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Recent advances in homogeneous enantioselective Diels–Alder reactions catalyzed by chiral transition-metal complexes

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Contents

Abstract

The homogeneous enantioselective Diels–Alder reactions catalyzed by chiral transition-metal complexes are reviewed. Special attention has been paid to the mechanistic aspects of

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the process in order to account for the stereochemical outcome of the reactions.

Keywords: Homogeneous reactions; Enantioselective Diels–Alder reactions; Transition metals

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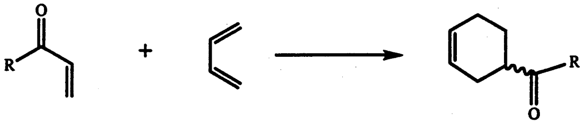
1. Introduction

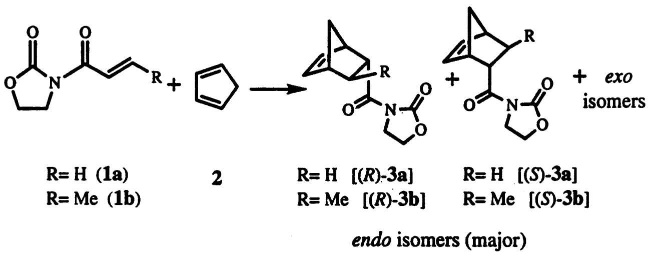
The Diels–Alder reaction is one of the most versatile and powerful synthetic transformations in organic chemistry (Scheme 1) [1]. Since the first reports on chiral Lewis acid catalyzed enantioselective Diels–Alder reactions [2] great progress has been made in the development of catalytic enantioselective versions of this reaction [3]. Although at a first stage aluminum and boron based catalysts with chiral ligands dominate in this chemistry, recent focus in this area has been on the use of chiral transition-metal-based Lewis acid catalysts. The fine tunning of the electronic properties and chiral environment of the coordination complexes involved could be easier by using transition metal complexes, allowing a better understanding of these reactions. This review will deal with recent advances in homogeneous enantioselective homo- and hetero-Diels–Alder reactions catalyzed by chiral transition metal complexes, covering the literature from the beginning of 1997 up to the middle of 1999. Nevertheless, previous literature, closely related to the recent advances reported here, will also be considered. Some previous reviews on this area are collected in Ref. [3].

2. Homo Diels–Alder reactions

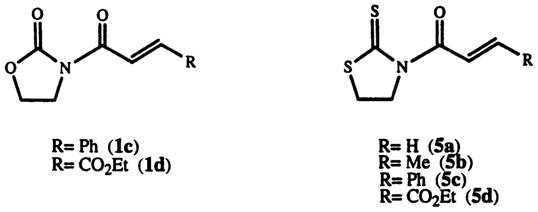
Corey and coworkers reported the first enantioselective Diels–Alder reaction between 3-acryloyl-1,3-oxazolidin-2-one (**1a**) as bidentate dienophile and cyclopentadiene (HCp, **2**) as diene catalyzed by chiral iron(III)- [4] and magnesium(II)- [5] bis(oxazoline) complexes (Scheme 2). The bis(oxazoline) used was 2,2-bis[2-{4(*S*)-phenyl-1,3-oxazolinyl}]propane (*S*)-**4e** and the catalyst was in situ prepared from the corresponding metal, iodine, and the chiral auxiliary (*S*)-**4e**. Shortly after that, Evans et al. published their results on the Diels–Alder reaction of unsubstituted **1a**, β-substituted acrylimides **1b**–**d** and thiazolidine-2-thione analogs **5a**–**d** with HCp catalyzed by chiral copper(II)–bis(oxazoline) complexes [6] (Scheme 3). With the bis(oxazolines) **4e**–**g** as chiral ligands diastereomeric excesses (de) up to 98:2



Scheme 1.



Scheme 2.

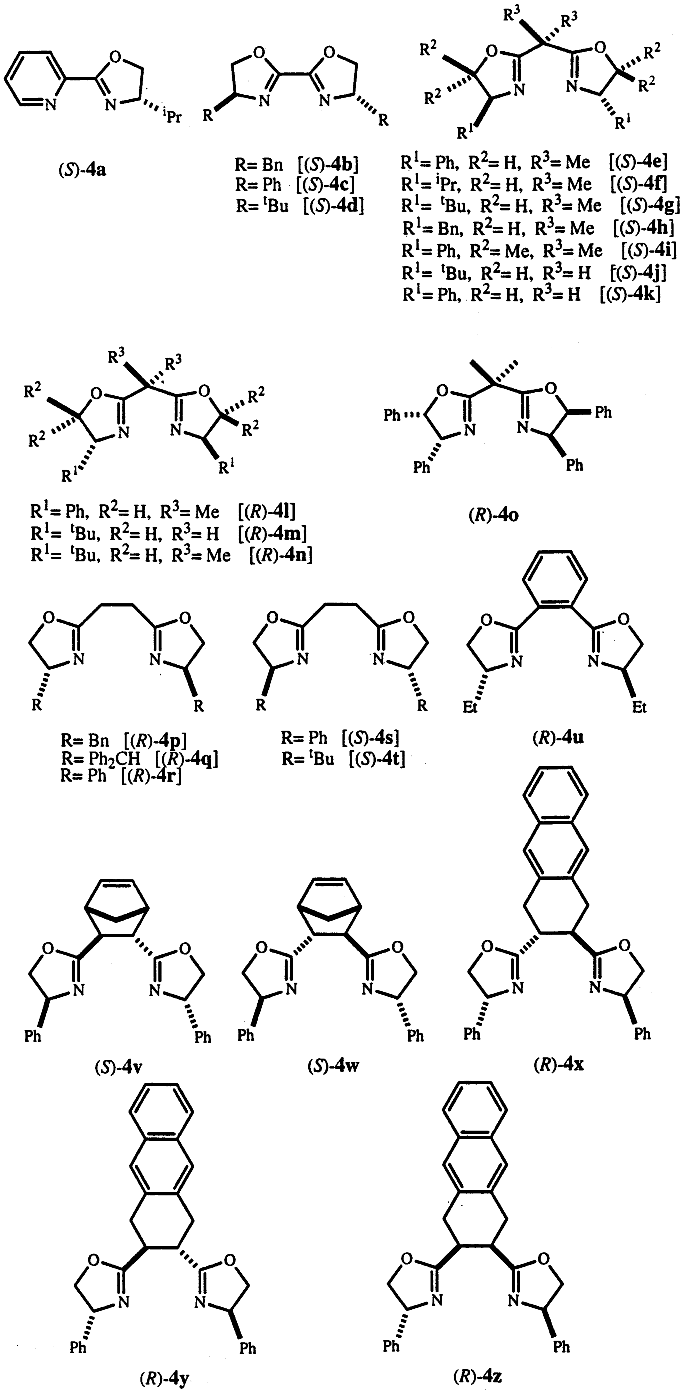


Scheme 3.

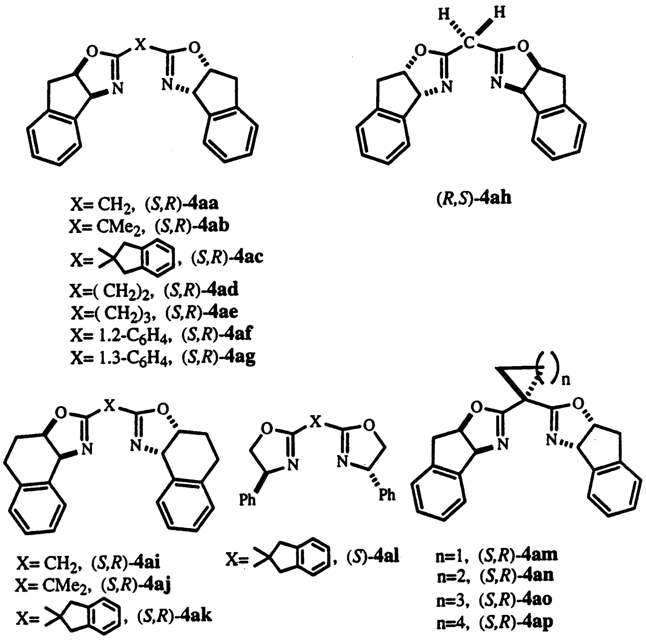
(*endo*:*exo* ratio) and enantiomeric excesses (ee) higher than 98% ((*R*)-**3a**) were achieved. The sense of the asymmetric induction was rationalized on the basis of square-planar rather than tetrahedral intermediate copper(II)–dienophile complexes [6].

Since then, a large number of efficient metal catalysts with bis(oxazoline) ligands were developed [7] and in particular in the last years some new results have appeared in this area. In this context, Takacs and coworkers reported the enantioselective Diels–Alder reaction of acrylimides **1a**,**b** with HCp catalyzed by zinc(II) or copper(II) triflates in conjunction with a variety of bis(oxazolines) (**4b**–**d**,**j**–**k**,**l**,**p**–**t**,**v**–**z**) as chiral auxiliaries [8,9]. Scheme 4 collects most of the bis(oxazoline) ligands involved in this review.

Conversions ranging from 60 to 99% were achieved after 24 h of reaction in CH_2Cl_2, at room temperature (r.t.), with a catalyst loading of 20 mol.% for the acrylimide **1b**. In general, the copper catalysts were faster than the zinc ones. Among the less constrained bis(oxazolines), **4b**–**d**,**j**–**k**,**l**,**p**–**t**, the best results with the zinc catalysts were achieved for the 1,4-bis(oxazolines) (*R*)-**4r** and (*S*)-**4s** (98% conversion, 8:1 *endo*:*exo* ratio, 72% ee (*R*)-**3b** [10] and 99% conversion, 8:1 *endo*:*exo* ratio, 78% ee (*S*)-**3b**, respectively), while the copper complex with the 1,3-bis(oxazoline) (*S*)-**4g** gave the best results (90% conversion, 6.7:1 *endo*:*exo* ratio, 76% ee (*S*)-**3b**). These results reflect the different optimal distances separating the two oxazoline moieties demanded by different metals [8]. For the more highly constrained and chiral at the backbone bis(oxazolines), **4v**–**z**, ee up to 88% (Cu-(*S*)-**4w** catalyst, (*S*)-**3b**) or 78% (Zn-(*S*)-**4v** catalyst, (*S*)-**3b**) were achieved. It is interesting to point out that the chirality present in the backbone of these


(S)-4a
R= Bn [(S)-4b]
R= Ph [(S)-4c]
R= ᵗBu [(S)-4d]
R¹= Ph, R²= H, R³= Me [(S)-4e]
R¹= ⁱPr, R²= H, R³= Me [(S)-4f]
R¹= ᵗBu, R²= H, R³= Me [(S)-4g]
R¹= Bn, R²= H, R³= Me [(S)-4h]
R¹= Ph, R²= Me, R³= Me [(S)-4i]
R¹= ᵗBu, R²= H, R³= H [(S)-4j]
R¹= Ph, R²= H, R³= H [(S)-4k]
R¹= Ph, R²= H, R³= Me [(R)-4l]
R¹= ᵗBu, R²= H, R³= H [(R)-4m]
R¹= ᵗBu, R²= H, R³= Me [(R)-4n]
(R)-4o
R= Bn [(R)-4p]
R= Ph₂CH [(R)-4q]
R= Ph [(R)-4r]
R= Ph [(S)-4s]
R= ᵗBu [(S)-4t]
(R)-4u
(S)-4v
(S)-4w
(R)-4x
(R)-4y
(R)-4z

Scheme 4.

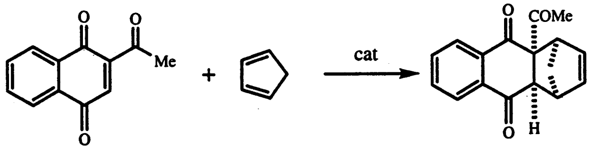


Scheme 4. (*Continued*).

bis(oxazolines) has no influence on the sense of asymmetric induction. Different diastereomers with the same absolute configuration within the oxazoline ring afforded, preferably, the same enantiomer of the product although, in some instances, differences in the degree of enantioselection have been observed [9]. In this context, it is remarkable that the *R* configurated bis(oxazoline)–copper catalysts, Cu-(*R*)-**4x** and Cu-(*R*)-**4y**, gave the (*S*)-**3b** adduct as major diastereomer (24 and 28% ee, respectively) instead of the (*R*)-**3b** one, predicted from a square-planar Cu(II) intermediate model [6].

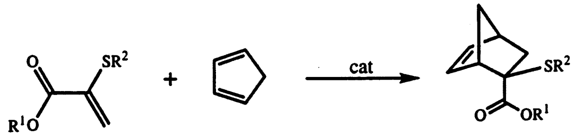
Conformationally constrained bis(oxazolines) **4aa**, **4ab**, and **4ad**–**4aj** and spiro bis(oxazolines) **4ac**, **4ak**, and **4al**–**4ap** have been used in the copper-catalyzed Diels–Alder reaction of acryloyl-*N*-oxazolidinone (**1a**) with HCp [11–14]. Thus, with an equimolar mixture of Cu(II) triflate and **4ah** as catalyst (4 mol.%) the *endo* (*R*)-**3a** adduct was obtained (CH_2Cl_2, −78°C, 8 h, 90% isolated yield) with virtually perfect diastereoselection and in 99% ee [11]. Analogously, with the related $Cu(OTf)_2$/**4ab** catalyst (10 mol.%) the (*S*)-**3a** adduct was obtained (CH_2Cl_2, −65°C) with an *endo*:*exo* ratio of 130:1 in 92% ee [12]. Among the spiro bis(oxazolines) the $Cu(OTf)_2$/**4am** catalyst afforded (*S*)-**3a** with the best *endo*:*exo* ratio, 44:1, and enantioselectivity, 96.3% ee [13]. In summary, by changing the phenyl group in the bis(oxazoline) ligand to the indane and introducing a spirocenter, the selectivity increased from 30 [6] to 96% [14].

As an exception, with the 1,2-benzo-indane ligand **4af** the *endo* (*R*)-**3a** adduct was obtained in 73% ee. The sense of induction was the opposed to the predicted from a square-planar Cu(II) intermediate [6].



6 2 7

Scheme 5.



R^1= Et, R^2= Me (**8a**)
R^1= Me, R^2= Ph (**8b**)
R^1= Et, R^2= Ph (**8c**)
R^1= ^{i}Pr, R^2= Ph (**8d**)
R^1= ^{t}Bu, R^2= Ph (**8e**)
R^1= CH_2CF_3, R^2= Ph (**8f**)

2 **9**

Scheme 6.

Brimble and McEwan investigated the use of copper derivatives of the chiral bis(oxazolines) **4k**–**o** as catalysts in the Diels–Alder reaction of HCp with the two point binding dienophile 2-acetyl-1,4-naphthoquinone (**6**) [15]. The reactions were carried out using 10–20 mol.% catalyst in CH_2Cl_2 at −78°C and were complete within 30 min. The best results (30% ee, 66% isolated yield) for the *endo* adduct **7** were obtained using bis(oxazoline) (*R*)-**4o** (Scheme 5).

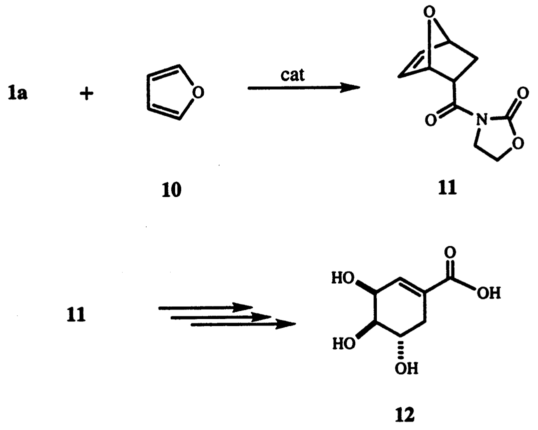
The complex formed from the phenyl-substituted bis(oxazoline) (*S*)-**4e** with $Cu(OTf)_2$ catalysed the asymmetric Diels–Alder cycloaddition of α-thioacrylates **8** with HCp to give the cycloadducts in up to 92% yield, 88% de and > 95% ee for the *endo* product [16]. The selectivity was highly dependent on the nature of the ester and thio substituent. The optimun reagents and conditions required ethyl α-phenylthioacrylate (**8c**) as dienophile, 20 mol.% of the copper catalyst and reaction at −78°C in CH_2Cl_2 (Scheme 6).

