)	ee (%)	ref
1	Ph	Ph	H	0	<i>p</i> -TsCl	47	72	47	74	447
2	Ph	4-Cl-C ₆ H ₄	H	0	<i>p</i> -TsCl	44	71	48	79	447
3	Ph	4-Me-C ₆ H ₄	H	0	<i>p</i> -TsCl	29	80	65	69	447
4	Ph	Cyclohex	H	0	<i>p</i> -TsCl	30	30	52	18	447
5	Ph	H	H	0	<i>p</i> -TsCl	28	90	61	43	447
6	Me	Ph	H	0	<i>p</i> -TsCl	26	90	70	24	447
7	Et	Ph	H	0	<i>p</i> -TsCl	44	83	44	61	447
8	<i>i</i> -Pr	Ph	H	0	<i>p</i> -TsCl	40	83	57	69	447
9	<i>t</i> -Bu	Ph	H	0	<i>p</i> -TsCl	30	78	66	36	447
10	cyclopentyl	Ph	H	0	<i>p</i> -TsCl	42	92	42	82	447
11	Me	Ph	H	1	PhCOCl	37	85	63	56	448
12	Me	4-Cl-C ₆ H ₄	H	1	PhCOCl	46	79	54	66	448
13	Me	3,5-Me-C ₆ H ₃	H	1	PhCOCl	47	78	53	65	448
14	Me	Me	Me	1	PhCOCl	46	76	7	31	448
15	Me	Ph	Me	1	PhCOCl	37	84	53	60	448
16	<i>n</i> -Pr	Ph	H	1	PhCOCl	34	68	64	45	448
17	Ph	Ph	H	1	PhCOCl	18	74	82	20	448
18	BocNH(CH ₂) ₃	Ph	H	1	PhCOCl	40	80	60	58	448

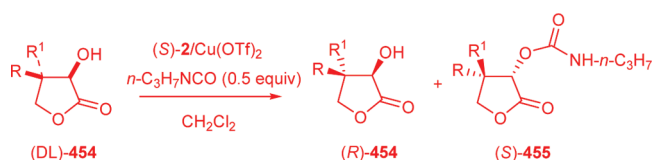
Scheme 172**Scheme 173**

as the fluorinating agent, and, not surprisingly, box complexes as the catalysts (Scheme 187).^{478–482}

It appears from some of the significant results reported in Table 112 that, after the screening of the boxes, Cu(II) salts, solvents, and halogenation reagents (Table 112, entries 1–5), the best catalyst for chlorination and bromination of β -ketoesters 174b was found to be [(*S*)-2/Cu(OTf)₂], either in Et₂O with NCS or in dioxane with NBS (Table 112, entries 5–7, 10, 12, and 14).⁴⁷⁸ For β -ketophosphonates, the same reaction conditions, except with THF as the solvent, were found to be optimum (Table 112, entries 24 and 25).⁴⁸¹ The formation of the (*S*)-enantiomer product, as described in entry 6 of Table 112, is in accordance with coordination of the β -ketoesters to the Cu(II)

Table 105. Carbamoylation of Racemic α -Hydroxy- γ -lactones 454 with *n*-Propyl Isocyanate⁴⁵¹

entry	R	R ¹	Box/CuX ₂	(<i>R</i>)-454 ee (%)	(<i>S</i>)-455 ee (%)
1	Me	Me	(<i>S</i>)-2/Cu(OTf) ₂	93	93
2	Me	Me	(<i>S</i>)-1/Cu(OTf) ₂	33	77
3	Et	Et	(<i>S</i>)-2/CuCl ₂	85	95
4	Ph	Ph	(<i>S</i>)-2/CuCl ₂	93	94
5	H	H	(<i>S</i>)-2/CuCl ₂	36	41
6	Ph	H	(<i>S</i>)-1/CuCl ₂	96	96
7	H	Ph	(<i>S</i>)-1/CuCl ₂	32	37

Scheme 174

catalysts in a bidentate fashion. Here the plane of the β -ketoesters is tilted from that of the box by approximately 45°. In the reacting intermediate, the ligand (*S*)-2 shields the Re face of the enolate leaving the Si face available for the attack.⁴⁷⁸

The fluorination of β -ketoesters differs from previous halogenations because it give the best enantioselectivities with [(*R*) or (*S*)-1/Cu(OTf)₂] (Table 112, entries 8, 9, 15–17, 22, and 23).^{479,482} However, [(*R*)-1/Ni(ClO₄)₂] was found to be a more selective catalyst (Table 112, entries 19–21).⁴⁸⁰ The most attractive feature of these fluorinations is that nickel and copper complexes give opposite enantiomers.

The fluorination of β -ketoesters 174b, performed with Select-fluor using CpTiCl₃ as the catalyst, is the first step in a consecutive catalytic enantioselective electrophilic fluorination/amination.

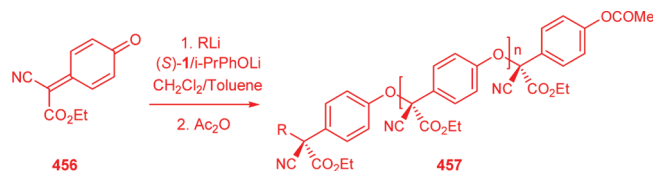
This is a result of the fluoroketoesters **483** reacting with the diazodicarboxylates **171** in the presence of [(*S*)-1/Cu(OTf)₂]. This step is actually an enantioselective catalytic Mannich reaction. It gives the α -fluoro- α -hydrazino- β -ketoesters **484** (Scheme 188), whose yields and ee's are reported in Table 113. Whereas it appears that the importance of substituents on stereoselectivity is irrelevant, the matching/mismatching effect is important as shown from entries 7 and 8 in Table 113.⁴⁸³

Three interesting reactions could be taken as examples of the flexibility and variety of box complexes as catalysts. However, the enantioselectivity is not comparable with that obtained using other chiral catalysts. For example, 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 obtained in 62% yield and 42% ee.⁴⁸⁴ Phenyl glyoxal **485** undergoes an intramolecular Canizzaro reaction in the presence of an alcohol and box/Cu(II) complexes to give the corresponding mandelate **486** (Scheme 189).⁴⁸⁵ The reaction requires the use of anhydrous glyoxal (Table 114, entry 1 vs 2), and although the steric hindrance of alcohol lowers the yields concomitantly, it increases the enantioselectivities (Table 114, entry 3 vs 2). However, the interesting feature was the double asymmetric induction (Table 114, entries 6–8), which found a matching pair in [(*S*)-2/Cu(SbF₆)₂] and [*D*-(+)-menthol].⁴⁸⁶

The Passerini three-component coupling reaction between benzoic acid, (benzyloxy)benzaldehyde, and *p*-methoxyphenyl isocyanide gives the amidoester **487** under catalysis with both [(*S*)-1/CuX₂] and [(*S*)-2/CuX₂] where X is OTf or SbF₆ (Scheme 190). Yields are excellent (up to 93%), and enantioselectivity good (50–64% ee), but pybox-based catalysts give the same yield with 97% ee.⁴⁸⁷

Previously unexplored fields have been recently investigated. The enantioselective formation of new C–X bonds using *n*-BuLi-generated α -sulfonyl or α -sulfinyl carbanions has been accomplished with the use of boxes. Two reactions of benzyl sulfones **488** are noteworthy: an aldol reaction with aromatic aldehydes that gives *syn*- and 3*anti*-**489**,⁴⁸⁸ and the electrophilic fluorination with NFSI that gives **490** (Scheme 191).⁴⁸⁹

Scheme 175



Both processes were performed using equimolar amounts of box, and some typical results are presented in Table 115.

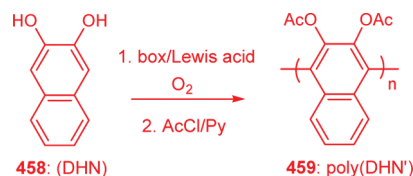
The deprotonation of *S*-cinnamyl thiocarbamate **491** with *n*-BuLi in the presence of stoichiometric amounts of (*R*)-**1** and subsequent alkylation with electrophiles R–X can be taken as an example of reactions involving α -sulfinyl carbanions to give the α -substituted products (*R*)-**492** in good yields and excellent enantioselectivities (Scheme 192).⁴⁹⁰ Other more exotic reactions are not quite as stereoselective as the example mentioned above.⁴⁹¹

In previous sections of this review, several enantioselective cyclizations have been discussed, but the intramolecular alkene cycloamination of **493** is of particular significance. Maybe because it is the key step in the synthesis of a natural product, or because it is an enantioselective oxidative cyclization that requires unusually drastic experimental conditions. This section will conclude with the reaction catalyzed by [(*R*)-1/Cu(OTf)₂] in which the sulfonamide **493** gives (*S*)-**494** in 64% yield. This sultam is transformed within two steps into the potent cancer cell growth inhibitor alkaloid (*S*)-(+)-tylophorine (**495**) with 81% ee (Scheme 193).⁴⁹²

5. OTHER BOX LIGANDS: EFFECT OF SUBSTITUENTS ON CATALYTIC BEHAVIOR

As seen in section 4, although both Ph- and *t*-Bu-boxes allow the catalysis of a wide range of reactions, other box ligands give catalysts that significantly improve efficiency and selectivity in the same or in other new reactions. As seen in Chart 1, more than 230 boxes have been synthesized. In the next few sections these

Scheme 176



Scheme 177

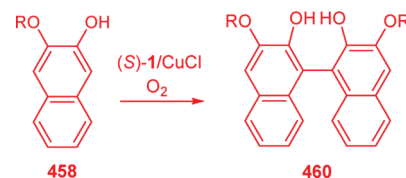


Table 106. Asymmetric Oxidative Coupling Polymerizations of 458 at Room Temperature

entry	458 R	box	Lewis acid	solvent	459 yield ^a (%)	<i>n</i>	[α] _D	460 ee (conf.)	ref
1	H	(<i>S</i>)-1	CuCl	THF	30	35 ^b	–40.3		456
2	H	(<i>S</i>)-1	CuOTf	THF	>99	30 ^b			456
3	H	(<i>S</i>)-2	CuCl	THF	27	25 ^b	+19.3		456
4	H	(<i>R</i>)-1	VOSO ₄	CH ₂ Cl ₂ /MeOH	58	8 ^b	–147		455
5 ^a	H	(<i>R</i>)-1	VOSO ₄	CH ₂ Cl ₂ /MeOH	4	6 ^b	–210		455
6	H	(<i>S</i>)-2	VOSO ₄	CH ₂ Cl ₂ /MeOH	93	15 ^b	+70		455
7	Bn	(<i>S</i>)-1	CuCl	THF	92 ^c			43 (<i>S</i>)	457
8	Me	(<i>S</i>)-1	CuCl	THF	61 ^c			71 (<i>S</i>)	457
9	MOM ^d	(<i>S</i>)-1	CuCl	THF	97 ^c			52 (<i>S</i>)	457

^a Reaction run at 0 °C. ^b Average number derived from *M_n* value. ^c Yield refers to product **460**. ^d MOM is CH₂OCH₃.

will be grouped into homogeneous classes whose behaviors will be discussed. Comparisons with those of **1** and **2**, considered as the prototypes of 4-aryl- and 4-alkyl-substituted boxes, will be made. Only those ligands whose complexes significantly improve or modify the selectivity of the catalysts derived from the prototypes will be discussed in detail.

5.1. 4-Aryl-Substituted Boxes

Two types of 4-aryl-substituted boxes have been used with the aim of preparing more bulky or more rigid catalysts: those with one or more substituents on the phenyl group and those with another aromatic group.

With one significant exception the success of the 4-aryl-box was very limited. Results showed that, in general, the enantioselectivity induced by catalysts based on these boxes was comparable, and sometimes even lower, than that obtained with **1**. The enantioselective mercuriocyclization of γ -hydroxy-*cis*-alkene to produce 2-substituted tetrahydrofuran with 4-(*o*-methoxyphenyl)-box (**S**)-**3z** gave enantioselectivities significantly lower than that with (*R*)-**1**, and both were surpassed in selectivities obtained using other types of ligands.⁴⁹³ The hetero Diels–Alder reaction of α,β -unsaturated acyl phosphonates **350b** with ethyl vinyl ether **351** gives results almost identical to those using (*S*)-**1** (Table S7, entry 2)

Table 107. Asymmetric Oxidative Coupling Polymerizations of 2,2'-Disubstituted-1,1'-binaphthalene-3,3'-diols **461**

entry	box	Lewis acid	461 (conf.)	R 461	462 yield (%)	462 (<i>S</i> / <i>R</i>)	$[\alpha]_D$	ref
1	(<i>S</i>)- 1	CuCl	racemate	MOM	30		−33	457
2	(<i>S</i>)- 1	CuCl	<i>S</i>	MOM	70		−136	457
3	(<i>R</i>)- 1	CuCl	<i>S</i>	MOM	66		−55	457
4	(<i>S</i>)- 1	CuCl	racemate	Me	84		−70	458
5	(<i>S</i>)- 1	CuCl	<i>S</i>	Me	63	76:24	−137	459
6	(<i>S</i>)- 1	CuCl	<i>R</i>	Me	50	80:20	+31	459
7	(<i>R</i>)- 1	CuCl	<i>S</i>	Me	41	23:77	−55	459
8	(<i>R</i>)- 1	CuCl	<i>R</i>	Me	58	23:77	+151	459

Scheme 178

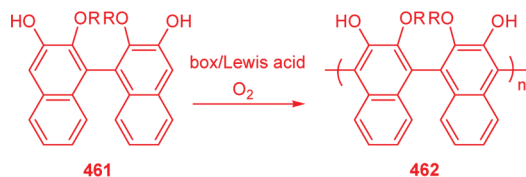


Table 108. Asymmetric Oxidative Cross-coupling of 2-Naphthol Derivatives **463 and **464** Catalyzed by [(*S*)-**1**/CuCl]**

entry	R	R ¹	R ²	X	Sc(OTf) ₃	coupling ratio [465 /(466 + 467)]	465 yield (%)	465 ee (%) (conf.)	ref
1	H	H	H	CO ₂ Me		96:4	87	10 (<i>S</i>)	460
2	H	H	H	CO ₂ Ph		86:14	72	55 (<i>R</i>)	460
3 ^a	H	H	H	CO ₂ Ph	0.2	≥99:1	98	59 (<i>R</i>)	461, 462
4	H	H	OBn	CO ₂ Ph		93:7	63	58 (<i>R</i>)	463
5	H	Br	H	CO ₂ Me		89:11	74	8 (<i>S</i>)	460
6	H	OAc	H	CO ₂ Me		≥99:1	94	10 (<i>S</i>)	460
7	H	OAc	H	CO ₂ Ph		97:3	76	46 (<i>R</i>)	460
8 ^a	H	OAc	H	CO ₂ Ph	0.2	≥99:1	85	55 (<i>R</i>)	461, 462
9	OBn	H	H	CO ₂ Ph		85:15	71	67 (<i>R</i>)	460, 461
10 ^a	OBn	H	H	CO ₂ Ph	0.2	97:3	93	86 (<i>R</i>)	461, 462

^a Ratio [(box/CuX)/**463**/**464**/Sc(OTf)₃] = [0.4:1.0:1.2:0.2].

when run with 4-OMe- or 4-Cl-phenyl box (*S*)-**3aa** and (*S*)-**3ab**.⁹¹ The enantioselectivity of the intramolecular cyclopropanation shown in Scheme 12 does not change when *o*-tolyl box (*S*)-**3y** is used instead of (*S*)-**1**.¹³⁹ Both the diastereo- and the enantioselectivities of the intermolecular cyclopropanation reaction catalyzed by [(*R*)-**1**/Cu(I)] and described in Table 3 (entry 3) are improved (from 40 to 68–80% de and from 65% up to 80% ee) using catalysts derived from the macrocyclic box (*R*)-**14a,b**.^{59a} The asymmetric cyclization–carbonylation of **251** to (*R*)-**253** that occurs with the [1/Pd(TFA)₂] complex (48% yield and 43% ee, Scheme 91) is significantly ameliorated (74% yield and 76% ee) when the ligand of the catalyst is (*S*)-**3aq**. Here the role of the electron-donating methoxy groups cannot be underestimated if even one methoxy group in **3aa** is enough to increase the enantioselectivity of the reaction to 51% ee.³⁷

The significant exception is given by a new class of box ligands containing the 4-(2',5'-disubstituted)-phenyl group (Scheme 194).^{32,98} These have been usefully applied to the Mukaiyama–aldol reactions between the α -ketoesters **106c** and silylketene acetal **123** to give dioxenones (*S*)-**124** (Scheme 34).³² Table 116 reports the comparison between (*S*)-**1** and **3z,ad–af** complexes of Cu(OTf)₂ and CuCl₂ in the reaction of methyl pyruvate.

The configuration of **124** is always (*S*). It is independent of the box and copper counterion, and the effect of the ortho substituent is limited (Table 116, entry 2 vs 1) as in previous examples. However, it was found that 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 116, entries 3 and 4). The asymmetric induction is strongly lowered by the modification of the OMe group in the ortho position (Table 116, entry 5). The catalyst [(*S*)-**3ad**/CuCl₂] was tested, **not only** on the Mukaiyama–aldol reaction of **123** with 13 different α -ketoesters **but also on the reaction of other TMS-ketene acetals with alkyl and aryl α -ketoesters**. The resulting yields and enantioselectivities of the (*S*) adducts are in the range 70–91% and 79–98% ee, respectively.^{32,98} From these results it seems reasonable to predict a positive impact of this new class of aryl boxes on future research in the field.

The next interesting class of boxes to be discussed are those with 1-naphthyl, 2-naphthyl, and 9-anthryl groups **3h**, **3i**, and **3ai** (Chart 2). These have all been used in different reactions, and the results were compared with those obtained by using **1** (Table 117). To discuss the enantioselectivities induced by these four boxes, all the reactions were considered to be performed with catalysts derived from (*S*)-box ligands. Hence, whenever the

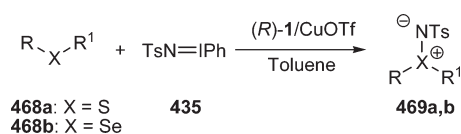
Scheme 179



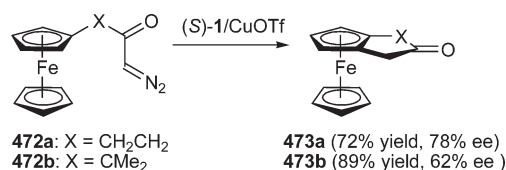
Table 109. Catalytic Asymmetric Imidation of Sulfides and Selenides 468a,b

entry	R	R ¹	X	box	Lewis acid	yield (%)	ee (%) (conf.)	ref
1	Ph	Bn	S	(R)-1	CuOTf	78	64	435, 436
2	Ph	Bn	S	(R)-2	CuOTf	68	34	436
3	Ph	Bn	S	(R)-1	Cu(OTf) ₂	74	25	435
4	Ph	Bn	Se	(R)-1	CuOTf	18	33	437
5	Ph(CH ₂) ₂	Bn	S	(R)-1	CuOTf	63	22	435, 436
6	1-Naph	Bn	S	(R)-1	CuOTf	75	71	435, 436
7	1-Naph	Bn	Se	(R)-1	CuOTf	23	29	437
8	PhCH=CHCH ₂	Ph	S	(R)-1	CuOTf	40	27	435, 436
9	PhCH=CHCH ₂	Ph	Se	(R)-1	CuOTf	63	20	437
10	1-NaphCH=CHCH ₂	Ph	S	(R)-1	CuOTf	80	58	436
11	<i>p</i> -Me-C ₆ H ₄	Me	S	(R)-1	CuOTf	82	13 (R)	436
12	<i>p</i> -Me-C ₆ H ₄	Me	S	(S)-1	Cu(acac) ₂ -MC	86	23	466
13	<i>p</i> -Me-C ₆ H ₄	Me	S	(S)-2	Cu(acac) ₂ -MC	84	12	466
14	<i>p</i> -Me-C ₆ H ₄	Me	S	(S)-1	Cu(acac) ₂ -IL	85	50	466
15	<i>p</i> -Me-C ₆ H ₄	Me	S	(S)-2	Cu(acac) ₂ -IL	82	15	466
16	<i>p</i> -Me-C ₆ H ₄	Me	S	(S)-1	Cu(OAc) ₂ -PVP	95	5	467
17	<i>p</i> -Me-C ₆ H ₄	Me	S	(S)-2	Cu(OAc) ₂ -PVP	95	68	467

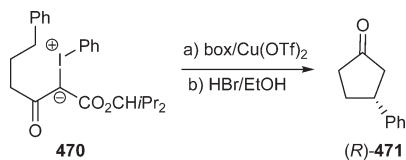
Scheme 180



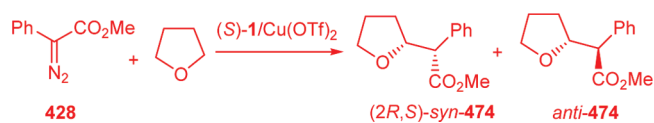
Scheme 182



Scheme 181



Scheme 183



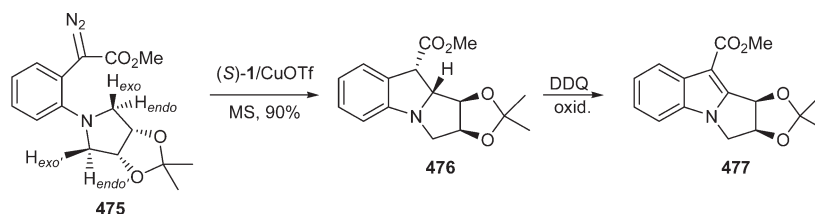
reaction was in fact performed with a (R)-box, the configuration of the products will be inverted. This is the only possibility for a homogeneous comparison of the enantioselectivities induced by the different ligands. To avoid any misunderstanding,⁴⁹⁴ a note will clarify this.

The majority of the reactions reported using the naphthyl-boxes, particularly those in which the reacting center is relatively remote from the coordination site, show a significant

improvement of the enantiomeric excess compared to those carried out using the phenyl-box (Table 117, entries 1–3 and 6–9). Similar results were obtained for 3ai (entry 4). In many other reactions (Table 117, entries 4, 5, 10, and 11) both 1 and 3h,i were found to induce the same enantioselectivity.

The most interesting reaction to be discussed in this section is the tandem oxa-Michael addition–Friedel–Crafts alkylation between *m*-anisole (204) and methyl 4-*p*-chlorophenyl-2-oxo-3-butenate

Scheme 184

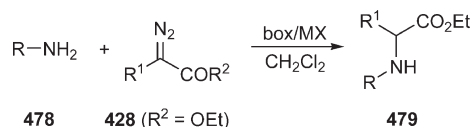
Table 110. Catalytic Enantioselective Insertion of α -Diazo compounds **428** into N–H Bond⁴⁷⁴

entry	R	R ¹	box	CuX	yield (%)	ee 479 (%) (conf.)
1	Ph	Me	(<i>R</i>)-1	CuPF ₆	62	20
2	Ph	Me	(<i>R</i>)-2	CuPF ₆	54	28
3	Ph	Me	(<i>R</i>)-2	AgOTf	5	48
4	Ph	Me	(<i>R</i>)-2	AgSbF ₆	8	25
5	Ph	Me	(<i>R</i>)-2	AgClO ₄	5	48
6	Ph	Ph	(<i>R</i>)-1	CuPF ₆	67	19
7	Ph	Ph	(<i>R</i>)-2	CuPF ₆	82	13
8	2-Naphth	Me	(<i>R</i>)-2	CuPF ₆	27	24
9	Bn	Me	(<i>R</i>)-2	CuPF ₆	27	10 (<i>R</i>)

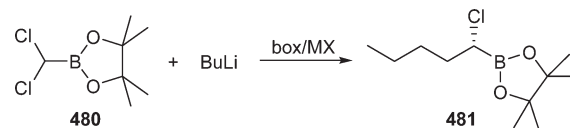
Table 111. Catalytic Enantioselective Insertion of BuLi into C–Cl Bond of **480**⁴⁷⁷

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

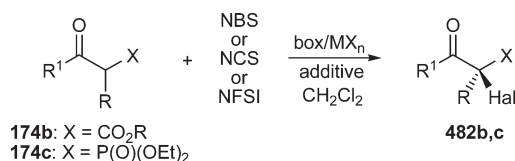
Scheme 185



Scheme 186



Scheme 187



(183). This is reported in Scheme 74 (Table 117, entry 8), not only because it is the reaction in which the catalysis was performed with the entire series of boxes (*S*)-1, **3h**, **3i**, and **3ai**, and hence allows a complete comparison of the different aromatic substituents, but also because on going from (*S*)-1 to (*S*)-3ai two aspects of the results data should be emphasized, namely, the enantioselectivity of the reaction increases on going from the phenyl-box to the 1-naphthyl-box, but not to the 2-naphthyl-box. It drops dramatically with the 9-anthryl-box. The reaction shows an anomalous induction of enantioselectivity within the series that is a unique example of the reaction discussed in Table 117. A reversal of the stereochemistry is observed on going from (*S*)-1 to (*S*)-3h; then it remains constant with the other boxes.²⁵

This section will conclude with a curious box, namely, the (*S*)-5aa with a phenyl and a methyl both in position 4 (Chart 2). Its CuOTf complex was tested in the catalyzed cyclopropanation of styrene (**29**) with ethyl diazoacetate (**30**) (Scheme 5), and the best ee reported was 30%.⁴⁶

5.2. 4-Aryl-5-Substituted Boxes

This section will present interesting information about the transfer of chiral information from the optically active catalyst to the product. A substituent in position 5 of the box may be either an aryl or an alkyl group and it may be either cis or trans to the 4-aryl group. The first comparison of 4,5-diaryl-substituted boxes

can be done between **1** with its 5-phenyl substituted cis and trans derivatives **5b** and **6b** (Chart 3). To deduce 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 configuration 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*SS*)-**5b** complexes including the Michael reaction,²³⁶ the Mannich reaction in Scheme 56,^{227b} the Claisen rearrangement in Scheme 159,²⁹⁸ the radical addition in Scheme 101,²⁹³ and the enantioselective desymmetrization in Scheme 171.⁴⁴⁴ All these reactions give nearly identical results in terms of enantioselectivity and the sense of induction.

On the other hand, the Friedel–Crafts reaction between anisole **158** and ethyl trifluoropyruvate **133** reported in Scheme 48²¹⁶ and the hetero Diels–Alder reaction between 5-bromo-*N*-oxypyridine-2-carbaldehyde **112** and the Danishefsky's diene **330** (Scheme 129),³⁶⁶

Table 112. Catalytic Enantioselective Halogenations of β -Ketoesters 174b and β -Ketophosphonates 174c

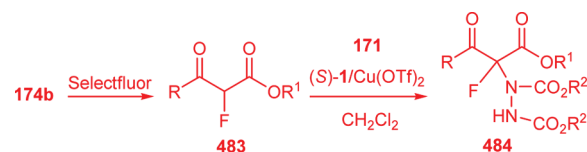
entry	R	R ¹	X	halogen source	box	MX _n	additive	solvent	yield (%)	ee % (conf.)	ref
1	Me	Me	CO ₂ Et	NCS	(R)-1	Cu(OTf) ₂		Et ₂ O	98	32	478
2	Me	Me	CO ₂ Et	NCS	(S)-2	Cu(OTf) ₂		Et ₂ O	n.r.	77	478
3	Me	Me	CO ₂ Et	NCS	(S)-2	Cu(OTf) ₂		dioxane	n.r.	62	478
4	Me	Me	CO ₂ Et	NCS	(S)-2	Cu(SbF ₆) ₂		Et ₂ O	n.r.	44	478
5	Me	Me	CO ₂ Et	NBS	(S)-2	Cu(OTf) ₂		dioxane	98	80	478
6	Me	Ph	CO ₂ Et	NCS	(S)-2	Cu(OTf) ₂		Et ₂ O	98	53 (S)	478
7	Me	Ph	CO ₂ Et	NBS	(S)-2	Cu(OTf) ₂		dioxane	95	41 (S)	478
8	Me	Bn	CO ₂ Et	NFSI	(S)-1	Cu(OTf) ₂		CH ₂ Cl ₂	78	17	482
9	Me	Bn	CO ₂ Et	NFSI	(S)-2	Cu(OTf) ₂		CH ₂ Cl ₂	50	5	482
10		(CH ₂) ₃	CO ₂ Et	NCS	(S)-2	Cu(OTf) ₂		Et ₂ O	96	72	478
11		(CH ₂) ₃	CO ₂ Bn	NFSI	(S)-1	Cu(OTf) ₂		CH ₂ Cl ₂	60	32	482
12		(CH ₂) ₄	CO ₂ Et	NCS	(S)-2	Cu(OTf) ₂		Et ₂ O	99	76	478
13		Tetralone	CO ₂ Bn	NFSI	(S)-1	Cu(OTf) ₂		CH ₂ Cl ₂	55	27	482
14		(CH ₂) ₄	CO ₂ Et	NBS	(S)-2	Cu(OTf) ₂		dioxane	85	82	478
15		(CH ₂) ₃	CO ₂ <i>t</i> -Bu	NFSI	(S)-2	Cu(OTf) ₂		Et ₂ O	91	20	479
16		(CH ₂) ₃	CO ₂ <i>t</i> -Bu	NFSI	(R)-1	Cu(OTf) ₂		Et ₂ O	82	72 (R)	479
17	(CH ₂) ₃	CO ₂ <i>t</i> -Bu	NFSI	(R)-1	Cu(OTf) ₂	HFIP		Et ₂ O	94	82 (R)	479
18	indanone	CO ₂ <i>t</i> -Bu	NFSI	(S)-1	Cu(OTf) ₂			CH ₂ Cl ₂	50	39 (S)	480
19	indanone	CO ₂ <i>t</i> -Bu	NFSI	(S)-1	Ni(ClO ₄) ₂			CH ₂ Cl ₂	92	76 (R)	480
20	indanone	CO ₂ <i>t</i> -Bu	NFSI	(S)-1	Ni(ClO ₄) ₂	MS		CH ₂ Cl ₂	87	93 (R)	480
21	indanone	CO ₂ (1-Adaman)	NFSI	(S)-1	Ni(ClO ₄) ₂	MS		CH ₂ Cl ₂	74	79	480
22		(CH ₂) ₄	CO ₂ <i>t</i> -Bu	NFSI	(R)-1	Cu(OTf) ₂	HFIP	Et ₂ O	92	63	479
23	Me	Ph	CO ₂ <i>t</i> -Bu	NFSI	(R)-1	Cu(OTf) ₂	HFIP	Et ₂ O	56	43 (S)	479
24	Me	Ph	P(O)(OEt) ₂	NCS	(S)-2	Cu(OTf) ₂		THF	>95	64	481
25	Me	Ph	P(O)(OEt) ₂	NCS	(S)-2	Zn(OTf) ₂		THF	>95	45	481

all show a slow increase in enantioselectivity on going from [(R)-1/Cu(OTf)₂] to [(4R,5S)-5b/Cu(OTf)₂]. The same trend was observed in the [4 + 3]-cycloaddition between furan and allenamides **402** (Scheme 156) with the ee of (S)-**404** going from 78% to 90% ee.⁴¹⁹

Two reactions deserve particular attention, both with α' -phosphoric enones **496** as substrates, in which the substrate is coordinated to the catalyst in a bidentate fashion through the carbonyl and the P=O groups. The first reaction is a radical conjugate addition of alkyl iodides catalyzed by the [(4R,5S)-5b/Zn(OTf)₂] complex (Scheme 195). The first step is the generation of a radical. When this is trapped by the hydrogen atom of tributylstannane (R² = H), (S)-**497** is obtained and the difference between the catalysts derived from box **1** and box **5b** with **496** [R = (CH₂)₂Ph] is noticeable because, against a yield of 56% and an enantioselectivity of 29% ee, the latter catalyst gives a yield of 85% and the ee is 91% (Table 118, entry 2).⁴⁹⁵ If the intermediate radical is generated in the presence of allyltributylstannane, it is trapped by an allyl group and the reaction affords *anti*-**497** (R² = allyl). The results of both these reactions with different substrates are reported in Table 118.

The second reaction again involves α' -phosphoric enones **496**. The nitron 1,3-dipolar cycloaddition with **362** is advantageously catalyzed by [(4R,5S)-5b/Cu(OTf)₂]. The increase in the ee with this catalyst, compared to that derived from box **1** (in the reaction where R = Me and R¹ = R² = Ph), is from 79% to 90% (Scheme 196).⁴⁹⁶ The catalyst derived from **5b** is very efficient because the cycloaddition of both diphenyl- and phenyl benzyl nitron, with several α' -phosphoric enones, is strongly endo-selective. The yields are in the range 82–92%, the diastereoselectivity is

Scheme 188



>98%, and the major product (3S,4R,5S)-**498** is obtained with an enantioselectivity in the range 84–99% ee.

The uniqueness of the above reactions (studied by the same authors) lies in the reacting complex involved in the catalytic process. The reaction in Scheme 195 has the complex [(4R,5S)-5b/Zn(OTf)₂/496] with a tetrahedral coordination, whereas the complex [(4R,5S)-5b/Cu(OTf)₂/496] involved in the reaction in Scheme 196 has a square-planar coordination. Both have the expected coordination geometry for Zn(II) and Cu(II), but the former has **496** coordinated in the *s*-cis form (as usual). On the other hand, the latter has **496** coordinated in the *s*-trans conformation.^{495,496} This interpretation serves obviously to rationalize the absolute configuration of the reaction products but probably neglects the aptitude of nitrones to behave as auxiliary ligands.

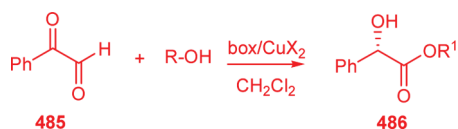
Some reactions have been catalyzed by both (R)-**1** and *trans*-(4R,5R)-**6b** complexes, and under both conditions, the hetero Diels–Alder reactions in Schemes 125, 128, and 130,^{361,365,367,375} do not change significantly. The Mukaiyama–Michael reaction in Scheme 82 does not change if the Lewis

Table 113. Enantioselective Fluorination/Amination of β -Ketoesters 174b Catalyzed by [(*S*)-1/Cu(OTf)₂]⁴⁸³

entry	R	R ¹	R ²	484 yield (%)	484 ee (%)
1	Me	Et	Et	90	93
2	Me	Et	Bn	73	91
3	Me	Me	Et	94	94
4	Ph	Et	Et	85	87
5	<i>t</i> -Bu	Et	Et	84	93
6	<i>t</i> -Bu	Et	Bn	84	93
7	Me	(-)-menthyl	Bn	75	75 ^b
8 ^a	Me	(-)-menthyl	Bn	95	97 ^b

^a Reaction catalyzed by [(*R*)-1/Cu(OTf)₂]. ^b Diastereomeric excess.**Table 114. Box/CuX₂-Catalyzed Enantioselective Intramolecular Canizzaro Reactions of Phenylglyoxal 485 and R–OH**

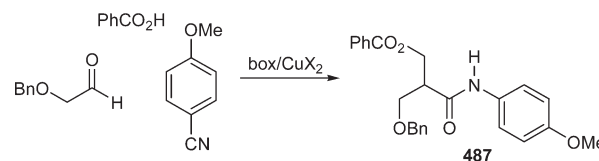
entry	box/CuX ₂	R–OH	yield (%)	486 ee (%) (conf.)	ref
1 ^a	(<i>S</i>)-1/Cu(OTf) ₂	<i>i</i> -PrOH	57	28 (<i>R</i>)	485
2	(<i>R</i>)-1/Cu(OTf) ₂	<i>i</i> -PrOH	89	23 (<i>S</i>)	486
3	(<i>R</i>)-1/Cu(OTf) ₂	<i>t</i> -BuOH	18	42 (<i>S</i>)	486
4	(<i>S</i>)-2/Cu(SbF ₆) ₂	<i>i</i> -PrOH	87	20 (<i>S</i>)	486
5	(<i>S</i>)-2/Cu(SbF ₆) ₂	<i>t</i> -BuOH	71	54 (<i>S</i>)	486
6	(<i>R</i>)-1/Cu(OTf) ₂	D-(+)-menthol	72	77 (<i>S</i>) ^b	486
7	(<i>R</i>)-1/Cu(OTf) ₂	L-(–)-menthol	81	35 (<i>R</i>) ^b	486
8	(<i>S</i>)-2/Cu(SbF ₆) ₂	D-(+)-menthol	81	90 (<i>S</i>) ^b	486

^a Reaction performed on hydrate phenylglyoxal. ^b Diastereomeric excess.**Scheme 189**

acid is Mg(ClO₄)₂. The enantioselectivity increases with the *trans*-box with Co(ClO₄)₂,²⁶¹ and the same increase is observed for the Mukaiyama–aldol reaction reported in Scheme 28.²⁵

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 119). The Mukaiyama–Michael reaction (MMR) in Scheme 83⁹⁶ and the intramolecular carboamination (ICA) in Scheme 109³⁰⁴ are extremes of the behavior of the catalysts based on *cis*-(4*R*,5*S*)-**5b** or *trans*-(4*R*,5*R*)-**6b**. In the MMR, whereas the former complex could be defined as the “ideal” catalyst, the latter gives bad results in terms of yield, diastereoselectivity, and enantioselectivity. The ICA reaction gives identical results with [**5b**/Cu(OTf)₂] or [**6b**/Cu(OTf)₂] complexes. This behavior is observed also both in the allylic substitution reported in Scheme 86 and in the allylic oxidation in Scheme 110. Both display higher enantioselectivities by using either the **5b** or **6b** box, with the same sense of induction irrespective of the configuration at C-5 (Table 119, entries 3 and 4).⁴⁹⁷

The Diels–Alder reaction between **216** and cyclopentadiene (Scheme 114) has been studied with the three boxes under different conditions. The results with Mg(ClO₄)₂, Mg(ClO₄)₂

Scheme 190

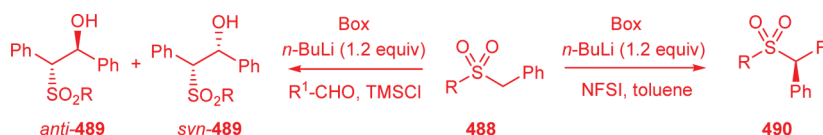
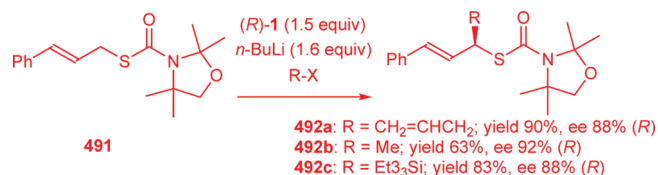
and 2 equiv of H₂O, and Mg(OTf)₂ are reported in Table 119, entries 5–7. In Figure 16 the reacting complexes of these reactions have been illustrated: tetrahedral with Mg(ClO₄)₂ and octahedral with either H₂O or OTf. If the reacting complex is tetrahedral, then the *cis*-box lowers the enantioselectivity, and the *trans*-box strongly increases both the diastereo- and enantioselectivities, but always with the same sense of induction. If the reacting complex is octahedral, then the *cis*-box increases the enantioselectivity with the same sense of induction. The *trans*-box not only lowers the enantioselectivity, but the absolute configuration also depends on the stereochemistry of the octahedron.^{319,322}

An important effect of the substituent on C-5 is observed in the 1,3-dipolar cycloaddition reaction between the nitron **362** and **53**. The three boxes (**1**, *cis*-**5b**, and *trans*-**6b**) and Mg(II), Ni(II), Co(II), and Zn(II) perchlorates as the Lewis acids were used (Table 119, entries 8–11). The (4*R*,5*S*)-**5b** complexes largely give the same sense of induction (with a lower enantioselectivity) as the corresponding complex with (4*R*)-**1** as the ligand. This is attributed to a preferred attack at the Re face for all the endo adducts and the exo adducts of magnesium and nickel and at 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. These results allowed the isolation of an exo enantiomer with 99% ee. Its unknown absolute configuration was established as (3*R*,4*R*)-**363** and is derived from a preferred attack at the Re face of the tetrahedral reacting intermediate **499** (Scheme 197). In conclusion, if the result in Table 119 (entry 12) is added to the above data, from two boxes with the same (4*R*)-configuration, clearly all stereoisomers can be obtained in very good yields and enantioselectivities: the endo enantiomers from [(*R*)-**1**/Ni(ClO₄)₂] and [(4*R*,5*R*)-**6b**/Zn(ClO₄)₂] (Table 119, entries 9 and 11), the exo enantiomers from [(4*R*,5*R*)-**6b**/Ni(ClO₄)₂] and [(*R*)-**1**/Co(ClO₄)₂] (Table 119, entries 9 and 10).³⁹⁰

Recently, (4*S*,5*R*)-4,5-di(2-naphthyl)-box (**5g**) (Chart 4) has been synthesized as the natural successor of **5b**.^{36,498} Even if its use is yet to be fully exploited, its usefulness can be understood by comparing the results of the cyclization carbonylation reaction performed on **254** (Scheme 92, Table 117, entry 11). Here the best result [quantitative yield, 77% ee of (*S*)-**255**] was obtained with the Pd(TFA)₂ complex of 4(2-naphthyl)-substituted box (*S*)-**3i**. Under the same conditions, using the **5e** complex,³⁶ the yield was again quantitative with 85% ee of the same (*S*) enantiomer. Box (4*S*,5*R*)-**5e** was also used in the parallel kinetic resolution of (±)-**500** with the box complex of Pd(TFA)₂, *p*-benzoquinone, *i*-BuOH, and CO, which, after oxidation that may involve only the product derived by (*R*)-**500**, gives (*R*)-**501** and (*S*)-**502** (Scheme 198).⁴⁹⁸ The different results obtained with catalysts derived from (*S*)-**1**, (*S*)-**3i**, and (4*S*,5*R*)-**5e** allow an appreciation of the advantages of using this last box.

Table 115. Enantioselective Reactions of α -Lithiated Sulfones 488 with Aldehydes and NFSI

entry	box	R	R ¹	yield (%)	syn/anti	syn-489 ee (%)	490 ee (%) (conf.)	ref
1	(S)-1	Ph	Ph	83	68:32	32		488
2	(S)-1	CF ₃	Ph	87	95:5	88		488
3 ^a	(S)-1	CF ₃	Ph	84	93:7	74		488, 489
4	(S)-2	CF ₃	Ph	55	>98:2	42		488, 489
5	(S)-1	Ph		50			99 (R)	488

^a Reaction performed with 0.3 mol box.**Scheme 191****Scheme 192**

Only a few boxes with a methyl group on the C-5 position are known. It is always *cis* to a 4-aryl group. To evaluate the methyl effect on the catalyst with the 5-aryl group only, a good model is the enantioselective substitution of the methoxy group of 1-(*p*-methoxybenzoyl)-3,4-dihydro-2-methoxypiperidine (**239**) with a malonate group catalyzed by complexes of Cu(OTf)₂ with boxes (S)-1, (S,R)-5c, (S,R)-5e, and (S,R)-5f, in which the last three ligands have a methyl group in position 4.⁴⁶ The reaction, which has already been discussed from a general point of view in Scheme 87 and is reported again for clarity in Scheme 199, gives in each case (R)-241. The yields are in the range 68–89% [the best result is obtained with (S,R)-5f], and the enantioselectivity is in the range 51–69% ee [the best result is obtained with (S,R)-5e]. Therefore, a 4-methyl group *cis* to a 5-aryl group does not significantly influence the sense of the stereoselection and, at best, may induce a small increase in the enantioselectivity of the new catalyst.

The enantioselective radical reaction of 3-(3-phenyl-2-propenyl)-2-oxazolidinone **216** (R = Ph) in Scheme 99 should be mentioned as further support of the above analysis because a comparison between the MgI₂-catalyzed reaction with (S)-1 or (4S,5R)-5c is evidence that (S)-267 is obtained with 47 and 31% ee, respectively.⁴⁵ This reaction allows the introduction of **9a**, an indene box synthesized in 1996,⁷³ which formally appears to be a 4-aryl-5-alkyl-substituted box (Chart 5). The (4S,5R)-**9a** box, applied to the same radical reaction, gives the product in 89% ee. However, 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 reacting intermediate since (R)-267 is the main enantiomer.⁴⁵

If the catalytic effects of **9a** complexes are compared with those of the prototype **1**, then sometimes the results are either negative

Table 116. Comparison between Different Cu(II)–Box Complexes in the Mukaiyama–Aldol Reaction between Methyl Pyruvate 106c (R = R¹ = Me) and Silylketene Acetal 123³²

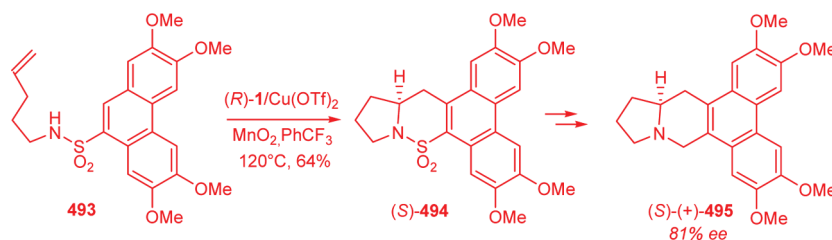
entry	Y	Y ¹	box	Cu(OTf) ₂		CuCl ₂	
				yield (%)	ee (%) (conf.)	yield (%)	ee (%) (conf.)
1			(S)-1	70	11 (S)	35	40 (S)
2	Me	H	(S)-3z	80	39 (S)	75	20 (S)
3	Me	Cl	(S)-3af			80	86 (S)
4	Me	<i>t</i> -Bu	(S)-3ad	78	76 (S)	81	94 (S)
5	(CH ₂) ₂ Cl	<i>t</i> -Bu	(S)-3ae	75	11 (S)	78	44 (S)

or almost the same; hence the commercial box remains the one of choice. This is the case for a range of reactions: the aldol reaction of **136** and benzaldehyde in Scheme 38,¹⁰² the Strecker-type reaction on 2-pyridinsulfonylimines **166** reported in Scheme 53,^{223,225} the Kharasch oxidations of cycloalkenes **290** or hexynes **294** with PhCO₃*t*-Bu in Schemes 110 and 111,^{309,312} the Diels–Alder reaction of α' -arylsulfonyl enones **307** with cyclopentadiene in Scheme 116,³³⁷ the [4 + 3]-cycloaddition between **403** and furan in Scheme 156,⁴¹⁹ and the enantioselective desymmetrization of **445** in Scheme 171.⁴⁴⁴

Sometimes, the stereoselectivity induced by **9a**-based catalysts is somewhat better than that obtained with those derived from **1**, but the overall balance does not justify a clear-cut choice. Two examples are the cyclopropanation of styrene with ethyl diazoacetate (Scheme 6), where **9a** is better than **1** (85% ee vs 60% ee),^{47a} and the classic Pd-catalyzed allylic alkylation of 3-acetoxy-1,3-diphenyl-1-propene **237** with dimethyl malonate (Scheme 86) where **1** works better than **9a** (93% ee vs 72% ee).⁴⁹⁹

An interesting test was made with the Diels–Alder reaction between **216** (R = H) and cyclopentadiene (Scheme 114) comparing the catalytic efficiency of the Cu(OTf)₂ complexes with (S)-1, (4S,5R)-**9a**, and (4S,5R)-**9b**.^{74,500,501} All reactions are endo-selective, (S)-**303** is the major product, and the enantiomeric excesses reported in Table 120 (entries 1–3) show for the conformationally constrained box **9a** an enhanced level of

Scheme 193



Scheme 194

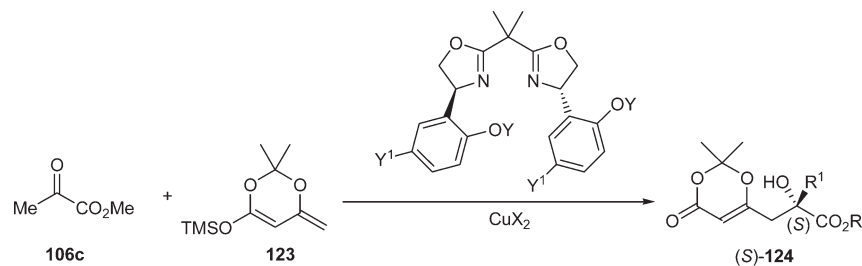


Chart 2

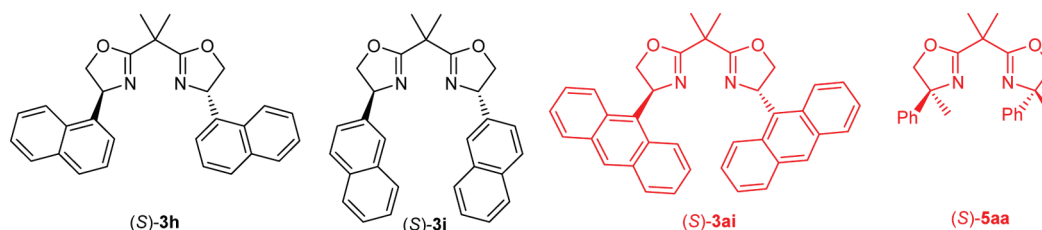


Table 117. Comparison of Ph-box (1) and Naphthyl-bo (3h,i) Complexes as Enantioselective Catalysts for Different Reactions

entry	reaction ^a	reagents	Lewis acid	(S)-1		(S)-3h		(S)-3i		(S)-3ai		ref
				yield (%)	ee % (conf.)	yield (%)	ee % (conf.)	yield (%)	ee % (conf.)	yield (%)	ee % (conf.)	
1	D.A.	216 + Cy ^b (Scheme 114)	Cu(OTf) ₂	92	30 (S)	92	44 (S)					93
2	D.A.	216 + Cy ^b (Scheme 114)	Mg(ClO ₄) ₂	>98	70 (R) ^c			>98	77 (R) ^c			26, 319
3	D.A.	216 + Cy ^b (Scheme 114)	Mg(OTf) ₂	>98	88 (S) ^c			>98	94 (S) ^c			26, 322
4	H.D.A.	106c + 330 (Scheme 125)	Cu(OTf) ₂	n.r.	13 (S)	n.r.	19 (S)			82	45 (S)	25, 33
5	M.A.R.	106c + 107 (Scheme 28)	Cu(OTf) ₂	73	24 (S)	n.r.	19 (S)	>95	31 (S)			25, 33
6	M.A.R.	106c + 123 (Scheme 34)	Cu(OTf) ₂	99	16 (R) ^c	73	51 (R)					25
7	M.Mi.R.	198 + 107 (Scheme 80)	Cu(SbF ₆) ₂	67	56 (S)	55	70 (S)	n.r.	79 (S)			33
8	O.Mi.R.	209 + 183 (Scheme 74)	Mg(OTf) ₂	75	65 (2R,4S)	39	74 (2S,4R)	67	62 (2S,4R)	n.r.	20 (2S,4R)	33, 44
9	F.C.R.	161 + 162 (Scheme 50)	Zn(OTf) ₂	10	19	22	27					218
10	A.S.R.	237 + MM ^d (Scheme 86)	Pd(SbF ₆) ₂	>95	96 (R)	>95	97 (R)	>95	97 (R)			33
11	C.C.R.	254 + CO (Scheme 92)	Pd(CO ₂ CF ₃) ₂	98	65 (S)	99	55 (S) ^c	99	77 (S) ^c			36

^a D.A., Diels–Alder reaction; H.D.A., hetero Diels–Alder reaction; M.A.R., Mukaiyama–aldol reaction; M.Mi.R., Mukaiyama–Michael reaction; O.Mi.R., Oxa-Michael reaction; F.C.R., Friedel–Crafts reaction; A.S.R., allylic substitution reaction; C.C.R., cyclization carbonylation reaction. ^b Cy is cyclopentadiene. ^c Reaction performed with (R)-box and configuration of the product inverted. ^d MM is methyl malonate.

