Review

Copper-Catalyzed Diels#Alder Reactions

Se#bastien Reymond, and Janine Cossy

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Copper-Catalyzed Diels−Alder Reactions

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1. Introduction

For 80 years, the Diels−Alder addition[1–3] has been one of the best methods for the preparation of six-membered carbocycles with control of up to four stereogenic centers in an atom-economical way. The typical [4+2]-cycloaddition condenses a diene moiety onto an alkene or alkyne system (dienophile) to afford a cyclohexene or cyclohexadiene derivative.

Since the report that thermal dimerizations of acrolein and methyl vinyl ketone are highly regioselective giving six-membered heterocycles,[4] the Diels−Alder additions of conjugated enols and enones to olefinic dienophiles has become a powerful method for the synthesis of 3,4-dihydro-2*H*-pyranes.[5,6] This cycloaddition was then generalized to other heterobutadienes such as azadienes and thiadienes (Scheme 1).

According to the Woodward−Hoffmann rules, the concerted suprafacial [$\pi 4_s + \pi 2_s$] cycloaddition of a diene and a dienophile is thermally allowed. The theory predicts that the rate and regioselectivity of cycloadditions are controlled by either the HOMO of the diene and the LUMO of the dienophile in the normal Diels−Alder and by the HOMO of the dienophile and the LUMO of the diene in the inverse electron-demand Diels−Alder.[7] Since the Woodward−Hoffmann rules, a diradicaloid transition state as well as a zwitterionic transition state were shown to also intervene in Diels−Alder reactions.[8]

In Diels−Alder reactions, the stereoselectivity is generally high due to the "*cis* principle", which states that Diels−Alder reactions require a cisoid conformation for the diene and suprafacial-suprafacial mode of reaction, meaning that both ends of the diene attack from the same face of the dienophile in a *syn* fashion. The Diels−Alder addition of dienophiles to dienes quite often gives the *endo* adducts.[2d,e] This is the "*endo* rule", first proposed by Alder and Stein.[9] The "*endo* rule" is usually rationalized as a result of the principle of "maximum accumulation of unsaturation". The polarizability of the diene and dienophile creates dispersive forces making the *endo* transition state more stable than the *exo* transition state. Secondary orbital overlaps are possible, leading to secondary binding forces that stabilize this transition state.[10,11] Solvents other than water have little effect on the *endo* selectivity;[12,13] however, temperature and/or the presence of a Lewis acid catalyst can affect it.[14]

Since 1942, it has been shown that the Diels−Alder reaction is catalyzed by Brönsted acids.[15] It was only later in 1960 that Yates and Eaton revolutionized the Diels−Alder reaction when they reported that a Lewis acid, $AlCl_3$, was able to catalyze Diels−Alder reactions under mild conditions.[16]

The very first Diels−Alder reaction promoted by copper species was presented by Bota et al.[17] In a short communication in 1961, they reported the Diels−Alder reaction of cyclopentadiene with acetylene to produce 2,5-norbornadiene by continuous flow reaction through a $CuCl/NH_4Cl$/activated carbon catalyst; however, the authors were not clear about the role of the catalyst. Corey et al. extended the use of copper salts as Lewis acid catalysts in the Diels−Alder reaction,[18] and in 1982, the $CuCl/NH_4Cl$ catalytic system was used for the second time (vide infra).[19]

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Sébastien Reymond was born in Valence, France in 1975. He received his diploma in 1999 from the Ecole Nationale Supérieure de Synthèses de Procédés et d'Ingénierie Chimiques d'Aix-Marseille (ENSSPICAM) and his Ph.D. in 2003 from the University of Aix-Marseille III in the group of Pr. Gérard Buono at ENSSPICAM. After a 1 year postdoctoral appointment with Pr. Jean-Pierre Genet at ENSCP in Paris, he was appointed Assistant Professor in 2004 at ESPCI in the group of Pr. Janine Cossy. His research interests include the development of eco-friendly synthetic organic methods, as well as the synthesis of biologically active compounds.

Janine Cossy was born in Reims (Champagne area), France and did her undergraduate and graduate studies at the University of Reims working on the photochemistry of ketones and enamino ketones under the supervision of Pr. Jean Pierre Pète. After a 2 year postdoctoral appointment with Pr. Barry M. Trost at the University of Wisconsin (USA), she returned to Reims in 1990 where she became a director of research for CNRS. In the same year she moved to Paris to become a professor of organic chemistry at ESPCI (Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris). Since 1991 she has also been Director of the CNRS unit, UMR 7084. She has more than 340 publications and 12 patents. She was President of the Organic Division of the French Chemical Society (from 2002 to Feb 2007), and since 2005 she has been an associate editor for *Organic Letters*.

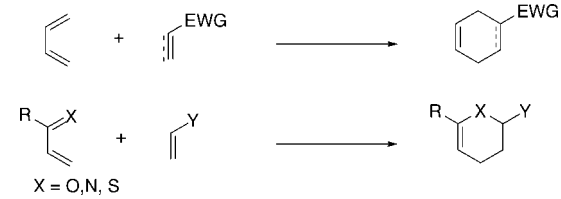
2. Carbo-Diels−Alder Reactions

2.1. Racemic Diels−Alder Reaction

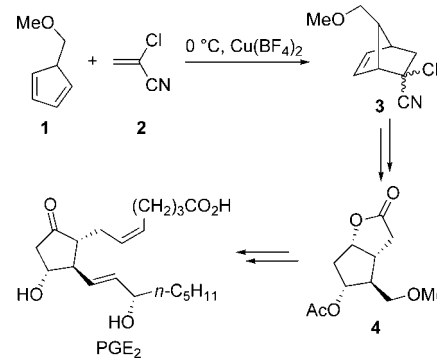
2.1.1. Diels−Alder Reaction in Organic Medium

In 1969 Corey et al. introduced the use of a copper salt [$Cu(BF_4)_2$] to catalyze the Diels−Alder reaction of diene **1** and 2-chloro-acrylonitrile **2**.[18,20,21] The use of this catalyst accelerated the Diels−Alder reaction at 0 °C without isomerization of diene **1**. The obtained cycloadduct **3** appeared to be an interesting precursor of lactone **4**, which was transformed to PGE_2 (Scheme 2). Later, Goering et al. observed that $Cu(BF_4)_2$ influenced not only the rate of the

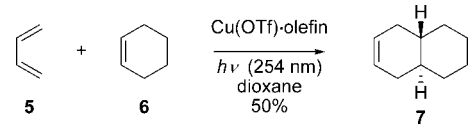
Scheme 1



Scheme 2



Scheme 3



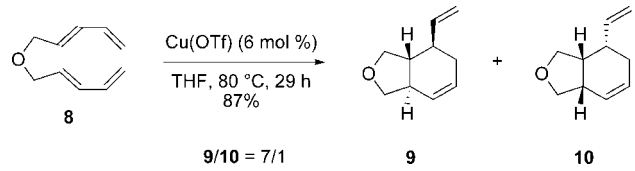
reaction between methylcyclopentadienes and **2** but also its regioselectivity.[22]

Mackor et al. reported that the copper(I)triflate·butadiene and copper(I)triflate·cyclohexene complexes were able to catalyze the photochemical Diels−Alder reaction of cyclohexene **6** and 1,3-butadiene **5** upon irradiation at 254 nm in 1,4-dioxane (Scheme 3).[23,24] In this reaction, copper(II) triflate and CuCl were also tested, but they displayed no catalytic behavior in the photochemical Diels−Alder reaction. Copper(OTf)·olefin complexes were proposed to play a role in both the *cis*/*trans* isomerization of cyclohexene and in bringing the diene and the dienophile closer by a template effect.

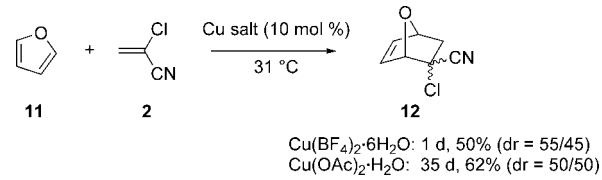
In 1991, Mattay et al. studied the copper(I)-catalyzed intramolecular cycloadditions of symmetrical bis-dienes under thermal and photochemical conditions.[25] The copper-catalyzed photochemical reaction of bis-dienes such as compound **8** did not favor [4+2]-cycloadducts and complex mixtures were obtained. However, under thermal conditions, the intramolecular Diels−Alder reaction of diene **8** catalyzed by 6 mol % of Cu(OTf) proceeded in good yields and with good stereocontrol (Scheme 4). Copper(II) complexes such as $Cu(OTf)_2$, $Cu(BF_4)_2 \cdot 6H_2O$, and $Cu(ClO_4)_2 \cdot 6H_2O$ also gave good stereocontrol (7/1), but longer reaction times were required and lower yields were obtained. These reactions were accelerated by adding a catalytic amount of hydroquinone, and this reaction was proposed to be catalyzed by copper(I) species (vide infra).[26]

Vogel et al. have used copper(I) and copper(II) complexes as Lewis acid catalysts for a Diels−Alder reaction involving furan.[27] The reactivity of furan **11** in a Diels−Alder reaction with 2-chloro-acrylonitrile **2** and 2-acetoxy-acrylonitrile was screened by using catalytic amounts of CuCl, $Cu(BF_4)_2 \cdot 6H_2O$, $Cu(OAc)_2 \cdot H_2O$ or Cu(tartrate)·$3H_2O$ with yields ranging from 19% to 62%. After 1 day at 31 °C with 10 mol %

Scheme 4



Scheme 5



$Cu(BF_4)_2 \cdot 6H_2O$, cycloadduct **12** was obtained in 50% isolated yield as a 55/45 mixture of stereoisomers. In contrast **12** was isolated in 62% yield after 35 days when $Cu(OAc)_2 \cdot H_2O$ was used (Scheme 5). Traces of hydroquinone and propylene oxide were reported to be useful to prevent polymerization during the course of this reaction. Moore et al. also studied the Diels−Alder reaction of **11** with various acrylic derivatives with copper(II) tetrafluoroborate in the presence of hydroquinone.[26] The authors revealed that under the reaction conditions, hydroquinone not only prevented polymerization but accelerated the Diels−Alder reaction. They proposed that the copper(II) species were reduced to copper(I) species by hydroquinone as the formation of quinone was characterized. In this study, tetrakis(acetonitrile)copper(I) tetrafluoroborate was also found to catalyze the Diels−Alder reaction with furan.

In general, $Cu(OTf)_2$ is the catalyst of choice for racemic Diels−Alder reactions. For example, $Cu(OTf)_2$ was used to prepare branched fatty acid derivatives through the Diels−Alder reactions of **13** with methyl vinyl ketone, crotonaldehyde, naphthoquinone, or *p*-benzoquinone (**14**).[28] The obtained cycloadducts were produced in good yields at moderate reaction temperature. For example, with *p*-benzoquinone (**14**), cycloadduct **15** was obtained as a mixture of isomers in 63% yield after 0.5 h (Scheme 6).

In the Diels−Alder reaction, the substrate plays an important role in the outcome of the cycloaddition. Narasaka et al. introduced the use of 3-acryloyl-1,3-oxazolidin-2-ones as dienophiles in Diels−Alder reactions.[29] These acrylimides possess a two-point binding mode to the Lewis acid, which allows them to form rigid complexes. The formation of such complexes was first postulated by Narasaka et al. in 1986 with Diels−Alder reactions promoted by chiral titanium complexes and confirmed by NMR studies in 1993 by Castellino et al.[30] The use of acrylimide dienophiles allows for faster reactions and increased *endo*/*exo* selectivities. Williams et al. have also reported that other chelating dienophiles were able to accelerate Diels−Alder reaction under Lewis acid promoted conditions. For example, the Diels−Alder reaction between cyclopentadiene (**18**) and (2-pyridyl)methyl acrylate (**17**) was faster than the competing reaction using benzyl acrylate (**16**). The best acceleration was obtained with $Cu(OTf)_2$ as the rate of the reaction was increased by a factor of 27 (Scheme 7).[31]

Other copper species are able to catalyze the Diels−Alder reaction. $Cu(NTf)_2 \cdot nH_2O$ (1 mol %) efficiently catalyzed the reaction of cyclopentadiene **18** with methyl vinyl ketone **21**.[32] In this case, the relative second-order rate constant was up to 1770 times higher than the one obtained with $CuCl_2 \cdot 2H_2O$ as the catalyst and *endo*-**22** was obtained as the major product (*endo*/*exo* = 13/1) (Scheme 8).

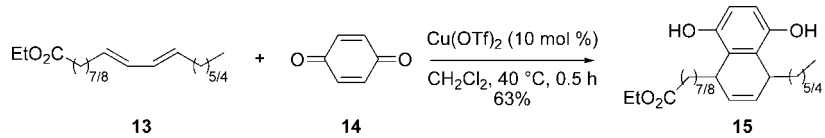
A heterobimetallic Fe/Cu complex was reported to catalyze the Diels−Alder reaction of **18** with methacrolein **23**.[33] The copper−iron complex **I** featuring two bridging phosphinooxazoline ligands allowed isolation of the bicyclic aldehyde **24** in 76% yield with moderate *exo* selectivity (*exo*/*endo* = 74/26) (Scheme 9).

2.1.2. Diels−Alder Reaction in Water

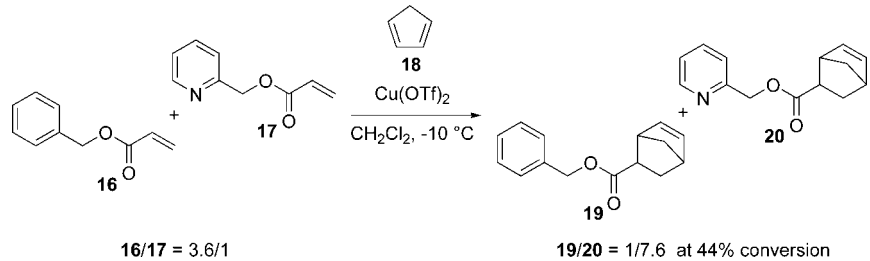
It is known that the Diels−Alder reaction is moderately sensitive to solvent effects;[2f,g,34] however, water was shown to have a positive effect on both the reaction rate and stereoselectivity.[35−37] Diels and Alder themselves reported that the cycloaddition works in water;[38] however, it was not until Breslow et al. revealed the details of the solvent effect that this reaction was well understood.[39] The positive effects of water are due to the hydrophobic packing and the enforced hydrophobic hydration in addition to the hydrogen-bonding effects.[37]

Engberts et al. reported that it was possible to obtain a great acceleration of the Diels−Alder reaction by using a catalytic amount of Lewis acids in water.[40−43] By using $Cu(NO_3)_2$ at low concentration in water (0.01 M), a synergistic effect provided great acceleration of the cycloaddition of diene **18** with the 2-pyridyl-propenoyl derivative **25** by a factor of 79,286 compared to the reaction in acetonitrile and by a factor of 287 compared to the reaction

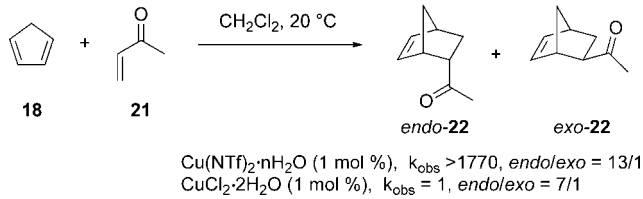
Scheme 6



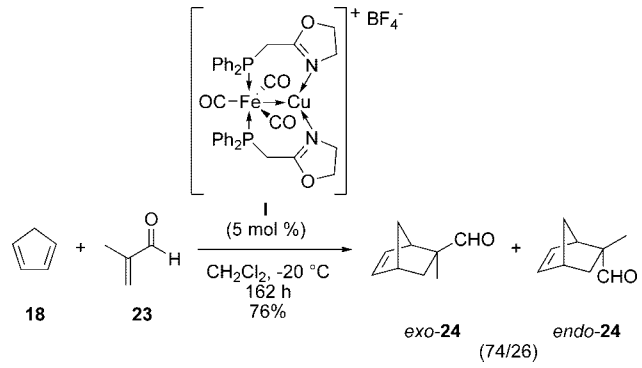
Scheme 7



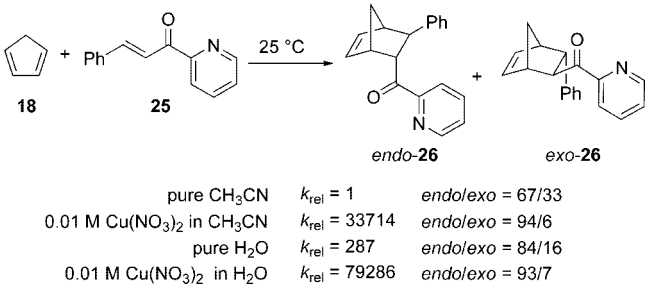
Scheme 8



Scheme 9



Scheme 10



in pure water.[41] Furthermore, by using $Cu(NO_3)_2$, the *endo*/*exo* ratio for cycloadduct **26** (93/7) was greater than the ratio obtained in pure water (84/16) (Scheme 10).

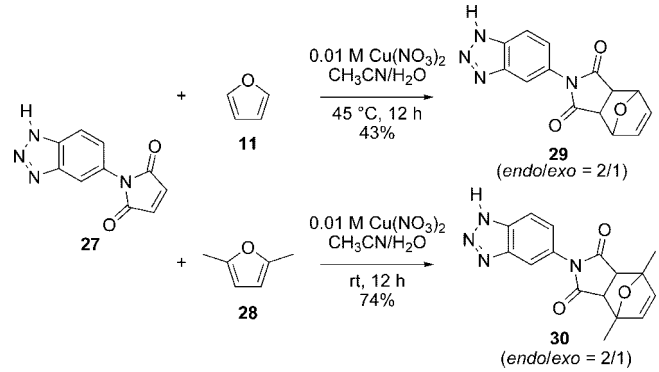
Engberts et al. also studied the effect of micelles on the Diels−Alder reaction of **18** with the 2-pyridyl-propenoyl derivative **25**. By using $Cu(DS)_2$ (DS = dodecyl sulfate) the relative second-order rate constant reached 425,000 (relative to the uncatalyzed reaction in pure CH_3CN).[44] In the case of a 2-pyridyl-propenoyl type dienophile featuring a quaternary ammonium substituent on the phenyl group, a rate enhancement of 1.8 million was observed. Later, copper(II) metallo-vesicles were also shown to be efficient catalysts.[45]

Based on the same idea, organo-aqueous solvents were reported to be good media in which to perform the Diels−Alder reaction. For example, Graham et al. were able to develop the Diels−Alder reaction of the benzotriazole maleimide dienophile **27** with various dienes.[46] In the case of furan **11** and dimethylfuran **28**, the corresponding cycloadducts **29** and **30** were obtained in 43% and 74% yield, respectively, by using $Cu(NO_3)_2$ (0.01 M in CH_3CN/H_2O) (Scheme 11).

2.1.3. Diels−Alder Reaction with Polymer-Supported Copper Catalysts

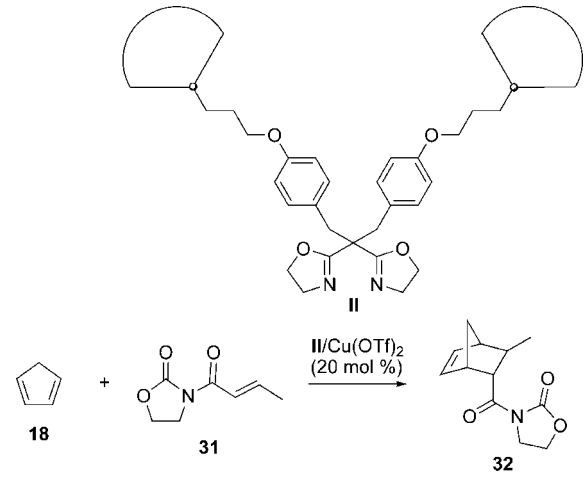
Polymer-supported Lewis acids are known to catalyze cycloadditions and polymer-loaded or dentritic-loaded copper catalysts have been reported to be promoters of Diels−Alder reactions.[47] Menger et al. described the synthesis of two copper-loaded polystyrene-based metallo-polymers and their

Scheme 11



use as catalysts in the reaction of **11** with **2** (see Scheme 5).[48] As a result, these metallo-polymers give better yields than the $Cu(OAc)_2$-catalyzed reaction.[27] Later, Chow et al. reported the synthesis of dendritic bis(oxazoline)**II**/Cu(II) complexes and their use as catalysts in the Diels−Alder reaction of **18** with **31**(Scheme 12).[49] For this reaction, the authors compared the influence of the dendritic character of the catalysts on both kinetics and selectivity. It appeared that the catalyzed reaction followed a Michaelis−Menten relationship with a fast and reversible formation of a dienophile−dendritic catalyst complex prior to the cycloaddition. Moreover, the size of the dendrimers had a strong influence on the kinetics of the reaction with a possible folding-back of the dendritic sectors toward the metallic site for higher-order dendrimers.

Scheme 12

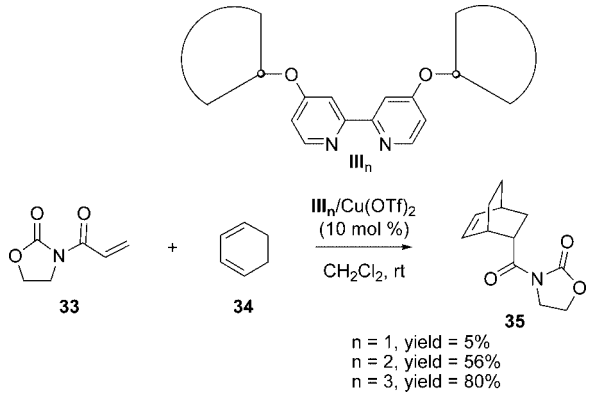


Later, Fujita et al. reported the use of dendritic bipyridines $\mathbf{III}_n$ as ligands of $Cu(OTf)_2$ in the Diels−Alder reaction of various dienes and dienophiles.[50] For example, the Diels−Alder reaction of **33** and **34** proceeded with excellent *endo* selectivity (no *exo* stereoisomer was detected), and a positive dendritic effect was observed as the yield of **35** increased with the size of the dendrimers. Indeed, the first-order dendrimer $\mathbf{III}_1$ led to a poor yield in **35** (5%), but $\mathbf{III}_2$ furnished **35** in 56% yield, and the third-order dendrimer $\mathbf{III}_3$ gave an optimal yield of 80% (Scheme 13).

2.1.4. Heterogeneous Diels−Alder Reaction

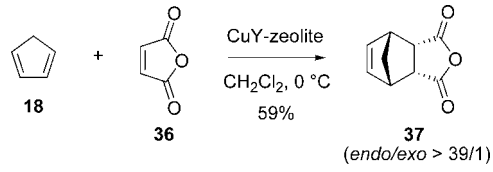
Copper-loaded zeolites and montmorillonites were developed and used as catalysts in the Diels−Alder reaction. The first example of a zeolite-based Cu(I) catalyst in the Diels−Alder

Scheme 13



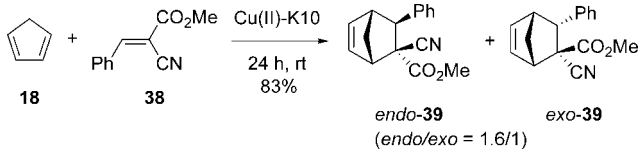
reaction was reported early in the 1970s by Ruiter et al.[51] A CuX-type zeolite (copper(I)) appeared to catalyze the reaction of acetylene with butadiene but in low yield. More recently, a copper(II)-based CuY-type zeolite was used in the Diels−Alder reaction of cyclopentadiene **18** with maleic anhydride **36**. Cycloadduct **37** was obtained in 59% yield with a high *endo*/*exo* ratio (>39/1) (Scheme 14).[52]

Scheme 14



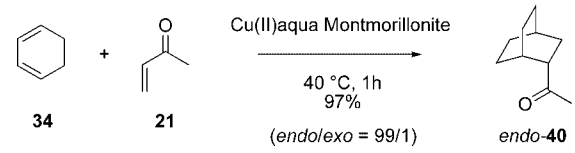
Metal-doped montmorillonites also found some applications as catalysts in Diels−Alder reactions. Worthy of note are Cu(II)-doped montmorillonites that were used as heterogeneous catayst in the Diels−Alder reaction. Mayoral et al. reported that the reaction of **18** with *trans*-anethole was catalyzed by an end-capped Cu(II)-K10 montmorillonite; however, the cycloadduct was obtained in low yield [as a 5/1 (*endo*/*exo*) mixture] because of the competitive polymerization of *trans*-anethole under these conditions.[53] In this study it was shown that an end-capped Fe(III)-K10 montmorillonite was the best catalyst for the reaction. When methyl (*E*)-2-cyanocinnamate **38** was used as the dienophile, a good yield in **39** was obtained (83%) after 24 h at room temperature by using a Cu(II)-K10 montmorillonite but with a modest ratio of *endo*/*exo*-cycloadducts **39** (1.6/1) (Scheme 15).[54]

Scheme 15



Recently, Kaneda et al. have shown that metal aqua complex-doped montmorillonites could be used as strong Lewis acids to catalyze various reactions and particularly the Diels−Alder reaction of dienes with deactivated dienophiles.[55] A Cu(II) aqua-doped montmorillonite has shown a good catalytic activity in the solvent-free Diels−Alder reaction, and for example, the reaction of **34** with **21** furnished cycloadduct **40** in 97% GC yield and with excellent *endo* selectivity (Scheme 16).

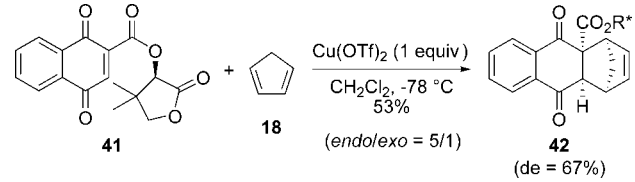
Scheme 16



2.2. Enantioselective Substrate-Directed Diels−Alder reaction

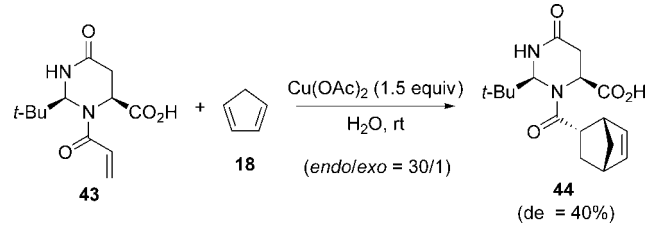
The major part of substrate-directed Diels−Alder reactions uses aluminum- or titanium-Lewis acid catalysts and the chiral induction is achieved by attaching a chiral auxiliary to the dienophile unit. Few examples of these types of Diels−Alder reactions catalyzed by copper have been reported. Brimble et al. have reported the asymmetric Diels−Alder reaction of **18** with a series of naphthoquinones featuring a chiral auxiliary.[56] In a systematic approach, the influence of various chiral auxiliaries and various Lewis acids was studied. In the case of copper(II) triflate, the best result was obtained by using (*R*)-pantolactone as the chiral auxiliary and cycloadduct **42** was obtained in 53% yield as a 5/1 *endo*/*exo* mixture in 67% diastereomeric excess (de) for the *endo* adduct (Scheme 17). It is worth noting that $ZnCl_2$ appeared to be a much better Lewis acid catalyst, and with this catalyst, **42** was obtained in 64% yield as a 45/1 *endo*/*exo* mixture (96% de).

Scheme 17



Negrete et al. reported the aqueous Diels−Alder reaction of **18** with a chiral acrylamide **43** derived from L-aspargine in the presence of metal salts.[57] When a copper(II) acetate solution was employed, cycloadduct **44** was obtained with excellent *endo* selectivity (*endo*/*exo* = 30/1) but with a poor diastereomeric excess of 40% (Scheme 18).

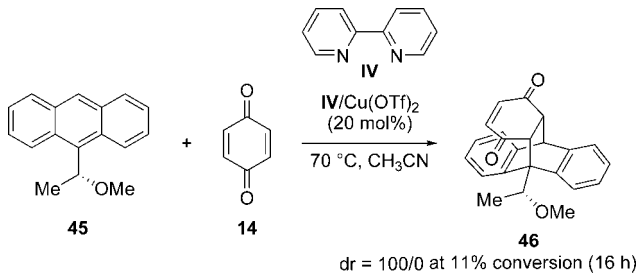
Scheme 18



An end-capped Cu(II)-K10 montmorillonite was also used in the Diels−Alder reaction of **18** with (−)-menthyl acrylate by Mayoral et al.[58] Although the *endo*/*exo* ratio was good (91/9), the conversion after 24 h was only of 47% with a poor diastereomeric excess for the major *endo*-cycloadduct.

One example of a copper-catalyzed Diels−Alder reaction of a chiral diene **45** with *p*-benzoquinone (**14**) was reported by Jones et al.[59] By using 20 mol % of Cu(OTf)$_2$ and 20 mol % of bipyridine (**IV**) as the copper ligand, a poor conversion was observed (11%) after 16 h at 70 °C in CH_3CN, but a single stereoisomer was obtained (compared

Scheme 19



to the 6/4 mixture obtained under thermal conditions) (Scheme 19).

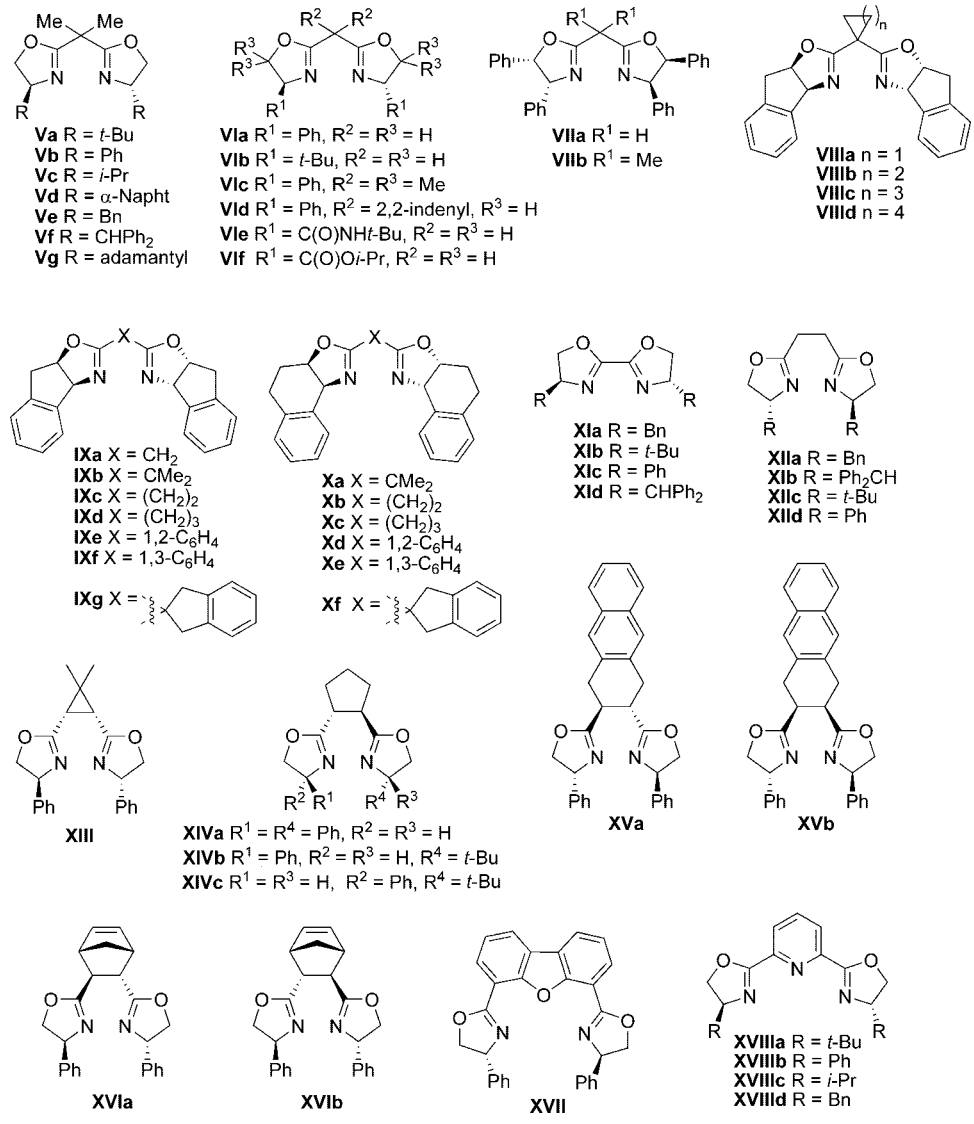
2.3. Enantioselective Diels−Alder Reaction Catalyzed by Chiral Copper Complexes

2.3.1. Bis(oxazoline) Ligands

Bis(oxazoline) ligands represent one of the major classes of chiral ligands for asymmetric catalysis. Their synthesis is quite easy and very flexible, giving the user access to a wide range of analogues for catalytic evaluations (ligands **V**−**XVIII**, see Chart 1). In addition, some of them are commercially available. A recent review emphasizes the scope of the applications of this class of C_2-symmetric ligands with more than 300 references cited.[60] Since the pioneering works of Evans and Corey in 1991 reporting, respectively, the copper-bis(oxazoline) catalyzed asymmetric cyclopropanation of olefins with diazoacetates[61] and the enantioselective iron-bis(oxazoline) catalyzed Diels−Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one and cyclopentadiene,[62] one can easily notice the booming development of bis(oxazoline)-based catalytic systems, and this area has also contributed to the exponential development of asymmetric catalysis.[63] These ligands find applications in very diverse metal-catalyzed asymmetric reactions such as cyclopropanations, aziridinations, aldol reactions, Mukaiyama reactions, allylic substitutions, radical reactions, and cycloadditions.

2.3.1.1. Diels−Alder Reaction with 3-Acryloyl-1,3-oxazolidin-2-ones. As mentioned previously (vide supra) the work of Narasaka et al. introduced the use of 3-acryloyl-1,3-oxazolidin-2-ones as dienophiles in the Diels−Alder reaction.[29,64] Because of their two-point binding modes to the Lewis acid, they form rigid complexes, allowing faster Diels−Alder reactions and better *endo*/*exo* selectivities. Moreover, by limiting the number of conformations for the dienophile coordinated to the Lewis acid, the enantioselection of the process is also dramatically influenced. For these

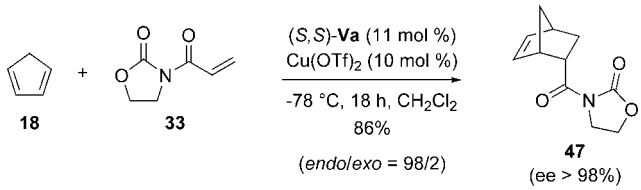
Chart 1



reasons, this class of dienophiles is of great interest for developing new copper-based catalytic systems in the Diels−Alder reaction with electron-rich dienes.