Evans et al. have accomplished several asymmetric syntheses of natural products following enantioselective Diels–Alder methodologies. Thus, for example, the Diels–Alder reaction between acrylimide **1a** and furan catalyzed by the complex formed from $CuCl_2$, the bis(oxazoline) (*S*)-**4g** and $AgSbF_6$ (5 mol.%, −78°C, CH_2Cl_2) afforded within 42 h cycloadduct **11** in 97% yield with *endo*:*exo* and ee (for the *endo* isomer) of 80:20 and 97%, respectively (Scheme 7). From **11** the unnatural enantiomer of shikimic acid **12** has been prepared in 55% yield [17]. The same copper bis(oxazoline) complex (2%, −20°C, CH_2Cl_2, 18 h) catalyzed the reaction of acrylimide **1a** and diene **13** affording cycloadduct **14** as a 73:27, *exo*:*endo* mixture of diastereomers where the major diastereomer, formed in 98% ee, was isolated in

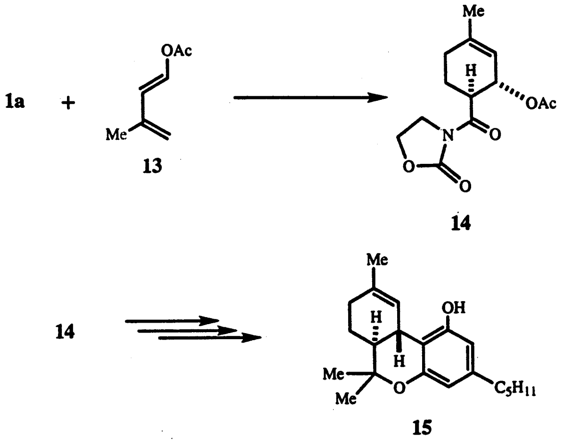
57% yield. From **14** the cannabinol *ent*-Δ^1-tetrahydrocannabinol (**15**) was synthesized in 37% yield [18] (Scheme 8).

Examples of enantioselective intramolecular Diels–Alder reactions are very scarce [19–21]. The aforementioned copper bis(oxazoline) complex also catalyzed enantioselectively the intramolecular Diels–Alder reaction of trienimides **16** [22]. Both [4.3.0]- and [4.4.0]-bicyclic ring systems (**17**) may be constructed with high levels of asymmetric induction. As the best result, cycloadduct **17b** was prepared from phenyl-substituted trienimide **16b**, in the presence of 5 mol.% of the catalyst, with complete diastereoselectivity in 86% yield after only 5 h and with 92% ee (Scheme 9).

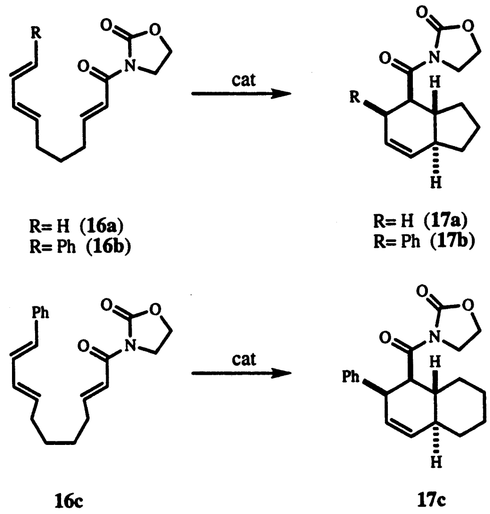
As an extension of this intramolecular enantioselective Diels–Alder reaction the asymmetric synthesis of (−)-isopulo'upone (**20**), a marine natural toxin, was



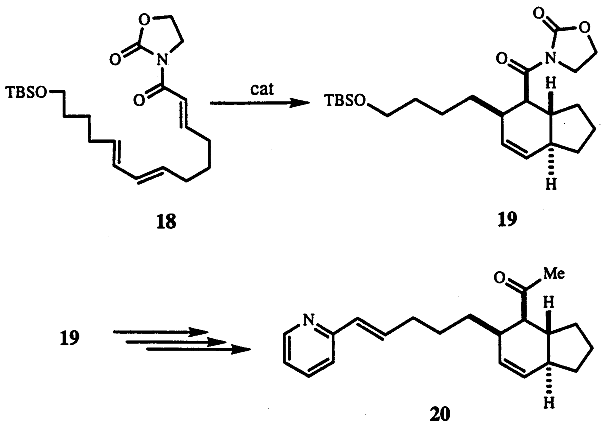
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

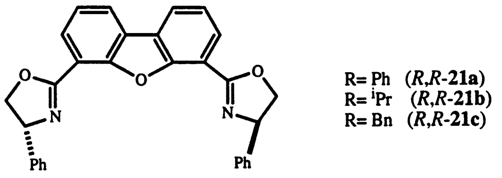
accomplished starting from the trienimide **18**. At 25°C, within 24 h, with as little as 5 mol.% of the copper–bis(oxazoline) (*S*)-**4g** catalyst the cycloadduct **19** was obtained in 81% yield. The cycloaddition proceeded with high diastereo- and enantioselectivity (> 99:1 *endo*:*exo*; 96% ee) to provide the bicyclic isopulo'upone precursor in the required relative and absolute configuration [22] (Scheme 10).

Kanemasa and coworkers [23,24] reported the new class of *trans*-chelating tridentate oxazoline containing ligands **21** (Scheme 11).

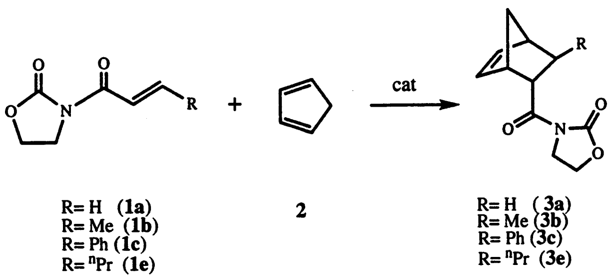
The totally insoluble in dichloromethane nickel perchlorate $Ni(ClO_4)_2 \cdot 6H_2O$ dissolved in the presence of (*R*,*R*)-**21a** and the derived bluish green complex exhibited a high catalytic activity. At a catalyst loading of 10 mol.%, a single enantiomer of *endo*-**3a** was obtained from the reaction of the acrylimide **1a** with HCp, when the reaction was carried out at −40°C (Scheme 12). Excellent *endo*:*exo* ratio (97:3) and chemical yield (96%, 14 h) were also achieved. Primary alkyl β-substituted dienophiles **1b**,**e** were much less reactive but, at r.t., produced **3b**,**e** in high chemical yield with good diastereo- and enantioselectivity (i.e. **3b**, 90% conversion, 20 h, 92:8 *endo*:*exo*, 93% ee). However, the phenyl substituted **1c** showed both low chemical yield (54%, 48 h, r.t.) and poor enantioselectivity (74%).

The crystal structure of the nickel complex ((*R*,*R*)-**22**) was solved by X-ray diffractometric methods. The compound consists of cations [Ni{(*R*,*R*)-**21a**}$(H_2O)_3]^{2+}$ and perchlorate anions. The structure of the octahedral nickel dication is schematically depicted in Scheme 13. The chiral ligand occupies three *mer* positions and three water molecules complete the octahedral arrangement. Interestingly, isolated crystals of (*R*,*R*)-**22** exhibited Diels–Alder features comparable to those of the aforementioned bluish green solution.

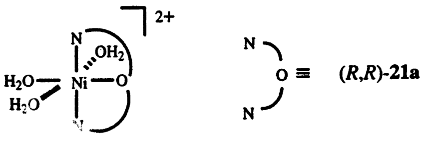
The sign of the observed enantioselectivity can be accounted for on the basis of a transition state structure such as that depicted in Scheme 14. The cata-



Scheme 11.

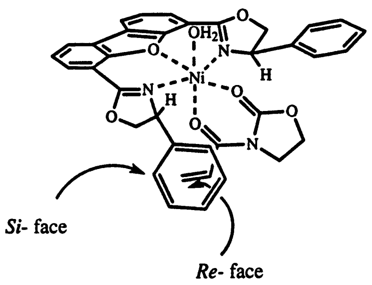


Scheme 12.

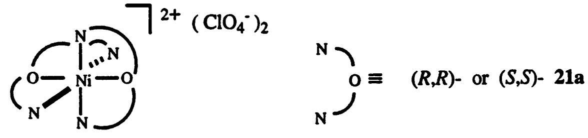


(*R*,*R*)-22

Scheme 13.



Scheme 14.



meso-23

Scheme 15.

lyst–dienophile complex possesses an octahedral geometry and adopts a conformation such that the *Re*-face of the unsaturated bond of the coordinated dienophile preferably participates in the catalyzed reaction.

The catalytic activity as well as enantioselectivity of the nickel perchlorate catalyst were maintained at satisfactory level after addition of variable amounts of water. Enantioselectivities of 93, 88 or 83% for the *endo*-**3a** product were achieved after addition of 5, 10 or 15 water equiv. to the reaction medium. Methanol and a variety of organic acids (MeCOOH, PhCOOH, *p*-$NO_2C_6H_4COOH$) or amines ($PhNH_2$, $PhCH_2NH_2$) were also tolerated by the catalyst without serious damage in its activity.

Complexes derived from $Co(ClO_4)_2{\cdot}6H_2O$, $Mn(ClO_4)_2{\cdot}6H_2O$, $Fe(ClO_4)_2{\cdot}3H_2O$, $Cu(ClO_4)_2{\cdot}3H_2O$, and $Zn(ClO_4)_2{\cdot}3H_2O$ or from their corresponding anhydrous salts and (*R*,*R*)-**21a** exhibited high catalytic activities resulting in excellent enantioselectivities in the *endo*-**3a** enantiomer for the Diels–Alder reaction between **1a** and **2**. Representative results are conversions around 95% at −40°C, with *endo*:*exo* ratios about 95:5 and ee usually greater than 90%. However, complexes derived from $CuI/AgClO_4$, $RhCl_3{\cdot}3H_2O/3AgClO_4$, $PdCl_2/2AgClO_4$, $PdCl_2(MeCN)_2/2AgBF_4$, $AgClO_4$, $Sn(OTf)_2$, $CeCl_3$, $La(OTf)_3$, $La(ClO_4)_3$, $Yb(ClO_4)_3$, $Gd(ClO_4)_3$ and (*R*,*R*)-**21a** were much less effective showing poor chemical conversions and no enantioselectivity in any case.

An interesting phenomenon of chiral amplification [25] was observed for the $Ni(ClO_4)_2$/**21a** catalytic system. When $Ni(ClO_4)_2{\cdot}6H_2O$ was treated with ligand **21a** of low enantiomeric purity ((*R*,*R*)-**21a** major isomer) [Ni{(*R*,*R*)-**21a**}$(H_2O)_3]^{2+}$ ((*R*,*R*)-**22**), [Ni{(*S*,*S*)-**21a**}$(H_2O)_3]^{2+}$ ((*S*,*S*)-**22**), and a pale precipitate of

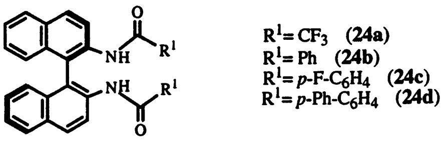
[Ni{(*R*,*R*)-**21a**}{(*S*,*S*)-**21a**}]$(ClO_4)_2$ (*meso*-**23**) were formed (Scheme 15). An X-ray single crystal analysis showed the presence of both enantiomers (*R*,*R*)-**21a** and (*S*,*S*)-**21a** in the complex cation of *meso*-**23**. Consistently, its CD spectrum was silent and the most straightforward access to it was treatment of [Ni{(*R*,*R*)-**21a**}$(H_2O)_3$]$(ClO_4)_2$ ((*R*,*R*)-**22**·$(ClO_4)_2$) with 1 equiv. of (*S*,*S*)-**21a**. However, the homochiral complex [Ni{(*R*,*R*)-**21a**}$_2$]$^{2+}$ can never be formed because of the severe steric hindrance between the 4-phenyl substituents of oxazoline rings [24]. As the formation of *meso*-**23** is irreversible and this saturated compound is catalytically inert an effective chiral amplification was produced. For example, under the standard conditions but, using **21a** with only 20% ee ((*R*,*R*)-**21a** major isomer), 95% of the cycloadduct **3a** was obtained in a 97:3 *endo*:*exo* ratio with an enantioselectivity of 96% for the *endo* isomer. Nevertheless, due to the relative formation constants for (*R*,*R*)-**22**, (*S*,*S*)-**22**, and *meso*-**23** from $Ni(ClO_4)_2\cdot 6H_2O$ and **21a**, the measured enantiomeric enrichment of the solution is lower than that needed to achieve the observed ee [24,26]. Then, a chirality enrichment mechanism other than that through the precipitation of *meso*-**23** has to exist in the solution.

In this context, the crystal structures of enantiopure (*R*,*R*)-**22**·$(ClO_4)_2$ and of a racemic mixture of (*R*,*R*)-**22**·$(ClO_4)_2$ and (*S*,*S*)-**22**·$(ClO_4)_2$ (prepared from equivalent amounts of both enantiopure components) have been solved by diffractometric means. They revealed that while two adjacent cations of (*R*,*R*)-**22**·$(ClO_4)_2$ are only linked by one hydrogen bond, established between coordinated water molecules and perchlorate anions, the same type of interaction between two differently configurated adjacent cations (*R*,*R*)-**22** and (*S*,*S*)-**22** occurs through two hydrogen bonds. It has been suggested [24] that the cation of the major enantiomer (*R*,*R*)-**22** would interact, even in solution, with the cation of the minor one (*S*,*S*)-**22** much more strongly than with itself. As a result, the minor complex is deactivated to enrich the enantiomeric purity of the solution. This is the second proposed mechanism to account for the observed chiral amplification. Support for this second mechanism stemmed from the observation that while addition of Et_2O maintained high levels of chiral amplification, a low level of amplification resulted in the presence of acetone; i.e. Et_2O only dissociated the weak chiral oligomers of (*R*,*R*)-**22** but acetone is powerful enough to dissociate both types of oligomers.

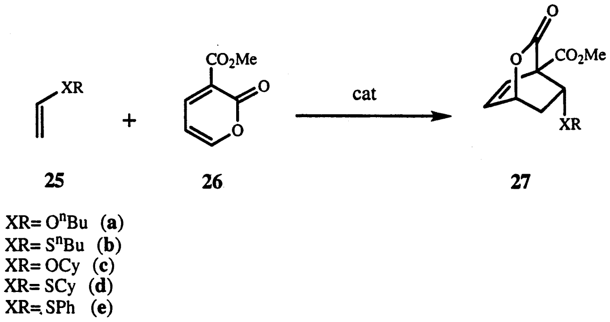
The Diels–Alder reaction between acrylimides **1a**,**b** and HCp was also catalyzed by an in situ prepared solution of chiral 1,1′-(2,2′-bisacylamino)binaphthalene **24a**–**d** and ytterbium(III) triflate in dichloromethane and in the presence of diisopropylethylamine. In the reaction **1b** + **2** the (*R*)-*endo* adduct was obtained essentially pure when the bis-benzoyl, bis-*p*-fluoro-benzoyl or bis-*p*-phenyl-benzoyl derivatives **24b**–**d** were used as chiral ligands [27]. At 0°C with 15–25 mol.% of catalyst conversions greater than 90% were obtained within 4 h and representative *endo*/*exo* ratios were greater than 90/10. However without diisopropylethylamine the product was essentially racemic. For the reaction **1a** + **2**, performed under similar conditions, quantitative yield, 91/9 *endo*/*exo* ratio and 88% ee for the (*R*)-*endo* adduct were obtained with the **24b** derived catalyst (Scheme 16).

Enantioselective inverse-electron demand Diels–Alder reactions of 3-carbomethoxy-2-pyrone (**26**) with various vinyl ethers or vinyl sulphides **25** are catalyzed by the $Yb(OTf)_3$/(*R*)-BINOL system [28] in the presence of diisopropylamine. Addition of small amounts of water, ^{t}BuOH or THF led to a remarkable increase of the optical purity of the bicyclic lactone adducts **27**. Enantiomeric excesses were greater than 60% for the (*R*)-*endo* adduct and in the case of the vinyl sulphides **25d**,**e** this product was obtained essentially pure (Scheme 17).