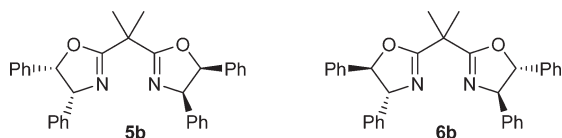
stereoselectivity. When **216** has R = 4-CF₃C₆H₄CO₂ (Table 120, entries 5–7),³²⁸ the enantiomeric excesses with (S)-1 and (4S,5R)-**9a** are comparable, but the enantioselection is the opposite, and the latter gives the same (R,R)-enantiomer obtained with (S)-2.

Even if the [(4R,5S)-**9a**/CuI] complex is not the best catalyst for the addition of ethyl propiolate to 1-acetylpyridinium salt **503**,

it gives (R)-methyl 2[2-(ethoxycarbonyl)ethynyl]pyridine-1(2H)-carboxylate (**504**) in 67% yield and 74% ee.⁵⁰² The reaction is interesting inasmuch as its product can be converted within four steps into (5R,9R)-indolizine **505** (Scheme 200).

The hetero Diels–Alder reactions of the α-carbalkoxy α,β-unsaturated carbonyl compounds **350a** with the vinyl ether **351**

Chart 3



(Scheme 201) were carried out with [(4*R*,5*S*)-**9a**/Cu(OTf)₂]. Both reactions were highly endo-selective (endo/exo = 95:5), and the products (4*S*,6*S*)-**352a** were obtained with 95% and 97% ee, respectively.⁵⁰³

The radical reaction performed on **216** with alkyl iodides in the presence of Et₃B/O₂ and Bu₃SnH, catalyzed by stoichiometric amounts of [box/MX₂] and already described in Scheme 99, was tested with the pyrazole template **317** (R = Ph), 2-iodopropane, and stoichiometric amounts of [(4*S*,5*R*)-**9a**/Zn(OTf)₂] (Scheme 202). (*S*)-**506** was obtained in 72% yield and 43% ee. The same result was obtained with box **10** using different alkyl iodides.⁵⁰⁴

Box (4*R*,5*S*)-**9a** finds three applications in the Henry reaction: The first, with Cu(OAc)₂ as the Lewis acid, concerns the synthesis of protected 4-hydroxyornithine **508**, a key constituent of the antibiotics clavalanine and biphenomycins, by the diastereoselective addition of MeNO₂ to the homoserine-derived aldehyde **507** (Scheme 203).⁵⁰⁵ 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 example of the Henry reaction has already been mentioned in Scheme 44 and concerns the addition of MeNO₂ to aldehydes. The catalyst of choice for this reaction is [(4*R*,5*S*)-**9a**/Cu(OAc)₂], which reacts with a variety of aldehydes to give **509** in very good yields and with excellent enantiomeric excesses (Scheme 204, Table 121). The absolute configuration can be compared to those obtained with (*S*)-**1** and (*S*)-**2**.^{100,506} If the crystal structure of the catalyst (Table 2, entry 27) is taken into account, then a distorted square-pyramidal configuration can be proposed for the reacting intermediate **510**, 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.¹⁰⁰

The last example of the Henry reaction made it possible to assign the correct absolute configuration to malynamide U, a secondary metabolite isolated from the marine cyanophyte *Lyngbya majuscula*. The (1'*R*,2'*S*,6'*R*)-cyclohexenyl carbaldehyde **511**, prepared from (*R*)-(-)-carvone, was submitted to an asymmetric Henry reaction with nitromethane, catalyzed by [(4*R*,5*S*)-**9a**/Cu(OAc)₂] complex, which gave (*S*)-**512** (Scheme 205).⁵⁰⁷ Within five steps this gave **513**, which was consistent with the data of the reported malynamide U and allowed for the subsequent revision of its structure.

The Friedel–Crafts alkylation of the indoles **196** with α'-phosphoric enones **496** gives the products **514** (Scheme 206). This is one of the reactions in which the [(4*R*,5*S*)-**9a**/Cu(OTf)₂] catalyst is undoubtedly more efficient in terms of yields and enantioselectivity than the analogous catalysts derived from (*R*)-**1** or (*R*)-**2** (all give the same enantiomer) (Table 122, entries 1–3).⁵⁰⁸ The reaction was compatible with several reagents (also with 1-methylpyrrole instead of indole), and the absolute configuration was determined to be (*S*)-**514** for the adduct described in entry 5 of Table 122.

As a consequence of the results presented in this section, it can be seen that, 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 121; Diels–Alder reaction with acryloyloxazolidinone **216** in Table 120, entries 1, 2, and 4; and Friedel–Crafts alkylation of indoles **196** with α'-phosphoric enones **496** in Scheme 206). In other cases **1** gives the opposite enantioselection to that of **9a** and **2** (Diels–Alder reaction with **216** (R = 4-CF₃C₆H₄CO₂) in Table 120, entries 5–7), and the 1-based complex becomes the best catalyst.

5.3. 4-Alkyl-Substituted Boxes

This is by far the section with the largest number of literature references, not only for the variety of substituents but also because two of them (4-isopropyl-box **3c** and 4-benzyl-box **3d**, Chart 6) are among the most popular boxes being used to catalyze several types of reactions. The benchmark for the box complexes in this section is the corresponding complex derived from **2**. A simple reference will be made to those reactions where 4-alkyl-substituted boxes do not significantly improve the efficiency of the benchmark. When the comparison of homogeneous reactions results in a significant improvement of the catalytic efficiency or gives a different result in terms of chirality transfer, the absolute configuration of the products (when available) will be referred to the box ligands with the (4*S*)-configuration.

The ligands **3c** and **3d** have been used as chiral ligands for copper-catalyzed intermolecular cyclopropanation reactions between alkenes and diazo-derivatives,^{115,117–119,132,509,510} and an example of a [3*e*/Cu(I)]-catalyzed intramolecular cyclopropanation is also reported.²⁹ The efficiency of these catalysts is, in general, lower than those derived from **1** or **2**. These results have already been reported in section 4.1.

The comparison of the catalytic effect of [2/Cu(OTf)₂] versus [3*c*/Cu(OTf)₂] on the reaction of methyl 2-furancarboxylic acid **39** and diazoester **30** (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 the diazoester **30** has R = *t*-Bu and the catalyst is [3*c*/Cu(OTf)₂] (95% ee), and the importance of this result may be appreciated since adduct **40** was converted to nephrosteranic acid, roccellaric acid, and protolichesterinic acid.¹²⁹

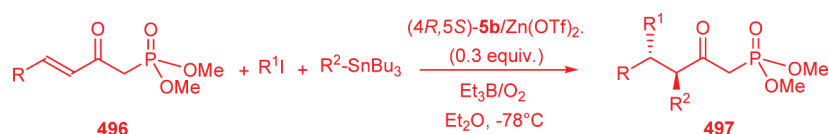
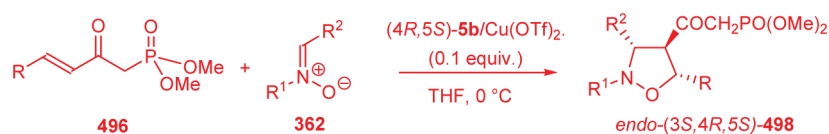
When phenyliodonium ylides are the source of the carbenoids involved in the intramolecular cyclopropanation reactions, the Cu(I) catalysts, derived from **3c** and **3f**, may be expected to give somewhat better results than those based on **2**. However, the values of the enantiomeric excesses show that these catalysts are not suitable for this reaction.^{511,512} The Cu(OTf)₂ **3c** and **3f** complexes should, however, be cited as catalysts for the intramolecular C–H insertion reaction of phenyliodonium ylide **470**, as illustrated in Scheme 181. After hydrolysis, 3-phenylcyclopentanone **471** is obtained with a yield of about 50% and with the same stereoselectivity for both catalysts. However, the enantioselectivities are 42% and 38% ee, respectively, with **3c** and **3f**, versus an ee of 23% obtained with **2**.⁴⁶⁹

An important difference between various 4-alkyl-substituted boxes regarding the enantioselectivity of the intramolecular cyclopropanation of α-diazo-β-ketosulfones **515**, in which R can be either a mesityl or an aryl group, has been reported. The results of catalysis with CuOTf complexes of (*S*)-**2**, (*S*)-**3c**, and (*S*)-**3d** to give the bicyclic reaction products **516** (Scheme 207) are reported in Table 123. The catalysts derived from these boxes induce the same enantioselection, and, in general, (*S*)-**3c** proved

Table 118. Enantioselective Radical Addition of Alkyl Iodides to α' -Phosphoric Enones **496** with [(4*R*,5*S*)-**5b**/Zn(OTf)₂] as Catalyst⁴⁹⁵

entry	R	R ¹	R ²	yield (%)	anti/syn	497 ee (%) (conf.)
1	(CH ₂) ₂ Ph	Et	H	76		89
2	(CH ₂) ₂ Ph	<i>i</i> -Pr	H	85		91
3	(CH ₂) ₂ Ph	<i>c</i> -hexyl	H	61		84
4	(CH ₂) ₂ Ph	<i>t</i> -Bu	H	77		91
5	Me	<i>i</i> -Pr	H	90		88
6	Ph	<i>i</i> -Pr	H	93		90 (<i>S</i>)
7 ^a	Ph	<i>i</i> -Pr	CH ₂ CH=CH ₂	71	20:1	91
8 ^a	Ph	<i>t</i> -Bu	CH ₂ CH=CH ₂	76	>50:1	99
9 ^a	Ph	Cl(CH ₂) ₂ CMe ₂	CH ₂ CH=CH ₂	71	>50:1	97

^a **497** (R² = H) side-products were obtained with yields in the range 7–10% and ee 58–71%.

Scheme 195**Scheme 196**

the most efficient ligand for all the substrates studied.^{142,513} The absolute configuration of **516** is as reported in Scheme 207 except where R¹ = Me (Table 123, entries 8 and 9).

The same stereochemical result as reported in Scheme 207 is obtained in the intramolecular cyclopropanation of 2-diazo-3-oxo-6-heptenoic acid esters. This reaction is analogous to **515** but with a CO₂R group instead of SO₂Me. (*S*)-**3c** is by far a better catalyst than (*S*)-**2**, and the analogous **516** has the (1*R*) configuration. The best result (77% ee) is obtained for the 2,6-di-*tert*-butyl-4-methylphenyl ester.¹⁴³

Among the reactions that use **3c** and **3d** boxes but do not merit specific attention, either because the enantioselectivity is not outstanding or because other boxes or even other chiral ligands give better results, are the hydrosilylation of ketones;⁵¹⁴ Heck-type reactions;⁵¹⁵ the asymmetric [2,3]-Wittig rearrangement of (*E*)-1-benzyloxy-2-TIPSO-but-2-ene **421**, which, as reported in Scheme 163, gives (1*R*,2*S*)-**422** with (*S*)-**3c** and *t*-BuLi (75% yield, 99% ee, a result identical to that obtained with **2**, Table 100, entry 5);⁴²⁸ and the oxidative cross-coupling of 2-naphthol and cross-coupling copolymerization of binaphthols.^{462,465}

Concerning the use of box complexes as chiral polymer catalysts, the Pd(Me)(MeCN) complex of (*S*)-**3c**, whose structure resembles closely that reported in entry 49 of Table 2, was tested in the asymmetric copolymerization of styrene and CO (Scheme 208). It led to the formation of the isotactic copolymer **517** with marked optical activity. One of the limits of using this catalyst is a significant loss of productivity.¹¹²

The aldol reaction between 3-propionyl-2-thiazolidinethione (**136**) and benzaldehyde can be catalyzed with [(*S*)-**3c**/Ni(OTf)₂]. The resulting enantiomeric excess, however, was lower than that for the **2**-based complex.¹⁰² This behavior cannot be generalized. The aldol reaction between the methyl malonic acid half thioester **130** 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 **131** (R = CH₂CH₂Ph) with 87% ee (Scheme 36). On the other hand, the more sterically demanding (*S*)-**2**-based complex gives only traces of the product.¹⁹⁶

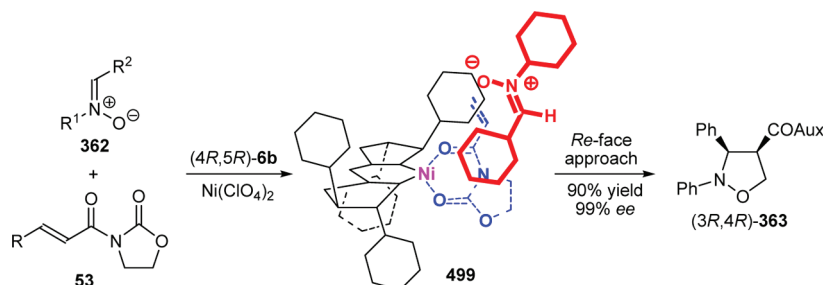
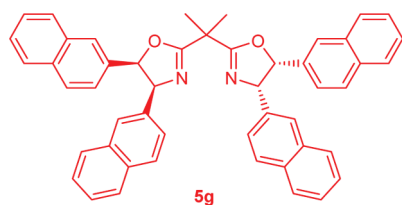
The results of the reactions between α -thio- and α -seleno-carbanions with aldehydes or ketones acting as electrophiles are reported in Table 26.^{199–204,205a} The lithium cation is the Lewis acid that coordinates the carbanion with the chiral ligand. It was found that the reaction of **139a,b** giving **141a,b** (Scheme 209) seldom gives better results with **3c,d** than with **2**.^{199–201} Table 124, which can be considered as a complement to Table 26, compares the results of 4-alkyl-substituted boxes with those for the benchmark **2** catalyst.

Even if the diastereoselectivity proves unsatisfactory (Table 124, entries 8, 9, 15, 20, and 26–29), the enantioselectivity is excellent. The sense of the induction depends on the nature of Ar. When it is a phenyl group, the anion is mono-coordinated to the lithium cation bound to the box, and the less hindered transition state gives the (*S*)-enantiomer (Table 124, entries 1–8 and 21–23). When Ar is either 2-pyridyl or

Table 119. Comparison between Complexes of 4-Ph-box (**1**) and 4,5-di-Ph-box (**5,6b**) as Enantioselective Catalysts for Different Reactions

entry	reaction ^a	reagents	Lewis acid	(4R)- 1			(4R,5S)- 5b			(4R,5R)- 6b			ref
				yield (%)	endo/exo (%)	ee (%) (conf.) ^b	yield (%)	endo/exo (%)	ee (%) (conf.) ^b	yield (%)	endo/exo (%)	ee (%) (conf.) ^b	
1	MMR	226 + 228b (Scheme 83)	Cu(OTf) ₂	99	98:2 ^c	98 (S,S)	95	>99:1 ^c	99 (S,S)	18	83:17 ^c	18 (S,S)	96
2	ICA	288 (Scheme 109)	Cu(OTf) ₂	97		83 (S) ^d	97		88 (S)	97		88 (S)	304
3	ASR	237 + Malon (Scheme 86)	PdCl ₂	23		95 (R)	90		98 (R)	70		97 (R)	48, 497
4	Rad.R.	290 + tBP (Scheme 110)	CuOTf	84		71 (R)	70		80 (R)	80		84 (R)	306, 497
5	DA	216 + Cy (Scheme 114)	Mg(ClO ₄) ₂	>98	96:4	73 (S) ^e	>98	96:4	30 (S) ^e	>98	>99:1	97 (S) ^d	319
6	DA	216 + Cy (Scheme 114)	Mg(ClO ₄) ₂ ^f	>98	95:5	73 (R) ^e	>98	96:4	89 (R) ^e	>98	98:2	78 (S) ^d	319
7	DA	216 + Cy (Scheme 114)	Mg(OTf) ₂	>98	92:8	88 (R) ^e	>98	94:6	93 (R) ^e	>98	89:11	60 (R) ^d	322
8	1,3-DC	53 + 362 (Scheme 138)	Mg(ClO ₄) ₂ ^g	>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)	390
9	1,3-DC	53 + 362 (Scheme 138)	Ni(ClO ₄) ₂ ^g	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)	390
10	1,3-DC	53 + 362 (Scheme 138)	Co(ClO ₄) ₂ ^g	>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)	390
11	1,3-DC	53 + 362 (Scheme 138)	Zn(ClO ₄) ₂ ^g	>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)	390
12	1,3-DC	53 + 362 (Scheme 138)	Mg(OTf) ₂	>98	97:3	86 (R,S)							390
13	IER ^h	385 (Scheme 149)	Mg(ClO ₄) ₂	61		30 (R,R,R)	48		51 (R,R,R)	75		88 (R,R,R)	408

^a MMR is Mukaiyama–Michael reaction; ICA is intramolecular carboamination; ASR is allylic substitution reaction; D is Diels–Alder reaction; 1,3-DC is 1,3-dipolar cycloaddition reaction; IER is intramolecular ene reaction. ^b Absolute configuration of endo/exo isomers. ^c The ratio refers to anti/syn diastereoselectivity, and the ee refers to the major diastereoisomer. ^d Reaction performed with (S)-box and configuration of the product inverted. ^e Absolute configuration of the endo isomer. ^f Plus 2 equiv of H₂O. ^g MS. ^h Stoichiometric conditions.

Scheme 197**Chart 4**

2-quinolyl, the anions behave in a bidentate fashion and the electrophile adds through the Re face, and (R) is the major enantiomer (Table 124, entries 10–14, 16–19, 24, and 25). Each diastereomer of the addition to 4-substituted cyclohexanones, obtained in high optical purity (Table 124, entries 27–29), afforded axially chiral benzylidenecyclohexanes with enantioselectivities of up to 99% ee.^{205a}

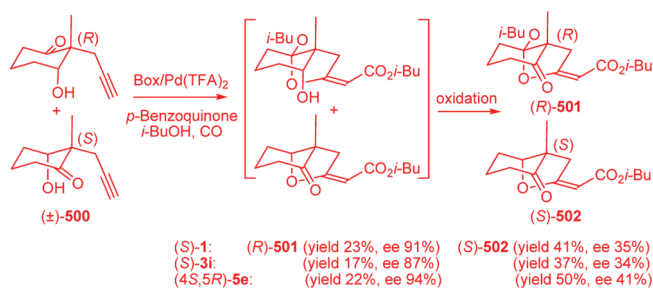
cis-Bicyclo[3.3.0]octane-3,7-dione monoethylene ketals **142** behave as electrophiles in reactions with α -thio- or α -seleno-carbanions derived from 1-phenyl-1-(phenylthio)-1-(tributylstannyl)methane **139a** and bis(phenylseleno)phenylmethane **139b**, respectively. The endo-selective aldol reaction can be catalyzed by BuLi and (S)-**3c** or (S)-**2** to afford (S)-**143**

(Scheme 210).^{205b} Table 25 compares the results for **3c** (entries 1, 3, 5, and 7) with those of the benchmark **2** catalyst, already reported in Table 26. Whereas **3c** is a better ligand for inducing 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*-vinylimines **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 the optically active 1-substituted tetrahydroisoquinolines (R)-**362** (Scheme 211).⁵¹⁶

Several additions to carbonyl groups, the majority of them already mentioned in section 4, take advantage of catalysts based on 4-alkyl-substituted boxes. The Henry reaction, carried out with MeNO₂ and *p*-nitrobenzaldehyde **149** in MeOH (Scheme 44),¹⁰⁰ is catalyzed by [box/Cu(OAc)₂], and (S)-**150** is obtained with 37%, 67%, and 45% ee, with (S)-**2**, (S)-**3c**, and (S)-**3d**, respectively. Again, the more sterically demanding **2** proves not to be the best ligand. It has also been observed that other Henry reactions exhibit similar behavior.^{210,506} Sometimes, the successful choice between two boxes is a matter of the solvent: The Friedel–Crafts/Michael reaction of the indole **196** with diethyl benzylidene malonate **198** (Scheme 212) gives **199** and can be catalyzed by either [(S)-**2**/Cu(OTf)₂] or [(S)-**3c**/Cu(OTf)₂]

Scheme 198



Scheme 199

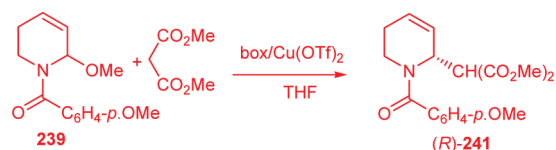
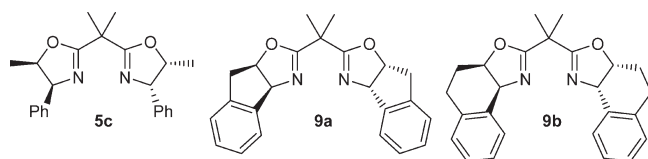


Chart 5



complexes.^{244,517} Table 126 shows the results for both catalysts in four different solvents, and the reverse of the enantioselection of the 3c complex in halogenated solvents appears evident (Table 126, entries 3 and 4).

The same Friedel–Crafts reaction between indole and **198** (but with R¹ = CO₂R) was catalyzed by [(S)-2/Cu(OTf)₂] or [(R)-3d/Cu(OTf)₂] complexes in THF. Taking into account the divergent configuration of the boxes, the results for four homogeneous pairs of **198** (R¹ = CO₂Et or CO₂t-Bu, and R = Me or Et) always give (R)-**199**. It should be noted, therefore, that this is the same configuration as that reported in Scheme 212, and [(R)-3d/Cu(OTf)₂] is always the best catalyst.²⁴⁵

Some aza-Michael reactions involving the addition of hydroxylamines to α,β-unsaturated carbonyl compounds were tested with 3c,d-based complexes and were found to give different results. The addition of O-benzyl-hydroxylamine to 3-(E)-crotonoyl-4,4-dimethyl-2-oxazolidinone **216** (R = R¹ = Me) gave racemates,²⁵³ whereas the reaction between N,O-bis(trimethylsilyl)hydroxylamine and alkylidene malonates **198**, 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 gives yields in the range 52–73% and up to 76% ee.^{257,518} The reaction between 1-benzyl-2-crotonoyl-4,4-dimethylpyrazolidin-3-one **220** and N-(4-methoxybenzyl)-hydroxylamine in Scheme 79 offers a comparison between [(S)-3c/Zn(OTf)₂] and [(S)-3d/Zn(OTf)₂] using [(S)-2/Zn(OTf)₂] as the benchmark. The yields of the chiral isoxazolidine (S)-**222** are

comparable (73–84%), but the enantioselectivities are 70% ee (3c), 50% ee (3d), and 17% ee (2).²⁵⁶

The Mukaiyama–Michael reactions between an activated α,β-unsaturated carbonyl derivative and silylketene acetals were catalyzed using 4-alkyl-box-based complexes with variable results: **107** (A = St-Bu, R² = H) and alkylidene malonates **198** lead to the formation of 3-substituted *tert*-butyl 4,4-dicarbomethoxybutanethioate **223** (Scheme 80). The best enantioselectivities are always obtained with the benchmark [2/Cu(OTf)₂].²⁵⁹ However, the results with the Cu(SbF₆)₂ complexes of (S)-**2**, (S)-**3c**, and (S)-**3d** give an interesting relationship between the box substituents and the selectivity of the reaction.^{95b} The reaction between the same silylketene acetal **107** and 3-[(E)-3-(ethoxycarbonyl)propenyl]-2-oxazolidinone **53** (R = CO₂Et) (Scheme 81) was catalyzed with [(S)-3c/Cu(SbF₆)₂] and the analogous complexes with (S)-**3d** and (S)-**2**.⁹⁴ Whereas the second complex gave a somewhat lower enantioselectivity (78% ee), the first catalyst gave a result identical with that of the benchmark: (S)-**225** is obtained in more than 80% yield and with 89% ee.

β-Lactams can be synthesized using the Kinugasa reaction between alkynes and nitrones. An enantioselective intramolecular example is reported in Scheme 213. Here the alkyne–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 [(S)-3c/CuBr] complex.⁵¹⁹

1,3-Dipolar cycloaddition reactions were 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 the enantioselectivity reported remains unsatisfactory for the moment. Such is the case for the reaction catalyzed by [(S)-3c/CuI] between azomethine imine **523** and ethyl propionate to give the bicyclic product **524** in excellent yield (98%) but with an enantioselectivity of only 19% ee (Scheme 214).⁵²⁰

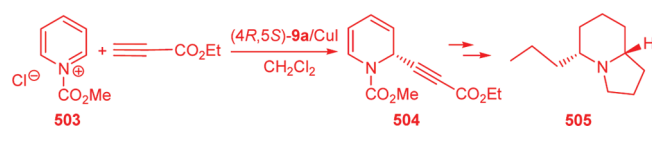
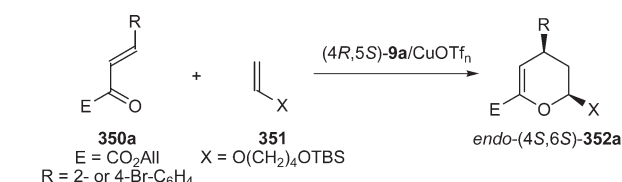
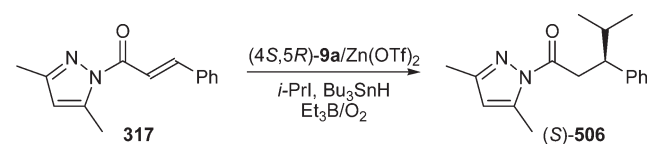
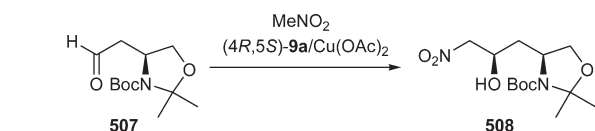
Among the pericyclic reactions, complex [(R)-3d/Cu(OTf)₂] was one of the catalysts tested in the [4 + 3]-cycloadditions reported in Scheme 156, but the enantiomeric excess of (S)-**404** was clearly unsatisfactory.⁴¹⁹ Analogously, only racemic products have been obtained both in the intramolecular ene reaction catalyzed by [(R)-3d/Fe(acac)₃/3 Et₃Al]⁵²¹ and in the aza-Claisen rearrangement of allyl imidates catalyzed by [(S)-3d/PdCl₂(MeCN)₂/AgBF₄].⁵²²

Among the radical reactions, the enantioselective intermolecular addition of ethyl radical to the endocyclic C=N double bond of 5-oxy-3-methyl-2*H*-benzo[*b*][1,4]oxazin-2-one (**525**), catalyzed by [box/Zn(OTf)₂] or [box/Cu(OTf)₂], was explored. Both 3-ethyl and 3,7-diethyl addition products were obtained (Scheme 215, Table 127).³⁰⁵ The best catalyst for the reaction of hydroxy-**525** was [(R)-3d/Zn(OTf)₂]. It gave the diethyl product (R)-**527** in 78% ee (Table 127, entry 3). On the other hand, [(R)-3d/Cu(OTf)₂] was the best catalyst in the reaction of methoxy-**525**, and (S)-**527** was obtained in 54% ee, inverting the enantioselectivity obtained with Zn(OTf)₂ (Table 127, entries 5 and 6).

An important radical reaction involved the 1-substituted 2-alkenyl-4,4-dimethylpyrazolidin-3-one **220**. This is a fruitful reagent that allows the application of the chiral relay strategy to the radical addition. If the process is a substrate-bound radical addition, then the chiral catalysts should 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

Table 120. Comparison between the Cu(OTf)₂ Complexes of Boxes 9a,b, 1, and 2 as Enantioselective Catalysts for the Diels–Alder Reactions between 216 and Cyclopentadiene

entry	R	box	yield (%)	endo/exo	endo ee (%) (conf.)	ref
1	H	(4 <i>S</i> ,5 <i>R</i>)-9a	n.r.	98:2	83 (<i>S</i>)	74, 499
2	H	(<i>S</i>)-1	92	95:5	30 (<i>S</i>)	93
3	H	(4 <i>S</i> ,5 <i>R</i>)-9b	n.r.	98:2	38 (<i>S</i>)	46
4	H	(<i>S</i>)-2	>98	98:2	>98 (<i>S</i>)	93
5	4-CF ₃ C ₆ H ₄ CO ₂	(4 <i>S</i> ,5 <i>R</i>)-9a	99	90:10	83 (<i>R</i> , <i>R</i>)	328
6	4-CF ₃ C ₆ H ₄ CO ₂	(<i>S</i>)-1	99	94:6	89 (<i>S</i> , <i>S</i>)	328
7	4-CF ₃ C ₆ H ₄ CO ₂	(<i>S</i>)-2	99	90:10	54 (<i>R</i> , <i>R</i>)	328

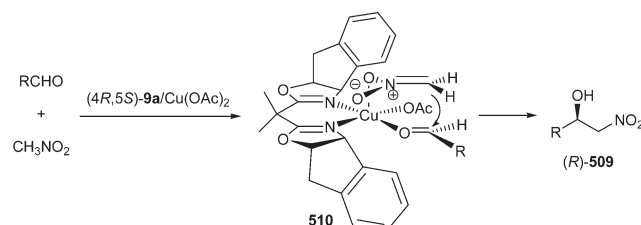
Scheme 200**Scheme 201****Scheme 202****Scheme 203**

R¹I promoted by Et₃B/O₂. The formation of the optically active 528 is catalyzed by Mg(II) and Cu(II) complexes of (*S*)-3a and (*S*)-3c (Scheme 216 and Table 128).⁵²³ Different substituents on the template and different radicals always give excellent yields and enantioselectivities. It was found that the larger the fluxional group in the template, the higher is the selectivity (Table 128, entries 1–4). If the configuration of the box is taken as constant, Co(II) and Mg(II) give opposite enantioselectivity to that induced by Cu(II) (Table 128, 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

Table 121. Comparison between the Cu(OTf)₂ Complexes of Boxes 9a, 1, and 2 as Enantioselective Catalysts for the Henry Reaction of Aldehydes and MeNO₂ in Scheme 204

entry	R	box	yield (%)	ee (%) (conf.)	ref
1	<i>p</i> -NO ₂ C ₆ H ₄	(4 <i>R</i> ,5 <i>S</i>)-9a	85	81 (<i>R</i>)	100
2	<i>p</i> -NO ₂ C ₆ H ₄	(<i>R</i>)-1 ^a	n.r.	43 (<i>R</i>)	100
3	<i>p</i> -NO ₂ C ₆ H ₄	(<i>R</i>)-2 ^a	n.r.	37 (<i>R</i>)	100
4	Ph	(4 <i>R</i> ,5 <i>S</i>)-9a	76	94 (<i>R</i>)	100, 506
5	<i>o</i> -MeOC ₆ H ₄	(4 <i>R</i> ,5 <i>S</i>)-9a	91	93 (<i>R</i>)	100
6	<i>o</i> -NOC ₆ H ₄	(4 <i>R</i> ,5 <i>S</i>)-9a	86	89 (<i>R</i>)	100
7	1-naphthyl	(4 <i>R</i> ,5 <i>S</i>)-9a	66	87 (<i>R</i>)	100
8	<i>i</i> -Pr	(4 <i>R</i> ,5 <i>S</i>)-9a	86	94 (<i>R</i>)	100
9	<i>n</i> -Bu	(4 <i>R</i> ,5 <i>S</i>)-9a	87	93 (<i>R</i>)	100
10	<i>t</i> -Bu	(4 <i>R</i> ,5 <i>S</i>)-9a	83	94 (<i>R</i>)	100

^a Ent-box used in these cases gave (*S*)-509.

Scheme 204

of the weakly directing box (*S*)-3a is enough to induce an enantioselectivity of 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 110 and the results with (*S*)-1 and (*S*)-2 that have been reported in Table 64, 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 for these two boxes give results comparable to those obtained with (*S*)-2.^{306,311} Only the oxidation of cyclohexene with *t*-BuO₂H/AcOH gives better results with the [(*R*)-3d/Cu(I)] catalyst than with the benchmark.³¹⁴

The Diels–Alder reaction between cyclopentadiene and different dienophiles (216, 315, 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 catalyst.^{20,106,316,320} As seen above for

Scheme 205

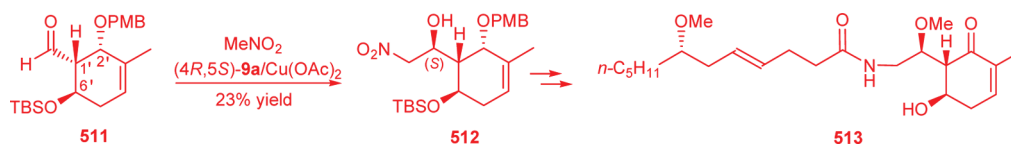


Table 122. Comparison between the $\text{Cu}(\text{OTf})_2$ Complexes of Boxes **9a**, **1**, and **2** as Catalysts for the Friedel–Crafts Alkylation of Indoles **196** with α' -Phosphoric Enones **496** in Scheme 206⁵⁰⁸

entry	R	R ¹	R ²	box	yield (%)	514 ee (%) (conf.)
1	Me	H	H	(4 <i>R</i> ,5 <i>S</i>)- 9a	98	95
2	Me	H	H	(<i>R</i>)- 1	95	35
3	Me	H	H	(<i>R</i>)- 2	34	31
4	<i>i</i> -Pr	H	H	(4 <i>R</i> ,5 <i>S</i>)- 9a	62	86
5	$\text{CH}_2\text{CH}_2\text{Ph}$	H	H	(4 <i>R</i> ,5 <i>S</i>)- 9a	98	97 (<i>S</i>)
6	Me	Me	H	(4 <i>R</i> ,5 <i>S</i>)- 9a	98	86
7	$\text{CH}_2\text{CH}_2\text{Ph}$	Me	H	(4 <i>R</i> ,5 <i>S</i>)- 9a	95	94
8	Me	H	OMe	(4 <i>R</i> ,5 <i>S</i>)- 9a	90	95
9	Me	H	Cl	(4 <i>R</i> ,5 <i>S</i>)- 9a	86	88
10	Me	H	Br	(4 <i>R</i> ,5 <i>S</i>)- 9a	85	86

the radical reactions, if the chiral relay strategy promoted by **216** ($\text{R} = \text{Me}$) is applied to the Diels–Alder reaction with cyclopentadiene (Scheme 217, Table 129), then the $\text{Cu}(\text{OTf})_2$ complexes of (*S*)-**3a**, (*S*)-**3c**, and (*S*)-**3d** give enantiomeric excesses of (2*S*,3*R*)-**529** that are comparable with the best values obtained with (*S*)-**2** and reported in the literature.^{20,326}

The role of the fluxional *N*-group in **220** was examined: When *R* is hydrogen, the products obtained are nearly racemic (Table 129, entry 2). When *R* is the bulky 1-naphthylmethyl group, the enantiomeric excesses obtained are up to 99% (Table 129, entry 6). With smaller groups, lower enantioselectivities were observed. Additional methyl groups on the C-5 position of the pyrazolinone were found to be of fundamental importance for increasing the enantioselectivity (Table 129, entries 6–9). When these conditions are satisfied, the pyrazolidinone templates are able to relay stereochemical information to the reacting center even from the small **3a** box. To evaluate the contribution of the template **220**, it is necessary to compare the difference between the enantiomeric excesses obtained (Table 129, entries 2–6) with those obtained using **216** ($\text{R} = \text{Me}$) (Table 129, entry 1).

The prototype of the allylic substitution reaction between *rac*-3-acetoxy-1,3-diphenyl-1-propene **237** and dimethyl malonate affords the optically active methyl (*E*)-2-methoxycarbonyl-3,5-diphenylpent-4-enoate **238** as reported in Scheme 86. Employing [(*R*)-**3d**]/ $\text{Pd}(\text{C}_3\text{H}_5\text{Cl})$ in CH_2Cl_2 , and KOAc with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as the base, (*R*)-**238** was obtained in 97% yield and 88% ee.^{21,51,524} Later, the same reaction was used to make a systematic comparison between a series of thiazoline and oxazoline ligands. The 4-alkyl-substituted boxes (*R*)-**3b**, (*R*)-**3c**, (*R*)-**3d**, and (*R*)-**2** all give (*R*)-**238**. Respective yields (and enantioselectivities) are 7% (4% ee), 8% (19% ee), 97% (88% ee), and 20% (33% ee).²⁶⁶

The allylic substitution reaction has several intramolecular versions where the reagent undergoing the cyclization is derived

using different routes. *N*-Tosyl-2-iodoaniline **242** ($\text{R}^1 = \text{H}$) reacts with 1,2-undecadiene **243** undergoing a palladium-catalyzed coupling to give a palladium complex that subsequently undergoes the intramolecular allylic substitution reaction affording *N*-tosyl-2,3-dihydro-3-methylene-2-*n*-octylindole **245** ($\text{R}^1 = \text{H}$) (Scheme 218).^{271,525} The yields (88% and 94%) and the enantioselectivities (67% and 82% ee) using (*S*)-**3c** and (*R*)-**3d**, respectively, suggest that the latter is the optimal ligand for this reaction. When the reaction was run using **242** ($\text{R}^1 = \text{Br}$), this not only allowed the determination of the absolute (*S*)-configuration of **245** ($\text{R}^1 = \text{Br}$, 64% yield, and 67% ee) but also made it possible to infer the catalytic mechanism of the intramolecular nucleophilic displacement. Using the catalyst based on (*R*)-**3d**, several heterocycles, either monocyclic or bicyclic, were obtained with enantioselectivities often >80% ee.^{271,525}

A somewhat similar reaction occurs between the 2,3-allenoic acids **530** and aryl iodides that, under conditions specific for the coupling cyclization, afford butenolides **531** (Scheme 219). 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**. For a series of aryl iodides and 2,3-allenoic acids using the same catalyst the enantiomeric excess is always around 50% ee.⁵²⁶

Not every intramolecular allylic substitution reaction is suitable for catalysis by the **3c,d**-palladium complexes, since several examples afford racemates or unsatisfactory enantioselectivities.^{274,275,279,527}

The radical addition arising from alkyl iodides with alkylidene sulfones bound to pyridyl, or even better to the benzimidazolyl moiety **275a,b**, gives the radical **276**. This can then be trapped either by allylation (with $\text{Bu}_2\text{Sn}(\text{allyl})_2$) or by hydrogen (with Bu_3SnH) (Scheme 104). The best catalyst is [(*S*)-**1**]/ $\text{Zn}(\text{OTf})_2$. The screening of the analogous complexes with (*S*)-**2**, (*S*)-**3c**, and (*S*)-**3d** gives enantiomeric compositions close to racemates.^{296,297}

Several box-catalyzed radical processes involve *N*-acyl substituted oxoheterocycles, which behave as bidentate reagents during the catalytic cycle. Among them, compounds **53** ($\text{R} = \text{Me}$ or Ph) react with the radical derived from the cleavage of R^2I to give **267**. This is formally the product of the conjugate addition of R^2H (Scheme 99). The best results using stoichiometric amounts of [(*S*)-**2**]/ MgBr_2 (Table 58) and [(*S*)-**3e**]/ MgI_2 were obtained with cinnamoyl-**53** (77% and 82% ee, respectively) and crotonoyl-**53** (82% and 74% ee, respectively). These results have been achieved only by using catalytic amounts of the **3e**-based catalyst.²⁸⁹

Some reactions require **3d**-box specific tailor-made catalysts. For example, there are several applications of the Mukaiyama–aldol reaction using 4-alkyl-substituted box-based catalysts.^{179,183,186} Among them, the reaction first mentioned in Scheme 28 but repeated for clarity in Scheme 220, between ethyl glyoxylate **106b** and silylketene acetals **107**, is strongly anti-selective. It gives **108b** and makes it possible to check the effect on the enantioselectivity of the $\text{Sn}(\text{OTf})_2$ complexes of (*S*)-**3c** and (*S*)-**3d** (Table 130),

Scheme 206

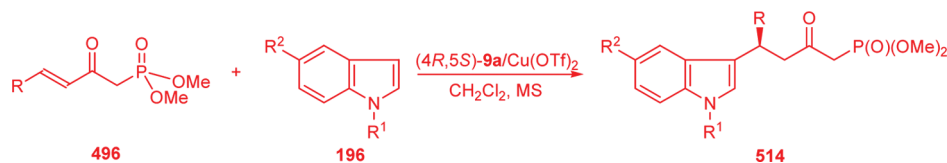


Chart 6

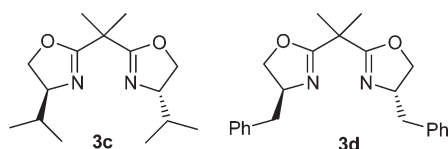
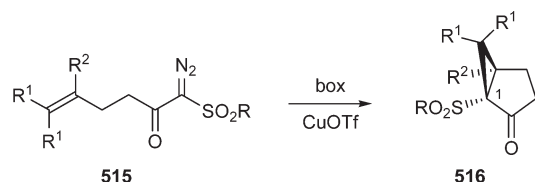


Table 123. Comparison between the CuOTf Complexes of Boxes 2, 3c, and 3d as Enantioselective Catalysts for the Intramolecular Cyclopropanation of α -Diazo- β -ketosulfones 515 in Scheme 207

entry	R ¹	R ²	R	box	yield (%)	516 ee (%) (conf.)	ref
1	H	H	mesityl	(S)-2	48	31 (1R)	513
2	H	H	mesityl	(S)-3c	93	83 (1R)	513
3	H	H	mesityl	(S)-3d	78	72 (1R)	513
4	H	Br	mesityl	(S)-3c	68	92 (1S)	513
5	H	Br	mesityl	(S)-3d	44	56 (1S)	513
6	H	CH ₂ OTr	mesityl	(S)-3c	91	78 (1R)	513
7	H	CH ₂ OTr	mesityl	(S)-3d	96	73 (1R)	513
8	Me	H	mesityl	(S)-3c	74	74 (1R)	513
9	Me	H	mesityl	(S)-3d	77	71 (1R)	513
10	H	H	1-naphthyl	(S)-2	59	45 (1R)	142
11	H	H	1-naphthyl	(S)-3c	95	72 (1R)	142
12	H	H	1-naphthyl	(S)-3d	91	71 (1R)	142
13	H	H	2,4-diMePh	(S)-2	89	37 (1R)	142
14	H	H	2,4-diMePh	(S)-3c	83	62 (1R)	142
15	H	H	2,4-diMePh	(S)-3d	75	72 (1R)	142

Scheme 207

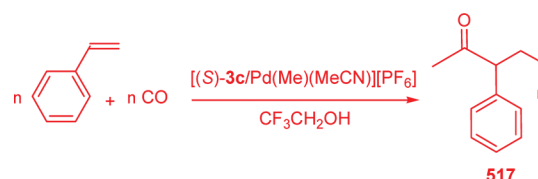


compared to the 91% ee obtained with [(S)-1/Sn(OTf)₂] (Table 20, entry 9).¹⁸⁰

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 **106b** and the silylketene acetals **107** (R = SPh; R¹ = (2R)-sec-butyl). The adduct (2S,3R)-**108b**, obtained with the same enantioselection reported 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.⁵²⁸

A new catalytic technology for the Mukaiyama–aldol reaction was developed by the Kobayashi group. First it consisted in running the reaction in H₂O–EtOH solutions.^{529,530} Later organic

Scheme 208



solvents were able to be completely avoided by using a combined Lewis acid–surfactant catalyst system [box/Cu(II)dodecyl sulfate],⁵³¹ in accordance with green chemistry paradigms. The reactions between several monodentate aldehydes and silylketene acetals **107** are all syn-selective and give **532** (Scheme 221, Table 131).

The best box proved to be (S)-3c, and the inversion of the stereoselection on going from 4-alkyl-substituted boxes [(S)-3c, **d,ag,ah**] to (S)-2, which is also the worst ligand in terms of the induced enantioselectivity, seems rather unusual (Table 131, entries 1, 2, and 4–7). Through the use of [(S)-3c/Cu(II)dodecyl sulfate] as the catalyst, the Lewis acid nature of the cation appears to exert a greater influence on yield than stereoselectivity (Table 131, entries 10, 11, 17, and 18).