The first example of the use of bis(oxazoline)/Cu(II) complexes as chiral catalysts for the enantioselective Diels−Alder reaction was reported by Evans et al. in 1993.[65] The in situ generated catalysts (5−10 mol %) were prepared by mixing the corresponding bis(oxazoline) ligands (*S*,*S*)-**Va**−**Vd** with $Cu(OTf)_2$ in CH_2Cl_2 at room temperature. Excellent results were obtained for the Diels−Alder cycloaddition of imides with cyclopentadiene (Table 1, entries 1−3), with the best result being the combination of **33** with bis(oxazoline) (*S*,*S*)-**Va** to afford the *endo* adduct **47** as the major product (*endo*/*exo* = 98/2) with an enantiomeric excess (ee) up to 98% (Scheme 20). The size of the bis(oxazoline) substituents appears to have a dramatic effect on the outcome of the reaction with 98% ee in the case of the *tert*-butyl substituents (**Va**, Table 1, entry 1) but only 30%, 58%, and 44% ee in the case of phenyl, isopropyl, and α-naphthyl groups, respectively (**Vb**,**Vc**, and **Vd**, Table 1, entries 2−4). Even (*S*,*S*)-**VIc**, which was previously reported to be an optimal ligand in Fe- and Mg-catalyzed asymmetric Diels−Alder reactions of **18** with **33**, furnished a poor enantiomeric excess and a poor *endo*/*exo* ratio when $Cu(OTf)_2$ was used (Table 1, entry 5).

Scheme 20



In general, bis(oxazoline)/Cu(II) complexes adopt distorted square-planar geometries as determined by several X-ray studies.[60] The bis(oxazoline) ligand acts as a bidentate ligand with a coordination number of four for copper(II).[66] Based on these results, computational studies have also been used to predict the geometry of the dienophile/bis(oxazoline)/Cu complex. In the case of bis(oxazoline) ligands **Va**−**Vc**, structure **A** is commonly proposed, and if a bis(oxazoline) of (*S*,*S*)-configuration is used, the sense of the asymmetric induction can be rationalized by a preferred approach of the diene on the α-*re* face of the dienophile producing the cycloadduct with the preferred (*S*)-configuration (Figure 1).[67−69]

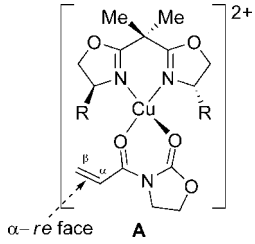


Figure 1.

In their seminal study, Evans et al. also envisaged double stereodifferentiation experiments.[65] By using chiral oxazolidinones (*R*)-**48** and (*S*)-**48** as the dienophiles and (*S*,*S*)-**Va**/$Cu(OTf)_2$ as the catalyst, diastereomeric cycloadducts **49** and **50** were obtained. Adduct **49** was obtained after full conversion with a dr (2*S*)-*endo*-**49**/(2*R*)-*endo*-**49** of more than 99/1, whereas the reaction with the enantiomeric dienophile (*S*)-**48** was a mismatched case that only led to a poor conversion of 20% of the dienophile and **50** was obtained with a modest dr (2*S*)-*endo*-**50**/(2*R*)-*endo*-**50** of 68/32 (Scheme 21). These matched/mismatched effects agreed with the predicted sense of asymmetric induction as well as with the calculated distorted square-planar geometry such as **A**.

Evans et al. investigated the role of the counterion on the outcome of the Diels−Alder reaction (Scheme 22).[67] At first, they employed $Cu(OTf)_2$ assuming that the triflate counterions would dissociate or would be displaced by the dienophile upon chelation to the copper center. Copper complexes (*S*,*S*)-**Va**/$Cu(BF_4)_2$, (*S*,*S*)-**Va**/$Cu(PF_6)_2$ and (*S*,*S*)-**Va**/$Cu(SbF_6)_2$ were surveyed in the Diels−Alder reaction of **18** with **33** (10 mol %) and interesting results were obtained (Table 1, entries 6−9). (*S*,*S*)-**Va**/$Cu(BF_4)_2$, (*S*,*S*)-**Va**/$Cu(PF_6)_2$ and (*S*,*S*)-**Va**/$Cu(OTf)_2$ gave similar results both in terms of stereoselectivity and kinetics. With (*S*,*S*)-**Va**/$Cu(SbF_6)_2$, the reaction was greatly accelerated and cycloadduct *endo*-**47** was obtained in >95% yield and with a >98% ee (Table 1, entry 8). Even with only 1 mol % of the catalyst (*S*,*S*)-**Va**/$Cu(SbF_6)_2$, an excellent enantiomeric excess for *endo*-**47** (96%) was obtained (Table 1, entry 9). Crystallographic studies on the bench-stable dihydrated catalysts have shown that in the case of (*S*)-**Va**/$Cu(OTf)_2(H_2O)_2$, in the solid state, one triflate was weakly bonded to the copper center while the other was fully dissociated, whereas in the case of complex (*S*)-**Va**/$Cu(SbF_6)_2(H_2O)_2$, both counterions were dissociated, leading to a distorted square-planar geometry for the copper complex.

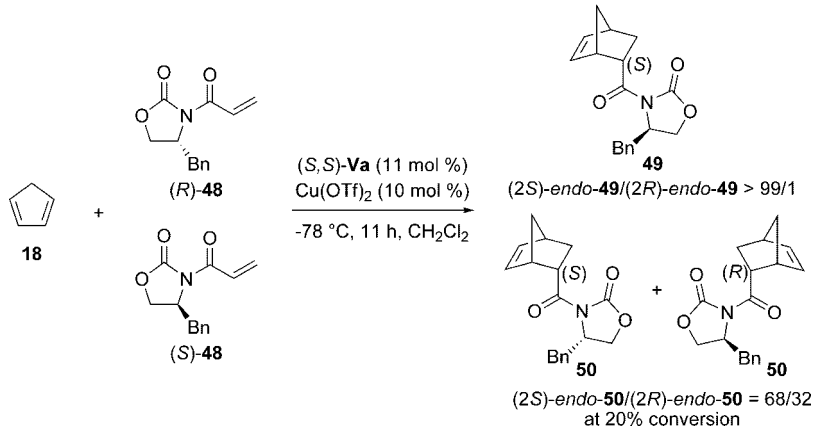
Other bis(oxazoline) ligands were also developed. For example, the use of (*S*,*S*)-**Vf**/$Cu(OTf)_2$ (10 mol %) in the Diels−Alder reaction of **18** with **33** led to a poor *endo*/*exo* ratio (72/28) and a poor enantiomeric excess for *endo*-**47** (35%) (Table 1, entry 10),[70] but by using catalyst (*R*,*R*)-**Vg**/$Cu(SbF_6)_2$, cycloadduct (*R*)-*endo*-**47** was obtained in 66% yield with an excellent enantiomeric excess of 98% and with a 92/8 *endo*/*exo* ratio (Table 1, entry 11).[71]

In the context of ligand optimization, a cyclopropane-based bis(oxazoline) ligand series was developed by Wang et al. and in the case of (*S*,*S*)-**XIII**/$Cu(OTf)_2$ as the catalyst, an enantiomeric excess of 77% was obtained in the best case for *endo*-**47**, and a 87/13 dr was obtained (Table 1, entry 12).[72] When substituents on the bis(oxazoline) other than phenyl groups were present, low enantiomeric excesses were obtained.

Ghosh et al. have reported the synthesis of a conformationally constrained bis(oxazoline) (1*S*,2*R*)-**IXa** derived from (1*S*,2*R*)-1-amino-2-indanol. This bis(oxazoline) was utilized as ligand of copper in the Diels−Alder reaction of **18** with **33** catalyzed by various metals and excellent results were obtained with copper triflate. When 8 mol % of (1*S*,2*R*)-**IXa**/$Cu(OTf)_2$ was used, an excellent *endo*/*exo* ratio (>99/1) for **47** was observed, and an enantiomeric excess of 94% was obtained for the *endo* cycloadduct (98% yield, Table 1, entry 13).[73]

Based on the same (1*S*,2*R*)-1-amino-2-indanol backbone, Davies et al. developed new bis(oxazoline) ligands **VIIIa**−**VIIId** and **IXb**−**IXg**.[74−76] In the case of ligands **VIIIa**−**VIIId** and **IXb**, the influence of the calculated bridge angle (Φ) and bite angle (θ) of the bis(oxazoline) on the

Scheme 21



Scheme 22

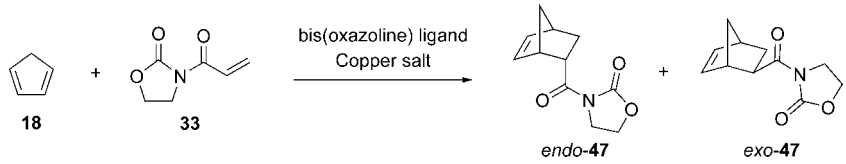
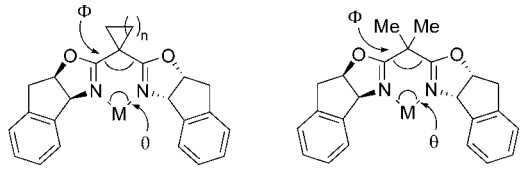


Table 1. Diels−Alder Reaction of 18 with 33 Catalyzed by Bis(oxazoline)/Cu(II) Complexes

entry	catalyst (mol %)	solvent (T, °C)	yield (%)	*endo*-**47**/*exo*-**47**	ee (%) *endo*-**47** (config)	ref
1	(*S*,*S*)-**Va**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−78)	86	98/2	>98 (2*S*)	65
2	(*S*,*S*)-**Vb**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−78)	92	95/5	30 (2*S*)	65
3	(*S*,*S*)-**Vc**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−78)	93	96/4	58 (2*S*)	65
4	(*S*,*S*)-**Vd**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−78)	92	94/6	44 (2*S*)	67
5	(*S*,*S*)-**VIc**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)		72/28	10 (2*S*)	67
6	(*S*,*S*)-**Va**/Cu(BF$_4$)$_2$ (10)	CH_2Cl_2 (−78)		98/2	>98 (2*S*)	67
7	(*S*,*S*)-**Va**/Cu(PF$_6$)$_2$ (10)	CH_2Cl_2 (−78)		97/3	>98 (2*S*)	67
8	(*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ (10)	CH_2Cl_2 (−78)	>95	96/4	>98 (2*S*)	67
9	(*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ (1)	CH_2Cl_2 (−78)		96/4	96 (2*S*)	67
10	(*S*,*S*)-**Vf**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−40)	98	79/21	35 (2*S*)	70
11	(*R*,*R*)-**Vg**/Cu(SbF$_6$)$_2$ (10)	CH_2Cl_2 (−84)	66	92/8	98 (2*R*)	71
12	(*S*,*S*)-**XIII**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−78)		87/13	77 (2*S*)	72
13	(1*S*,2*R*)-**IXa**/Cu(OTf)$_2$ (8)	CH_2Cl_2 (−78)	98	>99/1	94 (2*S*)	73
14	(1*S*,2*R*)-**VIIIa**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)	>90	44/1	96 (2*S*)	73
15	(1*S*,2*R*)-**VIIIb**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)	>90	38/1	92 (2*S*)	73
16	(1*S*,2*R*)-**VIIIc**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)	>90	37/1	90 (2*S*)	73
17	(1*S*,2*R*)-**VIIId**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)	>90	26/1	83 (2*S*)	73
18	(1*S*,2*R*)-**IXb**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)	>90	49/1	82 (2*S*)	74
19	(1*S*,2*R*)-**IXb**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−65)		130/1	92 (2*S*)	74
20	(1*S*,2*R*)-**IXb**/Cu(SbF$_6$)$_2$ (10)	CH_2Cl_2 (−75)	92	39/1	95 (2*S*)	74
21	(1*S*,2*R*)-**IXc**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)		8/1	13 (2*S*)	74
22	(1*S*,2*R*)-**IXd**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)		29/1	6 (2*S*)	74
23	(1*S*,2*R*)-**IXe**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)		22/1	73 (2*S*)	74
24	(1*S*,2*R*)-**IXf**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)		12/1	41 (2*S*)	74
25	(1*S*,2*R*)-**IXg**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−65)		39/1	96 (2*S*)	75
26	(1*S*,2*R*)-**VId**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)		23/2	46 (2*S*)	75
27	(1*S*,2*R*)-**Xa**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)		39/1	38 (2*S*)	75
28	(1*S*,2*R*)-**Xf**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−50)		24/1	49 (2*S*)	75
29	(*R*,*R*)-**XVa**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (25)		4/1	39 (2*S*)	79
30	(*R*,*R*)-**XVb**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (25)		10/1	75 (2*R*)	79
31	(*R*,*R*)-**XVII**/Cu(ClO$_4$)$_2$ + 3H$_2$O (10)	CH_2Cl_2 (−40)	99	97/3	96 (2*S*)	80
32	(*R*,*R*)-**XVII**/Cu(ClO$_4$)$_2$ (10)	CH_2Cl_2 (−40)	97	24/1	92	81
33	(*R*,*R*)-**XVII**/Cu(OTf)$_2$ (10)	CH_2Cl_2 (−40)	72	47/3	39	81
34	(*R*,*R*)-**XVII**(20% ee) /Cu(ClO$_4$)$_2$ + 3H$_2$O (10)	CH_2Cl_2 (−40)	96	97/3	87 (2*S*)	81
35	(1*S*,2*R*)-**IXa**/Cu(ClO$_4$)$_2$·6H$_2$O (10)	CH_2Cl_2 (−78)		99/1	98 (2*S*)	82
36	(1*S*,2*R*)-**IXa**/Cu(ClO$_4$)$_2$·6H$_2$O (10)	CH_2Cl_2 (0)	91	49/1	95 (2*S*)	82
37	(*S*,*S*)-**Va**/Cu(ClO$_4$)$_2$·6H$_2$O (10)	CH_2Cl_2 (0)	85	97/3	6 (2*S*)	82
38	(*S*,*S*)-**Vb**/Cu(ClO$_4$)$_2$·6H$_2$O (10)	CH_2Cl_2 (0)	84	97/3	41 (2*S*)	82

stereoselectivity of the Diels−Alder reaction was studied (Figure 2, Table 1, entries 14−18).[74,77] It appears that in the case of Cu(OTf)$_2$ complexes, larger bite angles resulted in higher enantioselectivity. In the series of spiro-ligands **VIIIa**−**VIIId**, the enantiomeric excess decreased from 96% to 83% as the bite angle (θ) was decreased from 97.7° to 94.9°, and bis(oxazoline) **IXb** with a bite angle of 95.4° led to 83% ee. Both bridge angle (Φ) and bite angle (θ) of the bis(oxazoline) were correlated to the complex geometry and to its distortion.[76]



VIIIa n = 1, Φ = 120.6°, θ = 97.7°
VIIIb n = 2, Φ = 115.8°, θ = 96.3°
VIIIc n = 3, Φ = 113.2°, θ = 95.7°
VIIId n = 4, Φ = 111.5°, θ = 94.9°

IXb, Φ = 112.8°, θ = 95.4°

Figure 2.

Later, Lipkowitz et al. further investigated this phenomenon by using the "computed chirality content" parameter of each complex **VIII**/Cu(OTf)$_2$. They found that the stereochemical outcome of the reaction was correlated to the ligand distortion, which was a function of the twist angle, the pucker angle, and the bite angle (in descending order of importance).[78]

Davies et al. also evaluated bis(oxazoline) ligands **IXb**−**IXf** in the cycloaddition of **18** with **33** catalyzed by Cu(OTf)$_2$ (Table 1, entries 18−24).[74] (1*S*,2*R*)-**IXb**/Cu(OTf)$_2$ (10 mol %) led to an enantiomeric excess of 82% at −50 °C, which was increased to 92% with an excellent *endo*/*exo* ratio of 130/1 by performing the reaction at −65 °C. The other catalytic systems (1*S*,2*R*)-**IXc**−**IXf**/Cu(OTf)$_2$ gave lower enantiomeric excesses ranging from 6% to 73%. With the same (1*S*,2*R*)-1-amino-2-indanol backbone as in (1*S*,2*R*)-**IXb**, only (1*S*,2*R*)-**IXg**, featuring a spiro 2,2-indenyl moiety, gave good stereocontrol in the Diels−Alder reaction with 96% ee at −65 °C and a 97/3 *endo*/*exo* ratio (Table 1, entry 25).[75] For this reason, bis(oxazoline) ligand **VId** featuring the same spiro-2,2-indenyl moiety, was prepared and evaluated, but in this case the enantiomeric excess of the *endo*-cycloadduct **47** was only 46% (Table 1, entry 26).

In their catalytic evaluation of new bis(oxazoline) ligands, Davies et al. replaced the (1*S*,2*R*)-1-amino-2-indanol chiral auxiliary with the (1*S*,2*R*)-1-amino-1,2,3,4-tetrahydro-naphthalene-2-ol.[75] However, (1*S*,2*R*)-**Xa**/Cu(OTf)$_2$ and (1*S*,2*R*)-**Xf**/Cu(OTf)$_2$ furnished only low enantioselectivities in the reaction of **18** with **33** (Table 1, entries 27 and 28).

Takacs et al. proposed several modifications of the bis(oxazoline) scaffold. Bis(oxazoline) ligands **XVa** and **XVb** were synthesized and used as ligands of Cu(OTf)$_2$.[79] With **XVa** as the ligand, *endo*-**47**was obtained in poor enantiomeric excess (39%) and with a 4/1 *endo*/*exo* ratio, whereas **XVb** gave an increased enantiomeric excess of 75% and a good *endo*/*exo*ratio (10/1) (Table 1, entries 29, 30).

Kanemasa et al. reported that bis(oxazoline) (*R*,*R*)-**XVII** was a good tridentate ligand of nickel-aqua complexes with catalytic activities in the Ni-catalyzed Diels−Alder reaction. This bis(oxazoline) also provided excellent results in the cycloaddition of **18** with **33** catalyzed by Cu(ClO$_4$)$_2$ in the presence of 3 equiv of water (relative to Cu).[80] In this case (Table 1, entry 31) *endo*-**47** was produced with 96% ee and a diastereomeric ratio of 97/3. Interestingly, a high chiral amplification was observed under these conditions. Indeed, when the enantiomeric excess of the (*R*,*R*)-**XVII** bis(oxazoline) ligand was only 20%, *endo*-**47** was produced with 96% ee. This enantiomeric excess was identical as the one obtained with the enantiomerically pure ligand (Table 1, entry 34). The supposed copper/aqua complex gave similar stereocontrol as the (*R*,*R*)-**XVII**/Cu(ClO$_4$)$_2$ system without addition of water, but in the latter case, the reaction was slowed down by a factor of 3 (Table 1, entry 32).[81] When bis(oxazoline) (*R*,*R*)-**XVII** was tested as the ligand of Cu(OTf)$_2$, the obtained enantiomeric excess for *endo*-**47** was only 39% (Table 1, entry 33).

Further studies concerning copper/aqua complexes were achieved by Ghosh et al. When (1*S*,2*R*)-**IXa**/Cu(ClO$_4$)$_2$·6H$_2$O was used as the catalyst (10 mol %) at −78 °C, an excellent enantiomeric excess of 98% was obtained with an excellent diastereomeric ratio (>99/1). Even at 0 °C, the enantioselection was still high (95% ee) (Table 1, entries 35 and 36).[82] As an extension, the use of bis(oxazoline) **Va** and **Vb** as ligands of such copper/aqua complexes were envisaged but unfortunately **Vb** gave a poor enantiomeric excess of 41%, and **Va**, reported to be one of the most efficient bis(oxazoline) ligands, led to a disappointing 6% ee (Table 1, entries 37 and 38).

The copper-catalyzed Diels−Alder reaction of dienophile **33** was also applied to other dienes. The use of cyclic dienes such as cyclohexadiene **34** or furan **11** was reported. When (*S*,*S*)-**Va**/Cu(OTf)$_2$ (10 mol %) was used with **34**, cycloadduct **35** was formed in 90% yield with 82% ee and with a 98/2 *endo*/*exo* ratio. The (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ complex allowed the isolation of *endo*-**35** in 93% ee and with a good *endo*/*exo* ratio (95/5) (Scheme 23, eq 1).[83,84]

Jørgensen et al. have shown that in this reaction, not only the counterion but also the solvent had an influence on the enantioselective outcome of the reaction.[85] Indeed (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ complex in nitromethane at 0 °C furnished *endo*-**35** in 96% ee, and an increased rate of reaction was observed with this solvent (Scheme 23, eq 1).

Evans et al. reported a concise route to *ent*-shikimic acid **52** in six steps from cycloadduct **51**. The key step in this synthesis was the cycloaddition of furan **11** with acrylimide **33**. By using (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ as the catalytic system at −78 °C in dichloromethane, the reaction proceeded with moderate diastereoselectivity (*endo*/*exo* = 8/2) but cycloadduct *endo*-**51** was obtained in 97% ee (Scheme 23, eq 2).[83] Furan, which was previously reported to be a poor diene, allowed in this case the isolation of cycloadduct *endo*-**51** in 67% yield. Interestingly, the cycloaddition of **11** with **33** appeared to be reversible. At a higher reaction temperature (−20 °C, 2.5 h), the stereoselectivity was decreased (*endo*/*exo* = 66/34; *endo*: ee = 59%), and when the reaction time was increased from 2.5 to 24 h, the diastereoselectivity was reversed (*endo*/*exo* = 1/9) and both *endo*- and *exo*-cycloadducts were obtained as racemic mixtures.

Scheme 23

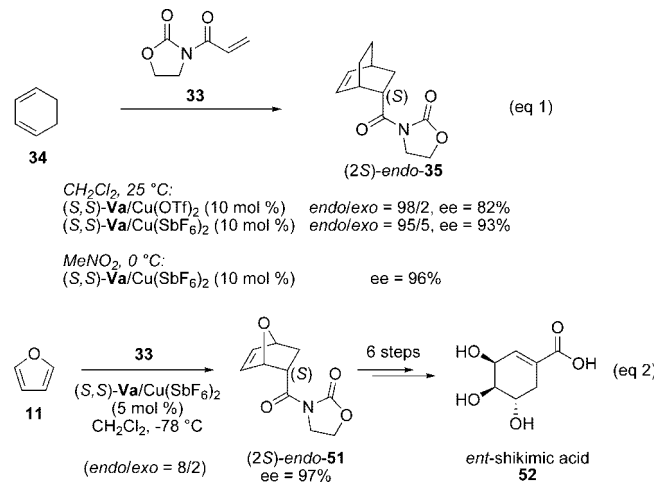
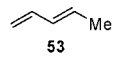
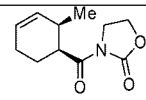
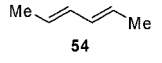
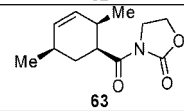
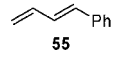
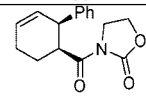
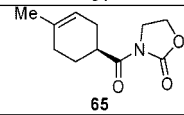
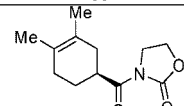
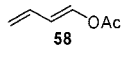
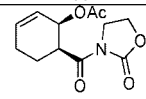
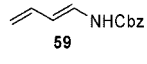
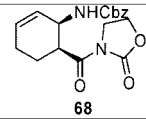
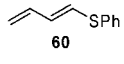
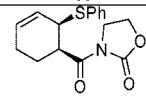
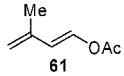
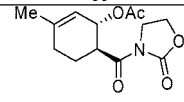


Table 2. Diels−Alder Reaction of 33 with Various Dienes Catalyzed by (*S*,*S*)-Va/Cu(SbF$_6$)$_2$ in CH$_2$Cl$_2$

entry	diene	mol % (T °C)	major cycloadduct	yield (%)	dr	ee (%)
1	 **53**	10 (25)	 **62**	89	83/17	94
2	 **54**	10 (25)	 **63**	59	77/23	93
3	 **55**	10 (25)	 **64**	95	85/15	97
4	 **56**	10 (25)	 **65**	81	-	59
5	 **57**	10 (25)	 **66**	78	-	65
6	 **58**	2 (0)	 **67**	75	85/15	96
7	 **59**	5 (0)	 **68**	54	72/28	90
8	 **60**	2 (-20)	 **69**	84	98/2	98
7	 **61**	2 (-20)	 **70**	57	73/27	98

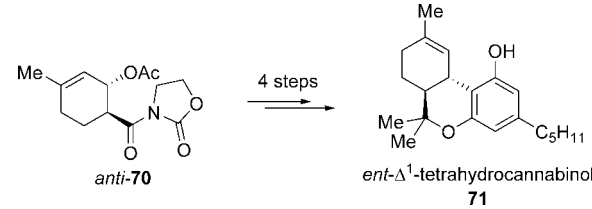
In the case of linear dienes, good to excellent stereoselectivities were obtained.[67,83,84] The Diels−Alder reaction of imide **33** with piperylene **53** catalyzed by various copper complexes using bis(oxazoline) **Va** as the ligand were studied, and the best result was obtained with catalyst (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$, which led to the synthesis of cycloadduct **62** in 94% ee and 83/17 *cis*/*trans* ratio (Table 2, entry 1).

On the basis of these results, linear dienes **54**−**61** were evaluated in the cycloaddition with **33** catalyzed by (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$. Optimal results are given in Table 2. The corresponding cycloadducts **63**−**70** were obtained in good to excellent enantiomeric excesses varying from 59% to 98% (Table 2, entries 2−7), and substituted *cis*-cyclohexenes **62**−**64** and **67**−**69** were obtained as the major products. In the case of diene **61**, cycloadduct **70** was obtained as the major product with *anti* relative stereochemistry for the substituents, which corresponds to an *exo* approach of the diene. This selectivity was explained by the authors as a result of steric hindrance generated by the methyl group at C3 on diene **61**. Cycloadduct *anti*-**70** was used as an advanced precursor of *ent*-Δ^1-tetrahydrocannabinol **71**, which was prepared in four steps from **70** (Scheme 24).[86]

Recently, Gouverneur et al. reported the Diels−Alder reaction of **33** with the silylated diene **72** catalyzed by 5 mol % of (*S*,*S*)-**Va**/Cu(OTf)$_2$.[87] Cycloadduct **73** was obtained with a 3/1 *exo*/*endo* ratio and in 89% ee for *exo*-**73**. This cycloadduct was stereoselectively fluorinated by Selectfluor leading to the fluorinated carbocycle **74** (Scheme 25).

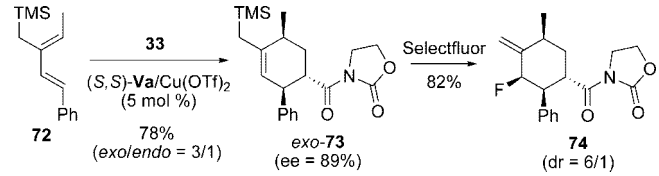
When β-substituted acryloyl-oxazolidinones were used as the dienophiles, good stereoselectivities were achieved in the

Scheme 24



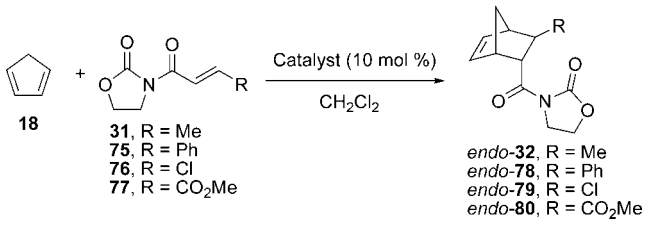
anti-**70** *ent*-Δ^1-tetrahydrocannabinol **71**

Scheme 25



Diels−Alder reaction with cyclopentadiene **18**. Evans et al. reported that (*S*,*S*)-**Va**/Cu(OTf)$_2$ and (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ catalyzed the reaction of dienophiles **31** and **75**−**77** (Scheme 26, Table 3, entries 1−8).[65,67,84] The reaction of **31** with **18** catalyzed by (*S*,*S*)-**Va**/Cu(OTf)$_2$ furnished predominantly cycloadduct *endo*-**32** with a 96/4 *endo*/*exo* ratio in 85% yield and 97% ee, while the use of catalyst (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ yielded *endo*-**32** (99%) with a 85/15 *endo*/*exo* ratio and with an excellent enantiomeric excess of 99% (Table 3, entries 1 and 2). When the cinnamoyl derivative **75** was used, the major product obtained was cycloadduct *endo*-**78**. When (*S*,*S*)-**Va**/Cu(OTf)$_2$ was used at 25 °C in CH_2Cl_2, **78** was obtained with a 9/1 *endo*/*exo* ratio in 85% yield and 90% ee for the major *endo*-adduct. By decreasing the temperature to −10 °C, the *endo*/*exo* ratio was enhanced to 93/7, but the enantiomeric excess was only raised to 94% and the yield was decreased considerably to 16% (Table 3, entries 3 and 4). In the case of catalyst (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ at 25 °C, the cycloaddition of **75** led to *endo*-**78** (*endo*/*exo* = 81/19) in good yield (96%) and in 96% ee (Table 3, entry 5). In the case of this more Lewis acidic catalyst, decreasing the temperature to −10 °C showed a mild influence on the yield as *endo*-**78** was isolated in 77% yield (*endo*/*exo* = 88/12) with a good enantiomeric excess of 98% (Table 3, entry 6). Starting with the chlorinated dienophile **76**, a low enantiomeric excess was obtained with catalyst (*S*,*S*)-**Va**/Cu(OTf)$_2$ (53%) whereas a good 96% ee was obtained with catalyst (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ at 25 °C (Table 3, entries 7 and 8). Here again, observing these results, the (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ catalyst led to increased stereoselectivities and increased yields, except in the case of fumarate derivative **77**. This may be due to the presence of the ester functionality that could interfer with the Lewis acid catalyst or to the presence of the background uncatalyzed reaction as a result of a low lying LUMO for the fumarate derivative. Compound **77** appeared to be very reactive and at −55 °C, the corresponding cycloadduct *endo*-**80** (*endo*/*exo* = 94/6) was obtained in 92% yield and 95% ee by using (*S*,*S*)-**Va**/Cu(OTf)$_2$ whereas (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ provided a lower enantiomeric excess (87%) (Table 3, entries 9 and 10).

Scheme 26



In the case of catalyst (1*S*,2*R*)-**IXa**/(CuOTf)$_2$, Ghosh et al. obtained moderate results in the reactions of dienophiles **31** and **75** (84% and 35% ee, respectively, Table 3, entries 11 and 12), but a better enantiomeric excess was obtained with dienophile **77** as cycloadduct *endo*-**80** (*endo*/*exo* = 93/7) was isolated in 75% yield and 94% ee (Table 3, entry 13).[73]

The copper/aqua complex (1*S*,2*R*)-**IXa**/Cu(ClO$_4$)$_2$·6H$_2$O appeared to be a good catalyst for the Diels−Alder reaction of imides **31** and **77**, and cycloadducts **32** and **80** were obtained with good diastereoselectivities (dr = 95/5 and 92/8) and with excellent enantiomeric excesses of 99% and 92% (Table 3, entries 14 and 15).[82]

Takacs et al. screened a series of bis(oxazoline) ligands/Cu(OTf)$_2$ to catalyze the Diels−Alder reaction of **31** with cyclopentadiene (**18**).[79,88] The use of ligands **XVa**, **XVIa**, **XIa**−**XIc**, **Vb**, **Ve**, **VIa**−**VIc**, and **XIIa**−**XIIc** led to a poor enantiomeric excess (0−34%) for *endo*-**32** obtained as the major cycloadduct and the use of bis(oxazoline) ligands **XIId**, **XVb**, and **XVIb** furnished moderate enantiomeric excesses for *endo*-**32** varying from 51% to 88% (Table 3, entries 16−18).

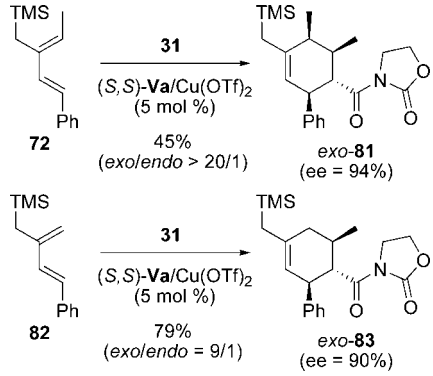
Bolm et al. have developed a new class of chiral bis(oxazoline) ligands based on a chiral 1,2-substituted cyclopentane backbone.[89] The best result in the Diels−Alder reaction of **31** with **18** was obtained with catalyst **XIVa**/Cu(OTf)$_2$, which led to **32** in 96% yield with a 77/23 *endo*/*exo* ratio and with 71% ee for *endo*-**32** (Table 3, entry 19). In the case of this ligand, no further improvement was obtained by changing the copper counterion as Cu(SbF$_6$)$_2$ or Cu(ClO$_4$)$_2$ gave similar diastereomeric ratios and lower enantiomeric excesses for *endo*-**32**.

Gouverneur et al. reported the Diels−Alder reaction of **31** with the silylated dienes **72** and **82** catalyzed by 5 mol % of (*S*,*S*)-**Ic**/Cu(OTf)$_2$.[87] Cycloadducts **81** and **83** were successfully obtained with excellent *exo* selectivities (dr = 20/1 and 9/1, respectively) and with good enantiomeric excesses of 94% and 90% (Scheme 27). These two cycloadducts were fluorinated like compound **73** to yield highly substituted fluoro carbocycles.