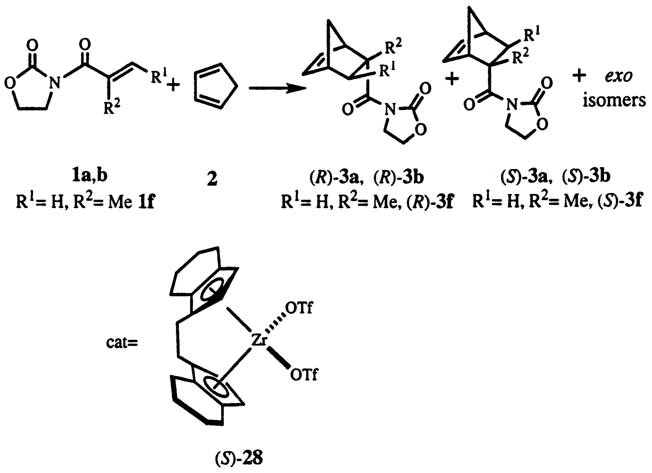
Chiral metallocene complexes have been also used as catalysts in enantioselective Diels–Alder reactions [29,30]. In particular, Collins and colleagues have studied the



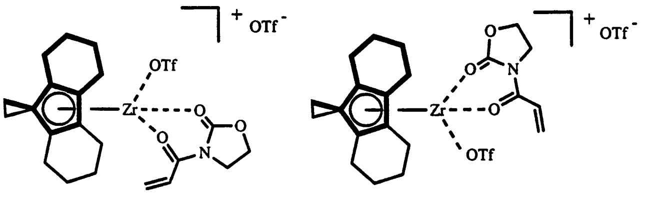
Scheme 16.



Scheme 17.



Scheme 18.



29a **29b**

Scheme 19.

Diels–Alder reactions of acrylimide dienophiles **1a**,**b**,**f** with HCp (Scheme 18) catalyzed by a chiral, linked bis(tetrahydroindenyl) bis(triflate) zirconium(IV) catalyst ((*S*)-**28**) [31]. The best levels of enantioselectivity were observed when the reactions were performed in nitroalkanes such as nitromethane or 2-nitropropane. Thus, for example 91% ee for the (*R*)-*endo* adduct was achieved in the reaction of **1a** with **2** with 1 mol.% of (*S*)-**28** at $-78°C$ in 2-nitropropane as solvent. The chemical yield after 1 h of reaction was 83% and the *endo*:*exo* ratio 92/8. The use of CH_2Cl_2 as the solvent afforded good *endo*:*exo* selectivity in most cases (up to 85:15) but the level of asymmetric induction was relatively low (up to 70% ee).

The binding of the dienophile **1a** to the catalyst (*S*)-**28** was studied by ^1H-, ^{13}C-, and ^{19}F-NMR spectroscopy. Two isomeric complexes **29a** and **29b** containing one triflate molecule and chetale **1a** in an *s-cis* conformation are formed. At $-30°C$, the ratio **29a**:**29b** was 1:2.4 in CD_3NO_2 but only 1:5.7 in CD_2Cl_2. It was suggested [31] that the minor isomer **29a** would react most rapidly and selectively with HCp, thus partially accounting for the important changes in enantioselectivity observed on going from nitroalkanes to dichloromethane solvent (Scheme 19).

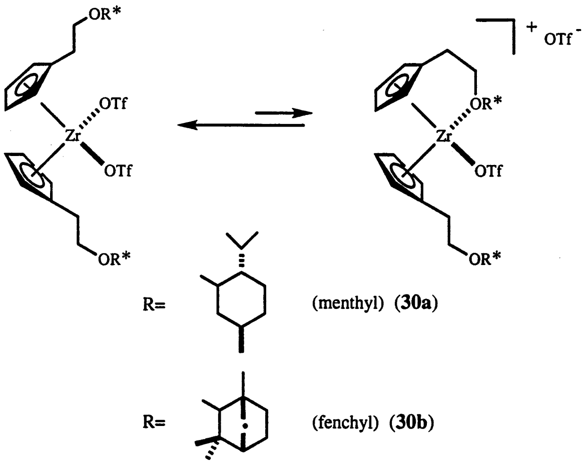
The chiral zirconocene complexes with *O*-functionalized side chains on the Cp ring **30** catalyzed the Diels–Alder reaction between methacrolein and HCp, but no asymmetric induction was observed probably because the chiral ether side chains are not coordinated during catalysis [32] (Scheme 20).

The related lanthanum and samarium complexes with chiral cyclopentadienyl ligands (*S*)-**31**-(*S*)-**34** exhibited activity for the Diels–Alder reaction between methacrolein and HCp. Total conversion was obtained within 24 h with *exo*:*endo* ratios greater than 90:10. However, the enantiomeric excesses are modest ($<15\%$) with all catalysts even at low temperature ($-30°C$) [33] (Scheme 21).

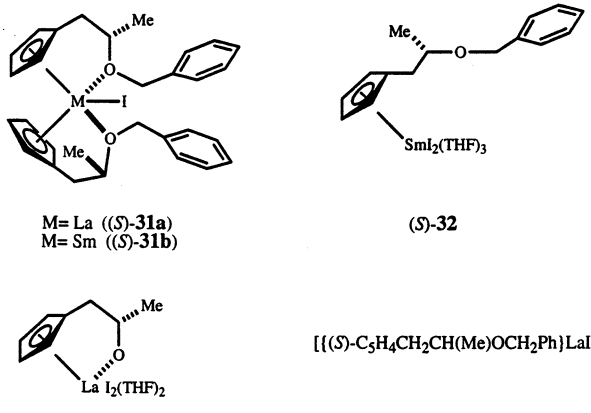
Half-sandwich d_6 metal complexes of general formula $[(\eta^n\text{-ring})M(L^1L^2)^*L^3]^{+x}$ where $(\eta^n$-ring)M is $(\eta^5\text{-}C_5H_5)Fe$ [34,35], $(\eta^5\text{-}C_5H_5)Ru$ [36], $(\eta^6\text{-}p\text{-}MeC_6H_4^iPr)Ru$ [37,38], $(\eta^6\text{-}1,3,5,\text{-}Me_3C_6H_3)Ru$ [39], $(\eta^5\text{-}C_5Me_5)Rh$ [38,40,41], $(\eta^5\text{-}C_5Me_5)Ir$ [42], $(L^1L^2)^*$ represents a chelate chiral ligand, and L^3 is a good leaving group have been tested as catalysts in enantioselective Diels–Alder reactions.

In this context, the iron compounds $[(\eta^5\text{-}C_5H_5)Fe((R,R)\text{-}\mathbf{35})(\text{acrolein})]BF_4$ (**36**) [34] and $[(\eta^5\text{-}C_5H_5)Fe((R,R)\text{-}\mathbf{37})(\text{acrolein})]BF_4$ (**38**) [35] (5 mol.%) readily catalyzed the reaction between methacrolein and HCp in CH_2Cl_2. At $-20°C$, isolated yields of 62 (**36**) and 69% (**38**) were achieved within 20 h with *exo*:*endo* diastereoselectivity ratios of 97:3 (**36**) and 98:2 (**38**) and enantiomeric excesses of 90 (**36**) and 97% (**38**) in the (1*S*,2*R*,4*S*)-2-methylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde ((*R*)-**39**) adduct (Scheme 22). 2,6-Di-*tert*-butylpyridine or 2,6-dimethylpyridine (2.5 mol.%) was added to scavenge residual acid impurities that adversely affected enantioselectivity by acting as achiral competing catalysts.

Compounds **36** and **38** also catalyzed the reactions of related α,β-enals such as acrolein or α-bromoacrolein with HCp as well as the reaction between α-bromoacrolein with other dienes such as 1,3-cyclohexadiene or 2,3-dimethyl-1,3-butadiene [34,35]. In general, ee greater than 90% were achieved and, in particular, a single enantiomer of the *endo*-formyl diastereomer was formed in the reaction of α-bromoacrolein with 1,3-cyclohexadiene.



Scheme 20.



M= La ((*S*)-**31a**)
M= Sm ((*S*)-**31b**)

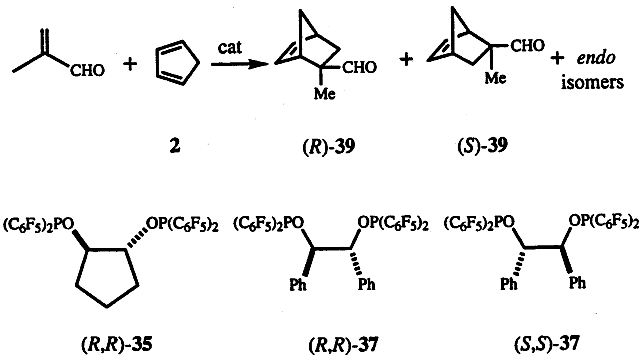
(*S*)-**32**

(*S*)-**33**

$[\{(S)\text{-}C_5H_4CH_2CH(Me)OCH_2Ph\}LaI_2]_x$

(*S*)-**34**

Scheme 21.



Scheme 22.

The related cyclopentadienyl ruthenium compound $[(\eta^5\text{-}C_5H_5)Ru((S,S)\text{-}\mathbf{37})(Me_2CO)]SbF_6$ (**40**) also catalyzed the Diels–Alder reaction of methacrolein with HCp (5 mol.% of catalyst, CH_2Cl_2, −20°C, 22 h) affording the cycloadduct (*S*)-**39** in 91% yield, with a diastereomeric *exo*:*endo* ratio of 97:3 and an enantioselectivity of 92% [36].

The nature of the counterion had a large effect on the rate ($TfO^- < BF_4^- < PF_6^- < SbF_6^- < TFPB^-$; $TFPB^-$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) but not on the enantioselectivity of the reaction. The solid state X-ray diffraction structure of the methacrolein compound $[(\eta^5\text{-}C_5H_5)Ru((S,S)\text{-}\mathbf{37})(\text{methacrolein})]SbF_6$ (**41**) revealed the existence of ion pairs between the cationic complex and the SbF_6 anion. This association is supported by three hydrogen bond interactions between three fluorine atoms of the anion and two hydrogen atoms of the cyclopentadienyl ring and the formyl hydrogen atom of the methacrolein moiety. These interactions between the anion and the Lewis acid–dienophile complex must be highly sensitive to the nature of the anion and could be responsible for the decrease of the turnover frequency [36].

The Diels–Alder reactions of α,β-enals with dienes are slower with the ruthenium catalyst **40** than those with the analogous iron catalyst **38** and, most probably due to the increased size of the chiral pocket on going from the first to the second row transition metal, afforded lower enantioselectivity [36]. Furthermore, the ruthenium catalyst became deactivated when α-bromoacrolein was used as dienophile, the bromo complex $[(\eta^5\text{-}C_5H_5)RuBr((S,S)\text{-}\mathbf{37})]$ being recovered from the reaction medium.

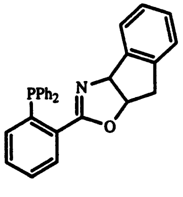
Examples of rhodium derivatives as enantioselective catalysts in Diels–Alder reactions are very scarce. The first examples reported were the chiral diphosphine aquo compounds $(S_{Rh},R_C)\text{-}[(\eta^5\text{-}C_5Me_5)Rh((R)\text{-prophos})(H_2O)]A_2$ ((*R*)-prophos) = (*R*)-(+)-1,2-bis(diphenylphosphino)propane, $A = BF_4$ (**42**), SbF_6 (**43**)) which are shown to be active catalyst for the reaction of methacrolein with HCp in CH_2Cl_2 [40]. With catalyst **42** the reaction occurred rapidly at r.t. (99% conversion in 50 min), the system operating at low catalyst loading (1 mol.%) but with poor enantioselectivity (< 5%). Both diastereo- and enantioselectivity were improved by increasing the catalyst ratio to 5–10 mol.% and operating at lower temperatures. A further improvement in both rate and enantioselectivity was obtained by using the SbF_6^- derivative **43** instead of the BF_4^- complex **42** as catalyst. Thus, 71% ee for the (*R*)-**39** isomer was achieved with **43** (10 mol.%) at −50°C, with an *exo*:*endo* ratio of 98:2 and a conversion of 73% within 27 h.

The first application of phosphino–oxazoline ligands [43] as chiral auxiliaries in transition-metal Lewis acid catalyzed Diels–Alder reactions was the use of the ruthenium aquo compounds (R_{Ru},S_C,R_C and S_{Ru},S_C,R_C)-[(η^6-*p*-$MeC_6H_4^iPr$)Ru((*S*,*R*)-**44**)(H_2O)](SbF_6)$_2$ (**45**) ((*S*,*R*)-**44**) = (*3aS*,*8aR*)-2-(2-diphenylphosphinophenyl)-3*a*,8*a*-dihydroindane[1,2-*d*]oxazole) as enantioselective catalyst for the reaction of methacrolein and HCp [37] (Scheme 23). At r.t., dichloromethane solutions of **45** catalyzed rapidly this reaction (91% conversion in 20 min) at 5 mol.% catalyst loading with good *exo*:*endo* selectivity (92:8) and moderate enantioselectivity (46% ee in the (*S*)-**39** *exo* adduct).

Chiral chelate dinitrogen donor ligands are also adequately suited to act as chiral auxiliaries in half-sandwich Lewis acid catalysts for Diels–Alder reactions. Thus, chiral pyridyl–imino Ir [42], Rh [38] or Ru [38] compounds of formulae (R_M,R_C and S_M,R_C)-[(η^5-C_5Me_5)M(L)(H_2O)]A_2 and [(η^6-*p*-$MeC_6H_4^iPr$)Ru(L)(H_2O)]A_2 (L represents an enantiopure chiral imine ligand derived from 2-pyridinecarbaldehyde (**46**–**51**), M is Ir or Rh, and A is the SbF_6, BF_4, PF_6 or (*1S*)-camphor-10-sulfonate anion) catalyzed the reaction of methacrolein and HCp in dichloromethane [38,42]. Good conversions and *exo*:*endo* ratios were achieved at 20 mol.% of catalyst loading although enantioselectivities were modest (up to 46%) (Scheme 24).

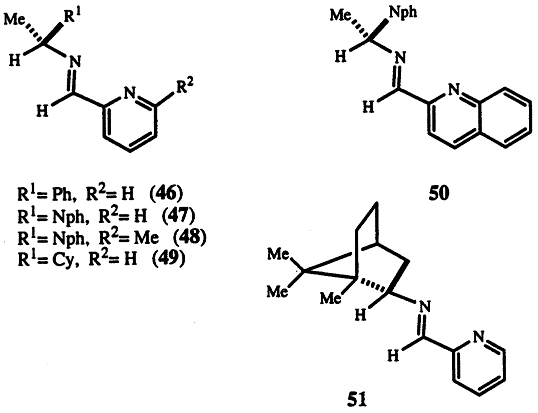
Analogously, the chiral pyridine–oxazolino ruthenium compound [(η^6-1,3,5-$Me_3C_6H_3$)Ru((*S*)-**4a**)(H_2O)](SbF_6)$_2$ catalyzed the model Diels–Alder reaction between methacrolein and HCp [39]. At a catalyst loading as low as 0.5 mol.%, essentially quantitative conversions within 45 min at r.t. with good *exo*:*endo* selectivity (95:5) and ee in the (*S*)-**39** adduct (70%) were achieved. Increasing the catalyst ratio to 5 mol.% had very little effect on the *exo*:*endo* ratio or on the enantioselectivity. However, reducing the temperature of reaction to −20°C led to small improvements in the enantioselectivity (up to 81%).

The chloride in the half-sandwich oxazoline complexes [(η^5-C_5Me_5)-RhCl(oxazoline)]SbF_6 (oxazoline = (*S*)-**4f** (**52**), (*R*)-**4u** (**53**), (*S*)-**4a** (**54**), see Scheme 4) is readily removed with $AgSbF_6$ to form dications. Solutions of these



(*S*,*R*)-44

Scheme 23.