The cyclization of optically active allenylhydrazine (R)-533 with organic iodides RI allows access to the pyrazoline derivatives *trans*-(3R,5S)- and *cis*-(3R,5S)-**248**. This is a class of heterocyclic compounds that have already been discussed in a previous section (Scheme 89). If the reaction is catalyzed by the [(R)-3d/Pd(OAc)₂] complex, the products are obtained in good yields, with high diastereoselectivities and high enantiopurities (Scheme 222).²⁷³ The results obtained by using different organic iodides are reported in Table 132. In addition, the correlation between the configuration of the chiral substrate, that of the catalyst, and the stereoselectivity of the reaction are also reported. From a comparison of these results, it is evident that the importance of matching/mismatching between substrate and box to determine the origin of the asymmetric induction cannot be underestimated.

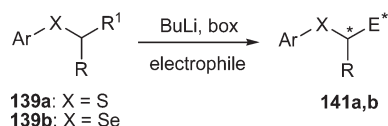
The complex [(R)-3d/CuCl₂] formed from 1.0 mol of PhCOCl and diisopropylethylamine is an excellent catalyst for the desymmetrization of *meso*-diols **438**, because monobenzoylated (1S,2R)-**440** products are obtained with very good enantiomeric excesses (Scheme 223).⁴⁴⁰

The complex [(R)-3d/Cu(OTf)₂] is a tailor-made catalyst for the alcohol dehydrogenase model reaction between the α -ketoesters **106** and the Hantzsch ester **534** that gives the α -hydroxyesters (S)-**535** with yields and enantiomeric excesses better than those achieved with other box-based catalysts (Scheme 224, Table 133). Among the different α -ketoester substituents, the best radical on the ester moiety is the *tert*-butyl group (Table 133, entries 3–5). On the other hand, a wider

Table 124. Enantioselective Addition of α -Sulfenyl and α -Selenyl Carbanions from **139a,b** to Various Carbonylic Electrophiles Catalyzed by LiBu and 4-Alkyl-Substituted Boxes

entry	Ar	X	R	R ¹	box	electrophile	yield (%)	anti/syn	ee (%) (conf)	ref
1	Ph	S	Ph	SnBu ₃	(S)- 3d	Ph ₂ CO	17		59 (S)	199, 200
2	Ph	S	Ph	SnBu ₃	(S)- 3c	Ph ₂ CO	79		99 (S)	199, 200
3	Ph	S	Ph	H	(S)- 3c	Ph ₂ CO	40		97 (S)	200
4	Ph	S	Ph	SePh	(S)- 3c	Ph ₂ CO	93		93 (S)	200
5	Ph	S	Ph	SnBu ₃	(S)- 3c	Me ₂ CO	71		>99 (S)	199, 200
6	Ph	S	Ph	SnBu ₃	(S)- 3c	Cyhex ^c	100		98 (S)	199, 200
7	Ph	S	Ph	SnBu ₃	(S)- 3c	CO ₂	87		74 (S)	200
8	Ph	S	Ph	SnBu ₃	(S)- 3c	PhCHO	100	40:60	87 (1S,2S) ^a	199, 200
9	Ph	S	Ph	SnBu ₃	(S)- 3c	EtCHO	51	62:38	96 ^b	199, 200
10	2-Pyr	S	Ph	H	(S)- 2	Ph ₂ CO	86		90 (R)	200
11	2-Pyr	S	Ph	H	(S)- 3d	Ph ₂ CO	13		58 (R)	200
12	2-Pyr	S	Ph	H	(S)- 3c	Ph ₂ CO	89		64 (R)	200
13	2-Pyr	S	Ph	H	(S)- 3c	Me ₂ CO	67		54 (R)	200
14	2-Pyr	S	Ph	H	(S)- 3c	CO ₂	60		70 (R)	200
15	2-Pyr	S	Ph	H	(S)- 3c	PhCHO	94	63:37	81 ^b	200
16	2-Quin	S	Ph	H	(S)- 2	Ph ₂ CO	99		71 (R)	201
17	2-Quin	S	Ph	H	(S)- 3c	Ph ₂ CO	95		89 (R)	201
18	2-Quin	S	Ph	H	(S)- 3c	Me ₂ CO	40		80 (R)	201
19	2-Quin	S	Ph	H	(S)- 3c	CO ₂	54		83 (R)	201
20	2-Quin	S	Ph	H	(S)- 3c	PhCHO	55	55:45	93 ^b	201
21	Ph	Se	Ph	Se-Ph	(S)- 2	Ph ₂ CO	63		70 (S)	203
22	Ph	Se	Ph	Se-Ph	(S)- 3c	Ph ₂ CO	60		85 (S)	203
23	Ph	Se	Ph	Se-Ph	(S)- 3d	Ph ₂ CO	51		67 (S)	203
24	2-Pyr	Se	Ph	Se-Ph	(S)- 2	Ph ₂ CO	51		41 (R)	203
25	2-Pyr	Se	Ph	Se-Ph	(S)- 3c	Ph ₂ CO	50		56 (R)	203
26	Ph	S	Ph	SnBu ₃	(S)- 2	4- <i>t</i> -Bu-cyhex ^c	68	64:36 ^d	92 ^e	205a
27	Ph	S	Ph	SnBu ₃	(S)- 3c	4- <i>t</i> -Bu-cyhex ^c	65	63:37 ^d	99 ^e	205a
28	Ph	Se	Ph	SnBu ₃	(S)- 3c	4-Me-cyhex ^c	71	65:35 ^d	99 ^e	205a
29	Ph	Se	Ph	SnBu ₃	(S)- 3c	4-Ph-cyhex ^c	53	52:48 ^d	99 ^e	205a

^a Configuration of the major syn isomer. ^b Configuration of the major anti isomer. ^c Cyhex = cyclohexanone. ^d Cis/trans. ^e Configuration of the major cis isomer.

Scheme 209

flexibility is compatible for the R substituent on the ketonic function.⁵³²

The complex [(S)-**3d**/Cu(OTf)₂] also proved to be the best catalyst for the Friedel–Crafts addition of indole **196** to *N*-sulfonyl aldimines **164** to give (S)-**536** (Scheme 225).⁵³³ Table 134 (entries 1–4) reports the results with the most common boxes and Cu(II). The comparison of the yield and the enantioselectivity obtained with [(S)-**2**/Cu(OTf)₂] (entry 2) with those obtained with the same catalyst in the Friedel–Crafts reaction of indole with diethyl benzylidene malonate **198** (Scheme 212, Table 126)^{244,245,517} justifies the term “tailor-made catalyst”. The enantioselectivity is always excellent, and the steric hindrance of the sulfonyl group has some minimal influence on the yield of the reaction only (Table 134, entries 6, 7, and 9).

In addition to the above example, the majority of the results reported in this section all suggest that the isopropyl, benzyl, and *tert*-butyl boxes are the only 4-alkyl-substituted boxes suitable for inducing good or excellent enantioselective reactions. The only exception seems to be the Diels–Alder reaction between **220** and cyclopentadiene (Scheme 217). Here even the small **3a** box is able to induce a good enantiomeric excess. This exception is

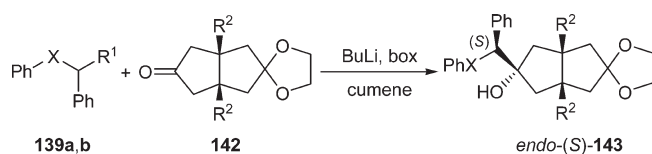
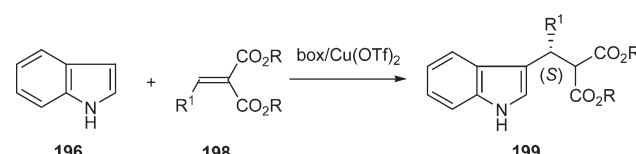
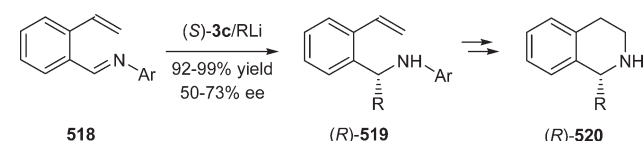
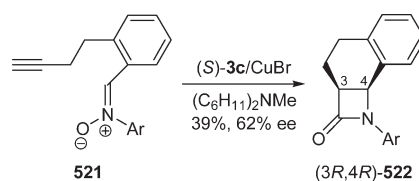
certainly due to the fluxional *N*-groups of the pyrazolidinone templates, which are able to relay stereochemical information to the reacting center. This could also be because boxes with small alkyl groups like **3a**, **3b**, or **3e** are usually forgotten when choosing the ligand for the catalyst.

Already the radical additions to α,β -unsaturated 2-pyridyl ketones **269** to give **270** have been catalyzed with the [(S)-1/Zn(OTf)₂] complex (Scheme 101). The reaction was tested with different (S)-4-alkyl boxes, which all gave (S)-**270**.²⁹³ Different (S)-4-alkyl boxes have been used in the *n*-butyl lithium-catalyzed asymmetric intramolecular hydroamination of aminoalkenes **537**, and all reactions gave (S)-**538**.³⁴ The enantioselective desymmetrization of 2,2-disubstituted *meso*-1,3-diols **445** with CuCl₂–box complexes, benzoyl chloride, and triethylamine, already mentioned in Scheme 171, was catalyzed using a series of 4-alkyl-substituted boxes either on derivatives with a 2-hydroxy substituent **446a**⁴⁴⁴ or with derivatives having the 2-benzoylamino substituent **446b**.⁴⁴⁵ The above reactions are reiterated in Scheme 226, and their enantioselectivities are reported in Table 135. The different boxes are listed in the order of the Taft steric parameter *E*_S of the alkyl group because it is a measure of its steric hindrance.^{534,535}

Obviously one cannot expect the same trend of enantioselectivities for such varied reactions, catalyzed by such different Lewis acids. However, some common aspects are certainly unexpected. Surprisingly, the worst ligand for all four reactions is box **2** (Table 135, entry 9). Again unexpectedly, the best box for reactions 3 and 4 (the only ones for which it was tested) is the ethyl box **3b** (Table 135, entry 2). With two exceptions—entry 4,

Table 125. Comparison between Boxes (S)-3c and (S)-2 in the Enantioselective Addition of α -Sulfenyl and α -Selenyl Carbanions Derived from 139a,b^{205b}

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 210**Scheme 212****Scheme 211****Scheme 213****Table 126.** Enantioselective Additions of 198 (R = Et, R¹ = Ph) to Indole: Relationship between Solvent, Box, and Enantioselectivity

entry	solvent	(S)-2/Cu(OTf) ₂		(S)-3c/Cu(OTf) ₂		ref
		yield (%)	ee (%) (conf.)	yield (%)	ee (%) (conf.)	
1	THF	77	60 (S)	99	46 (S)	244
2	<i>i</i> -BuOH	95	40 (S)	99	83 (S)	244, 517
3	CH ₂ Cl ₂	71	57 (S)	88	67 (R)	244
4	(CHCl ₂) ₂	20	27 (S)	89	71 (R)	244

reaction 1, and entry 3, reaction 4—the overall result could be interpreted as a balance between a positive effect of the alkyl steric hindrance in differentiating the enantioface of the favored attack and the negative effect of the alkyl steric hindrance in the selective coordination of the reagent to the catalyst. A short comment regarding the results of reaction 2, reported in entries 7 and 8, in which the box ligands have a chiral alkyl group in position 4, is necessary. Box (S)-3ak has a *sec*-butyl group with an (S) configuration, and the enantiomeric excess of (S)-538 (66%) is in agreement with the series of other results. Box (R)-3al again has the *sec*-butyl group with an (S) configuration, but the product is (R)-538, and the enantioselectivity is 91% ee, which is the result of a matching pair situation.

Despite the above considerations, this section is still based on a comparison between the results obtained from catalysts with 4-alkyl-substituted boxes as ligands and the benchmark, which is

the corresponding complex derived from 2. One box that reproduces the results of the benchmark is 2,2'-isopropylidenebis[(R)-(1-adamantyl)-2-oxazoline] 3g (Chart 7).²⁴ Four reactions have been tested following the protocols reported in the literature for (S)-2, the cyclopropanations of styrene and 1,1-diphenylethylene with ethyl diazoacetate (Scheme 6, Table 3, entries 1 and 9), the Kharasch reaction between cyclopentene and *tert*-butylperbenzoate (Scheme 110, Table 64, entry 1), and the Diels–Alder reaction between 216 and cyclopentadiene (Scheme 114, Table 65, entry 7). For each reaction the result was the same as that obtained with the benchmark catalyst.

5.4. 4-Alkyl-5-Substituted Boxes

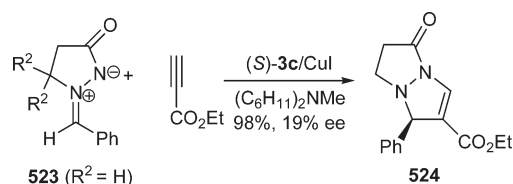
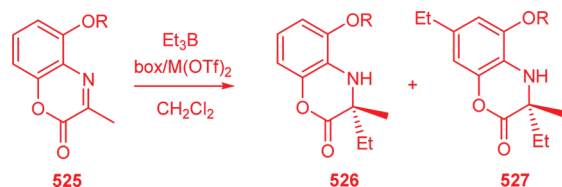
Very few examples are known of boxes with an alkyl group in position 4 and an additional group in position 5. If those boxes with heteroatoms in the substituents are excluded (since these will be considered in a next section), then only ligands 5a and 6a, prepared from norephedrine,¹⁵ (Chart 8) have found rare applications in such catalysis. Since with only the methyl group in position 4 a weakly directing box results, with a phenyl group in position 5, a strong influence on the sense of the induction could be expected. However, the results were disappointing.

[(4S,5R)-5a/Cu(OTf)₂] was tested as a catalyst for the enantiotopic differentiation of pro-R or pro-S chlorines in (dichloromethyl)borate 480 by BuLi (Scheme 186): The resulting (1-chloropentyl)boronate 481 was a racemate.⁴⁷⁷ [(4S,5S)-6a/Mg(ClO₄)₂] catalyzed the intramolecular ene reaction of (E)-1-acetyl-3-[2-(3-methyl-2-butenyloxy)benzylidene]-2-oxindole 385 (Scheme 149),

Table 127. Effect of Box and Triflates on the Enantioselective Ethyl Radical Addition to Ketimine **525**³⁰⁵

entry	OR	box ^a	M(OTf) ₂	526 yield %	526 ee (%) (conf.)	527 yield %	527 ee (%) (conf.)
1	OH	(<i>R</i>)- 2	Zn(OTf) ₂	50	6	38	22 (<i>R</i>)
2	OH	(<i>R</i>)- 3c	Zn(OTf) ₂	36	3	31	racemate
3	OH	(<i>R</i>)- 3d	Zn(OTf) ₂	49	33	35	78 (<i>R</i>)
4	OH	(<i>R</i>)- 3d	Cu(OTf) ₂	32	72	trace	
5	OMe	(<i>R</i>)- 3d	Zn(OTf) ₂	<i>b</i>		31	28 (<i>R</i>)
6	OMe	(<i>R</i>)- 3d	Cu(OTf) ₂	<i>b</i>		35	54 (<i>S</i>)

^a The configuration is that illustrated in the reference. ^b Monoethylated product **526** was also obtained in 21–34% yield.

Scheme 214**Scheme 215**

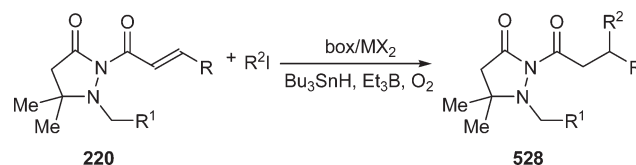
and (3*S*,3'*S*,4'*S*)-**386** was obtained in 63% yield and 47% ee. This is not a bad result, first because a reaction that usually requires stoichiometric amounts of catalysts can be run under catalytic conditions (ratio reagent/catalyst = 3:1), and second because this is one of the most chemoselective catalysts since the ratio hetero Diels–Alder/intramolecular ene reaction is 91:9.⁴⁰⁸

Two unusual boxes have been recently synthesized (Chart 8): The first is the 5-phenyl box (*R*)-**5h**, which was tested in the Cu(I)-catalyzed cyclopropanation of styrene and ethyl diazoacetate (Scheme 5) and gave no more than 30% ee.^{47a} The second is box **5i**, synthesized from (2*S*,3*R*)-aminoisoborneol, the use of which was limited to the cyclization of **537** to (*R*)-**538** (Scheme 226, reaction 2), even though the yield and the enantiomeric excess were excellent (98% and 86% ee, respectively).³⁴

More recently, another new box has been synthesized:⁷⁹ (3*aR*,3'*aR*,8*bS*,8'*bS*)-2,2'-isopropylidene-bis[3*a*,8*b*-dihydro-4*H*-indeno[2,1-*d*]oxazole (**9h**). If this is compared with its isomer (3*aS*,3'*aS*,8*bR*,8'*bR*)-2,2'-isopropylidene-bis[3*a*,8*a*-dihydro-8*H*-indeno[1,2-*d*]oxazole (**9a**) (Chart 8), then overall it can be considered as a 4-alkyl-5-aryl-substituted box vs a 4-aryl-5-alkyl-substituted box. To evaluate the difference between the two catalysts with the same Lewis acid derived from these boxes for the same reaction, a comparison was done between the catalytic efficiency of their Pd complexes on the classic allylic alkylation of 1,3-disubstituted 3-acetoxy-1-propene **237** with dimethyl malonate to give **238** (Scheme 227, Table 136).⁷⁹

Table 128. Enantioselective Additions of a Radical to **220**: Effect of Box and Lewis Acid on the Enantioselectivity⁵²³

entry	R	R ¹	R ²	box	MX ₂	yield (%)	528 ee (%) (conf.)
1	Ph	<i>n</i> -Pr	<i>i</i> -Pr	(<i>S</i>)- 3a	Cu(OTf) ₂	95	52 (<i>S</i>)
2	Ph	<i>i</i> -Pr	<i>i</i> -Pr	(<i>S</i>)- 3a	Cu(OTf) ₂	95	58 (<i>S</i>)
3	Ph	1-Naphth	<i>i</i> -Pr	(<i>S</i>)- 3a	Cu(OTf) ₂	91	90 (<i>S</i>)
4	Ph	Ph	<i>i</i> -Pr	(<i>S</i>)- 3a	Cu(OTf) ₂	92	82 (<i>S</i>)
5	Ph	Ph	<i>i</i> -Pr	(<i>S</i>)- 3a	Co(ClO ₄) ₂	87	58 (<i>R</i>)
6	Ph	Ph	<i>i</i> -Pr	(<i>S</i>)- 3c	Mg(NTf ₂) ₂	90	62 (<i>R</i>)
7	Ph	Ph	<i>i</i> -Pr	(<i>S</i>)- 3c	Cu(OTf) ₂	94	98 (<i>S</i>)
8	Ph	Ph	Et	(<i>S</i>)- 3c	Cu(OTf) ₂	83	92
9	Ph	Ph	<i>t</i> -Bu	(<i>S</i>)- 3c	Cu(OTf) ₂	92	98
10	Me	Ph	<i>i</i> -Pr	(<i>S</i>)- 3c	Cu(OTf) ₂	80	95 (<i>S</i>)
11	Et	Ph	<i>i</i> -Pr	(<i>S</i>)- 3c	Cu(OTf) ₂	84	98 (<i>S</i>)
12	3-furyl	Ph	<i>i</i> -Pr	(<i>S</i>)- 3c	Cu(OTf) ₂	60	95 (<i>S</i>)
13	CO ₂ Et	Ph	<i>i</i> -Pr	(<i>S</i>)- 3c	Cu(OTf) ₂	52	58 (<i>S</i>)

Scheme 216

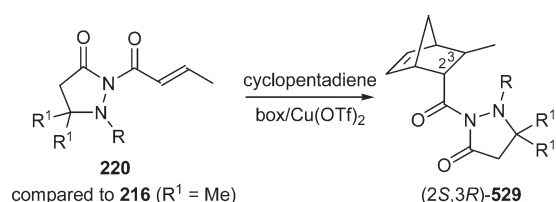
The shielding of **9a** and **9h** is somewhat unexpected: it looks similar for 3-acetoxy-1,3-diphenyl-1-propene (Table 136, entries 1 and 2), but it is deeply different for 4-acetoxy-2-pentene (entries 3 and 4). Adversely, the sense of the stereoselection is that generally expected because **9a** and **9h** give the opposite enantiomers with both substrates.

A new class of carbohydrate-based box ligands was prepared with excellent yields starting from D-glucosamine **539** to give boxes with either 3-*O* substituents of varying steric and electronic demand **16a–d**^{11,12} or others either with or without a cyclic acetal group in a pyranose conformation **17a–g** (Scheme 228).^{12,13}

These ligands were tested in an asymmetric Cu(I)-catalyzed cyclopropanation reaction. Results revealed a strong dependence of the enantioselectivity on both the steric and electronic demands of R as well as on the ligand conformation.^{11,13} The model reaction between styrene **29** and ethyl diazoacetate **30** (Scheme 229) with the new box complexes was used to evaluate the results of the induced enantioselectivity on the trans and cis products **31** and **32** (Figure 19). Results were compared with those obtained using the two classic boxes, (*S*)-**3c** and (*R*)-**2**.^{9,16} The latter was used as the benchmark for the reaction.

Table 129. Enantioselective Diels–Alder Reactions between Cyclopentadiene and 220: Effect of Dienophile Substituents and Box on Enantioselectivity^a

<i>n</i>	220: R	220: R ¹	[(<i>S</i>)-3a/Cu(OTf) ₂]		[(<i>S</i>)-3c/Cu(OTf) ₂]		[(<i>S</i>)-3d/Cu(OTf) ₂]		[(<i>S</i>)-2/Cu(OTf) ₂]		ref
			endo/exo	ee (%)	endo/exo	ee (%)	endo/exo	ee (%)	endo/exo	ee (%)	
1	216		88:12	38	87:13	23	86:14	17	81:19	54	20, 326
2	H	Me	91:9	29	95:5	8	86:14	3			20
3	Ethyl	Me	91:9	64	96:4	56	88:12	55	93:7	77	20, 326
4	Benzyl	Me	93:7	71	92:8	84	91:9	71	92:8	97	20, 326
5	CH ₂ –(2-naphthyl)	Me	93:7	79	91:9	65	90:10	69	93:7	99	20, 326
6	CH ₂ –(1-naphthyl)	Me	90:10	86	93:7	95	87:13	85	90:10	99	20, 326
7	CH ₂ –(1-naphthyl)	H			71:29	63					326
8	CH ₂ –(1-naphthyl)	(CH ₂) ₄			88:12	97					326
9	CH ₂ –(1-naphthyl)	benzyl			87:13	96					326

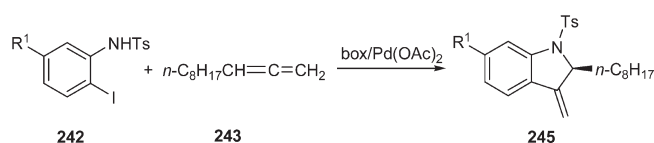
^a All products are (1*S*,2*S*,3*R*,4*R*)-366.**Scheme 217**

The diastereoselectivity was found to be nearly constant for all 11 reactions studied (31/32 = 71:29 ± 6%). The three new boxes (16a, 16d, and 17d), however, gave excellent enantiomeric excesses very close to those obtained with the benchmark catalyst. In several cases they proved even better than those achieved with the 3c-based catalyst.

5.5. 4-Aryl- and 4-Alkyl-5,5-Disubstituted boxes

The boxes 4a–j and 4m–o shown in Chart 1 have either an aryl or an alkyl group in position 4 as well as 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, soon after the very first two papers,^{9,10} Corey and Ishihara reported the synthesis of (*S*)-4g. Its complexes with Fe(III) and Mg(II) were tested on the Diels–Alder reaction between 216 (R = R¹ = H) and cyclopentadiene as seen in Scheme 114.⁴² The results with [(*S*)-4g/FeI₃/I₂] (yield 87%, endo/exo 95:5, and 85% ee of (*R*)-303) are slightly higher than those for the parallel experiments for the complex with (*S*)-1 (Table 66, entry 1). However, the most interesting result is obtained with [(*S*)-4g/MgI₂/I₂]: yield 82%, endo/exo 97:3, and 91% ee of (*R*)-303. For the first time the reacting intermediate of a box-catalyzed reaction is found to have only one arrangement of the box and the dienophile, namely, a well-defined tetrahedral geometry (Figure 20). Clearly this is the key to interpreting the transmission of the chiral information from the ligand to the product.

The addition of two substituents into position 5 rarely has a beneficial effect on the 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 reaction, which yields sirenin where the 4g-based catalyst gives a racemate.¹³⁹ The same results were found in the intramolecular allylic substitution carboannulation of allenes²⁷¹

Scheme 218

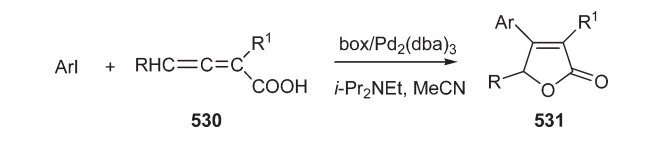
and in the enantioselective mercuriocyclization of γ-hydroxy-*cis*-alkenes.⁴⁹³ If the enantiomeric excesses of the Kharasch reaction on cyclopentene, cyclohexene, and cyclooctene (Scheme 110) catalyzed by [(*S*)-2/Cu(OTf)₂] (Table 64, entries 1, 7, and 15) are compared with those from [(*S*)-4e/Cu(OTf)₂], the results demonstrate an ineffectual effect of the 5-substituents. On the other hand, [(*S*)-4g/Cu(OTf)₂], which fails with cyclohexene and cyclooctene, is in fact the best catalyst for cyclopentene (49% yield and 81% ee of (*S*)-291 (Ar = Ph, *n* = 1)).^{307,308}

The addition of (*E*)-styrylzirconocene chloride 540 to 3,4-dihydroisoquinoline 541 in the presence of (Boc)₂O is catalyzed by [(*S*)-4e/Cu(MeCN)₄PF₆] and gives (*S*)-542 in 65% yield and 75% ee (Scheme 230). As can be seen from the results, there is a decrease in yield but a marked improvement of the enantioselectivity (90 and 50% ee) when compared to the 5,5-unsubstituted catalyst derived from (*S*)-2.⁵³⁶

Sometimes the presence of a *gem*-dimethyl group in the 5-position of the box has a negative effect on the enantioselectivity of the cyclopropanation reactions between styrene and ethyl diazoacetate 30 (R = Et) (Scheme 6). The 4c,d,f,h–j complexes with Cu(OTf)₂ give both diastereo- and enantioselectivities lower than those of the corresponding copper complexes of the 4-alkyl and 4-aryl 5-unsubstituted boxes (Table 3).⁴¹ On the contrary, both the *trans*-selectivity and enantioselectivity of the cyclopropanation of 2,5-dimethyl-2,4-hexadiene (29) with 30 (R = *t*-Bu) (Scheme 231)^{43,71b} are remarkably enhanced. The results can be appreciated by considering the results shown in Table 137. Here the ratio [*trans*-(1*R*,3*R*)-543]/[*cis*-(1*R*,3*S*)-544], the products of the reaction, and their enantiomeric excesses obtained using the CuOTf complex with unsubstituted (*R*)-1, compared to those with (*R*)-4g and (*R*)-4m–o, are reported.

The most interesting effect of the 5-substituents is observed in the [2,3]-Wittig rearrangement of benzyl prenyl ether 545, which enantioselectively gives 546 with BuLi and a box (Scheme 232).⁵³⁷ The reaction with (*S*)-3c affords a good enantiomeric excess of (*S*)-546 (Table 138, entry 1), the 5,5-dimethyl-box (*S*)-4a gives a lower

Scheme 219



enantiomeric excess, and the *S,S*-diphenyl-box (*S*)-**4b** gives a slightly higher enantiomeric excess. However, the most interesting result is that the sense of the asymmetric induction is now reversed and (*R*)-**546** is obtained (Table 138, entries 2 and 3).

5.6. Heteroatoms in the 4- or 5-Substituent Groups

The aim of designing boxes containing heteroatoms in one of the oxazoline substituents is always motivated by the somewhat remote hope that the new ligand will allow two simultaneous binding interactions, one with the heterocyclic nitrogen (standard for a box) and one with the heteroatom in the chains. The bifunctional ligand, in addition to the standard formation of the reacting 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. This in turn may assist the reaction and promote a specific stereochemical outcome.

This overall goal explains the variety of boxes that fall into this section: **3j–av**, **4k–m**, and **6c–ar**, several with a hydroxy group in the chains, which is the most promising substituent since its hydrogen bonds may lead to realization of the scope of the design.

Unfortunately, the majority of these boxes do not satisfy any of the expectations. The substituent carrying the heteroatom is found to behave only as a more or less sterically congested substituent. This is the role of $\text{CMe}_2\text{OSiMe}_3$ in the complex $[(S)\text{-3o}/\text{CuOTf}]$. The catalyst is much better than those based on either **1** or **2** (Table 10, entries 9 and 10), which are used for the intramolecular cyclopropanation of **547**. This reaction gives 92% ee of (*1R,6S*)-**548** (Scheme 233).²⁹ The role of $\text{CH}_2\text{OSiMe}_2t\text{-Bu}$ in the complex $[(S,S)\text{-6m}/\text{Pd}(\text{OAc})_2]$ is the same. It catalyzes the reaction of *N*-tosyl-2-iodoaniline **242** ($R^1 = \text{H}$) with 1,2-undecadiene **243** and affords *N*-tosyl-2,3-dihydro-3-methylene-2-*n*-octylindole **245** ($R^1 = \text{H}$) (Scheme 218) in an excellent (for this reaction) 87% yield and 78% ee.²⁷¹

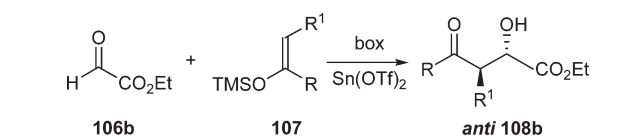
Several cyclopropanations have also been tested. It was found that the reaction between styrene and methyl or ethyl diazoacetate (Scheme 6), catalyzed by the CuOTf complexes of **3s–3x**³¹ or the $\text{Cu}(\text{I})$ complexes of **6k**, **6n**, or **6t**,⁵⁰ cannot compete with the enantiomeric excesses induced by $[\text{2}/\text{CuOTf}]$ (Table 3). The enantioselective cyclopropanation of furan and methyl furan carboxylates (**39**) with methyl or ethyl diazoacetate (**30**), already mentioned in Scheme 8 and now again illustrated in Scheme 234, is more fruitful because of their use as synthons of natural products. The catalysts were prepared from several boxes, $\text{Cu}(\text{OTf})_2$, and phenylhydrazine, leading to the formation of cyclopropanes (*1S,5S,6S*)-**40**. The results are reported in Table 139. The following conclusions can be made: Furan-2- and -3-carboxylates proved to be the best substrates (Table 139, entry 1 vs 2 and 3), and **6k** and **6n** are not the ligands of choice for the reaction (Table 139, entries 2–4). It is, therefore, difficult to imagine **6k** as an active participant via the hydroxy group in the catalytic cycle. Of the **6s–6v** candidates, on the other hand, **four**

Table 130. Enantioselective Catalysis of the Mukaiyama–Aldol Reactions between 106b and Trimethylsilylketene Acetals 107 with $\text{Sn}(\text{OTf})_2$ Complexes of Box's 3c and 3d¹⁸⁰

entry	R	R ¹	box	yield (%)	anti/syn	108b ee (%) (conf.)
1	SPh	H	(<i>S</i>)- 3c	<i>a</i>		93 (<i>S</i>)
2	SPh	H	(<i>S</i>)- 3d	90		98 (<i>S</i>)
3	SPh	Me	(<i>S</i>)- 3d	87	90:10	95 (2 <i>R</i> ,3 <i>S</i>)
4	SPh	Et	(<i>S</i>)- 3d	90	92:8	95 (2 <i>R</i> ,3 <i>S</i>)
5	SPh	<i>i</i> -Pr	(<i>S</i>)- 3d	72	93:7	95 (2 <i>R</i> ,3 <i>S</i>)
6	SPh	<i>i</i> -Bu	(<i>S</i>)- 3d	88	92:8	98 (2 <i>R</i> ,3 <i>S</i>)
7	SEt	<i>i</i> -Bu	(<i>S</i>)- 3d	83	92:8	92 (2 <i>R</i> ,3 <i>S</i>)
8	<i>St</i> -Bu	<i>i</i> -Bu	(<i>S</i>)- 3d	83	96:4	96 (2 <i>R</i> ,3 <i>S</i>)

^a Not reported.

Scheme 220



of them (Table 139, entries 5–8) induce excellent enantioselections.⁵⁰

The reaction of *rac*-3-acetoxy-1,3-diphenyl-1-propene **237** with dimethyl malonate to give the optically active **238** (Scheme 86) is a benchmark for asymmetric allylic alkylations. It is pertinent to discuss it yet again because several palladium complexes of boxes with heteroatoms in the 4- or 5-substituents (Chart 9) have been used as catalysts. The results are listed in Table 140.

An early investigation compared the palladium complexes of (*R*)-**3d** and (*4S,5S*)-**6m**, and the base was either BSA or KOAc (Table 140, entries 1 and 2). The latter catalyst gave excellent yields and enantioselectivities. It appears that the enantioselection is being driven by the 4-substituents, and if $\text{CH}_2\text{OSiMe}_2t\text{-Bu}$ can be considered as a substituent that is more sterically hindered than the benzyl group, then the increased enantioselectivity can be rationalized.⁵¹ Some results, however, cast doubt on this simple interpretation: The palladium complexes of (*4S,5S*)-**6k** and (*4S,5S*)-**6l** give the same enantioselection (Table 140, entries 3 and 4), but here the best substituent is the smallest hydroxymethyl group as found in **6k**.⁵³⁸ The investigation of the complex pairs with (*S*)-**3j**, (*R*)-**3k**, (*R*)-**4k**, and (*R*)-**4l** (which despite their descriptors have the same absolute configuration depicted in Chart 9) always gives (*S*)-**238** (Table 140, entries 5–8).²⁷ When the homogeneous series of (*S*)-boxes 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, results showed that **3u** gave no reaction, three led to (*R*)-selectivity, and the hydroxymethyl derivative **3s** led to (*S*)-selectivity with 92% ee (Table 140, entries 10, 12, and 13 vs 9).¹¹³ This inversion of the enantioselection requires the presence of a second chiral center in the substituent (see the results for entries 5–8, which have been discussed already). 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 140, entries 14 and 15 vs 16 and 17).²⁷

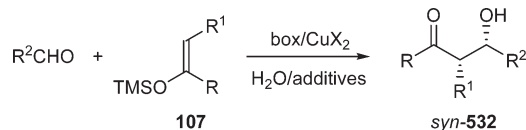
Table 131. Enantioselective Catalysis of the Mukaiyama–Aldol Reactions between Aldehydes and Trimethylsilylketene Acetals 107 Run in Aqueous Media

entry	R	A	R ² (conf.) ^a	box	X ₂	solvent/additives	yield (%)	syn/anti	359 ee (%) (conf.)	ref
1	Ph	Ph	Me (Z)	(S)-2	OTf	<i>b</i>	92	90:10	15 (2R,3R)	181, 529
2	Ph	Ph	Me (Z)	(S)-3c	OTf	<i>b</i>	74	76:24	67 (2S,3S)	181, 529
3	Ph	Ph	Me (Z)	(S)-3c	DS ^c	C ₁₁ H ₂₃ CO ₂ H	38	63:37	56 (2S,3S)	530
4	Ph	Ph	Me (Z)	(S)-3d	OTf	<i>b</i>	>99	67:33	61 (2S,3S)	181, 529
5	Ph	Ph	Me (Z)	(S)-3e	OTf	<i>b</i>	98	72:28	37 (2S,3S)	181
6	Ph	Ph	Me (Z)	(S)-3ag	OTf	<i>b</i>	63	58:42	31 (2S,3S)	181
7	Ph	Ph	Me (Z)	(S)-3ah	OTf	<i>b</i>	86	64:36	47 (2S,3S)	181
8	Ph	Et	Me (E)	(S)-3c	OTf	<i>b</i>	32	62:38	32	181, 529
9	Ph	Et	Me (Z)	(S)-3c	OTf	<i>b</i>	81	78:22	81	181, 529
10	Ph	Et	Me (Z)	(S)-3c	DS ^c		23	76:24	58	530, 531
11	Ph	Et	Me (Z)	(S)-3c	DS ^c	C ₁₁ H ₂₃ CO ₂ H	76	74:26	69	530, 531
12	Ph	<i>i</i> -Pr	Me (Z)	(S)-3c	OTf	<i>b</i>	17	80:20	67	181, 529
13	2-Naph	<i>i</i> -Pr	Me (Z)	(S)-3c	OTf	<i>b</i>	97	80:20	81	181, 529
14	2-furyl	Et	Me (Z)	(S)-3c	OTf	<i>b</i>	86	80:20	76	181, 529
15	2-thienyl	Et	Me (Z)	(S)-3c	OTf	<i>b</i>	78	85:15	75	181, 529
16	<i>c</i> -C ₆ H ₁₁	Ph	Me (Z)	(S)-3d	OTf	<i>b</i>	77	82:18	42	181, 529
17	Ph	Et	Me (Z)	(S)-3c	DS ^c	HCl	31	73:27	61	530
18	Ph	Et	Me (Z)	(S)-3c	DS ^c	(+)-CSA ^d	34	75:25	63	530
19	2-Naph	Et	Me (Z)	(S)-3c	DS ^c	C ₁₁ H ₂₃ CO ₂ H	75	76:24	66	530

^a Main configuration. ^b EtOH–H₂O 9:1. ^c Dodecyl sulfate. ^d (+)-Camphorsulfonic acid.

Table 132. [Pd(OAc)₂/3d]-Catalyzed Asymmetric Coupling-Cyclization Reactions of Allenylhydrazine 533 with Different Organic Iodides²⁷³

entry	533 (conf.)	R	box	yield (%)	trans/cis	trans-248 ee (%) (conf.)	cis-248 ee (%) (conf.)
1	(R)	4-Me-C ₆ H ₄	(R)-3d	81	92:8	99 (3R,5S)	nr
2	(R)	4-MeO-C ₆ H ₄	(R)-3d	85	94:6	99 (3R,5S)	nr
3	(R)	4-MeO ₂ C–C ₆ H ₄	(R)-3d	83	95:5	97 (3R,5S)	nr
4	(R)	2-thienyl	(R)-3d	67	95:5	99 (3R,5S)	nr
5	(R)	C ₆ H ₅	(R)-3d	81	94:6	99 (3R,5S)	73 (3R,5R)
6	(R)	C ₆ H ₅	(R)-3d	81	35:65	90 (3R,5S)	97 (3R,5R)
7	(S)	C ₆ H ₅	(S)-3d	80	39:61	94 (3S,5R)	99 (3S,5S)
8	(S)	C ₆ H ₅	(S)-3d	85	96:4	99 (3S,5R)	85 (3S,5S)

Scheme 221

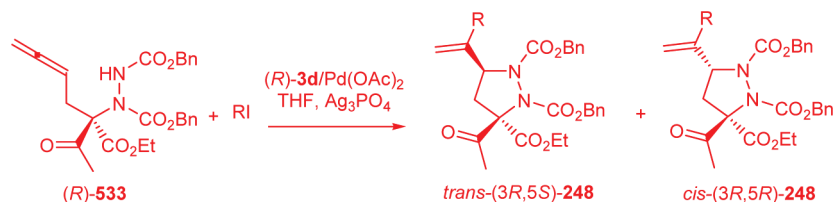
The results in Table 140, entries 5–17, are obtained when the base is NaH, and the nucleophile attacking the palladium π -allyl complex **549** is the Na salt of dimethylmalonate (Figure 21). When the box has a hydroxy group [(S,S)-3s], the interaction of the hydroxy group with the nucleophile assists the attack and governs the regioselectivity affording (S)-238. Assistance is impossible when the hydroxy group is protected (Table 140, entries 10, 12, and 13 vs 9). The base BSA/KOAc affords different results, the most intriguing being the opposite enantioselection obtained using (S,S)-3s (Table 140, 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 **549**, and (R)-238 is the product. To confirm this hypothesis, the reaction was carried out using an equimolar amount of tetrabutylammonium fluoride. Here the fluorine traps the TMS group and again affords (S)-238 (Table 140, entry 18 vs 19). These experiments, together with DFT calculations of **549**

both before and after the nucleophilic attack,⁵³⁸ demonstrate that sometimes a heteroatom in the box substituents may be involved in an interaction that assists the reaction and promotes a specific enantioselectivity.

In closing the argument, a series of palladium complexes with a homogeneous set of 4,5-disubstituted boxes deserve mention due to the fact that the substituent carrying the heteroatom is now in position 5 (Table 140, entries 20–35).^{35a,48} The only complex derived from a cis-disubstituted box (4R,5R)-**5d** afforded no reaction (entry 20). All other boxes have a trans-(4R,5S) and, except **6h** where the 4-mesityl could have proven too sterically demanding, gave catalysts that afforded excellent yields and enantiomeric excesses. A comparison of the catalysts deriving from (4R,5S)-**6c** and (4S,5S)-**6l** where the Ph and the CH₂OMe groups are interchanged and the absolute configuration of the substituents is opposite (Table 140, entry 21 vs 4) suggests that perhaps only the hydroxy group can interfere. It assists the catalytic reaction; otherwise the overall steric hindrance could play a fundamental role in determining the stereoselectivity.

In conclusion, the range of results focused on the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**237**) with dimethyl malonate, and reported in Tables 119, 136, and 140, allow the suggestion that the [allyl/PdCl]₂ complex of type **6** box is the catalyst of choice for this type of reaction. In addition, the results presented make it possible to propose this reaction as a true benchmark for evaluating any new type of 4,5-disubstituted box.

Scheme 222



Scheme 223

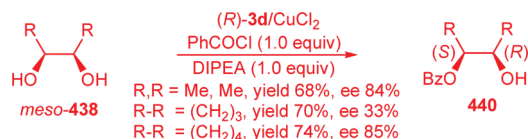
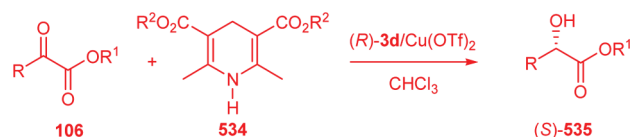


Table 133. Asymmetric Alcohol-Dehydrogenase Mimic Reactions between α -Ketoesters 106 and the Hantzsch Ester 534 Catalyzed by [Box/Cu(OTf)₂]⁵³²

entry	R	R ¹	box	yield (%)	(S)-535 ee (%)
1 ^a	Ph	Et	(R)-1	20	82
2 ^a	Ph	Et	(R)-2	<5	nd
3	Ph	Et	(R)-3d	90	82
4	Ph	Bn	(R)-3d	96	78
5	Ph	<i>t</i> -Bu	(R)-3d	89	92
6	4-NO ₂ -C ₆ H ₄	<i>t</i> -Bu	(R)-3d	94	80
7	4-MeO-C ₆ H ₄	<i>t</i> -Bu	(R)-3d	83	94
8	2-naphthyl	<i>t</i> -Bu	(R)-3d	82	94
9	2-furyl	<i>t</i> -Bu	(R)-3d	80	94
10	cyclohexyl	<i>t</i> -Bu	(R)-3d	72	80

^a Reaction run in CH₂Cl₂.

Scheme 224



Attempts to introduce more sophisticated residues containing a second binding site with a crown ethers moiety,⁴⁹ substituents with pendant sulfides suitable to assist a carbenic reagent in the addition to a carbonyl and promote enantioselective epoxidation,³⁰ or the addition of MeLi to aromatic aldimines²⁸ into the substituents did not afford any remarkable improvement in selectivity, at least none superior to those catalysts with the corresponding naked scaffold.

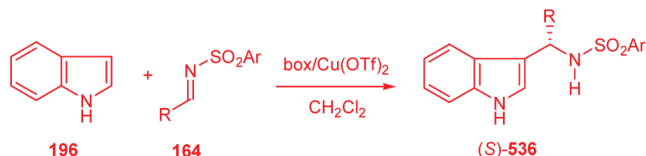
Is it therefore possible to postulate that a bifunctional box may be involved in a second interaction, which can assist the reaction and promote a specific enantioselectivity? The answer for specific reactions appears positive in the presence of a hydroxy-containing pendant. The enantioselective addition of ZnR₂ to aldehydes can be catalyzed by (4*S*,5*S*)-6k and (4*S*,5*S*)-6y to give optically

Table 134. Asymmetric Friedel–Crafts Additions between Indole 196 and *N*-Sulfonyl Aldimines 164⁵³³

entry	R	SO ₂ Ar	box	yield (%)	(S)-536 ee (%)
1	4-NO ₂ -C ₆ H ₄	tosyl	(S)-1	39	racemate
2	4-NO ₂ -C ₆ H ₄	tosyl	(S)-2	33	–6 ^a
3	4-NO ₂ -C ₆ H ₄	tosyl	(S)-3c	50	32
4	4-NO ₂ -C ₆ H ₄	tosyl	(S)-3d	94	95
5	4-Cl-C ₆ H ₄	tosyl	(S)-3d	75	94
6	2-Cl-C ₆ H ₄	tosyl	(S)-3d	72	94
7	2,6-Cl ₂ -C ₆ H ₃	tosyl	(S)-3d	47	93
8	Ph	Ns ^b	(S)-3d	86	94
9	2-Me-C ₆ H ₄	Ns ^b	(S)-3d	63	89
10	1-naphthyl	Ns ^b	(S)-3d	85	81

^a (R)-536 is obtained. ^b Ns is *p*-nitrobenzenesulfonyl group.

Scheme 225



active 1-phenylpropanol (Scheme 235), and Table 141 compares these results with those obtained with (S)-2.⁵³⁹

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 are found to give excellent enantiomeric excesses without any additive (see Table 141, entries 2–6), with heptanal the yield and enantioselectivity can be increased by the addition of catalytic amounts of BuLi, with an optimum of 2 mol % (Table 141, entries 7–9). The most probable effect appears to be on the deprotonation of the alcohol functionality of the box.

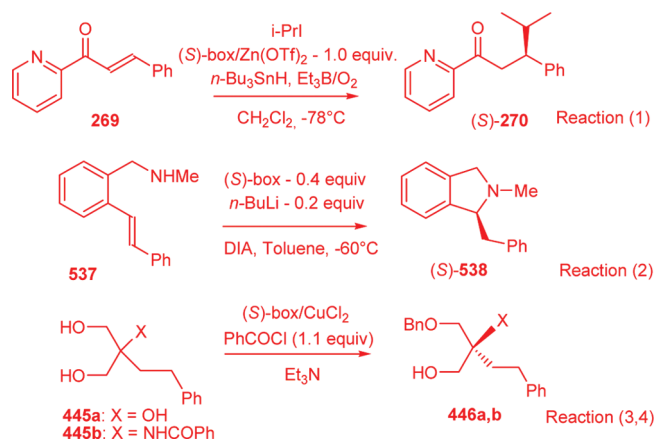
Further experiments investigating the hydroxy-functionalized boxes gave different results. The dioxomolybdenum complex of (4*S*,5*S*)-6k failed as catalyst for the enantioselective epoxidation of olefins.⁵⁴⁰ Yet the same box found useful applications in the Michael addition of ZnR₂ to cycloalkanones to afford 4-substituted cycloalkanones 551 (Scheme 236 and Table 142).⁵³⁹ 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 142, entries 2 and 3 vs 1). The efficiency of the catalyst allowed the first enantioselective 1,4-asymmetric phenyl transfer to an enone with diphenylzinc as the reagent (Table 142, entry 6).