Table 3. Diels−Alder Reaction of 18 with Imides 31 and 75−77 Catalyzed by Bis(oxazoline)/Cu(II) Complexes

entry	dienophile	catalyst	*T* (°C)	yield (%)	*endo*/*exo*	ee (%) (*endo*)
1	**31**	(*S*,*S*)-**Va**/Cu(OTf)$_2$	−15	85	48/2	97
2	**31**	(*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$	−15	99	85/15	99
3	**75**	(*S*,*S*)-**Va**/Cu(OTf)$_2$	25	85	9/1	90
4	**75**	(*S*,*S*)-**Va**/Cu(OTf)$_2$	−10	16	93/7	94
5	**75**	(*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$	25	96	81/19	96
6	**75**	(*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$	−10	77	88/12	98
7	**76**	(*S*,*S*)-**Va**/Cu(OTf)$_2$	25	96	93/7	53
8	**76**	(*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$	25	96	87/13	96
9	**77**	(*S*,*S*)-**Va**/Cu(OTf)$_2$	−55	92	94/6	95
10	**77**	(*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$	−55	88	82/18	87
11	**31**	(1*S*,2*R*)-**IXa**/Cu(OTf)$_2$	0	77	9/1	84
12	**75**	(1*S*,2*R*)-**IXa**/Cu(OTf)$_2$	23	78	8/2	35
13	**77**	(1*S*,2*R*)-**IXa**/Cu(OTf)$_2$	−45	75	93/7	94
14	**31**	(1*S*,2*R*)-**IXa**/Cu(ClO$_4$)$_2$·6H$_2$O	−30	85	95/5	99
15	**77**	(1*S*,2*R*)-**IXa**/Cu(ClO$_4$)$_2$·6H$_2$O	−78	95	92/8	92
16	**31**	(*S*,*S*)-**XIId**/Cu(OTf)$_2$	25		13/5	51
17	**31**	(*S*,*S*)-**XVIb**/Cu(OTf)$_2$	25		88/12	88
18	**31**	(*S*,*S*)-**XVIb**/Cu(OTf)$_2$	25		89/11	72
19	**31**	(*S*,*S*)-**XIVa**/Cu(OTf)$_2$	25	96	77/23	71

Scheme 27



Evans et al. developed the use of β-substituted acryloyl-oxazolidinones **84**−**87** featuring a dienic moiety on the side chain. The asymmetric copper-catalyzed intramolecular Diels−Alder reaction of these trienes catalyzed by (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ allowed access to chiral bicycles **88**−**91** with good *endo* selectivity (Scheme 28, eq 1).[83,90] The intramolecular cycloaddition of triene **84** furnished the bicyclic compound *endo*-**88** with excellent *endo*/*exo* selectivity (>99/1) in 89% yield and 86% ee. In the case of imide **85** possessing a phenyl substituent on the dienic moiety, *endo*-**89** was obtained in 86% yield in a good 92% ee (*endo*/*exo* >95/5). It is noteworthy that in the case of **84**, catalyst (*S*,*S*)-**Va**/Cu(OTf)$_2$ displayed poor reactivity (17% conversion after 5 days). Triene **86** also led to excellent results (*endo*/*exo* >99/1), with a 96% ee and a yield of 81% for bicycle *endo*-**90**. This compound was used by Evans et al. as a precursor of (−)-isopulo'upone **92** (Scheme 28, eq 2). Finally, the use of triene **87** possessing a longer lateral chain was also possible and yielded the corresponding bicyclic compound *endo*-**91** (97%, *endo*/*exo* = 84/16) with a good enantiomeric excess of 97%.

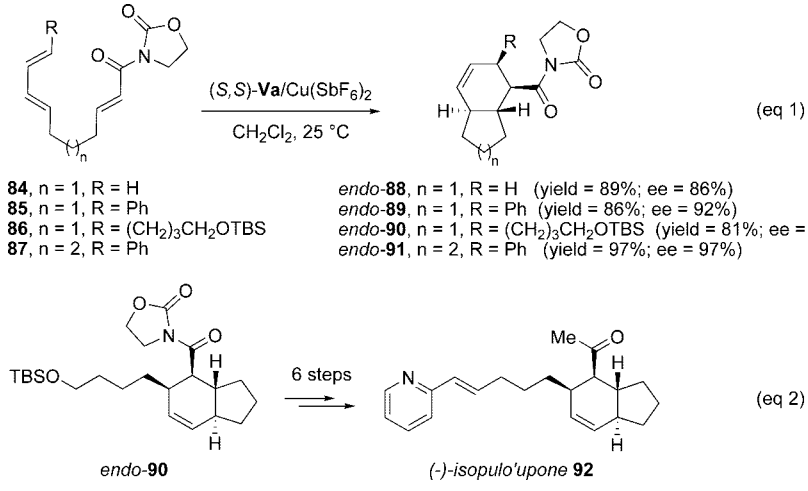
2.3.1.2. Diels−Alder Reaction with Other Dienophiles. In the context of their study and in order to increase the reactivity of β-substituted acryloyl-oxazolidinones, Evans et al. evaluated other dienophiles such as the thiazolidine-2-thiones **93**, **94**, and **95**, which are the thio-analogs of acryloyl-oxazolidinones **76**, **77**, and **78**.[65,67] It appeared that the reactivity of the thio analogues was greatly enhanced by using catalyst (*S*,*S*)-**Va**/Cu(OTf)$_2$, while (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ was poisoned by the thio-compounds leading to low catalytic turnover. The Diels−Alder reaction of **93** with **18** occurred at −45 °C and yielded *endo*-**96** (82%, *endo*/*exo* = 96/4) with a good enantiomeric excess of 94%. Dienophile **94** displayed good reactivity at −35 °C, and *endo*-**97** (86%, *endo*/*exo* = 92/8) was obtained with 97% ee, whereas the analogous dienophile **75** was nearly unreactive at−10 °C (Table 3, entry 4). The fumarate derivative **95** was very reactive, the reaction proceeded at −55 °C with only 5 mol % of (*S*,*S*)-**Va**/Cu(OTf)$_2$ yielding cycloadduct **98** (88%) as a 84/16 mixture of the *endo*/*exo* diastereoisomers (96% ee for *endo*-**98**) (Scheme 29).

Renaud et al. also studied a modification of the dienophile partner. The variation of the 4-substituent on *N*-acryloyl-1,3-benzoxazol-2-(*3H*)-ones **99**−**101** had an influence on the enantioselective outcome of the Diels−Alder reaction with **18** catalyzed by zinc, copper, and magnesium triflates.[91] In the case of Cu(OTf)$_2$ and by using the bis(oxazoline) ligand (*R*,*R*)-**Vb**, cycloadducts **102**−**104** were obtained in enantiomeric excesses increasing with the size of the 4-substituent (Scheme 30). The reaction of dienophile **99** with **18** catalyzed by (*R*,*R*)-**Vb**/Cu(OTf)$_2$ produced cycloadduct **102** in 96% yield with excellent diastereoselectivity (*endo*/*exo* = 100/1) but with low enantioselectivity (ee = 44%). A methyl group on the 4-position in **100** furnished an increased enantiomeric excess (55%) as well as with dienophile **101**, whose reaction led to 64% ee for cycloadduct **104**. The chiral relay effect of the 4-substituent in this reaction could be explained by the creation, in the dienophile/catalyst complex, of a novel element of chirality (a chiral axis), resulting in double stereoselective induction.

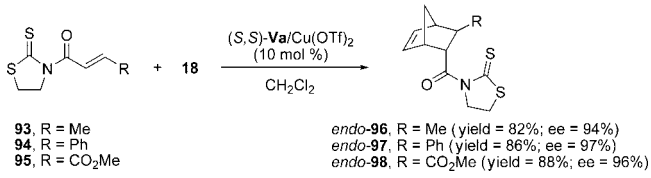
Sibi et al. have also reported that an achiral template on the acryloyl dienophile had an influence on both reactivity and selectivity of the Diels−Alder reaction. After optimization of the structure of the pyrazolidinones, they have reported that the pyrazolidinone substituents dramatically influenced the enantioselection of the reaction with **18**.[92] When dienophile **105** was reacted with **18** in the presence of 15 mol % of catalyst (*S*,*S*)-**Vc**/Cu(OTf)$_2$, the cycloaddition furnished adduct **106** (dr = 90/10) with an enantiomeric excess of 92%, whereas under the same conditions, the reaction with dienophile **31** gave a 23% ee for the corresponding cycloadduct (Scheme 31).

By comparison with the Diels−Alder reaction of oxazolidinone **33** with **18** catalyzed by (1*S*,2*R*)-**VIIIa**/Cu(OTf)$_2$, a series of achiral templates was evaluated (Scheme 32).[93] The reaction of **33** yielded, after 10 min at 0 °C, cycloadduct **47** with a 19/1 *endo*/*exo* ratio and in 88% ee (Scheme 32,

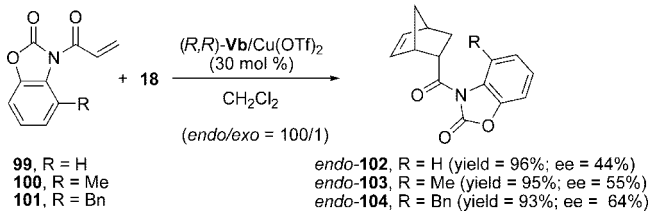
Scheme 28



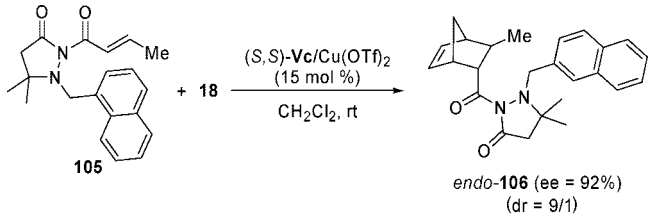
Scheme 29



Scheme 30



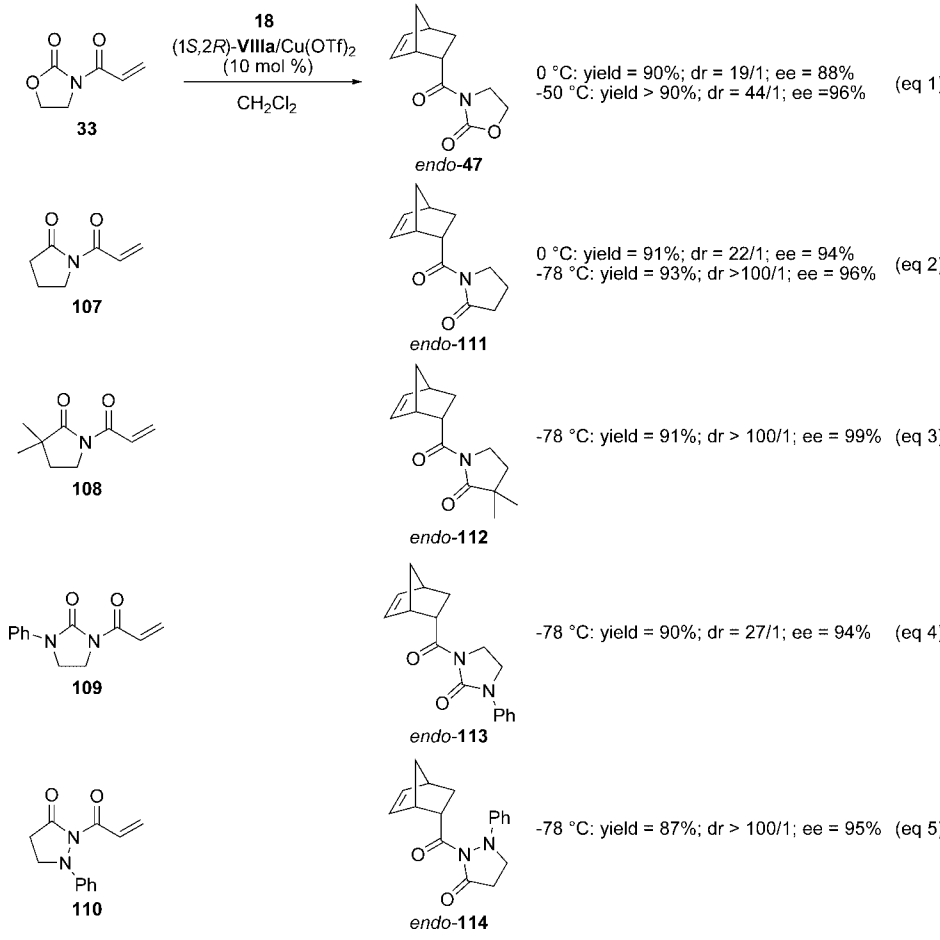
Scheme 31



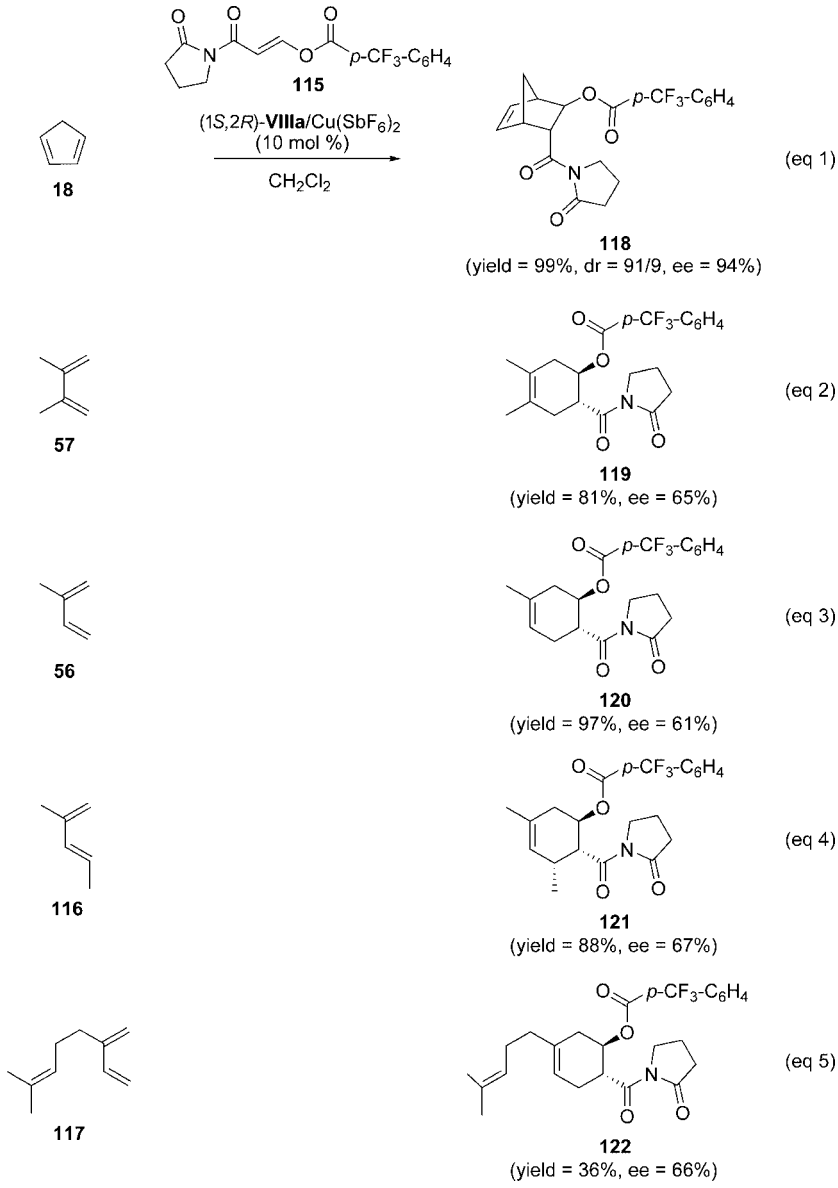
eq 1). At −50 °C, this reaction gave cycloadduct **47** with a 44/1 *endo*/*exo* ratio and with 96% ee (Table 1, entry 14).[73] When the oxygen atom of the oxazolidinone ring was replaced by a methylene group such as in dienophile **107**, after 10 min at 0 °C, the cycloaddition furnished adduct *endo*-**111** as the major product (*endo*/*exo* = 22/1) with 94% ee. At −78 °C, this reaction produced *endo*-**111** in 93% yield (*endo*/*exo* > 100/1) with 96% ee (Scheme 32, eq 2). With dienophile **108** featuring a *gem*-dimethyl group, excellent stereoselectivity was achieved (dr >100/1) and *endo*-**112** was isolated in 91% yield and 99% ee (Scheme 32, eq 3). Imidazolidinones such as **109** and pyrazolidinones such as **110** appeared to be good templates for Diels−Alder reactions with **18**. Cycloadducts **113** and **114** were obtained with good enantiomeric excesses of 94% and 95%, respectively (Scheme 32, eqs 4 and 5). In this study, the cycloaddition of crotonate derivatives also led to good enantioselectivities.

Starting from 1-acryloyl-pyrrolidin-2-one template such as in **107**, Sibi et al. developed the Diels−Alder reaction of 3-(acyloxy)acrylates, which allowed the formation of chiral hydroxy-functionalized cycloadducts in one step.[94] It is worth noting that the oxazolidinone template showed lower reactivity in this reaction. Good results were obtained in the Diels−Alder reaction of the fluoro dienophile **115** with various dienes in the presence of catalyst (1*S*,2*R*)-**VIIIa**/$Cu(SbF_6)_2$ (Scheme 33). Cycloaddition of cyclopentadiene **18** led to the formation of adduct **118** with *endo* selectivity (dr = 91/9) and with a 94% ee for the major *endo* product (Scheme 33, eq 1). With dienes **57** (Scheme 33, eq 2), **56** (Scheme 33, eq 3), and **116** and **117** (Scheme 33, eq 4 and 5), good diastereoselectivities were obtained but with modest enantiomeric excesses for the adducts **119**−**122** (61−67% ee).

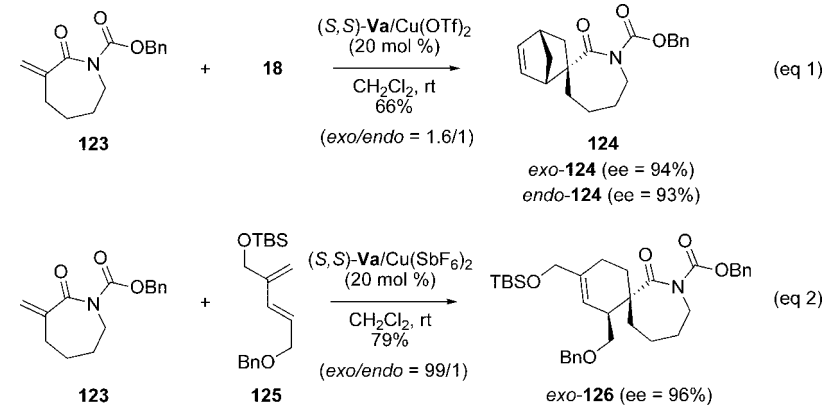
Scheme 32



Scheme 33

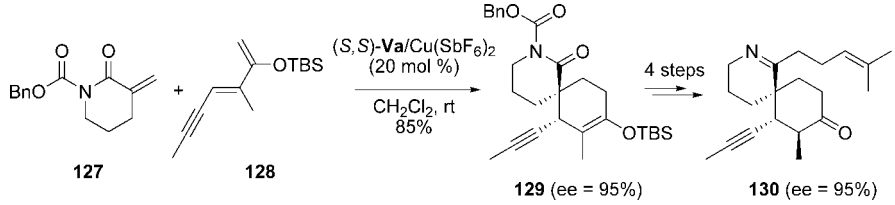


Scheme 34



Murai et al. have reported an access to the azaspiro[5,6]dodec-9-ene from cyclic imide **123**.[95] Such azaspiro compounds represent an interesting framework for the synthesis of the pinnatoxin or the pteriatoxin families. The Diels−Alder reaction of **123** with **18** catalyzed by (*S*,*S*)-**Va**/Cu(OTf)$_2$ yielded spirocyclic compound **124** (66%) with a moderate diastereoselectivity (*exo*/*endo* = 1.6/1) and good enantiomeric excesses for both cycloadducts *exo*-**124** (94%) and *endo*-**124** (93%) (Scheme 34, eq 1). The reactivity of noncyclic dienes with **123** was evaluated, and high *exo*

Scheme 35

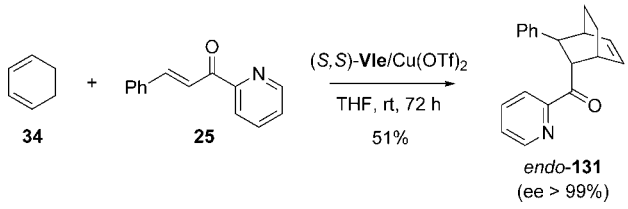


selectivities were obtained. For example, the cycloaddition of diene **125** catalyzed by (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ led to spirocycloadduct *exo*-**126** with 99/1 dr and 96% ee (Scheme 34, eq 2).

Further to this study, Romo et al. have used a six-membered cyclic imide **127** in the Diels−Alder reaction with diene **128** catalyzed by (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ to build spirolactam **129** in 85% yield as a single diastereomer in 95% ee (Scheme 35).[96] Spirolactam **129** was transformed in four steps to ketimine **130**, which can be a key intermediate for the synthesis of gymnodimine, a cytotoxic spirolide.

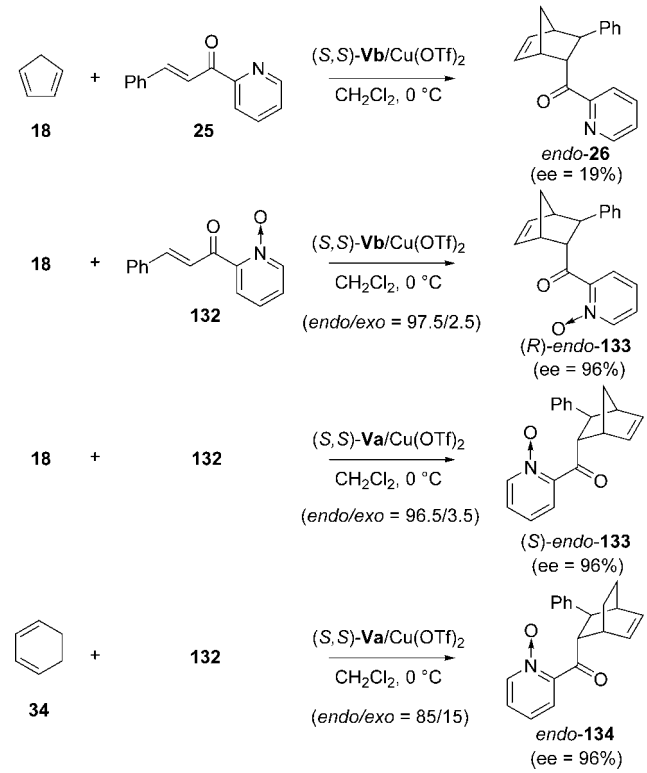
Enantioselective versions of the Diels−Alder reaction with 2-pyridyl-propenoyl dienophiles such as **25** were studied. The cycloaddition of **25**, capable of two-point binding to the Lewis acid, with cyclohexadiene **34** was catalyzed by (*S*,*S*)-**VIe**/Cu(OTf)$_2$ yielding *endo*-**131** (*exo* isomer not detected) in more than 99% ee and 51% isolated yield (78% HPLC yield) (Scheme 36).[97] CH−π Interactions and hydrogen bonding between the bis(oxazoline) ligand and the dienophile in the catalyst/dienophile complex were suspected by the authors to account for the catalytic activity. Indeed, when **VIf** or **Va** was used as the bis(oxazoline) ligand, an excellent enantiomeric excess was obtained (>99%), but poor catalytic activity led only to the formation of **131** in 4% HPLC yield after 3 days at 20 °C.

Scheme 36



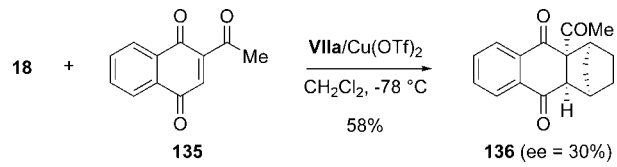
Starting from the same 2-pyridyl-propenoyl template, Pedro et al. disclosed that the Diels−Alder reaction with **18** was much more stereoselective when the pyridyl moiety was oxidized as a pyridine *N*-oxide (Scheme 37).[98] Indeed, when **25** reacted with **18** in the presence of 10 mol % of catalyst (*S*,*S*)-**Vb**/Cu(OTf)$_2$, **26** was obtained with a 86/14 *endo*/*exo* ratio, with low enantiolselectivity [ee (*R*)-*endo*-**26** = 19%; ee (*R*)-*exo*-**26** = 11%]. In contrast, when *N*-oxide **132** was used as the dienophile, the cycloaddition led to **133** with a good *endo*/*exo* ratio (97.5/2.5) and with a good enantiomeric excess [ee (*R*)-*endo*-**133** = 96%; ee (*R*)-*exo*-**133** = 81%]. When the bis(oxazoline) ligand was changed to (*S*,*S*)-**Va**, *endo*-**133** was obtained as the major cycloadduct (dr = 96.5/3.5) with reversed enantioselectivity as both (*S*)-*endo*-**133** and (*S*)-*exo*-**133** were obtained with excellent enantiomeric excesses (96% and 94%, respectively). In the case of diene **34**, the Diels−Alder reaction with **132** led to cycloadduct **134** with a 85/15 *endo*/*exo* ratio, and the *endo*-cycloadduct was produced with a 96% ee. Other dienes such as **53** and **55**−**57** were also successfully applied in this reaction and gave rise to enantiomeric excesses between 92% and 94%.

Scheme 37



In the context of their study on the Diels−Alder reaction of naphthoquinone derivatives, Brimble et al. have studied the cycloaddition of 2-acetyl-1,4-naphthoquinone (**135**) with dienes catalyzed by a series of bis(oxazoline)/Cu catalysts.[99] However, this reaction afforded a low level of enantioselection, and the best observed enantiomeric excess of 30% was obtained in the case of the cycloaddition of **18** with **135** catalyzed by **VIIa**/Cu(OTf)$_2$ (Scheme 38). Other Lewis acids furnished racemic compounds.

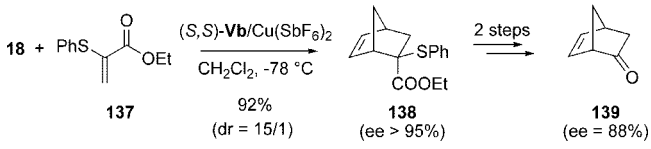
Scheme 38



In the aim of developing ketene equivalents for Diels−Alder reaction, Aggarwal et al. have introduced the use of α-thioacrylates.[100,101] The obtained thio-cycloadducts can be easily transformed to the corresponding norbornenone **139**. Moreover, these dienophiles also have the advantage of exhibiting a two-point binding mode to the Lewis acid via coordination of the α-sulfur atom. After a screening of acrylates, the best result was obtained in the reaction of thioacrylate **137** with **18** catalyzed by (*S*,*S*)-**Vb**/Cu(SbF$_6$)$_2$, and cycloadduct **138** was produced in 92% yield with a 15/1

endo/*exo* ratio and with an excellent enantiomeric excess (>95%). Other bis(oxazoline) ligands were tested in this reaction but only (*S*,*S*)-**VId**/Cu(SbF$_6$)$_2$ yielded the cycloadduct with similar levels of stereoselection. Adduct **138** (>95% ee, *endo*/*exo* = 15/1) was transformed after two steps to norbornenone **139**, which was obtained in 68% yield in only 88% ee because the *exo*-cycloadduct was transformed in this reaction to the opposite enantiomer (Scheme 39).

Scheme 39



In addition to the dienophiles possessing a two-point binding mode to the Lewis acid, more simple acryloyl derivatives were also screened in the Diels−Alder reactions of electron-rich dienes. To do so, Evans et al. have used tridentate bis(oxazolinyl)pyridine ligands **XVIIIa**−**XVIIId** that have the advantage of leaving a single vacant coordination site to the copper center upon coordination with copper(II) complexes.[84,83] As such, acrolein **140**, methacrolein **23**, and 2-bromoacrolein **141** were reacted with **18** in the presence of 5 mol % of catalyst **XVIIIa**/Cu(SbF$_6$)$_2$ leading to excellent diastereoselectivities and good enantiomeric excesses varying from 85% ee in the case of acrolein to 96% ee in the case of **141** (Scheme 40).

With acrylate dienophiles, the optimal substrate appeared to be *tert*-butyl acrylate **144** (Scheme 41). From a ligand screening (**XVIIIa**−**XVIIId**), bis(oxazolinyl)pyridine ligand **XVIIId** was found to give the highest enantioselectivities. For example, cycloadduct *endo*-**147** was obtained with high diastereoselectivity (98/2) and an enantiomeric excess of 92%.

When the reactivity of acetylenic dienophile **150** was studied in the Diels−Alder reaction with **18**, low reactivities were observed with both catalysts (*S*,*S*)-**Va**/Cu(OTf)$_2$ and (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ even at 25 °C. Furthermore, low enantiomeric excesses of 41% and 52% were obtained for the norbornadiene-derived cycloadduct **151**, respectively (Scheme 42).[67] However, the β-chloro acrylimide **76**, which is a good acetylenic surrogate, participated in a high-yielding and enantioselective Diels−Alder reaction (Table 3, entry 8). Indeed, chloro-cycloadducts such as **79** are known to be easily transformed into the corresponding substituted norbornadienes.

2.3.1.3. Heterogeneous Bis(oxazoline) Ligands. In a recent review, Lemaire et al. focused on the enantioselective reactions catalyzed by heterogeneous bis(oxazoline) ligands.[102] We present here a summary of the results that were reported in the field of asymmetric heterogeneous-bis(oxazoline) mediated copper-catalyzed Diels−Alder reactions. The aim of such heterogeneous reactions is the recycling of the chiral catalyst.

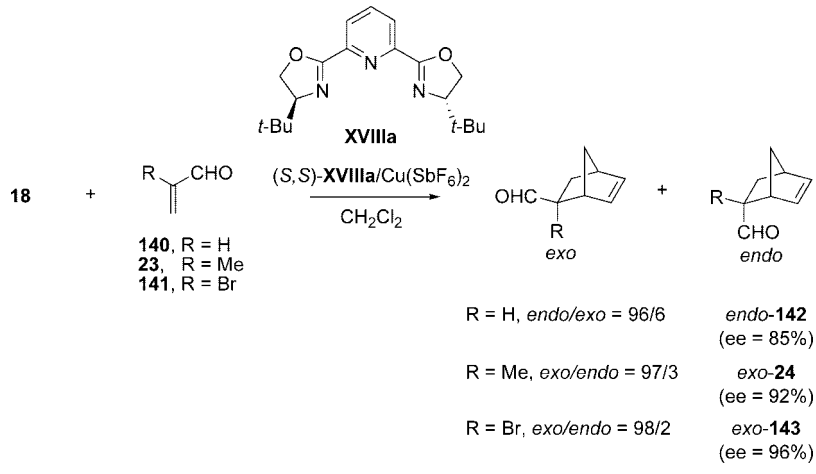
Cozzi et al. reported the use of a chiral PEG-supported bis(oxazoline) **XIX** as the copper ligand in the cycloaddition of **18** with **33**, but low enantiomeric excesses were observed probably because of a competitive coordination of the PEG oxygens to the copper center. When Cu(OTf)$_2$ was used, cycloadduct *endo*-**47** was obtained in 83% yield with 45% ee (Scheme 43).[103]

For the immobilized ligands, most of the studies were dedicated to the preparation and use of bis(oxazoline)/copper complexes immobilized on surfaces through covalent[104−110] or ionic[111,112] linkages. For instance, Lemaire et al. reported the heterogenization of bis(oxazoline) ligand (1*R*,2*S*)-**IXa** grafted on a silica surface (ligand **XX**). With Cu(ClO$_4$)$_2$·6H$_2$O as the copper source, the obtained catalyst was robust and could be recycled. A good ee of 92% was obtained for cycloadduct *endo*-**47** (*endo*/*exo* = 86/14) with this system at −78 °C in CH$_2$Cl$_2$ (Scheme 44).[105]

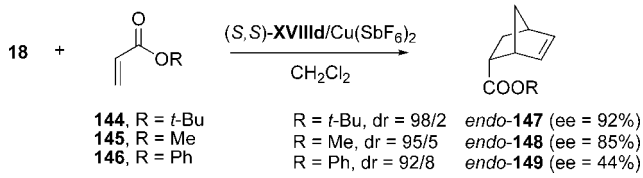
Noncovalent heterogenization of the bis(oxazoline)/copper catalyst is also possible, but the major drawback in this case is the difficulty in recycling the catalyst.[102] However, Li et al. recently reported the application of hydrogen bonding heterogeneous copper catalysts such as **XXI** in the Diels−Alder reaction of **31** with **18**.[112] Cycloadduct **32** was produced (98% conversion after 22 h) with a 9/1 *endo*/*exo* ratio and 91% ee for the *endo* adduct when 10 mol % of **XXI** was used in toluene in the presence of molecular sieves 3Å (Scheme 45). After three runs, the catalyst furnished the same stereochemical results with a slightly diminished conversion (83% after 22 h).