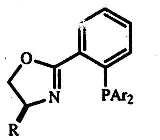


R^1= Ph, R^2= H **(46)**
R^1= Nph, R^2= H **(47)**
R^1= Nph, R^2= Me **(48)**
R^1= Cy, R^2= H **(49)**

50

51

Scheme 24.



R= Me, Ar= Ph **(55a)**
R= ^{i}Pr, Ar= Ph **(55b)**
R= ^{t}Bu, Ar= Ph **(55c)**
R= ^{t}Bu, Ar= Mes **(55d)**
R= ^{t}Bu, Ar= 2-Naph **(55e)**
R= ^{t}Bu, Ar=1-Naph **(55f)**
R= ^{t}Bu, Ar= 1-Anth **(55g)**

Scheme 25.

dications in CH_2Cl_2 catalyzed the Diels–Alder reaction between methacrolein and HCp [41]. The dications derived from **52** and **53** gave only modest results in terms of activity and enantioselectivity. However, the dication from **54** is a reasonable catalyst even at fairly low catalyst loading (1 mol.%) showing good *exo*:*endo* selectivity (94:6, r.t.) with moderate enantioselectivity (52%). At 0°C with 2 mol.% of catalyst the ee increased to 68%.

Chiral (phosphino–oxazoline)copper(II) complexes have been applied as catalysts for the Diels–Alder reaction of substituted *N*-acylamide dienophiles with HCp [44]. The catalysts were in situ prepared from $Cu(OTf)_2$ and the appropriate ligand **55a**–**g**. At -78°C, in CH_2Cl_2 isolated yields around 90% were achieved for the **1a** + **2** reaction at 10 mol.% of catalyst loading. Diasteroselection favored the formation of the *endo* products and the (*S*)-*endo* adduct was enantioselectively prepared (Scheme 25). Enantioselectivity was found to depend strongly on the size of the substituents of the chiral ligand increasing with the steric bulk of both the substituent R and the aryl group Ar. The best result (97% ee) was obtained with ligand **55f**.

Interestingly, with the bulky anthryl–tertbutyl ligand **55g** the *endo*:*exo* selectivity was reversed and the *R* configuration at C_2 of the *endo* adduct was preferentially formed. In order to explain these changes in stereoselectivity, a distortion of the coordination around the copper atom from planar towards tetrahedral caused by the steric bulk of the chiral ligand **55g** was proposed.

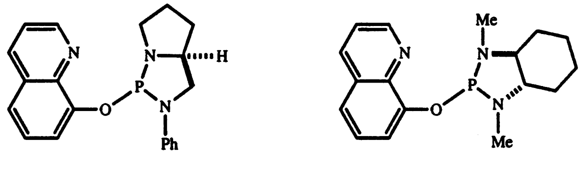
Taking the $Cu(OTf)_2$/**55f** system as model catalyst, the effect of changes in the solvent, catalyst concentration, dienophile, and counterion was studied. In general, reactions were significantly faster in $EtNO_2$ than in CH_2Cl_2, with other solvents such as THF, Et_2O, toluene, EtCN, DMF, ethyl acetate being inferior. However, enantioselectivity was slightly higher in CH_2Cl_2 than in $EtNO_2$. Only 1 mol.% of catalyst in $EtNO_2$ at −78°C furnished complete conversion in 44 h with 92% ee. At −20°C in CH_2Cl_2 the reaction proceeded to completion with 0.1 mol.% of catalyst within 5 h with 81% ee. The *N*-crotonoyl-oxazolidinone (**1b**) reacted at −20°C with good enantioselectivity (86%) while the *N*-cinnamoyl-oxazolidinone (**1c**) underwent the reaction with reversed *endo*:*exo* selectivity (*endo*:*exo* ratio = 40:60) and good *exo* (85% ee) and low *endo* enantioselectivity (32%). The *N*-fumaroyl-oxazolidinone (**1d**) afforded the cycloadduct **3d** with moderate *endo*:*exo* selectivity (60:40) and good enantioselectivity (75%). In CH_2Cl_2, slightly lower enantioselection was obtained with the $Cu(SbF_6)_2$/**55f** catalyst compared to that with the corresponding triflate catalyst. However, in $EtNO_2$ the SbF_6 salt induced low degrees of enantioselection [44].

The $Cu(OTf)_2$/**55f** system also catalyzed the reaction between **1a** and 1,3-cyclohexadiene. At 0°C in CH_2Cl_2 a conversion of 82% was achieved within 48 h with a catalyst loading of 10 mol.%. Essentially perfect diastereoselection and 79% ee in the (*S*)-*endo* isomer were obtained.

Reaction **1a** + **2** was also catalyzed by copper complexes derived from the chiral pyridine–phosphine ligand **56**. The catalyst (10 mol.%) was in situ prepared by treatment of $Cu(OTf)_2$ with the ligand. The *endo* product (*S*)-**3a**, in quantitative yield (3 h), was the sole product in CH_2Cl_2 operating from −78 to 25°C [45] (Scheme 26).

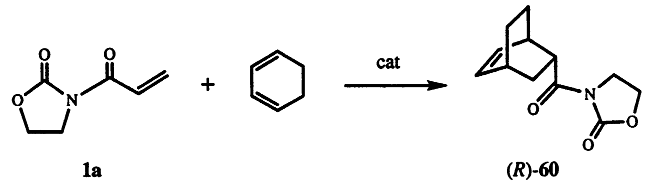
Enantioselectivities varying from 2 to 32% were obtained with other solvents such as THF, toluene or $EtNO_2$. The corresponding Cu(I) triflate complex led to a low enantiomeric excess (14%) and the use of ligand **57** led to a complete conversion but the adduct (*S*)-**3a** (> 95:5 *endo*:*exo* ratio) was obtained in only 36% ee.

The cationic palladium(II) compound $[Pd((S)\text{-BINAP})(PhCN)_2](BF_4)_2$ (**58**) catalyzed the Diels–Alder reaction of *N*-acryloyloxazolidinone (**1a**) with HCp [46]. At −50°C in CH_2Cl_2, 95% isolated yield was obtained within 24 h operating at a catalyst loading of 10 mol.%. The *endo* (*R*)-**3a** adduct was obtained (95:5 *endo*:*exo* ratio) in 99% ee. Lower enantioselection (77%) was obtained by changing the counterion in the catalyst from BF_4 to PF_6.

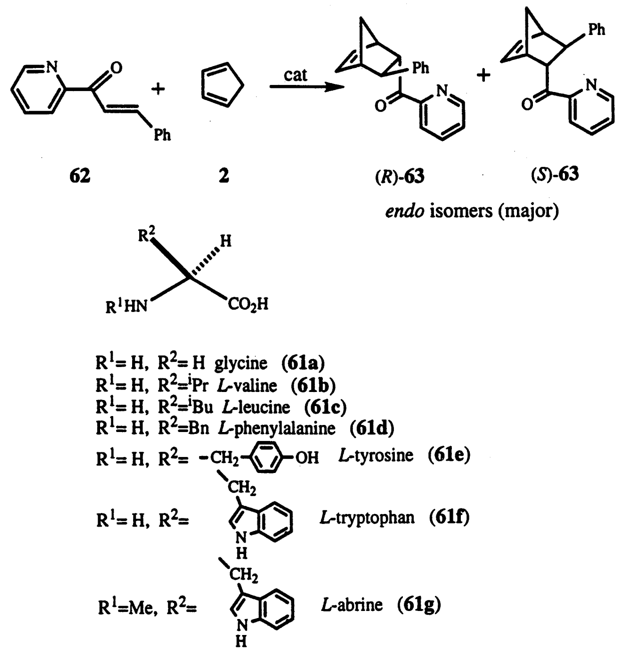


(*S*)-56 **(*S*,*S*)-57**

Scheme 26.



Scheme 27.



Scheme 28.

The reaction of **1a** with 1,3-cyclohexadiene was slower than that **1a** with **2** yielding the *endo* cycloadduct **60** in 43% yield with an ee of 92% in the (R) at the C_2 isomer (Scheme 27).

The first example of an enantioselective Lewis-acid-catalyzed Diels–Alder reaction in water was recently reported by Engberts and coworkers [47]. In the presence of 10 mol.% of copper(II) complexes of a variety of α-amino acids (**61a**–**g**), the dienophile 3-phenyl-1-(2-pyridyl)-2-propen-1-one (**62**) reacted with HCp to afford the Diels–Alder adduct **63** in yields generally exceeding 90% after 48 h of treatment. In particular, with L-abrine (**61g**) an enantiomeric excess of 74% for the major *endo* adduct was achieved (the absolute configuration of **63** has not been determined). Enantioselectivity clearly decreased in other solvents such as chloroform (44%), ethanol (39%), THF (24%) or MeCN (17%) (Scheme 28).

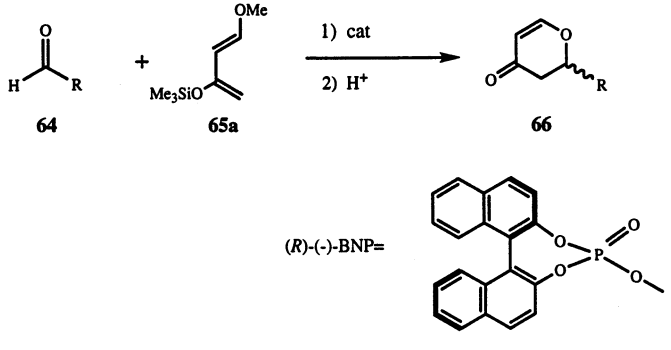
Only α-amino acids containing aromatic side groups showed significant enantioselectivities (**61d**, 14%; **61e**, 26%; **61f**, 25%). This result has been explained assuming that an attractive interaction between the aromatic ring of the α-amino acid and the pyridine ring of **62** is involved in the transition-state complex.

3. Hetero Diels–Alder reactions

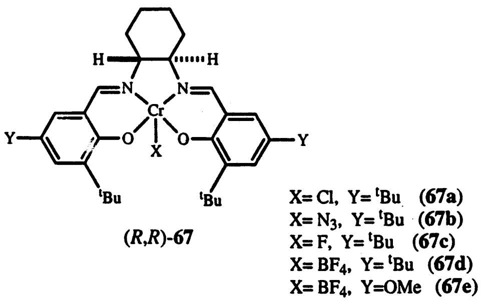
3.1. Oxa Diels–Alder reactions

The trivalent lanthanoids (La, Pr, Sm, Gd, Dy, Er, Yb), scandium, and yttrium tris-(*R*)-(−)-1,1′-binaphthyl-2,2′-diyl phosphonate (BNP) have been cited as chiral Lewis acids for the hetero Diels–Alder reaction of benzaldehyde with the Danishefsky's diene [1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene] [48] (Scheme 29). The degree of asymmetric induction was found to be highly sensitive to the ionic radius of the metal ion and the best results were obtained with the ytterbium complex [Yb{(*R*)-(−)BNP}$_3$] (73% ee). The reaction proceeded under heterogeneous conditions but, in dichloromethane, addition of pyridine or substituted pyridines dissolved the catalyst and, in most cases, chemical and/or optical yields were improved. The best result, 94% conversion and 89% ee, was obtained after 16 h of reaction at r.t. by employing 2,6-lutidine (1:1, lutidine:ytterbium complex ratio) and 10% of catalyst [49]. At 3°C the ee increased to 91% (79% chemical yield) but further lowering of temperature no longer improved the ee. The optimal conditions were applied to other aldehydes. Aromatic, hetero-aromatic, and conjugated aldehydes gave satisfactory results with conversions ranging from 59 to 86% and ee from 65 to 93%. However, the aliphatic non-conjugated aldehyde $PhCH_2CH_2CHO$ gave only an 11% ee. The existence of π–π interactions between the carbonyl substrate and the binaphthyl ring of the catalyst has been proposed to play an important role in attaining a high asymmetric induction [49].

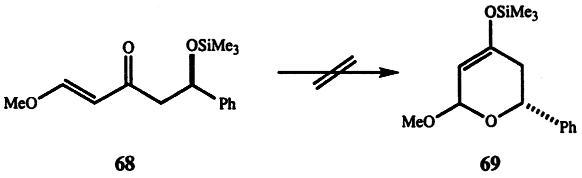
The chiral (salen)Cr(III) complexes **67** also catalyzed the hetero Diels–Alder reaction depicted in Scheme 1 [50]. The best results for the model reaction with



Scheme 29.



Scheme 30.



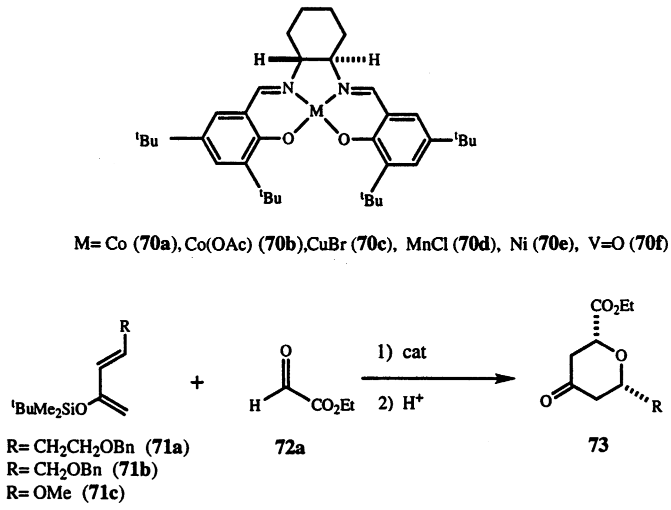
Scheme 31.

benzaldehyde (85% conversion, 87% ee) were achieved with only 2 mol.% of **67d**, at − 30°C, in TMBE and in the presence of oven-dried powdered molecular sieves 4Å (MS4Å) (Scheme 30). The conversion was obtained after 24 h of reaction at a 5.0 M concentration for the diene and benzaldehyde. Noncoordinating ethers such as Et_2O or TMBE afforded the highest yield and enantioselectivity and catalyst bearing less coordinating counteranions proved to be much less reactive and less enantioselective.

The scope of the asymmetric reaction of **65a** with aldehydes catalyzed by the (salen)Cr(III) compounds **67d** and **67e** is broad. Under the conditions aforementioned, not only aromatic, heteroaromatic and conjugated but also aliphatic and cycloaliphatic aldehydes gave satisfactory results with conversions ranging from 65 to 98% and ee from 62 to 93%.

In some instances, it has been shown that the reaction of Danishefsky's diene with simple aldehydes does not involve a formal cycloaddition reaction but rather to proceed via a two step Mukaiyama aldol condensation–cyclization sequence [51,52]. To test the possible intermediacy of an aldol condensation adduct, silyl ether **68** was synthesized independently and subjected to the conditions of the (salen)Cr(III)-catalyzed reaction. Cyclization of **68** to **69** was not detected, this result pointing toward a concerted [4 + 2] mechanism for the (salen)Cr catalyzed reaction (Scheme 31).

Catalysts based on a variety of salen–metal complexes (**70**) have been tested in the hetero Diels–Alder reaction between ethyl glyoxylate and 1-(2-benzyloxyethyl)-3-(*tert*-butyldimethylsilyl)oxy-1,3-butadiene **71a** (Scheme 32) [53].

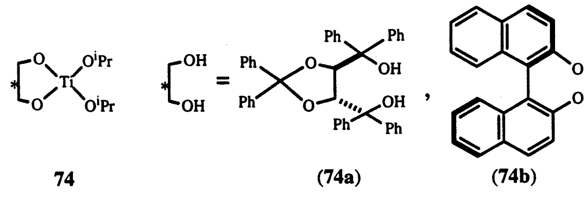


Scheme 32.

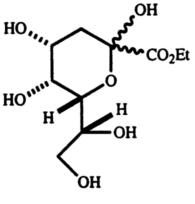
Under the best conditions (10 mol.% of **70a**, $-78°C$, CH_2Cl_2) *endo*:*exo* ratios $>99:1$ and conversions of 75% were achieved with ee values for the *endo* isomer of 52%. The presence of MS4Å did not cause any changes in the outcome of the reaction. When using ether solvents (Et_2O, THF) to replace CH_2Cl_2, not only the ee value decreases (24 and 25%, respectively), but also the *endo*:*exo* ratio (80:20 and 90:10, respectively).