Table 135. Enantioselectivity of the Reactions in Scheme 226 As a Function of 4-Alkyl Boxes

entry	box			ee (%)			
	no.	4-substituent	$-E_S^a$	(S)-270 ^b	(S)-538 ^c	(S)-446a ^d	(S)-446b ^e
1	3a	Me	0.00	17		86 ^f	20 ^f
2	3b	Et	0.07			90 ^f	84 ^f
3	3d	Bn	0.38	45		91 ^f	44 ^f
4	3c	<i>i</i> -Pr	0.47	9	84	76	78
5	3e	<i>i</i> -Bu	0.93		79		
6	3f	CH ₂ -C ₆ H ₁₁	0.98		76		
7	3ak	(S)-CH(CH ₃)CH ₂ CH ₃	1.13		66		
8	3al	(R)-CH(CH ₃)CH ₂ CH ₃	1.13		91 (R) ^g		
9	2	<i>t</i> -Bu	1.54	19	19	14	15
10	3aj	CH ₂ - <i>t</i> -Bu	1.74		71		

^a Ref 534. ^b Ref 293. ^c Ref 34. ^d Ref 444. ^e Ref 445. ^f Reaction performed with (*R*)-box, configuration of the product inverted. ^g Reaction performed with (*R*)-box, configuration of the product NOT inverted.

Scheme 226

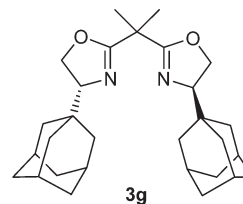


The stringent requirements of two coordinating sites for two different metals allows the postulation of **550** as the reacting intermediate in the catalytic cycle.

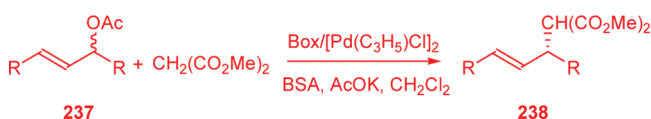
Recently, by applying a common modification, the TIPS functionalization of the hydroxy group of (4*S*,5*S*)-**6k**, the new box (4*S*,5*S*)-**6aa** was obtained. Using it in some classic applications of box-based catalysts made it possible to infer and clarify the catalytic cycle involved. The Cu(OTf)₂ complex of (4*S*,5*S*)-**6aa** (**552**) was isolated, and its X-ray structure was determined (Figure 9). It was found to have one water and one triflate in the equatorial position, thus completing the pentacoordination with the axial triflate.⁵⁵

The complex **552** was used as a catalyst in a series of reactions: in the Diels–Alder reaction and in the 1,3-dipolar cycloaddition of acryloyl oxazolidinone **216** (R = R¹ = H) with cyclopentadiene to give *endo*-(*S*)-**303** and *exo*-(*R*)-**304**, as well as with 1,3-diphenylnitrone **362** to give *endo*-(3*R*,4*R*)-**363** and *exo*-(3*S*,4*R*)-**363** (Scheme 237). The different reaction conditions and results are reported in Table 143. For entries 1–4, both diastereo- and enantioselectivities are seen to be constant under the conditions reported, which suggests that the catalyst is **552**. There is a slight but significant increase for the Diels–Alder reaction under nonanhydrous conditions as reported in entries 5 and 6. The

Chart 7



Scheme 227

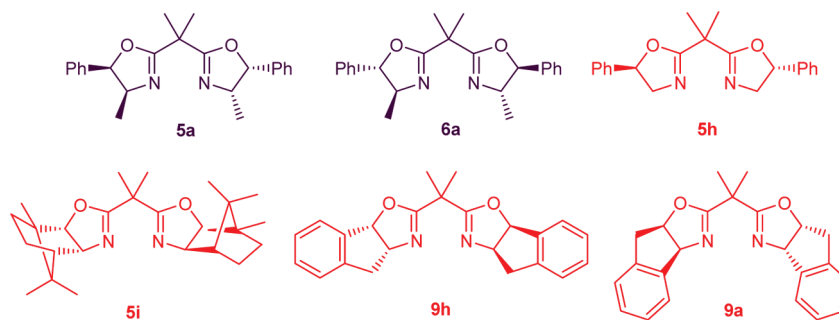


catalyst should then react with **216** to give the reacting intermediate **553**, which was in fact isolated and its structure determined by X-ray analysis. The favored attack of either cyclopentadiene or diphenylnitrone to **553** is at the Re face of complexed **216**. This gives rise to (*S*)-**303** and (3*R*,4*R*)-**363**, respectively. The overall catalytic cycle is reported in Figure 22. Here, although the *s*-cis conformation of **216** is emphasized, it must be acknowledged that this is always supposed or assumed but has never been structurally demonstrated. The importance of the role of the axial water molecule in **552** in favoring the Re face approach can be easily understood from the results of the experiments in Table 143, entries 5 and 6.

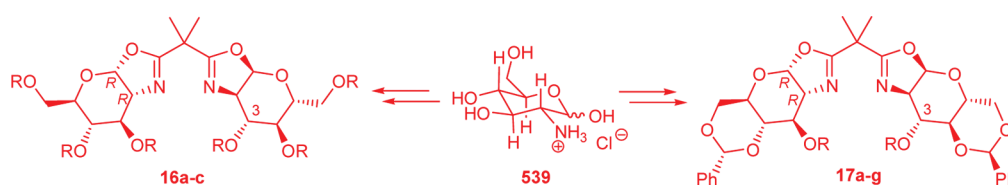
The same complex **552** was used as a catalyst for the Diels–Alder reaction and the 1,3-dipolar cycloaddition of **310** with cyclopentadiene and diphenylnitrone (Scheme 238).⁹⁹ The results of the Diels–Alder reaction with the Cu(II) complex of (*S*)-**1** and (*S*)-**2** have been previously reported in Scheme 117 and Table 72.

Both reactions give excellent diastereo- and enantioselectivities (Table 144), and the previously unknown absolute configurations of **311** and **363** were determined by X-ray analysis. The reaction intermediate **556**, derived by a ligand substitution

Chart 8



Scheme 228

Table 136. Pd-Catalyzed Asymmetric Alkylation of **237** Mediated by Ligands (3a*R*,8b*S*)-**9h** and (3a*S*,8b*R*)-**9a**⁷⁹

entry	box	R	yield %	238 ee % (conf.)
1	(3a <i>R</i> ,8b <i>S</i>)- 9h	Ph	>99	93 (<i>R</i>)
2	(3a <i>S</i> ,8b <i>R</i>)- 9a	Ph	>99	98 (<i>S</i>)
3	(3a <i>R</i> ,8b <i>S</i>)- 9h	Me	18	47 (<i>R</i>)
4	(3a <i>S</i> ,8b <i>R</i>)- 9a	Me	16	8 (<i>S</i>)

reaction of **310** onto **552**, was isolated and its structure also determined by X-ray analysis.⁹⁹ The favored *Re* face approach of either cyclopentadiene or diphenylnitrone to coordinated **310** rationalizes the stereochemistry of the products. The importance of the triflate axial ligand of **556** in favoring the *Re* face approach is further evidenced by the experimental results shown in Table 144, entry 3.

A number of new boxes have been recently synthesized with N- and P-heteroatomic groups incorporated into the substituents in the 4-position.^{17,18,38,39} The addition of Et₂Zn to benzaldehyde was catalyzed by (*R*)-**3as–u** boxes with a CH₂NHAr group in position 4. The Lewis acid was the Zn(II) cation.³⁸ The ZnI₂ complex of the new box (*S*)-**3av** (with an unusual CH₂POPh₂ group in position 4) was the catalyst for an enantioselective allylation of the aldehydes **106** with allyltrichlorosilane. Discrete enantiomeric excesses were obtained (Scheme 239).³⁹ For both reactions, yields and enantiomeric excesses of the secondary alcohol **557** are reported in Table 145.

The Cu(OTf)₂ or Cu(NTf₂)₂ complexes of boxes **6aq** and **6ar**, with NHSO₂Me and NHSO₂CF₃ groups, have been tested in the Diels–Alder reaction between **216** (R = R¹ = H) and cyclopentadiene. The results (Table 146, entries 4 and 5) have been compared to those obtained with the analogous Cu(II) complexes of the oxygenated boxes **6an**, **6ao**, and **6ap** (Table 146, entries 1–3).^{18b} The excellent results in entries 4 and 5 suggest the key role of the

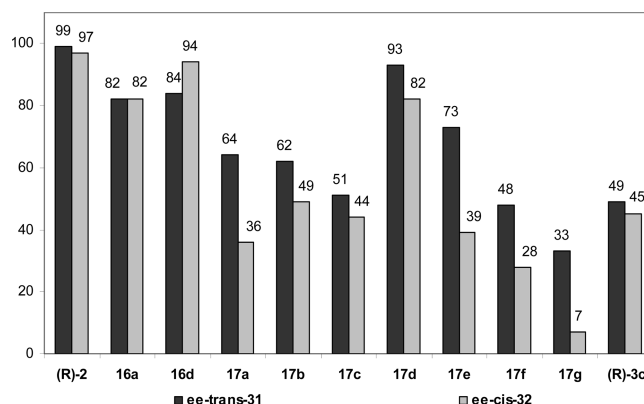
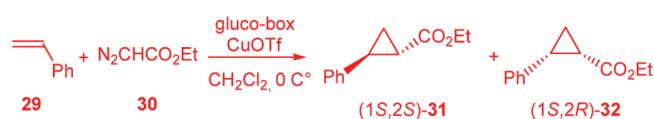


Figure 19. Impact of boxes **16** and **17** on the enantioselectivity of the Cu(I)-catalyzed cyclopropanation reaction in Scheme 229, compared with those obtained using (*R*)-**2** and conventionally (*R*)-**3c** (reaction performed with (*S*)-**3c**, configuration of the product inverted).

Scheme 229



sulfonamido group in the construction of an efficient asymmetric environment through coordination of the sulfonyl oxygen atom with the Cu(II) cation. This rationale is supported by theoretical calculations.

This example is proof that a bifunctional ligand, in addition to the standard formation of the reacting intermediate with the Lewis acid and one reagent, may also be involved in a second interaction, which increases the catalyst selectivity.

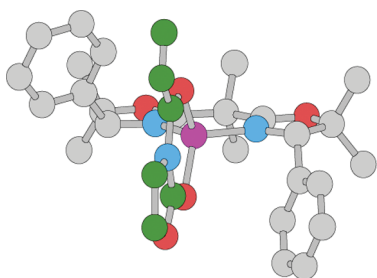


Figure 20. Tetrahedral magnesium complex of **216** and (S)-**4g**.⁴²

Scheme 230

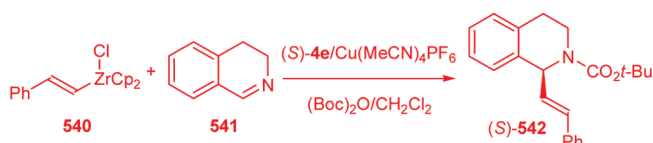


Table 137. Cu(I)-Catalyzed Asymmetric Cyclopropanations of 2,5-Dimethyl-2,4-hexadiene (**29**) with **30**, Mediated by Boxes Both with and without 5,5-Dimethyl Substitution^{43,71b}

entry	box	yield %	[543]/[544]	(1 <i>R</i> ,3 <i>R</i>)- 543 ee %	(1 <i>R</i> ,3 <i>S</i>)- 544 ee %
1	(<i>R</i>)- 1	92	81:19	83	62
2	(<i>R</i>)- 4g	93	84:16	88	68
3	(<i>R</i>)- 4m	88	85:15	93	69
4	(<i>R</i>)- 4n	92	86:14	95	69
5	(<i>R</i>)- 4o	91	79:21	85	69

5.7. Substituents Other Than Methyls on the Methylene Bridge

In the above sections only those boxes with an isopropylidene bridge were discussed. However, several different substituents have also been placed at the carbon connecting the oxazoline rings. Chart 1 reports boxes **7**, **9**, and **13–15** that still retain the C_2 -symmetry. In addition to these boxes with substituents other than methyls on the methylene bridge, there is a class of spirocyclic boxes in which the substituents, which are obviously different than methyls, induce strain in the ligand. The angle Φ between the heterocycles and the bridge (C_2-C-C_2') is changed. These, however, will be the topic of the next section, and therefore **8** and **10–12** will not be discussed in this section.

For many reasons these classes are among those whose development was more tumultuous in recent years. This is because, once the different substitutions on the isoxazoline ring were exhausted, the only other box position where researchers could exploit their fantasy and imagination in inventing new substituents is the carbon spacer. Because the spacer is the possible point of anchorage for solid-supported boxes, substituents suitable for the intended applications or those that mimic the linker or the support have all been extensively introduced.

To evaluate the effect of the bridge substituent, the efficiency and selectivity promoted by the catalyst derived from these boxes will be compared to the selectivities exerted by the catalysts derived from the corresponding benchmark isopropylidene boxes. Obviously, the more selective the new catalyst, the more promising the substituent will be in the development of

new box ligands. Although many of these boxes behave very similarly to the benchmark, some intriguing results have been reported. One of these is the Kharasch reaction of the cycloalkenes **221** with *tert*-butyl *p*-nitroperbenzoate, catalyzed by CuPF₆ complexes of eight boxes: (S)-**1**, (S)-**2**, (S)-**3c**, and (S)-**3d**, taken as the benchmark, and the corresponding *gem*-diethyl-boxes (S)-**7a**, (S)-**7c**, (S)-**7d**, and (S)-**7e** (Scheme 240, Table 147).³¹¹

All eight Cu(I) box complexes give the same (S)-enantiomer, but yields and enantioselectivities change significantly (Table 147). The reaction with cyclohexene **290** ($n = 2$) gives better enantiomeric excesses with the methyl-substituted boxes, whereas cyclopentene **290** ($n = 1$) gives better enantiomeric excesses with (S)-**7a,d,e** than with the corresponding benchmark catalysts. Few reactions of cycloheptene **290** ($n = 3$) and 1,5-cyclooctadiene **290** ($n = 4$) have been compared: (S)-**7e** for the former substrate and (S)-**7a** for the latter give better enantioselectivity than the corresponding benchmarks. Again, it is difficult to draw general conclusions for reactions where each of them have a specific tailor-made box, but to test boxes with different substituents on the methylene bridge may give pleasant surprises.

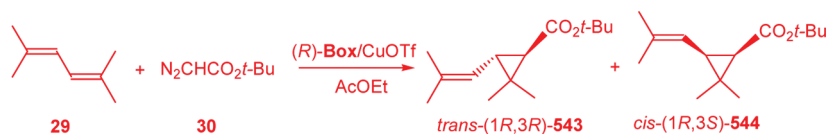
Recently, the complexes between Cu(OTf)₂ and boxes with different groups on the carbon spacer have been tested. These results have been incorporated into Table 147. The catalyst derived from (S)-**7ao** (two phenyl groups) cannot compete with that of (S)-**7c** (two methyl groups) (Table 147, entry 9 vs 3).⁵⁴¹ However, that derived from (S)-**7s** (two benzyl groups) gives results better than those obtained with (S)-**3c** and (S)-**7a** (two methyl and two ethyl groups, respectively) (Table 147, entry 10 vs 3 and 4). Excellent analogous results were obtained with catalysts involving box (S)-**7ap–s**.⁶⁵ The complex derived from box (S)-**7aq** with two CH₂–(2-pyridyl) side arms is interesting because the pyridyl group could be involved as an auxiliary ligand in the copper complexation. The crystal structure of the [(S)-**7aq**/Cu(OTf)₂] complex was determined and found to be octahedral. The acetates behave as bicoordinating anions (Table 2, entry 26); therefore, the pyridyls are not involved in the coordination. This conclusion is to be expected if the results in Table 147, entries 11–13, are compared.⁶⁵

Among the less significant applications of boxes **7**, their nontraditional use in asymmetric anionic polymerization of maleimides⁵⁴² and the low enantiomeric excesses obtained in the allylic substitution/allene cycloannulation reaction,²⁷¹ in the cyclopropanation of α,β -unsaturated carbonyl compounds with diazomethane,⁵⁷ in the radical addition to pyrazole template **317** ($R = Ph$) (Scheme 202),⁵⁰⁴ and in the kinetic resolution of pyridyl alcohols⁴³⁹ should be mentioned. In the kinetic resolution of racemic diols **438** (Scheme 169) or in the cyclopropanation of styrene (Scheme 5), the results are lower or at the best overlap those obtained with the analogous isopropylidene boxes.^{82,439,440,543}

Using (*R*)-**1** as the chiral catalyst, the deprotonation with *n*-BuLi of primary carbamoyl-protected substituted methanethiols **491** ($X = S$) and the alkylation with electrophiles $R-Y$ to give the α -substituted products **492** has been briefly reported in Scheme 192.⁴⁹⁰ An efficient enantioselective process has been realized with a catalyst derived from (S)-**7c**.

The deprotonation step of **491** generates two labile enantiomeric lithiated species, (*R*)- and (S)-**558**. When these are generated in the presence of (S)-**7c**, they can easily epimerize by a temperature-dependent process, which can be monitored by ¹H- and ⁶Li NMR spectroscopy. Under these conditions, a dynamic thermodynamic resolution of [(S)-**7c**/Li/**558**] occurs.

Scheme 231

Table 138. Effect of 5-Substituents on the [2,3]-Wittig Rearrangement of 545⁵³⁷

entry	box	yield (%)	546 ee (%) (conf.)
1	(S)-3c	31	62 (S)
2	(S)-4a	11	25 (R)
3	(S)-4b	39	66 (R)

The epimeric complex involving (R) -558 is strongly favored, and this can be stabilized upon cooling when $k_{1,2\text{epi}} \ll k_{3,4\text{ret/inv}}$, thus becoming the enantiodetermining step of the entire process. The substitution reaction on the electrophile R–Y can occur through two stereochemical pathways either with retention or inversion of configuration. The overall process is depicted in Scheme 241. By using trimethylsilyl chloride as the electrophile, when R^1 is a phenyl group, the silylated S -benzyl thiocarbamate (R) -492 is obtained in 90% yield and 96% ee by a substitution reaction with inversion of configuration.^{490,544,545} The results with different reagents are listed in Table 148.

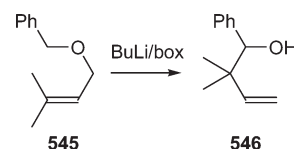
O -benzyl carbamates 491 ($X = O$) can also be deprotonated with s -BuLi, and the configurationally labile lithiated species 558 (O instead of S) can react with electrophiles. The enantiodetermining step was proven to be the dynamic thermodynamic resolution of 558 (Scheme 241).⁵⁴⁶ These results have been incorporated into Table 148. From entry 1 vs 9, it can be seen that (S) -7c proved to be a better enantioselective catalyst than (S) -7a.

The sulfones 488 ($R = CF_3$) are the third class of compounds that undergo n -BuLi-promoted deprotonation to form α -sulfonyl carbanions. These subsequently react enantioselectively with electrophiles in the presence of boxes. This reaction has already been mentioned in Scheme 191, and the results with boxes 1 and 2 were reported in Table 149. However, since many more stereoselective results can be obtained with substituents other than methyl on the methylene bridge, the reaction will now be reconsidered (Scheme 242).^{488,489} The aldol reaction with aromatic and heterocyclic aldehydes is strongly syn selective, and syn -489 is by far the major product. The box substituents have a strong influence on the enantioselectivity; a phenyl in position 4 is the best group, whereas two benzyl substituents on the spacer as in (S) -7u have a beneficial effect on the enantioselectivity.

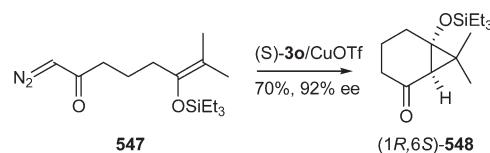
A further class of reagents, the benzyl ethers 559, undergoes enantioselective lithiation at the benzyl carbon atom with $[(S)$ -7a/ t -BuLi] as the catalyst. This is followed by reaction with either CO_2 or aldehydes as the electrophiles to give phenylacetic acids 560⁵⁴⁷ or the anti and syn adducts 561 (Scheme 243).⁵⁴⁸ The results are reported in Table 150. 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 using benzyl ethers, the reaction can also be run over phthalan or isochroman 562 ($n = 1$ or 2, respectively), the

Scheme 232



Scheme 233



cyclic analogues of benzyl ether, with alkyl halides or carbonyl derivatives as the electrophiles. The results are reported in Table 151. Scheme 244 shows the reaction with methyl bromoacetate to give (R) -563, which, upon reduction with $LiAlH_4$, mesylation with $MsCl/Et_3N$, and reaction with 4-(piperazin-1-yl)benzenesulfonamide, furnishes the (R) -enantiomer of the dopamine D_4 antagonist U-101387.⁵⁴⁹

The lithiation of 1',2,2',3',4',5,5'-heptamethylazaferrocene 564 can be achieved with $[(S)$ -7a/ sec -BuLi]. The subsequent enantioselective reaction with electrophiles affords the methyl-functionalized product 565 in excellent enantiomeric excess. The only limitation is the amount of catalyst required (Scheme 245, Table 152).⁵⁵⁰

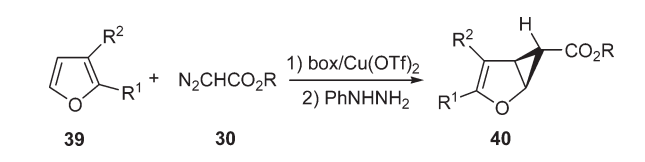
$[(S)$ -7a/ t -BuLi] is an unsatisfactory enantioselective catalyst (18% ee) of the [2,3]-sigmatropic rearrangement that transforms (Z) -cyclic furfuryl ether 419 into syn -420 (Scheme 162). But when $[(S)$ -7c/ t -BuLi] is used as the catalyst for the same reaction, the 93% ee exceeds the 91% ee obtained with the benchmark $[(S)$ -2/ t -BuLi].⁴²⁶

The [2,3]-sigmatropic rearrangement of allyl ethers 566 (Scheme 246) with (E) - or (Z) -configuration of the double bond, and with A being either phenyl, 1-propynyl, or TMS-ethynyl, have all been extensively studied with $[(S)$ -7a/ t -BuLi]. Both the erythro/threo ratios of 567 and the enantiomeric excesses of the major diastereoisomer are reported in Table 153.^{537,551,552}

Even if stoichiometric amounts of $[box/t-BuLi]$ are required, the rearrangement of propynyl ether occurs with very good diastereomeric and enantiomeric excesses (Table 153, entry 4). The configuration of the double bond strongly changes the erythro/threo ratio (Table 153, entries 4 and 5). Although the reaction run under catalytic conditions lowers the enantiomeric excesses (Table 153, entry 3), it demonstrates that selectivity is promoted by the reacting complex $[(S)$ -7a/Li(I)/566] involved in the catalytic cycle. If the same experimental conditions are

Table 139. Enantioselective Cyclopropanation of Furan Carboxylates 40 with Diazoacetates 30

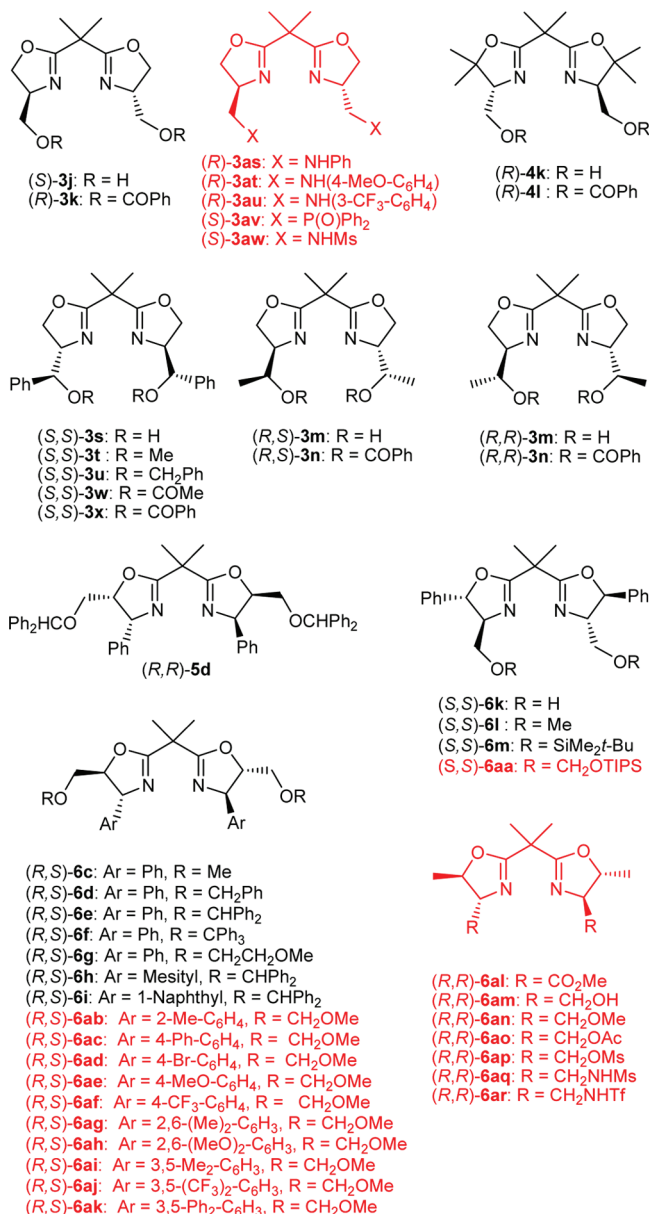
entry	R ¹	R ²	R	box	yield (%)	40 ee (%)	ref
1	H	H	Me	(4 <i>S</i> ,5 <i>S</i>)-6k	7	51	129
2	H	CO ₂ Me	Et	(4 <i>S</i> ,5 <i>S</i>)-6k	27	74	129
3	CO ₂ Me	H	Me	(4 <i>S</i> ,5 <i>S</i>)-6k	45	69	50, 129
4	CO ₂ Me	H	Me	(4 <i>S</i> ,5 <i>S</i>)-6n	46	45	50
5	CO ₂ Me	H	Et	(4 <i>S</i> ,5 <i>S</i>)-6s	33	85	50
6	CO ₂ Me	H	Et	(4 <i>S</i> ,5 <i>S</i>)-6t	42	83	50
7	CO ₂ Me	H	Et	(4 <i>S</i> ,5 <i>S</i>)-6u	36	91	50
8	CO ₂ Me	H	Me	(4 <i>S</i> ,5 <i>S</i>)-6u	39	88	50, 53
9	CO ₂ Me	H	Me	(4 <i>S</i> ,5 <i>S</i>)-6v	41	62	50

Scheme 234

applied to the deprotonable ethers 568, then the enantioselective version of the [1,2]-Wittig rearrangement gives 569 (Scheme 247). The results of some selected examples are reported in Table 154. Here the benzyl-type group migrates and the enantioselectivity might be determined in the radical recombination step involving the box/Li(I)-bound radical anion.⁵⁵³

Useful applications for 7 have been found in some Diels–Alder reactions. The cycloaddition of cyclopentadiene and ethyl α -phenylthioacrylate 314 (R = Et, R¹ = Ph), catalyzed by [(*S*)-1/Cu(SbF₆)₂], is reported in Table 73, entry 6. It shows an endo/exo ratio of 94:6 and >95% ee of the (*R*)-adduct. This excellent performance can be replicated with [(*S*)-12a/Cu(SbF₆)₂] (endo/exo ratio 92:8 and enantioselectivity >95% ee).³⁴¹ The Diels–Alder reaction between 216 (R = R¹ = H) and cyclopentadiene (Scheme 114) was catalyzed with Cu(OTf)₂ complexes of (*S*)-12a, (*S*,*R*)-11b, and (*S*,*R*)-11a. All catalysts are endo-selective, but the enantioselectivity is disappointing except with the last catalyst (97% de and 96% ee of (*S*)-303). This result is better than that obtained with the corresponding benchmark catalyst derived from (4*S*,*S*,*R*)-9a (Table 120, entry 1).⁷⁴ The third Diels–Alder reaction, between 1,1-dicarbonyl ethenes 570a,b and cyclopentadiene, when catalyzed by [(*R*)-7e/MgI₂/I₂], is very selective both for R = OEt (570a) (since (*R*)-571a is obtained in 81% yield, diastereomeric excess >99:1, and 85% ee) and for R = Me (570b) ((*S*)-571b, 77% yield, diastereomeric excess 98:2, and 78% ee) (Scheme 160).⁵⁵⁴

The asymmetric Mukaiyama–aldol reaction between 1-oxypyridine-2-carbaldehyde 112 and silylketene acetal 113a, catalyzed by [box/Cu(OTf)₂] complexes and already reported in Scheme 30, was run with the box (4*R*,5*S*)-5b, and results were compared with the analogous catalyst derived from the box with two benzyl groups in the spacer. The product from both catalysts was methyl (*S*)-3-hydroxy-2,2-dimethyl-3-(1-oxypyridin-2-yl)-propionate (114a) (Scheme 249). Although with the latter catalyst the yield was somewhat lower, the enantiomeric excess showed significant improvement (from 89 to 96% ee).¹⁸²

Chart 9

The best catalysts for the Henry reaction between *p*-nitrobenzaldehyde 140 and nitromethane (already mentioned in Scheme 44) were found to be the complexes between Cu(OAc)₂ and boxes with two ethyl groups in the spacer. Because a series of isopropylidene and 3-pentylidene boxes were compared, this reaction is reiterated in Scheme 250. The results for a critical evaluation of both series are listed in Table 155.⁶⁶

With the exception of the results presented in Table 155, entry 3, the 3-pentylidene boxes (with two ethyl groups on the spacer) always give better enantiomeric excesses than those obtained with the traditional isopropylidene analogues. Thus, (*S*)-7a was the box of choice for carrying out the Henry reaction with a range of aldehydes.⁶⁶

Ligand (*S*)-7a proved to be the optimal box in three other reactions. The first, whose target is the desymmetrization of *meso*-epoxide 572, is the reaction of organolithium in the

Table 140. Enantioselective Allylic Alkylations of 1,3-Diphenyl-2-Propenyl Acetate 237 with Dimethyl Malonate

entry	box	base	yield (%)	238 ee (%) (conf.)	ref
1	(R)-3d	BSA, ^a KOAc	97	88 (R)	33
2	(4S,5S)-6m	BSA, ^a KOAc	97	97 (S)	51
3	(4S,5S)-6k	BSA, ^a KOAc	^b	96 (S)	538
4	(4S,5S)-6l	BSA, ^a KOAc	^b	89 (S)	14
5	(S)-3j	NaH	100	80 (S)	27
6	(R)-3k	NaH	100	80 (S)	27
7	(R)-4k	NaH	88	77 (S)	27
8	(R)-4l	NaH	80	85 (S)	27
9	(S,S)-3s	NaH	98	92 (S)	27, 113
10	(S,S)-3t	NaH	65	85 (R)	113
11	(S,S)-3u	NaH	0	113	113
12	(S,S)-3w	NaH	99	77 (R)	113
13	(S,S)-3x	NaH	98	90 (R)	27, 31, 113
14	(R,S)-3m	NaH	90	72 (S)	27
15	(R,S)-3n	NaH	95	97 (S)	27
16	(R,R)-3m	NaH	90	63 (R)	27
17	(R,R)-3n	NaH	90	68 (S)	27
18	(S,S)-3s	BSA, ^a KOAc	70	91 (R)	27
19	(S,S)-3s	BSA, ^a NBu ₄ F	75	52 (S)	27
20	(4R,5R)-5d	BSA, ^a KOAc	0	48	48
21	(4R,5S)-6c	BSA, ^a KOAc	>95	96 (R)	35a, 48
22	(4R,5S)-6d	BSA, ^a KOAc	16	95 (R)	48
23	(4R,5S)-6e	BSA, ^a KOAc	60	96 (R)	48
24	(4R,5S)-6f	BSA, ^a KOAc	94	96 (R)	48
25	(4R,5S)-6g	BSA, ^a KOAc	81	93 (R)	48
26	(4R,5S)-6h	BSA, ^a KOAc	8	50 (R)	48
27	(4R,5S)-6i	BSA, ^a KOAc	100	96 (R)	48
28	(4R,5S)-6ac	BSA, ^a KOAc	58	94 (R)	35a
29	(4R,5S)-6ad	BSA, ^a KOAc	41	95 (R)	35a
30	(4R,5S)-6af	BSA, ^a KOAc	>95	95 (R)	35a
31	(4R,5S)-6ag	BSA, ^a KOAc	63	94 (R)	35a
32	(4R,5S)-6ah	BSA, ^a KOAc	59	94 (R)	35a
33	(4R,5S)-6ai	BSA, ^a KOAc	60	95 (R)	35a
34	(4R,5S)-6aj	BSA, ^a KOAc	43	91 (R)	35a
35	(4R,5S)-6ak	BSA, ^a KOAc	70	96 (R)	35a

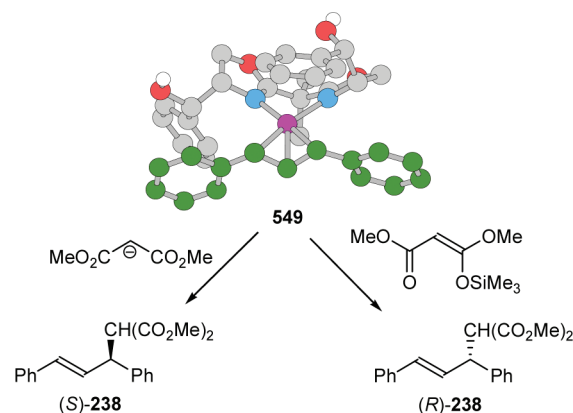
^a *N*,*O*-bis(trimethylsilyl)acetamide. ^b Not reported.

presence of (S)-7a/BF₃/diethylether. Both *n*-butyl and phenyl lithium give 573 (Scheme 251). However, only the latter reagent furnishes the product in the (1*R*,2*S*) absolute configuration with 54% ee.⁵⁵⁵

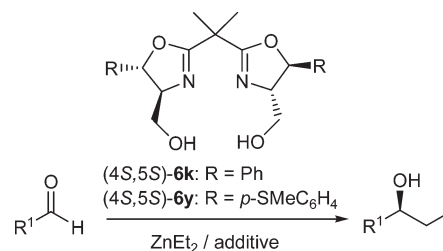
The second reaction is again a desymmetrization. This time *meso*-silyl ethers 574 are opened by organolithium reagents in the presence of (S)-7a to give chiral silanol derivatives 575. These can be easily debenzylated to realize the enantioselective synthesis of the target silanols (Scheme 252).⁵⁵⁶ The yields and the enantiomeric excesses of two examples of such a reaction, whose limitation is the use of 3.0 equiv of [(S)-7a/R²Li], are reported in Scheme 252.

The asymmetric resolution of racemic nine-membered diallyl ethers 576 is another example that requires 3.0 equiv of [(S)-7a/*t*-BuLi] (Scheme 253). The remarkably stable planar chirality of 576 allows it to undergo a transannular [2,3]-Wittig rearrangement on one enantiomer. Catalysis with [(S)-7a/*t*-BuLi] affords the rearranged product (R,R)-577 and allows isolation of the enantiomerically enriched (S)-576.⁵⁵⁷ This resolution allows further transformations such as epoxidations, hydroborations, and Cope rearrangement of the optically active ether, which all increase the value of this elegant research.

Not all substituents are positioned at the carbon atom connecting the box oxazoline rings with the aim of synthesizing a

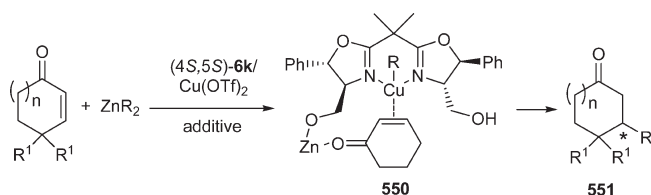
**Figure 21.** Different enantioselective attacks of the palladium π -allyl complex 549 by the Na salt of dimethylmalonate and by the silyl ketene acetal of malonate.**Table 141. Enantioselective Additions of ZnEt₂ to Aldehydes⁵³⁹**

entry	R ¹	box	additive (mol %)	yield (%)	ee (%) (conf.)
1	Ph	(S)-2		60	20 (S)
2	Ph	(4S,5S)-6k		96	93 (S)
3	Ph	(4S,5S)-6y		56	83 (S)
4	<i>p</i> -OMeC ₆ H ₄	(4S,5S)-6k		99	95 (S)
5	<i>p</i> -ClC ₆ H ₄	(4S,5S)-6k		76	83 (S)
6	<i>p</i> -FC ₆ H ₄	(4S,5S)-6k		74	88 (S)
7	<i>n</i> -C ₆ H ₁₃	(4S,5S)-6k		31	36 (S)
8	<i>n</i> -C ₆ H ₁₃	(4S,5S)-6k	<i>n</i> -BuLi (2)	60	66 (S)
9	<i>n</i> -C ₆ H ₁₃	(4S,5S)-6k	<i>n</i> -BuLi (6)	68	47 (S)

Scheme 235

more efficient ligand that is competitive with respect to the benchmark. Sometimes the substituents become the linkers of solid-supported or polymer-immobilized boxes. Their performance in the cyclopropanation reaction of styrene with diazoacetate esters (Scheme 5) constitutes the critical test for homogeneous versus heterogeneous catalysis. Since the benchmark of these homogeneous catalysts is [(S)-2/CuOTf] (Table 3, entry 1, 99% ee), the enantioselectivity promoted by Cu(I) or Cu(II) complexes of 7j,k,⁵¹⁰ 7t,u,^{60a,b,558} 7v-x,^{60b} 7af,⁶² 13a-c,e,⁸³ and 14a-d,^{59a} must be taken as the results of model catalysts. Recently several macrocyclic boxes of the general formula 14 and 15 have been synthesized, and 16 of them have been tested in the Cu(I)-catalyzed cyclopropanation

Scheme 236

Table 142. Enantioselective [Box/Cu(OTf)₂]-Catalyzed Michael Additions of ZnR₂ to Cycloalkenones⁵³⁹

entry	R ¹	n	R	box	yield (%)	551 ee (%) (conf.)
1	H	1	Et	(S)-2	65	racemate
2	H	1	Et	(4S,5S)-6k	93	94 (S)
3	H	1	Et	(4S,5S)-6y	81	90 (S)
4	H	2	Et	(4S,5S)-6k	71	41
5	Me	1	Et	(4S,5S)-6k	42	8
6	H	1	Ph	(4S,5S)-6k ^a	53	69 (S)

^a In the presence of 1 equiv of Et₂Zn as an additive.

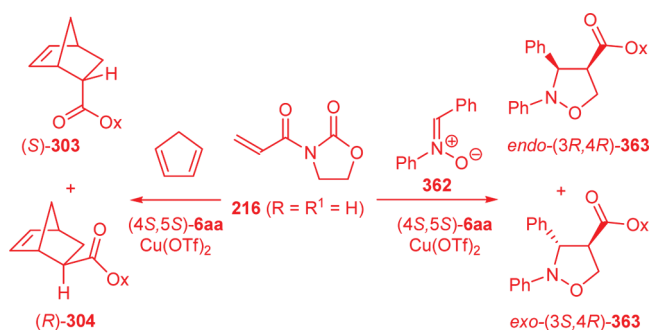
of styrene with ethyldiazoacetate.⁷⁰ The best catalyst proved to be that derived from box **14g**. It gives a *cis/trans* ratio of 6:94, but the enantiomeric excess of *trans*-**31** is only a disappointing 75% ee.

The cyclopropanation of methyl cinnamate with diazo-methane is 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).¹³² In view of the application of supported boxes to the catalysis of the carbonyl–ene reaction between α -methylstyrene and the Mukaiyama–aldol reaction between **107**, both with **106b**, the Cu(OTf)₂ complexes with **7af** and **7am** were tested. Their selectivities were taken as the results for the model catalysts.^{62,63} The comparison between diastereomeric excess and enantiomeric excess obtained in the catalysis of the aza-Henry reaction, between **164** (R = CO₂Et) and nitroalkanes R²CH₂NO₂ with [7an/Cu(OTf)₂] (R² = 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 **237** with dimethyl malonate to give optically active **238** (Scheme 86) was catalyzed (in the presence of BSA and KOAc) by several palladium complexes of the box with substituents on the spacer. Boxes **7d,e,j,k**, **14a**, and (S)-**15a–e** induce good enantioselectivities (80–92% ee), and taking their configurations as a constant (S), all ligands afford (S)-**238**.⁸⁶ The only exception is possibly (S)-**7d** (86% ee of (R)-**238**), since the enantioselection induced by (R)-**3d** (88% ee of (R)-**238**) is the opposite.⁵¹ 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)-**238**.⁵⁵⁹

Literature reports covering a homogeneous series of reactions differing only by the substituent on the spacer are important for making a clean evaluation of this factor. One of the few examples is the intramolecular cyclopropanation already discussed in Scheme 207. Here α -diazo- β -ketosulfones **578a** and α -diazo- β -carboxylates **578b** react with bicyclic ketosulfones **579a** and

Scheme 237



esters **579b** (Scheme 254). Reactions are catalyzed by CuOTf complexes of (S)-**3c**, (S)-**7a**, and (S)-**7s**, all *i*-Pr-substituted boxes, with methyl (the benchmark), ethyl, and benzyl groups on the bridge (Table 156).^{141,143,513,560,561}

From the point of view of this section, it is important to note that a clear effect of the different substituents on the spacer emerges. In most cases, the yield of α -diazo- β -ketosulfones **578a** is better with the benchmark, but enantioselectivity in general increases on going from methyl to ethyl, and the enantiomeric excess obtained with (S)-**7a** is not far from that achieved with (S)-**7s**.^{141,143,513,560}

With respect to enantioselectivity, a great influence emerges from consideration of three other parameters. First, a substitution on the sulfone phenyl group has a beneficial effect on enantioselectivity (Table 156, entries 1–5). The second important parameter depends on R¹. Excellent enantiomeric excesses were obtained with methyl, bromine, or a CH₂OTr group (Table 156, entries 6–8).⁵¹³ If R¹ is an aryl group, then the enantiomeric excesses strongly depend on the substituents on the aromatic ring (Table 156, entries 9–12).¹⁴¹ The third factor is the chain length (Table 156, entries 14–16). When *n* is 2, the enantioselectivity is excellent also with (S)-**3c**, but the reactions give byproduct as a result of C–H insertion.⁵⁶⁰ Solvents other than toluene afford lower enantioselectivities. The enantioselectivity in the α -diazo- β -carboxylate **578b** reaction depends on the bulkiness of the ester moiety. A methyl ester (Table 156, entry 17) gives unsatisfactory enantiomeric excesses, independent of the nature of the box. The phenyl ester is better than its methyl counterpart, but the best results are obtained with 2,6-di-*tert*-butyl-4-methylphenyl ester (Table 156, entries 18–20).¹⁴³

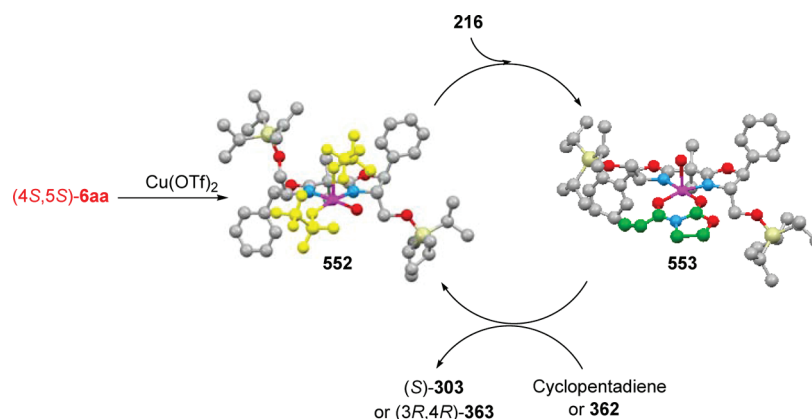
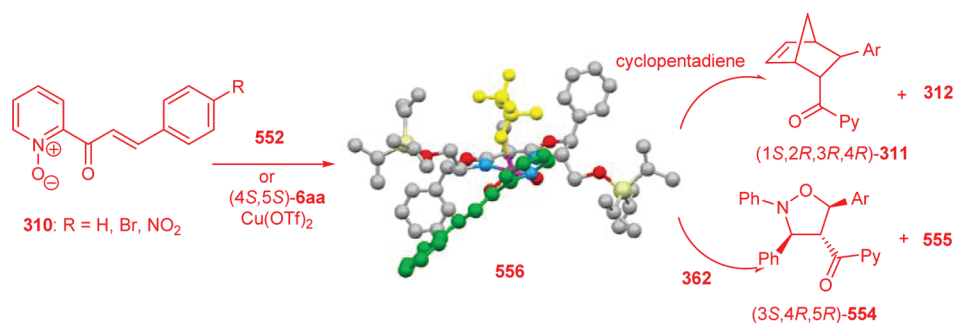
The reaction was also run with 2,5-cyclohexadien- α -diazo- β -ketosulfones. Tricyclic products were obtained with the same excellent enantioselectivities.^{141,513,560}

The copper/box-catalyzed asymmetric intramolecular cyclopropanation reaction (AIMCPR) of α -diazo- β -ketosulfones to yield bicyclic or tricyclic ketosulfones is a protocol useful for the synthesis of several natural products. (–)-Malyngolide **582**, isolated from the lipid extract of a shallow-water variety of *Lyngbya majuscula*, possesses a δ -lactone incorporating two stereogenic centers. These can be generated by the AIMCPR of **580** with [(R)-**7s**/CuOTf] to give (1S,5S)-**581** with the expected absolute configuration, which is converted into the target after several routine synthetic steps (Scheme 255).⁵⁶²

A new asymmetric total synthesis of (–)-methyl jasmonate was accomplished starting from the product (1R,5R)-**579** described in entries 3 and 4 of Table 156. It contains the ester chain

Table 143. Diels–Alder and 1,3-Dipolar Cycloaddition Reactions of **216** Catalyzed by $[\text{Cu(II)}]/(4\text{S},5\text{S})\text{-6aa}]^{55}$

entry	catalyst	Diels–Alder reaction			1,3-dipolar cycloaddition		
		(endo)/(exo)	(S)- 303 ee (%)	(R)- 304 ee (%)	(endo)/(exo)	(3R,4R)- 363 ee (%)	(3S,4R)- 363 ee (%)
1	552	93:7	74	60			
2	552 /MS	90:10	76	50	98:2	84	>90
3	$[(4\text{S},5\text{S})\text{-6aa}/\text{Cu}(\text{OTf})_2]$	92:8	76	55	98:2	86	>90
4	$[(4\text{S},5\text{S})\text{-6aa}/\text{Cu}(\text{ClO}_4)_2]/\text{MS}$	92:8	73	52	98:2	86	>90
5	$[(4\text{S},5\text{S})\text{-6aa}/\text{Cu}(\text{ClO}_4)_2(\text{H}_2\text{O})_6]$	93:7	82	57			
6	552 + $5\text{H}_2\text{O}$	91:9	81	55			

**Figure 22.** Catalytic cycle of the Diels–Alder reaction and of the 1,3-dipolar cycloaddition of **216** catalyzed by **552**.**Scheme 238**

in the correct configuration and the sulfonate group critical for the introduction of the (*Z*)-pentene group.¹⁴²

(–)-Scabrosine A, a potent stimulator of nerve growth factor isolated from the mushroom *Scardon scabrosus*, has a complex structure with seven stereogenic centers. The chiral building block **585**, which incorporates four stereogenic centers in the correct configuration and two suitably placed carbonyl groups, represents an important step toward the target. The AIMCPR allows the conversion of **583** into (1*R*,5*R*)-**584** with excellent enantioselectivity. This was further modified to give **585** (Scheme 256).⁵⁶³

The AIMCPR, run with 2,5-cyclohexadien- α -diazo- β -ketosulfones, can be performed on the analogous carboxylates **586** to give the tricyclic products **587**. These are versatile intermediates for the enantioselective synthesis of a range of natural products.