2.3.1.4. Diels−Alder Reaction in Ionic Liquids. Still with the aim of recycling the bis(oxazoline)/copper catalyst, ionic liquids have been used as solvents for Diels−Alder reactions. Oh et al. performed the cycloaddition of **18** with **31** catalyzed by (*S*,*S*)-**Va**/Cu(OTf)$_2$ in 1,3-dibutylimidazolium tetrafluoroborate (DiBuIm) and obtained **32** with a diastereomeric ratio of 93/7 and 92% ee for the major cycloadduct *endo*-**32**

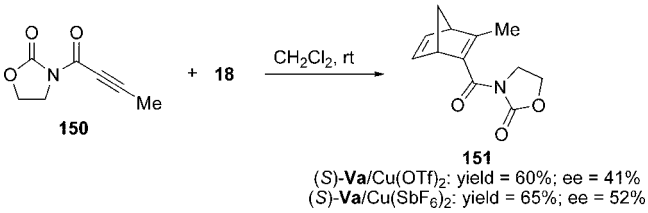
Scheme 40



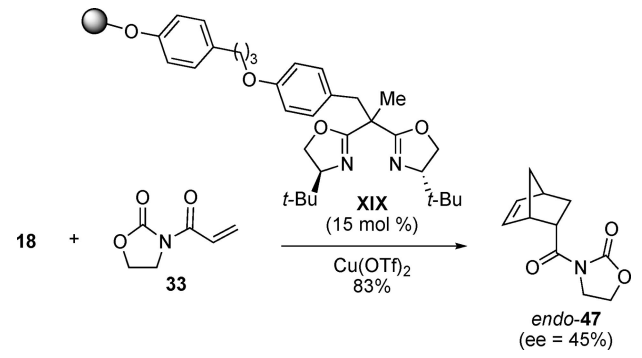
Scheme 41



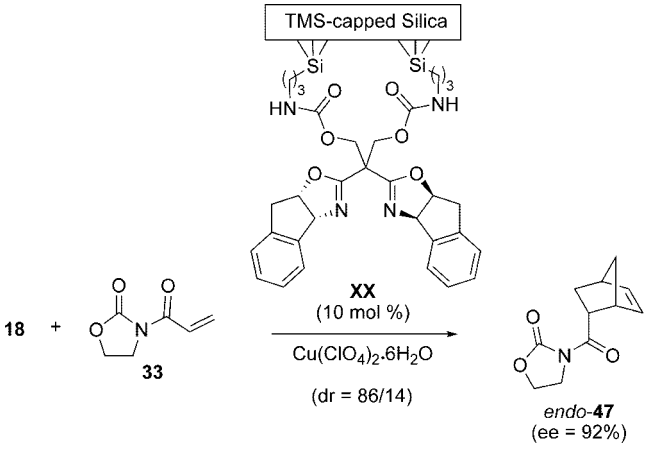
Scheme 42



Scheme 43



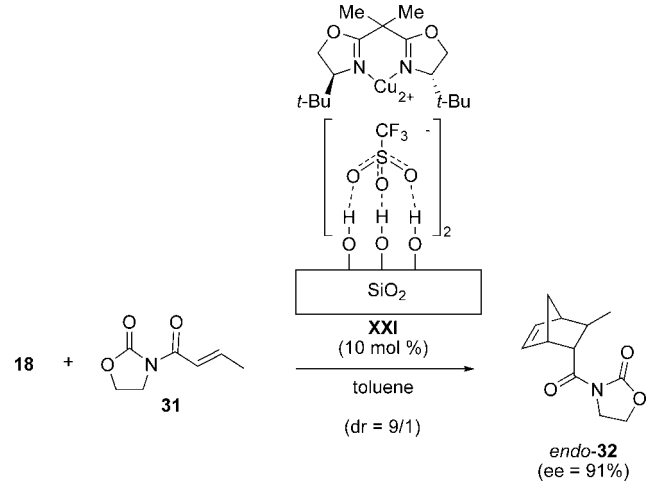
Scheme 44



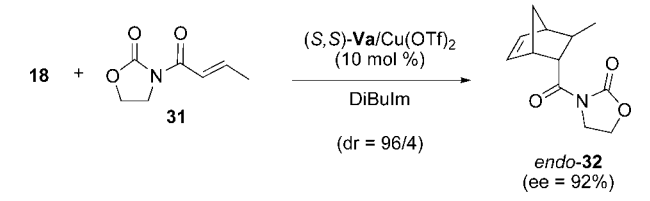
(Scheme 46).[113] It is worth noting that ionic liquids accelerated the Diels−Alder reaction with respect to the one performed in CH_2Cl_2.[67]

Recently, Kim et al. reported that the Diels−Alder reaction of **18** with **33** was efficiently catalyzed by (1*S*,2*R*)-**IXa**/$Cu(OTf)_2$ in [Bmim]SbF_6 (Bmim = 1-*N*-butyl-3-methylimidazolium) even at low catalytic loading (0.6 mol %).[114] Under these conditions, *endo*-**47** (dr = 97/3) was produced in 93% yield with an enantiomeric excess of 94% (Scheme 47). Moreover, the recycling of the [Bmim]SbF_6 containing the catalyst was possible. After four runs both the diastereomeric ratio and enantiomeric excess of the cycloaddition remained unchanged, and after the 17th run, the diastereomeric ratio was 93/7 with 84% ee for *endo*-**47**. To perform Diels−Alder reactions in ionic liquids ([emim]NTf_2) (emim = 1-ethyl-3-methylimidazolium), Doherty et al. have recently

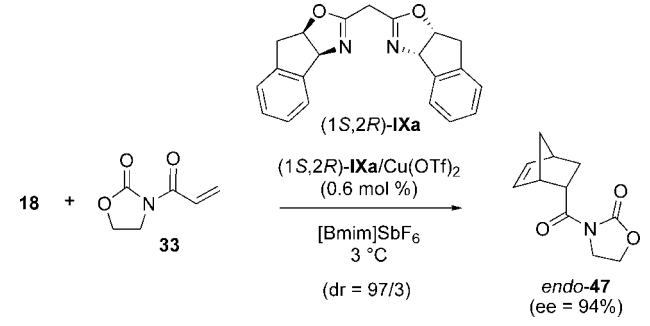
Scheme 45



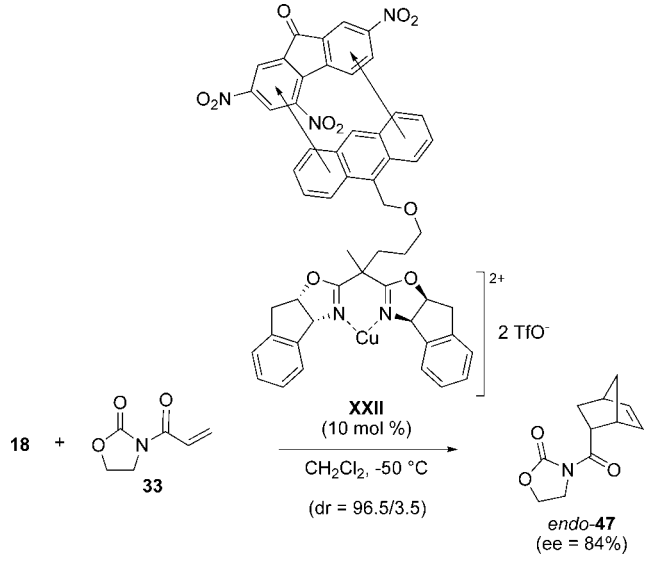
Scheme 46



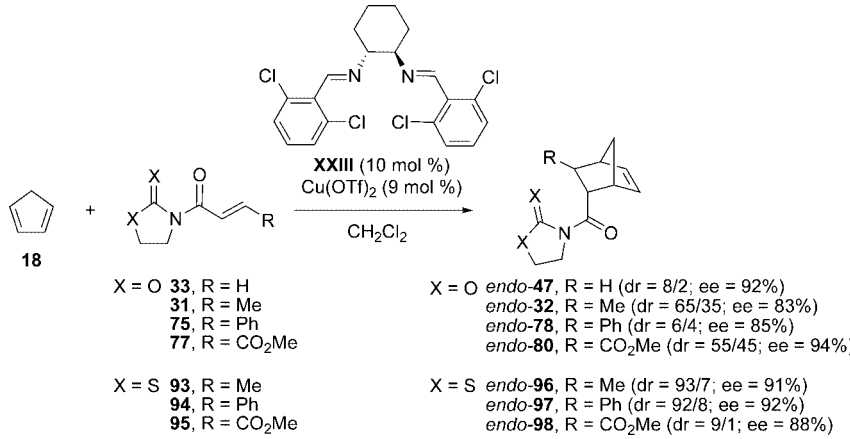
Scheme 47



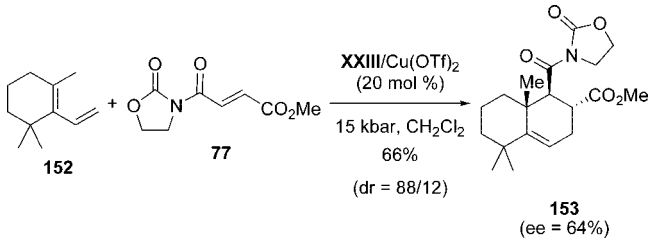
Scheme 48



Scheme 49



Scheme 50



2.3.1.5. Miscellaneous. To recycle the bis(oxazoline)/copper catalyst, Schulz et al. recently introduced a new method based on the formation of charge-transfer complexes and their subsequent precipitation.[116,117] With catalyst **XXII**, which in turn derives from (1*R*,2*S*)-**IXa**, the Diels−Alder reaction of **18** with **33** in CH_2Cl_2 at −50 °C provided cycloadduct *endo*-**47** with 84% ee (*endo*/*exo* = 96.5/3.5) (Scheme 48). The catalyst was precipitated with pentane and reused 11 times with no loss of stereoselectivity or yield.

From the examples of Section 2.3.1, it is clear that the tuning of the catalytic systems based on bis(oxazoline) ligands has allowed for the achievement of high stereoselectivities in the Diels−Alder reaction. When structural modifications were made to the bis(oxazoline), disappointing results were observed. Indeed, the use of mono-oxazoline ligands possessing a lateral chain that incorporated a nitrogen atom capable of coordination to the copper center provided low enantioselectivity.[92,118] Poor enantioselectivities were also observed when the two oxazolidinyl moieties of the bis(oxazoline) were not able to bind the same copper center because of the spacer used.[119]

Tris(oxazoline) ligands were also designed and applied in the copper-catalyzed Diels−Alder reaction, but they do not compete with the excellent enantioselectivities given by the related bis(oxazoline) ligands.[120]

2.3.2. Bis(imine) Ligands

Evans et al. were the first to apply chiral bis(imine) as ligands of copper to promote asymmetric Diels−Alder reactions.[121] After optimization of the bis(imine) substituents, **XXIII**, with a (1*R*,2*R*)-diaminocyclohexane backbone, appeared to give the best results in the cycloaddition of **18** with **33** catalyzed by $Cu(OTf)_2$ providing adduct *endo*-**47** in 92% ee (*endo*/*exo* = 8/2). Imides **31**, **75**, and **77** as the dienophiles led to good enantiomeric excesses for the corresponding cycloadducts, but with moderate diastereoselectivities. This problem was remedied through the use of the thio-dienophiles **93**−**95**, which formed cycloadducts **96**−**98** with a good *endo*/*exo* ratio (>9/1) and good enantiomeric excesses for the major *endo* products (88−92%) (Scheme 49).

Feringa et al. used this methodology for the construction of a drimane sesquiterpene precursor.[122] The Diels−Alder reaction of diene **152** with imide **77** under high pressure (15 kbar) furnished the bicyclic product **153** in 66% yield as a 88/12 mixture of diastereomers and a 64% ee for the major cycloadduct (Scheme 50).

Other more complicated bis(imine) ligands such as **XXIV**[123] or **XXV**[124] only furnished poor enantiomeric excesses (Figure 3).

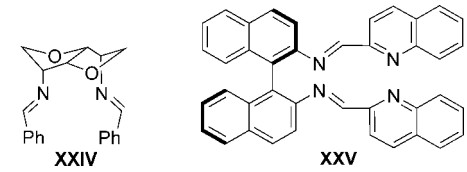


Figure 3.

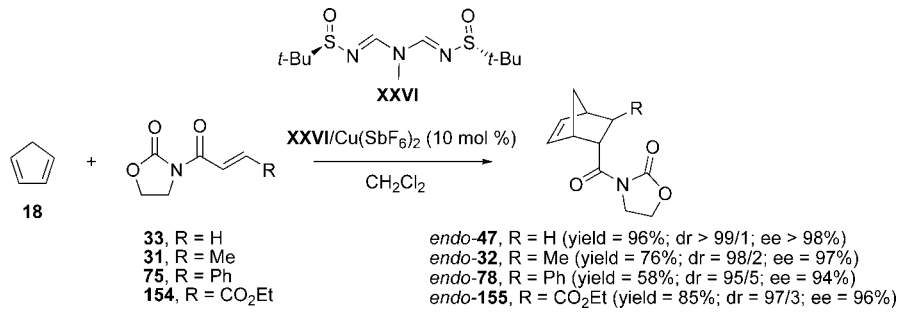
2.3.3. Organosulfur-Based Ligands

Ellman et al. developed a new C_2-symmetric bis(sulfinyl)imidoamidine ligand possessing stereogenic sulfur atoms **XXVI**.[125,126] This ligand predominantly binds copper in solution via the oxygen atom of the sulfinyl group. Ligand **XXVI** appeared to be an excellent ligand of $Cu(SbF_6)_2$ catalyzing the Diels−Alder reaction of **18** with imides **33**, **31**, **75**, and **154** with excellent enantio- and diastereoselection (Scheme 51). Cycloadduct *endo*-**47** was obtained in 96% yield with an excellent diastereomeric ratio (>99/1) and an excellent enantiomeric excess (>98%). Cycloadducts **32**, **78**, and **155** were also produced in good yields (58−85%) with high diastereomeric ratios (>95/5) and high enantiomeric excesses (>94%) (Scheme 51).

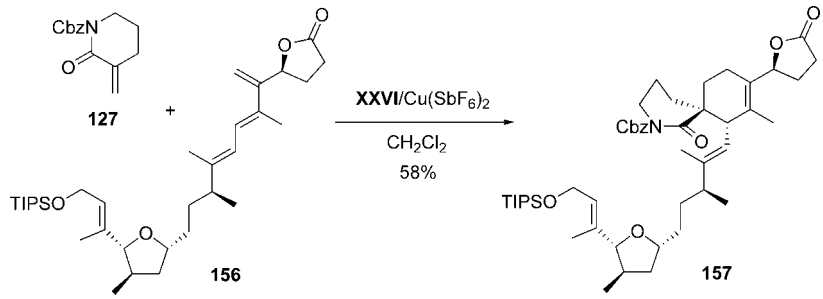
In the context of their studies on the construction of azaspiro compounds, Murai et al. reported the preparation of an azaspiro[5,5]undec-8-ene system required for the synthesis of gymnodimine.[127] The Diels−Alder reaction of cyclic imide **127** with the elaborated diene **156** catalyzed by **XXVI**/$Cu(SbF_6)_2$ produced the azaspirocyclic compound **157** in 58% corrected yield as a single diastereoisomer, whereas an approach to this fragment applying a bis(oxazoline) as the copper ligand appeared to be ineffective (Scheme 52).

Bolm et al. developed a class of bis(sulfoximine) ligands with stereogenic sulfur atoms for the copper-catalyzed

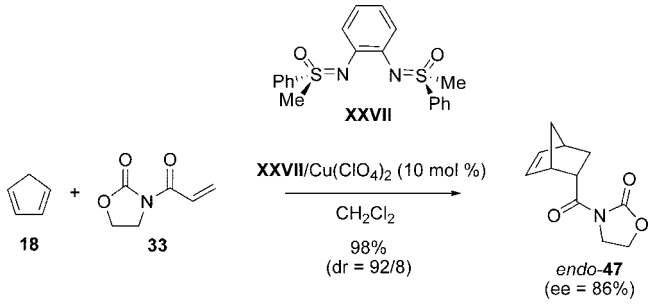
Scheme 51



Scheme 52



Scheme 53



Diels−Alder reaction.[128] From spectroscopic investigations, it was shown that these ligands binded to the copper center via the sulfoximine nitrogens.[129,130] The best catalytic system was found to be **XXVII**/$Cu(ClO_4)_2$, promoting the reaction of **18** with imide **33** to yield cycloadduct *endo*-**47** as the major product (98% yield, 92/8 dr) in 86% ee (Scheme 53).

Sulfoxide-oxazoline ligands were also studied as ligands of copper in the Diels−Alder reaction of **18** with **33** by Hiroi et al., but they led to poor enantioselectivity with a maximum 66% ee and 94/6 diastereoselectivity when **XXVIII**/$Cu(SbF_6)_2$ was used as the catalyst (Figure 4).[131]

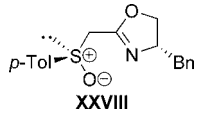


Figure 4.

2.3.4. Bifunctional Organophosphorous Ligands

P,*N* and *P*,*S* ligands are versatile ligands for asymmetric catalysis, and their use was envisaged as ligands of copper to promote Diels−Alder reactions. Helmchen et al. reported that (phosphino-oxazoline)/copper(II) complexes such as **XXIX**/$Cu(OTf)_2$ were able to catalyze this reaction.[132] Cycloaddition of **18** with dienophile **33** provided adduct *endo*-**47** as the major diastereoisomer (92% yield, 94/6 dr) with an excellent enantiomeric excess of 97%. With imides **31** or **154** as the dienophiles, lower diastereoselectivities were observed (88/12 and 6/4, respectively), as well as lower enantiomeric excesses of 86% for *endo*-**32** and 75% for *endo*-**155** (Scheme 54).

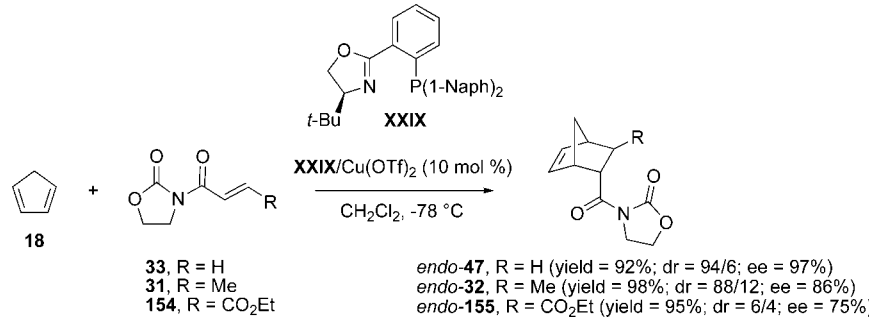
Later, Yamakuchi et al. reported the synthesis of sterically congested phosphino-thiazolines as illustrated by **XXX**.[133] When **XXX** was used as ligand of $Cu(OTf)_2$ in the Diels−Alder reaction of **33** with **18**, an enantiomeric excess of 92% was obtained for the major adduct *endo*-**47** (*endo*/*exo* = 97/3). Buono et al. reported the use of a diazaphospholidine-quinoline compound as a ligand of copper in the Diels−Alder reaction of imide **33**.[134] Ligand **XXXI** features the chirality on both the phosphorus atom and on the C_1-diamine linked to the phosphorus center. Catalyst **XXXI**/$Cu(OTf)_2$ produced cycloadduct *endo*-**47** with high diastereoselection (*endo*/*exo* >98/2) and with an excellent enantiomeric excess (>99%). A phosphino-sulfenylferrocene ligand **XXXII** was applied by Carretero et al. in the reaction of imide **33** with **18**, but even if catalyst **XXXII**/$Cu(BF_4)_2$ gave a high diastereomeric ratio (99/1), the reaction only provided **47** with a moderate enantiomeric excess of 54% (Scheme 55).[135]

2.3.5. Miscellaneous Nitrogen-Containing Ligands

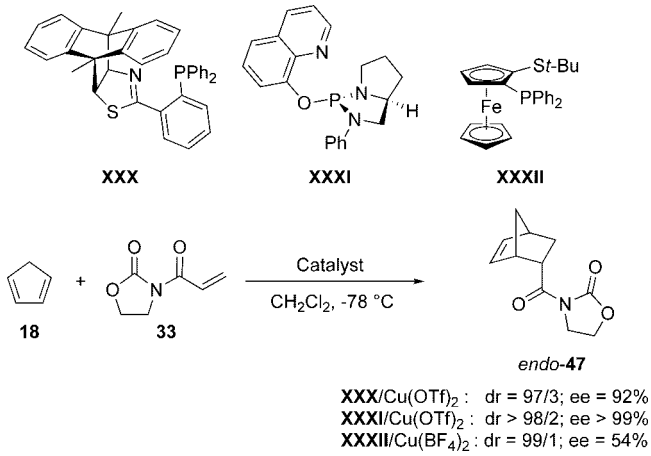
Fernández et al. developed a new class of C_2-symmetric bis(hydrazone) ligands, from which **XXXIII** was shown to be a good ligand of $Cu(OTf)_2$ in the Diels−Alder reaction of dienophile **33** with various dienes (Scheme 56).[136] The reaction with **18** provided adduct *endo*-**47** with a diastereomeric ratio of 98/2 and an enantiomeric excess of 95% (Scheme 56, eq 1). When dienes **34**, **56**, and **57** were involved in the cycloaddition with **33**, adducts **35**, **65**, and **66** were isolated in good yields, with high diastereoselectivity and good enantiomeric excesses varying from 84% to 92% (Scheme 56, eq 2−4). With furan **11** as the diene, a 87/13 dr was obtained and cycloadduct *endo*-**51** was produced with a high enantiomeric excess of 96% (Scheme 56, eq 5).

A class of amino-alcohol-derived dihydropyrazole was developed by Sibi et al. and applied to the Diels−Alder

Scheme 54



Scheme 55



reaction.[137] For example, **XXXIV**/Cu(OTf)$_2$ (Figure 5) catalyzed the cycloaddition of **18** with **33** yielding **47** with moderate diastereoselectivity (*endo*/*exo* = 2.4/1) and an enantiomeric excess of 92% for the *endo* product. These bifunctional compounds were revealed to be better ligands of zinc, leading to increased enantioselectivities in this cycloaddition.

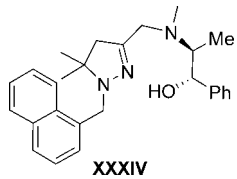


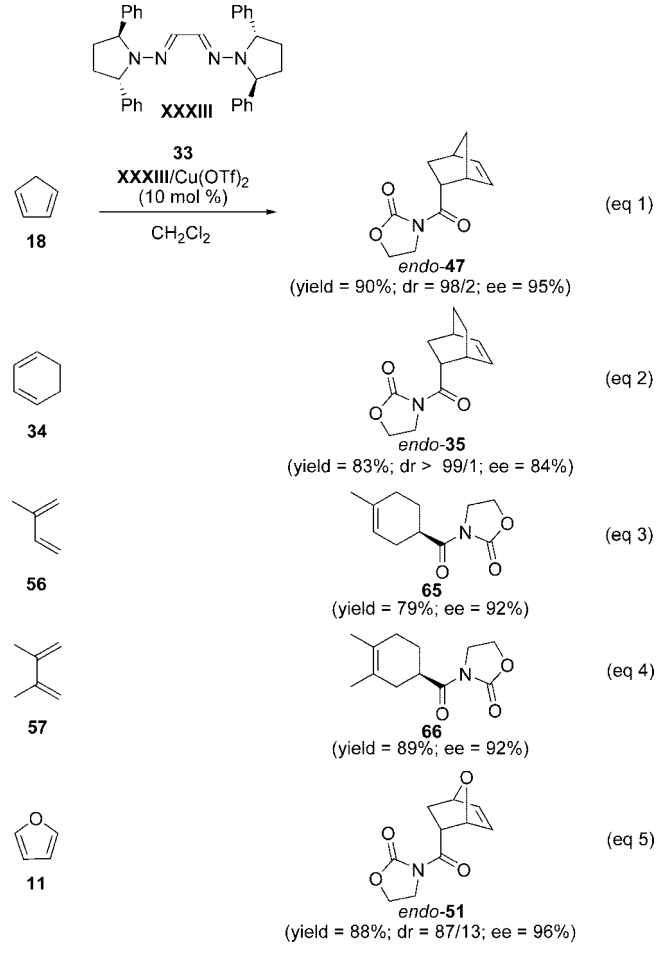
Figure 5.

As mentioned previously (vide supra), Engberts et al. reported the beneficial role of water in the copper-catalyzed Diels−Alder reaction and they also devised an enantioselective version of the this reaction.[138,139] To do so, they screened a series of amino acids as ligand of copper(II) in the reaction of **18** with **25**. Interestingly, amino acids featuring an aromatic group allowed the isolation of *endo*-**26** as the major product (dr >9/1) with enantiomeric excesses varying from 17% to 74%. For example, *N*-methyl-L-tryptophan (L-abrine) and *N*-methyl-L-tyrosine (**XXXV**) led to a 74% ee, and the authors proposed that the enantioselectivity could be attributed to the folding back of the aromatic side-chain of the amino acid and $\pi-\pi$ interactions with the dienophile (see complex **B**, Scheme 57). Such interactions would result in the shielding of one face of the dienophile from attack by **18**.

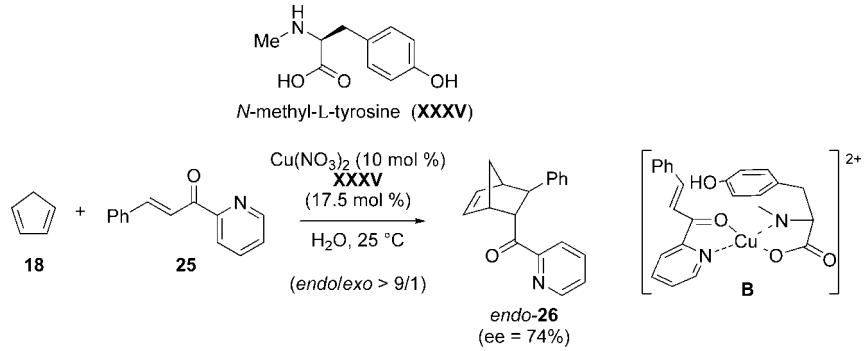
Adding to this pioneering work, Ishihara et al. optimized the catalyst's structure and reported the highly stereoselective Diels−Alder reaction of imide **158** with **18** in MeCN catalyzed by **XXXVI**/Cu(OTf)$_2$ to produce cycloadduct **159** with high diastereoselection (dr = 99/1) and 98% ee for *endo*-**159** (Scheme 58).[140] This catalytic system was also successfully applied in Diels−Alder reactions of **158** with other dienes. To account for the high stereoselectivity of this system, the authors proposed transition state **C** in which a copper(II) cation$-\pi$ interaction occurs between the aromatic system of the chiral ligand and the copper center. Such interaction was previously reported by Helm et al. in the crystal structure of the bis(L-tyrosinato)/Cu(II) complex.[141]

Recently, Feringa et al. demonstrated that it was possible to transfer the chirality of DNA to a copper-catalyzed Diels−Alder reaction by positioning an achiral ligand between the DNA double helix and the copper(II) center.[142] An optimization of the achiral ligand used to connect both DNA and copper(II) led to 99/1 *endo*/*exo* selectivity in the

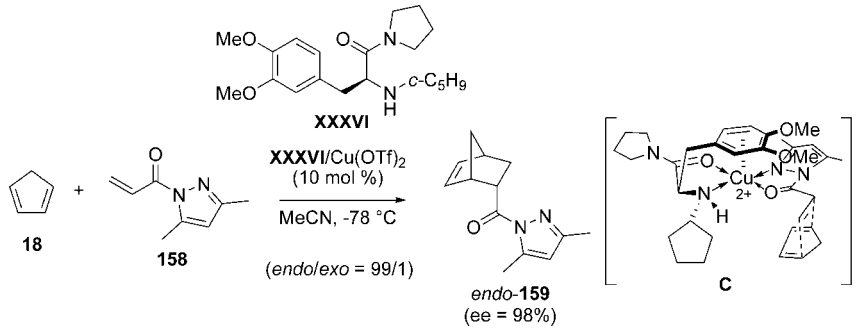
Scheme 56



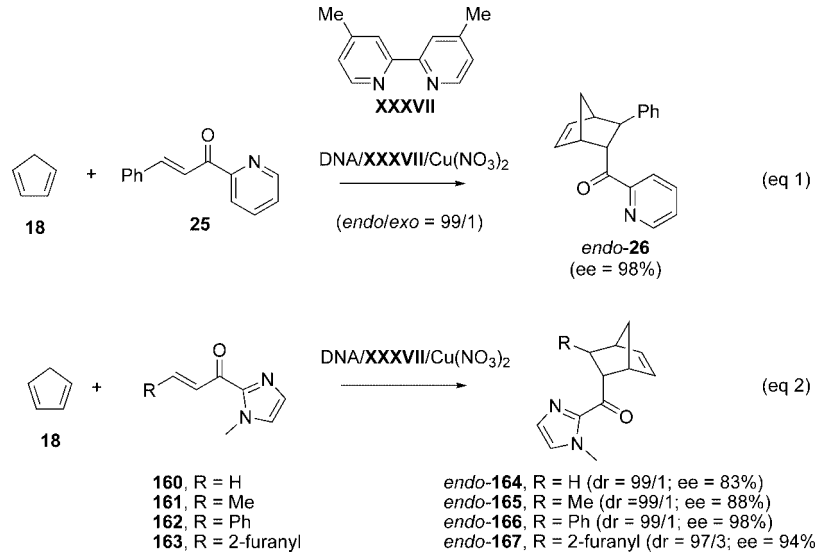
Scheme 57



Scheme 58



Scheme 59



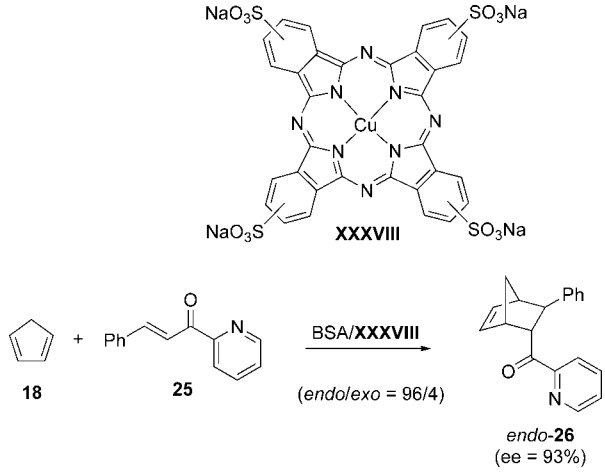
cycloaddition of **18** with **25** catalyzed by DNA/**XXXVII**/$Cu(NO_3)_2$ with an excellent enantiomeric excess of 98% for *endo*-**26**.[143] Very recently, by tuning both the achiral ligand and the dienophile template, good enantioselectivities (83−98% ee) and excellent diastereoselectivities (99/1) were obtained in the DNA-mediated Diels−Alder reaction of **18** with **160**−**163** (Scheme 59).[144]

Finally, Reetz et al. also reported recently a bioinspired Diels−Alder reaction catalyzed by a catalytic system composed of the water-soluble phthalocyanine/copper complex **XXXVIII** and the protein BSA (bovine serum albumine).[145] For example, this system catalyzed the cycloaddition of **18** with **25** to produce *endo*-**26** as the major product (dr = 96/4) in 93% ee (Scheme 60).

3. Hetero-Diels−Alder Reactions

During the past decade, the hetero-Diels−Alder (HDA) reaction has been the subject of intense research that has resulted in the synthesis of numerous heterocyclic compounds and in the introduction of efficient catalysts. Different metal catalysts have been used to perform hetero-Diels−Alder reactions, and great progress has been achieved in developing catalysts that perform enantioselective reactions with unactivated and activated heteroatomic compounds (carbonyl, imine, aza, thia, etc. compounds). The enantioselectivity of these reactions is often affected by chiral ligands, and the most common ligands used to obtain heterocyclic adducts in high enantioselectivity, as in the carbo Diels−Alder reaction, include C_2-symmetric bis(oxazolines).[60,63,146] The

Scheme 60

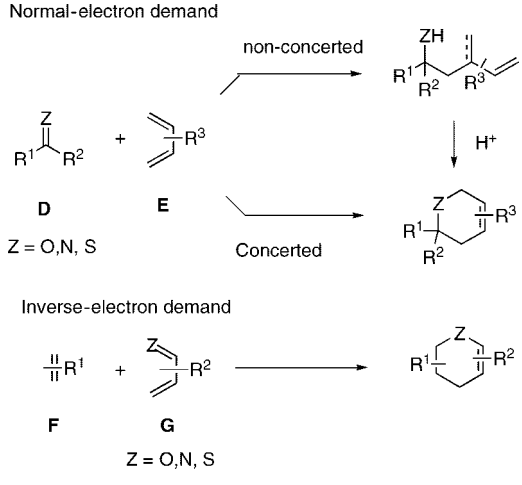


hetero-Diels−Alder field has been reported in recent reviews.[147–149]

There are two types of hetero-Diels−Alder reactions: the normal-electron cycloaddition and the inverse-electron demand cycloaddition that can be catalyzed by copper catalysts. For the normal-electron demand hetero-Diels−Alder reactions, compounds of type **D** containing the heteroatom react with conjugated 1,3-dienes of type **E**, and in order to drive the reaction, either pressure or a catalyst is needed. In general, for normal-electron demand hetero-Diels−Alder reactions, the LUMOs of compounds of type **D** interact with the HOMOs of the dienes. The activation of compounds of type **D**, by the coordination of the heteroatom with a Lewis acid, lowers the energy of the LUMOs and HOMOs of compounds of type **D**, and better interactions with dienes of type **E** can take place.

The inverse-electron demand hetero-Diels−Alder reaction is achieved with dienes of type **G** containing a heteroatom. These dienes can react with electron-rich alkenes of type **F**. The reaction is controlled by the LUMOs of compounds of type **G** that interact with the HOMOs of alkenes of type **F**. This reaction can also be catalyzed by Lewis acid. The catalytic properties of the Lewis acid for inverse-electron demand hetero-Diels−Alder reactions are due to the coordination of the Lewis acid to a heteroatom of the 1,3-diene, leading to a decrease of the energy of the LUMOs and HOMOs of the dienes; thus, a more favorable interaction with electron-rich alkenes can take place (Scheme 61).

Scheme 61



The mechanism of the hetero-Diels−Alder reaction is determined by several factors such as the nature of the catalyst, the solvent, and the structural features of the reactants. These factors affect the stereochemical outcome of the reaction. Compared to the normal Diels−Alder reaction, very few theoretical calculations have been published, and there are even fewer on Lewis acid catalyzed hetero-Diels−Alder reactions.[68,150] We have to point out that two mechanisms can operate for metal-catalyzed hetero-Diels−Alder reactions, either a stepwise mechanism or a concerted nonsynchronous mechanism, involving in many cases an unsymmetrical transition state.

One factor that can affect the diastereoselectivity of the hetero-Diels−Alder reaction is the presence of a Lewis acid. For example, in the case of aldehydes, the uncatalyzed reaction displays *endo*-selectivity for the carbonyl substituent.[151] When the reaction is performed in the presence of a Lewis acid catalyst, the Lewis acid is oriented *trans* to the carbonyl substituent and the modest *endo* selectivity observed is probably the result of the preference for the solvated Lewis acid to be *exo* because of its size.[152] It is worth noting that the configuration of the diene in the ground state does not have to be the same as that of the reacting diene.[153] For example, the four different approaches for the hetero-Diels−Alder reaction of a β,γ-unsaturated α-ketoester with a vinyl ether lead to four diastereomers, as the β,γ-unsaturated α-ketoester can be in both the *E*- and *Z*-configuration. These four possibilities are reported in Scheme 62. The *cis*-adduct can come from either the *endo-E-syn* or *exo-Z-syn* orientation and the *trans*-adduct can come from either the *exo-E-anti* or the *endo-Z-anti* orientation.

3.1. Oxa-Diels−Alder Reaction

The hetero-Diels−Alder reaction between aldehydes or ketones with 1,3-dienes is an elegant access to dihydropyrans that can be transformed into carbohydrates or included in the synthesis of natural products.[2c,154,155] In hetero-Diels−Alder reactions, carbonyl compounds have limited reactivity because only electron-deficient carbonyl can react with 1,3-dienes possessing electron-donating groups. However, when a Lewis acid or high pressure are used, hetero-Diels−Alder adducts can be obtained in good yields.

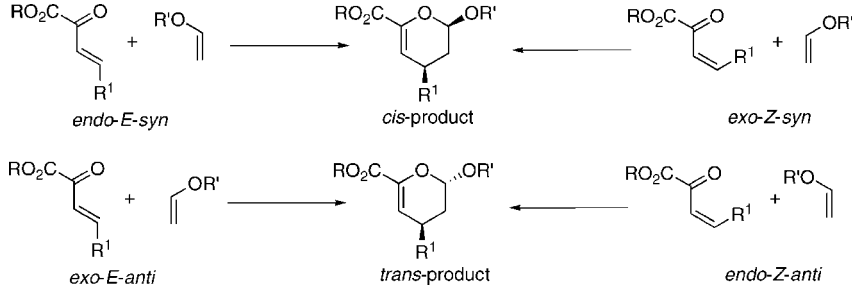
When the oxa-Diels−Alder reaction is catalyzed by a Lewis acid, two mechanistic pathways have to be taken into consideration for the formation of the hetero-Diels−Alder cycloadducts as these compounds can be formed through the traditional Diels−Alder cycloaddition pathway or through a Mukaiyama-aldol reaction followed by an acidic workup (Scheme 63).

The reaction pathway depends on the reactant as well as on the Lewis acid complex. Depending on the Lewis acid used, the reaction can proceed through a stepwise mechanism or a concerted mechanism. Furthermore, when the diene contains an allylic C−H bond, a hetero-Diels−Alder as well as an ene reaction can take place.