The diene **71b** was also tested in place of **71a**. Comparable results (*endo*:*exo* $>99:1$, 45% ee for the *endo* isomer) could be detected, but conversion was lowered to 45%.

Chiral additives such as 5,5′-dichloro-4,4′,6,6′-tetramethylbiphenol (5-Cl-BIPOL) or BINOL activate the enantiopure TADDOL- or BINOL-derived titanium diisopropoxide catalyst **74** for the hetero Diels–Alder reaction between the Danishefsky diene **71c** and *n*-butyl glyoxylate (Scheme 33). For example, the addition of a further 1 equiv. of BINOL to a catalyst prepared by mixing BINOL and [Ti(O^{i}Pr)$_4$] at a ratio of 1:1, in toluene, increased the conversion from 40 to 50% and, more importantly, enhanced the ee from 5 to 84% [54]. Thus, this strategy could be used to significantly improve the levels of catalytic efficiency and enantioselectivity of enantiopure catalysts.

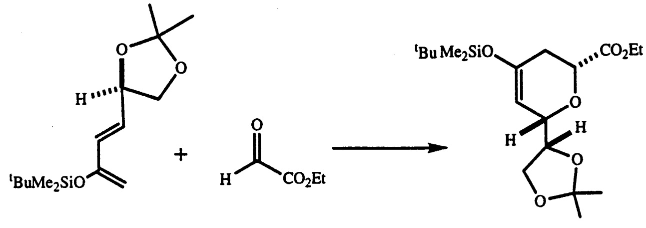


Scheme 33.



KDO (75)

Scheme 34.



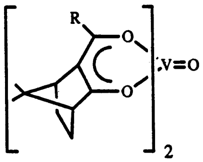
76 **72** ***77-endo-si***

Scheme 35.

The incorporation of 3-deoxy-D-*manno*-2-octulosonic acid (KDO) to the outer membrane lipopolysaccharide of Gram-negative bacteria is highly likely to be a vital step in the growth of this type of micro-organisms [55] (Scheme 34). A formal total synthesis of KDO has been completed [55], the key step being the oxa Diels–Alder reaction between the chiral diene **76** and ethyl glyoxylate catalyzed by (salen)Co complex **70a** to selectively render the **77**-*endo*-*si* isomer (Scheme 35).

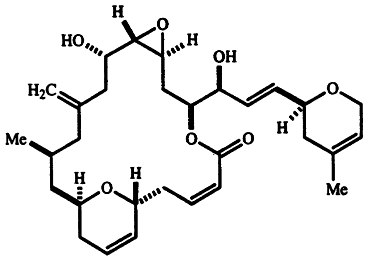
In the absence of catalyst, it was necessary to increase the reaction temperature to 60°C, in order to obtain satisfactory conversions (90%). At this temperature, the chiral induction from the substrate was not enough to obtain the desired stereoselectivity and all four possible diastereomers were obtained (35:20:21:24 ratio for the *endo*-*si*, *exo*-*si*, *endo*-*re*, and *exo*-*re* isomers, respectively). Catalysts based on strong Lewis acids such as $BF_3 \cdot OEt_2$ or $AlCl_3$ led to decomposition of the diene **76**. $ZnCl_2$ or Et_2AlCl increased the rate of the reaction but selectivities remained poor: 45% of the desired *endo*-*si* isomer. Good results were obtained when chiral catalysts based on transition-metal complexes were tried. Interestingly, the use of the chiral vanadium catalyst **78** [56] produced the expected rate acceleration but reversed the *re*/*si* selectivity [57] (Scheme 36). This experimental result was attributed to the mismatched chiral induction effect of the catalyst, i.e. the chiral induction effect of the catalyst worked against that of the substrate [55]. Finally, with the (salen)Co complex **70a**, at 20°C, a total conversion of 85% was achieved with 80% yield in the required **77**-*endo*-*si* isomer. It seems that now the asymmetric induction effect of the catalyst **70a** matched that of the substrate **76**, so that the desired isomer predominated over the others.

Laulimalide **79** is a 20-membered macrolide with potential utility as an anticancer agent [58] (Scheme 37). The asymmetric synthesis of its C_3–C_{14} segment has been achieved by a chiral bis(oxazoline)–metal complex catalyzed oxa Diels–Alder reaction [58]. Dihydropyranone derivatives **81** and **83** are appropriately functionalized for the synthesis of the aforementioned laulimalide segment. Cyclocondensation of aldehyde **80** and Danishefsky's diene, at −78°C, in the presence of 10% Cu(II)–bis(oxazoline) complex [59] provided 62–76% yield of **81** in enantiomeric



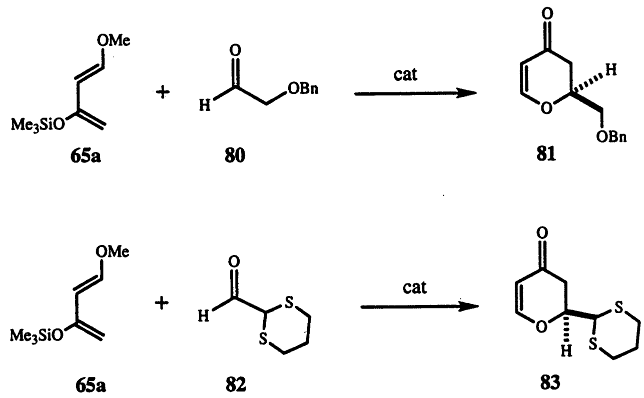
R= $CF_2CF_2CF_3$ (78)

Scheme 36.



79

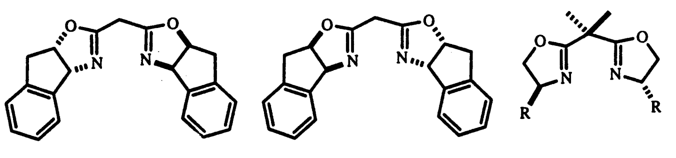
Scheme 37.



65a **80** **81**

65a **82** **83**

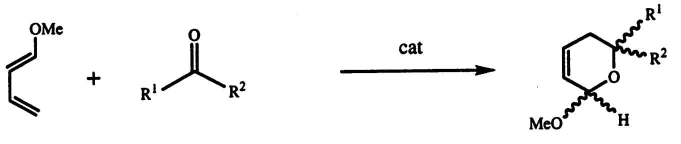
Scheme 38.



(*R*,*S*)-**4ah** (*S*,*R*)-**4ah**

R= Ph [(S)-**4e**]
R= ^{t}Bu [(S)-**4g**]

Scheme 39.



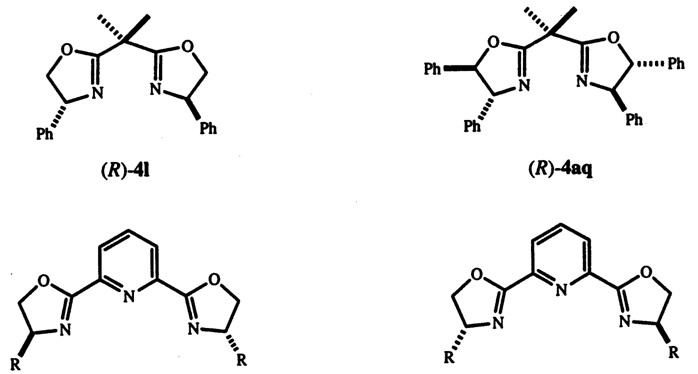
84 $R^1 = CO_2Et$, $R^2 = CO_2Et$ (**85a**)
$R^1 = H$, $R^2 = CO_2Bu$ (**85b**) **86**

Scheme 40.

excesses ranging from 38 to 87% (Scheme 38). The more constrained oxazolines (*R*,*S*)-**4ah** and (*S*,*R*)-**4ah** afforded higher enantioselectivities (85% ee, *S* at C_2 and 87% ee, *R* at C_2, respectively) (Scheme 39). Compound **81** can be prepared on a multigram scale by this method. Cyclocondensation of 1,3-dithianecarboxaldehyde **82** with the Cu(II)–bis(oxazoline) complex derived from (*S*,*R*)-**4ah** afforded the dihydropyranone **83** in 46% yield and 81% ee for the *S* enantiomer at C_2.

Examples of asymmetric hetero Diels–Alder reactions of ketones catalyzed by chiral transition-metal Lewis acids are very scarce. In 1987, Quimpère and Jankowski reported the reaction of diene **84** with the carbonyl dienophiles **85** using the lanthanide NMR chiral shift reagent tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$] as catalyst [60]. Good conversions in the dihydropyran carboxylate adducts **86** were obtained but with moderate ee (up to 64%) (Scheme 40).

The latter was the only reported example until Jørgensen and coworkers, very recently, published their results on catalytic Diels–Alder reactions of α-dicarbonyl compounds [61,62]. A variety of bis(oxazolines) ((*S*)-**4g**, (*R*)-**4l**, (*R*)-**4aq**, (*S*)-**4ar**, (*S*)-**4as**, (*R*)-**4at**) and metallic salts [$Cu(SbF_6)_2$, $Cu(OTf)_2$, $Zn(OTf)_2$, $Mg(OTf)_2$] were tested as catalysts (Scheme 41). The combination of the bis(oxazoline) (*S*)-**4g** with $Cu(OTf)_2$ (10 mol.%) gave the best results for the reaction between ethyl piruvate **87a** and Danishefsky's diene **65a** (Scheme 42). The hetero-Diels–Alder product **88a** was prepared in 78% isolated yield with 99% ee working at − 40°C in CH_2Cl_2. It is interesting to note that although the absolute stereochemistry of the two ligands, (*S*)-**4g** and (*R*)-**4l**, is opposite, the same absolute stereochemistry was found in product **88a**. Among nitromethane, Et_2O, CH_2Cl_2, and THF, the latter was the solvent of choice.



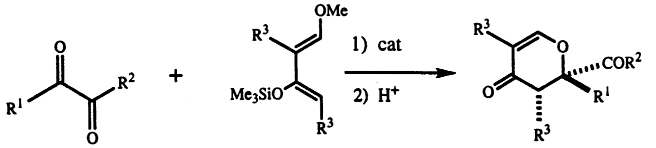
(*R*)-4l

(*R*)-4aq

R= ^{i}Pr [(*S*)-4ar]
R= ^{t}Bu [(*S*)-4as]

(*R*)-4at

Scheme 41.



R^1= Me, R^2= OEt **(87a)**
R^1= Me, R^2= OMe **(87b)**
R^1= Et, R^2= OMe **(87c)**
R^1= ^{i}Pr, R^2= OEt **(87d)**
R^1= Ph, R^2= OEt **(87e)**
R^1= Me, R^2= Me **(87f)**
R^1= Me, R^2= Et **(87g)**
R^1= Et, R^2= Et **(87h)**
R^1= Me, R^2= Ph **(87i)**

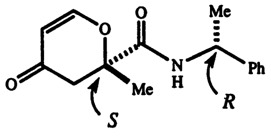
R^3= H **(65a)**
R^3= Me **(65b)**

R^1= Me, R^2= OEt, R^3= H **(88a)**
R^1= Me, R^2= OMe, R^3= H **(88b)**
R^1= Et, R^2= OMe, R^3= H **(88c)**
R^1= ^{i}Pr, R^2= OEt, R^3= H **(88d)**
R^1= Ph, R^2= OEt, R^3= H **(88e)**
R^1= Me, R^2= Me, R^3= H **(88f)**
R^1= Me, R^2= Et, R^3= H **(88g)**
R^1= Et, R^2= Et, R^3= H **(88h)**
R^1= Me, R^2= Ph, R^3= H **(88i)**
R^1= Me, R^2= OMe, R^3= Me **(88j)**
R^1= Ph, R^2= OEt, R^3= Me **(88k)**
R^1= Me, R^2= Me, R^3=Me **(88l)**

Scheme 42.

The $Cu(OTf)_2$-catalyzed reaction was developed to a general reaction between α-keto esters **87a**–**e** or α-diketones **87f**–**i** and the dienes **65a**,**b**. Under standard conditions (THF, 10 mol.% catalyst) conversions between 77 and 96% with ee ranging from 77 to 99% were achieved for diene **65a**. Only the sterically more demanding isopropyl compound **87d** reacted with diene **65a** giving poorer results: 42% yield of **88d** with 37% ee. Among the α-diketones, remarkably, the catalytic system distinguished between the methyl and ethyl or phenyl fragments of **87g** and **87i** reacting essentially at the methyl fragment in both cases.

The absolute stereochemistry of the major enantiomer **88b** was assigned by determining the molecular structure of its derivative **89** (Scheme 43). According to this analysis the absolute stereochemistry of the newly formed quaternary carbon



89

Scheme 43.

center of **88b** is *S* and, most probably, all adducts **88** have the same three-dimensional structure.

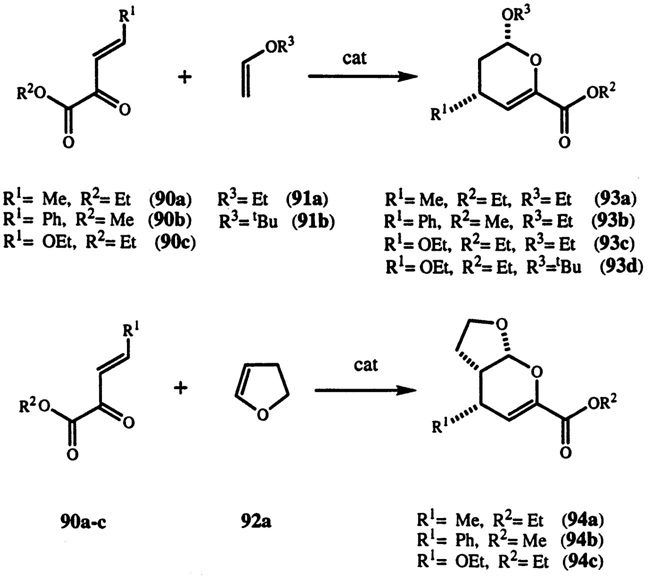
Diene **65b** reacted diastereoselectively with the methyl pyruvate **87b** giving in 75% isolated yield with 96% ee the endo product **88j** as shown by X-ray diffractometric measurements [62]. The phenyl-substituted α-keto ester **87e** and the dione **87f** reacted with diene **65b** with de of 67 and 80% and ee, in the major diastereomer, of 99 and 91%, respectively.

Interestingly, the reaction between ketones **87** and dienes **65**, catalyzed by the Cu(OTf$_2$)-(*S*)-**4g** system, can proceed to complete conversion with catalyst loadings as low as 0.05 mol.% without significative decrease in either turnover numbers nor enantioselectivity. It has been pointed out that this behavior is beginning to be enzyme-like and, therefore, the Cu(OTf)$_2$-(*S*)-**4g** catalytic system has been called ‘chemzyme’ [62].

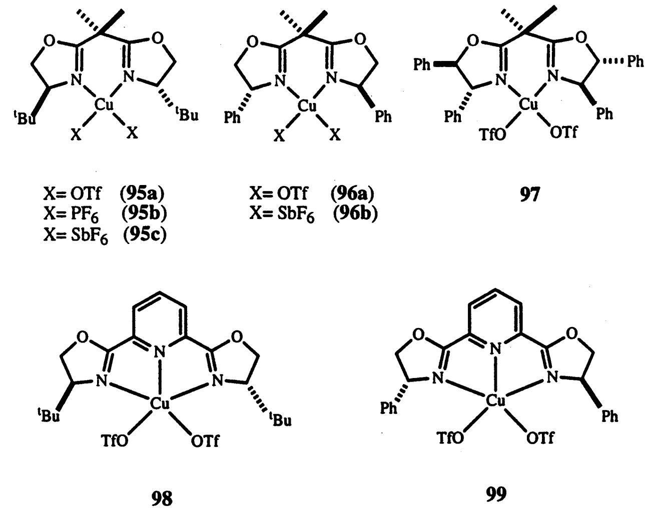
The enantioselective addition of electron-rich alkenes to α,β-unsaturated carbonyl compounds with chiral Lewis acids as catalysts is still a relatively unexplored field and only very few reactions have been reported. A recent example is the synthesis of dihydropyran adducts **93**, **94** achieved by the catalytic hetero-Diels–Alder reaction of β,γ-unsaturated α-keto esters **90** with acyclic **91** or cyclic enol ethers **92a** [63] (Scheme 44). A highly diastereo- and enantioselective conversion was obtained by using chiral bis(oxazoline) ligands in combination with copper(II) triflate or hexafluorophosphate salts. The best results for the reaction between **90a** and **91a** were obtained with complex **95a** (10 mol.%) at −78°C, in THF: 100% conversion, 99.7 ee (Scheme 45). Also complete conversions and ee greater than 95.6% were obtained in CH$_2$Cl$_2$. The related copper bis(oxazoline) complexes **96**–**99** gave good conversions with moderate ee (**96**, **97**) and poor conversions and ee (**98**, **99**). It is interesting to point out that ligands with opposite stereochemistry such as those of complexes **95a** and **96** led to the same absolute stereochemistry in the product.