The data shown in Scheme 257 are evidence of both the importance of the bulkiness of the ester moiety and the matching/mismatching between the box chirality and the chiral ester residue.⁵⁶⁴

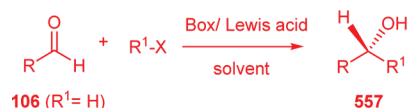
Important applications of the boxes discussed in this section are found in the addition of organometallic reagents to aldehydes and imines. The addition of organolithium (R^1Li) to $\text{R}-\text{CH}=\text{N}-\text{PMP}$ (**164**) to give the amine **165** in Scheme 258 has been already discussed (Scheme 51). The results with the spacer-substituted boxes and the comparison with the (*S*)-**2** as the benchmark are reported in Table 157.^{22,56,220} In the reaction between iminobenzaldehyde **164** ($\text{R} = \text{Ph}$) and MeLi, run under stoichiometric conditions and without changing the substituent (Table 157, entries 1–3 and 5–11), the benchmark is found to not be the best catalyst (entry 1 vs 3). In the first series of results,

Table 144. Diels–Alder and 1,3-Dipolar Cycloaddition Reactions of **310** Catalyzed by **552**⁹⁹

entry	310 R	catalyst	Diels–Alder reaction		1,3-dipolar cycloaddition	
			(endo)/(exo)	(2 <i>R</i> ,3 <i>R</i>)- 311 ee (%)	(endo)/(exo)	(3 <i>S</i> ,4 <i>R</i> ,5 <i>R</i>)- 554 ee (%)
1	H	552 /MS	99:1	97	88:12	93
2	H	[(4 <i>S</i> ,5 <i>S</i>)- 6aa /Cu(OTf) ₂]	99:1	98	87:13	94
3	H	552 /LiOTf/MS	99:1	97	94:6	96
4	Br	552 /MS	99:1	96		98
5	NO ₂	552 /MS	98:2	97		

Table 145. Enantioselective Alkylation of Aldehydes **106** (Scheme 239)

entry	R	R ¹ –X	box	Lewis acid	yield (%)	557 ee (%) (conf.)	ref
1	Ph	Et ₂ Zn	(<i>R</i>)- 3as		83	45	38
2	Ph	Et ₂ Zn	(<i>R</i>)- 3at		72	25	38
3	Ph	Et ₂ Zn	(<i>R</i>)- 3au		93	54	38
4	Ph	CH ₂ =CHCH ₂ SiCl ₃	(<i>S</i>)- 3av	ZnI ₂	74	86 (<i>R</i>)	39
5	<i>p</i> -NO ₂ C ₆ H ₄	CH ₂ =CHCH ₂ SiCl ₃	(<i>S</i>)- 3av	ZnI ₂	73	79 (<i>R</i>)	39
6	<i>p</i> -ClC ₆ H ₄	CH ₂ =CHCH ₂ SiCl ₃	(<i>S</i>)- 3av	ZnI ₂	65	76 (<i>R</i>)	39
7	<i>p</i> -MeOC ₆ H ₄	CH ₂ =CHCH ₂ SiCl ₃	(<i>S</i>)- 3av	ZnI ₂	52	39 (<i>R</i>)	39
8	PhCH ₂ CH ₂	CH ₂ =CHCH ₂ SiCl ₃	(<i>S</i>)- 3av	ZnI ₂	48	68 (<i>S</i>)	39
9	(<i>E</i>)-PhCH=CH	CH ₂ =CHCH ₂ SiCl ₃	(<i>S</i>)- 3av	ZnI ₂	54	64 (<i>R</i>)	39

Scheme 239

with boxes having a 3-pentylidene group as the spacer (Table 156, entries 2–8), the best box is (*S*)-**7m**. It has a rather unusual CMePh₂ group (entry 4), which balances the exaggerated steric hindrance of (*S*)-**7n** (entry 8) with that of the second efficient box (*S*)-**7c**. To evaluate efficiency and synthetic difficulties, a series of *t*-Bu boxes with different spacers was therefore tested (Table 157, entries 9–11). The best box proved to be (*S*)-**7p**, with the 2,4-dimethyl-3-pentylidene group as the spacer. The reactions of different aldimines with various organolithium compounds are also possible (Table 157, entries 12–19), giving appreciable enantioselectivities.

A somewhat related reaction is the addition of alkyllithium to quinoline **588**, which can be catalyzed by three 3-propenylidene boxes (*S*)-**7a**, **c**, **d**. The addition intermediate was trapped by methyl chloroformate to give (*S*)-**589** (Scheme 259). The enantiomeric excesses depend on the box, the solvent, and the amount of ligand. The results in toluene are reported in Table 158, and the best box is seen to be (*S*)-**7a**.⁵⁶⁵

The addition of diethylzinc to aldehydes affording chiral secondary alcohols (Scheme 235) was studied in the presence of four spiro-boxes bearing dibenzo[*a,c*]cycloheptadiene as the spacer: (*S*)-**13d**, (*S*)-**13f**, (*S*)-**13g**, and (*S*)-**13h**. The best result for benzaldehyde is obtained with (*S*)-**13g** (Table 159, entry 3 vs 1, 2, and 4), and the interesting results of this box with some aldehydes are reported in entries 5–10.⁸⁴

Chart 1 reported a great number of boxes with somewhat bizarre substituents on the spacer that have not yet found any

Table 146. Enantioselective [box/Cu(OTf)₂]-Catalyzed Diels–Alder Reactions between **216** and Cyclopentadiene^{18b}

entry ^a	box	4-R	yield (%)	endo/exo	303 ee (%) (conf.)
1	(4 <i>R</i> ,5 <i>R</i>)- 6an	CH ₂ OMe	63	90:10	8 (<i>R</i>)
2	(4 <i>R</i> ,5 <i>R</i>)- 6ao	CH ₂ OAc	99	98:2	24 (<i>R</i>)
3	(4 <i>R</i> ,5 <i>R</i>)- 6ap	CH ₂ OMs	18	98:2	84 (<i>R</i>)
4	(4 <i>R</i> ,5 <i>R</i>)- 6aq	CH ₂ NHMs	95	99:1	98 (<i>R</i>)
5	(4 <i>R</i> ,5 <i>R</i>)- 6ar	CH ₂ NHTf	97	98:2	96 (<i>R</i>)

^a Reactions run in CH₂Cl₂ or EtNO₂.

practical application. An exception is (*R*)-2,2'-(2,3-dihydro-1*H*-phenalene-2,2-diyl)bis-(4-phenyl-4,5-dihydrooxazole) (*R*)-**13aa**. Its Ni(II) complex is an interesting catalyst for the Kumada reaction. This is the enantioselective coupling between Grignard reagents and organic electrophiles **590** to give **591** (Scheme 260).⁸⁵ The box (*R*)-**13aa** is in competition with box (*R*)-**1** as catalyst of choice for this reaction (Table 160). Strictly speaking it should therefore have been discussed in the previous section 4. The reason why both ligands are discussed here is because (*R*)-**13aa** proves to be the best box for the Kumada reaction of dialkyl ketones (Table 160, entries 1–5). (*R*)-**1** gives the catalyst of choice for the reaction of aryl alkyl ketones (Table 160, entries 6–10). The reaction reported in entry 5, performed with both catalysts, supports this conclusion.

The Kumada reaction reports the only known use of the new box (*R*)-**13aa**, and it is astonishing that no emphasis has been given to such an unexpected result: The NiCl₂ complexes of two boxes, (*R*)-**13aa** and (*R*)-**1**, which have the same configuration, give opposite enantiomers, (*R*)-**591** and (*S*)-**591**, respectively.⁸⁵

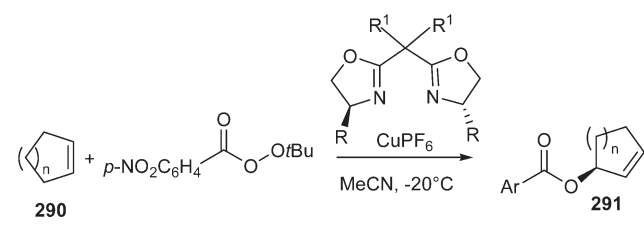
At the beginning of this section, dedicated to the substituents at the box spacer, the efficiency and selectivity promoted by the catalyst compared to the selectivity exerted by the catalyst derived from the corresponding isopropylidene box taken as

Table 147. Enantioselective [Box/CuPF₆]-Catalyzed Kharasch Reactions of Cycloalkenes 290 Yielding (S)-291

entry	box	R	R ¹	n = 1		n = 2		n = 3		n = 4 ^a		ref
				yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)	
1	(S)-1	Ph	Me	49	82	44	96	23	56	46	74	311
2	(S)-7e	Ph	Et	41	99	50	75	12	86	34	59	311
3	(S)-3c	<i>i</i> -Pr	Me	42	51	40	82	14	99	25	36	311
4	(S)-7a	<i>i</i> -Pr	Et	36	83	26	78			27	78	311
5	(S)-3d	Bn	Me	25	75	30	71					311
6	(S)-7d	Bn	Et	28	80	50	53					311
7	(S)-2	<i>t</i> -Bu	Me	52	79	61	84	3	95	13	94	311
8	(S)-7c	<i>t</i> -Bu	Et	31	38	25	16					311
9	(S)-7ao	<i>i</i> -Pr	Ph			75	48					541
10 ^b	(S)-7s	<i>i</i> -Pr	Bn			52	85					65
11 ^b	(S)-7ap	<i>i</i> -Pr	CH ₂ -(2-naphthyl)			42	84					65
12 ^b	(S)-7aq	<i>i</i> -Pr	CH ₂ -(2-pyridyl)			60	82					65
13 ^b	(S)-7ar	<i>i</i> -Pr	CH ₂ -(3-pyridyl)			47	85					65
14 ^b	(S)-7as	<i>i</i> -Pr	CH ₂ -(4-pyridyl)			49	65					65

^a 1,5-cyclooctadiene. ^b Reaction performed with Cu(OTf)₂ as Lewis acid; absolute configuration of 291 not reported.

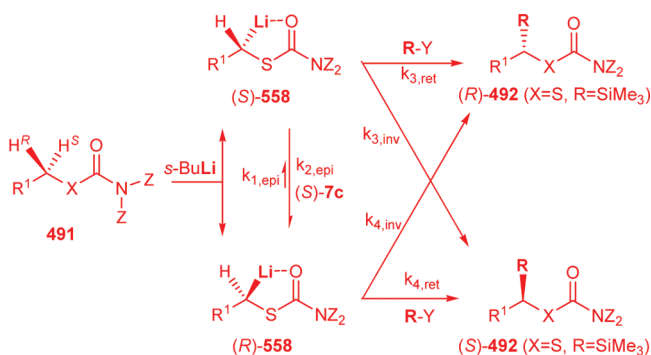
Scheme 240



the benchmark were chosen as the most important parameters to evaluate the effects of the bridge substituents. We close this sections with **ten** boxes ((S)-7ag, (S)-7ah, (S)-7ak, (S)-7ai, (S)-7aj, (R)-7al, (S)-7ay, (S)-7az, (S)-7ba, and (S)-7bb) (Chart 10) bearing two “fluorous ponytails” on the spacer. These are substituents that influence the behavior of the ligand.^{61,68,69,269,566}

The complexes of these ligands have been tested as catalysts for **selected** reactions. The palladium complexes are the catalysts for the allylic substitution reaction of *rac*-3-acetoxy-1,3-diphenyl-1-propene 237 with dimethyl malonate (in the presence of BSA and KOAc) to afford 238 (Scheme 86). The conversions are in the range 89–100%, and the enantioselectivities are in the range 89–96% ee. The enantioselection with six boxes, which have all the same absolute configuration, affords (S)-238 with the 4-Ph- and 4-*i*-Pr-box ((S)-7ai, (S)-7aj, (S)-7ag, and (S)-7ah) and the enantiomer (R)-238 with boxes containing the oxygen atom in the oxazolinic substituents ((S)-7ak and (R)-7al).^{61,566} The same reaction, performed with (S)-7bb, a “bisfluorous ponytail” box with “tails” on the spacer and on the substituent, gives (S)-238 in 92% ee.⁶⁹ The Cu(I) complexes (except that of (S)-7ak, which is inactive) are the catalysts for the Kharasch reaction of cyclohexene 290 (n = 2) with *tert*-butyl perbenzoate to give always (S)-cyclohexenyl-2-benzoate 291 (Scheme 110) with yields in the range of 37–67% and 50–73% ee.^{61,69} The above results are in the range of the box catalysts discussed in previous sections. The Cu(I) complexes of (S)-7ag, (S)-7ai, and (S)-7ay were also tested. The reaction used was the standard cyclopropanation of

Scheme 241



styrene with ethyl diazoacetate (Scheme 5), with quite good results.⁶⁸ Finally, the Cu(II) complexes of (S)-7ag and (S)-7ai have all been applied to several asymmetric glyoxylate–ene reactions between 106b and 373 (Scheme 143). They give products in moderate to high enantiomeric excesses.^{69,269} The peculiar characteristic of these ligands, 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, and they retain the same enantioselectivities.^{61,566}

5.8. Effect of Strained Cyclic Substituents on the Box Geometry

This section is dedicated to the spiro-boxes 8, 10, and 11 in which the substituents induce strain in the ligand, changing the angle Φ between the heterocycles and the bridge (C₂–C–C₂).

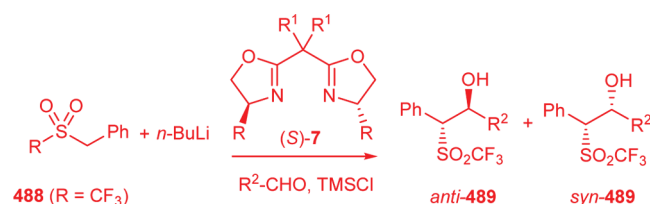
A few years after the discovery of the first boxes, Davies et al. synthesized four boxes (S,R)-10a–d (Chart 11) with cyclopropylidene, cyclobutylidene, cyclopentylidene, and cyclohexylidene groups as spacers.⁸¹ Their aim was to prepare a series of ligands having different bridge angles Φ and to compare their Cu(II) catalysts with those derived from isopropylidene-box 9a.⁷³

Table 148. Deprotonation of *O*- or *S*-Substituted Carbamates **491** with *s*-BuLi/Boxes and Substitution Reactions with Electrophiles RY

entry	R ¹	X	NZ ₂	RY	box	yield (%)	492 ee (%) (config.)	ref
1	Ph	O	N(<i>i</i> -Pr) ₂	Bu ₃ SnCl	(<i>S</i>)- 7c	98	98 (<i>S</i>)	544, 546
2	Ph	O	N(<i>i</i> -Pr) ₂	allylBr	(<i>S</i>)- 7c	75	62 (<i>S</i>)	544
3	Ph	O	N(<i>i</i> -Pr) ₂	MeOC(O)Cl	(<i>S</i>)- 7c	95	91 (<i>R</i>)	544
4	Ph	O	N(<i>i</i> -Pr) ₂	<i>t</i> -BuCOCl	(<i>S</i>)- 7c	87	63 (<i>R</i>)	544
5	Ph	O	N(<i>i</i> -Pr) ₂	<i>p</i> -BrPhCOCl	(<i>S</i>)- 7c	24	96 (<i>R</i>)	544
6	Ph	O	N(<i>i</i> -Pr) ₂	Me ₂ CO	(<i>S</i>)- 7c	28	54 (<i>S</i>)	544
7	1-naphth.	O	N(<i>i</i> -Pr) ₂	MeI	(<i>S</i>)- 7c	77	93 (<i>S</i>)	544
8	<i>o</i> -EtPh	O	N(<i>i</i> -Pr) ₂	Me ₃ SiCl	(<i>S</i>)- 7c	97	>98 (<i>S</i>)	544
9	Ph	O	N(<i>i</i> -Pr) ₂	Bu ₃ SnCl	(<i>S</i>)- 7a	88	90 (<i>R</i>)	546
10	Ph	O	N(<i>i</i> -Pr) ₂	Me ₃ SiCl	(<i>S</i>)- 7c	98	>98 (<i>S</i>)	546
11	Ph	O	N(<i>i</i> -Pr) ₂	CO ₂	(<i>S</i>)- 7c	99	95 (<i>R</i>)	546
12	1-naphth.	O	N(<i>i</i> -Pr) ₂	Me ₃ SiCl	(<i>S</i>)- 7c	96	98 (<i>S</i>)	546
13	1-naphth.	O	N(<i>i</i> -Pr) ₂	Bu ₃ SnCl	(<i>S</i>)- 7c	91	99 (<i>S</i>)	546
14	Ph	S	N(<i>i</i> -Pr) ₂	Ph ₂ CO	(<i>S</i>)- 7c	99	98 (<i>R</i>)	545
15	Ph	S	N(<i>i</i> -Pr) ₂	MeOTf	(<i>S</i>)- 7c	98	96 (<i>S</i>)	545
16	Ph	S	N(<i>i</i> -Pr) ₂	CO ₂	(<i>S</i>)- 7c	53	98 (<i>R</i>)	545
17	cinnamyl	S	TMox ^a	Me ₃ SiCl	(<i>S</i>)- 7a	95	84 (<i>S</i>)	490

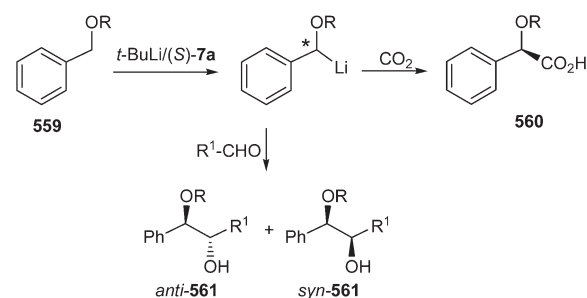
^a TMox is 2,2,5,5-tetramethyl-1,3-oxazole.**Table 149.** Enantioselective Reactions of α -Lithiated Sulfoxones **488** with Aldehydes

entry	box	R	R ¹	R ²	yield (%)	syn/anti	syn- 489 ee (%)	ref
1	(<i>S</i>)- 1	Ph	Me	Ph	84	93:7	74	488, 489
2	(<i>S</i>)- 7e	Ph	Et	Ph	74	93:7	94	488, 489
3	(<i>S</i>)- 7	Ph	<i>i</i> -Pr	Ph	74	92:8	94	488, 489
4	(<i>S</i>)- 7u	Ph	Bn	Ph	87	96:4	94	488, 489
5	(<i>S</i>)- 7u	Ph	Bn	<i>p</i> -MeOPh	57	97:3	98	488, 489
6	(<i>S</i>)- 7u	Ph	Bn	2-naphthyl	80	94:6	96	488, 489
7	(<i>S</i>)- 7u	Ph	Bn	2-furyl	58	93:7	90	488, 489
8	(<i>S</i>)- 7u	Ph	Bn	2-thienyl	95	97:3	92	489
9	(<i>S</i>)- 7u	Ph	Bn	(<i>E</i>)-styryl	94	85:15	98	489

Scheme 242

to establish the influence of the bite angle θ in the complex on the diastereo- and enantioselectivities.

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. These values were checked with the data of the corresponding crystal structures, and the agreement between theory and experiment was found to be good.⁵⁶⁷ Table 161 reports the calculated values of Φ and θ and the diastereomeric and enantiomeric excesses of the Diels–Alder reaction between acryloyloxazolidinone **216** (R = R¹ = H) and cyclopentadiene at

Scheme 243

−50 °C reported in Scheme 114. 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 is the enantioselectivity (and the same for Φ), at least for Cu(II) catalysts.

The influence of the spiro group on the enantioselectivity of the Diels–Alder reaction was further investigated. By correctly assuming that chirality is a property of the whole molecule, the parameter “computed chirality content” (CCM) was determined for the **10a–d** catalysts. A linear relationship was found between CCM and the enantioselectivity of the Diels–Alder reaction. 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.⁵⁶⁸

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

The results of attempts to catalyze intramolecular cyclopropanation of both phenyliodonium ylides with [(*R,S*)-**10a**/Cu(I)]⁵¹² and diazoketones with the Cu(II) complexes of (*S*)-**8a**,

Scheme 244

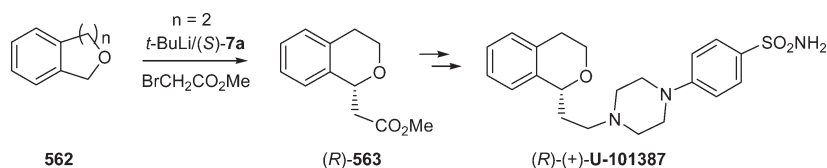


Table 150. Reactions of Benzyl Ethers 559 with Electrophiles Catalyzed by [(S)-7a/t-BuLi]

entry	R	electrophiles CO ₂ or R ¹ (CHO)	solvent	yield (%)	anti/syn	560 ee (%) (conf.)	anti-561 ee (%) (conf.)	syn-561 ee (%) (conf.)	ref
1	Me	CO ₂	hexane	>95		95 (R)			547
2	Me	CO ₂	THF	85		17 (S)			547
3	Me	CO ₂	ether	>95		racemate			547
4 ^a	CH ₂ OMe	CO ₂	hexane	46		30 (R)			547
5	Me	Ph	hexane	>95	88:12		90 (1R,2S)	60 (1R,2R)	548
6	Me	<i>n</i> -C ₈ H ₁₇	hexane	77	71:29		61	47	548
7	Me	cyclohexyl	hexane	68	58:42		78	61	548
8	Me	(<i>E</i>)-PHCH=CH	hexane	17	64:36		37	15	548
9	Me	Ph—C≡C	hexane	>95	90:10		>98 (1R,2S)	84 (1R,2R)	548
10	Me	<i>t</i> -BuPh ₂ Si—C≡C	hexane	>95	91:9		>98 (1R,2S)	86 (1R,2R)	548

^a *s*-BuLi.Table 151. Reactions of Phthalan and Isochroman (562) with Electrophiles Catalyzed by [(S)-7a/t-BuLi] in Hexane⁵⁴⁹

entry	<i>n</i>	electrophiles	yield (%)	563 ee (%) (conf.)
1	1	MeI	68	36 (R)
2	1	PhCH ₂ Br	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 ₂ Br	37	30
7	2	CH ₂ =CHCH ₂ Cl	63	34
8	2	CO ₂	75	89 (S)
9	2	PhCHO	94 ^c	97 ^b

^a 76:24 Mixture of diastereoisomers. ^b Ee of the major diastereoisomer.^c 60:40 Mixture of diastereoisomers.

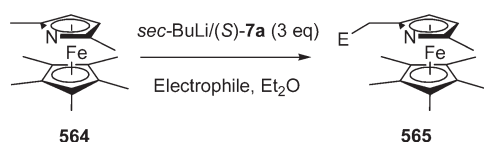
Table 153. [2,3]-Sigmatropic Rearrangements of 566 Catalyzed by [(S)-7a/t-BuLi]

entry	A	R	R ¹	yield (%)	erythro/threo	567 ee (%) (conf.) ^a	ref
1	Ph	Me	Me	74		33 (S)	537
2	Ph	H	Me	<i>b</i>	89:11	40 (1R,2S)	551, 552
3 ^c	Ph	H	Me	<i>b</i>	89:11	23 (1R,2S)	552
4	Me—C≡C	Me	H	<i>b</i>	<5:>95	89 (1S,2S)	551, 552
5	Me—C≡C	H	Me	<i>b</i>	94:6	39 (1S,2R)	551, 552
6	TMS—C≡C	Me	H	<i>b</i>	80:20	32 (1S,2R)	551, 552
7	TMS—C≡C	H	Me	<i>b</i>	95:5	45 (1S,2R)	551, 552
8	TMS—C≡C	H	Ph	48	45 ^d :55	73 (1S,2R)	552

^a Ee's of the major diastereoisomer. ^b >90%. ^c Catalytic version run with 0.2 eq [box/*t*-BuLi]. ^d 12% ee (1S,2S).Table 152. Reactions of 1',2,2',3',4',5,5'-Heptamethylazaferrocene 564 with Electrophiles Catalyzed by [(S)-7a/sec-BuLi] in Ether⁵⁵⁰

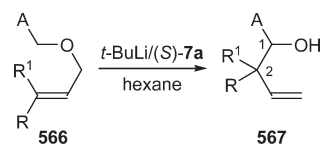
entry	electrophiles	<i>E</i>	yield (%)	565 ee (%) (conf.)
1	Ph ₂ CO	C(OH)Ph ₂	57	99
2	(TMSO) ₂	OH	17	99 (R _p)
3	(PhS) ₂	SPh	46	99
4	TMSCH ₂ N ₃	NH ₂	46	96

Scheme 245

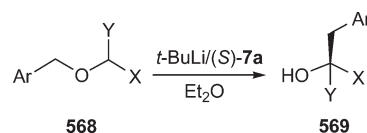


(*S*)-8b, and (*S*)-8g⁷² show enantioselectivities lower than those obtained with the benchmark. Even worse results were obtained for the intramolecular C—H insertion of phenyliodonium

Scheme 246

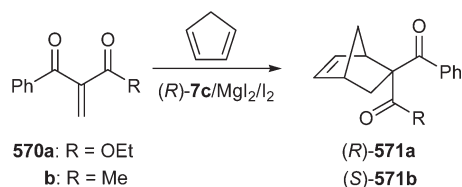


Scheme 247



ylides⁴⁶⁹ and the intermolecular insertion of methyl diazo acetate into the N—H bond of aniline.⁴⁷⁴ The cyclopropanation of methyl cinnamate with diazomethane catalyzed by [(*S*)-8a/Cu(I)] gave a positive result, since the enantioselectivity (77%)

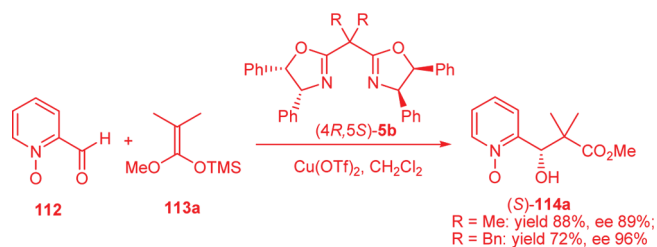
Scheme 248

Table 154. [1,2]-Wittig Rearrangements of 568 Catalyzed by [(S)-7a/*t*-BuLi]⁵⁵³

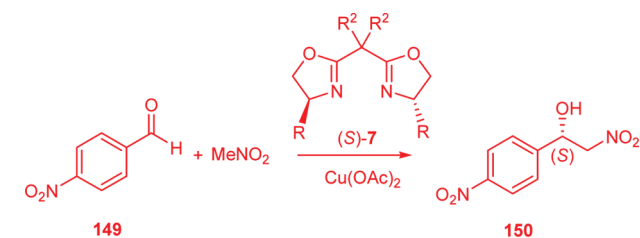
entry ^d	Ar	X	Y	yield (%)	569 ee (%) (conf.)
1	Ph	Ph	H	86	60 (S)
2	<i>m</i> -diMeC ₆ H ₃	3,5-diMeC ₆ H ₃	H	65	56
3	Ph	TMS-C≡C	Ph	55	54 (R)
4	Ph	TIPS-C≡C	Ph	65	65 (R)

^a *t*-BuLi 2 equiv, (S)-7a 0.1 equiv.

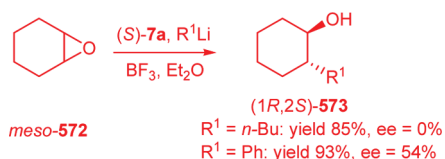
Scheme 249



Scheme 250



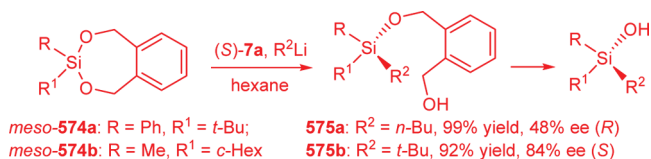
Scheme 251



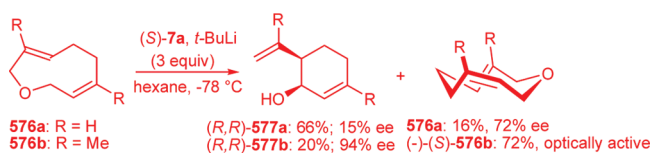
ee) was better than that obtained with the complex of (S)-1 (Table 7, entry 1).¹³² As a whole, carbenoids are not the best reagents for [cyclopropylidene-box/Cu] catalysts.

During the extensive research to check the best catalyst for the addition of organometallic reagents to imines, 10a was tested

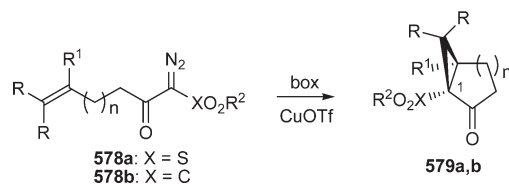
Scheme 252



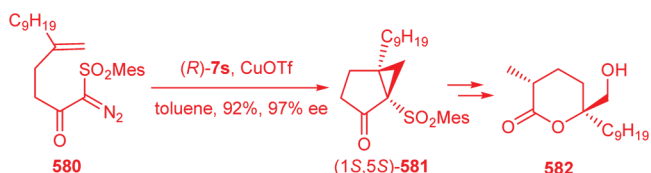
Scheme 253



Scheme 254



Scheme 255



with formation of racemates.²²¹ The Mannich reaction between *N*-tosyl- α -iminoester 101 and β -ketophosphonates 174c^{228b} to afford 175c (Scheme 57) was tested with the Cu(OTf)₂ complexes of (R,S)-10a and (S)-8b. The former catalyst gave racemates. Although the latter gave a good selectivity (2.2:1 dr, 74% ee), it was lower than that obtained with the corresponding benchmark (S)-2 (Table 28, entry 23).^{228b} The radical addition of *i*-PrI to 269 (Scheme 101) exhibits the same behavior but with different Lewis acids: Zn(OTf)₂ and (R,S)-10a give racemates, and Mg(NTf₂)₂ and the same box give (S)-270 in 35% ee, but the enantiomeric excess is lower than that obtained with other boxes.²⁹³

Other spiro-cyclopropylidene boxes were tested with disappointing results; [(S)-8c/Cu(OTf)₂] catalyzed the aza-Henry reaction of 164 and 177 (Scheme 60), but *anti*-178 was obtained with only 36% ee.²³⁴ The Mannich reaction of isothiocyanatoacetyl-2-oxazolidinone 256 and tosyl imine 164, which gives an interesting intermediate for the enantioselective synthesis of protected anti- α,β -diamino acids 593 (Scheme 261), can be catalyzed by the Mg(ClO₄)₂ complexes of (R)-8b or (R)-8h.

Table 155. Enantioselective Henry Reactions between 149 and Nitromethane Yielding (S)-150, Catalyzed by the Cu(OAc)₂ Complexes of Isopropylidene and 3-Pentylidene Boxes⁶⁶

entry	isopropylidene-box				3-pentylidene-box			
	(S)-box	R	yield (%)	ee (%)	(S)-box	R	yield (%)	ee (%)
1	3c	<i>i</i> -Pr	91	67	7a	<i>i</i> -Pr	93	72
2					7b	<i>i</i> -Bu	94	57
3	2	<i>t</i> -Bu	60	47	7c	<i>t</i> -Bu	87	25
4					7d	Bn	88	69
5	1	Ph	97	42	7e	Ph	85	71
6					7au	<i>sec</i> -Bu	92	63

Table 156. Intramolecular Cyclopropanations of α -Diazo- β -ketosulfones 578a and α -Diazo- β -carboxylates 578b Catalyzed by CuOTf Complexes of Boxes (S)-3c, (S)-7a, and (S)-7s

entry	578	R	R ¹	XO ₂ R ²	<i>n</i>	(S)-7s			(S)-7a			(S)-3c			ref
						yield (%)	ee (%)	(conf.)	yield (%)	ee (%)	(conf.)	yield (%)	ee (%)	(conf.)	
1	a	H	H	SO ₂ Ph	1	61	73 (1R)		67	72 (1R)		91	65 (1R)		513, 561
2	a	H	H	SO ₂ -2,3-Me ₂ Ph	1	82	91 (1R)		95	93 (1R)					561
3	a	H	H	SO ₂ -2,6-Me ₂ Ph	1	82	91 (1R)		83	90 (1R)					561
4	a	H	H	SO ₂ -(1-Naphth)	1	82	79 (1R)		93	83 (1R)					561
5	a	H	H	SO ₂ Mes	1	87	93 (1R)		89	90 (1R)		93	83 (1R)		513
6	a	H	Me	SO ₂ Mes	1	90	98 (1R)		94	87 (1R)		96	81 (1R)		513
7	a	H	Br	SO ₂ Mes	1	63	98 (1S)		43	95 (1S)		68	92 (1S)		513
8	a	H	CH ₂ OTr	SO ₂ Mes	1	98	91 (1R)		75	84 (1R)		91	78 (1R)		513
9	a	H	Ph	SO ₂ Mes	1	95	96 (1R)		quant	87 (1R)		quant	82 (1R)		141
10	a	H	3,4-(OMe) ₂ Ph	SO ₂ Mes	1	55	racemate		86	racemate		44	racemate		141
11	a	H	3,4-(OTBS) ₂ Ph	SO ₂ Mes	1	77	55 (1R)		73	64 (1R)		80	30 (1R)		141
12	a	H	3,4-(OBz) ₂ Ph	SO ₂ Mes	1	96	93 (1R)		55	80 (1R)		75	69 (1R)		141
13	a	Me	H	SO ₂ Mes	1	84	92 (1R)		54	76 (1R)		74	74 (1R)		513
14	a	H	H	SO ₂ Ph	2	41 ^a	89 (1R)		28 ^a	88 (1R)		58 ^a	92 (1R)		560
15	a	H	H	SO ₂ Mes	2	31 ^a	98 (1R)		23 ^a	94 (1R)		36 ^a	90 (1R)		560
16	a	H	Me	SO ₂ Mes	2	43 ^a	98 (1R)		26 ^a	94 (1R)		41 ^a	90 (1R)		560
17	b	H	H	CO ₂ Me	1	57	35 (1R)		57	38 (1R)		68	56 (1R)		143
18	b	H	H	CO ₂ CMe ₂ Ph	1	90	52 (1R)		87	50 (1R)		77	48 (1R)		143
19	b	H	H	CO ₂ Mes	1	87	69 (1R)		82	66 (1R)		74	53 (1R)		143
20	b	H	H	CO ₂ -2,6-(<i>t</i> -Bu) ₂ -4-MePh	1	53	74 (1R)		56	78 (1R)		92	77 (1R)		143

^a C–H insertion byproduct.

Unfortunately, the enantiomeric excesses were only 8% and 39%, respectively. This is enormously far from the values obtained with catalysts derived from the DBFox, a ligand not included in this review.⁵⁶⁹

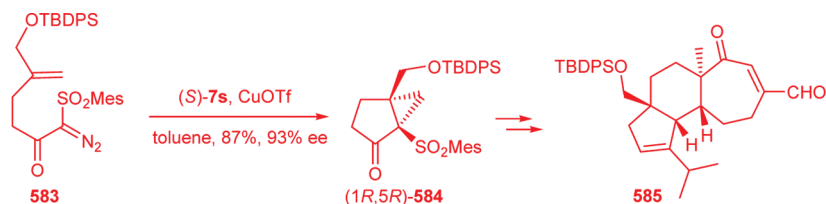
(S)-8b and Cu(OTf)₂ are the catalysts in the Mukaiyama–aldol reaction between 112 and 113a (Scheme 30), but the 64% ee of (S)-114a is too far from the 90% ee obtained with (S)-2.¹⁸² Hence, a spiro-cyclopropylidene spacer appears to have a negative effect on the enantioselectivity of this reaction. This spacer has the same negative effect on the radical addition of *i*-PrI on α' -phosphoric enone 496 [R = (CH₂)₂Ph] also (Scheme 195), because the Zn(OTf)₂ complexes of (R,S)-8g and (R,S)-5b give 497 in 73% and 88% ee, respectively.⁴⁹⁵

The above examples are clear results of a negative effect of the spiro-cyclopropylidene spacer. Before examining reactions in which this spacer makes a box the base of a tailor-made catalyst, an equivocal result must be mentioned because,

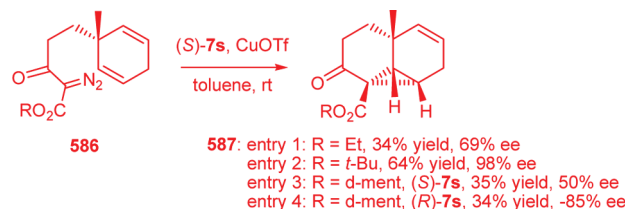
although enantioselective catalysis is an art, surprises always lie behind the corner. Among the dozens of [box/Cu(I)] catalysts used for the standard cyclopropanation of styrene with ethyl diazoacetate (Scheme 5), two pairs of boxes were tested. They had the same substituents with the same configuration: one box with isopropylidene, the other with cyclopropylidene as spacer, (S)-2 vs (S)-8b and (R)-4o vs (R)-8aa.^{71a} The results of the *trans*-31 and *cis*-32 adducts are reported in Table 162. (R)-8aa depresses the enantioselectivity observed for both isomers with (R)-4o (Table 162, entry 2 vs 1); on the contrary, (S)-8b gives even better enantiomeric excesses than the excellent ones obtained with (S)-2, (Table 162, entry 4 vs 3).

The α' -hydroxy enones 188 have been used as electrophiles in some reactions catalyzed by box complexes with cyclopropylidene as the spacer. One example is the enantioselective Friedel–Crafts alkylation/Michael reaction of indole 196 (R² = R³ = H) with 188, which occurs at position 3 and affords 594

Scheme 256



Scheme 257



(Scheme 262).²⁴⁹ Table 163 reports the selectivity induced by $[(S)\text{-8b}/\text{Cu}(\text{OTf})_2]$ as catalyst, compared with the results obtained for the benchmark $[(S)\text{-2}/\text{Cu}(\text{OTf})_2]$. The effect of cyclopropylidene as spacer in box **8b** is to increase both yields and enantioselectivities (Table 163, entries 1 and 3 vs 2 and 4).

The α' -Hydroxy enone **188** (R = $\text{CH}_2\text{CH}_2\text{Ph}$) adds benzyl-carbamate **212**, in accordance with an aza-Michael reaction, to give the β -amino-protected carbonyl adduct **213** (Scheme 75).²⁵¹ The $\text{Cu}(\text{OTf})_2$ complex of $(S)\text{-2}$ is an excellent catalyst (Table 50, entry 2, yield 86%, 96% ee (*S*)). However, the strained analogue $(S)\text{-8b}$ does not prove to be inferior since the yield is 90% and the enantiomeric excess of $(S)\text{-213}$ is 98%.

The α' -hydroxy enones **188** also behave as electrophiles in the enantioselective Michael addition with nitromethane, giving the adducts **595**. This is only with the complex between $(S,R)\text{-10a}$ and $\text{Mg}(\text{OTf})_2$ (Scheme 263) because, using $(S,R)\text{-10b}$ or $(S)\text{-8b}$, the products were found to be racemates.⁵⁷⁰ The use of different surrogates of the CMe_2OH substituents emphasizes the importance of the tertiary sp^3 -carbon atom. Under these conditions the enantioselectivities are excellent with different types of alkyl or aryl α -hydroxy enones (Table 164).

The above reaction is a good example of the core topic of this section: The extensive use of the box **10a** often improves the performance compared to its unstrained analogue **9a**. The addition of ethyl propiolate to the 1-acylpyridinium salt **503** that gives (R) -methyl 2-[2-(ethoxycarbonyl)ethynyl]pyridine-1(2*H*)-carboxylate **504**, which was briefly discussed in Scheme 200, can be catalyzed by the CuI complex of $(4R,5S)\text{-9a}$ (67% yield and 74% ee). Even better it can be catalyzed by the same complex with $(4R,5S)\text{-10a}$: here the yield is 63% but the enantiomeric excess is improved to 87%.⁵⁰²

N-Substituted alkenoys, 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 **596** (**216** when Z is O and R = R^1 = Me)

(Scheme 77), with $(S)\text{-1}$ and $(S)\text{-2}$, gives low enantiomeric excesses of **597**, which can be easily converted into protected β -amino acids. Since the best catalyst is $[(S,R)\text{-10a}/\text{MgBr}_2]$, Table 165 reports the results with different β -substituted templates (**596**, Scheme 264).²⁵³

This reaction not only gives good enantiomeric excesses of **597** with different enones, but the face selectivity in these additions is temperature-dependent, and it shows an unusual reversal of enantioselection between 0 and -60°C .

When the $[(S,R)\text{-10a}/\text{MgX}_2]$ -catalyzed conjugate addition to enones **598** is performed with *N*-substituted-hydroxylamines (Scheme 265), the addition product **599** undergoes elimination of the template and gives the chiral isoxazolidinones **222** with yields and enantioselectivities as reported in Table 166.^{256,571}

Several enones of the type **598** give excellent enantiomeric excesses with complexes of $(S,R)\text{-10a}$, which seems to be the tailor-made ligand for the reaction (Table 166, entries 1, 3, and 6–9). Among them, the 1-substituted 2-alkenoyl-4,4-dimethylpyrazolidin-3-ones **220** (Z = CH_2 , R^1 = Me, Y = NBn) and their analogues in Table 166 (entries 11–13) are achiral templates that relay and amplify the stereochemistry induced by $(S,R)\text{-10a}$. 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 achieved with the 2-substituted *N*-acyl-2-enimides **600**. They proved ideal for the easy preparation of the cheap template and the flexibility of the reaction (Table 167), which allows the preparation of chiral 3,4-disubstituted isoxazolinones **601** with high diastereo- and enantioselectivities. Using hydrogenation, the isoxazolinones can then be converted into the α,β -disubstituted- β -amino acids **602** (Scheme 266).⁵⁷² The best catalyst has $\text{Mg}(\text{NTf}_2)_2$ as the Lewis acid (Table 167, entry 4 vs 3). It gives high diastereomeric and enantiomeric excesses and allows the preparation of enantiopure disubstituted β -amino acids.

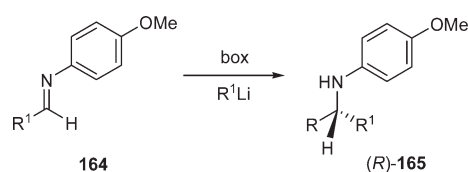
The conjugate addition of monosubstituted hydrazines to enones was investigated with the aim of providing access to optically active pyrazolidinones. Because the cleavage of the template during the reaction results in a direct synthesis of the chiral heterocycle, much effort was concentrated on the search for the best template. The reaction of several α,β -unsaturated amides **603**, in which the templates **A–D** were bound by a nitrogen atom, was tested with $(R,S)\text{-10a}$ and different Lewis acids. Among them, the best was magnesium perchlorate. A sample of the different reaction conditions, templates, and substituents tested is reported in Table 168. Among the different templates, the *N*-benzoyl-2-enimides used in the reaction shown in Scheme 266 are notable for their excellent results as well as their easy preparation. At low temperatures, a better control of the nucleophilicity of the hydrazine nitrogen atoms is realized, and the more nucleophilic and bulky nitrogen adds selectively

Table 157. Asymmetric Additions of Organolithiums to Imines 164 (Scheme 51)

entry	R	R ¹	box	yield (%)	(R)-165 ee (%)	ref
1 ^a	Ph	Me	(S)-2	90	67	22, 220
2 ^a	Ph	Me	(S)-7a	90	70	56, 220
3 ^a	Ph	Me	(S)-7c	95	75	22, 56, 220
4 ^b	Ph	Me	(S)-7c	98	68	56
5 ^a	Ph	Me	(S)-7d	91	34	56, 220
6 ^a	Ph	Me	(S)-7l	75	64	56, 220
7 ^a	Ph	Me	(S)-7m	99	81	56, 220
8 ^a	Ph	Me	(S)-7n	0		56, 220
9 ^a	Ph	Me	(S)-7p	87	89	22, 220
10 ^a	Ph	Me	(S)-7q	95	85	22, 56, 220
11 ^a	Ph	Me	(S)-7z	85	85	22, 220
12 ^b	1-naphthyl	Me	(S)-7c	97	60	56
13 ^a	(E)-PhCH=CH	Me	(S)-7c	90	80	220
14 ^b	(E)-PhCH=CH	Me	(S)-7c	92	68	56
15 ^a	(E)-PhCH=CH	Me	(S)-7p	77	81	220
16 ^b	PhCH ₂ CH ₂	Me	(S)-7c	81	82	56
17 ^a	PhCH ₂ CH ₂	Me	(S)-7p	77	87	220
18 ^b	PhCH ₂ CH ₂	<i>n</i> -Bu	(S)-7c	92	51	56
19 ^b	PhCH ₂ CH ₂	CH ₂ =CH	(S)-7c	82	82	56

^a Stoichiometric amounts of catalyst. ^b Catalytic amounts of catalyst.

Scheme 258



to the β -carbon, giving **604**. This, upon ring closure and loss of the template, gives **605** as the main product: **606** becomes a byproduct (Table 167, entries 4–6) (Scheme 267).⁵⁷³ Two short observations will emphasize the role of **603** with **D** as a simple and efficient template: It is compatible with the majority of the R substituents (Table 167, entries 4–7 vs 8 and 9), and it coordinates to the [Mg(II)/(*R,S*)-**10a**] catalyst to give an octahedral complex rationalizing the (*R*) configuration obtained for **605**.

The chiral relay methodology can be applied to templates without a carbonyl group, if the framework allows a bidentate coordination to the catalyst. These characteristics can be found in 1-alkenoyl-3,5-dimethylpyrazoles **317** (where N(2) is the second binding site of the reagent). It adds *O*-benzylhydroxylamine to give **607** (Scheme 268).⁵⁷⁴ The limitation of the reaction lies in the amount of catalyst [(*S,R*)-**10a**/MgBr₂] required, namely, 30 mol %. At lower catalytic loadings selectivity was found to decrease; for this reason Table 169 reports the results run under these conditions.

The Michael reaction of active methylene compounds to α,β -nitro alkenes **608** gave almost racemic products with (*S*)-**1** or (*S*)-**2** and several Cu, Ni, Fe, or Mg salts. Where the classic boxes failed, success was achieved with the 1,3-dicarbonyl compounds **174a,b** by using [(*S,R*)-**10a**/Mg(OTf)₂] (Scheme 269, Table 170).^{236,575}

Two points deserve attention: the comparison of the catalysts [(*S,R*)-**10a**/Mg(OTf)₂] and [(*S,R*)-**9a**/Mg(OTf)₂] (Table 170, entry 1 vs 2), which identifies the positive effect of the strain induced by the 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 some biologically active molecules. Endothelin-A is the receptor of the potent vasoconstrictive endothelin-1. Its antagonist ABT-546 (**615**) is used in the treatment of cancer and congestive heart failure. The asymmetric conjugate addition of the ketoester **174b** (R = Et, R¹ = CH₂C(Me)₂*n*-Pr) to nitroolefin **610**, catalyzed by [(*S,R*)-**10a**/Mg(OTf)₂], gives the adduct **611** with 82% yield and 88% selectivity (Scheme 270). The reduction of the nitroketone, first with H₂–Raney/Ni, then with NaBH(OAc)₃, delivers the hydride syn to the 3-carboxylate and provides the enantiomerically enriched *trans,trans*-pyrrolidine **612**. The pure (*2S,3R,4S*)-enantiomer **613** was obtained as the tartrate salt, which was transformed with standard reactions, through **614**, into the target **615**.⁵⁷⁵

Rolipram **618** 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 **174a** and nitrostyrene derivative **616** was achieved following the above-described protocol. The adduct **617** was reduced with H₂–Raney/Ni in the presence of a catalytic amount of H₃PO₄ to the corresponding pyrrolidone, which was then saponified and decarboxylated to give (*R*)-**618** with excellent overall yield and selectivity (Scheme 271).⁵⁷⁵

The same enantioselective Michael addition of α -methylmalonate **174a** to the nitrostyrene derivative **619**, catalyzed by the [(*R,S*)-**10a**/Mg(OTf)₂] complex, generates **620** with a stereocenter (*S*) at the benzylic carbon and an adjacent prochiral center. The reduction of the nitro group and cyclization

gives (3*S*,4*S*)-**621**, which is easily transformed into **622**, the phosphodiesterase type 4 (PDE4) potent inhibitor IC86518 (Scheme 272).⁵⁷⁶ Additional examples of such enantioselective malonates/ β -nitrostyrene Michael additions, catalyzed by [(*R,S*)-**10a**/Mg(OTf)₂], are reported with enantioselectivities well above 90%.