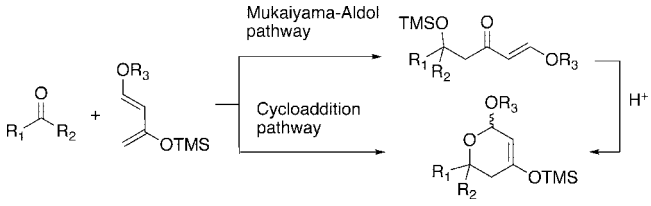
3.1.1. Oxygenated Dienophiles

3.1.1.1. Aldehydes. The majority of the recent work dealing with hetero-Diels−Alder reaction involving aldehydes has concentrated on asymmetric catalysis. In 1995, Jørgensen et al.[156] demonstrated that chiral C_2-symmetric bis(oxazoline)/Cu(II) complexes were efficient catalysts for hetero-Diels−Alder reaction of alkyl glyoxylates with

Scheme 62



Scheme 63



1,3-dienes to produce hetero-Diels−Alder adducts and ene compounds in high yields, with excellent enantiomeric excesses. The hetero-Diels−Alder adduct/ene product ratio depends on the chiral ligands bound to copper. For example, the reaction of methyl glyoxylate **168a** with 2,3-dimethylbutadiene **57** in the presence of (*S*,*S*)-**Va**/Cu(OTf)$_2$ or (*R*,*R*)-**Vb**/Cu(OTf)$_2$ catalyst at 20 °C led to hetero-Diels−Alder adduct **169** and ene adduct **170** in a ratio of 1.0/0.6 to 1.0/1.8 (Scheme 64).

It is surprising that the absolute configuration of the stereogenic center in product **169** remained (*S*) by utilizing either catalyst (*S*,*S*)-**Va**/Cu(OTf)$_2$ or catalyst (*R*,*R*)-**Vb**/Cu(OTf)$_2$. More experiments were necessary in order to rationalize these results (vide infra).

A diverse array of substituted noncyclic and cyclic conjugated 1,3-dienes can be involved in hetero-Diels−Alder reactions with alkyl glyoxylates.[156] In the case of noncyclic substituted dienes, when the hetero-Diels−Alder reaction is catalyzed by complexes of type **V**/Cu(II), the hetero-Diels−Alder adducts were obtained in modest yields, with good enantiomeric excesses and were in general accompanied by ene-adducts. In contrast, in the case of cyclic 1,3-dienes such as 1,3-cyclohexadienes, the ene-adducts were not observed and the yields of the hetero-Diels−Alder adducts were good (Scheme 65).[156] As a result, most of the studies of oxa-Diels−Alder reactions involve 1,3-cyclohexadiene (**34**).

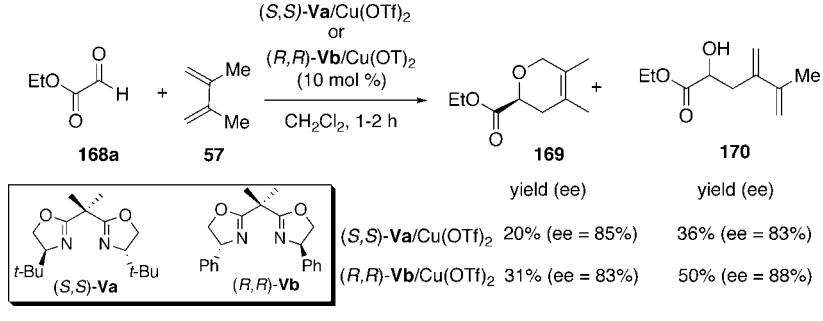
In the oxa-Diels−Alder reaction, both the counter-anion of the catalyst and the solvent influence the reaction.[157,158] The rate of the reaction as well as the enantioselectivity depend on these two factors. The use of polar solvents such as acetonitrile or 2-nitropropane led to significant improvements in the catalytic properties of the cationic copper-Lewis acid involved in the hetero-Diels−Alder reaction of alkyl glyoxylates with dienes. For example, for the oxa-Diels−Alder reaction between ethyl glyoxylate **168a** and 1,3-cyclohexadiene (**34**), it was observed that the use of CH_3NO_2 as the solvent enhances the reactivity of the (*S*,*S*)-**Va**/Cu(OTf)$_2$ catalyst compared to the reactivity of the same catalyst in CH_2Cl_2. It is worth noting that changing the counter-anion of the catalyst from TfO^-[(*S*,*S*)-**Va**/Cu(OTf)$_2$] to SbF_6^-[(*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$] leads to an increase of the reaction rate (Scheme 66). However, the enantiomeric excess is the lowest found (93%), whereas for all the other combinations, the enantiomeric excess is up to 97% (Scheme 66). It has been rationalized that the reactive **Va**/Cu(II) catalyst is a dicationic species. The dissociation of the two counter-ions from copper is necessary to activate the catalyst, and more polar solvents stabilize the dissociated ligand/copper cations.

It has been observed that the absolute configuration of the hetero-Diels−Alder adduct obtained from ethyl glyoxylate **168a** and 1,3-cyclohexadiene (**34**), in the presence of the chiral (*R*,*R*)-**Vb**/Cu(OTf)$_2$, depends on the nature of the solvent.[157] A linear relationship between the enantiomeric excess and the dielectric constant of the solvent was observed; however, the enantiomeric excess of the adduct obtained with the chiral complex (*R*,*R*)-**Va**/Cu(OTf)$_2$ is independent of the nature of the solvent (Scheme 67, Table 4).[158]

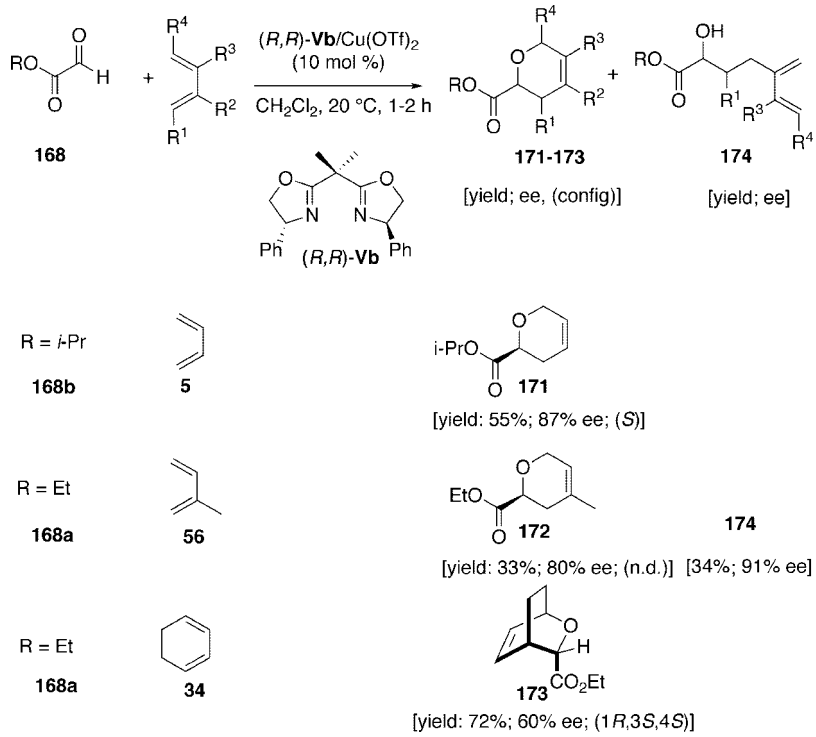
On the basis of the experimental results, X-ray diffraction, and ab initio calculations, it has been suggested that among the 17-, 19-, and 21-electron bis(oxazoline)/Cu(II)/substrate complexes, the 17-electron complex is the most stable and the most reactive (Figure 6).[68]

It seems that the reactive 17-electron **Va**/Cu(II) and **Vb**/Cu(II) complexes probably exist in conformations between a static square-planar and a tetrahedral intermediate (Figure 7). The flexibility and dynamics of the ligands are important as a result of the ability of the substituents to rock between a pseudoaxial and a pseudoequatorial position. According to Jørgensen et al. the same absolute configuration for the

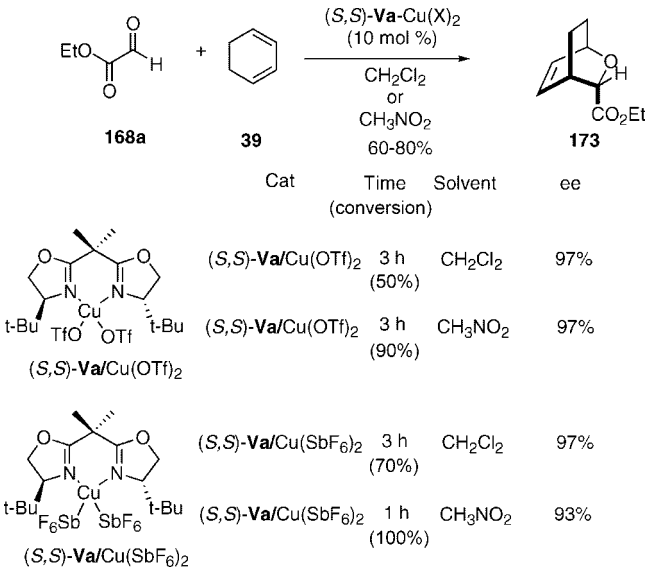
Scheme 64



Scheme 65



Scheme 66



stereogenic centers in the obtained hetero-Diels−Alder products, when changing from the (*S*,*S*)-**Va**/Cu(II) to the (*R*,*R*)-**Vb**/Cu(II) system, is caused by a steric geometrical change that allows the diene to approach on the same face of the carbonyl (Figure 7).[68]

A wide range of ligands can be used to perform hetero-Diels−Alder reactions between ethyl glyoxylate **168a** and 1,3-cyclohexadiene (**34**). In general, the C_2-symmetric ligands give better enantiomeric excesses than the unsymmetrical ligands. It is worth noting that the replacement of $Cu(OTf)_2$ by $Cu(SbF_6)_2$, $Cu(PF_6)_2$, or $Cu(ClO_4)_2$ does not modify the *endo*/*exo* ratio, the yield, or the enantiomeric excess of the hetero-Diels−Alder adducts.[160−163] Some examples are reported in Scheme 68.

The hetero-Diels−Alder reaction between alkyl glyoxylates and substituted 1,3-cyclohexadiene **175** has been used to synthesize (*R*)-dihydroactinidiolide, a major component of the pheromone for red fire ant colonies (*Soleneopsis invicta*).[157,164] The hetero-Diels−Alder reaction of ethyl glyoxylate **168a** with 2,6,6-trimethyl-1,3-cyclohexadiene (**175**) in the presence of (*S*,*S*)-**Va**/$Cu(SbF_6)_2$ led to **176** with very high regio-, diastereo-, and enantioselectivity. After saponification of **176** and treatment with HCl, the bicyclic lactone **178** was produced with an enantiomeric excess of 95% via intermediate **177** and was then transformed into the natural lactone, (*R*)-dihydroactinidiolide (Scheme 69).

It seems that the catalytic enantioselective formation of bicyclic lactones of type **178** works only with 1,3-cyclohexadiene derivatives and alkyl glyoxylate. With 1,3-cyclopentadiene derivatives, compounds resulting from an ene reaction are produced.[165]

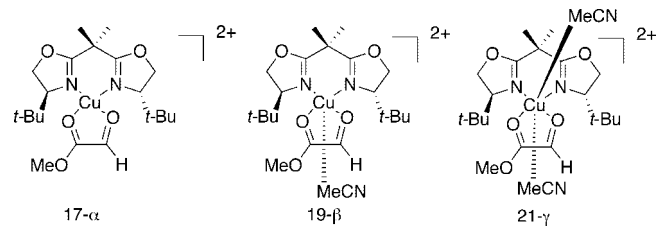


Figure 6. Calculated (ab initio) minimum energy geometries for 17-, 19-, and 21-electron species with [(*S*,*S*)-**Va**/Cu(II)-(methyl glyoxylate)] coordinated to zero, one, and two MeCN molecules.

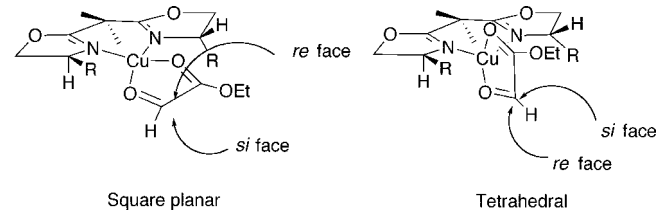
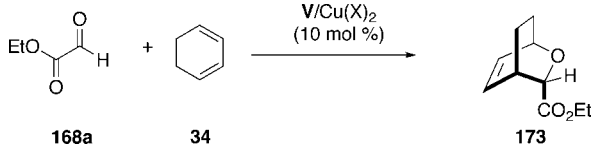


Figure 7. Square planar and tetrahedral Cu(II) stereochemical models.

Scheme 67

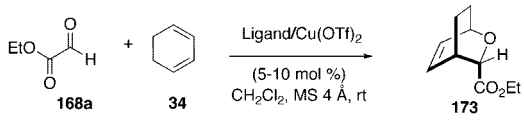


168a 34 173

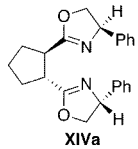
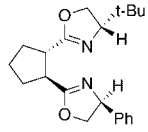
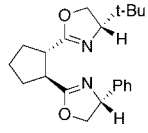
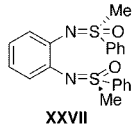
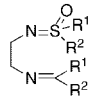
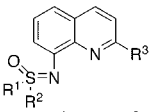
Table 4

solvent	dielectric constant	ee (%) (**173**) (*R*,*R*)-**Vb**/Cu(OTf)$_2$	ee (%) (**173**) (*R*,*R*)-**Va**/Cu(OTf)$_2$
$CDCl_3$	4.80	−79	97
$CHCl_3$	4.89	−78	97
THF	7.47	−47	99
CH_2Cl_2	9.08	−59	97
$EtNO_2$	36.00	11	97

Scheme 68

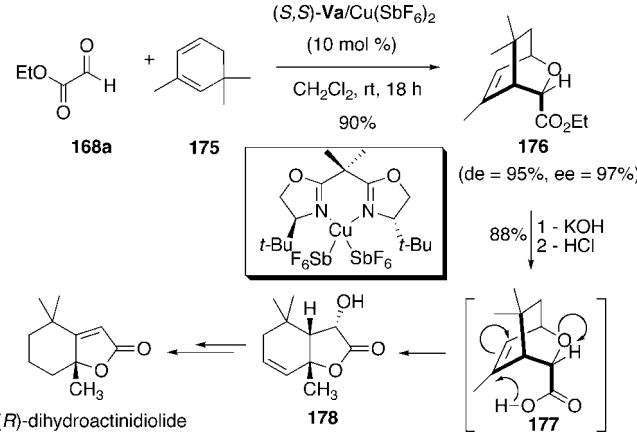


168a 34 173

Ligand	*endo*/*exo*	yield	ee	configuration
 **XIVa**	97/3	65%	39%	(1*S*,3*R*,4*R*)
 **XIVb**	97/3	70%	45%	(1*S*,3*R*,4*R*)
 **XIVc**	98/2	50%	30%	(1*S*,3*R*,4*R*)
 **XXVII**	99/1	81%	98%	(1*S*,3*R*,4*R*)
 (*S*,*S*)-**XXXIXa** (R^1= Me, R^2= Ph)	99/1	73%	93%	(1*R*,3*S*,4*S*)
(*R*,*R*)-**XXXIXb** (R^1= 2-OMe-C_6H_4, R^2= Me)	99/1	62%	91%	(1*S*,3*R*,4*R*)
 (*S*)-**XLa** (R^1= CH_3, R^2= Ph, R^3 = Bu)	99/1	93%	63%	(1*R*,3*S*,4*S*)
(*R*)-**XLb** (R^1= CH_3, R^2= 2-MeO-Ph, R^3 = H)	98/2	98%	91%	(1*S*,3*R*,4*R*)

Electron-rich dienes, particularly Danishefsky-type dienes, were used to synthesize functionalized optically active six-membered oxygenated heterocycles. Ghosh et al.[166] investigated the hetero-Diels−Alder reaction, catalyzed by chiral constrained bis(oxazolines)/Cu(OTf)$_2$ such as catalyst (1*R*,2*S*)-**IXa**/Cu(OTf)$_2$. In order to compare the properties of this

Scheme 69



168a 175 176 178 177

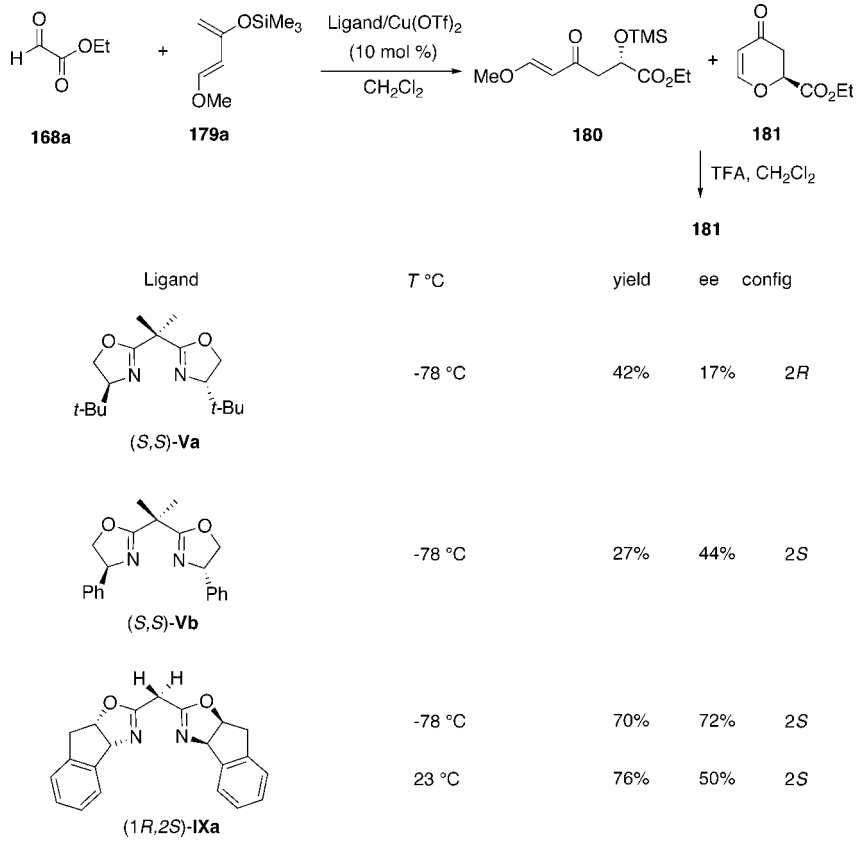
catalyst with (*S*,*S*)-**Vb**/Cu(OTf)$_2$ and (*S*,*S*)-**Va**/Cu(OTf)$_2$, a hetero-Diels−Alder reaction was performed between ethyl glyoxylate **168a** and Danishefsky's diene **179a**. After completion of the reaction, a mixture of Mukaiyama-aldol product **180** and pyranone **181** was obtained, and after treatment of the reaction mixture with trifluoroacetic acid, pyranone **181** was isolated. The best yield and enantiomeric excess of **181** were obtained with (1*R*,2*S*)-**IXa**/Cu(OTf)$_2$, as **181** was obtained in 70% yield and with an enantiomeric excess of 72% at −78 °C versus 27−42% yield and 17−44% enantiomeric excess when (*S*,*S*)-**Vb**/Cu(OTf)$_2$ and (*S*,*S*)-**Va**/Cu(OTf)$_2$ were used. It is worth noting that the use of (1*R*,2*S*)-**IXa**/Cu(OTf)$_2$ at 23 °C led to a decrease in the enantiomeric excess of **181** (50% at 23 °C versus 76% at −78 °C) (Scheme 70).

The oxa-Diels−Alder reaction between aldehyde **182** and Danishefsky's diene **179a** catalyzed by (1*S*,2*R*)-**IXa**/Cu(OTf)$_2$ was used to synthesize the C4−C13 fragment of laulimalide. The chiral constrained complex (1*S*,2*R*)-**IXa**/Cu(OTf)$_2$ afforded the dihydropyranone **183** in good yield and enantiomeric excess. Compound **183** was then transformed into the C4−C13 fragment of laulimalide, compound **184**, by using a Ferrier rearrangement, and this latter compound led to the synthesis of laulimalide after a few steps (Scheme 71).[166b]

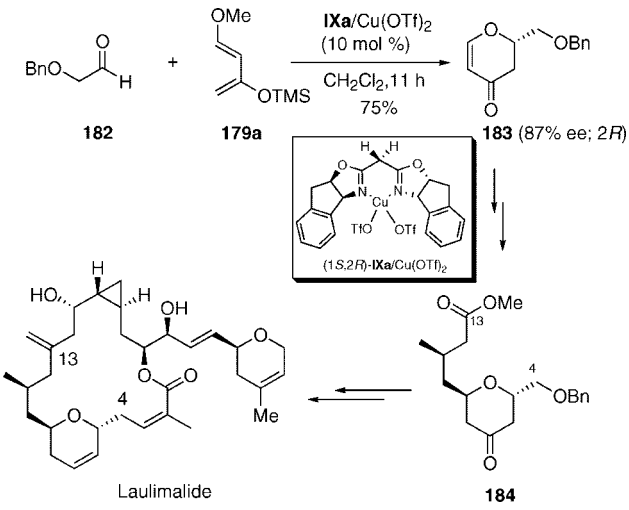
Jørgensen et al.[167] developed a general catalytic oxa-Diels−Alder reaction of prochiral *N*-oxy-pyridine aldehydes. The catalytic asymmetric oxa-Diels−Alder reaction of electron-rich dienes with *N*-oxy-pyridine-2-carboxaldehyde derivatives, catalyzed by chiral **Va**/Cu(II) or **Vb**/Cu(II) complexes, gave the oxa-Diels−Alder adducts after treatment with TFA. In this reaction, the Mukaiyama-aldol products were also formed. The oxa-Diels−Alder adducts were obtained in moderate to good yields and with excellent enantiomeric excesses. In the case of the hetero-Diels−Alder reaction of 5-bromo-*N*-oxy-pyridine-2-carbaldehyde **185a** with **179a**, different catalysts were tested such as (*S*,*S*)-**Va**/Cu(OTf)$_2$, (*S*,*S*)-**Vb**/Cu(OTf)$_2$, and (4*R*,5*S*)-**VIIb**/Cu(OTf)$_2$, in different solvents. The best enantiomeric excess of **186a** was obtained when the reaction was run in a mixture of toluene/CH_2Cl_2 (4/1) in the presence of (4*R*,5*S*)-**VIIb**/Cu(OTf)$_2$ (Scheme 72).

The reaction is general, and different *N*-oxy-pyridine-2-carboxaldehyde derivatives of type **185** were also involved in the oxa-Diels−Alder reaction with Danishefsky's diene **179a** in the presence of (4*R*,5*S*)-**VIIb**/Cu(OTf)$_2$. The yields of the hetero-Diels−Alder adducts of type **186** were modest

Scheme 70



Scheme 71



to good, and the enantiomeric excesses were good to excellent.[167] Some examples are reported in Scheme 73.

For *N*-oxy-pyridine-2-carboxaldehyde derivatives, both the oxygen atoms of the aldehyde and of the *N*-oxide probably coordinate to the copper(II) center in a bidentate fashion. This leads to the formation of a distorted square planar intermediate in which the *si* face of the reacting carbonyl functionality is available for the Mukaiyama approach of the diene (Figure 8).

It is interesting to note that the reaction of **185b** with the 1,3-dimethoxy-1-(trimethylsiloxy)butadiene (Brassard's diene) (**187a**) in an oxa-Diels−Alder fashion gave only the vinylogous Mukaiyama-aldol compound **188** in 81% yield with an enantiomeric excess of 85% and no trace of the cyclic hetero-Diels−Alder adduct was observed (Scheme 74).[167]

On the contrary, nonactivated aldehydes of type **189** reacted with the Brassard's diene **187b** to produce the hetero-Diels−Alder adducts with good diastereo- and enantioselectivity when the reaction was catalyzed by chiral copper(II) Schiff base complexes. When the oxa-Diels−Alder reaction was performed with aldehydes of type **189** and diene **187b** in the presence of **XLI**/Cu(OTf)$_2$ or **XLII**/Cu(OTf)$_2$, followed by treatment with TFA, 5-methyl α,β-unsaturated δ-lactones of type **190** were obtained in modest to good yields, good diastereoselectivities (*anti*/*syn* = 95/5), and good to excellent enantiomeric excesses (Table 5).[168] For aldehyde **189a**, the chiral copper(II)/Schiff base complex derived from **XLI** was a better catalyst than the chiral copper(II)/Schiff base complex derived from **XLII**. However, with other aromatic aldehydes **189b** and **189d**, ligand **XLII** was better than **XLI** in terms of diasteroselectivity and enantioselectivity (cf. *o*-MeC$_6$H$_4$CHO **189b**, 1-naphthylaldehyde **189d**). It is worth noting that unsaturated aldehydes such as **189e** can be involved in oxa-Diels−Alder reactions with Brassard's diene **187b**, leading to the hetero-Diels−Alder adduct in moderate yields and enantioselectivities. In the case of linear aldehydes such as *n*-butyraldehyde **189f**, the hetero-

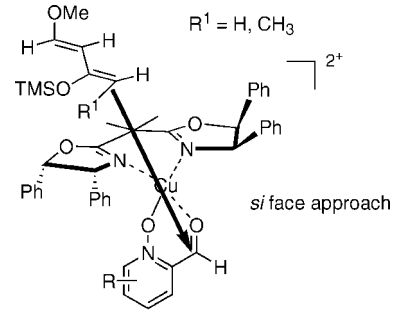
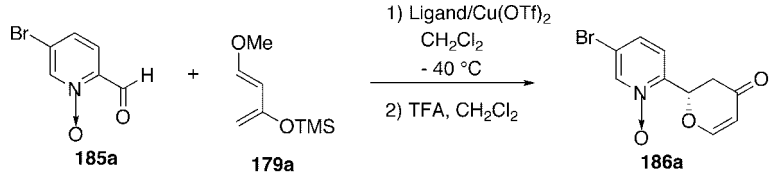
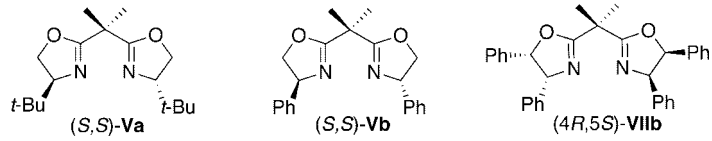


Figure 8.

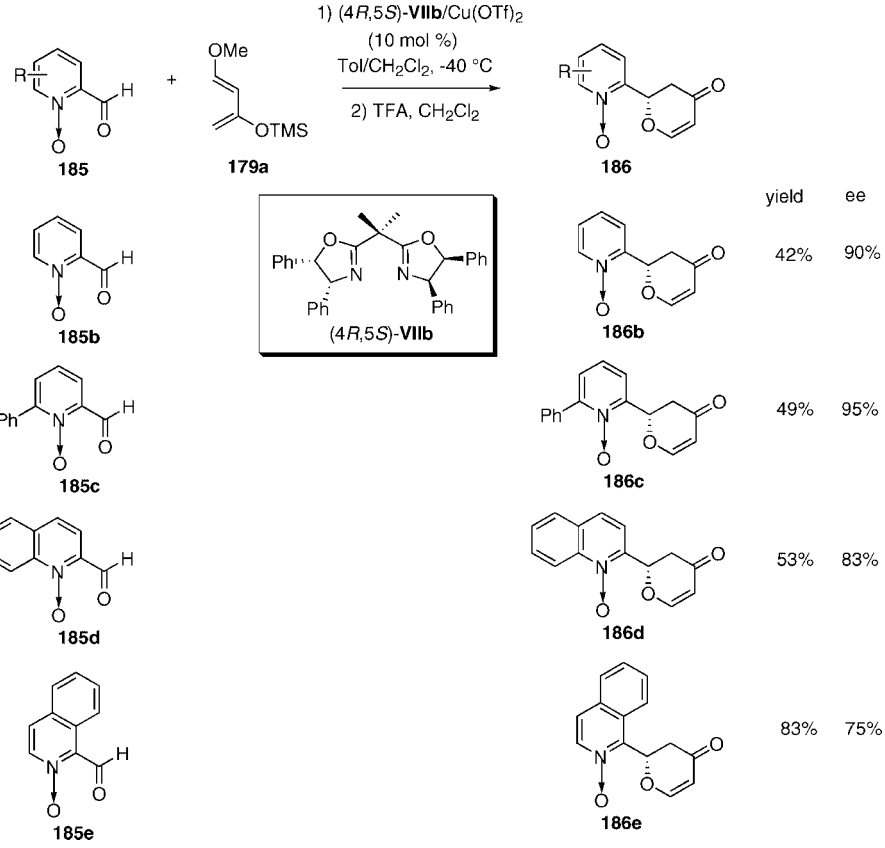
Scheme 72



Ligand	solvent	yield	ee
(*S*,*S*)-**Va**	CH_2Cl_2	30%	80%
(*S*,*S*)-**Va**	Toluene	49%	76%
(*S*,*S*)-**Vb**	CH_2Cl_2	30%	-78%
(4*R*,5*S*)-**VIIb**	CH_2Cl_2	32%	87%
(4*R*,5*S*)-**VIIb**	Toluene/CH_2Cl_2	47%	93%



Scheme 73



	yield	ee
185b → **186b**	42%	90%
185c → **186c**	49%	95%
185d → **186d**	53%	83%
185e → **186e**	83%	75%

Diels−Alder adduct was obtained in low yield, low diastereoselectivity, and with modest enantioselectivity (Scheme 75, Table 5).[168]

As in the reaction involving Brassard's diene **187b** with aldehydes of type **189**, the cyclized product was observed before treatment with TFA, thus it seems that the reaction might proceed via a Diels−Alder pathway. On the basis of this hypothesis and the observed absolute configurations of the products **190a**−**190d**, a possible transition-state model for asymmetric induction in this catalytic system could be postulated (Figure 9). The carbonyl group of the aldehyde is prevented from binding to the Cu(II) center via the coordination shown in models **H** and **I** represented in Figure 9, due to the large steric hindrance between two phenyl subunits (model **H**) or between the phenyl and OTf groups (model **I**). The favored one is suggested as model **J**. In this transition state, the steric hindrance of the indanyl subunit shields the *re* face of the aldehyde, while the *si* face is much more available to accept the attacking diene to give the products with the (5*R*,6*S*) configuration as expected. On the

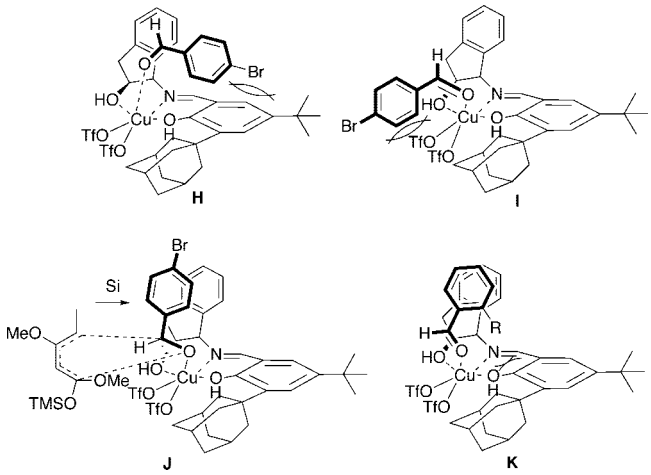
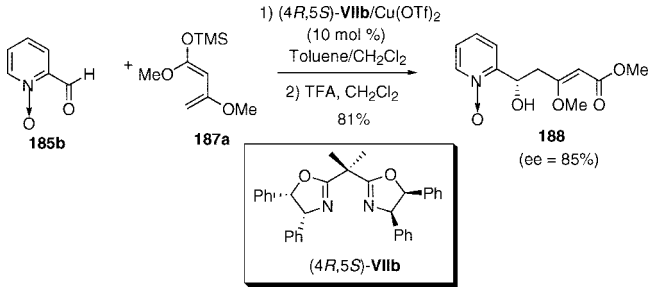


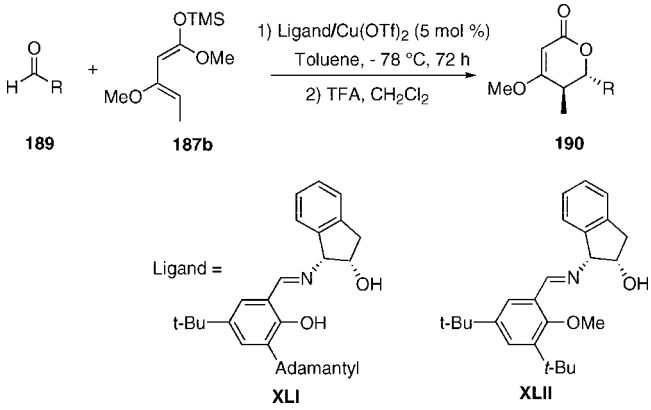
Figure 9. Proposed model for the hetero-Diels−Alder reaction of diene **187b** with aldehydes of type **189** catalyzed by Cu(II)/**XLI** complex.

Scheme 74

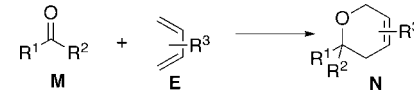


other hand, the *ortho* substituent present on the aromatic aldehyde could cause larger steric hindrance with the adamantyl group (model **K**), while the *t*-Bu group in **XLII** was suitable. This model could well explain the absolute

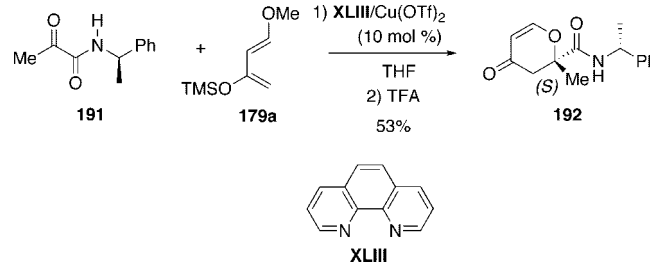
Scheme 75



Scheme 76



Scheme 77



configuration and the phenomenon that ligand **XLII** was efficient with *ortho*-substituted substrates, whereas **XLI** was more successful with the other ones (Figure 9).[168]

3.1.1.2. Ketones. Ketones are, in general, less reactive than aldehydes, and hetero-Diels−Alder reactions with ketones should be more difficult to achieve. To work, a direct-electron demand hetero-Diels−Alder reaction of conjugated dienes with ketones requires a catalyst or the reaction conditions have to be forced by using pressure. Ketones of type **M** can react with dienes of type **E** to produce cyclic compounds of type **N** (Scheme 76).

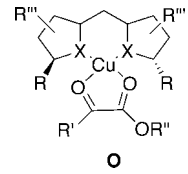
An important aspect of hetero-Diels−Alder reactions with ketones is the construction of heterocyclic compounds of type **N** possessing a quaternary center. The challenge, for chemists, is to control this quaternary center.[169] Most of the hetero-Diels−Alder reactions of ketones involve dienes such as 1,3-cyclohexadiene derivatives or more electron-rich dienes such as Danishefsky's or Brassard's dienes. We have to point out that, depending on the diene, the ene or Mukaiyama aldol reactions can compete with the oxa-Diels−Alder reaction. In hetero-Diels−Alder reactions involving ketones, the chirality can come from the substrate or from the catalyst.