The scope of this reaction was demonstrated for the reaction of various γ-substituted β,γ-unsaturated α-keto esters **90b**,**c** with the electron-rich alkenes **91**, **92** catalyzed by the copper–bis(oxazoline) compounds **95a**,**b** (10 mol.%). Good diasteroselectivities, ee greater than 90.4%, and conversions above 51% were achieved in all cases.

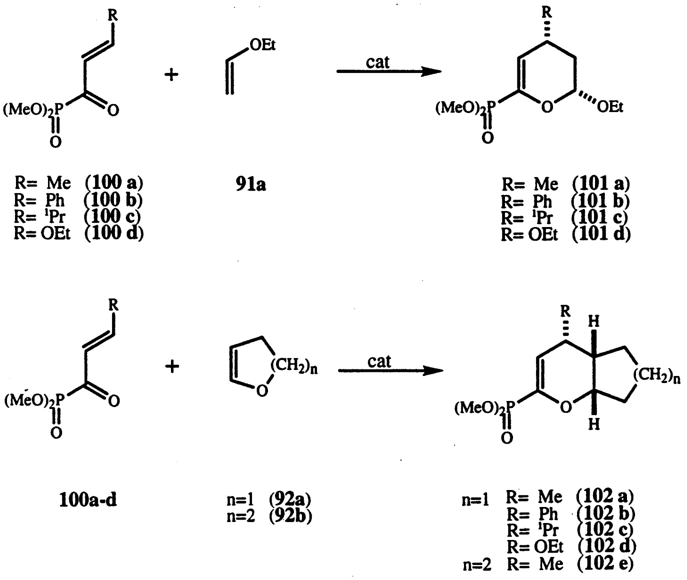
The stereoselective hetero Diels–Alder reaction between α,β-unsaturated acyl phosphonates **100** and enol ethers **91** and **92** catalyzed by the *C*$_2$-symmetric copper(II)–bis(oxazoline) complexes **95a**,**c** and **96a**,**b** was reported by Evans and Johnson [64]. In particular, the reaction of the ethyl vinyl ether **91a** with crotonyl phosphonate **100a** in the presence of **95a** (10 mol.% catalyst, CH_2Cl_2, 48 h, − 78°C) afforded cycloadduct **101a** in 89% yield with an *endo*/*exo* ratio of 99/1 and in 99% ee (Scheme 46). The hexafluoroantimonate catalyst **95c** accelerates the reaction (84% conversion in 22 h) but afforded adduct **101a** in lower diastero- and enantioselectivities (*endo*/*exo*, 69/1; 93% ee). Catalysts **96a**,**b** gave comparable



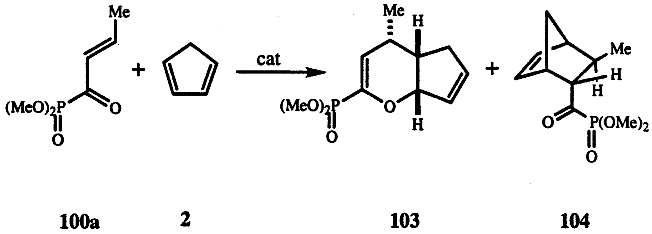
Scheme 44.



Scheme 45.



Scheme 46.

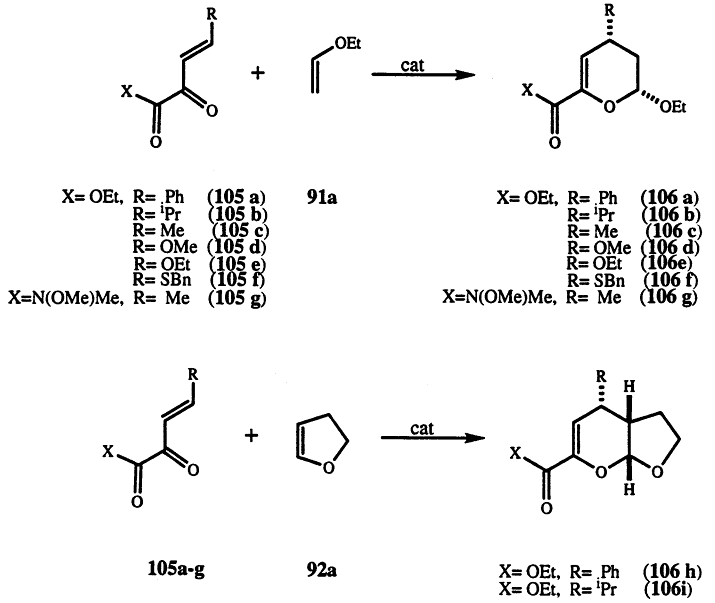


Scheme 47.

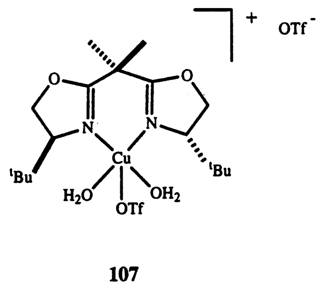
results as **95a**,**c** and led to the same stereochemistry in the products in spite of their opposite stereochemistry. Interestingly, the stereoselectivities and yield of the reaction could be almost maintained (93% yield, *endo*/*exo*: 99/1, 93% ee) using only 0.2 mol.% of catalyst **96b**. Furthermore, this reaction tolerates a broad range of temperatures (from -78 to $+25$°C) without important decrease in stereoselectivities: catalyst **95a**; -78°C, *endo*/*exo* = 99/1, 99% ee; 25°C, *endo*/*exo* = 95/5, 89% ee. Any of the four catlysts, **95a**,**c** and **96a**,**b**, also catalyzed the cycloaddition of cyclic enol ethers **92a**,**b** with acyl phosphonate **100a** in $>80\%$ ee.

Acyl phosphonates **100** also reacted with dienes. Surprisingly, the major product of the reaction of **100a** with HCp in the presence of **95c**, compound **103** (65% yield, *endo*/*exo* $>$ 95/5, 95% ee), results from an inverse electron demand hetero-Diels–Alder reaction in which HCp acted as the dienophile. The expected Diels–Alder adduct **104** was obtained as minor product (35% yield, *endo*/*exo* = 87/13, 84% ee) (Scheme 47).

The scope of the reactions depicted in Scheme 46 was expanded to cycloaddition reactions of β,γ-unsaturated α-keto esters **105** using the same type of bis(oxazoline)–copper(II) compounds (**95a** and **107**) as catalysts [65]. The ethyl vinyl ether **91a** reacted with unsaturated keto ester **105a** in the presence of catalyst **95a** (2 mol.%, THF, 0°C) providing cycloadduct **106a** in 93% yield, with an *endo*/*exo* ratio greater than 20:1 and in 97% ee (Scheme 48). The same reaction performed in the presence of catalyst **107** afforded identical results if MS3Å was present in the reaction medium. While the anhydrous complex **95a** is hygroscopic, the related bis(aquo) complex **107** is stable enough to be stored indefinitely without special precaution. Thus, a combination of **107** with MS3Å is a plausible alternative to **95a** (Scheme 49).

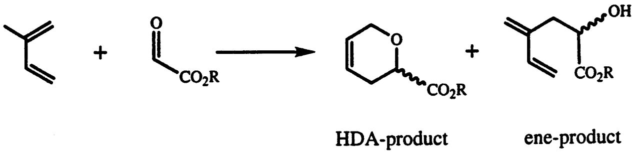


Scheme 48.



107

Scheme 49.



Scheme 50.

The structure of complex **107** has been determined by X-ray diffractometric methods [65]. The copper atom displays a distorted square pyramidal geometry with one of the triflate anions bound to the metal (Cu–O, 2.624 Å) in the apical position. The two water molecules and the two nitrogens of the bis(oxazoline) ligand occupy the equatorial positions, the remaining triflate anion being fully dissociated.

Complex **107** is an effective catalyst over a broad range of temperature and solvents with excellent results. In THF, the ee varies from 94 to > 99% between + 25 and − 40°C. At 0°C the ee achieved in THF, Et_2O, toluene, dioxane, and CH_2Cl_2 were 97, 97, 98, 93, and 89%, respectively.

Alkyl, alkoxy, and thiobenzyl keto esters **105b–f** as well as amide **105g** reacted with the vinyl ethyl ether **91a** affording the corresponding dihydropyrans **106** with excellent yield (greater than 87%) and diastero- and enantioselectivities (*endo*/*exo* = 16:1, = 95% ee) under standard conditions (2 mol.% of **107**, MS3Å, THF, 0°C). In particular, 96% ee was achieved in the reaction of **105c** with **91a** with only 0.5 mol.% of **107** in the presence of MS3Å.

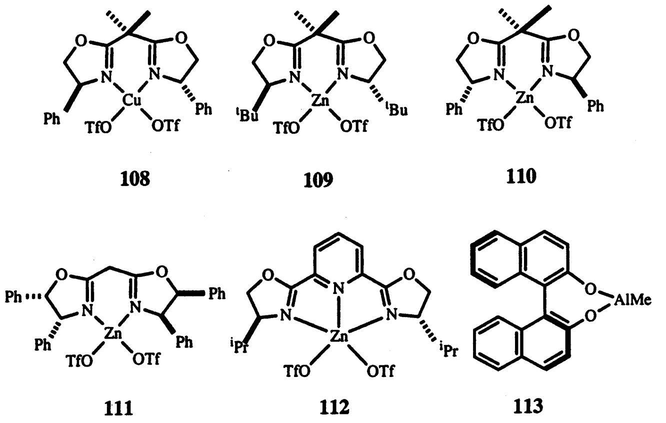
Interestingly, catalyst **107** can be recovered and reused five times without significant diminution in yield or selectivity.

Jørgensen et al. have developed a catalytic asymmetric hetero-Diels–Alder methodology for the reaction of unactivated dienes with glyoxylates. Unactivated dienes having an allylic C–H bond can react with electron-deficient aldehydes in two different ways leading to either the hetero-Diels–Alder or the hetero-ene product (Scheme 50). Good hetero-Diels–Alder:ene product ratios, can be obtained by using the copper(II) [66] **95a**, **96a** and **108** or the zinc(II) [67] **109–112** bis(oxazoline) compounds as catalysts [68] (Scheme 51). Scheme 52 summarizes the tested reactions. Under standard conditions (10 mol.%, CH_2Cl_2, r.t.) and using copper(II) based catalysts, the highest hetero-Diels–Alder:ene ratio (1:1) was achieved for catalyst **95a** in the reaction between **114c** and **72c** with 77% ee for the hetero-Diels–Alder product. The temperature has a significant influence on the hetero-Diels–Alder product:ene product ratio. Thus, for the reaction between **114a** and **72a** this ratio was 1:1.8 and 1:0.8 at 20 and − 30°C, respectively. Reducing the temperature also led to a substantial increase in ee. For example, in the presence of **95a** as catalyst, at 20°C the ee for the hetero-Diels–Alder product **115d** was 85% and at − 30°C it was 95%.

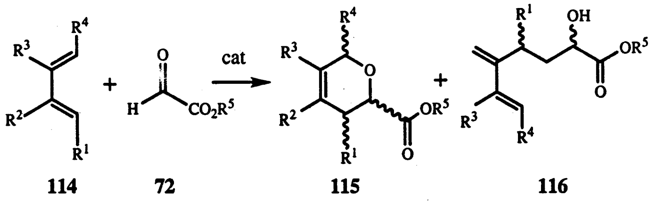
Reaction of 1,3-cyclohexadiene **114d** with **72a** using **96a** as catalyst produced only the *endo* isomer of the bicyclic product **115f** in 60% ee. Compound **115f** can be converted into enantiomerically pure lactone **117**, a highly interesting synthon for natural product synthesis [66] (Scheme 53).

The hetero-Diels–Alder reaction between the substituted 1,3-cyclohexadiene **118** and **72a** using the bis(oxazoline)–copper(II) catalyst **95c** was used as a key step in the first total synthesis of (*R*)-dihydroactinidiolide (**119**) [69] and (*R*)-actinidiolide (**120**) identified as flavor components in many plants such as tobacco and tea [70] (Scheme 54).

The use of bis(oxazoline)–zinc(II) catalyst produced greater hetero-Diels–Alder product:ene product ratios than the use of their copper analogues. Thus, an 1:0.6 hetero-Diels–Alder product:ene product ratio was obtained in the reaction of **114c** with **72a** using the zinc compound **110** as catalyst. Under the standard conditions above mentioned, an overall yield of 67% was achieved with 81% ee for the hetero-Diels–Alder *S* adduct. The use of nitromethane as solvent, instead of CH_2Cl_2, produced, in general, a decrease in the ee of the products [67]. The reaction



Scheme 51.



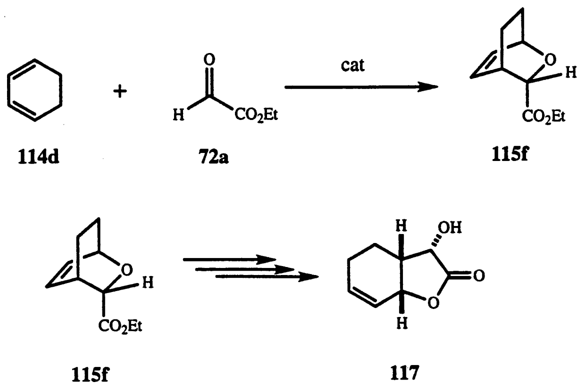
R^1=R^2=R^3=R^4= H (**114a**)
R^1=R^3=R^4= H; R^2=Me (**114b**)
R^1=R^4= H; R^2=R^3=Me (**114c**)
R^1=R^4= -CH_2-; R^2=R^3=H (**114d**)

R^5= Et (**72a**)
R^5= Me (**72b**)
R^5= ⁱPr (**72c**)

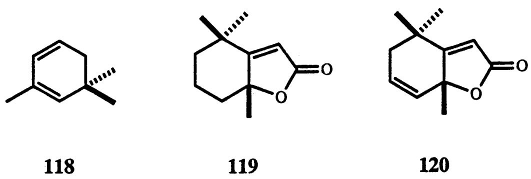
R^1=R^2=R^3=R^4= H; R^5=ⁱPr (**115a**)
R^1=R^3=R^4= H; R^2=Me; R^5=Et (**115b**)
R^1=R^4= H; R^2=R^3=Me; R^5= Me (**115c**)
R^1=R^4= H; R^2=R^3=Me; R^5=Et (**115d**)
R^1=R^4= H; R^2=R^3=Me; R^5= ⁱPr (**115e**)
R^1=R^4= -CH_2-; R^2=R^3=H; R^5= Et (**115f**)

R^1=R^3=R^4= H; R^5=Et (**116a**)
R^1=R^4= H; R^3=Me; R^5=Me (**116b**)
R^1=R^4= H; R^3=Me; R^5=Et (**116c**)
R^1=R^4= H; R^3=Me; R^5=ⁱPr (**116d**)

Scheme 52.



Scheme 53.



Scheme 54.

between 1,3-cyclohexadiene **114d** and glyoxylate **72a** in the presence of the zinc catalysts **109**–**112** gave the hetero-Diels–Alder product **115f** in yield ranging from 19 to 84% with moderate ee ($\leq 65\%$).

It is interesting to remark that for both copper and zinc based catalysts changing the substituent from *tert*-butyl to phenyl and changing the absolute stereochemistry of the chiral carbon atom in the bis(oxazoline) ligand led to the same absolute configuration in the products. Furthermore, in some instances, the enantiomer obtained depends on the solvent used. This is the case for the reaction between **114d** and **72a** catalyzed by the zinc compound **110**. While in CH_2Cl_2 the 1*R*,3*S*,4*S* diastereomer was obtained in nitromethane as solvent its 1*S*,3*R*,4*R* eanantiomer was the product.