The enantioselective malonates/ β -nitrostyrenes Michael addition between **174a** and **623** was catalyzed by [(*R,S*)-**10a**/

Table 158. Enantioselective Additions of Organolithium Reagent to Quinoline **588 in the Presence of Box**⁵⁶⁵

entry	R ¹ Li	box	equiv. box	yield (%)	(<i>S</i>)- 589 ee (%)
1	Me	(<i>S</i>)- 7a	1	47	63
2	Me	(<i>S</i>)- 7a	0.2	30	62
3	<i>n</i> -Bu	(<i>S</i>)- 7a	1	85	79
4	<i>n</i> -Bu	(<i>S</i>)- 7a	0.2	63	67
5	Me	(<i>S</i>)- 7c	0.2	<5	n.d.
6	<i>n</i> -Bu	(<i>S</i>)- 7c	0.2	70	37
7	Me	(<i>S</i>)- 7d	0.2	69	21
8	<i>n</i> -Bu	(<i>S</i>)- 7d	0.2	79	41

Scheme 259

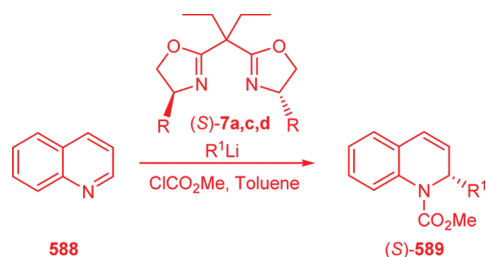


Table 159. Asymmetric Additions of Diethylzinc to Aldehydes in Toluene–Hexane 1:1 at 0 °C (Scheme 235)⁸⁴

entry	RCHO	box	yield (%)	ee (%) (conf.)
1	Ph	(<i>S</i>)- 13d	28	18 (<i>R</i>)
2	Ph	(<i>S</i>)- 13f	81	racemate
3	Ph	(<i>S</i>)- 13g	86	87 (<i>R</i>)
4	Ph	(<i>S</i>)- 13h	38	50 (<i>R</i>)
5	<i>p</i> -Me ₂ NC ₆ H ₄	(<i>S</i>)- 13g	86	74 (<i>R</i>)
6	<i>p</i> -MeOC ₆ H ₄	(<i>S</i>)- 13g	91	95 (<i>R</i>)
7	<i>p</i> -ClC ₆ H ₄	(<i>S</i>)- 13g	90	96 (<i>R</i>)
8	<i>p</i> -NO ₂ C ₆ H ₄	(<i>S</i>)- 13g	84	75 (<i>R</i>)
9	1-naphthyl	(<i>S</i>)- 13g	90	90 (<i>R</i>)
10	(<i>E</i>)-Ph–CH=CH	(<i>S</i>)- 13g	86	61 (<i>R</i>)

Table 160. Enantioselective Kumada Reactions between α -Bromo Ketones **590 and Grignard Reagents Catalyzed by NiCl₂ Complex of Boxes (*R*)-**13aa** or (*R*)-**1****⁸⁵

entry	R	R ¹	Ar	(<i>R</i>)- 13aa		(<i>R</i>)- 1	
				yield (%)	ee (%) (config.)	yield (%)	ee (%) (config.)
1	PhCH ₂	Me	4-Cl–C ₆ H ₄	90	82 (<i>R</i>)		
2	Cy-hexCH ₂	Me	Ph	85	73 (<i>R</i>)		
3	Cy-hexCH ₂	Et	3-Br–C ₆ H ₄	78	70 (<i>R</i>)		
4	<i>i</i> -Pr	Me	Ph	84	83 (<i>R</i>)		
5	Et	Me	Ph	73	90 (<i>R</i>)	24	23
6	Ph	Me	4-MeO–C ₆ H ₄			82	91 (<i>S</i>)
7	Ph	Me	3-CN–C ₆ H ₄			91	95 (<i>S</i>)
8	3-Cl–C ₆ H ₄	Me	Ph			72	80 (<i>S</i>)
9	2-thienyl	Me	Ph			91	87 (<i>S</i>)
10	Ph	(CH ₂) ₂ Cl	Ph			73	86 (<i>S</i>)

Mg(OTf)₂] and afforded (*R*)-**624** in quantitative yield and >95% ee. This reacted with paraformaldehyde and RNH₂ and, after reduction with Zn/AcOH, gave a series of 1-substituted (*R,R*)-**625** piperidinones. These are selective dipeptidyl peptidase IV (DPP4) inhibitors (Scheme 273).⁵⁷⁷

The enantioselective Mukaiyama–Michael reaction of silylketene acetals **107** with β -enamido malonates **198** ($R^1 = R^3OCHN$) (Scheme 80), which fails with complexes based on **1** and **2** ($\leq 60\%$ ee), can be usefully catalyzed by [(*S,R*)-**10a**/Cu(OTf)₂]. Table 171 reports some significant results where either the substituent in α position to the OTMS group of **107** or the R^3 group of **198** are changed.²⁵⁹

Radical reactions are often marginally discussed in reviews dealing with enantioselective catalysis because of the common misconception about radicals as a species being too reactive to be used in stereoselective processes. Hence, it is not surprising that this proved to be a most fertile field to test the performance of

Scheme 260

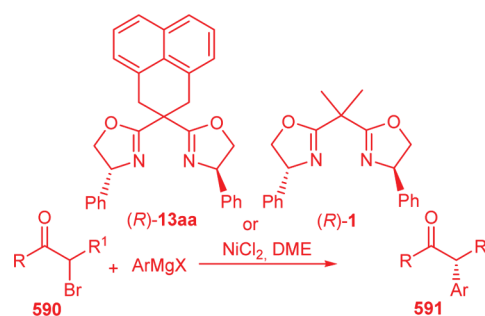


Chart 10

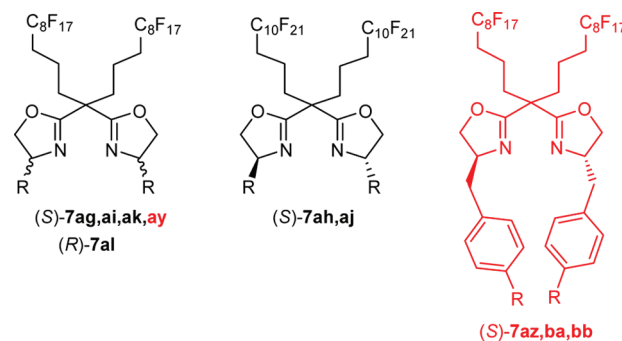


Chart 11

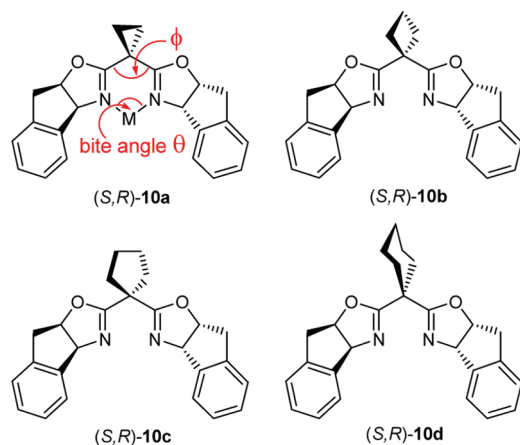


Table 161. Calculated Values of Φ and θ of (S,R)-10a–d and (S,R)-9a Cu(II) Complexes and Observed Selectivity of the Diels–Alder Reactions between 216 ($R = R^1 = H$) and Cyclopentadiene (Scheme 114)^{81,567}

entry	box	Φ (deg)	θ (deg)	de (endo) (%)	(S)-303 ee (%)
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

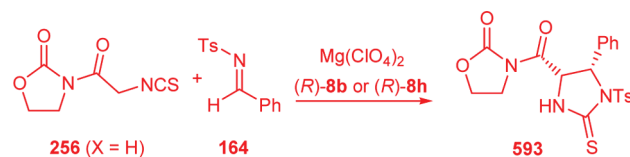
spirocyclic boxes in which the substituents induce strain in the ligand.

An early example concerns the fragmentation, promoted by Et_3B , of *N*-(2-bromo-4,4-dimethylpentanoyl)-2-oxazolidinone **258**. It loses bromine to give a radical that is trapped by trimethylallylsilane (Scheme 95).²³ The effect of the cyclopropylidene as a spacer in the box is shown by a 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)-261 (82 vs 88% ee) is obtained with the 8b complex.

A frequently applied radical reaction concerns the addition of radicals derived from alkyl iodides, which are cleaved by $\text{Et}_3\text{B}/\text{O}_2$ and add to a substrate catalyzed by a Lewis acid/box (normally 10a) complex. An example is the reaction of 4-oxo-4*H*-pyran-3-yl pivalate **626** that adds an *i*-Pr radical in position 2 or 6, giving **627** or **628**, respectively (Scheme 274). In the presence of [(S,R)-10a/ $\text{Mg}(\text{NTf}_2)_2$], (S,R)-627 is obtained with discrete diastereo- and enantioselectivity.⁵⁷⁸

The most important application in the field concerns the addition of the radical derived from the cleavage of R^2I to the alkenoyl derivative of an heterocyclic template (**629**) 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 **630**, which is formally the product of the conjugate addition of R^2H and can be a useful source of the optically active carboxylic acids **631** (Scheme 275). The results with nine different heterocyclic templates (A–I), and the effects of the different parameters that influence the selectivity of the reaction, are reported in Table 172.

Scheme 261



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

- the strain induced in the box by cyclopropylidene is not enough to produce excellent catalysts (Table 172, entries 2 and 4 vs 1 and 3); the box substituent is far more important;
- the ligands belonging to the family of the so-called Indaboxes (**9**, **10**) (entries 5–8) give very good enantiomeric excesses; among them the best is **10a**;
- the last statement is true for Mg(II) complexes, not for those with Zn(II) (Table 172, entries 26–29);
- Mg(II) and Fe(II) are the best cations with (S,R)-10c, and triflimide is the best counterion (Table 172, entries 10 and 11);
- the heterocyclic templates in **629** (het = A–I) (Table 172, entries 12–19) strongly influence the enantioselectivity;
- the templates with a carbonyl group (A–D) and those with a nitrogen lone pair (E–G) promote an opposite sense of induction;
- the radical R^2 (COMe excluded, entry 23) has a small effect on enantioselectivity.

Considering the different possibilities illustrated in Table 172, with judicious choice of template and catalyst these radical reactions have a large range of applications.

The above radical addition is the key step in the synthesis of (+)-Ricciocarpin A, which is a furanosesquiterpene lactone active against schistosomiasis. The reaction between 4-bromo-1-chloro-4-methylpentane and **629** (Scheme 276), catalyzed by [(S,R)-10a/ MgI_2], gives (R)-632 in excellent yield and enantioselectivity. This in turn is converted, through **633**, into the substituted methyl (1*S*,2*R*)-cyclohexanecarboxylate **634**. After deprotection and oxidation to give the aldehyde **635** and the introduction of the furyl substituent under specifically controlled conditions to optimize both yield and diastereomeric excess, the desired natural ricciocarpin **636** was successfully obtained.⁵⁸⁰

When the reaction in Scheme 275 is run with allyltributyltin, the radical formed by the addition of R^2 to **629** adds an allyl group and the addition occurs anti to R^2 to afford **637** (Scheme 277). The box of choice is (S,R)-10a and the best Lewis acid, after testing several cations and counterions, proved to be MgI_2 and $\text{Cu}(\text{OTf})_2$. These catalysts not only give good enantiomeric excesses but also have an additional important property: MgI_2 and $\text{Cu}(\text{OTf})_2$ are able to afford an opposite sense of induction (Table 173).⁵⁸¹

The radical addition to α,β -unsaturated carbonyl compounds can occur on the alkenoyl derivatives of amides **600**. This is in fact a nonheterocyclic template. The catalyst is a Mg(II) complex of (S,R)-10a, and excellent results (with the exclusion of the example in Table 174, entry 6) were obtained both in terms of diastereoselectivity, which favors the anti isomer **638**, and enantioselectivity (Scheme 278).⁵⁸²

Table 162. Asymmetric Cyclopropanations of Styrene and Ethyl Diazoacetate with CuOTf Complexes of Box with Isopropylidene and Cyclopropylidene Spacers^{71a}

entry	box	spacer	yield (%)	[trans/cis]	31 ee (%) (conf.)	32 ee (%) (conf.)
1	(R)-4o	isopropylid.	80	62:38	77 (1R,2R)	66 (1R,2S)
2	(R)-8aa	cyclopropylid.	79	68:32	65 (1R,2R)	43 (1R,2S)
3	(S)-2	isopropylid.	85	75:25	99 (1R,2R)	99 (1R,2S)
4	(S)-8b	cyclopropylid.	85	84:16	>99.9 (1R,2R)	>99.9 (1R,2S)

This protocol has 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. The α -acylamido acrylates **639** first add **R**³ to the β -position, then the radical is trapped by Bu₃SnH to give **640**, which is the protected form of chiral α -amino acids (Scheme 279). The best catalyst is [(*S,R*)-**10a**/Mg(ClO₄)₂] (Table 175), the only limit being the stoichiometric amount of complex required.⁵⁸³

All the previous radical reactions discussed follow a protocol that begins with the cleavage of the alkyl iodide **R**³-I by borane/O₂, followed by the addition of **R**³ to the β -position of enone. The resulting radical is then trapped by Bu₃SnH to give the final product. Because of the nature of the weak Sn–H bond, a tin hydride reagent is very popular for carrying out chain radical reactions. However, alternate reagents can also be usefully applied to deliver the final H radical. Among them, different silanes have a suitable Si–H bond, and after screening of silyl reagents with different alkenoyl derivatives of amides **600**, interesting yields and enantiomeric excesses of **638** were obtained (Scheme 280, Table 176) using hexyl-SiH₃ as hydrogen source and a pyvaloyl group at the amide.⁵⁸⁴

The [**10a**/Lewis acid]-catalyzed conjugate addition of suitable nucleophiles to enones (Scheme 265–267) can undergo subsequent elimination of the template to give chiral heterocycles. This promising protocol may be usefully applied to radical reactions performed on **317** if the alkyl iodide has a β - or γ -hydroxy group and therefore the intermediates **641** can undergo ring closure to give chiral lactones **642** (Scheme 281). Varying the substituent **R** in **317** does not discriminate either reactivity or enantioselectivity (Table 177). If the best box is accepted as the well-known (*R,S*)-**10a**, then careful optimization of the Lewis acid led to the choice of Mg(NTf₂)₂.⁵⁸⁵

Radical addition to β -acylamido acrylates **643**, followed by hydrogen atom transfer, led to a source of the protected form of the chiral β -amino acids **644** (Scheme 282, Table 178). The enantioselectivity depends on the protection of the nitrogen (Table 178, entries 1, 4, and 6). The best protective group proved to be the phthalimidyl one (Table 178, entries 6–12).^{586,587} The effect of **R** and the configuration of the product suggest that the tetrahedral reacting intermediate **645**, where the Mg cation coordinates the box and **643**, is an eight-membered chelate. After the **R**² radical addition, the hydrogen atom transfer to **646** depends on the steric hindrance of the box and on **R**, which determines the face selectivity. This reaction works with a substoichiometric amount of catalyst.⁵⁸⁷

The radical addition to α -hydroxymethyl acrylates **647** is an interesting route to the β -hydroxy esters **648** (Scheme 283). A detailed investigation of ligand, Lewis acid, and substrate led to the choice of [(*R,S*)-**10a**/MgI₂] as the catalyst and demonstrated the importance of the size of the ester substituent (Table 179).⁵⁸⁸

Table 163. Enantioselective Friedel–Crafts Alkylations of Indole with α' -Hydroxy Enones **188²⁴⁹**

entry	R	box	yield (%)	(<i>R</i>)- 594 ee (%)
1	<i>i</i> -Pr	(<i>S</i>)- 8b	68	93
2	<i>i</i> -Pr	(<i>S</i>)- 2	44	85
3	cyclohexyl	(<i>S</i>)- 8b	80	96
4	cyclohexyl	(<i>S</i>)- 2	32	85
5	4-Cl–C ₆ H ₄	(<i>S</i>)- 8b	95	83

The addition of secondary and tertiary **R**² groups gave better enantiomeric excesses than the ethyl radical. Methyl ester gave the best enantioselectivity (Table 179, entries 1, 4, 6, and 8), whereas the medium-sized benzyl ester was inferior. The bulky *tert*-butyl group gave the opposite sense of induction (Table 179, entries 3, 5, 7, and 9). This radical reaction has been the topic of much intense discussion. It is catalyzed by complexes of **10a** and was tested on vinyl sulfones but gave nearly racemic products.^{296,297}

We close the discussion of radical reactions with three enantioselective cascade addition–cyclization–trapping processes starting from *N*-allyl-*N*-(benzyloxy)methacrylamide **649** (**R** = Me, **R**¹ = Bn), which reacts with a radical **R**² derived from an alkyl iodide under [(*R,S*)-**10a**/Zn(OTf)₂] catalysis to give *N*-(benzyloxy)pyrrolidine **650**. The overall process incorporates **R**² into the acrylamide double bond and iodine into the allylic double bond after the ring closure from **652** to **653**.⁵⁸⁹ The sequence of reactions involves the coordinated intermediates **651**, **652**, and **653**. The latter is trapped by the residue iodine radical to give **650** in the relative configuration reported (Scheme 284). Some reactions between **649**, containing different **R** and **R**¹ substituents, and different alkyl iodides are reported in Table 180. Yields of the methacryloyl derivatives (**R** = Me) are better than those obtained with the acryloyl derivatives (**R** = H) (Table 180, entries 1–6 vs 7–9), but the enantiomeric excesses are better in the last three entries.

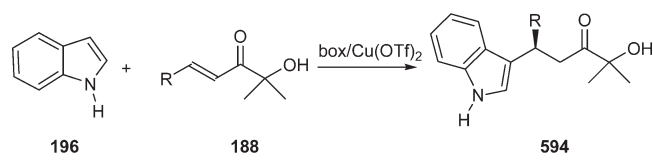
Two variations of this reaction have been reported. The first involves a triple bond instead of the allylic bond of **649**. The alkynes **654** react with 30 mol % of chiral Lewis acid to give **655** with >80% ee and high *Z/E* selectivity (Scheme 285).⁵⁸⁹

The last radical cascade reaction involves the *N*-(benzyloxy)-*N*-(2-alkoxyiminoethyl) acrylamides **656** that undergo the addition of the isopropyl radical, ring closure, and the trapping of other radicals, other than iodine, to give the aminoderivative **657** with excellent enantiomeric excesses. However, only discrete diastereoselectivities are achieved (Scheme 286).⁵⁹⁰

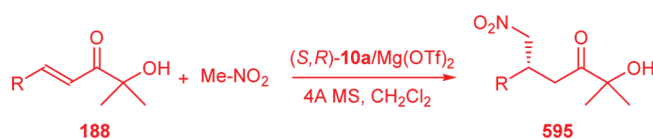
The Kharasch reaction between *tert*-butyl perbenzoate and cyclohexene (Scheme 110), catalyzed by CuPF₆ and (*R,S*)-**10a**, gave the same results (65% yield, 74% ee) obtained with (*R,S*)-**9a**.³⁰⁹

Boxes with cyclopropylidene as the spacer found useful applications in 1,3-dipolar cycloadditions. The reaction between the nitrones **362** and 1-benzyl-2-alkenoyl-5,5-dimethylpyrazolidin-3-ones **220**, the achiral template already mentioned in

Scheme 262



Scheme 263

Table 164. Enantioselective Michael Reactions between α -Hydroxy Enones **188** and Nitromethane Catalyzed by $(S,R)\text{-10a}$ and $\text{Mg}(\text{OTf})_2$ ⁵⁷⁰

entry	R	yield (%)	595 ee (%) (conf.)
1	PhCH_2CH_2	>99	94 (S)
2	hexyl	60	92
3	ethyl	60	88
4	cyclohexyl	74	86
5	Ph	93	74
6	4-Cl- C_6H_4	77	78 (R) ^a

^a Note the change in priority.

Scheme 139, was performed with $[(S,R)\text{-10a/Cu}(\text{OTf})_2]$ as the catalyst (Scheme 287). The results, good in terms of diastereoselectivity and always excellent in terms of enantioselectivity, are reported in Table 181.³⁹²

The same catalyst was later tested in the reaction between the nitrones **362** and α,β -disubstituted acrylamides **600** (Scheme 288), which is a nonheterocyclic template already used in radical reactions. The exo-selective reaction gives **658**, and some significant results are collected in Table 182.⁵⁹¹

Few examples are known of 1,3-dipolar cycloadditions with nitrile oxides. In these examples, the catalysts of choice are the complexes of $(S,R)\text{-10a}$. Several nitrile oxides (**659**) have been tested, with different acrylamides **603** carrying the templates **T1–T7**, and two different regioisomers have been obtained, **660** and **661** (Scheme 289).^{396,591} The excellent results are reported in Table 183.

The selectivity largely depends on the nature of **T**; good results are obtained with **T3**, **T6**, and **T7**. Among them, **T3** deserves attention for its easy preparation. However, **T6** proved to be the template of choice with all kinds of nitriloxides, both those stable ($\text{R}^2 = \text{mesityl}$ and $p\text{-Cl-C}_6\text{H}_4$) and unstable (Table 183, entries 10–12); it gave excellent regio- and enantioselectivities. The absolute stereochemistry of the product in Table 183 (entry 8) was determined to be $(S,S)\text{-660}$, and this can be rationalized by assuming the octahedral reacting intermediate in Figure 23. This allows the attack of **659** onto the C_α Si face of the coordinated dipolarophile.

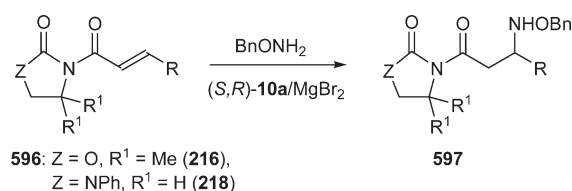
The first examples of 1,3-dipolar cycloadditions of nitrile imines have been recently reported. The reactions are between

Table 165. Addition of *O*-Benzylhydroxylamines to **596** Catalyzed by $[(S,R)\text{-10a/MgBr}_2]$ ²⁵³

entry	R	Z	R ¹	T (°C)	yield (%)	597 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	$\text{CH}_2\text{C}_5\text{H}_{11}$	O	Me	0	89	29 (−) ^a
6	$\text{CH}_2\text{C}_5\text{H}_{11}$	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 264



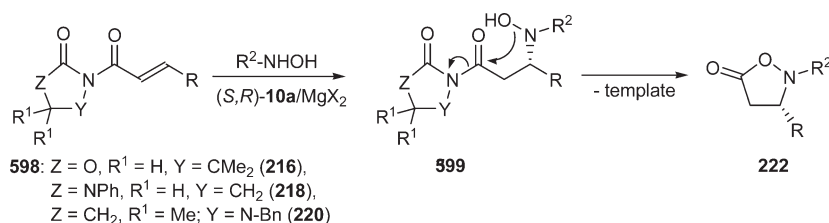
α,β -disubstituted acrylamides **603** with templates **A–C** and **663**, prepared in situ from hydrazonyl halides **662** in the presence of base (Scheme 290, Table 184). The best catalyst is $[(R,S)\text{-10a/Mg}(\text{NTf}_2)_2]$ (Table 184, entries 1–3) or $[(R,S)\text{-10a/MgI}_2]$ (Table 184, entries 13–26). The base has also a relevant role in the success of the reaction (Table 184, entries 3–5 and 23–26), but the template is what probably ultimately decides the success or failure of the chiral induction (Table 184, entries 13–15). The cycloaddition is completely regioselective and gives **664** with excellent enantioselectivity, and the adducts are easily reduced to **665**.^{592,593}

The absolute stereochemistry of the product in Table 184 (entry 10) was determined as $(4S,5S)\text{-664}$, and this can be rationalized by assuming the same octahedral reacting intermediate. This allows the attack of **663** onto the C_α Si face of coordinated **603A**, as already reported in Figure 23 for the 1,3-dipolar cycloaddition with nitrile oxide.

The dipolarophiles **220**, with 5,5-dimethylpyrazolidinone as the template, react with azomethine imine **523**; $[(R,S)\text{-10a/Cu}(\text{OTf})_2]$ proved to be the best catalyst. The reaction is exo-selective and the cycloadducts **666**, with three chiral centers, have been isolated with high diastereoselectivities and with excellent enantiomeric excesses (Scheme 291, Table 185). The best template is 5,5-dimethyl-1-methyl(1-naphthyl)pyrazolidin-3-one (Table 185, entries 1–3). However, the easy preparation of 1-benzyl derivative suggests it could be a reasonable compromise.⁵⁹⁴ If the *gem*- R^2 substituents influence yield more than the stereoselectivity (Table 185, entries 4–6), and the aryl group in azomethyne exerts little influence on the reaction (Table 185, entries 1,7–9), then a dramatic effect is observed for the β -substituents of the dipolarophile; these sometimes inhibit the reaction (Table 185, entries 11 and 12).

Besides the different 1,3-dipoles described above, the diazoesters **30** also react with the dipolarophiles **220**. This has 5,5-dimethylpyrazolidin-3-one as the template, and they give the cycloadducts **667**

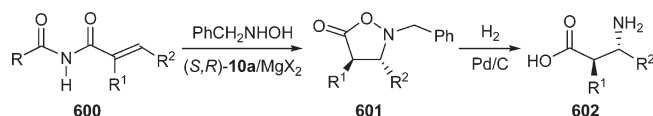
Scheme 265

Table 166. Addition of *N*-Benzylhydroxylamines to 598 Catalyzed by [(*S,R*)-10a/MgX₂]

entry	R	Z	Y	R ¹	R ²	X	yield (%)	ee (%) (conf.)	ref
1	Me	O	CH ₂	H	CH ₂ Ph	Br	74	92 (R)	571
2	Me	CH ₂	CH ₂	H	CH ₂ Ph	Br	80	86 (R)	571
3	Me	CMe ₂	CH ₂	H	CH ₂ Ph	Br	55	89 (R)	571
4	Me	CH ₂	CH ₂	H	CHPh ₂	Br	90	85	571
5	Me	CH ₂	CH ₂	H	<i>p</i> -MeOC ₆ H ₄ CH ₂	Br	78	86 (R)	571
6	Ph	CH ₂	CH ₂	H	CH ₂ Ph	ClO ₄	80	96 (S) ^a	571
7	<i>p</i> -NO ₂ C ₆ H ₄	CH ₂	CH ₂	H	CH ₂ Ph	ClO ₄	60	91	571
8	<i>p</i> -ClC ₆ H ₄	CH ₂	CH ₂	H	CH ₂ Ph	ClO ₄	87	96	571
9	3-furyl	CH ₂	CH ₂	H	CH ₂ Ph	I	80	91	571
10	Me	CH ₂	NH	Me	<i>p</i> -MeOC ₆ H ₄ CH ₂	ClO ₄	75	76 (R)	256
11	Me	CH ₂	NCH ₂ Ph	H	<i>p</i> -MeOC ₆ H ₄ CH ₂	ClO ₄	67	78 (R)	256
12	Me	CH ₂	NCHPh ₂	H	<i>p</i> -MeOC ₆ H ₄ CH ₂	ClO ₄	77	96 (R)	256
13	Me	CH ₂	NCH ₂ -1-Nap	Me	<i>p</i> -MeOC ₆ H ₄ CH ₂	ClO ₄	76	96 (R)	256

^a Note the change in priority.

Scheme 266



(Scheme 292). The best catalyst is [(*R,S*)-10a/Mg(NTf₂)₂], and for R¹ = hydrogen the reaction occurs with very good yields and enantioselectivities generally >95%, independent of the substituents.⁵⁹⁵ Cycloadditions utilizing the less-reactive α,β-disubstituted dipolarophiles require temperatures higher than room temperature. Yields are in the range 40–60%, and the enantiomeric excesses are always >95% ee. Finally, when R = H and R¹ = Me, the adduct **667** is converted in four steps into (–)-manzacidin A (**668**) (Scheme 292). The absolute stereochemistry of this compound allows the absolute configuration (5*R*) to be assigned to its precursor **667**.⁵⁹⁵

Among the cycloadditions described above, the “*pseudo*-1,3-dipolar cycloaddition” involving the reaction between *N*-tosyl aldimines **164** and 2-methylenecyclopropane carboxylic acid diphenylamide (**669a**) merits mention. The ring expansion of the monoactivated methylenecyclopropane giving **670** can be formally considered a process involving the cycloaddition of **669b** where the charge-affinity pattern of the dipolar cyclopropane complements that of the aldimines **164** (Scheme 293).⁵⁹⁶ The reaction is performed in THF at 60 °C with [(*R,S*)-10a/MgI₂] as the catalyst and gives (2*R*,3*R*)-**670** with yields in the range 50–60% and enantioselectivities between 70% and 80% ee.

In the previous Scheme 157, the enantioselective Nazarov cyclization, the cationic electrocyclic 4*π* conrotatory process of a divinyl ketone that gives a cyclopentenone, has been reported as

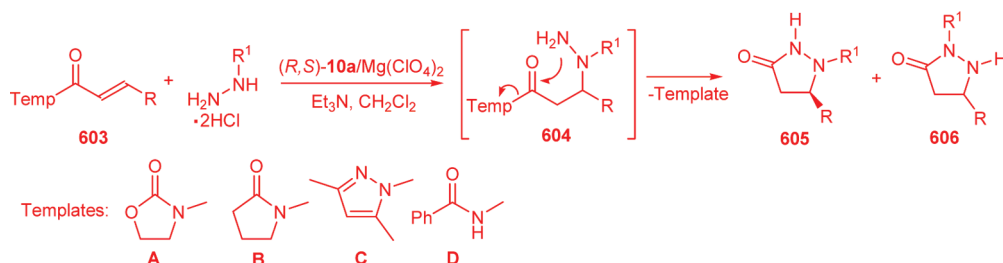
Table 167. Addition of *N*-Benzylhydroxylamines to 600 Catalyzed by [(*S,R*)-10a/MgX₂]⁵⁷²

entry	R	R ¹	R ²	X	yield (%)	de (%)	601 ee (%) (conf.)
1	Ph	Me	Me	ClO ₄	47	94	75 (2 <i>R</i> ,3 <i>R</i>)
2	<i>t</i> -Bu	Me	Me	ClO ₄	45	92	57 (2 <i>R</i> ,3 <i>R</i>)
3	cyclohexyl	Me	Me	ClO ₄	76	92	88 (2 <i>R</i> ,3 <i>R</i>)
4	cyclohexyl	Me	Me	NTf ₂	66	90	96 (2 <i>R</i> ,3 <i>R</i>)
5	<i>i</i> -Pr	Me	Me	NTf ₂	72	96	96 (2 <i>R</i> ,3 <i>R</i>)
6	<i>i</i> -Pr	Ph	Me	NTf ₂	90	95	90
7	<i>i</i> -Pr	Me	Ph	NTf ₂	38	95	76 (2 <i>R</i> ,3 <i>S</i>)
8	<i>i</i> -Pr	Ph	Ph	NTf ₂	49	93	84

being catalyzed by the [box/Cu(SbF₆)₂] complexes. A further extension of this pericyclic process is the reaction of methyl 2-arylidene-3-(2-methylcyclohex-1-enyl) (or 1,3-dienyl)-3-oxopropanoates **671** catalyzed by [(*S,R*)-10a/Cu(SbF₆)₂].⁵⁹⁷ The complex reaction pathway gives two products depending on the substituents. Although none of them is the actual Nazarov product, this electrocyclic process still furnishes **672**. After a 4*π* conrotatory process, the oxyallyl cation undergoes ring contraction leading to the spirocyclic cation **673**. Then, depending on the migratory ability of the substituent, either a hydride shift to give **674** or an sp²-carbon shift to **675** occurs (Scheme 294). The reaction products were isolated with excellent yields and enantiomeric excesses ranging from 29% to 64% ee (depending on the substituents).⁵⁹⁷

At the end of this fruitful section two fundamental questions need to be asked. Do indanyl substituents induce the ability of boxes to behave as alkyl- or as aryl-substituted ligands? Furthermore, is the trend illustrated in Table 161 for Cu(II)

Scheme 267

Table 168. Addition of Hydrazines to **603** Catalyzed by $[(R,S)\text{-10a}/\text{Mg}(\text{ClO}_4)_2]$ ⁵⁷³

entry	598 template	R	R ¹	T (°C)	yield (%)	605/606	605 ee (%) (conf.)
1	A	Me	Bn	amb. t.	92	45:55	55 (S)
2	B	Me	Bn	amb. t.	84	69:31	67 (S)
3	C	Me	Bn	amb. t.	93	70:30	58 (S)
4	D	Me	Bn	amb. t.	86	59:41	69 (S)
5	D	Me	Bn	−30	87	92:8	79 (S)
6	D	Me	Bn	−50	92	98:2	84 (S)
7	D	CH ₂ Ph	Bn	−50	74	98:2	89
8	D	Ph	Bn	−50	43	90:10	37
9	D	CO ₂ <i>t</i> -Bu	Bn	−50	80	99:1	67
10	D	Me	Me	−50	88	99:1	80
11	D	CH ₂ OBn	<i>c</i> -Hex	−50	61	99:1	79 (R) ^a
12	D	CH ₂ OBn	<i>i</i> -Pr	−50	67	99:1	99 (R) ^a

^a Note the change of priority.

Scheme 268



catalysts, namely, “the larger the bridge angle Φ , the higher is the enantioselectivity induced in the reaction”, a general effect valid for every cation involved with the reagent and the boxes in the reacting intermediate?

The Diels–Alder reaction between cyclopentadiene and **53** ($\text{R} = 4\text{-CF}_3\text{C}_6\text{H}_4\text{CO}_2$) gives *endo*-**676** as main adduct (Scheme 295). Both the enantioselectivity and the face selectivity of the cycloaddition are a function of several factors (Table 186).³²⁸

When the copper counterion is OTf, the presence of 4 Å MS is strongly negative with respect to the enantioselectivity (Table 186, entry 1 vs 2). On the other hand, this additive has no effect with $\text{Cu}(\text{SbF}_6)_2$. If the presence of cyclopropylidene as a spacer promotes a better enantioselection (Table 186, entry 1 vs 5), then the comparison of two boxes with the same configuration at the C(4) center, $(S,R)\text{-10a}$ and $(S)\text{-1}$ (Table 186, entry 1 vs 7), affords a most important result since the enantiomeric excess values are the same. However, it must be noted that 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.

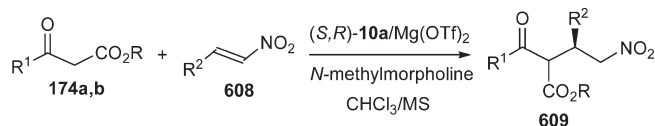
The complexes derived from box **10a** containing a spirocyclic cyclopropyl group are the catalysts of choice for the reactions involving the acrylamides **603** carrying different templates. It is

therefore clear that Diels–Alder reactions would be promising candidates for these chiral catalysts. Great effort has been dedicated to testing different dienophiles with a great variety of templates (**T1**–**T8**) to find the best reagent in terms of yield, diastereoselectivity, and enantioselectivity of the adducts *endo*-**677** and *exo*-**678** (Scheme 296).⁵⁹⁸ Table 187 reports the most interesting results obtained with $[(S,R)\text{-10a}/\text{Cu}(\text{OTf})_2]$ as the catalyst. There are several templates (**T1**, **T3**, **T6**, and **T7**) that give **677** with enantioselectivities $\geq 95\%$ ee. One final suggestion is to exclude templates lacking a carbonyl group. This is because if not all templates with a carbonyl group give excellent enantiomeric excesses, then templates without a carbonyl group give negligible selectivities (Table 187, entry 7).⁵⁹⁸

An interesting extension of the above Diels–Alder reaction is its application to the kinetic resolution of chiral pyrazolidinones. These are incorporated as racemic templates into the crotonoyl dienophiles **679**. Their reaction with cyclopentadiene, catalyzed by $[(S,R)\text{-10a}/\text{Cu}(\text{OTf})_2]$, should, ideally, be stopped at 50% conversion. Then a mixture of the unreacted dienophile (*S*)-**679**, nearly enantiomerically pure (97–99% ee), and the product *endo*-**680** incorporating (*R*)-**679**, diastereomerically enriched (about 70% dr), are chromatographically separated. These products are treated with lithium *p*-methoxybenzyl alcoholate (LiOPMB). This allows the isolation of the enantiomeric pairs (*S*)-**681** and (*R*)-**681**, respectively (Scheme 297). To focus on the limits of this kinetic resolution, the acryloyl derivative of *rac*-**679** ($\text{R} = \text{H}$) is too reactive and the cinnamoyl derivative ($\text{R} = \text{Ph}$) is too inactive for an optimal reaction. Thus, crotonoyls are the best compromise. Using this approach, three racemic templates with $\text{R}^1 = i\text{-Pr}$, *t*-Bu and Ph have been kinetically resolved.⁵⁹⁹

Table 169. Addition of *O*-Benzylhydroxylamines to **317** Catalyzed by 0.3 equiv [(*S,R*)-**10a**/MgBr₂]⁵⁷⁴

entry	R	yield (%)	607 ee (%) (conf.)
1	Me	80	92 (R)
2	Et	74	92
3	CH ₂ C ₆ H ₁₁	53	90
4	CH ₂ Ph	80	95
5	<i>i</i> -Pr	76	87
6	Ph	24	83

Scheme 269

The addition of MeLi to the imines **164** to give the amines **165** (Scheme 298), whose results have been already mentioned in Table 32, was studied in detail in the presence of (*S*)-**8b**–**e**. These four 4-*t*-Bu-substituted boxes have cycloalkylidenes as the spacer (Chart 12). 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 188).^{22,220}

The common result in each of the three examples is that the enantiomeric excess is lower for the most strained box (*S*)-**8b**. This is in sharp contrast with the enantioselectivities reported previously for the Cu(II) complexes of (*S,R*)-**10a**–**d**, which were used as catalysts for the Diels–Alder reaction (Table 161). If on the same graph both the enantiomeric excesses of the MeLi addition to imine **164** (R = Ph), catalyzed by [(*S*)-**8b**–**e**/MeLi] and [(*S*)-**2**/MeLi], and the enantiomeric excesses of the Diels–Alder reaction between **216** and cyclopentadiene, catalyzed by [(*S,R*)-**10a**–**d**/Cu(OTf)₂] and [(*S*)-**9a**/Cu(OTf)₂], are plotted versus the bridge angle Φ , the correlations shown in Figure 24 are obtained. This figure can be interpreted perhaps as suggesting that strongly strained cyclopropylidene boxes with large bridge angles prefer cations with large radii, whereas cations with small radii do not suit this kind of box.

6. COMPLEXES OF PHENYL- AND *tert*-BUTYL-BOXES WITH DIFFERENT INORGANIC SALTS AND THEIR BEHAVIOR AS EFFICIENT ASYMMETRIC CATALYSTS

Two families of catalysts, based on phenyl- and *tert*-butyl-boxes, are the core of this review. An understanding and knowledge of their behavior regarding different reactions may help the reader either find a well-tested [box/cation] combination already successful for a certain class of reactions or discover unusual catalysts whose potentialities are not yet fully explored. Among the many hundreds of results, the choice was limited to those complexes with **1** and **2** as ligands capable of inducing at least 50% enantiomeric excess in the catalyzed reaction. The cluster of reactions satisfying this limitation includes a total of 474 examples, and its breakdown is reported in Figure 25.

Table 170. Michael Reactions between 1,3-Dicarbonyl Compounds **174a,b** and Nitroalkenes **608** Catalyzed by [(*S,R*)-**10a**/Mg(OTf)₂]^{236,575}

entry	R	R ¹	R ²	yield (%)	609 ee (%) (conf.) ^a
1	Et	Me	Ph	95	90
2 ^b	Et	Me	Ph	44	77
3	<i>i</i> -Bu	Me	Ph	92	88
4	<i>t</i> -Bu	Me	Ph	94	29
5	Et	<i>i</i> -Pr	Ph	90	94
6	Me	OMe	Ph	96	93
7	Et	OEt	Ph	92	95 (S)
8	<i>t</i> -Bu	O <i>t</i> -Bu	Ph	88	33
9	Et	OEt	<i>n</i> -C ₅ H ₁₁	93	89 (R)
10	Et	OEt	<i>i</i> -Bu	88	90

^aThe adducts of **174b** with nitrostyrenes are formed as 1:1 mixtures of diastereomeric compounds due to equilibration under the reaction conditions. ^bReaction catalyzed by [(*S,R*)-**9a**/Mg(OTf)₂].

The result of this simple analysis is that phenyl- and *tert*-butyl-boxes are seen to give virtually the same contribution to the world of box catalysts.

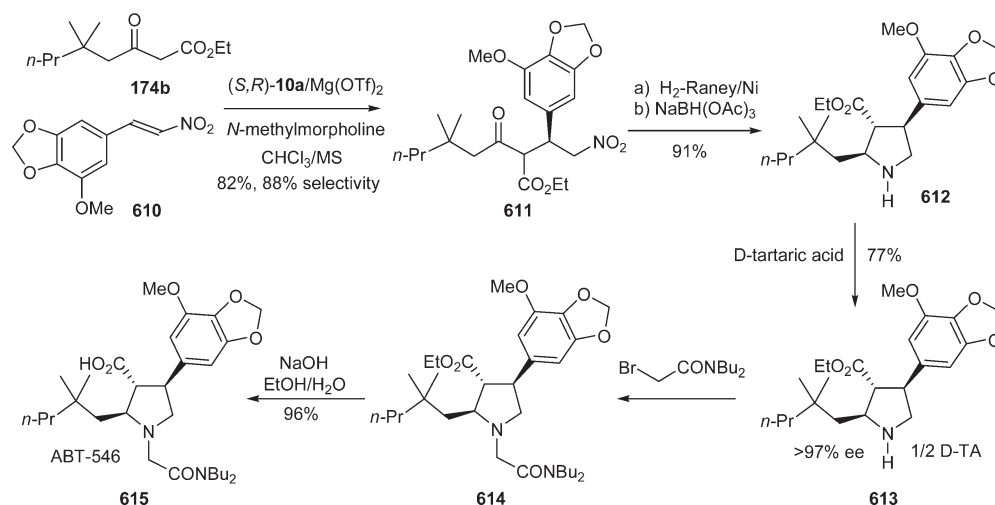
The above cluster of 474 selected examples was further analyzed, and the types of reactions catalyzed by complexes of **1** and **2** are reported in Figure 26. The most developed applications concern aldol, Diels–Alder, hetero Diels–Alder, and cyclopropanation reactions. Some reactions prefer to be catalyzed by complexes of **1**: allylic substitutions (100%), radical reactions (71%), aziridinations (67%), and 1,3-dipolar cycloadditions (64%). Some other reactions prefer complexes involving **2** as the chiral ligand: cyclopropanations (65%) and Michael reactions (70%). The remaining reactions (and in particular the aldol reactions) can be usefully catalyzed by complexes involving both ligands.

To find evidence for the best fit between cation and box, the next step was the analysis of the data obtained using the different cations that give catalysts with **1** and **2** in terms of relative composition of their corresponding clusters (Figure 27).

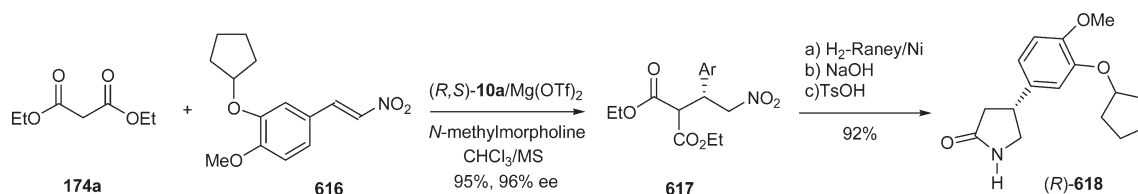
The graph in Figure 27 clearly suggests that the *tert*-butyl-box has a specific affinity with copper, since about 80% of the catalysts with this ligand involve the copper cation. The importance of other cations in the **2**-based catalysts is marginal since the second relevant cation is lithium (8%), which 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 the most diffused cation (56%)) is the not negligible presence of catalysts derived from the Zn(II) (14%) and Mg(II) (9%) cations. This diffusion (a total of 23% with **1** vs 11% with **2**) is important because it makes the phenyl-box a more flexible ligand that is compatible with different cations. This in turn allows a more extended use of its box-based catalysis. A clear example is given by the relative diffusion of palladium-based catalysts that suggests phenyl-box as the ligand of choice for asymmetric allylic substitutions.

A further step is to look more deeply 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 28). In the present state of the art approach to running cyclopropanations, aziridinations, Diels–Alder, and oxidation reactions, the use of copper complexes is strictly required. The same approach is strongly recommended with Michael, hetero Diels–Alder, ene,

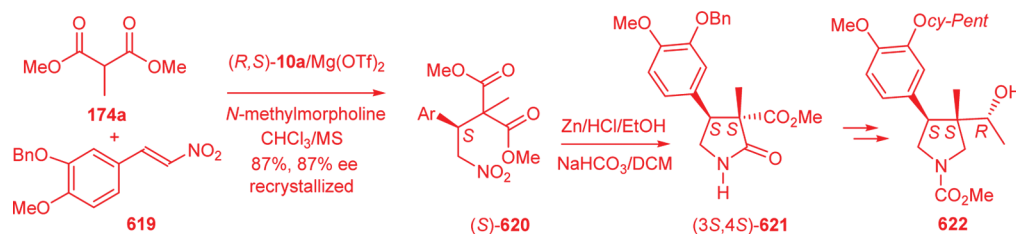
Scheme 270



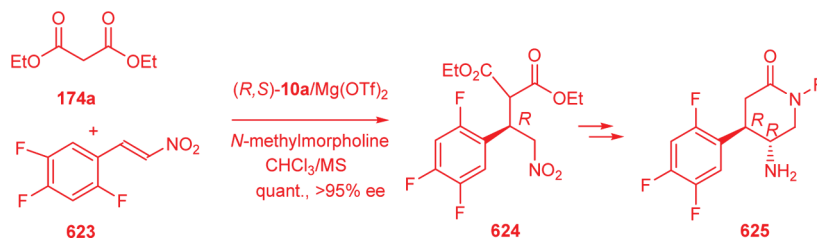
Scheme 271



Scheme 272



Scheme 273



and rearrangement reactions. On the other hand, 1,3-dipolar cycloadditions, as well as aldol and radical reactions, tolerate the use of complexes with other cations.

The same type of analysis has been applied to the cluster of reactions catalyzed by complexes of **1** with copper (Figure 29). Again, to carry out cyclopropanations, aziridinations, Michael,

hetero Diels–Alder, ene, oxidation, and rearrangement reactions, the use of copper complexes is strongly recommended. The main difference with the reaction distribution observed for **2** is that in some reactions the contribution of catalysts based on other cations (47% of Diels–Alder and 34% of aldol or aldol-like reactions) can become important or even predominant (88% in radical, 78% in allylic substitution reactions, and 67% in 1,3-dipolar cycloadditions).

Given the important contribution of cations other than copper to the preparation of efficient enantioselective catalysts with phenyl-box as the ligand (30% of the cluster), the contribution of

Table 171. Mukaiyama–Michael Reactions between Silylketene Acetals **107** and β -Enamidomalonates **198** (Scheme 80) Catalyzed by [(*S,R*)-**10a**/Cu(OTf)₂]²⁵⁹

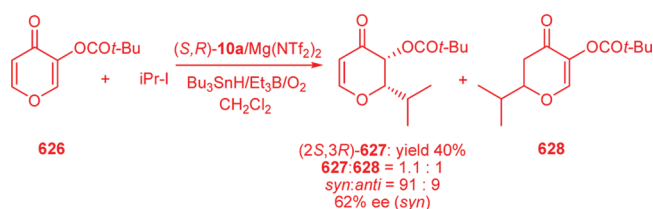
entry ^a	A	R ³	yield (%)	223 ee (%) (conf.)
1	<i>t</i> -BuS	Ph	96	89 (R)
2	Ph	Ph	97	64
3	<i>t</i> -Bu	Ph	39	40
4	<i>t</i> -BuS	<i>t</i> -Bu	97	83
5	Ph	<i>t</i> -Bu	74	73
6	<i>t</i> -BuS	CF ₃	74	54
7	Ph	CF ₃	95	67

^a Reactions run in the presence of hexafluoro-2-propanol.

the most diffused candidates (Zn(II), Mg(II), and Pd(II)) to the different reactions was analyzed (Figure 30).