One of the few examples in hetero-Diels−Alder reactions where the chirality originates from the substrate is illustrated by α-ketoamide **191**. This compound reacts diasteroselectively with **179a** to give **192** in 53% yield when the reaction is catalyzed by 1,10-phenanthroline/$Cu(OTf)_2$ [**XLIII**/$Cu(OTf)_2$] (10 mol %) (Scheme 77).[170]

Except for the previous example, where the chirality is coming from the substrate, in most cases, the chirality in hetero-Diels−Alder reactions involving ketones is coming from the catalyst. The catalysts described for the hetero-Diels−Alder reaction involving aldehydes can also be used to catalyze highly enantioselective hetero-Diels−Alder cycloadditions of α-ketoesters or α-diketones with conjugated

Table 5

		compounds **190a−f**		
aldehydes **189**	ligand	yield (%)	*anti*/*syn*	*anti* ee (%); (config)
PhCHO **189a**	**XLI**	70	95/5	98; (5*R*,6*S*)
PhCHO **189a**	**XLII**	68	71/29	92; (nd)
o-MeC_6H_4CHO **189b**	**XLI**	35	92/8	54; (5*R*,6*S*)
o-MeC_6H_4CHO **189b**	**XLII**	52	99/1	94; (5*R*,6*S*)
m-$NO_2C_6H_4CHO$ **189c**	**XLI**	53	88/12	90; (5*R*,6*S*)
1-naphythylaldehyde **189d**	**XLI**	30	92/8	24; (5*R*,6*S*)
1-naphythylaldehyde **189d**	**XLII**	57	98/2	92; (5*R*,6*S*)
(*E*)-MeCH═CH-CHO **189e**	**XLI**	58	90/10	62; (nd)
n-butyraldehyde **189f**	**XLI**	15	59/41	73; (nd



O

Figure 10.

dienes. Dicarbonyl derivatives are set up for bidentate coordination to a chiral Lewis acid. This coordination of the ketone derivatives implies at first, the activation of the ketone functionality and second the discrimination of one of the faces of the ketone by the chiral ligand. For example, by using a chiral ligand, a complex of type **O** is formed and the *re* face of the ketone is shielded by the C_2-symmetric chiral ligand (Figure 10).

The hetero-Diels−Alder reaction between 1,3-cyclohexadiene (**34**) and ethyl ketomalonate (**193**), employing C_2-symmetric bis(oxazolines) of type **V** as the chiral ligands and Cu(II) as the Lewis acid, led to cycloadduct **194** in good yields and in enantiomeric excesses up to 93% (Scheme 78).[171]

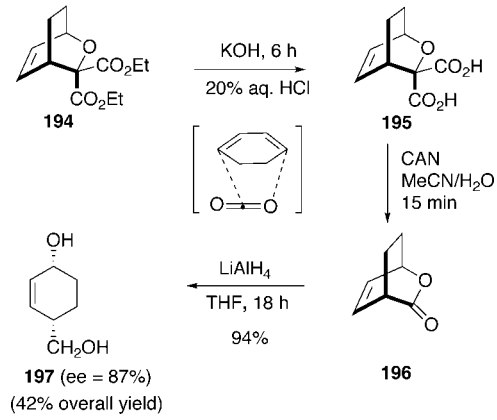
The adduct **194** obtained from this reaction is equivalent to the adduct obtained from an enantioselective addition of 1,3-cyclohexadiene to CO_2. The saponification of the adduct **194** followed by acidic treatment furnishes dicarboxylic acid **195**, which after treatment with cerium ammonium nitrate (CAN) gives the chiral lactone **196**. Reduction of **196** produces diol **197** in 94% yield with an enantiomeric excess of 87% (Scheme 79).[171]

By using cyclopentadiene **18**, the reaction also proceeds well at low temperature, but increasing the temperature leads to a retro-Diels−Alder reaction (Scheme 80).[171]

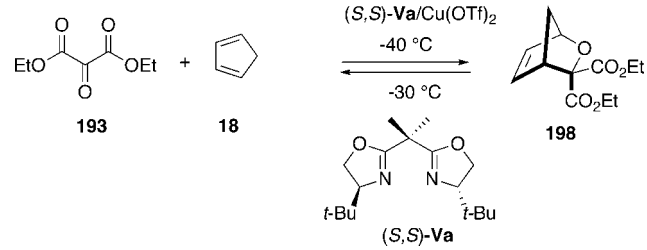
Bolm et al. have successfully used chiral bis(sulfoximines) as the ligands and $Cu(OTf)_2$ as the Lewis acid to perform hetero-Diels−Alder reactions.[162] Catalyst (*S*,*S*)-**XXVII**/$Cu(OTf)_2$, promoted the hetero-Diels−Alder reaction between ketomalonate **193** and 1,3-cyclohexadiene (**34**). The adduct **194** was produced in excellent yield and enantioselectivity. The absolute configuration of **194** was established to be (1*S*,4*R*) when (*S*,*S*)-**XXVII**/$Cu(OTf)_2$ was used (Scheme 81).[162]

Later on, the same group successfully employed a quinoline-based C_1-symmetric monosulfoximide ligand [(*S*)-**XLb**]

Scheme 79



Scheme 80

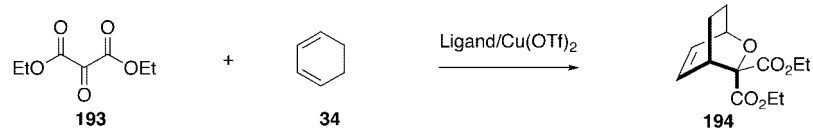


in combination with $Cu(OTf)_2$ to perform the hetero-Diels−Alder reaction between **193** and **34**, and (1*R*,4*S*)-**194** was obtained with an enantiomeric excess of 89% (Scheme 82).[163]

On the basis of X-ray analysis of the chiral ligand/$CuCl_2$ complex, it was proposed that only one transition state is favored in this reaction, e.g., **P** over **Q** as diene **34** can approach only from the less sterically hindered side (Figure 11).[163] As a result of this analysis, Bolm et al.[163] proposed an optimal ligand where the sulfoximine unit bears a small alkyl substituent and an aryl moiety having a bulky group in the *ortho* position. This prediction was confirmed with the (*R*)-*N*-(8-quinolyl)-*S*-(2-isopropyloxyphenyl)-*S*-methylsulfoximine ligand, which led to **194** in 94% yield and with an enantiomeric excess of 93%.

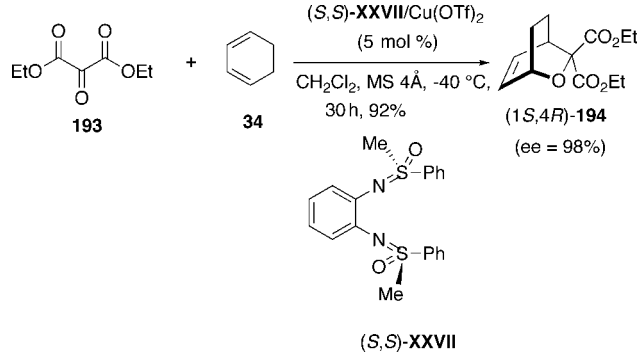
In 1997, the first example of the enantioselective catalytic hetero-Diels−Alder reaction of activated ketones with ac-

Scheme 78



Ligand	Ligand/Cu(II)	cat. loading (mol %)	solvent	*T* °C	yield	ee
(*S*,*S*)-**Va**	(*S*,*S*)-**Va**/$Cu(OTf)_2$	5	CH_2Cl_2	-40 °C	20%	40%
	(*S*,*S*)-**Va**/$Cu(SbF_6)_2$	5	CH_2Cl_2	-40 °C	11%	64%
(*R*,*R*)-**Vb**	(*R*,*R*)-**Vb**/$Cu(OTf)_2$	10	CH_2Cl_2	rt	76%	84%
	(*R*,*R*)-**Vb**/$Cu(OTf_2)_2$	20	Et_2O	-20 °C	64%	93%

Scheme 81



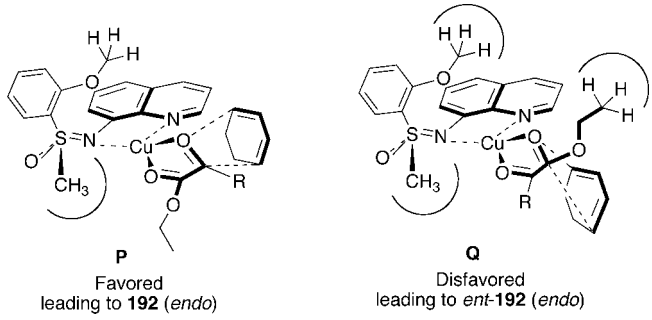
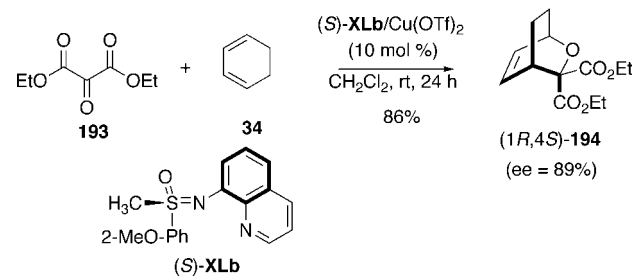
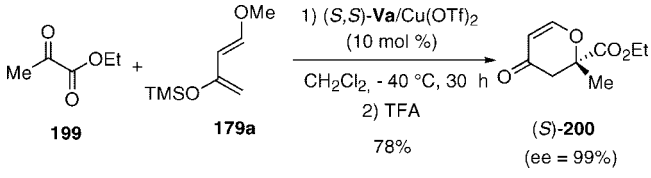


Figure 11. Transition states.

Scheme 82



Scheme 83



tivated dienes was reported.[172] The reaction of ethyl pyruvate **199** with *trans*-1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene (Danishefsky's diene) (**179a**) was examined. The yield and the enantiomeric excess of the hetero-Diels−Alder adduct **200** depend on the catalyst. Different C_2-symmetric bis(oxazoline) ligands were tested,[172−174] and the best yields and enantiomeric excesses were obtained with catalyst (*S*,*S*)-**Va**/Cu(OTf)$_2$(10 mol %), which afforded **200** in 78% yield and 99% enantiomeric excess (−40 °C; CH_2Cl_2) (Scheme 83).[172] To form (*S*)-**200**, the diene has to approach the *si* face of the ketone. It is assumed that both the chiral ligand and ethyl pyruvate **199** are coordinated to the copper(II) center, with the ligand and the substrate in the same plane producing a complex in which the carbonyl *re* face of **199** is shielded by the *tert*-butyl groups of the ligand. As usual, when the Danishefsky's diene is used, a traditional hetero-Diels−Alder reaction and/or a Mukaiyama aldol condensation can take place, but after acidic treatment of the reaction mixture, the dihydropyranones were exclusively obtained.

Scheme 85

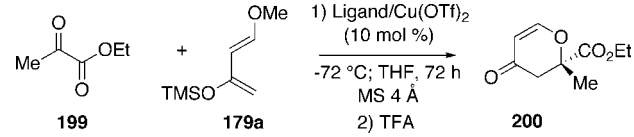
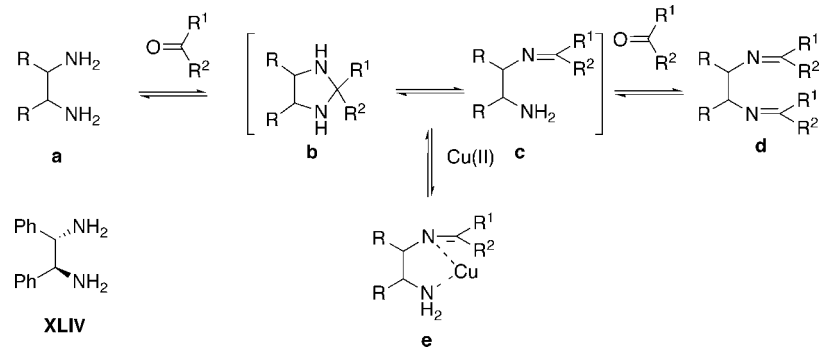


Table 6

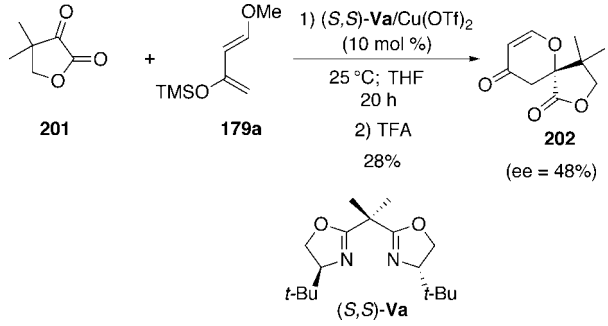
Ligand **XLIV** + ketone (ratio: 1/1)		**200**	
	Ketone	yield	ee
XLIV	Cyclohexanone	72%	70%
XLIV	Cyclopentanone	85%	91%
XLIV	Cyclobutanone	85%	94%

Ligands other than bis(oxazolines) have been prepared very easily by condensing chiral vicinal diamines with 1 equiv of different carbonyl compounds. The catalyst preparation was based on the condensation of 1,2-diamines of type **a** with ketones and aldehydes to afford imidazolidines **b** in equilibrium with the open form **c**. The corresponding bis(imines) **d** and the starting diamines **a** are often present with **b** and **c** in the reaction mixture. Chelating metals such as Cu(II) shift the equilibrium toward the metallacyclic form by forming a bidentate complex, and the resulting adducts are then complexed with Cu(OTf)$_2$ to form **e** (Scheme 84). These complexes were then tested in hetero-Diels−Alder reactions using ethyl pyruvate **199** and Danishefsky's diene **179a**. The best results were obtained with **XLIV**/Cu(OTf)$_2$ (Scheme 85, Table 6).[175]

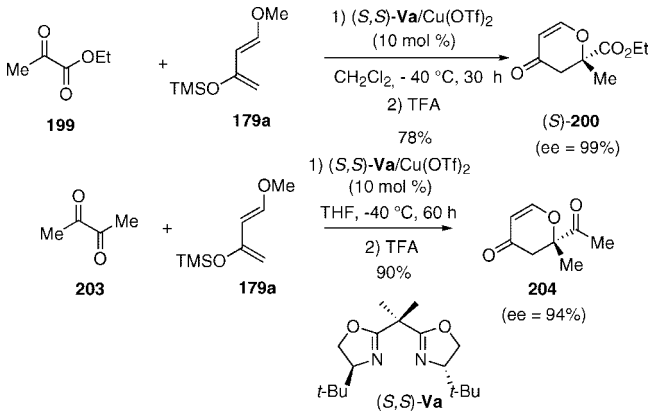
Scheme 84



Scheme 86



Scheme 87



The Cu(II)/ligand stoichiometry was critical for selectivity and reactivity. Whereas a 1/1 ratio of cyclohexylidine ligand derived from (−)-diphenyl ethylamine **XLIV**, cyclohexanone, and $Cu(OTf)_2$ afforded the hetero-Diels−Alder adduct **200** in 92% ee, from **199** and **179a**, an increase in the Cu(II)/ligand ratio to 2/1 resulted in only 73% ee in **200**. Furthermore, when a two-fold molar excess of ligand relative to Cu(II) salt was used, the catalytic activity of the complex was inhibited. Upon decreasing the ring size of the ketone component from six to four carbon atoms, the enantiomeric excess of the cycloadduct **200** was increased to 94% (Scheme 85, Table 6).[175]

Spirolactones can also be formed starting from cyclic α-ketoesters. For example, when **201** and **179a** were involved in a hetero-Diels−Alder reaction, catalyzed by Cu-complexes, the spirolactone **202** was obtained in modest yield. The best enantiomeric excess of **202** (ee = 48%) was obtained with the (*S*,*S*)-**Va**/$Cu(OTf)_2$ catalyst (Scheme 86).[174]

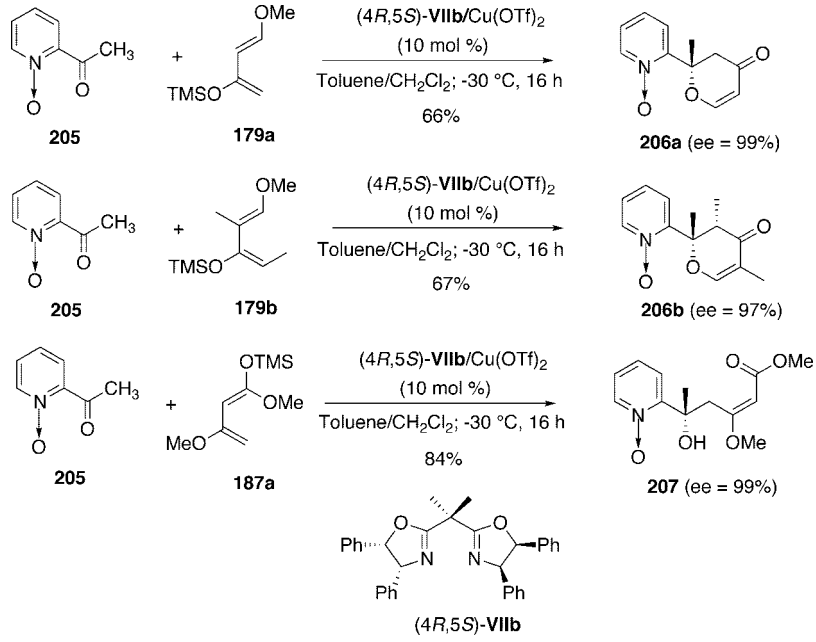
Other dicarbonyl compounds such as α-diketones can also be involved in hetero-Diels−Alder reactions. For example, when the hetero-Diels−Alder between α-diketone **203** and **179a** was performed in the presence of (*S*,*S*)-**Va**/$Cu(OTf)_2$, cycloadduct **204** was obtained in good yield and excellent enantiomeric excess (94%). It has been noted that lowering the amount of catalyst in this reaction from 10 mol % to 0.05 mol % does not affect both the yield and enantiomeric excess (Scheme 87).[172]

As for aldehydes, pyridine-*N*-oxides can be good activating groups and *N*-oxy-pyridine-2-ketone derivatives can be involved in oxa-Diels−Alder reactions catalyzed by chiral bis(oxazoline)/Cu(II) complexes to give unsaturated pyrones with one quaternary center. The hetero-Diels−Alder adducts were isolated in good yields and with good enantiomeric excesses. Among the C_2-symmetric bis(oxazoline) ligands tested, bis(oxazoline) (4*R*,5*S*)-**VIIb** gave the best results when the reaction was performed in toluene/CH_2Cl_2 (4/1) at −30 °C for 16 h, and the hetero-Diels−Alder reaction worked perfectly when Danishefsky-type dienes were utilized. For example, the cycloadducts **206a** and **206b** were obtained from **205**, but when Brassard-type dienes were used, only the Mukaiyama aldol product **207** was formed (Scheme 88).[167]

3.1.2. Oxygenated Dienes: α,β-Unsaturated Carbonyl Compounds

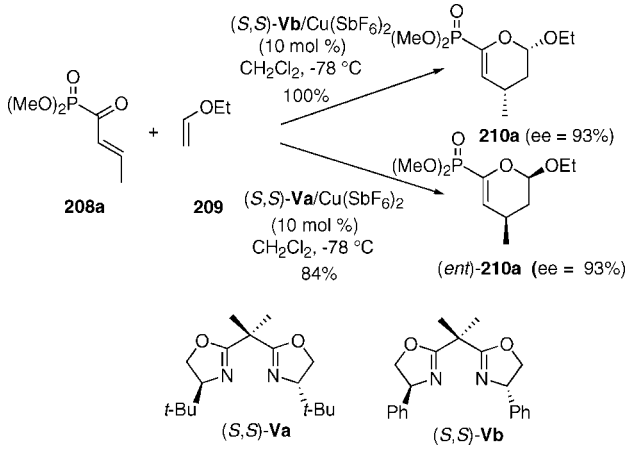
When α,β-unsaturated carbonyl compounds are involved in a hetero-Diels−Alder reaction as heterodienes, an inverse-electron demand reaction takes place and the catalytic enantioselective hetero-Diels−Alder reaction of α,β-unsaturated carbonyl compounds with electron-rich alkenes allowed access to 2-substituted 3,4-dihydro-2*H*-pyrans. In this case, there is a dominant interaction between the LUMO of the 1-oxa-1,3-butadienes of type **R** and the HOMO of the

Scheme 88

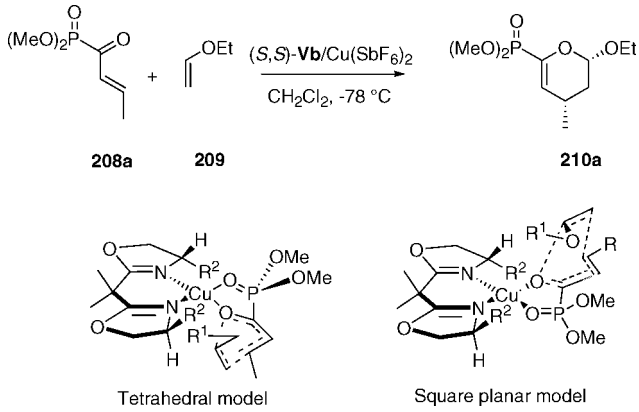


Scheme 89

Scheme 90



Scheme 91

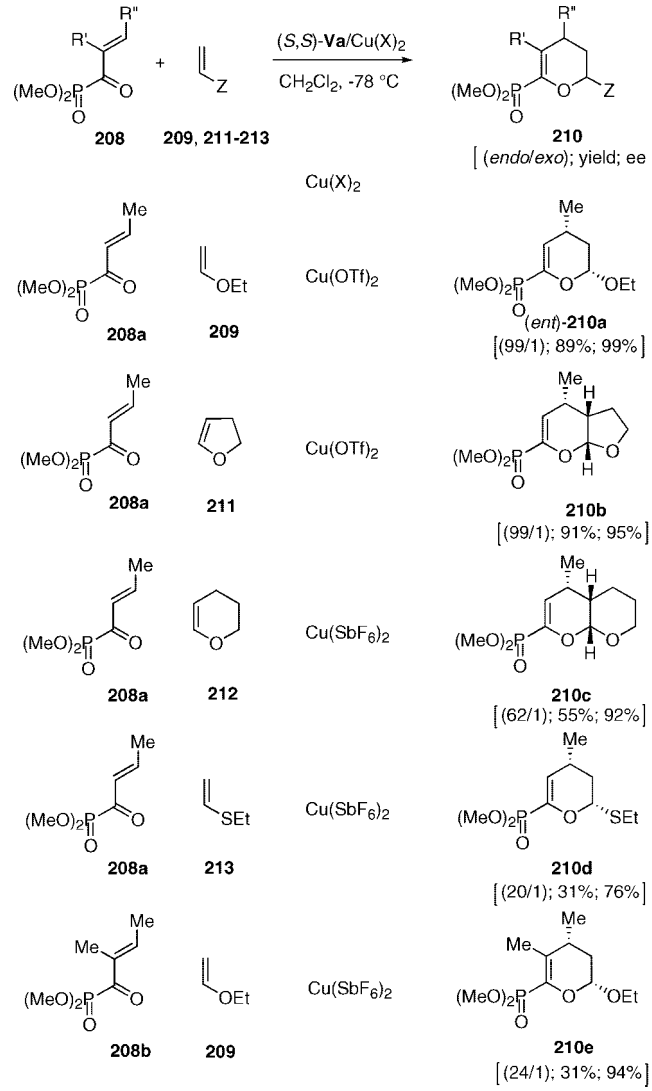


alkenes. This reaction is in general a concerted nonsynchronous process, and a retention of the configuration of the dienophile is observed, as well as high regioselectivity, which can be further improved by adding a Lewis acid (Scheme 89).

Chiral bis(oxazoline)/Cu(II) complexes were used to induce highly enantioselective hetero-Diels−Alder reactions of β,γ-unsaturated α-keto-esters, β,γ-unsaturated acyl phosphonates and also α,β-unsaturated oxazolidinones, with electron-rich olefins such as enol ethers. The high level of enantio-induction might be related to the coordination of the substrate to the chiral bis(oxazoline)/Cu(II) catalysts leading to the formation of chiral complexes of type **T**. In Figure 12, the chiral ligand discriminates one face of the ketone, e.g., the *re* face, which is shielded by the C_2-symmetric chiral ligand of (*S*,*S*)-configuration.

The first examples of hetero-Diels−Alder reaction of α,β-unsaturated carbonyl compounds such as acyl phosphonate **208a** with electron-rich heterodienophiles such as **209**, catalyzed by chiral bis(oxazolines)/Cu(II) complexes, were investigated by Evans et al., who used (*S*,*S*)-**Vb**/$Cu(X)_2$ and (*S*,*S*)-**Va**/CuX_2 (X = OTf or X = SbF_6) catalysts. Dihydrofuran **210a** and its enantiomer (*ent*)-**210a** were, respectively, obtained in 93% enantiomeric excess by employing either the (*S*,*S*)-**Va**/$Cu(SbF_6)_2$ or (*S*,*S*)-**Vb**/$Cu(SbF_6)_2$ catalysts (Scheme 90).[176,177]

Scheme 92



The stereochemical course of these enantioselective reactions catalyzed by (*S*,*S*)-**Va**/$Cu(SbF_6)_2$ and (*S*,*S*)-**Vb**/$Cu(SbF_6)_2$ is accounted for the intermediacy of a distorted square planar bis(oxazoline)/Cu(II)/substrate complex rather than by a tetrahedral bis(oxazoline)/Cu(II)/substrate complex. For the achievement of high enantioselectivity, the substrate undergoing activation must be capable of bidentate coordination to the chiral Lewis acid (Scheme 91).[176]

The hetero-Diels−Alder reaction between various α,β-unsaturated acyl phosphonates of type **208** and various types of electron-rich alkenes such as **209** and **211**−**213** led to cycloadducts in high yields and with excellent stereo- and enantioselectivities when they were catalyzed by bis(oxazoline)/Cu(II) catalysts. In general, better *endo*/*exo* selectivities and enantiomeric excesses were obtained with bis(oxazoline)/$Cu(OTf)_2$ catalysts than with bis(oxazoline)/$Cu(SbF_6)_2$ cata-

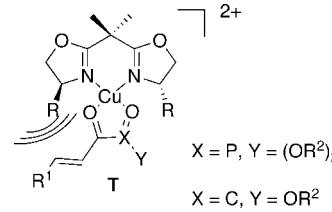
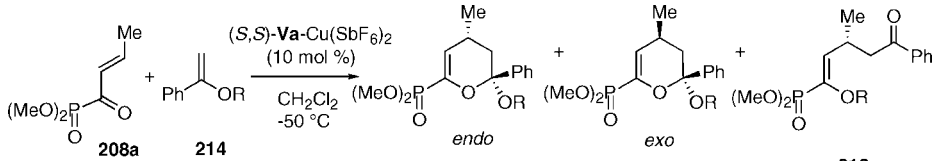


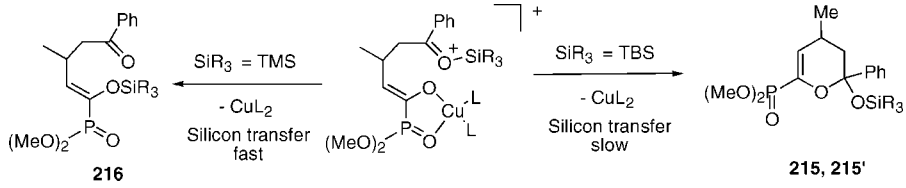
Figure 12.

Scheme 93

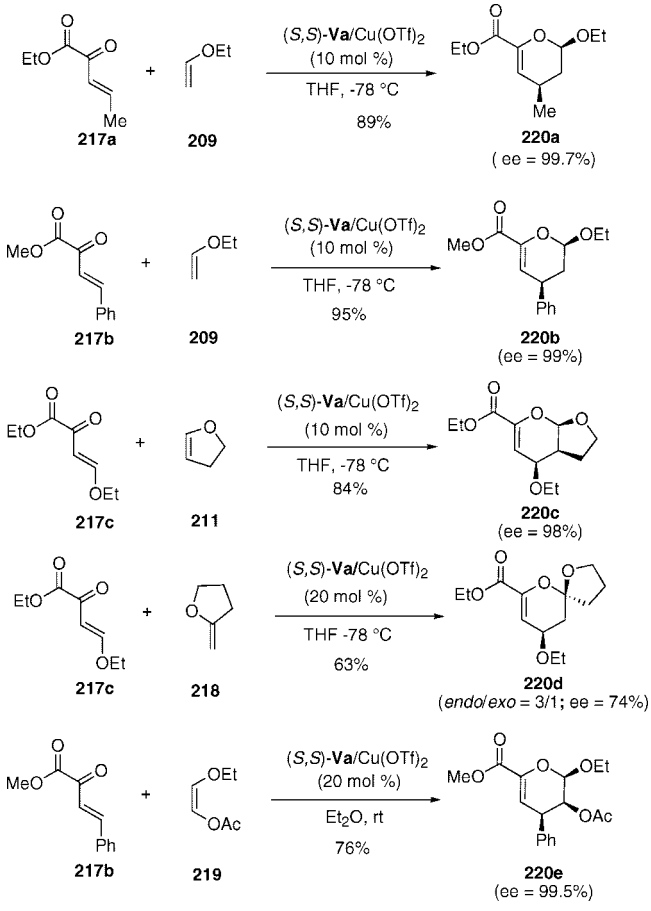


214	215/215'/216	215 [ee(%)]	215' [ee(%)]	216 [ee (%)]
214a R = TMS	57/5/38	99	74	70
214b R = TBS	93/7/0	99	82	

Scheme 94



Scheme 95



lysts. Some examples catalyzed by (*S*,*S*)-**Va**/Cu(OTf)$_2$ and (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ are reported in Scheme 92.[178,179]

The hetero-Diels−Alder reaction of acyl phosphonates can also be performed with silyl enol ethers derived from acetophenone.[179] The cycloaddition of crotylphosphonate **208a** with **214** led to a mixture of dihydropyrans **215**, **215′**, and Michael adduct **216**. The *endo*-isomer was formed preferentially using (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ or (*S*,*S*)-**Vb**/Cu(SbF$_6$)$_2$. In contrast to the results obtained with the monosubstituted enol ethers, the same major enantiomers were obtained with the (*S*,*S*)-**Va**/Cu(SbF$_6$)$_2$ and (*S*,*S*)-**Vb**/Cu(SbF$_6$)$_2$ catalysts. While alteration of the reaction conditions (solvent, temperature) did not affect the product distribution, the change of the silyl group in the silyl enol ether, such as the exchange of a TMS group to a TBS group, modified the ratio of the cycloadducts and the Michael adduct (Scheme 93).[179] Silyl transfer to a putative Cu(II) enolate is presumably retarded when using the bulkier silyl group, e.g., the *tert*-butyldimethylsilyl group, and the formal cycloaddition pathway becomes dominant. This result implicates a nonconcerted process for cycloadditions of this heterodienophile (Scheme 94).[179]

The extension of this hetero-Diels−Alder reaction to α-β-unsaturated α-ketoester of type **217** was achieved with various electron-rich dienophiles. β,γ-Unsaturated α-ketoesters are somewhat more reactive than α,β-unsaturated acyl phosphonates in catalytic hetero-Diels−Alder reactions.[180,181] In general, good yields and high diastereo- and enantioselectivities were obtained for the hetero-Diels−Alder adducts of type **220** when the reaction was catalyzed by (*S*,*S*)-**Va**/Cu(OTf)$_2$. Some examples are reported in Scheme 95.

The (*S*,*S*)-**Va**/Cu(II) complex is theorized to have a square-planar geometry at the copper(II) center. This square-planar intermediate was calculated by PM3 from the X-ray structure analysis of the chiral bis(oxazoline)/Cu(OTf)$_2$·(H$_2$O)$_2$ complex. The γ-substituted β,γ-unsaturated α-ketoesters of type **217** are coordinated in a bidentate fashion through the carbonyl oxygen atom to the (*S*,*S*)-**Va**/Cu(II) catalyst. The approach of the alkene to the α-substituted β,γ-unsaturated

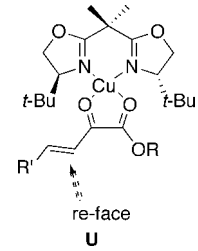
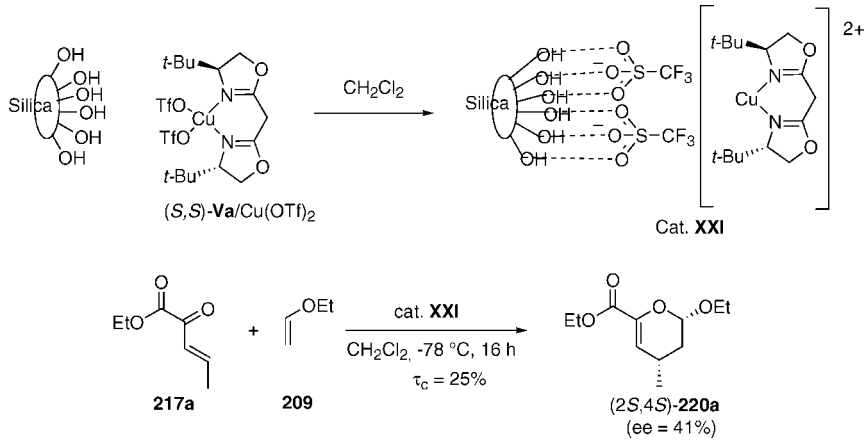
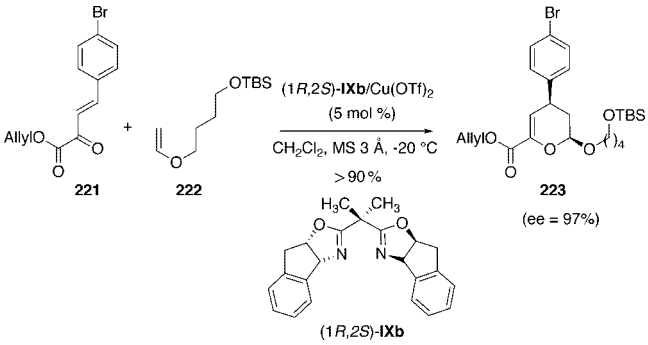


Figure 13. Transition state.