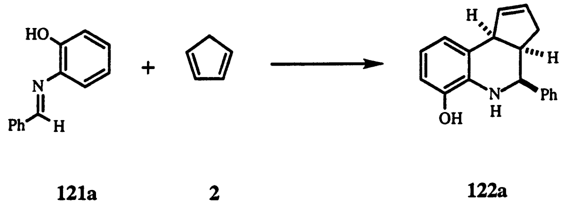
3.2. *Aza Diels–Alder reactions*

The asymmetric catalytic aza Diels–Alder reactions provide a useful route to optically active substituted piperidine and tetrahydroquinoline heterocycles holding enormous potential in alkaloid synthesis. Examples of chiral transition-metal Lewis acid catalyzed asymmetric aza Diels–Alder reactions are rare. This could be due to the fact that the basic nitrogen atom of the substrate would irreversibly coordinate to the metallic catalyst precluding the completion of the catalytic cycle. Consequently, stoichiometric amounts of the chiral Lewis acid were needed [71].

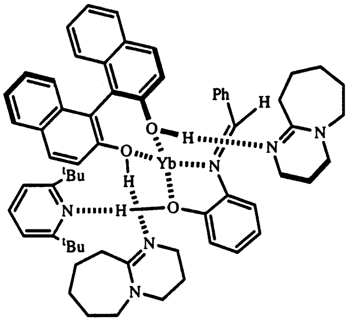
Ishitani and Kobayashi have reported the first catalytic enantioselective aza Diels–Alder reaction between *N*-benzylidene-2-hydroxyaniline and HCp (Scheme 55) [72]. The catalyst was prepared in situ from [Yb(OTf)$_3$] and (*R*)-(+)-1,1′-bi-2-naphthol [(*R*)-(+)-BINOL]. The best results (92% chemical yield and > 99/1 *cis*/*trans* and 71% ee selectivities) were achieved in CH_2Cl_2, at − 15°C, with 20% of catalyst, MS4Å, diaza bicyclo[5.4.0]undec-7-ene (DBU), and 2,6-di-*tert*-butylpyridine (DTBP) as additive. In order to achieve reasonable chiral induction the bidentate coordination of the diene to the chiral Lewis acid plays an important role [73]. The proposed transition state that accounts for the experimental results is depicted in Scheme 56.

DBU forms hydrogen bonds with the coordinated (*R*)-(+)-BINOL transferring the axial chirality of the alcohol to the azadiene region and favoring the chiral induction. The top face of the azadiene is shielded by a DBU molecule and the diene preferably approaches from the bottom face achieving the selectivity. However, the phenolic hydrogen of the azadiene would also interact with DBU decreasing selectivity. This undesirable effect can be reduced by using additives such as *N*-methylimidazole (NMI), DTBP, 2,6-dimethylpyridine (DMP), or 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), that can form N···H–O hydrogen bonds of the dienophile.

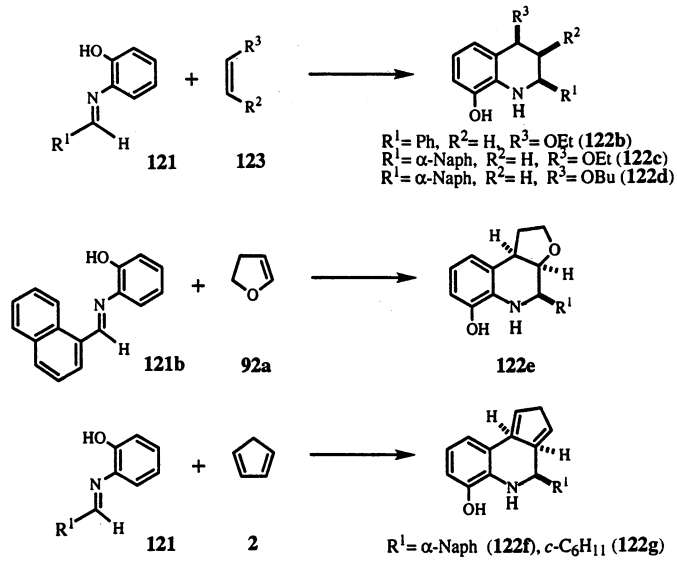
Other dienes and dienophiles were tested under similar conditions (Scheme 57). The results range from 58 to 90% chemical yield in the corresponding tetrahydroquinoline, with a typical *cis*/*trans* selectivity greater than 90/10 and an ee in the major isomer ranging from 61 to 91%.



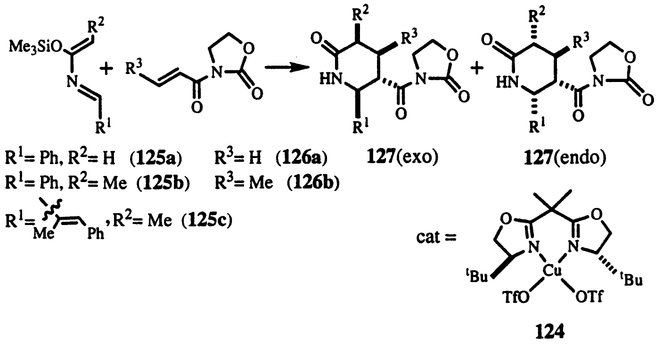
Scheme 55.



Scheme 56.



Scheme 57.



Scheme 58.

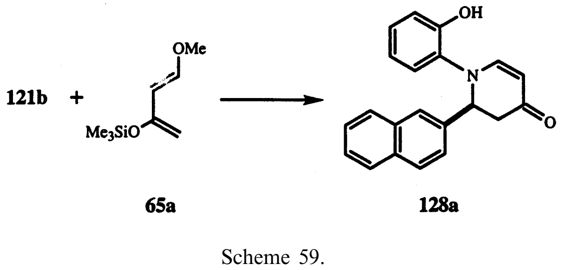
The above reactions are not only the first asymmetric aza Diels–Alder reactions achieved using a chiral metal-based catalyst but are also remarkable as rare examples in which the chiral Lewis acid activates not the dienophile but the diene.

Jnoff and Ghosez recently reported Diels–Alder reactions between electron-rich 2-azadienes and olefinic dienophiles activated by the Evans' Lewis acid **124**, prepared in situ from copper(II) triflate and (*S*,*S*)-*tert*-butyl-bis-oxazoline [74]. Azadiene **125** cycloadded to *trans*-crotonimide **126** in the presence of **124** to give, after methanolysis, the corresponding substituted 2-piperidones (Scheme 58).

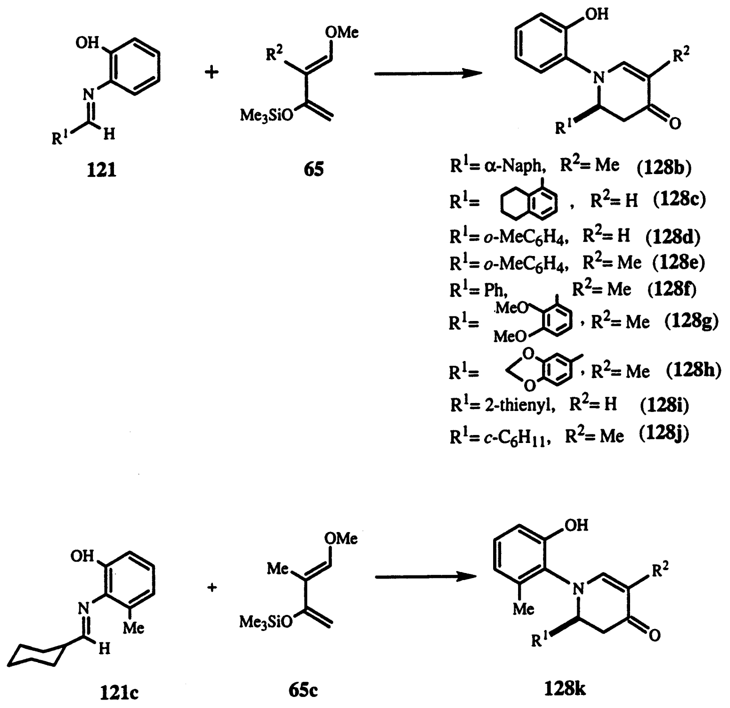
The reaction was performed in CH_2Cl_2, with 5–8 mol.% of catalyst, between −45°C and r.t., and in the presence of MS4Å. Under these conditions the *exo*-selectivity was practically perfect (>99:1), except in the case **125a** + **126a** (*exo*/*endo*, 6.1/1), and the ee in the *exo* isomer was greater than 90% in all cases (98.3% for **125a** + **126a** and **125b** + **126a**). The configuration of the new stereogenic centers has been predicted from the transition-state model proposed by Evans et al. for other Diels–Alder reactions catalyzed by **124** [75].

The enantioselective synthesis of chiral piperidine derivatives has been achieved by reacting aldimines, as imino dienophiles, with Danishefsky's diene. A chiral zirconium compound (10 mol.%) prepared from $[Zr(O\text{-}t\text{-}Bu)_4]$, (*R*)-6,6′-dibromo-1,1′-binaphthol [(*R*)-Br-BINOL, 2 equiv.] and an additive (NMI, 2-methylimidazole, 1,2-dimethylimidazole, oxazolidine, and 2-methyloxazolidine, 2–3 equiv.) [76] catalyzed the reactions. The reaction of aldimine **121b** [77] and Danishefsky's diene **65a**, at −45°C, was investigated as the model reaction [78] (Scheme 59). The actual structure of the catalyst is not known yet but it seems that it is strongly influenced by the solvent in which it was prepared. It has been proposed that two molecules of the additive are coordinated to the zirconium [78]. Among additives, NMI gave the best results. Dichloromethane, benzene, and toluene have been tried as solvents and the best results were obtained when the catalyst was prepared in toluene and the catalytic reaction was performed in toluene as well. Under these conditions an 86% of chemical yield of **128a** with 82% ee were achieved. Higher catalyst loading (20 mol.%) improved both yield (96%) and ee (88%).

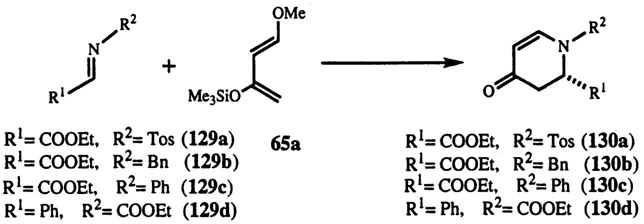
The use of catalysts based on the other two Group 4 metals, titanium and hafnium, was also examined. Under similar conditions the corresponding hafnium system gave high yields and enantioselectivities (20 mol.% catalyst, 96 and 84%, respectively) in the model reaction. Lower yields and enantioselectivities were obtained with the related titanium catalyst (70% yield, 62% ee). The chiral zirconium catalyst was also tested in several related aza Diels–Alder reactions (Scheme 60) under the standard conditions (5–20 mol.% catalyst, toluene, NMI, −45°C). In general, high chemical yields (51–98%) and good to high enantioselectivities (64–93%) were obtained. **65c** was also examined as diene and gave the corresponding dihydropyridone (51–93% yield) with ee of 65% ($R^1 = Ph$), 93% ($R^1 = \alpha$-Naph), 77% ($R^1 = o\text{-}MeC_6H_4$), and 86% ($R^1 = c\text{-}C_6H_{11}$, $R^3 = Me$). Dienophiles with *ortho*-substituted arenes as R^1 group gave higher selectivities than those with unsubstituted arenes. The reaction of **121** ($R^1 = c\text{-}C_6H_{11}$) with **65c** occurs, under standard conditions, with a low ee. It has been argued [78] that this low ee was due to the isomerization of the *cis* and *trans* forms of the aldimine. In fact, the aldimine **121c**



Scheme 59.



Scheme 60.



Scheme 61.

(R^3 = Me), in which the isomerization is restricted, gave the desired pyridone with 86% ee.

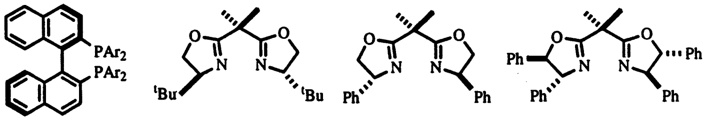
Following a Diels–Alder methodology Jørgensen and coworkers have prepared attractive precursors for optically active nonnatural α-amino acids of the piperidine type [79]. Reaction of imines derived from ethyl glyoxylate (**129**) with the activated dienes **65a**,**b** gave the optically active aza Diels–Alder adducts **130** (Scheme 61). The bidentate coordination of the dienophile through the imino nitrogen and one the oxygen of the ester functionality could originate a fixed chiral environment around the aldimino group.

A variety of metal complexes derived from the chiral diphosphines **131a**,**b** or bisoxazoline ligands (*S*)-**4g**, (*R*)-**4l**, and (*R*)-**4aq** and transition-metal Lewis acid such as $Zn(OTf)_2$, $Cu(OTf)_2$, CuOTf, $CuClO_4$, $AgSbF_6$, AgOTf, $AgClO_4$, $Pd(SbF_6)_2$, $Pd(ClO_4)_2$, $Pd(OTf)_2$, and $RuSbF_6$ ($Tf = F_3CSO_2$) were examined. Under the standard conditions (−78°C, THF, 10 mol.% of catalyst) only the α-imino ester **129a**, reacted enantioselectively with the activated diene **65a** to yield **130a** when copper(I)–BINAP complexes were used as catalyst with conversions greater than 60% in all cases. The highest ee, 80%, was obtained by using the 2,2′-bis(ditolylphosphanyl)-1,1′-binaphthyl ligand (**131b**) with $CuClO_4 \cdot 4MeCN$ (Scheme 62). Results are almost independent of the counterion used, but when CH_2Cl_2 was used as the solvent the ee strongly diminished [80]. Silver(I) and palladium(II) catalyst gave ee values of about 33% and ruthenium(I) led to a racemic product. Catalyst based on the bisoxazoline ligands (*S*)-**4g**, (*R*)-**4l**, and (*R*)-**4aq** with copper(I), copper(II) or zinc(II) salts gave ee values lower than 20%.

The absolute stereochemistry of **130a** was assigned using the anomalous X-ray scattering for sulfur: the Rogers parameter refined best for the isomer with *S* stereochemistry at C_1 [81].

The use of the $CuClO_4 \cdot 4MeCN$-tol-BINAP catalytic system, under the standard conditions, for the reaction between **129a** and **65b** resulted in a significant improvement in the ee value of the major diastereomer **130e**-*trans*: 94% ee, diastereoselectivity ratio 10:1. The relative configuration of the minor diastereomer **130e**-*cis* was also assigned by X-ray crystallography [79] (Scheme 63).

It is worthy of mention that the aza Diels–Alder reaction **129a** + **65b** can be performed on gram scale with only 1 mol.% of catalyst. The diastereomer **130e**-*trans* was isolated in 90% yield with a diastereoselective ratio of 4:1 and an ee of 93%. Under the standard conditions, THF is the solvent of choice. In all other tried solvents, the enantioselectivity of **130e**-*trans* decrease: THF, 94% ee; Et_2O, 79%; CH_2Cl_2; 80%, toluene, 65%; DMF, 0%.



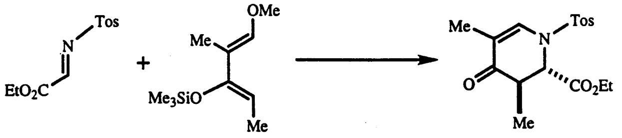
Ar= Ph (**131a**)
Ar= Tol (**131b**)

(*S*)-**4g**

(*R*)-**4l**

(*R*)-**4aq**

Scheme 62.

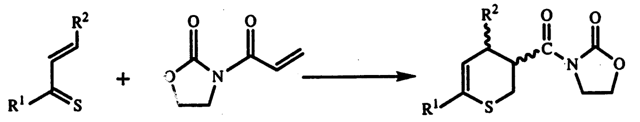


129a

65b

130e-*trans*

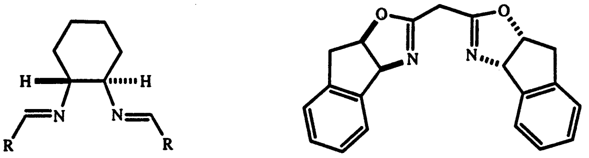
Scheme 63.