If Pd(II) is the obvious cation of choice for allylic substitutions, then Zn(II) is best employed in hetero Diels–Alder, aldol, and aldol-like reactions. On the other hand, Mg(II) and Zn(II)

Scheme 274



Scheme 275

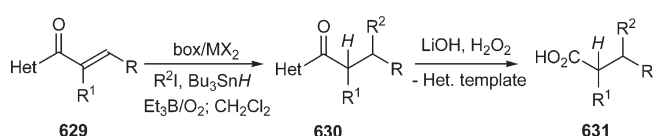
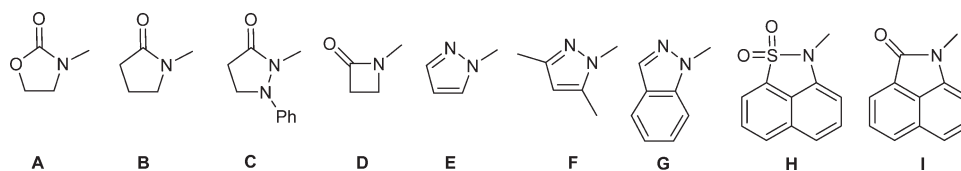
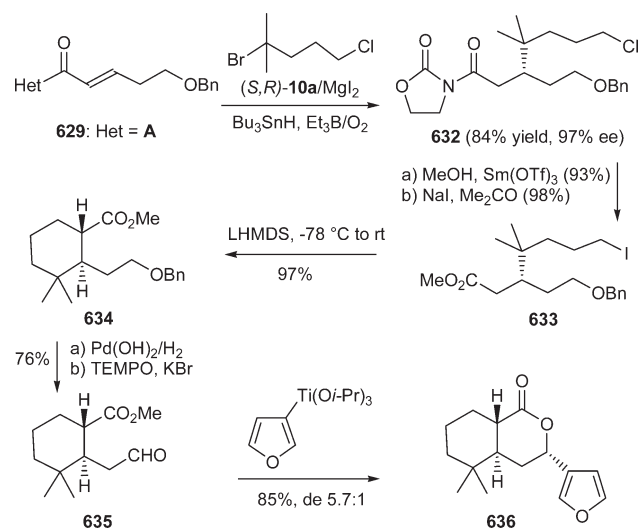


Table 172. Enantioselective Radical Additions of R²I to Alkenyl Heterocycles **629**

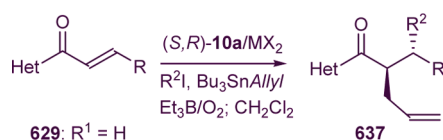


entry	R	R ¹	Het.	R ²	box	MX ₂	yield (%)	630 ee (%) (conf.)	ref
1	Ph	H	A	<i>i</i> -Pr	(<i>S</i>)- 1	MgI ₂	88	47 (S)	45
2	Ph	H	A	<i>i</i> -Pr	(<i>S</i>)- 8a	MgI ₂	87	37 (S)	45
3	Ph	H	A	<i>i</i> -Pr	(<i>S,R</i>)- 5c	MgI ₂	79	31 (S)	45
4	Ph	H	A	<i>i</i> -Pr	(<i>S,R</i>)- 8f	MgI ₂	88	36 (S)	45
5	Ph	H	A	<i>i</i> -Pr	(<i>S,R</i>)- 9a	MgI ₂	88	89 (R)	45
6	Ph	H	A	<i>i</i> -Pr	(<i>S,R</i>)- 10c	MgI ₂	92	82 (R)	45
7	Ph	H	A	<i>i</i> -Pr	(<i>S,R</i>)- 10b	MgI ₂	90	82 (R)	45
8	Ph	H	A	<i>i</i> -Pr	(<i>S,R</i>)- 10a	MgI ₂	95	96 (R)	45
9	Ph	H	A	<i>i</i> -Pr	(<i>S,R</i>)- 10a	Mg(ClO ₄) ₂	91	94 (R)	290
10	Ph	H	A	<i>i</i> -Pr	(<i>S,R</i>)- 10a	Mg(NTf ₂) ₂	99	98 (R)	290
11	Ph	H	A	<i>i</i> -Pr	(<i>S,R</i>)- 10a	Fe(NTf ₂) ₂	95	98 (R)	290
12	H	Me	A	<i>i</i> -Pr	(<i>S,R</i>)- 10a	MgBr ₂	80	65 (S)	579
13	H	Me	B	<i>i</i> -Pr	(<i>S,R</i>)- 10a	MgBr ₂	76	42 (S)	579
14	H	Me	C	<i>i</i> -Pr	(<i>S,R</i>)- 10a	MgBr ₂	67	28 (S)	579
15	H	Me	D	<i>i</i> -Pr	(<i>S,R</i>)- 10a	MgBr ₂	54	15 (S)	579
16	H	Me	E	<i>i</i> -Pr	(<i>S,R</i>)- 10a	MgBr ₂	52	15 (R)	579
17	H	Me	F	<i>i</i> -Pr	(<i>S,R</i>)- 10a	MgBr ₂	54	38 (R)	579
18	H	Me	G	<i>i</i> -Pr	(<i>S,R</i>)- 10a	MgBr ₂	66	15 (R)	579
19	H	Me	H	<i>i</i> -Pr	(<i>S,R</i>)- 10a	MgBr ₂	59	88	579
20	H	Me	H	<i>t</i> -Bu	(<i>S,R</i>)- 10a	MgBr ₂	84	89	579
21	H	Me	H	cyhex	(<i>S,R</i>)- 10a	MgBr ₂	96	89	579
22	H	Me	H	CH ₂ OMe	(<i>S,R</i>)- 10a	MgBr ₂	89	90	579
23	H	Me	H	COMe	(<i>S,R</i>)- 10a	MgBr ₂	<25	18	579
24	H	Me	I	CH ₂ OMe	(<i>S,R</i>)- 10a	MgBr ₂	61	6	579
26	Ph	H	F	<i>i</i> -Pr	(<i>S,R</i>)- 9a	Zn(OTf) ₂	72	43 (S)	504
27	Ph	H	F	<i>i</i> -Pr	(<i>S,R</i>)- 10c	Zn(OTf) ₂	90	50 (S)	504
28	Ph	H	F	<i>i</i> -Pr	(<i>S,R</i>)- 10b	Zn(OTf) ₂	81	44 (S)	504
29	Ph	H	F	<i>i</i> -Pr	(<i>S,R</i>)- 10a	Zn(OTf) ₂	76	51 (S)	504

Scheme 276



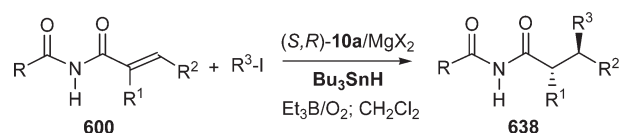
Scheme 277

Table 173. Enantioselective Tandem Radical Additions of R² and Allyl Groups to Alkenoyl Heterocycles 629 Catalyzed by Complexes of (S,R)-10a⁵⁸¹

entry	R	Het.	R ²	MX ₂	yield (%)	dr (anti/syn)	637 ee (%) (conf.)
1	Ph	A	<i>i</i> -Pr	MgI ₂	93	97:3	93
2	Ph	A	<i>i</i> -Pr	Zn(OTf) ₂	69	97:3	−43
3 ^a	Ph	A	<i>i</i> -Pr	Cu(OTf) ₂	93	97:3	−79
4	Ph	A	<i>t</i> -Bu	MgI ₂	84	99:1	97 (<i>R,R</i>)
5 ^a	Ph	A	<i>t</i> -Bu	Cu(OTf) ₂	90	99:1	96 (<i>S,S</i>)
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	<i>t</i> -Bu	Mg(ClO ₄) ₂	85	95:5	92
10 ^a	Me	B	<i>t</i> -Bu	Cu(OTf) ₂	66	98:2	−83

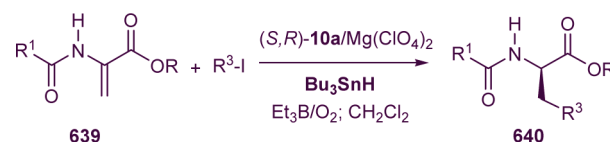
^a Allyltriphenyltin was used.

Scheme 278

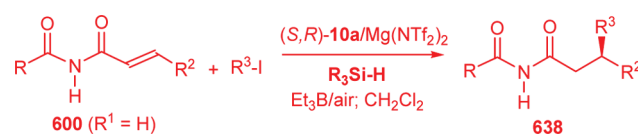


frequently participate in the development of enantioselective catalysts for Diels–Alder reactions, radical reactions, and 1,3-dipolar cycloadditions.

Scheme 279



Scheme 280



7. RELATION BETWEEN THE DIFFERENT REAGENTS COORDINATED TO SOME [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 during the course of the text. This is because they have been successfully applied as substrates in several reactions. An important 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 greatly influence the enantioselectivity of the reaction (solvent, counterion, additive, temperature, etc.). Therefore, this investigation will be limited to a few ordinary reagents that may give a bidentate coordination with phenyl- and *tert*-butyl-box metal catalysts: α -oxoesters **106b,c**, β -oxoesters (**174a–c**, **185**, **198**, **246**, **278**, **280**, **282**, and **405**), and 3-alkenoyl-2-oxazolidinones **216**. A few assumptions will be made: e.g., the cisoid conformation of **216** and the reacting 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 198a and 223b and in the 1,3-dipolar cycloadditions), but the answer being sought in this section is simply to which face of the above coordinated reagents the attack preferentially occurs. With these limitations in mind, the face selectivity with (*S*)-**1** and (*S*)-**2** in different reactions with different cations and different counterions will be discussed.

One further limit should be considered: Of the hundreds of results available, insofar as it is feasible, only those reactions with dichloromethane as solvent will be considered. The reason for this selection with α -oxoesters **106b,c** can be shared if the results of the hetero Diels–Alder reaction between ethyl glyoxylate **106b** (R = Et) and 1,3-cyclohexadiene **333** to give **334** (Scheme 123) are considered.⁹² The enantioselectivity, in different modes with different catalysts, strongly depends on the solvent, and Table 189 recalls these results.

Whereas the reactions in CHCl₃, CH₂Cl₂, and THF show opposite face selectivities when catalyzed by [(*S*)-**1**/Cu(OTf)₂] or [(*S*)-**2**/Cu(OTf)₂], in EtNO₂ the attack of the uncomplexed diene to the complexed α -oxoester occurs at the same face.

Taking into consideration the above assumptions (with the exception of the nine reactions run in Et₂O or THF and incorporated with a view to broadening the variety of reactions considered), all of the references dealing with reactions run with **106b,c** have been analyzed. One significant example for each reaction and for each catalyst is reported in Table 190. In addition, the cations and anions used, the typical enantiomeric excesses obtained, and (the most important information) the face under attack (keeping in mind the previous assumptions) are also presented. To avoid any misunderstanding,⁴⁹⁴ in this and in the following analyses (Tables 190–194) the face selectivity of a

Table 174. Enantioselective Radical Additions of R³I to Diamides **600** Catalyzed by Mg(II) Complexes of (S,R)-**10a** in the Presence of Bu₃SnH⁵⁸²

entry	R	R ¹	R ²	R ³	MgX ₂	yield (%)	dr (anti/syn)	anti- 638 ee (%)
1	<i>i</i> -Pr	Me	Me	<i>t</i> -Bu	Mg(NTf ₂) ₂	69	97:3	69
2	cyhex	Me	Me	<i>t</i> -Bu	Mg(NTf ₂) ₂	67	98:2	65
3	Ph	Me	Me	<i>t</i> -Bu	Mg(NTf ₂) ₂	78	98:2	74
4	<i>t</i> -Bu	Me	Me	<i>t</i> -Bu	MgI ₂	83	99:1	94
5	<i>t</i> -Bu	Me	Me	Cyhex	MgI ₂	62	98:2	79
6	<i>t</i> -Bu	Me	Me	CH ₂ OMe	MgI ₂	59	75:25	56
7	<i>t</i> -Bu	Me	Et	<i>i</i> -Pr	MgI ₂	37	95:5	80
8	<i>t</i> -Bu	Me	Ph	<i>i</i> -Pr	MgI ₂	71	99:1	93
9	<i>t</i> -Bu	Et	Me	<i>i</i> -Pr	MgI ₂	50	87:13	74

Table 175. Enantioselective Radical Additions of R³I to Amidoesters **639** Catalyzed by [(S,R)-**10a**/Mg(ClO₄)₂] in the Presence of Bu₃SnH⁵⁸³

entry	R	R ¹	R ³	yield (%)	640 ee (%) (conf.)
1	Me	OBn	Et	61	22
2	Bn	2-Naph	Et	57	68
3	<i>t</i> -Bu	2-Naph	Et	56	71
4	Me	2-Naph	Et	72	85 (R)
5	Me	2-Naph	<i>i</i> -Pr	62	83 (R)
6	Me	2-Naph	cyhex	62	55 (R)
7	Me	2-Naph	<i>t</i> -Bu	54	27 (R)

Scheme 281

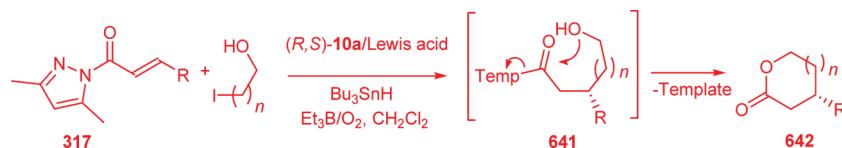


Table 176. Enantioselective Radical Additions of R³I to Diamides **600** Catalyzed by Mg(NTf₂)₂ Complexes of (S,R)-**10a** in the Presence of Silanes⁵⁸⁴

entry	R	R ²	R ³	R ₃ SiH	yield (%)	638 ee (%)
1	Ph	Me	<i>i</i> -Pr	(TMS) ₃ SiH ^a	91	81
2	Ph	Me	<i>i</i> -Pr	hexylSiH ₃	76	80
3	4-Cl-C ₆ H ₄	Me	<i>i</i> -Pr	hexylSiH ₃	62 ^b	77
4	<i>t</i> -Bu	Me	<i>i</i> -Pr	(TMS) ₃ SiH	83	83
5	<i>t</i> -Bu	Me	<i>i</i> -Pr	hexylSiH ₃	56	90
6	<i>t</i> -Bu	Me	<i>t</i> -Bu	hexylSiH ₃	81	86
7	<i>t</i> -Bu	Et	Cl(CH ₂) ₃ CMe ₂	hexylSiH ₃	95	82
8	<i>t</i> -Bu	Ph	<i>t</i> -Bu	hexylSiH ₃	71	91
9	<i>t</i> -Bu	4-Cl-C ₆ H ₄	<i>t</i> -Bu	hexylSiH ₃	89	94
10	<i>t</i> -Bu	4-MeO-C ₆ H ₄	<i>t</i> -Bu	hexylSiH ₃	88	90

^a (TMS)₃SiH is tris(trimethylsilyl)silane. ^b Ethyl radical addition byproduct formed in amount >10%.

reaction catalyzed by a complex of the enantiomer (R)-**1** will be reversed.

Fifty reactions were considered, and some specific results were obtained:

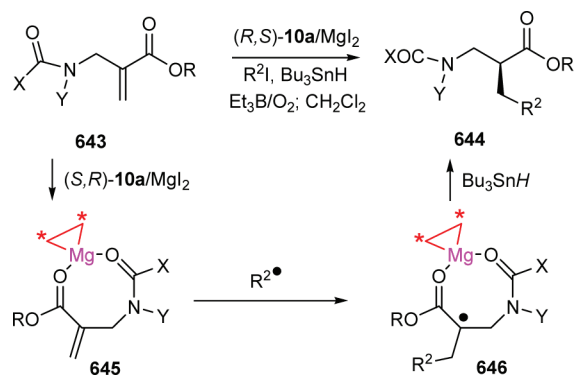
- 34 reactions were catalyzed with (S)-**1** complexes, **40** with (S)-**2** complexes, and of these **24** reactions were catalyzed with both (S)-**1** and (S)-**2** complexes, which allows the derivation of a significant comparison between these two classes of catalysts;
- 46 reactions were run with Cu(II) as the Lewis acid, **2** with Mg(II), **1** with Sn(II), and **1** with Zn(II); hence copper seems to be the cation of choice for α-oxoesters;
- several types of reactions (aldol, Mukaiyama–aldol, Friedel–Crafts, Mannich, Michael, hetero Diels–Alder, and hetero ene are the most significant ones) have all been successfully performed.

Table 177. Enantioselective Radical Synthesis of Lactones **642** from **317**, Through Addition–Cyclization Catalyzed by Complexes of (R,S)-**10a**⁵⁸⁵

entry	R	n	Lewis acid	yield (%)	642 ee (%) (conf.)
1	(CH ₂) ₂ Ph	1	Zn(OTf) ₂	40	55
2	(CH ₂) ₂ Ph	1	Zn(NTf ₂) ₂	40	10
3	(CH ₂) ₂ Ph	1	Yb(OTf) ₃	54	10
4	(CH ₂) ₂ Ph	1	Mg(OTf) ₂	58	32
5	(CH ₂) ₂ Ph	1	Mg(NTf ₂) ₂	50	85 (R) ^a
6	Ph	1	Mg(NTf ₂) ₂	48	85 (S) ^a
7	2-furyl	1	Mg(NTf ₂) ₂	40	79
8	2-thienyl	1	Mg(NTf ₂) ₂	52	80
9	4-CF ₃ -C ₆ H ₄	1	Mg(NTf ₂) ₂	81	80 (S) ^a
10	cyclohexyl	1	Mg(NTf ₂) ₂	68	81 (S) ^a
11	(CH ₂) ₂ Ph	2	Mg(NTf ₂) ₂	68	92
12	4-CF ₃ -C ₆ H ₄	2	Mg(NTf ₂) ₂	64	87

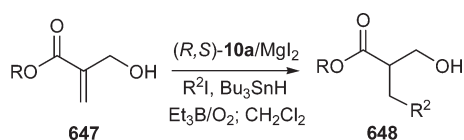
^a Note the change of priority from entry 5 to entries 6, 9, and 10.

Scheme 282

Table 178. Enantioselective Radical Additions of R^2I to β -Acylamido Acrylates **643** Catalyzed by $[(R,S)$ -**10a**/ MgI_2]

entry	R	Y,COX	R^2	yield (%)	644 ee (%) (conf.)	ref
1	Me	succinimidyl	<i>i</i> -Pr	66	33	S86
2	<i>t</i> -Bu	succinimidyl	<i>i</i> -Pr	50	39	S86
3	Me	H,Boc	Et	90	60	S86
4	Me	H,Boc	<i>i</i> -Pr	95	35	S86
5	Me	H,Boc	cyclohexyl	85	10	S86
6	Me	phthalimidyl	<i>i</i> -Pr	91	40 (S)	S87
7	<i>t</i> -Bu	phthalimidyl	<i>i</i> -Pr	95	84 (S)	S87
8	Me	phthalimidyl	<i>t</i> -Bu	81	20	S87
9	<i>t</i> -Bu	phthalimidyl	<i>t</i> -Bu	88	71	S87
10	<i>t</i> -Bu	phthalimidyl	Et	83	62	S87
11	<i>t</i> -Bu	phthalimidyl	cyclohexyl	86	90	S87
12	<i>t</i> -Bu	phthalimidyl	1-adamantyl	72	61	S87

Scheme 283

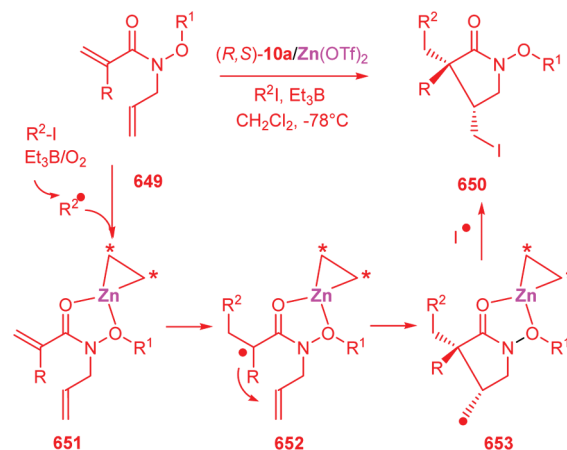
Table 179. Enantioselective Radical Additions of R^2I to α -Hydroxymethyl Acrylates **647** Catalyzed by $[(R,S)$ -**10a**/ MgI_2]^{S88}

entry	R	R^2	yield (%)	648 ee (%) (conf.)
1	Me	Et	51	75
2	Bn	Et	85	40
3	<i>t</i> -Bu	Et	58	–62
4	Me	<i>i</i> -Pr	69	88 (S)
5	<i>t</i> -Bu	<i>i</i> -Pr	53	55 (R)
6	Me	cyclohexyl	52	78 (S)
7	<i>t</i> -Bu	cyclohexyl	75	71 (R)
8	Me	<i>t</i> -Bu	77	92
9	<i>t</i> -Bu	<i>t</i> -Bu	80	–53

The analysis of this large set of data gives some important information:

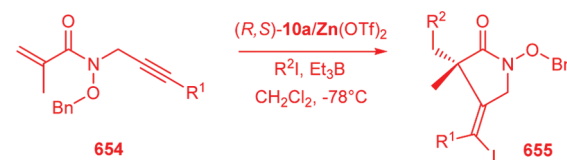
- in 37 of the 40 reactions catalyzed by $[(S)$ -**2**/ CuX_2] the nucleophile approaches the Si face of the complexed α -oxoester; this is independent of the reaction, the counterion,

Scheme 284

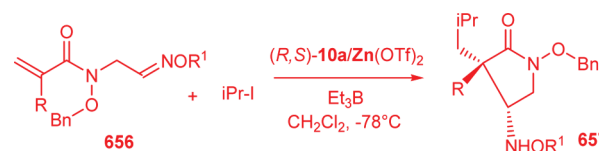
Table 180. Enantioselective Cascade Radical Addition–Cyclization–Trapping Reactions of *N*-Allyl-*N*-(alkoxy)methacrylamides **649** with R^2I Catalyzed by $[(R,S)$ -**10a**/ $Zn(OTf)_2$]^{S89}

entry	R	R^1	R^2	yield (%)	d.r.	650 ee (%)
1	Me	Bn	<i>i</i> -Pr	71	>98:2	77
2	Me	Me	<i>i</i> -Pr	75	>98:2	82
3	Me	<i>t</i> -Bu	<i>i</i> -Pr	71	>98:2	75
4	Me	2-naphthylmethyl	<i>i</i> -Pr	75	>98:2	73
5	Me	diphenylmethyl	<i>i</i> -Pr	52	>98:2	racemate
6	Me	Me	<i>t</i> -Bu	78	>98:2	88
7	H	Bn	<i>i</i> -Pr	52	92:8	92
8	H	Bn	<i>c</i> -Hex	57	94:6	91
9	H	Bn	<i>c</i> -Pent	35	94:6	91

Scheme 285



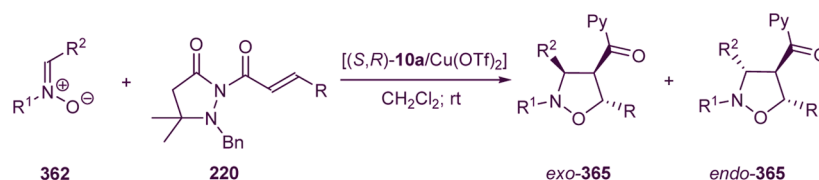
Scheme 286



and the type of reagent; 2 of the 3 exceptions give a negligible enantioselectivity, and 1 was performed in nitromethane;

- 22 of the 30 reactions catalyzed by $[(S)$ -**1**/ CuX_2] occur with the attack on the Re face of the complexed α -oxoester, and 6 of the 8 exceptions gave very low enantioselectivities or were not run in CH_2Cl_2 ;

Scheme 287

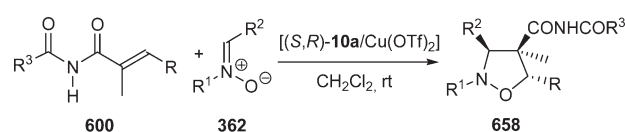
Table 181. Enantioselective 1,3-Dipolar Cycloadditions between Nitrones 362 and 220 Catalyzed by [(S,R)-10a/Cu(OTf)₂]³⁹²

entry	R	R ¹	R ²	yield (%)	365 exo/endo	exo ee (%) (conf.)
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 ₂ Et	Me	Ph	44	67:33	85
5	Me	Bn	Ph	92	93:7	99
6	Me	Bn	<i>p</i> -Cl-C ₆ H ₄	52	85:15	98
7	Me	Bn	<i>p</i> -MeO-C ₆ H ₄	45	95:5	98
8	Me	Ph	Ph	85	52:48	99 (3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)

Table 182. Enantioselective 1,3-Dipolar Cycloadditions between Nitrones 362 and α,β-Disubstituted Acrylamides 600 Catalyzed by [(S,R)-10a/Cu(OTf)₂]⁵⁹¹

entry	R	R ³	R ¹	R ²	yield (%)	exo/endo	exo ee (%)
1	H	<i>t</i> -Bu	Me	Ph	57	81:19	89
2	Me	<i>t</i> -Bu	Me	Ph	60	99:1	94
3	Et	<i>t</i> -Bu	Me	Ph	63	99:1	91
4	Me	<i>t</i> -Bu	Me	<i>p</i> -Br-C ₆ H ₄	62	99:1	98
5	Me	<i>t</i> -Bu	Ph	Ph	50	85:15	86

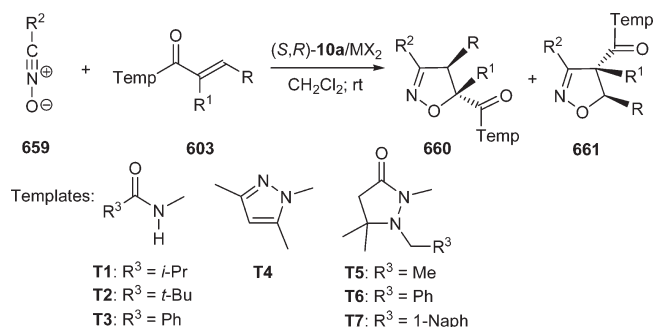
Scheme 288



- 18 of the 22 reactions catalyzed by both [(S)-1/CuX₂] and [(S)-2/CuX₂] show attack of the nucleophile on opposite faces of **106b,c**; hence these catalysts, with chiral ligands having the same configuration, give opposite stereochemical outcomes;
- the 18 examples reported above include the 3 exceptions of attack on the Re face realized with [(S)-2/CuX₂] (Table 190, entries 4, 14, and 25). This means that the same unexpected inversion of attack occurs with both (S)-1- and (S)-2-based catalysts;
- the hetero Diels–Alder reaction catalyzed by both [(S)-1/Zn(OTf)₂] and [(S)-2/Zn(OTf)₂] (Table 190, entry 36) gives 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 excess obtained with (S)-1 when Zn(II) is the cation.

The second class of potentially bidentate reagents concerns the β-oxoesters **174b,c**, **245**, **278**, **280**, and **282** or their 2-ylidene derivatives **185**, **198**, and **405** (including their variants allowing intramolecular reactions) as well as the corresponding β-keto-phosphonates. Clearly the 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 86). Twenty reactions were considered, and one significant example for each for them is reported in Table 191. Cations and anions, typical enantiomeric excesses

Scheme 289



obtained with the catalysts, and the solvent for the few reactions not performed in CH₂Cl₂ are all given. To have a homogeneous comparison between the stereochemical results of the reactions, the preferred face of attack for the reagent in the first step of the reaction will be considered: (a) to the β-carbon atom in 2-ylidene-substituted β-oxoesters and, independently on the nature of R¹ (Scheme 299), the face selectivity will be determined by assigning to this group the second priority, and (b) to the α-carbon atom in 2-substituted β-oxoesters and the face selectivity will be conventionally that reported in Scheme 299.

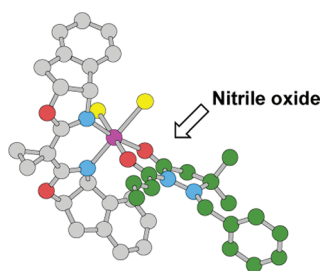
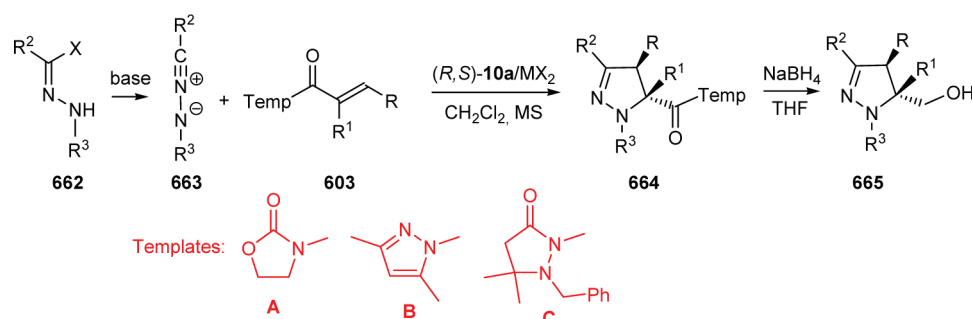
Seven of the 20 reactions concern 2-sp²-β-oxoesters (the 2-ylidene derivatives, Table 191, entries 1–7), and the face of approach will be that concerning the β-carbon atom of the CC double bond. In the 13 reactions concerning 2-sp³-β-oxoesters (Table 191, entries 8–20), the considered face of approach will be that involving the α-carbon with the conventional priority reported in Scheme 299.

All 7 reactions on 2-sp²-β-oxoesters have been performed with Cu(II)-based catalysts, all with (S)-2 complexes; 5 of them are with (S)-1-based catalysts also. Copper is therefore the cation of choice for β-oxoesters.

Seven of the 13 reactions concerning 2-sp³-β-oxoesters were performed with Cu(II) as the Lewis acid, 3 with Mg(II), 2 with

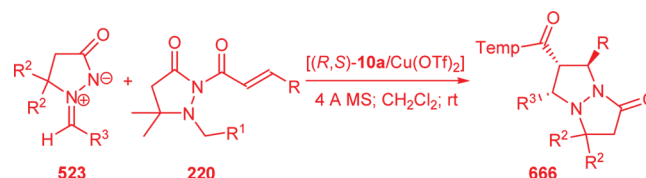
Table 183. Enantioselective 1,3-Dipolar Cycloadditions between Nitrile Oxides **659** and α,β -Disubstituted Acrylamides **603** Catalyzed by [(*S,R*)-**10a**/MX₂] (Scheme 289)

entry	R	R ¹	temp	R ²	MX ₂	yield (%)	660/661	ee 660 (%) (conf.)	ref
1	Me	H	T4	mesityl	MgI ₂	61	17:83	37	396
2	Me	H	T5	mesityl	MgI ₂	88	99:1	95	396
3	Me	H	T6	mesityl	MgI ₂	84	99:1	99	396
4	Me	H	T7	mesityl	MgI ₂	98	99:1	99	396
5	Et	H	T6	mesityl	MgI ₂	86	99:1	95	396
6	Ph	H	T6	mesityl	MgI ₂	85	99:1	99	396
7	CO ₂ Et	H	T6	mesityl	MgI ₂	75	99:1	99	396
8	Me	H	T6	Ph	MgI ₂	75	99:1	99 (<i>S,S</i>)	396
9	Me	H	T6	<i>p</i> -Cl-C ₆ H ₄	MgI ₂	70	99:1	96	396
10	Me	H	T6	<i>p</i> -MeO-C ₆ H ₄	MgI ₂	61	91:9	99	396
11	Me	H	T6	<i>i</i> -Bu	MgI ₂	63	97:3	79	396
12	Me	H	T6	<i>t</i> -Bu	MgI ₂	44	99:1	92	396
13	Me	Me	T1	mesityl	Mg(ClO ₄) ₂	56	>99:<1	83	591
14	Me	Me	T2	mesityl	Mg(ClO ₄) ₂	0			591
15	Me	Me	T3	mesityl	Mg(ClO ₄) ₂	79	>99:<1	81	591
16	Me	Me	T3	mesityl	Mg(NTf ₂) ₂	51	>99:<1	82	591
17	Me	Me	T3	mesityl	Ni(ClO ₄) ₂	99	>99:<1	77	591
18	Me	Me	T7	mesityl	Mg(ClO ₄) ₂	12	>99:<1	95	591

Scheme 290**Figure 23.** Stereochemical model of the 1,3-dipolar cycloaddition reaction of nitrile oxide with crotonyl-amide in Table 183, entry 8.

Zn(II), and **1** with Ni(II). (*S*)-**1** complexes are the catalysts for 9 reactions; in addition an analogous 9 reactions are catalyzed by (*S*)-**2** complexes, and 5 reactions are catalyzed with both (*S*)-**1** and (*S*)-**2** complexes.

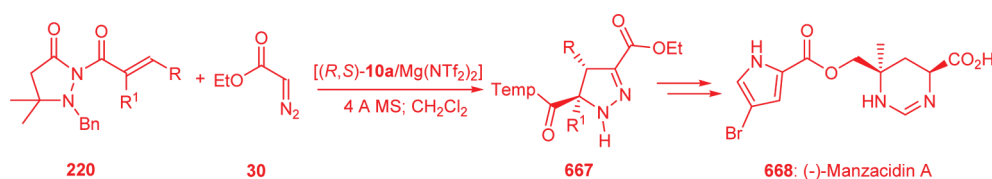
Even if the results reported in Table 191 appear less homogeneous than those concerning the glyoxylates (Table 190), some interesting information can be derived from their analysis:

Scheme 291

- several types of reactions (halogenations, Friedel–Crafts, Mannich, Michael, Nazarov, α -aminations, and intramolecular radical reactions) have all been successfully performed with these reagents;
- all 7 reactions with 2-sp²- β -oxoesters (Table 191, entries 1–7) give enantioselectivities ranging from good to excellent with [(*S*)-**2**/CuX₂] as the catalyst and a preference for β -Si face selectivity;
- all seven reactions with 2-sp³- β -oxoesters catalyzed by Cu(II) (Table 191, entries 8–11, and 13–15) have (*S*)-**1** as the chiral

Table 184. Enantioselective 1,3-Dipolar Cycloadditions between Nitrile Imines **663** and α,β -Disubstituted Acrylimides **603** Catalyzed by [(*R,S*)-**10a**/MX₂] (Scheme 290)

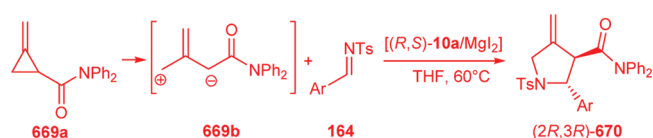
entry	temp	R	R ¹	R ²	R ³	X	base	MX ₂	yield (%)	ee (%) (conf.)	ref
1	A	Me	H	Ph	<i>p</i> -BrC ₆ H ₄	Br	<i>i</i> -Pr ₂ NEt	Ni(ClO ₄) ₂	61	28	592
2	A	Me	H	Ph	<i>p</i> -BrC ₆ H ₄	Br	<i>i</i> -Pr ₂ NEt	Mg(ClO ₄) ₂	92	96	592
3	A	Me	H	Ph	<i>p</i> -BrC ₆ H ₄	Br	<i>i</i> -Pr ₂ NEt	Mg(NTf ₂) ₂	93	99	592
4	A	Me	H	Ph	<i>p</i> -BrC ₆ H ₄	Br	Et ₃ N	Mg(NTf ₂) ₂	99	95	592
5	A	Me	H	Ph	<i>p</i> -BrC ₆ H ₄	Br	DABCO	Mg(NTf ₂) ₂	51	98	592
6	A	Ph	H	Ph	<i>p</i> -BrC ₆ H ₄	Br	<i>i</i> -Pr ₂ NEt	Mg(NTf ₂) ₂	95	97	592
7	A	2-furyl	H	Ph	<i>p</i> -BrC ₆ H ₄	Br	<i>i</i> -Pr ₂ NEt	Mg(NTf ₂) ₂	94	99	592
8	A	CO ₂ <i>t</i> -Bu	H	Ph	<i>p</i> -BrC ₆ H ₄	Br	<i>i</i> -Pr ₂ NEt	Mg(NTf ₂) ₂	92	91	592
9	A	Me	H	<i>i</i> -Pr	<i>p</i> -BrC ₆ H ₄	Br	<i>i</i> -Pr ₂ NEt	Mg(NTf ₂) ₂	98	99	592
10	A	Me	H	<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Br	<i>i</i> -Pr ₂ NEt	Mg(NTf ₂) ₂	95	95 (4 <i>S</i> ,5 <i>S</i>)	592
11	A	Me	H	Ph	Ph	Cl	<i>i</i> -Pr ₂ NEt	Mg(NTf ₂) ₂	92	95	592
12	A	<i>p</i> -BrC ₆ H ₄	H	Ph	Ph	Cl	<i>i</i> -Pr ₂ NEt	Mg(NTf ₂) ₂	97	97	592
13	A	H	Me	<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Br	Et ₃ N	Mg(NTf ₂) ₂	78	22	593
14	B	H	Me	<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Br	Et ₃ N	Mg(NTf ₂) ₂	88	racemate	593
15	C	H	Me	<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Br	Et ₃ N	MgI ₂	80	99	593
16	C	Me	Me	<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Br	Et ₃ N	MgI ₂	97	99	593
17	C	Ph	Me	<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Br	Et ₃ N	MgI ₂	56	99	593
18	C	–(CH ₂) ₃ –		<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Br	Et ₃ N	MgI ₂	83	98	593
19	C	–(CH ₂) ₄ –		<i>p</i> -BrC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	Br	Et ₃ N	MgI ₂	83	98	593
20	C	Me	Me	Ph	<i>p</i> -BrC ₆ H ₄	Br	Et ₃ N	MgI ₂	96	99	593
21	C	H	Me	BnOCH ₂	<i>p</i> -MeOC ₆ H ₄	Br	Et ₃ N	MgI ₂	48	80	593
22	C	H	Me	BnOCH ₂	<i>p</i> -MeOC ₆ H ₄	Br	Et ₃ N	MgI ₂	61	79	593
23	C	H	Me	Ph	<i>p</i> -MeOC ₆ H ₄	Br	Et ₃ N	MgI ₂	47	91	593
24	C	H	Me	Ph	<i>p</i> -MeOC ₆ H ₄	Br	TBTP ^a	MgI ₂	94	95	593
25	C	H	Me	PhCH=CH	Ph	Br	Et ₃ N	MgI ₂	39	89	593
26	C	H	Me	PhCH=CH	Ph	Br	TBTP ^a	MgI ₂	78	94	593

^a TBTP is [*tert*-butylimino-tris(dimethylamino)phosphorane].**Scheme 292**

ligand and prefer the α -Re face selectivity; this occurs with good or excellent enantioselectivity;

- Mg(II), Ni(II), and Zn(II) complexes (Table 191, entries 12, and 16–20) always give the same sense of induction, and the face of the attack is α -Re, independent of the type of box involved in the formation of the catalyst. It is noteworthy that [(*S*)-**2**/Mg(ClO₄)₂] gives the same sense of induction in the intramolecular radical reaction performed on three different substrates.

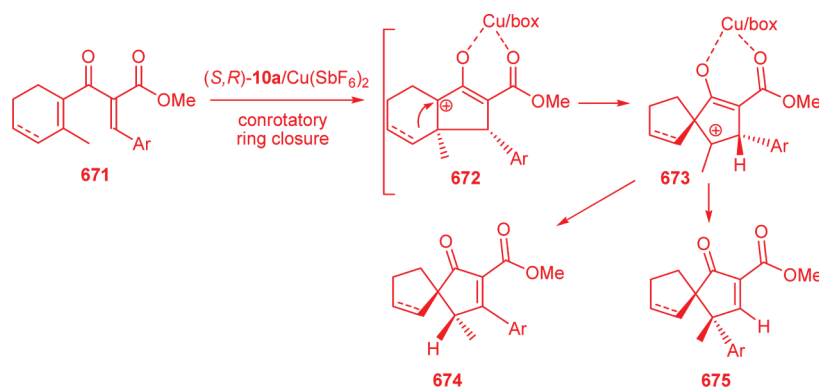
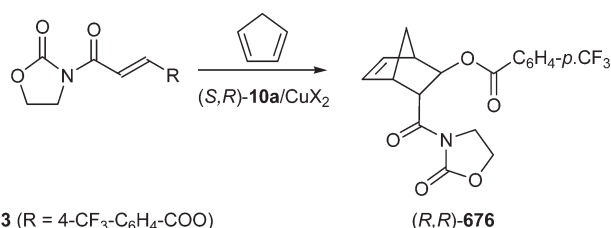
Even if the data in Table 191 do not allow an unambiguous prediction of the face selectivity, an interesting consideration can be derived from entries 3 and 4 of Table 191 (the reactions involving **198** as β -oxoester). A rationalization of the Mukaiyama–Michael reaction between **198** and **107** has been reported on the basis of the crystal structure of the reacting complexes

Scheme 293

with [(*S*)-**1**/Cu(SbF₆)₂] (**21**) and [(*S*)-**2**/Cu(SbF₆)₂] (**22**) (Figure 14).⁹⁵ This favored attack at the β -Re face of the former catalyst and at the β -Si face of the latter one (Figure 31). The above analysis rationalizes the sense of stereinduction observed in the Mukaiyama–Michael reaction of the enamidomalonate in entries 3 and 4 but does not explain the stereinduction

Table 185. Enantioselective 1,3-Dipolar Cycloadditions between Azomethine Imine **523 and β -Substituted Acrylimides **220** Catalyzed by [(*R,S*)-**10a**/Cu(OTf)₂]⁵⁹⁴ (Scheme 291)**

entry	R	R ¹	R ²	R ³	yield (%)	exo/endo	exo- 666 (%) (conf.)
1	H	Ph	Me	Ph	90	88:12	94
2	H	Me	Me	Ph	86	92:8	98
3	H	1-naphthyl	Me	Ph	79	95:5	98
4	H	Ph	H	Ph	79	>96:4	95
5 ^a	H	Ph	Et	Ph	75	88:12	94 (SS,6R)
6 ^a	H	Ph	-(CH ₂) ₅ -	Ph	65	86:14	95 (SS,6R)
7	H	Ph	Me	<i>p</i> -MeOC ₆ H ₄	81	96:4	98
8	H	Ph	Me	<i>p</i> -BrC ₆ H ₄	83	93:7	98
9 ^a	H	Ph	Me	<i>p</i> -CNC ₆ H ₄	81	87:13	96
10	H	Ph	Me	<i>i</i> -Pr	72	88:12	78
11	Me	Ph	H	Ph	77	>96:4	67 (SS,6R,7R)
12	Me	Ph	Me	Ph	0		

^a Reaction performed without 4 Å MS.**Scheme 294****Scheme 295**

observed, not only in the Friedel–Crafts reaction with indole reported in entries 5 and 6 but also in the Mukaiyama–Michael reaction (Table 191, entry 2), which is performed on a β -enamido malonate whose structure does not allow the exclusion of a different type of coordination to the catalyst.

The reader of this review will have become acquainted with the fact that 3-alkenyl-2-oxazolidinones **216** are by far the most popular reagents tested with box catalysts in a variety of reactions. These reagents 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 **216** in the cisoid conformation was assumed on the basis of recent X-ray

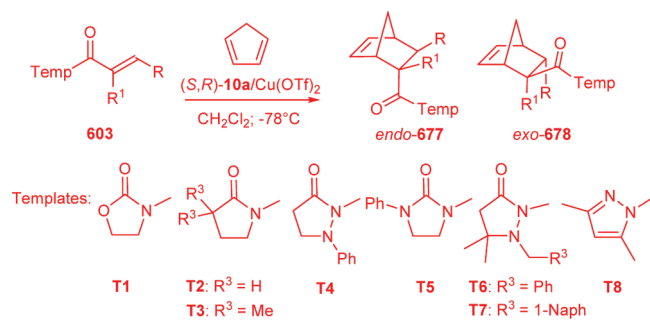
crystal data.⁵⁵ Again the solvents other than CH₂Cl₂ are excluded. This is in spite of the fact that, at least for (*S*)-**2** complexes with Cu(OTf)₂ or Cu(SbF₆)₂, the enantioselectivity of the reactions involving these reagents seems to be slightly affected by solvent.⁹³ The reactions involving **216** may occur either on its α,β -positions (Diels–Alder reaction and 1,3-dipolar cycloadditions) or in the β -position (Mukaiyama–Michael and radical reactions). To achieve a homogeneous comparison between the stereochemical results of these substrates and those of the previously discussed ones, the preferred approached face is referred to the alkenyl carbonyl group of complexed **216** (Scheme 300).

If the Diels–Alder reaction involving **216** is taken as the benchmark for all the catalysts under consideration, it is therefore not unexpected that 35 different reactions that have been found in the literature, 1,3-dipolar nitron cycloadditions, Michael reactions and their variations, and radical reactions led to a total of 58 different examples catalyzed by (*S*)-**1**- and (*S*)-**2**-based catalysts. In this large number of reactions three clusters can be detected that are homogeneous with respect to the cation acting as the Lewis acid: Cu(II), Mg(II), Ni(II), and other divalent cations.

First the cluster of **21** reactions characterized by Cu(II) is reported in Table 192. It consists of Diels–Alder cycloadditions and Mukaiyama–Michael reactions with three different counterions of

Table 186. Enantioselective Diels–Alder Reactions between 53 ($R = 4\text{-CF}_3\text{-C}_6\text{H}_4\text{CO}_2$) and Cyclopentadiene³²⁸

entry	box	CuX ₂	additive	yield (%)	endo/exo	676 ee (%) (conf.)
1	(<i>S,R</i>)-10a	Cu(OTf) ₂		99	90:10	90 (<i>R,R</i>)
2	(<i>S,R</i>)-10a	Cu(OTf) ₂	4 Å MS	99	92:8	50 (<i>R,R</i>)
3	(<i>S,R</i>)-10a	Cu(SbF ₆) ₂		99	88:12	91 (<i>R,R</i>)
4	(<i>S,R</i>)-10a	Cu(SbF ₆) ₂	4 Å MS	99	91:9	90 (<i>R,R</i>)
5	(<i>S,R</i>)-9a	Cu(OTf) ₂		99	90:10	83 (<i>R,R</i>)
6	(<i>S</i>)-2	Cu(OTf) ₂		99	90:10	54 (<i>R,R</i>)
7	(<i>S</i>)-1	Cu(OTf) ₂		99	94:6	89 (<i>S,S</i>)

Scheme 296

Cu(II): ClO₄, SbF₆, and OTf. **Twenty** reactions are run with complexes of (*S*)-2, and it is an exception to obtain an enantioselectivity lower than 95%. This is a clear demonstration that Cu(II), when coupled with (*S*)-2, gives a tailor-made catalyst for 3-alkenyl-2-oxazolidinones **216**. This complex works nicely for Diels–Alder and Mukaiyama–Michael reactions, although its behavior in other reactions was rarely tested and is currently therefore unknown. The reaction in entry 16 occurs with 6% ee, and the catalyst is [(*S*)-2/Cu(ClO₄)₂]. It is prepared from the hexahydrate salt; hence the anomalous result can be due to water that competes in the formation of the reacting intermediate. Molecular sieves do not influence the enantioselectivity of the Mukaiyama–Michael reactions (Table 192, entry 21). Seven reactions are run with complexes of (*S*)-1; the favored approach is on the Si face, and the enantioselectivity is in general poor. One exception is the Diels–Alder reaction in entry 5 that occurs with very good enantioselectivity through a favored Re face approach.