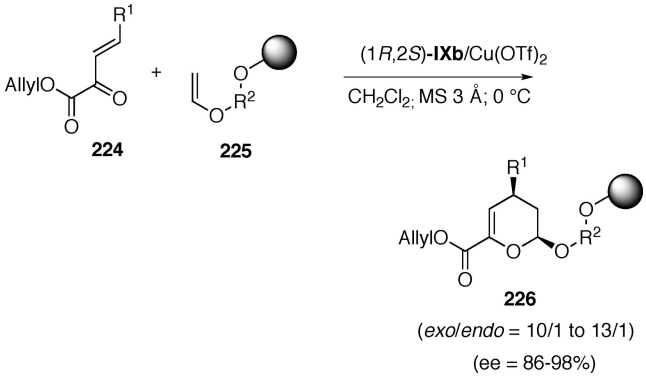
Scheme 96



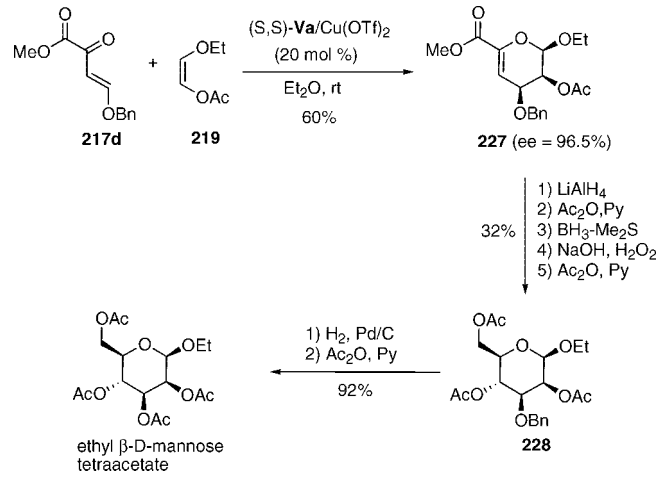
Scheme 97



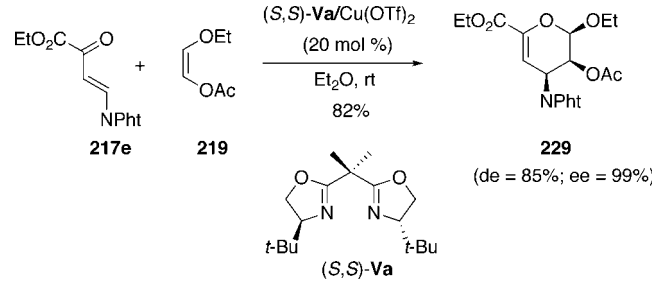
Scheme 98



Scheme 99



Scheme 100



α-ketoester thus takes place on the *re* face of the reacting carbonyl functionality (Figure 13).[180,181]

The bis(oxazoline)/Cu(II) catalysts can be immobilized on silica gel via electrostatic interactions and are still active in hetero-Diels−Alder reactions.[182] With the immobilized (*S*,*S*)-**Va**/Cu(OTf)$_2$ catalyst (catalyst **XXI**), the predominant enantiomer formed, from **217a** and **209**, was (2*S*,4*S*)-**220a** with an enantiomeric excess of 41% when the reaction was performed at −78 °C (Scheme 96).[182]

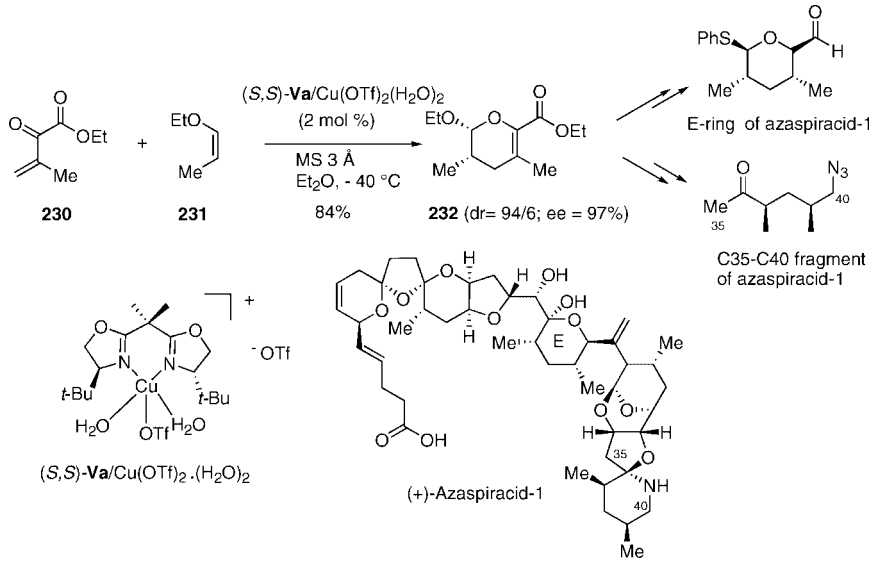
Other catalysts such as (1*R*,2*S*)-**IXb**/Cu(OTf)$_2$ can be used to produce dihydropyrans such as **223**, from α,β-unsaturated keto-ester **221** and dienophile **222**, in high enantiomeric excesses (Scheme 97).[183] We have to point out that the dienophile can be supported on solid phase, and the (1*R*,2*S*)-**IXb**/Cu(OTf)$_2$ complex is still very efficient as the adducts of type **226** were obtained in good to excellent enantiomeric excesses (86−98%) (Scheme 98).[183]

The main applications of the hetero-Diels−Alder reaction of β,γ-unsaturated α-ketoesters with electron-rich dienophiles is the formation of carbohydrates. The hetero-Diels−Alder adduct **227**, issued from the γ-oxygenated β,γ-unsaturated α-ketoesters **217d** and **219**, was transformed in a few steps to the carbohydrate derivative ethyl β-D-mannose tetraacetate via **228** (Scheme 99).[181]

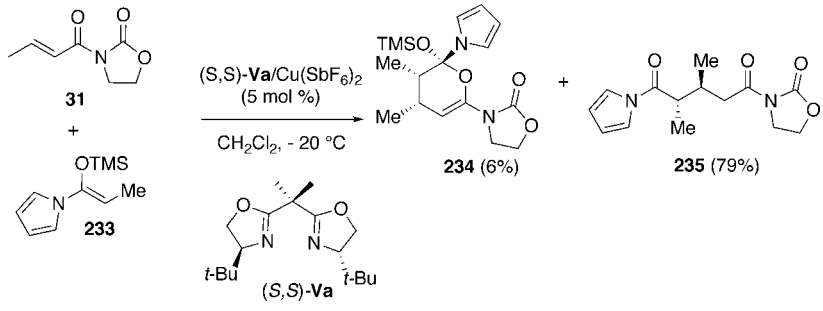
Carbohydrates containing nitrogen atoms can be synthesized from γ-amino-protected β,γ-unsaturated α-keto esters. The hetero-Diels−Alder adduct **229**, precursor to aminosugars, was obtained from **217e** and alkene **219** in good yield with high diastereo- and enantioselectivity and with full control of the stereocenter bearing the amino group when the reaction was performed with (*S*,*S*)-**Va**/Cu(OTf)$_2$ (Scheme 100). Compound **229** can be the precursor of carbohydrates containing nitrogen atoms.[184]

The hetero-Diels−Alder reaction of β,γ-unsaturated α-ketoesters catalyzed by (*R*,*R*)-**Va**/Cu(OTf)$_2$ has been used to synthesize a library of substituted dihydropyrans for

Scheme 101



Scheme 102



protein-binding assays.[185] Furthermore, both the E ring and the C35−C40 fragment of the (+)-azaspiracid-1 were synthesized by using a hetero-Diels−Alder reaction between **230** and the electron-rich olefin **231** using the (*S*,*S*)-**Va**/$Cu(OTf)_2 \cdot 2H_2O$ complex as the catalyst to produce **232** with good diastereo- and enantioselectivity (Scheme 101).[186]

We have to point out that α-*β*-unsaturated *β*-keto-oxazolidinones are not good dienes, as when α-*β*-unsaturated *β*-keto-oxazolidinones **31** and electron-rich olefin **233** were treated with (*S*,*S*)-**Va**/$Cu(SbF_6)_2$, adduct **234** was produced in only 6% yield; the major compound **235** (79% yield) corresponds to the Mukaiyama−Michael product.[187]

Hetero-Diels−Alder reactions can also be performed intramolecularly. A series of articles by Wada et al. were dedicated to this subject.[188,189] The enantioselective reaction of methyl (*E*)-4-methoxy-2-oxo-(3-butenoate) (**236**) with (*rac*)-6-methyl-5-hepten-2-ol (**237**) produced hetero-Diels−Alder compounds with an effective kinetic resolution. At −78 °C, high diastereoselectivities (de = 86%) and high enantioselectivities (97%) were observed in the presence of (*S*,*S*)-**Va**/$Cu(SbF_6)_2$ and molecular sieves 5Å (Scheme 103).

3.2. Aza-Diels−Alder Reaction

Nitrogen-containing compounds are present in a great variety of natural products and/or biologically active compounds. Hetero-Diels−Alder reactions are a good way to obtain these heterocyclic compounds, and the nitrogen atom can be present either in the dienophile or in the diene.

3.2.1. Imines

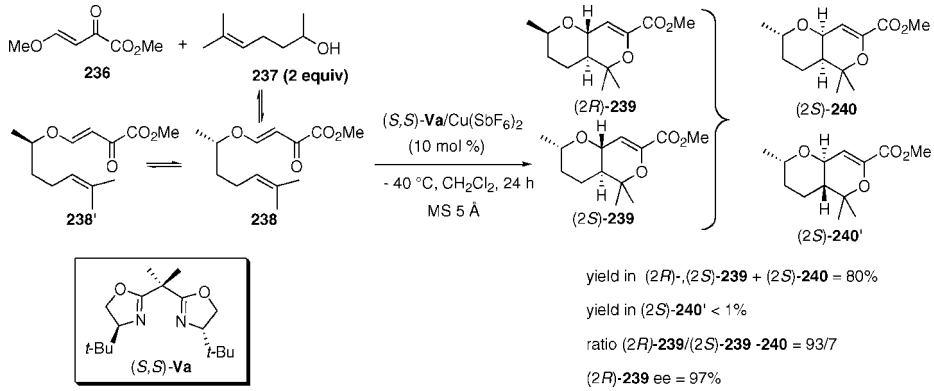
Similarly to carbonyl derivatives, imines can be involved in hetero-Diels−Alder reactions, Mannich, and ene reactions. When a Lewis acid catalyzed hetero-Diels−Alder reactions, two pathways generally have to be taken into considerations: the traditional Diels−Alder cycloaddition and the Mannich-type reaction (Scheme 104).

Furthermore, when the substrate contains an allylic C−H bond, both the hetero-Diels−Alder reaction and the ene reaction take place as illustrated by *N*-tosyl α-iminoester **241**. When *N*-tosyl α-aminoester **241** reacted with **57** in the presence of the Tol-BINAP/Cu(I) complex [**XLV**/$CuClO_4$], the hetero-Diels−Alder adduct **245** (64% yield; 65% ee) and the ene-adduct **246** (7% yield; 86% ee) were formed in a 9/1 ratio, respectively.[190] By using other ligands such as **XLVI** and **XLVII** in combination with $CuClO_4$, the aza-Diels−Alder adduct is the only compound formed, but unfortunately as a racemate (Scheme 105).

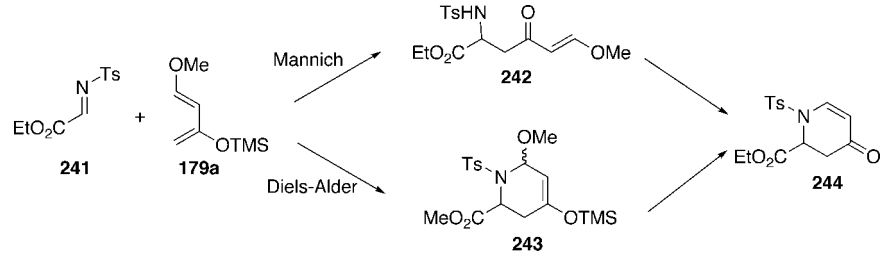
Considerable attention has been paid to the development of asymmetric hetero-Diels−Alder reactions involving imines. Chiral ligands, similar to those used in oxa-Diels−Alder reactions, were utilized to obtain optically active amino heterocyclic compounds.

3.2.1.1. Aza-Dienophiles. Simple non-activated Schiff bases display low reactivities in hetero-Diels−Alder reactions. However, imino-Diels−Alder reactions of 2-amino-1,3-butadienes of type **248** with imines of type **247**, in the presence of a catalytic amount of $Cu(OTf)_2$, led to 2,6-disubstituted 4-piperidinones of type **249** in good yields and with good diasteroselectivities (Scheme 106).[191]

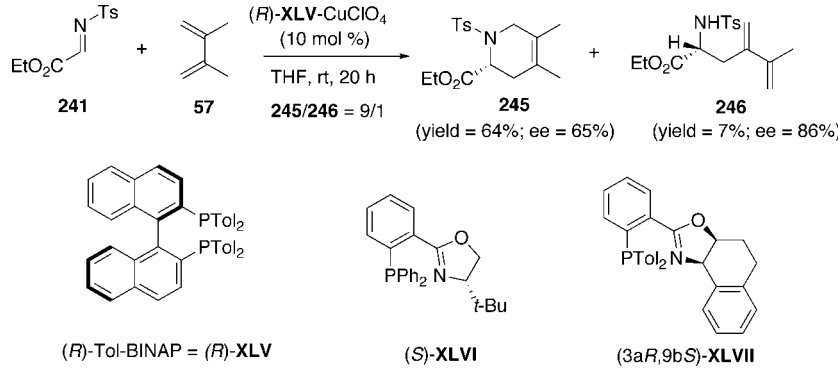
Scheme 103



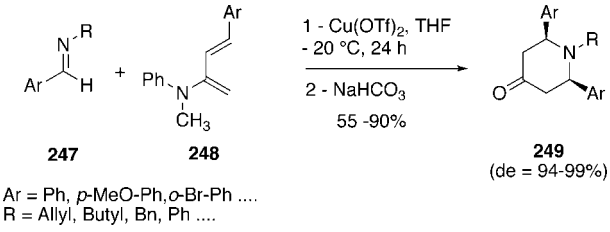
Scheme 104



Scheme 105



Scheme 106



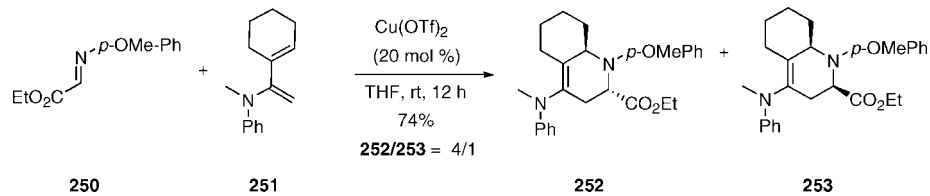
Imines derived from glyoxylic esters such as **250** can react with electron-rich dienes. In the case of 2-amino-1,3-butadiene (**251**), 4-amino tetrahydropyridines **252/253** were obtained in good yields and in a ratio of 4/1 in favor of **252** when $Cu(OTf)_2$ was used as the catalyst (Scheme 107).[192]

It is worth nothing that, when dienophile **254** and diene **179a** were treated with the optically active diamine **XLIV**/$Cu(OTf)_2$, the hetero-Diels−Alder adduct **255** was obtained with an enantiomeric excess of 88% (Scheme 108),[193] but when **250** and **179a** were treated with the cyclic amine **XLIX**/$CuCl_2$, the hetero-Diels−Alder adduct **256** was obtained as a racemate (Scheme 109).[194]

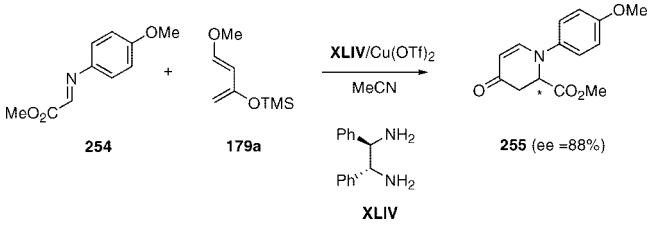
N-Tosylimines as well as *N*-carbamate imines proved to be efficient dienophiles and most of the hetero-Diels−Alder reactions with these imines were performed with the Danishefsky's diene **179a** in the presence of a chiral catalyst in order to access optically active dihydropyridinones.

In the case of *N*-tosyl imines, it appears that (*R*)-**XLV**/$CuClO_4$ can catalyze the hetero-Diels−Alder reaction of *N*-tosylimine **257** with Danishefsky's diene **179a** to produce

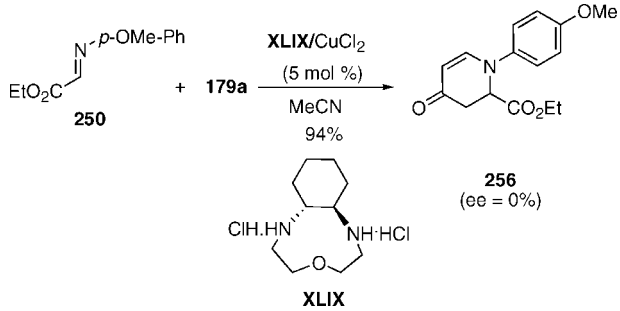
Scheme 107



Scheme 108



Scheme 109



the dihydropyridinone **258** in moderate yield (65%) and in moderate enantiomeric excess (48%) (Scheme 110).[190]

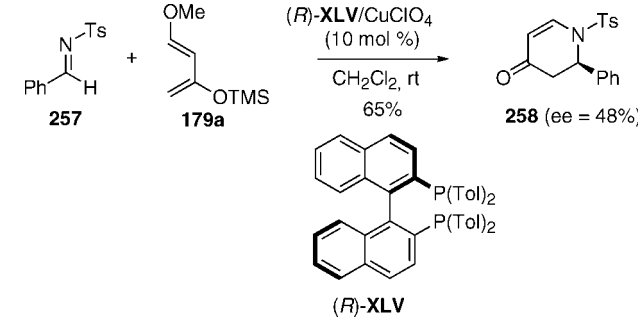
The yield and the enantiomeric excess of dihydropyridinone **258** can be increased when the reaction was performed in the presence of the Fesulphos/Cu(I) complex such as [**XLVIII**/CuBr]$_2$ as the catalyst. Under these conditions, the Mannich compound **259** was formed and transformed under acidic conditions to the cycloadduct **258** in good yield (90%) and excellent enantiomeric excess (93−97%). A great variety of chiral catalysts have been prepared, and the best one seems to be [**XLVIII**/CuBr]$_2$ in the presence of $AgClO_4$ (Scheme 111).[194,195]

Catalyst [**XLVIII**/CuBr]$_2$ can tolerate a great variety of substrates, and the aza-Diels−Alder adducts were obtained in good yields (65%−90%) and enantiomeric excesses (73−93%). It is also worth noting that a high yield and high enantioselectivity were obtained for adduct **261** when the aza-Diels−Alder reaction, involving the tosylimine of cinnamaldehyde **260** and diene **179a**, was catalyzed by a mixture of [**XLVIII**/CuBr]$_2$/$AgClO_4$, as **261** was isolated in yield 66% with an enantiomeric excess of 83%. Similarly, aldimine **262** issued from enolizable aliphatic aldehyde was transformed to **263** in 65% yield with an enantiomeric excess of 73% (Scheme 112).[195,196]

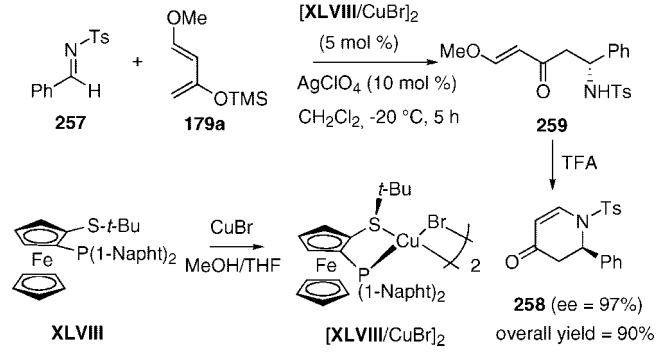
More activated dienophiles such as *N*-tosyl- and *N*-alkyl carbamate imines derived from glyoxylic esters were also involved in aza-Diels−Alder reactions. In the case of *N*-tosylimines derived from ethyl glyoxylate, different chiral copper catalysts were tested, such as (*R*)-**XLV**/Cu(I), (*S*)-**XLVI**/Cu(I), (3a*R*,9b*S*)-**XLVII**/Cu(I) complexes, as well as different solvents. It appeared that the use of (*S*)-**XLVI**/$CuClO_4$·4MeCN, as the catalyst in THF, gave the best stereochemical result for the aza-Diels−Alder product. Compound **244** was obtained in 82% yield with an enantiomeric excess of 87% when *N*-tosylimine **241** and diene **179a** were treated with 10 mol % of catalyst (*S*)-**XLVI**/$CuClO_4$ in THF. When this reaction was carried out in CH_2Cl_2, a better yield of 96% was obtained, but the enantiomeric excess of **244** was decreased to 77% (Scheme 113).[190]

The results for the reaction of the *N*-tosylimino ester **241** with *trans*-1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-

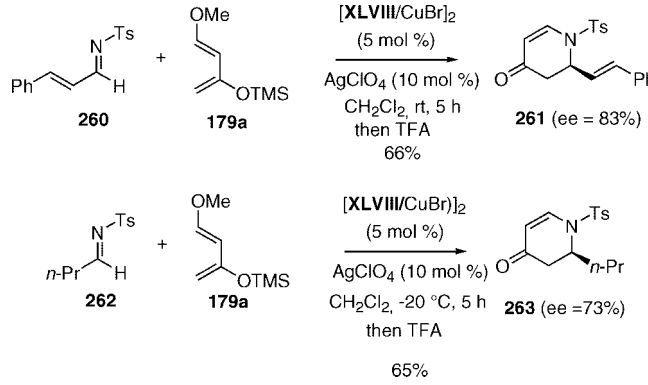
Scheme 110



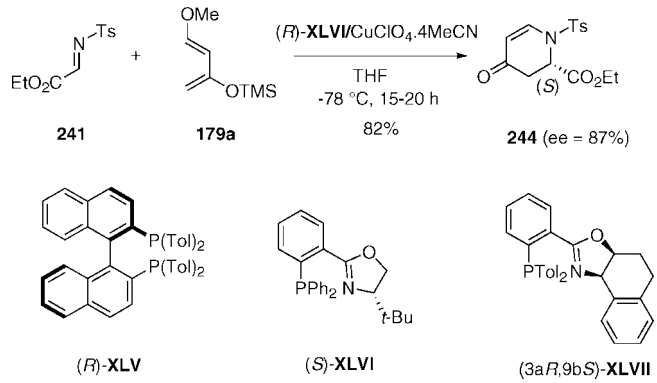
Scheme 111



Scheme 112



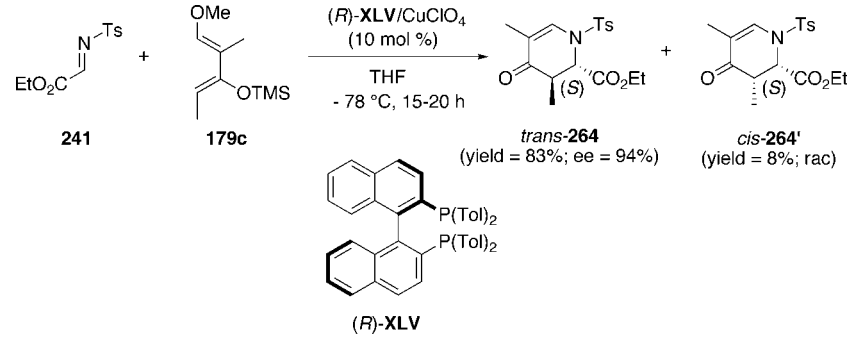
Scheme 113



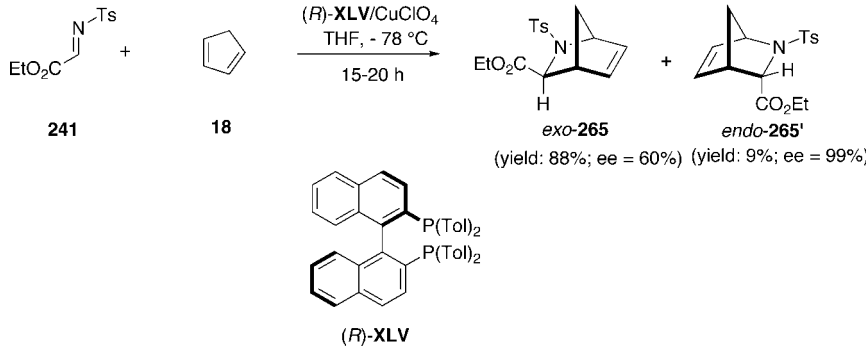
pentadiene (**179c**) show that the (*R*)-**XLV**/$CuClO_4$ catalyst gave the highest diastereoselectivity as a 10/1 ratio of *trans*-**264**/*cis*-**264′** was obtained. The diastereomer *trans*-**264** is formed in 83% yield and with 94% ee by using 10 mol % of catalyst (Scheme 114).[190]

Other dienes can react with **241** to produce aza-Diels−Alder compounds. When **241** reacts with 1,3-cyclopentadiene (**18**), unsaturated bicyclic compounds **265**/**265′**

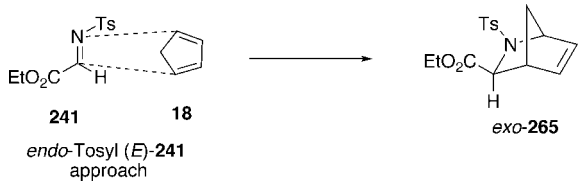
Scheme 114



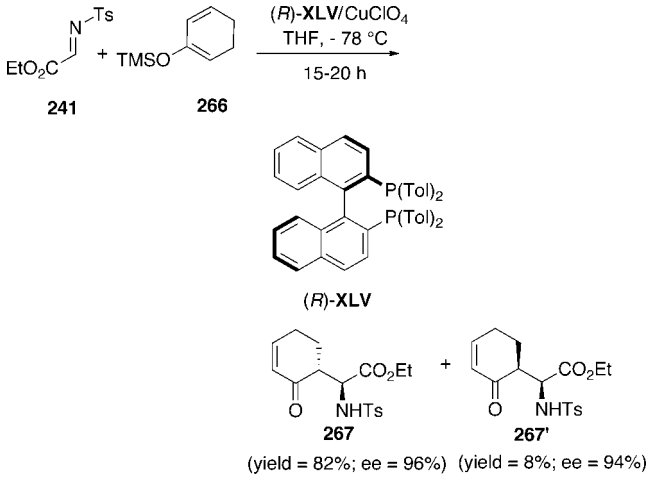
Scheme 115



Scheme 116



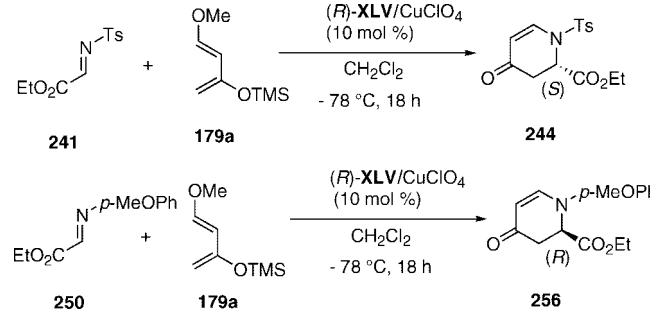
Scheme 117



are obtained with good *exo*-selectivity (ratio 10/1) when the reaction is catalyzed by **XLV**/$CuClO_4$ in THF.[190] 1,3-Cyclohexadiene (**34**) can also be used in aza-Diels−Alder even if the yield is slightly low; the enantiomeric excess of the *exo*-cycloadducts is up to 90% (Scheme 115).

For the *exo* preference in this catalytic enantioselective reaction, it was postulated that the reaction proceeds via the (*E*)-form of the *N*-tosyl α-iminoester **241** with the *N*-tosyl group oriented *endo* relative to the diene, thus leading to the *exo* adduct **265** (Scheme 116).[190]

Scheme 118

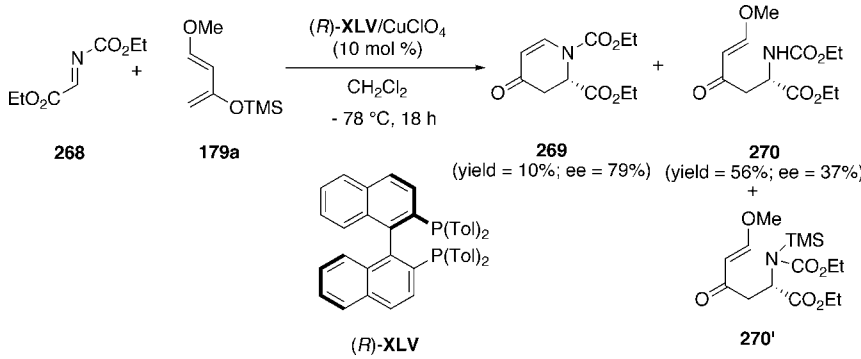


A wide array of 2-aminobutadienes can be used to perform an aza-Diels−Alder with *N*-alkyl- and *N*-aryliminoesters in the presence of copper catalysts, the aza-Diels−Alder adducts are obtained in good yields. On the contrary, the reaction did not lead to the aza-Diels−Alder products when *N*-tosyl α-imino esters such as **241** reacted with diene **266** as substituted cyclohexenones resulting from a Mannich-type reaction were obtained. When **241** reacted with **266** in the presence of catalyst (*R*)-**XLV**/$CuClO_4$, the substituted cyclohexenones **267/267′** were formed (dr = 10/1; ee >94%) (Scheme 117).[190]

It is worth noting that by using the same catalyst, (*R*)-**XLV**/$CuClO_4$, the absolute configuration of the aza-Diels−Alder adduct **244**, obtained from **241** and **179a**, is (*S*) and the absolute configuration of **256**, obtained from **250** and **179a**, is (*R*) (Scheme 118).[190,197]

In the case of imine **241**, the *N*-tosyl group can participate in the coordination of the chiral Lewis acid, whereas for imine **250**, the *N*-*p*-methoxyphenyl substituent cannot participate in the coordination and a bidendate chelate of type **Y** is formed. For the *N*-tosyl glyoxylate imine, several coordination modes are possible. It was proposed that the *N*-tosyl α-iminoester coordinates in a tridentate fashion, whereas the *N*-*p*-methoxylphenyl glyoxylate imine coordi-

Scheme 119



nates in a bidentate fashion leading to a tetrahedral intermediate (Figure 14).[190]

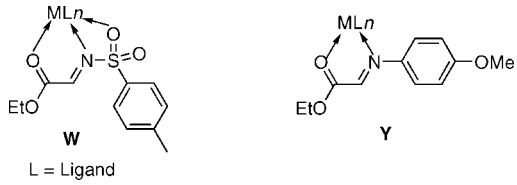


Figure 14. Transition states.

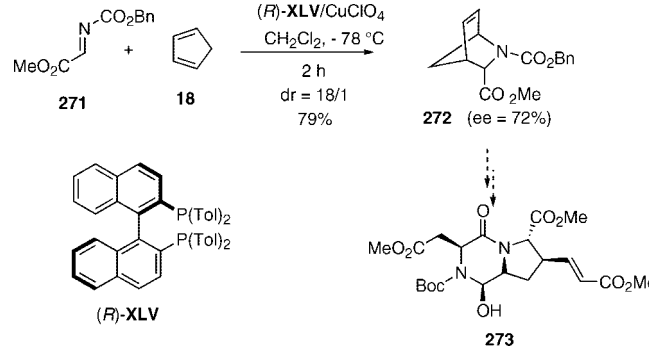
Contrary to the results with *N*-tosylimine **241**, in the reaction of the *N*-carbamate imine **268** derived from ethyl glyoxylate with Danishefsky's diene **179a**, the aza-Diels−Alder and the Mannich-type addition products were both isolated. For the reaction of imine **268**, the aza-Diels−Alder adduct **269** was formed with a 79% ee, while the isolated yield was low (10% yield). In contrast to this, the Mannich-type addition product **270** was formed as the major product (56% yield), however, with low enantiomeric excess (37%). Furthermore, a certain amount of the Mannich-type adduct **270′**, with a TMS-group on the nitrogen atom, was also formed. It is worth noting that **270** and **270′** were transformed slowly into the aza-Diels−Alder compound **269** with a low enantiomeric excess by treatment with diluted TFA in CH_2Cl_2. These results indicate that two different reaction pathways are taking place simultaneously. One reaction pathway gives the aza-Diels−Alder product with good chiral induction, whereas the other pathway leads to the Mannich-type addition product **270** in low enantiomeric excess (Scheme 119).[190]

N-Carbamate iminoesters, derived from glyoxylic esters, such as **271** can also react with 1,3-cyclopentadiene (**18**) to produce unsaturated bicyclic heterocycles such as **272** in good enantiomeric excesses when the reaction was catalyzed by (*R*)-**XLV**/$CuClO_4$. These heterocyclic compounds were versatile intermediates in the synthesis of different dipeptide mimetics (Scheme 120).[198]

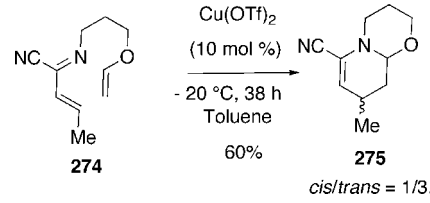
3.2.1.2. Azadienes. The hetero-Diels−Alder reaction of azadienes represents both a direct and convergent strategy for the construction of functionalized six-membered ring amino heterocyclic compounds. 1-Azadienes, 2-azadienes, and peculiar azadienes such as tetrazines can be involved in hetero-Diels−Alder reactions to produce heterocyclic compounds.

To be involved in the hetero-Diels−Alder reaction, it is crucial that 1-azadienes are activated and the introduction of electron-donating (NMe_2)[199] or -withdrawing (*N*-OAc[200] or *N*-SO_2AR[201,202]) groups onto the azadiene nitrogen has proven to be effective, as well as the substitution at the C2 position of 1-azadienes by a cyano group.[203,204]

Scheme 120



Scheme 121



3.2.1.2.1. 1-Azadienes. 2-Cyano-1-azadienes bearing either a *N*-acyl or *N*-phenyl substituent react under thermal conditions with both electron-rich (LUMO azadiene-controlled) and electron-poor (HOMO azadiene-controlled) dienophiles.[203,204]

The $Cu(OTf)_2$-catalyzed intramolecular Diels−Alder reaction of 2-cyano-1-azadiene **274**, containing an electron-rich enol ether dienophile component, undergoes cycloaddition to give the oxazino-piperidines **275** in 60% yield with a *cis*/*trans* ratio of 1/3.7 (Scheme 121)[204,205].