The most prominent observation derived from the results shown in Table 192 is the sense of the stereoinduction obtained in the 21 reactions. All reactions catalyzed by [(*S*)-2/CuX₂], independent of the counterion X, occur with the attack at the Si face. Six of the seven reactions catalyzed by [(*S*)-1/CuX₂] occur with the same sense of stereoinduction. The exception (Table 192, entry 5) has an unusual R substituent (OCOMe) that could interfere with the coordination of **216** to the catalyst, promoting the favored approach to the Re face.

If those Cu(II) complexes with boxes have a distorted square-planar geometry, then the results with [(*S*)-2/CuX₂] can be rationalized by assuming that for both reactions the reacting intermediate is that illustrated in Figure 32. The stereoinduction given by [(*S*)-1/CuX₂] would not be supported by a reacting intermediate with the opposite tilt.³²⁸

Table 187. Enantioselective Diels–Alder Reactions between Substituted Acrylimides 603 Carrying Templates T1–T8 with Cyclopentadiene Catalyzed by [(*S,R*)-10a/Cu(OTf)₂]⁵⁹⁸

entry	R	R ¹	template	yield (%)	677/678	677 ee (%) (conf.)
1	H	H	T1	>90	99:1	98 (<i>S</i>)
2	H	H	T2	93	>99:1	96 (<i>S</i>)
2	H	H	T3	91	>99:1	99 (<i>S</i>)
3	H	H	T4	87	>99:1	95 (<i>S</i>)
4	H	H	T5	90	96:4	94 (<i>S</i>)
5	H	H	T6	95	>99:1	98 (<i>S</i>)
6	H	H	T7	95	>99:1	97 (<i>S</i>)
7	H	H	T8	85	97:3	28 (<i>S</i>)
8	Me	H	T1	>90	93:7	95 (2 <i>S</i> ,3 <i>R</i>)
9	Me	H	T3	>90	94:6	96 (2 <i>S</i> ,3 <i>R</i>)
10	Me	H	T6	>90	94:6	98 (2 <i>S</i> ,3 <i>R</i>)

The second cluster of 18 reactions, characterized by Mg(II) as the Lewis acid, is reported in Table 193. It consists of Diels–Alder reactions, nitron 1,3-dipolar cycloadditions, and radical reactions with four different counterions: Br, I, ClO₄, and OTf. The main difference with Cu(II) is that 17 of the 18 reactions are run with complexes involving (*S*)-1 and only 3 with [(*S*)-2/MgX₂]. The latter is an interesting ligand only in radical reaction catalysis (Table 193, entry 18). The sense of the stereoinduction is not constant (and this is the second difference with Cu(II)) and depends on two factors: the type of anion and the presence of additives. The effect of these variables is further complicated by the potential coordination ability of nitron in 1,3-dipolar cycloadditions.

The nitron 1,3-dipolar cycloadditions occur with attack at the Si face of the coordinated dipolarophile and are independent of the anions (I, ClO₄, or OTf, Table 193, entries 1, 4, and 7). In the case of catalysts having iodide or perchlorate as the counterions, the addition of water does not change this sense of induction (Table 193, entries 3 and 6). However, the presence of MS does reverse the stereochemical outcome (Table 193, entries 2 and 5). In the case of the catalyst having triflate as the counterion, the addition of either H₂O or MS determines the loss of any catalytic activity.³⁸⁹

The behavior of the Diels–Alder reaction with Mg(II) is not the same. The stereochemical outcome is deeply influenced by the nature of both counterion and additives: ClO₄ (with or without MS) and OTf give opposite sense of induction (Re the former, Si the latter, Table 193, entries 8–11 vs 13 and 14). Among the additives, the addition of water to Mg(ClO₄) reverses the sense of induction from Re to Si (Table 193, entry 12 vs 8) but does not influence either the catalytic activity or the stereochemical induction with Mg(OTf)₂.³²² A new interesting result was obtained by adding 1-benzyl-2-benzoyl-5,5-dimethylpyridazine (BDMP) and MS to the Mg(ClO₄)₂-based catalyst because the enantioselectivity is strongly increased but the favored attack still remains at the Re face (Table 193, entry 11 vs 10). Hundreds of crystal structures with Mg(II) are known to have the coordination number either 4 or 6.³²⁵ The rationalization of the different enantioselections induced by counterion and by water in Diels–Alder reactions has already been illustrated in Figure 16. This is due to the formation of different reacting complexes with tetrahedral or octahedral geometries.^{318–320} Whereas one single tetrahedral complex can be obtained by

Scheme 297

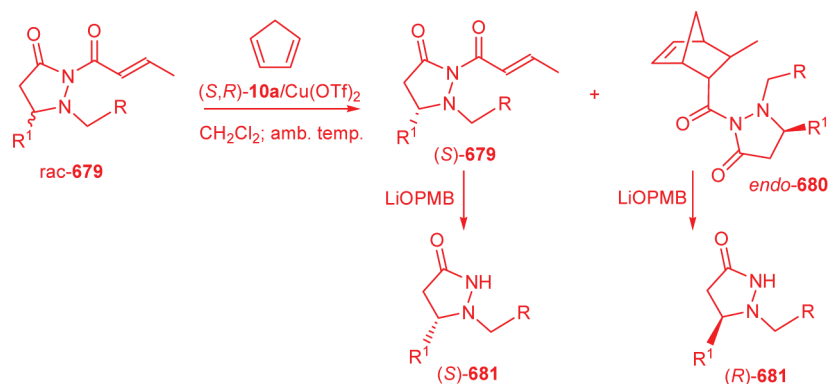


Chart 12

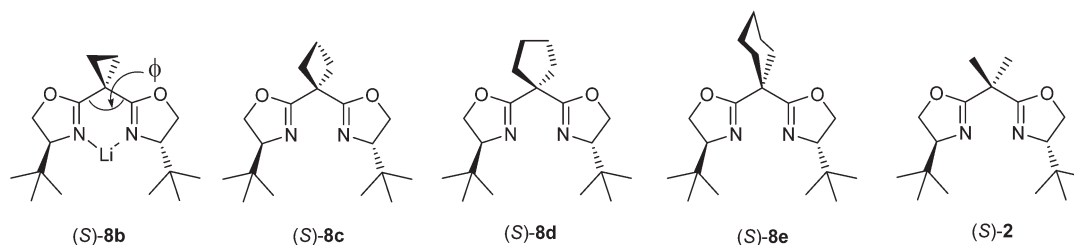


Table 188. Calculated Bridge Angles (Φ) of [Box/LiMe] Complexes and Enantiomeric Excess of MeLi Additions to Imines **164**^{22,220}

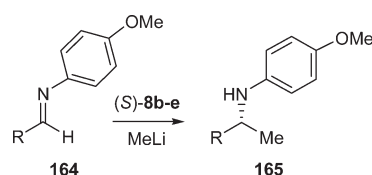
box	(S)-8b	(S)-8c	(S)-8d	(S)-8e	(S)-2
bridge angle Φ (deg)	122.7	110.0	111.8	106.8	109.7
ee for R = Ph	51	73	71	70	67
ee for R = (E)-PhCH=CH	2	84	90	91	94
ee for R = PhCH ₂ CH ₂	44	90	91	75	93

mixing (S)-**1**, Mg(II), and **216** (Table 193, entries 8–10), and one single octahedral is obtained by adding two triflate anions in the axial positions (Table 193, entries 13 and 14), more than one octahedral complex can be obtained from the tetrahedral [(S)-**1**/Mg(ClO₄)₂] complex by adding auxiliary ligands in the axial and equatorial positions. Whereas 2 H₂O molecules give rise to the octahedral complex reported in Figure 16 (Table 193, entry 12) that is seen to favor attack at the Si face, the addition of 1 equiv of BDMP, which again coordinates with the axial and equatorial carbonyls, gives a different octahedron that favors attack at the Re face (Table 193, entry 11).³²⁵

The last cluster of 19 reactions, characterized by Ni(II) and other bivalent cations acting as Lewis acids and with ClO₄, SbF₆, OTf, and Cl as counterions, is reported in Table 194. This cluster consists of Diels–Alder reactions, nitron 1,3-dipolar cycloadditions, Mukaiyama–Michael, and radical reactions, all run with (S)-**1** complexes; (S)-**2** has only a very marginal use.

The most significant effect is shown in the nitron 1,3-dipolar cycloadditions where MS induces the change of the Si face selectivity into the opposite Re one with three different cations

Scheme 298



Ni(II), Mn(II), and Co(II) (Table 194, entries 1, 6, and 8 vs 2, 7, and 9). This has already been seen for the Mg(II) cation. The Diels–Alder reactions catalyzed by perchlorates of different cations (Ni(II), Co(II), Fe(II), and Zn(II)) give interesting results. Ni(II) and Zn(II), without MS, favor the Si face selectivity (Table 194, entries 3 and 15), but with MS Ni(II), Co(II), Fe(II), and Zn(II) favor the Re face selectivity (Table 194, entries 4, 10, 13, and 16). These results, which seem compatible with a four-coordinated reaction intermediate, are strongly ameliorated for Ni(II), Co(II), and Fe(II) when 1-benzyl-2-benzoyl-5,5-dimethylpyridazine (BDMP) is added. This is probably due to the change of the coordination from tetrahedral to octahedral (Table 194, entries 5, 11, and 14). For historical reasons the Re face selectivity induced by [(S)-**1**/FeCl₂] must be mentioned.¹⁰

At least in the case of the 3-alkenoyl-2-oxazolidinones **216**, [(S)-**2**/CuX₂] is the steady catalyst that gives products with high enantiomeric excesses. However, there are very few possibilities for changing the canonical face selectivity derived from the predictable distorted square-planar geometry. On the contrary, [(S)-**1**/MgX₂] is the fancy catalyst that gives products, albeit in

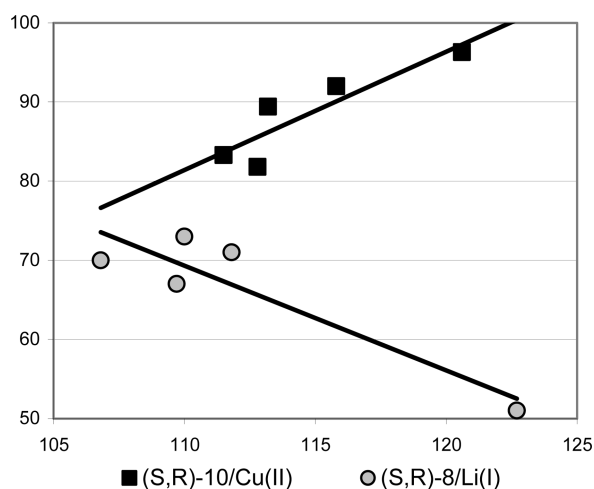


Figure 24. Relationships between the bridge angle Φ of the box complex and the enantiomeric excess of both the MeLi addition to imine **164** ($R = Ph$) (Table 188) and the Diels–Alder reaction between **216** and cyclopentadiene (Table 161).

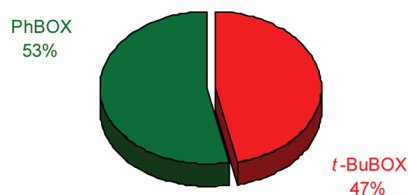


Figure 25. Composition of the cluster of reactions catalyzed by complexes of phenyl- and *tert*-butyl-box (**1** and **2**) inducing at least 50% enantiomeric excess in the catalyzed reaction.

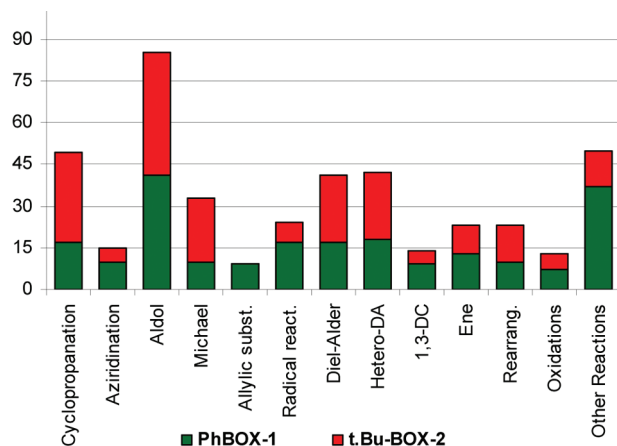


Figure 26. Types of reactions, catalyzed by complexes of **1** and **2**, occurring with at least 50% enantiomeric excess.

lower enantiomeric excesses, but with much wider possibilities of influencing the sense of the stereoinduction through a change in the anion or the addition of an achiral additive. The possibility of changing the structure of the intermediate complex from tetrahedral to different octahedral geometries allows the opposite enantiomers to be obtained while still using the same chirality source.

Because during the “golden years” of this research the box applications to enantioselective catalysis concerned mainly the

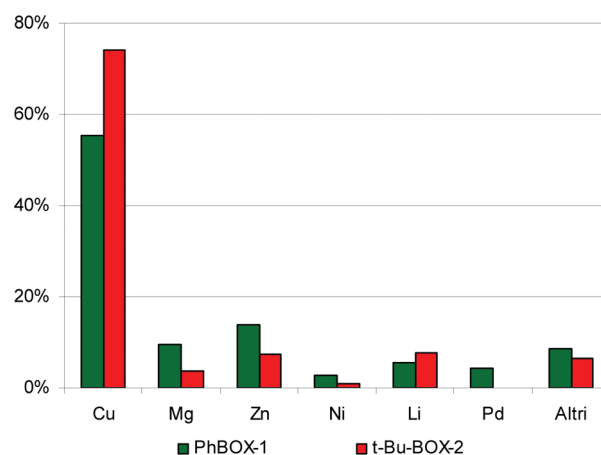


Figure 27. Most important cations giving complexes with **1** and **2** catalyzing reactions with at least 50% enantiomeric excess.

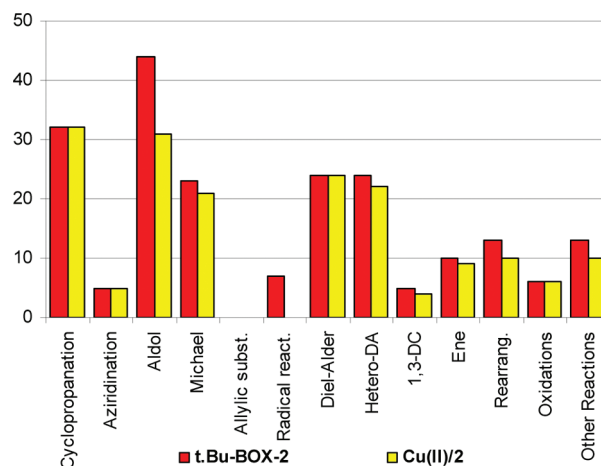


Figure 28. Types of enantioselective reactions catalyzed by complexes of **2** with copper.

boxes **1** and **2**, this section dealt with the relationship between the different reagents coordinated to phenyl- and *tert*-butyl-box metal catalysts and the relative stereochemical outcomes. Nowadays new boxes are becoming so familiar that dozens of applications allow the development of a relationship between coordination and stereochemical outcome for other ligands. For their intrinsic structures, these boxes add new possibilities to the above-mentioned canonic ligands. Among the less traditional boxes, one particular position can be assigned to **10a**. First, because the spiro-cyclopropylidene spacer induces an intrinsically different geometry to the box backbone (Chart 11), second because section 5.8 showed the wide range of applications of this ligand. For these reasons the different reactions of the substituted acryloyl derivatives **603** carrying a variety of templates (**T1**–**T17**, all having the possibility of a bidentate coordination to the cationic core of the catalyst) and catalyzed by complexes of different cations and counterions of box (*S,R*)-**10a**, will be analyzed and their stereochemistry will be discussed (Scheme 301). The results of a cluster of 55 different reactions, performed under different conditions and giving at least 50% ee, are reported in Table 195.

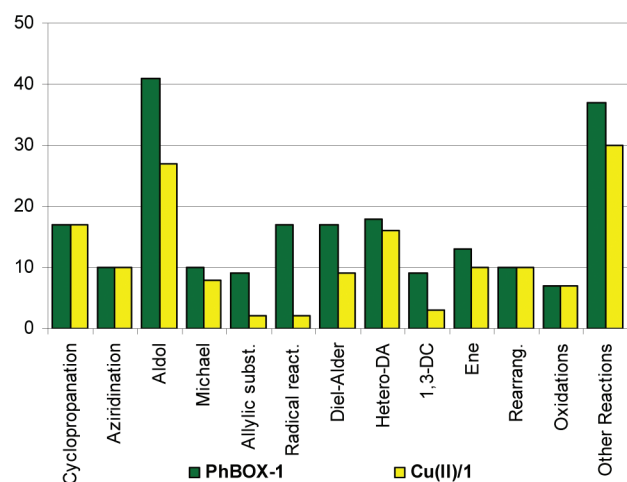


Figure 29. Type of enantioselective reactions catalyzed by complexes of 1 with copper.

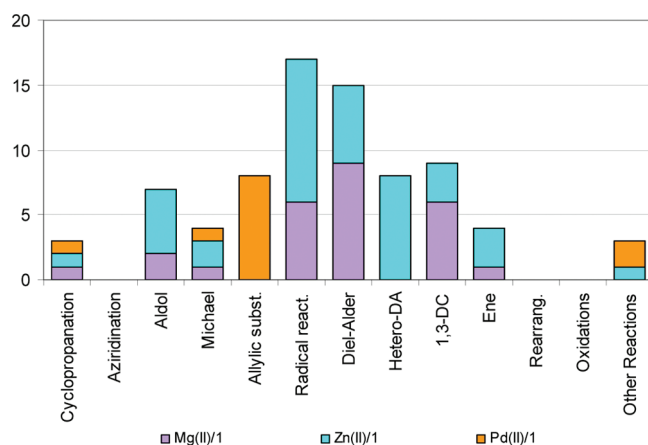
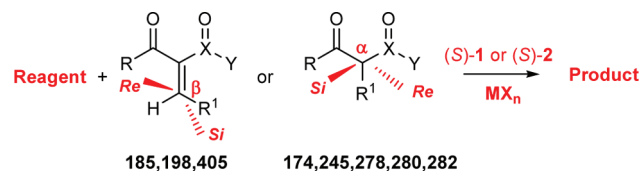


Figure 30. Type of enantioselective reactions catalyzed by complexes of 1 with Zn(II), Mg(II), and Pd(II).

Scheme 299



Again, to achieve a homogeneous comparison between the stereochemical results of the substrates, the preferred approached face of the first step of the reaction will always refer to the α -carbon atom, whether this is one of the couple of carbon atoms involved in the reaction (Diels–Alder reactions and 1,3-dipolar cycloadditions), or if the first step of the reaction occurs at the β -position (Michael and radical reactions).

Table 195 reports 34 results of different reactions with substituted acryloyl derivatives **603**, carrying 12 different templates (entries 1–31, 33, 35, and 36), catalyzed by complexes of Mg(II) with different counterions: In all the reactions the attack on the complexed **603** is at its α -Si face. This is

Table 189. Effect of the Solvent on the Enantioselectivity of the Hetero Diels–Alder Reactions between 1,3-Cyclohexadiene and Ethyl Glyoxylate **106b** (Scheme 123)⁹²

solvent	334 ee (%) and configuration	
	[(S)-1/Cu(OTf) ₂]	[(S)-2/Cu(OTf) ₂]
CHCl ₃	78 (R)	97 (S)
CH ₂ Cl ₂	59 (R)	97 (S)
THF	47 (R)	99 (S)
EtNO ₂	11 (S)	97 (S)
MeCN	60 (S)	

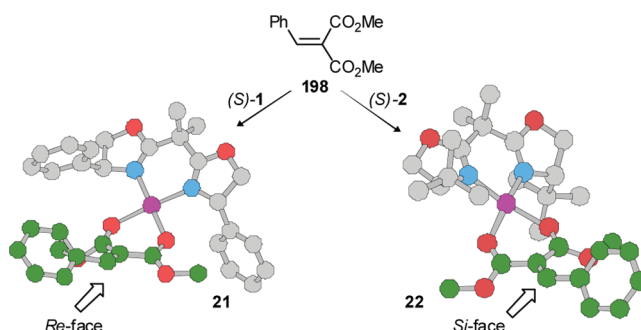


Figure 31. Reaction complexes between **198** and the Cu(II) complexes of (S)-1 and (S)-2 promoting opposite sense stere inductions.

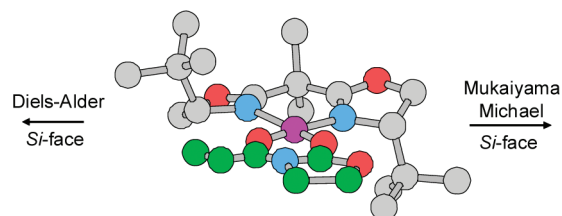
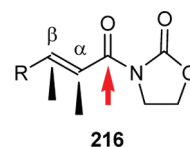


Figure 32. Reaction complexes of **216** and [(S)-2/CuX₂] promoting the Si sense of stere induction.

Scheme 300



independent of the type of reaction (radical, aza-Michael, 1,3-dipolar cycloadditions of nitrile oxides, nitrile imines, or diazoesters), the substitution on the double bond, or the template.

One of the above reactions, the tandem radical reaction reported in Scheme 277 on **603** (T1) and catalyzed by MgI₂ (Table 195, entry 33),⁵⁸¹ was also performed with Cu(OTf)₂ as the catalyst (Table 195, entry 34). The most noteworthy outcome of this experiment was that magnesium and copper Lewis acid complexes gave the opposite enantiomers using the same chiral source. With Cu(II) as the cation, the attack occurred at the α -Re face of the bound reagent. This is the

Table 190. Face Selectivity of the Reactions with Glyoxylates **106b,c** Catalyzed by (S)-1 and (S)-2 Box Complexes

n	reaction	cation	anion	(S)-1		(S)-2		ref
				ee (%)	face	ee (%)	face	
1 ^{a,b}	aldol	Cu(II)	OTf	12	Re	90	Si	213
2 ^c	aldol	Cu(II)	OTf			99	Si	212
3	aldol	Cu(II)	OTf			93	Si	198a
4 ^{b,d}	aldol—Henry	Cu(II)	OTf	14	Si	92	Re	209
5 ^c	Mukaiyama—aldol	Cu(II)	Cl			91	Si	32
6 ^b	Mukaiyama—aldol	Cu(II)	OTf	16	Re	49	Si	25
7	Mukaiyama—aldol	Cu(II)	OTf			99	Si	180, 185
8	Mukaiyama—aldol	Cu(II)	OTf			98	Si	183
9	Mukaiyama—aldol	Cu(II)	OTf	43	Si	98	Si	186
10 ^b	Mukaiyama—aldol	Cu(II)	OTf	88	Re			405
11	Mukaiyama—aldol	Cu(II)	OTf	31	Si	65	Si	98
12	Mukaiyama—aldol	Cu(II)	OTf			90	Si	188
13	Mukaiyama—aldol	Sn(II)	OTf	91	Si			180
14 ^b	Mannich	Cu(II)	OTf	89	Si	33	Re	227a
15 ^a	Michael	Cu(II)	OTf			99	Si	215
16 ^{a,b}	Michael	Cu(II)	OTf	77	Si	84	Si	238
17 ^a	Friedel—Crafts	Cu(II)	OTf	42	Re	97	Si	242
18 ^b	Friedel—Crafts	Cu(II)	OTf	54	Re	80	Si	214
19	Friedel—Crafts	Cu(II)	OTf			93	Si	215
20 ^c	Friedel—Crafts	Cu(II)	OTf	79	Si			216
21 ^f	hetero Diels—Alder	Cu(II)	OTf	94	Re	99	Si	91, 400
22	hetero Diels—Alder	Cu(II)	OTf	59	Re	97	Si	92
23	hetero Diels—Alder	Cu(II)	OTf			97	Si	329
24 ^b	hetero Diels—Alder	Cu(II)	OTf	83	Re	85	Si	354, 355, 358
25	hetero Diels—Alder	Cu(II)	OTf	44	Si	17	Re	357
26 ^b	hetero Diels—Alder	Cu(II)	OTf	26	Re	92	Si	361
27	hetero Diels—Alder	Cu(II)	OTf			91	Si	362
28	hetero Diels—Alder	Cu(II)	OTf			99	Si	363
29 ^b	hetero Diels—Alder	Cu(II)	OTf	64	Re	98	Si	375
30 ^{b,f}	hetero Diels—Alder	Cu(II)	OTf	93	Re	99	Si	377
31 ^c	hetero Diels—Alder	Cu(II)	OTf			99	Si	364
32 ^c	hetero Diels—Alder	Cu(II)	OTf	94	Re	99	Si	376
33 ^{a,b}	hetero Diels—Alder	Cu(II)	OTf	12	Re	99	Si	97
34 ^f	hetero Diels—Alder	Cu(II)	SbF ₆	93	Re	93	Si	90
35	hetero Diels—Alder	Cu(II)	SbF ₆			97	Si	359
36 ^b	hetero Diels—Alder	Zn(II)	OTf	81	Re	23	Si	354, 356
37	hetero ene	Cu(II)	OTf	94	Re			89
38	hetero ene	Cu(II)	OTf	87	Re			90, 399
39	hetero ene	Cu(II)	OTf	92	Re			401
40 ^b	hetero ene	Cu(II)	OTf	92	Re			403
41	hetero ene	Cu(II)	OTf	31	Si	73	Si	406
42	hetero ene	Cu(II)	SbF ₆			98	Si	89
43	hetero ene	Cu(II)	SbF ₆			97	Si	90, 399
44	hetero ene	Cu(II)	SbF ₆	70	Re	96	Si	400
45	hetero ene	Cu(II)	SbF ₆			98	Si	403
46	hetero ene	Cu(II)	SbF ₆	90	Re			404
47	intramolecular hetero ene	Cu(II)	OTf	91	Re			410
48	[2 + 2]-cycloaddition	Cu(II)	OTf	17	Re	69	Si	412
49	oxa-Michael	Mg(II)	OTf	65	Si	18	Si	33
50	radical addition	Mg(II)	Br	52	Re			294

^a Et₂O as the solvent. ^b Reaction catalyzed by (R)-1, and therefore the reported face of attack is reversed. ^c THF as the solvent. ^d Nitromethane as the solvent. ^e For analogy with glyoxylates, the Si face is defined by assigning to the CF₃ group the lowest priority. ^f For analogy with glyoxylates, the face is defined by considering the phosphonate group as a carboxylate.

same as that found for nothing else among the 17 reactions with **603** carrying 11 different templates, and catalyzed by complexes of Cu(II), as reported in Table 195 (entries 34 and 38–53). All these reactions occur with an attack to the α -Re face of the coordinated **603**.

The formation of the enantiomeric products with Cu(II) or Mg(II) must be the result of a different geometry for the ternary reacting complexes. An attack at the less-hindered

α -Re face of the coordinated **603** accounts for the observed absolute configuration of the products obtained with [(S,R)-**10a**/Cu/**603**] and involving a reaction intermediate having a square-planar structure (Figure 33).

Tetra- and hexacoordinated Mg(II) complexes are well-known in box-catalyzed processes. To account for the observed absolute configuration of the products obtained with [(S,R)-**10a**/MgX₂] as the catalyst, an attack at the

Table 191. Face Selectivity of the Reactions with β -Oxoesters Catalyzed by (S)-1 and (S)-2 Box Complexes

n	reaction (β -oxoester)	cation	anion	(S)-1		(S)-2		ref
				ee (%)	face	ee (%)	face	
1 ^a	Michael (185)	Cu(II)	OTf	10	β -Si	72	β -Si	239
2	Mukaiyama–Michael (198)	Cu(II)	OTf	32	β -Si	60	β -Si	259
3	Mukaiyama–Michael (198)	Cu(II)	SbF ₆			91	β -Si	89, 95a
4 ^b	Mukaiyama–Michael (198)	Cu(II)	SbF ₆	52	β -Re	93	β -Si	95b
5	Friedel–Crafts (198)	Cu(II)	OTf			57	β -Re	244
6 ^c	Friedel–Crafts (198)	Cu(II)	OTf	44	β -Si	68	β -Re	245
7	Nazarov (405)	Cu(II)	SbF ₆	86	β -Si	87	β -Si	420
8 ^c	Mannich (174b)	Cu(II)	OTf	68	α -Re	92	α -Re	228a
9 ^c	Mannich (174c)	Cu(II)	OTf	56	α -Si	84	α -Re	228b
10	α -amination (174b)	Cu(II)	OTf	98	α -Re			230, 229a
11	α -amination (246)	Cu(II)	OTf	99				272, 273
12 ^d	Mannich (174c)	Zn(II)	OTf			67	α -Re	228b
13 ^{c,d}	chlorination (174b)	Cu(II)	OTf	32	α -Re	77	α -Si	478
14 ^{c,d}	fluorination (174b)	Cu(II)	OTf	72	α -Re	20	α -Si	479
15	fluorination (174b)	Cu(II)	OTf	39	α -Si			480
16	fluorination (174b)	Ni(II)	ClO ₄	71	α -Re			480
17	α -amination (174c)	Zn(II)	OTf	92	α -Re	12	α -Re	229b
18	intramolecular radical (278)	Mg(II)	ClO ₄			71	α -Re	298
19	intramolecular radical (280)	Mg(II)	ClO ₄			33	α -Re	300
20 ^e	intramolecular radical (282)	Mg(II)	ClO ₄			89	α -Re	301

^a DCE as the solvent. ^b Toluene/CH₂Cl₂ 3:1 as solvent. ^c Reaction catalyzed by (R)-1, and therefore the reported face of attack is reversed. ^d Et₂O as the solvent. ^e Toluene as solvent.

Table 192. Face Selectivity of the Reactions with 3-Alkenoyl-2-oxazolidinones 216 Catalyzed by (S)-1 and (S)-2 Cu(II) Complexes

entry	reaction	cation	anion	additive	(S)-1		(S)-2		ref
					ee (%)	face	ee (%)	face	
1	Diels–Alder	Cu(II)	OTf		30	Si			74
2	Diels–Alder	Cu(II)	OTf		30	Si	98	Si	93
3	Diels–Alder	Cu(II)	OTf		30	Si	98	Si	316
4 ^a	Diels–Alder	Cu(II)	OTf		22	Si	76	Si	320
5	Diels–Alder	Cu(II)	OTf		89	Re	54	Si	328
6	Diels–Alder	Cu(II)	OTf				99	Si	324
7	Diels–Alder	Cu(II)	OTf				89	Si	333
8	Diels–Alder	Cu(II)	OTf				88	Si	334
9	Diels–Alder	Cu(II)	SbF ₆				98	Si	93
10	Diels–Alder	Cu(II)	SbF ₆				98	Si	178
11	Diels–Alder	Cu(II)	SbF ₆				96	Si	317
12	Diels–Alder	Cu(II)	SbF ₆				93	Si	329
13	Diels–Alder	Cu(II)	SbF ₆				97	Si	330
14	Diels–Alder	Cu(II)	SbF ₆				98	Si	331
15	Diels–Alder	Cu(II)	SbF ₆				96	Si	332
16	Diels–Alder	Cu(II)	ClO ₄	6H ₂ O	41	Si	6	Si	323
17	intramolecular Diels–Alder	Cu(II)	SbF ₆				92	Si	347
18	aza-Diels–Alder	Cu(II)	OTf				98	Si	382
19	Mukaiyama–Michael	Cu(II)	SbF ₆		57	Si	89	Si	94
20	Mukaiyama–Michael	Cu(II)	SbF ₆				97	Si	260
21	Mukaiyama–Michael	Cu(II)	OTf	MS-HFIP			95	Si	262, 263

^a Reaction catalyzed by (R)-1, and therefore the reported face of attack is reversed.

less-hindered α -Si face of the bicoordinated **603** in a *s*-cis conformation is necessary. This occurs if the ternary reacting complex adopts an octahedral geometry with the two auxiliary ligands (reasonably the counterions) having a *cis*

orientation and one of them being *trans* to the more Lewis basic carbonyl oxygen (Figure 34).

The analysis of 51 reactions involving **603** carrying 17 different templates as reagents, catalyzed by complexes of

Table 193. Face Selectivity of the Reactions with 3-Alkenoyl-2-oxazolidinones 216 Catalyzed by (S)-1 and (S)-2 Mg(II) Complexes

<i>n</i>	reaction	cation	anion	additive	(S)-1		(S)-2		ref
					ee (%)	face	ee (%)	face	
1 ^a	nitroene 1,3-DC	Mg(II)	I		46	Si			387, 388
2 ^a	nitroene 1,3-DC	Mg(II)	I	MS	79	Re			387, 388
3	nitroene 1,3-DC	Mg(II)	I	H ₂ O	50	Si			388
4 ^a	nitroene 1,3-DC	Mg(II)	ClO ₄		48	Si			389, 390
5	nitroene 1,3-DC	Mg(II)	ClO ₄	MS	70	Re			389, 390
6	nitroene 1,3-DC	Mg(II)	ClO ₄	H ₂ O	45	Si			389
7	nitroene 1,3-DC	Mg(II)	OTf		86	Si			389, 390
8 ^a	Diels–Alder	Mg(II)	ClO ₄		72	Re			114
9 ^a	Diels–Alder	Mg(II)	ClO ₄	MS	70	Re			114, 318, 319
10	Diels–Alder	Mg(II)	ClO ₄	MS	56	Re			325
11	Diels–Alder	Mg(II)	ClO ₄	MS, BDMP ^b	84	Re			325
12 ^a	Diels–Alder	Mg(II)	ClO ₄	H ₂ O	73	Si			318, 319
13 ^a	Diels–Alder	Mg(II)	OTf		73	Si			320
14 ^a	Diels–Alder	Mg(II)	OTf		88	Si			322
15	aza-Michael	Mg(II)	Br		47	Si	14	Si	253
16	radical	Mg(II)	I		47	Si			45
17	radical	Mg(II)	I		47	Si	61	Re	289
18	radical	Mg(II)	I				93	Re	291

^a Reaction catalyzed by (R)-1, and therefore the reported face of attack is reversed. ^b BDMP is 1-benzyl-2-benzoyl-5,5-dimethylpyrazolidine.

Table 194. Face-Selectivity of the Reactions with 3-Alkenoyl-2-oxazolidinones 216 Catalyzed by (S)-1 and (S)-2 Complexes of Ni(II) and Other Different Cations

entry	reaction	cation	anion	additive	(S)-1		(S)-2		ref
					ee (%) ^a	face	ee (%)	face	
1 ^b	nitroene 1,3-DC	Ni(II)	ClO ₄ ^c		74	Si			390
2 ^b	nitroene 1,3-DC	Ni(II)	ClO ₄ ^c	MS	85	Re			390
3 ^b	Diels–Alder	Ni(II)	ClO ₄		52	Si			321
4	Diels–Alder	Ni(II)	ClO ₄	MS	66	Re			325
5	Diels–Alder	Ni(II)	ClO ₄	MS, BDMP ^d	92	Re			325
6 ^b	nitroene 1,3-DC	Mn(II)	ClO ₄ ^c		52	Si			390
7 ^b	nitroene 1,3-DC	Mn(II)	ClO ₄ ^c	MS	14	Re			390
8 ^b	nitroene 1,3-DC	Co(II)	ClO ₄ ^c		47	Si			390
9 ^b	nitroene 1,3-DC	Co(II)	ClO ₄ ^c	MS	42	Re			390
10	Diels–Alder	Co(II)	ClO ₄ ^c	MS	69	Re			325
11	Diels–Alder	Co(II)	ClO ₄ ^c	MS, BDMP ^d	95	Re			325
12	Diels–Alder	Fe(II)	Cl		80	Re			10
13	Diels–Alder	Fe(II)	ClO ₄ ^c	MS	60	Re			325
14	Diels–Alder	Fe(II)	ClO ₄ ^c	MS, BDMP ^d	85	Re			325
15 ^b	Diels–Alder	Zn(II)	ClO ₄ ^c		20	Si			114
16 ^b	Diels–Alder	Zn(II)	ClO ₄ ^c	MS	73	Re			114
17	Diels–Alder	Zn(II)	SbF ₆		92	Re			178
18 ^b	Mukaiyama–Michael	Zn(II)	ClO ₄ ^c	MS	31	Re			261
19	radical	Zn(II)	OTf		61	Si	37	Re	289

^a Referred to the *endo*-isomer. ^b Reaction catalyzed by (R)-1, and therefore the reported face of attack is reversed. ^c The perchlorates were hexahydrate.

^d BDMP is 1-benzyl-2-benzoyl-5,5-dimethylpyrazolidine.

(S,R)-10a with Mg(II) or Cu(II), suggests that the reagents are always bicoordinated with a *s-cis* conformation. The choice of magnesium or copper as the Lewis acid induces the opposite enantioselectivity and leads to the conclusion that this is a powerful

tool to customize the enantioselective reaction with a foreseen and defined configuration.

Three further cations are marginally involved in the catalytic processes reported in Table 195: the Yb(OTf)₃ complex

Table 195. Enantioselective Reactions of Substituted Acryloyl Derivatives 603 Carrying Templates T1–T17, Catalyzed by (*S,R*)-10a Complexes with Different Cations

entry	reaction (Scheme)	R	R ¹	T	cation	anion	(<i>S,R</i>)-10a		ref
							ee (%)	α-face	
1	radical addition (Scheme 99)	Ph	H	T1	Mg(II)	I	93	Si	45
2	aza-Michael (Scheme 264)	Me	H	T1	Mn(II)	Br	66	Si	253
3	aza-Michael (Scheme 264)	Me	H	T3	Mn(II)	Br	68	Si	253
4	aza-Michael (Scheme 264)	Me	H	T2	Mn(II)	Br	50	Si ^a	253
5	aza-Michael (Scheme 265)	Me	H	T1	Mg(II)	Br	92	Si	571
6	aza-Michael (Scheme 265)	Me	H	T3	Mg(II)	Br	85	Si	571
7	aza-Michael (Scheme 265)	Me	H	T4	Mg(II)	Br	89	Si	571
8	aza-Michael (Scheme 265)	Me	H	T9	Mg(II)	ClO ₄	96	Si	256
9	aza-Michael (Scheme 265)	Me	H	T10	Mg(II)	ClO ₄	96	Si	256
10	aza-Michael (Scheme 265)	Me	H	T13	Mg(II)	Br	73	Si	571
11	aza-Michael (Scheme 266)	Me	Me	T14	Mg(II)	N(Tf) ₂	96	Si	572
12	aza-Michael (Scheme 266)	Me	Et	T14	Mg(II)	N(Tf) ₂	86	Si	572
13	aza-Michael (Scheme 266)	Ph	Ph	T14	Mg(II)	N(Tf) ₂	84	Si	572
14	aza-Michael (Scheme 266)	Me	Me	T16	Mg(II)	ClO ₄	75	Si	572
15	aza-Michael (Scheme 266)	Me	Me	T17	Mg(II)	N(Tf) ₂	96	Si	572
16	aza-Michael (Scheme 267)	Me	H	T1	Mg(II)	ClO ₄	55	Si ^b	573
17	aza-Michael (Scheme 267)	Me	H	T3	Mg(II)	ClO ₄	67	Si ^b	573
18	aza-Michael (Scheme 267)	Me	H	T13	Mg(II)	ClO ₄	58	Si ^b	573
19	aza-Michael (Scheme 267)	Me	H	T15	Mg(II)	ClO ₄	84	Si ^b	573
20	radical addition (Scheme 276)	(CH ₂) ₂ OBn	H	T1	Mg(II)	I	97	Si	580
21	radical addition (Scheme 276)	(CH ₂)OCOMe	H	T3	Mg(II)	I	84	Si	580
22	radical addition/trapping (Scheme 278)	Me	Me	T14	Mg(II)	I	94	Si	582
23	radical addition/trapping (Scheme 278)	OCOPh	Me	T16	Mg(II)	ClO ₄	82	Si	582
24	nitroxide 1,3-DC (Scheme 289)	Me	H	T8	Mg(II)	I	99	Si	396
25	nitrile imine 1,3-DC (Scheme 290)	Me	H	T1	Mg(II)	N(Tf) ₂	99	Si ^b	592
26	nitrile imine 1,3-DC (Scheme 290)	H	Me	T8	Mg(II)	I	99	Si ^b	593
27	nitrile imine 1,3-DC (Scheme 290)	Ph	Me	T8	Mg(II)	I	99	Si ^b	593
28	diazoester 1,3-DC (Scheme 292)	H	H	T8	Mg(II)	N(Tf) ₂	97	Si ^b	595
29	diazoester 1,3-DC (Scheme 292)	CH ₂ Ph	H	T8	Mg(II)	N(Tf) ₂	95	Si ^b	595
30	diazoester 1,3-DC (Scheme 292)	Me	Me	T8	Mg(II)	N(Tf) ₂	99	Si ^b	595
31	aza-Michael (Scheme 268)	Me	H	T13	Mg(II)	Br	92	Si	574
32	aza-Michael (Scheme 268)	Me	H	T13	Yb(III)	OTf	59	Re	574
33	radical addition/trapping (Scheme 277)	Ph	H	T1	Mg(II)	I	93	Si	581
34	radical addition/trapping (Scheme 277)	Ph	H	T1	Cu(II)	OTf	79	Re	581
35	nitroxide 1,3-DC (Scheme 289)	Me	Me	T9	Mg(II)	N(Tf) ₂	95	Si	591
36	nitroxide 1,3-DC (Scheme 289)	Me	Me	T16	Mg(II)	N(Tf) ₂	82	Si	591
37	nitroxide 1,3-DC (Scheme 289)	Me	Me	T16	Ni(II)	ClO ₄	77	Si	591
38	nitron 1,3-DC (Scheme 287)	Me	Me	T15	Cu(II)	OTf	94	Re	591
39	Diels–Alder (Scheme 114)	H	H	T1	Cu(II)	OTf	96	Re	81, 598
40	Diels–Alder (Scheme 114)	H	H	T3	Cu(II)	OTf	96	Re	598
41	Diels–Alder (Scheme 114)	H	H	T4	Cu(II)	OTf	99	Re	598
42	Diels–Alder (Scheme 114)	H	H	T5	Cu(II)	OTf	95	Re	598
43	Diels–Alder (Scheme 114)	H	H	T6	Cu(II)	OTf	94	Re	598
44	Diels–Alder (Scheme 114)	H	H	T8	Cu(II)	OTf	98	Re	598
45	Diels–Alder (Scheme 114)	H	H	T10	Cu(II)	OTf	97	Re	598
46	Diels–Alder (Scheme 114)	<i>p</i> -CF ₃ PhCO ₂	H	T3	Cu(II)	SbF ₆	94	Re	328
47	nitron 1,3-DC (Scheme 287)	Me	H	T7	Cu(II)	OTf	78	Re	392
48	nitron 1,3-DC (Scheme 287)	Me	H	T8	Cu(II)	OTf	98	Re	392
49	nitron 1,3-DC (Scheme 287)	Me	H	T11	Cu(II)	OTf	79	Re	392
50	nitron 1,3-DC (Scheme 287)	Me	H	T12	Cu(II)	OTf	93	Re	392
51	azomethine imine 1,3-DC (Scheme 291)	H	H	T7	Cu(II)	OTf	98	Re	594
52	azomethine imine 1,3-DC (Scheme 291)	H	H	T8	Cu(II)	OTf	94	Re	594
53	azomethine imine 1,3-DC (Scheme 291)	H	H	T10	Cu(II)	OTf	98	Re	594
54	radical addition (Scheme 202)	Ph	H	T13	Zn(II)	OTf	51	Re	504
55	radical addition (Scheme 202)	Ph	H	T1	Zn(II)	OTf	51	Si	504

^a Reaction performed at 0 °C; the same reaction at –60 °C gives reversal of stereochemistry (43% ee) with attack to the α-Re face. ^b Reaction catalyzed by (*R,S*)-10a, and therefore the reported face of attack is reversed.

(Table 195, entry 32) gives a stereochemical induction opposite to that promoted by MgBr₂ in the aza-Michael reaction (Table 195, entry 31) as reported in Scheme 268.⁵⁷⁴ On the contrary, catalysts with Ni(ClO₄)₂ or Mg(NTf₂)₂ (Table 195, entries 37 and 36) give the same stereochemical result in the

nitroxide 1,3-dipolar cycloaddition reported in Scheme 289.⁵⁹¹ This is not unexpected if the usual coordination numbers of these complexes are considered.

Finally, the [(*S,R*)-10a/Zn(OTf)₂] complex is an exception among the reactions reported in Table 195, because it is the only catalyst able to

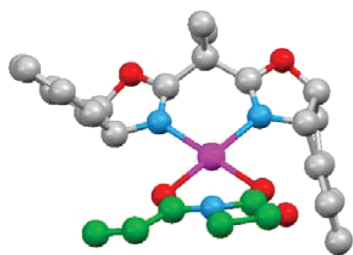


Figure 33. Reaction complex of **603** and $[(S,R)\text{-}10a/\text{CuX}_2]$ promoting the Re sense of stereoinduction.

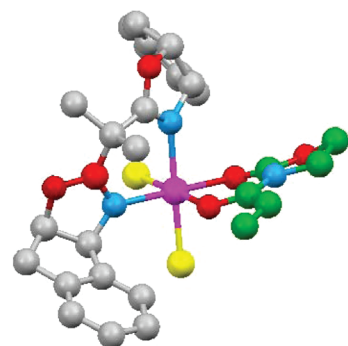
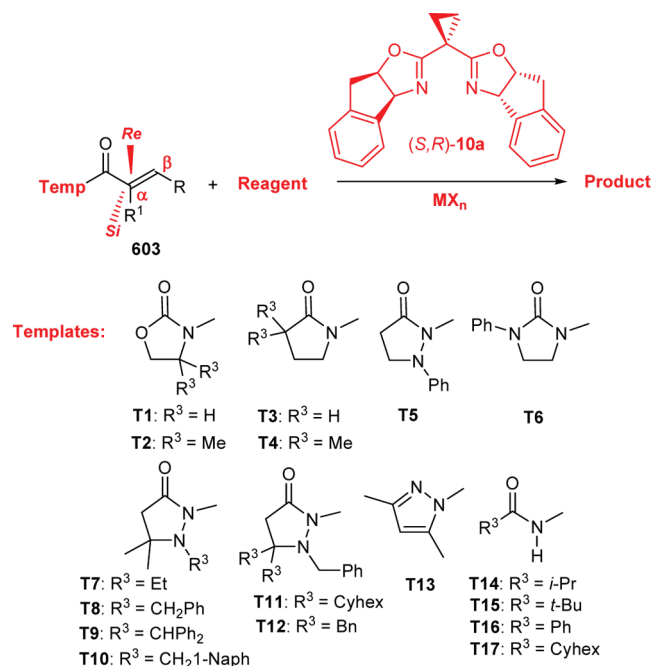


Figure 34. Reaction complex of **603** and $[(S,R)\text{-}10a/\text{MgX}_2]$ promoting the Si sense of stereoinduction.

Scheme 301



induce an opposite sense of stereoinduction when two different templates (**T1** and **T13**, Table 195, entries 54 and 55) are attached to **603**.^{5b4}

8. CONCLUSIONS

This review reports the history of boxes since their invention in 1991 by Corey and Evans. The capacity of boxes to behave as chiral ligands in the formation first of complexes with inorganic salts and then of reacting 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 is certainly due to their simple preparation. This has made available **more than 200** different structures, each of them tested in the enantioselective catalysis of a wide range of organic reactions. This 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 relevant sections. This capability makes the box-based catalysts not only efficient but also clever *molecular robots*,⁶⁰⁰ whose behavior can also be predicted.

In enantioselective catalysis with box complexes there are still unanswered questions, but given the spectacular developments in the field, the authors are confident that these will be solved in the near future.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: giovanni.desimoni@unipv.it; kaj@chem.au.dk.

BIOGRAPHIES



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. Since 2010 he is Professor emeritus at the University of Pavia.



Giuseppe Fata was born in 1962 and received his degree in Chemistry in 1986 at the University 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.



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.

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