We have to point out that the asymmetric version of this intramolecular cycloaddition catalyzed by (*S*,*S*)-**Va**/$Cu(OTf)_2$ was not efficient as **275** was obtained with an enantiomeric excess of 8%. This results suggests that the cyano group is not coordinated to the copper cation and that the reaction could proceed via a single-point diene/catalyst complex **Z** (Figure 15).[204]

3.2.1.2.2. 2-Azadienes. 2-Azadienes were also involved in hetero-Diels−Alder reactions, and *N*-arylimines, which react

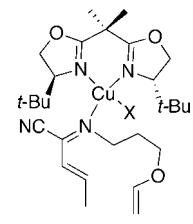
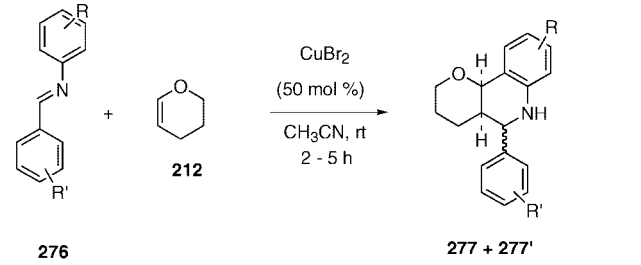
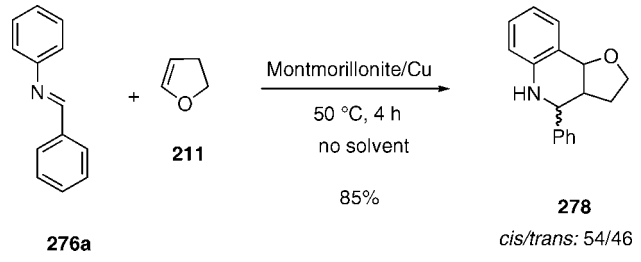


Figure 15.

Scheme 122



Scheme 123



with nucleophic olefins, can be considered to be 2-azadienes providing an easy access to substituted tetrahydroquinolines. $CuBr_2$ was used as the Lewis acid to catalyze the hetero-Diels−Alder reaction between *N*-benzylidene-anilines of type **276** and dihydropyran **212** in acetonitrile at room temperature, to produce the corresponding pyrano-tetrahydroquinoline adducts (**277** and **277′**) in poor to good yields (46−76%). Mixtures of *cis*- and *trans*-isomers **277** and **277′** were obtained in ratios that varied from 21/79 to 38/62 depending on the substituents (Scheme 122).[206]

Other copper catalysts such as montmorillonite-enwrapped copper catalysts (Cu^{2+}-montmorillonite) were also used to perform the hetero-Diels−Alder reaction between **276a** and dihydrofuran **211**, leading to the tetrahydroquinoline **278** in high yield (85%) and with an *endo*/*exo* ratio of 54/46 (Scheme 123).[55]

Ghosez et al. prepared enantiomerically pure piperidones by using a hetero-Diels−Alder reaction involving electron-rich 2-azadienes and olefinic dienophiles activated by the chiral (*S*,*S*)-**Va**/$Cu(OTf)_2$ complex.[208] Thus, the copper(II) catalyst (*S*,*S*)-**Va**/$Cu(OTf)_2$ effectively produced piperidinone **280** at −45 °C from **279** and **33** with high regio- and *exo*-selectivity (99/1) and in high enantioselective excess (Scheme 124).[208]

The observed adduct results from an *exo*-approach of the diene to the less hindered face of the square-planar complex of **Va**/Cu(II) with the dienophile (Figure 16).

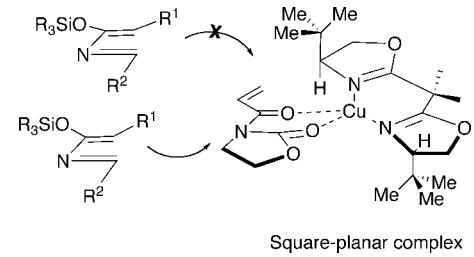
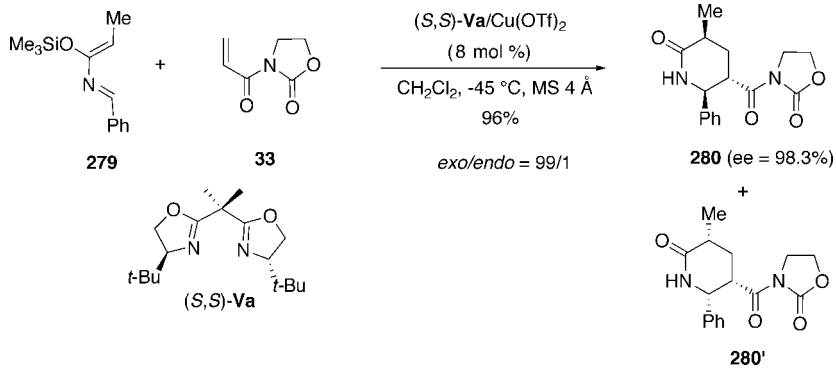


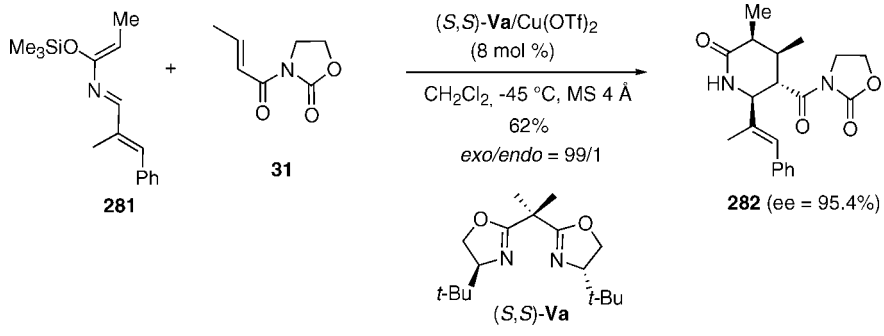
Figure 16.

We have to point out that 2-azadienes bearing a substitutent at C1 other than a phenyl group were difficult to prepare.[209] This limitation was overcome by preparing azatrienes such as **281**.[208] When this latter diene was involved in a hetro-Diels−Alder reaction with diene **31**, a good *exo*/*endo* selectivity was also observed for the hetero-Diels−Alder cycloadduct **282**. A good yield and excellent enantiomeric excess were obtained for this latter compound (Scheme 125).[208]

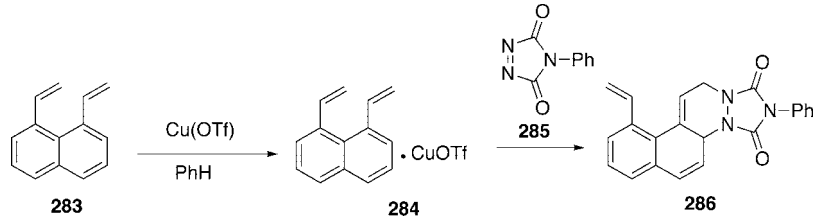
Scheme 124



Scheme 125



Scheme 126



3.2.2. Azo Compounds

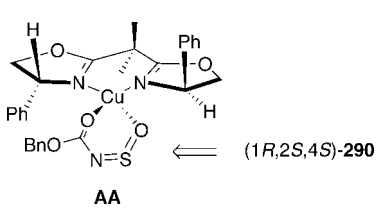
Azo compounds can be involved in hetero-Diels−Alder reactions and can react as dienophiles. When diene **283** was treated with copper trifluoromethane sulfonate (CuOTf), a 1/1 complex **283**/CuOTf (complex **284**) was formed in which both the vinyl groups appeared to be complexed to the Cu(I) ion. By treating *N*-phenyl triazolinedione **285** with complex **284**, the same cycloadduct **286** was formed as when **283** was reacted with **285** without Cu(OTf). From these results, it is not clear if *N*-phenyltriazoline dione **285** reacts with complex **284** or directly with compound **283** (Scheme 126).[209]

Azodicarboxylates can also react as dienophiles in hetero-Diels−Alder reactions. 1,3-Cyclopentadiene (**18**) reacts with {[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]diazenyl} formate (TOCDF) **287**. When the reaction was catalyzed by (*R*,*R*)-**Vb**/Cu(OTf)$_2$ (10 mol %), the hetero-Diels−Alder adduct **288** was isolated in high yield (92%) but in low enantiomeric excess (∼20%). Changing the chiral ligand to a more sterically hindered ligand did not improve the enantioselectivity (Scheme 127).[210]

3.2.3. N-Sulfinyl Dienophiles

Asymmetric hetero-Diels−Alder reactions of 1,3-cyclohexadiene (**34**) with *N*-sulfinyl dienophile **289**, promoted by a stoichiometric amount of chiral ligand/Cu(II) complexes, afforded *endo*-adducts in good yields. Among the different chiral catalysts tested, catalyst (*R*,*R*)-**Vb**/Cu(OTf)$_2$ turned out to be the best. By using 100 mol % of this catalyst at −85 °C, **290**/**290′** (*endo*/*exo* adducts) were obtained in a ratio of 95/5 in 63% yield; the *endo*-adduct was obtained with an enantiomeric excess of 92% (Scheme 128). The absolute configuration (1*R*,2*S*,4*S*) of **290** was determined by X-ray diffraction.[211]

The postulated intermediate, represented Figure 17, is based on the assumption that the *N*-sulfinyl dienophile **289** engages in a bidentate coordination to the chiral Lewis acid with the *N*-sulfinyl oxygen and the carbonyl oxygen or one of the sulfonyl oxygen, respectively. A tetrahedral metal center can explain the stereochemical outcome of the reaction (Figure 17).

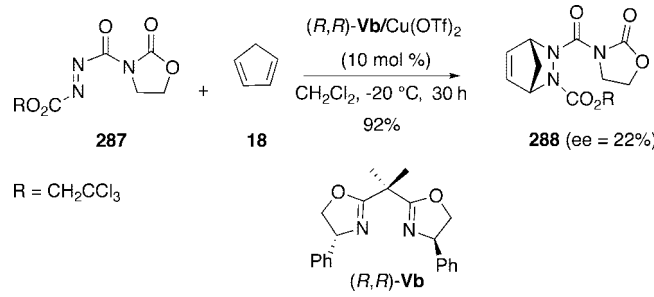


AA

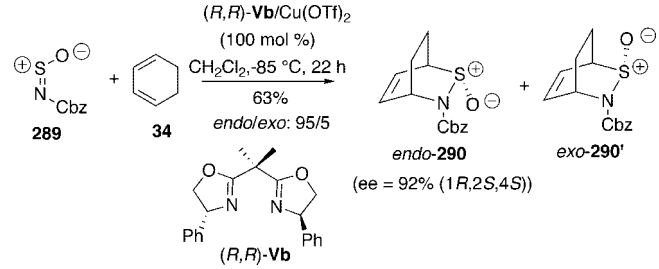
Figure 17. Transition state.

N-Sulfinyl derivatives were also reacted with acyclic 1,3-dienes to produce hetero-Diels−Alder adducts. We have

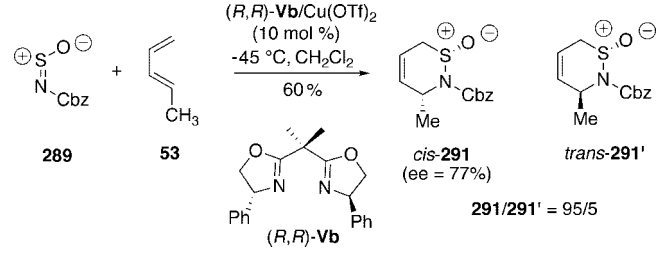
Scheme 127



Scheme 128



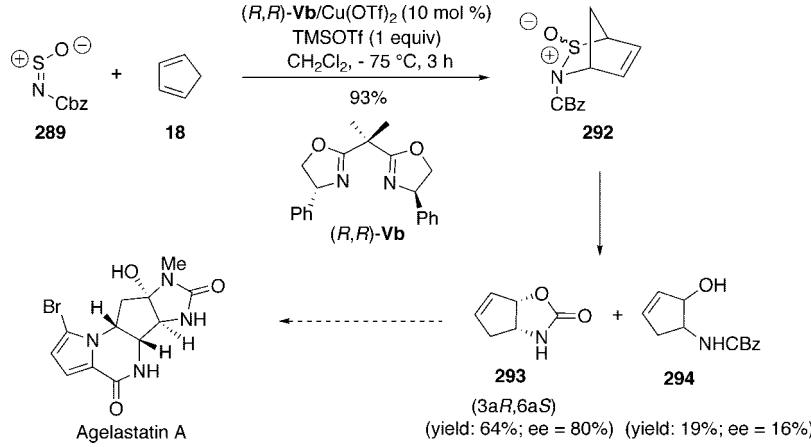
Scheme 129



to point out that symmetrical and unsymmetrical 1,3-dienes can also be involved in hetero-Diels−Alder reactions with sulfoximines. Sulfoximine **289** reacted with the 1,3-diene **53** to produce the *cis*-**291** adduct and the *trans*-**291′** adducts in 93% yield and in a ratio of 95/5. When the reaction was performed with 10 mol % of (*S*,*S*)-**Vb**/Cu(OTf)$_2$, the adduct *cis*-**291** was obtained with an enantiomeric excess of 77% (Scheme 129).[212]

A catalytic version in (*R*,*R*)-**Vb**/Cu(OTf)$_2$ was possible when 1 equiv of TMSOTf was added to the reaction media. When the hetero-Diels−Alder reaction of 1,3-cyclohexadiene (**34**) with **289** was performed in the presence of 10 mol % of (*R*,*R*)-**Vb**/Cu(OTf)$_2$ and 1 equiv of TMSOTf, the hetero-Diels−Alder adduct was obtained with excellent diastereoselectivity (dr = 95/5) and the enantiomeric excess of the *endo*-adduct was excellent (∼ 89%). The role of the additive was unclear, but the authors hypothesized that it was involved in the breakdown of catalyst−sulfoximine aggregates and assisted in the release of the catalyst from the hetero-Diels−Alder adducts.[213]

Scheme 130



A precursor to the C-ring of agelastatin A was obtained from **289** and 1,3-cyclopentadiene (**18**) using (*R*,*R*)-**Vb**/$Cu(OTf)_2$ (10 mol %) and TMSOTf (1 equiv) in CH_2Cl_2 (Scheme 130).[212]

3.2.4. Nitroso Dienophiles

A wide range of nitroso compounds, which are very reactive hetero-dienophiles, can undergo hetero-Diels−Alder reactions at low temperatures.[214,215] The disproportionation of Boc-NHOH to produce Boc-N═O can be activated by Cu-catalyst such as CuBr·Me_2S, and the resulting Boc-N═O can be involved in hetero-Diels−Alder reaction with 1,3-dienes. When Boc-NHOH **295** and 1,3-cyclohexadiene (**34**) were treated with 10 mol % of CuBr·Me_2S, acylnitroso **296** was efficiently trapped to afford the corresponding hetero-Diels−Alder adduct **297**. Compound **297** was produced after 65 h in 41% yield. A dramatic improvement in the efficiency of the hetero-Diels−Alder cycloaddition was achieved when the reaction was conducted by using a stoichiometric oxidant such as H_2O_2, as the reaction proceeded at 20 °C within a few hours with CuCl as the catalyst. A possible catalytic pathway is outlined in Scheme 131.[216]

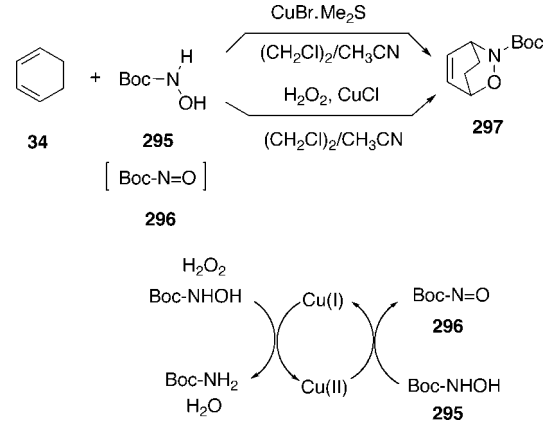
The α-acyloxy nitroso **299** was also examined. This compound was easily prepared from oxime **298** by treatment with (diacetoxyiodo)benzene and was then involved in a hetero-Diels−Alder reaction with 1,3-cyclohexadiene (**34**) in the presence of $Cu(OTf)_2$. After treatment with HCl and Boc_2O in basic conditions, the expected bicyclic oxazine **297** and the hydroxycarbamate **300** were formed. Compound **300** resulted from the N−O bond cleavage of **297** under the conditions used (Scheme 132).[217]

The hetero-Diels−Alder reaction was performed between **299** and a diverse array of cyclic 1,3-dienes and 1,3-acyclic dienes.[217] This reaction can also be performed in water with a ratio **297**/**300** (90/10) in favor of **297** but in a low yield (23%).[218]

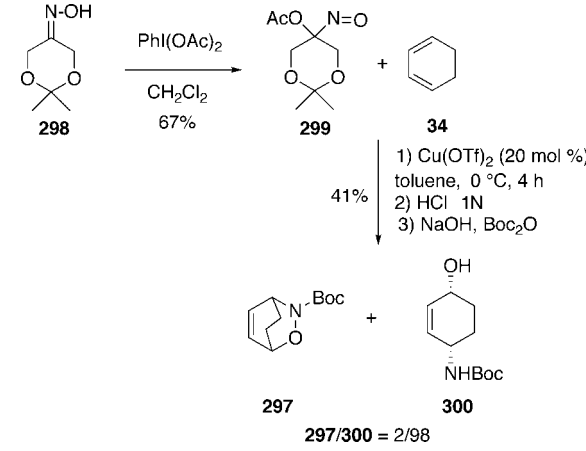
The acylnitroso Diels−Alder cycloadducts were transformed to 4-acylamino analogues of LY 35470, a selective agonist for group II metabotropic glutamate receptors.[219] The synthesis of a unique cyclopentenyl hydroxamic acid based inhibitor of 5-lipoxygenase was also achieved through this method.[220]

Less reactive nitroso dienophiles such as arylnitroso derivatives were better suited for Lewis acid mediated catalysis in the nitroso Diels−Alder cycloaddition. Several complexes of arylnitroso compounds with metals have been

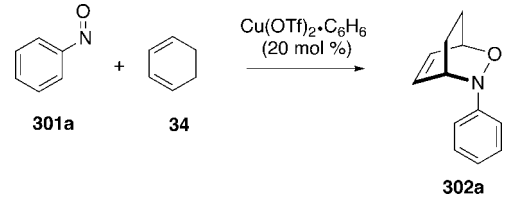
Scheme 131



Scheme 132

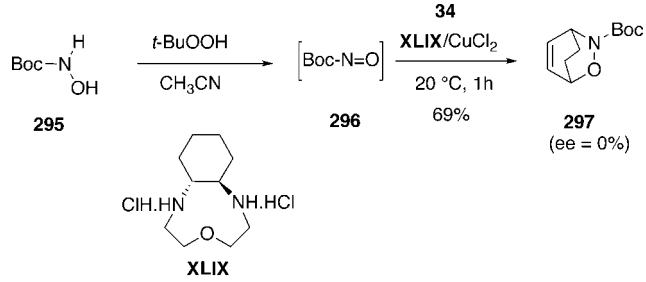


Scheme 133

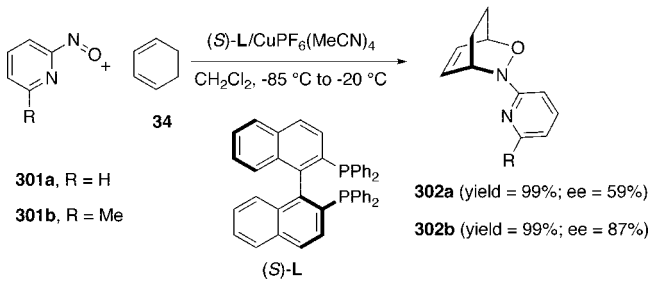


reported. Unfortunately, Lewis acids such as $Cu(OTf)_2.C_6H_6$ failed to affect the rate of arylnitroso **301a** cycloaddition with 1,3-cyclohexadiene (**34**),[221] and the corresponding Diels−Alder adduct **302a** was obtained at the same rate as in the normal process (Scheme 133).[222]

Scheme 134



Scheme 135



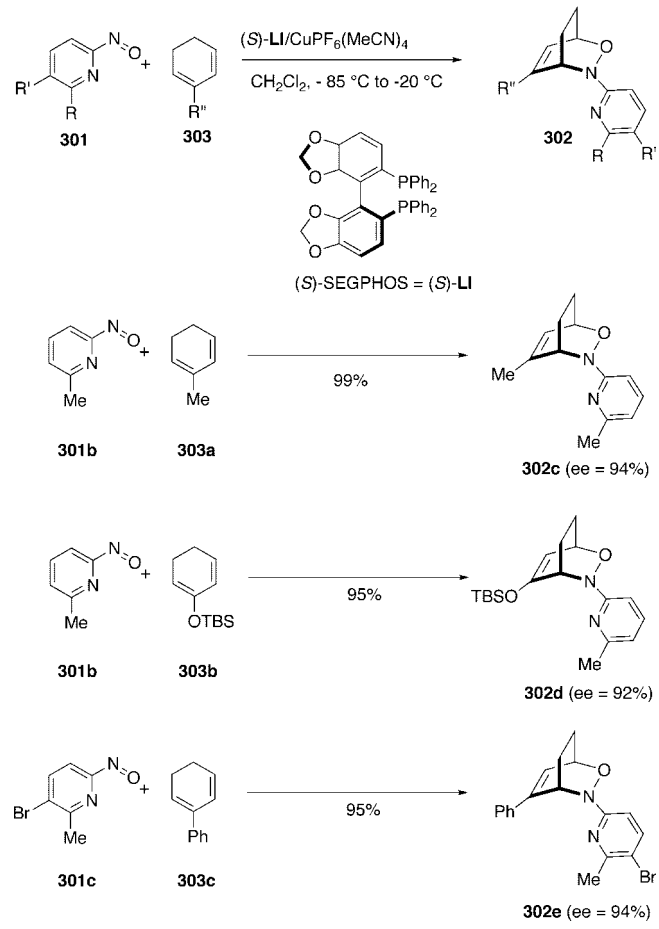
The first attempt to obtain optically active cycloadducts from arylnitroso derivatives and 1,3-dienes was achieved by Watkinson et al. in 2003.[193] The enantiomerically pure complex **XLIX**/$CuCl_2$ was used as the oxidizing agent. Unfortunately, no enantioselectivity was detected. These results indicate that the dissociation of the acylnitroso **297** from the chiral metal complex occurs before the [4+2]-cycloaddition (Scheme 134).[193]

Difficulties for successful enantioselective hetero-Diels−Alder with nitroso compounds are also probably due to the fact that nitroso compounds exist in organic solvents as a monomer−azetoxy dimer equilibrium[223] and that Lewis acids are able to form stable complexes with the azetoxy dimer of arylnitroso compounds.[221,224] Recently, a breakthrough in this series was achieved by Yamamoto et al.[225] They generated chelated monomeric 2-nitrosopyridine derivatives with suitable Lewis acid catalysts that produced hetero-Diels−Alder adducts with good enantiomeric excesses when a chiral Cu/ligand complex is used. When **301a**and **34** were treated with catalyst (*S*)-**L**/$CuPF_6(MeCN)_4$ at −85 °C, cycloadduct **302a** was produced quantitatively in 59% ee. By increasing the steric hindrance at the C6 position of the 2-nitrosopyridine, higher enantioselectivities were obtained (77−87%). The best enantiomeric excess for the cycloadduct was obtained with 6-methyl 2-nitrosopyridine **301b** as **302b** was isolated in 99% yield and with an enantiomeric excess of 87% (Scheme 135).[225]

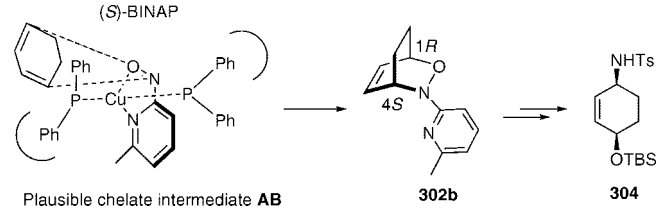
Different ligands were tested, and the best ligand is (*S*)-SEGPHOS, (*S*)-**LI**. The cycloadduct **302c** was isolated in quantitative yield and with an enantiomeric excess of 94% when the hetero-Diels−Alder reaction, involving **301b** and diene **303a** was carried out in the presence (*S*)-SEGPHOS/$CuPF_6(MeCN)_4$ [(S)-**LI**/$CuPF_6(MeCN)_4$]. Different cyclic 1,3-dienes of type **303** can be involved in this hetero-Diels−Alder reaction as well as different substituted 6-alkyl 2-nitrosopyridines of type **301**, producing cycloadducts of type **302** in excellent yield and with enantiomeric excesses up to 90% (Scheme 136).[225]

The copper catalyst is very effective, and these reactions proceed via a highly organized transition state. A plausible chelate intermediate **AB** has been proposed to explain the

Scheme 136



Scheme 137



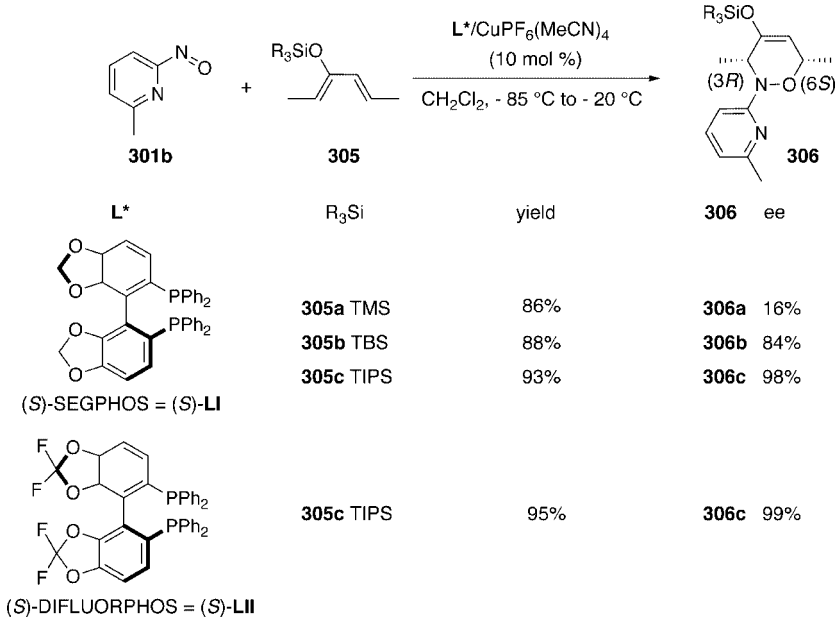
absolute configuration of the stereogenic centers. The cycloadducts of type **302** can be transformed to the corresponding protected amino alcohols of type **304** by treatment with $Mo(CO)_6$ and $NaBH_4$ (cleavage of the N−O bond) (Scheme 137).[225]

It is worth noting that under the previous conditions with (*S*)-(SEGPHOS)/$CuPF_6$·$(MeCN)_4$ [(S)-**LI**/$CuPF_6(MeCN)_4$], the (2*Z*,4*E*)-3-trimethylsilyloxy-2,4-hexadiene gave the hetero-Diels−Alder adduct with complete regioselectivity[226,227] but in very low enantiomeric excess (16%). However, the low enantioselectivity was improved by simply increasing the size of the silyl group (R^3 = TMS < TBS < TIPS). Furthermore, by using diene **305c**, the enantiomeric excess of the hetero-Diels−Alder adduct **306c** was increased to 99%[227] by using (*S*)-DIFLUORPHOS/$CuPF_6(MeCN)$[228] [**LII**/$CuPF_6(MeCN)$] (Scheme 138).

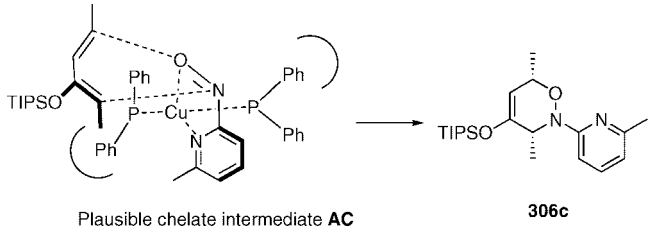
A transition state such as **AC** was envisioned to explain the absolute configuration of the cycloadduct **306c** (Scheme 139).

Kinetic resolution to obtain enantio-enriched compounds from racemic dienes was achieved with catalyst **LIII**/$[Cu(MeCN)_4]PF_6$ (10 mol %) and applied to the nitroso-

Scheme 138



Scheme 139



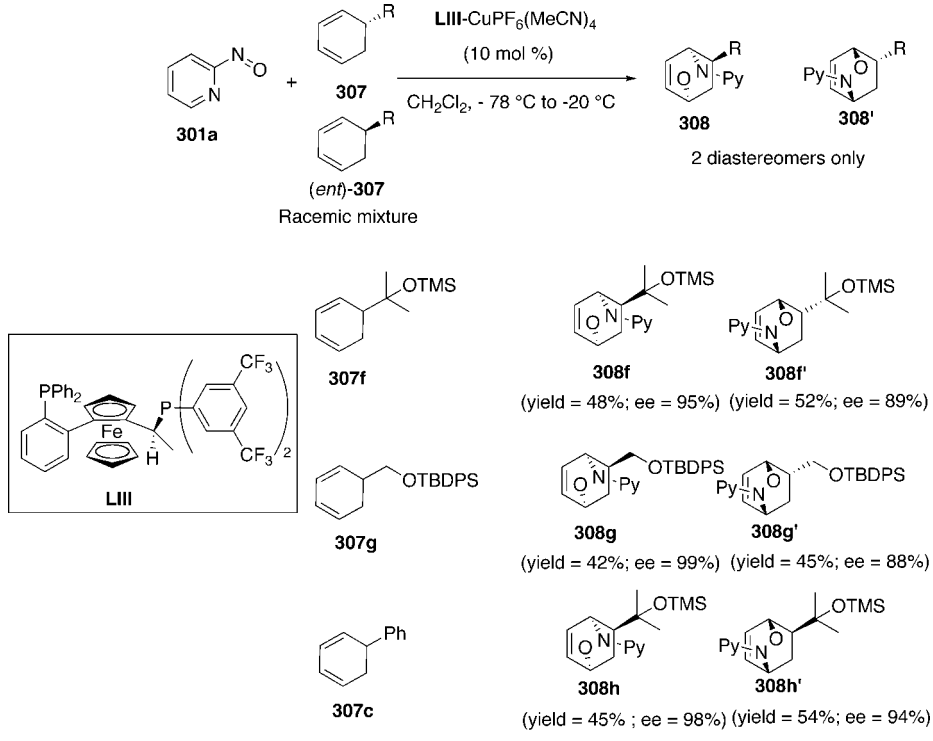
Diels−Alder reaction involving **301a**. The racemic starting material **307** was selectively converted to two of the eight possible diastereomers **308** and **308′**. Both diastereomers were obtained in high yields and enantiomeric excesses (Scheme 140).[229]

3.3. Thia-Diels−Alder Reaction

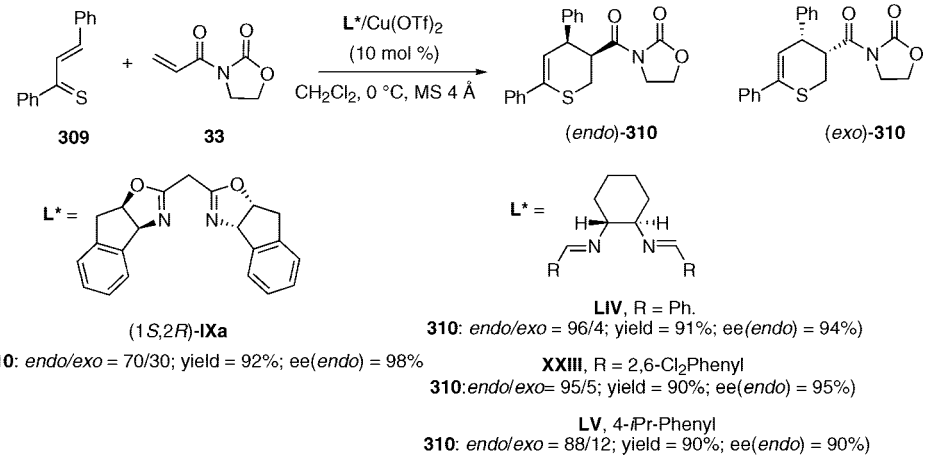
Despite its promising utility, the asymmetric hetero-Diels−Alder reaction of thio-carbonyl compounds has received less attention than oxa- and aza-Diels−Alder reactions. A few reports on the thia-Diels−Alder reaction exist.[230–232]

At first, the enantioselective thia-Diels−Alder was achieved with thiabutadiene **309** as the heterodiene and oxazolidinone **33** as the dienophile by using a stoichiometric amount of Lewis acid bis(imine)/Cu(OTf)$_2$ complexes.[233] Among the different bis(imine)/Cu(OTf)$_2$ complexes tested, **LIV**/Cu(OTf)$_2$ was revealed to be the best catalyst. Furthermore by adding molecular sieves 4Å in the reaction media, the amount of the catalyst can be decreased

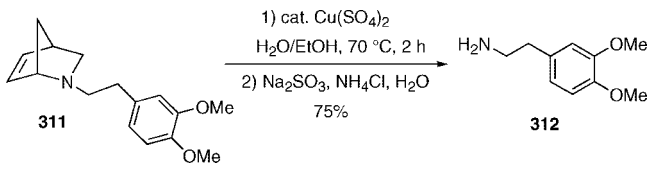
Scheme 140



Scheme 141



Scheme 142



to 10 mol % and the hetero-Diels−Alder adduct, dihydrothiopyrane **310**, was obtained, from **309** and oxazolidinone **33**, with a high *endo*/*exo* ratio of 96/4, in good yield (91%) and in 94% ee for the *endo*-adduct.[233] Other catalysts, such as **IXa**/Cu(OTf)$_2$, were also tested, and it was found that the hetero-Diels−Alder adducts **310** were formed, at room temperature, with an *endo*/*exo* ratio of 70/30. When **IXa**/Cu(OTf)$_2$ was used the enantiomeric excess was excellent as the major *endo* compound **310** was isolated with an enantiomeric excess of 98% (Scheme 141).[234]

3.4. Miscellaneous

Retro hetero-Diels−Alder reactions can take place and Cu(I) or Cu(II) can catalyze these cycloreversions (Scheme 142). For example, the Cu(II)-catalyzed cycloreversions are best conducted at 70 °C in aqueous ethanol or aqueous methanol. The general process is illustrated below for the cycloreversion of the 2-azanorbornene **311** derived from homoveratrylamine **312** (Scheme 142).[235]

4. Conclusion

Diels−Alder reactions, catalyzed by copper salts, are very important reactions that have been used to construct unsaturated carbocyclic six-membered rings and heterocyclic six-membered rings. In order to carry out asymmetric reactions, a great number of optically active ligands have been developed. The most common and efficient ligands are typically the optically active C_2-symmetric bis(oxazolines); however, 5−10 mol % of the ligand/Cu complexes are used, and it would be beneficial to find other chiral ligands that would be able to increase the turnover of the catalyst. By using the catalyzed Diels−Alder reaction, up to four stereogenic centers can be controlled, even quaternary centers, and the resulting six-membered rings are very useful intermediates that can be involved in the syntheses of natural and/or biologically active compounds.

5. Acknowledgments

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