R^1= Ph, R^2= Ph **(132a)**
R^1= Ph, R^2= *p*-Tol **(132b)**
R^1= *p*-Tol, R^2= *p*-Tol **(132c)**
R^1= *p*-$MeOC_6H_4$, R^2= Ph **(132d)**
R^1= SMe, R^2= Ph **(132e)**

R^1= Ph, R^2= Ph **(133a)**
R^1= Ph, R^2= *p*-Tol **(133b)**
R^1= *p*-Tol, R^2= *p*-Tol **(133c)**
R^1= *p*-$MeOC_6H_4$, R^2= Ph **(133d)**
R^1= SMe, R^2= Ph **(133e)**

Scheme 64.



R= Ph **(134a)**
R= 2,6-$Cl_2C_6H_3$ **(134b)**
R= 4-$^iPrC_6H_4$ **(134c)**

(*S*,*R*)-4ah

Scheme 65.

3.3. Thia Diels–Alder reactions

The asymmetric thia Diels–Alder reaction is a useful and powerful synthetic method which can provide access to sulfur containing heterocycles and their derivatives with high enantiomeric excess. In spite of their promising utility, chiral transition-metal Lewis acid catalyzed versions of this reaction are very rare. As far as we know, there is only two communications on this subject [82,83] (Scheme 64).

Saito et al. [82] reported the first homochiral Lewis acid-induced enantioselective thia Diels–Alder cycloaddition between the thiabutadiene **132a** and the dienophile **1a**. The best results were achieved by employing as Lewis acid catalyst a 1.0:1.1 mixture of $Cu(OTf)_2$ and a chiral bisimine (**134**). The reaction was performed in CH_2Cl_2, at 0°C or r.t. and isolated yields up to 99% were obtained with all the three ligands **134a**–**c**, after 3 h of treatment. *Endo*:*exo* ratios range from 69:31 to 91:9 and, under catalytic conditions, ee between 40 and 64% in the *endo*-(3*R*,4*R*) adduct were achieved. However, the highest ee values (73%, **134a**; 76%, **134b**; 74%, **134c**) were obtained under stoichiometric conditions (Scheme 65).

It is interesting to note that, when the reaction was performed in the presence of MS4Å under the optimized conditions (100 mol.% catalyst, CH_2Cl_2, 0°C, 3 h of reaction) conversions around 90% and *endo*:*exo* ratios of 96:4, 95:5 and 88:12 and *endo*-(3*R*,4*R*) ee of 94, 95, and 90% for **134a**, **134b**, and **134c**, respectively, were achieved.

In order to accomplish a better catalytic version for the process of Scheme 64, the bisoxazoline ligand (*S*,*R*)-**4ah** was selected [83]. $Cu(OTf)_2$, $Cu(ClO_4)_2$, and

$Ni(ClO_4)_2$ were the Lewis acids of choice; $Co(ClO_4)_2$, $NiCl_2{\cdot}6H_2O$ or $Zn(OTf)_2$ were found to be inferior. At 10 mol.% of catalyst loading, both $Cu(OTf)_2$ or $Ni(ClO_4)_2$ in combination with homochiral (*S*,*R*)-**4ah** (1.0:1.1 ratio), at r.t., gave 80 (nickel salt) or 92% (copper salt) conversions until 3 h of reaction. The *endo*:*exo* molar ratios obtained were 78:22 and 70:30 and the ee, in the *endo*-(3*S*,4*S*) isomer, were 80 and 98% for the nickel and copper salts, respectively. The $Cu(ClO_4)_2$ catalyst also induced good enantioselectivities (93 and 89% ee) with the use of only 5 mol.% loading.

These copper and nickel catalytic systems were also active for the reactions between thiabutadienes **132b–d** and **1a**. In general, ee values greater than 80% were attained using 50 mol.% catalyst loadings. The copper catalyst is also efficient at 5–10 mol.% ratios (74% ee). In particular, the reaction with the *p*-methoxyphenyl-substituted thiabutadiene **132d** showed 96% ee with 20 mol.% of $Cu(OTf)_2$-(*S*,*R*)-**4ah** as catalyst.

The reaction between the α,β-unsaturated dithiocarboxylic acid **132e** and the dienophile **1a** is catalyzed by $Ni(ClO_4)_2$-(*S*,*R*)-**4ah** (20 mol.%) at r.t., in CH_2Cl_2, to afford the *endo*:*exo* isomers in a 70:30 ratio with a 82% ee in the *endo*-(3*S*,4*S*) adduct. Analogously, with only 5 mol.% of $Cu(OTf)_2$-(*S*,*R*)-**4ah** catalyst, 74% conversion with 74% ee were achieved. Interestingly, the use of the chiral bisimine **134b** in combination with the copper Lewis acid catalyst produced at −78°C almost perfect enantioselectivity ($>99\%$) when the reaction was performed in the presence of powdered MS4Å.

4. Mechanistic considerations

4.1. The bis(oxazoline)-based catalytic systems

Most of the stereochemical results obtained from the Diels–Alder reaction of acrylimides **1** and HCp (Scheme 2) catalyzed by C_2-symmetric bis(oxazoline) complexes of Fe^{3+}, Mg^{2+}, Zn^{2+} or Cu^{2+} have been rationalized by assuming that the reaction proceeds via the intermediacy of octahedral [4] $[FeX_2\{bis(oxazoline)\}\mathbf{1}]^+$, tetrahedral $[M\{bis(oxazoline)\}\mathbf{1}]^{2+}$, (M = Mg [5,11,84], Zn [85]) or square-planar [6,11–14] $[Cu\{bis(oxazoline)\}\mathbf{1}]^{2+}$ complexes in which the dienophile **1** chelates to the metal in a C=C/C=O *s-cis* conformation [86]. Furthermore, in octahedral structures chelation of the dienophile has to occur at an equatorial and axial site [4]. For *S*,*S* configurated bis(oxazolines) (see Scheme 4) [87], the octahedral and tetrahedral geometries favor the attack of the HCp on the *Si*-face but, in the square-planar arrangement the sterically accessible dienophile diastereoface is the *Re* one. In the former case, (*R*)-**3** adducts would be formed and, in the second, (*S*)-**3** products would be obtained. Conversely, when catalysts with *R*,*R* configurated bis(oxazolines) [87] adopt the octahedral or tetrahedral geometries, (*S*)-**3** products would be obtained and, if they are square-planar, (*R*)-**3** adduct would be expected [4–6,11–14,84,85].

Analogously, the stereochemical outcome of the hetero Diels–Alder reactions between the unactivated dienes 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene [66,67] or Danishefsky's diene [88] with glyoxylate esters catalyzed by C_2-symmetric bis(oxazoline) complexes of Cu^{2+} or Zn^{2+} was similarly explained [89]. In this case, the square-planar geometry proposed for the copper–dienophile complex [66,88] favor the diene attack on the *Re*-face of the dienophile when *R*,*R* configurated bis(oxazolines) [87] were used as chiral auxiliaries and, consequently, *R* adducts were obtained. However, with this type of bis(oxazolines), the assumed tetrahedral environment of the zinc–dienophile intermediate [67] originated *S* adducts via attack of the diene on the unencumbered *Si*-face of the dienophile. On the contrary, *S*,*S* configurated bis(oxazolines) [87] in square-planar geometries afforded *S* adducts but in tetrahedral structures yielded *R* products.

However, several exceptions to these simplistic rules have been reported. Thus, for example, the reaction of acrylimide **1a** with HCp catalyzed by the $Cu(OTf)_2$/**4af** complex afforded the *endo* (*R*)-**3a** adduct in 73% ee instead of the expected *endo* (*S*)-**3a** adduct according to a square-planar intermediate copper complex [12]. Similarly, **1b** + HCp yielded the unexpected *endo* (*S*)-**3b** product in 24% or 28% ee, when the $Cu(OTf)_2$/**4x** or $Cu(OTf)_2$/**4y** complexes, respectively, were used as catalysts [9]. Analogously, $M(OTf)_2$/bis(oxazoline) catalysts (M = Mg, Zn) afforded **3b** adducts with predominant configurations opposite to the expected from tetrahedral intermediates [8] $[M\{(bis(oxazoline)\}(\mathbf{1b})]^{2+}$.

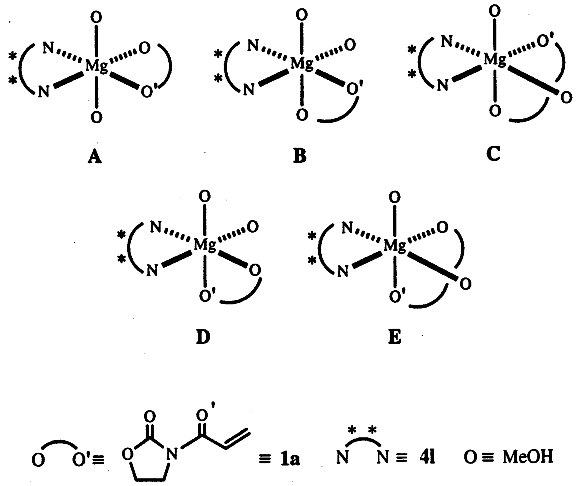
Some exceptions have also been reported for hetero Diels–Alder reactions [62–64,66,67]. Thus, for example, the reaction of 2,3-dimethyl-1,3-butadiene with ethyl glyoxylate (see Scheme 52) catalyzed by $Cu(OTf)_2$/**4l** or $Cu(OTf)_2$/**4e** complexes afforded the dihydropyran derivatives (*S*)- or (*R*)-**115d**, respectively, in both cases with opposite configuration to that expected from a square-planar intermediate of the type [66] $[Cu\{(bis(oxazoline)\}(ethyl\ glyoxylate)]^{2+}$. Similarly, using the $Zn(OTf)_2$/**4g** complex as catalyst the (*S*)-**115d** isomer was obtained instead of the (*R*)-**115d** enantiomer predicted from a $[Zn\{(bis(oxazoline)\}(ethyl\ glyoxylate)]^{2+}$ tetrahedral intermediate.

In order to account for these exceptions, changes in the geometry of the involved intermediates has been proposed [67], i.e. tetrahedral instead of square-planar copper(II)–bis(oxazoline)–dienophile complexes or square-planar or octahedral instead of tetrahedral M–bis(oxazoline)–dienophile (M = Mg, Zn) intermediates.

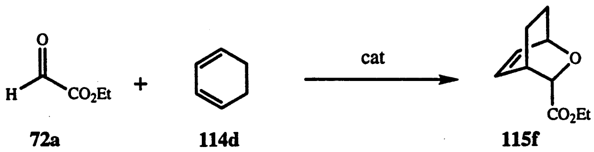
In this context, it is interesting to point out that for the reaction between **1a** and HCp it has been reported the enantioselective synthesis of both Diels–Alder enantiomers *endo* (*S*)-**3a** and *endo* (*R*)-**3a** by using the same bis(oxazoline)-based catalyst, $Mg(ClO_4)_2$/**4l** [90]. Thus, while in dry CH_2Cl_2 the *endo* (*S*)-**3a** adduct was obtained in 68–73% ee, when the same reaction was run in the presence of 2 equiv. of hydroxylic ligands (water or alcohols) the opposite enantiomer *endo* (*R*)-**3a** was preferably obtained. The intermediacy of an 1:1, metal:bis(oxazoline) complex was supported by the linear relationship between the ee of the product and the ee of the bis(oxazoline) [90]. The effect of water or alcohols in inverting enantioselectivity of the reaction was assigned to a change in the coordination around the Mg(II) center from tetrahedral $[Mg(\mathbf{4l})(\mathbf{1a})]^{2+}$ to octahedral $[Mg(\mathbf{4l})(\mathbf{1a})(ROH)_2]^{2+}$. The tetrahedral coordination leaves the *Re* diastereoface of the dienophile more accessible to the diene and (*S*)-**3a** was the preferred enantiomer obtained. Variable temperature ^{1}H-NMR data of 1:1:1:2, $Mg(ClO_4)_2$:**4l**:**1a**:MeOH mixtures strongly indicated first, that the acryloyl group was in the *s-cis* conformation and second, that from the five possible isomers of the octahedral species $[Mg(\mathbf{4l})(\mathbf{1a})(ROH)_2]^{2+}$ (**A**–**E**, Scheme 66) only isomer **B** was present in solution. Complex **B**, with the acryloyl group in the *s-cis* conformation, will give the (*R*)-**3a** enantiomer preferentially, while isomers **C**–**E** will give the opposite enantiomer.

Similarly, the absolute stereochemistry of the hetero Diels–Alder product *endo*-**115f** of the reaction between 1,3-cyclohexadiene and ethyl glyoxylate using $Zn(OTf)_2$/**4l** [67] or $Cu(OTf)_2$/**4l** [91] as catalyst changed from 1*R*,3*S*,4*S* to 1*S*,3*R*,4*R* when the solvent was changed from CH_2Cl_2 to $MeNO_2$. This change can be accounted for by assuming a change of the intermediate from a tetrahedral $[M(glyoxylate)(\mathbf{4l})]^{2+}$ to an octahedral $[M(glyoxylate)(\mathbf{4l})(MeNO_2)_2]^{2+}$ geometry with the two solvent molecules coordinated at the axial sites (Scheme 67).

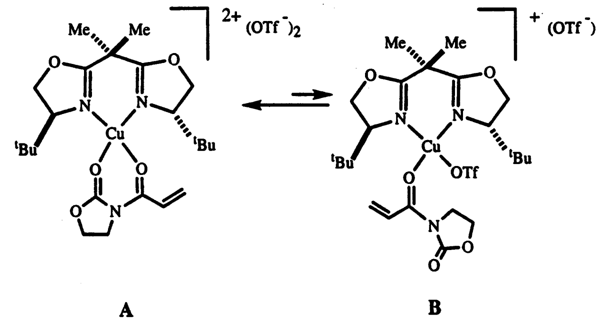
Besides the solvent, the counterion also affected in some instances the enantioselectivity and the conversion of certain of Diels–Alder reactions. For example, the rate of the reaction of acrylimide **1a** with HCp catalyzed by $Cu(SbF_6)_2$/**4g** was approximately 20 times faster than the rate of the analogous reaction promoted by



Scheme 66.



Scheme 67.



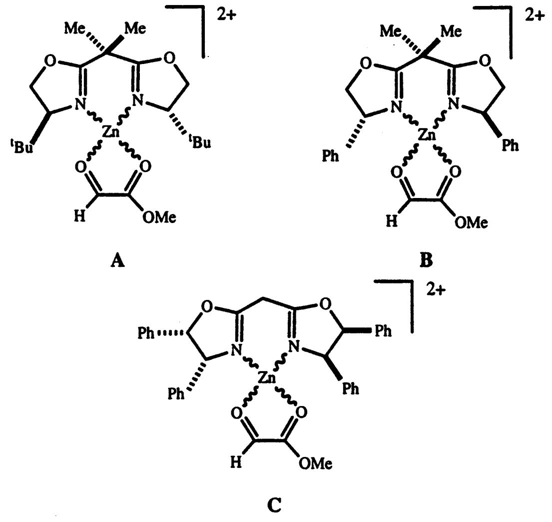
Scheme 68.

the homologous triflate catalyst. A selection of cyclic and acyclic dienes was probed in the aforementioned reaction. In all instances, the hexafluoroantimonate catalyst afforded higher levels of asymmetric induction than the analogous triflate catalyst. For example, in the Diels–Alder reaction between **1a** and 1,3-cyclohexadiene catalyzed by $Cu(OTf)_2$/**4g** a 90% yield of the *endo* (*S*)-**3a** adduct having an ee of 82% was formed after 48 h. Changing the counterion in the catalyst from OTf to SbF_6 led to an increase of the ee from 82 to 93%. Furthermore the reaction rate was also increased: 90% yield of the *endo* (*S*)-**3a** adduct was obtained in 5 h [92]. Similarly, the rate of the reaction of glyoxylate **72a** (see Scheme 67) with 1,3-cyclohexadiene catalyzed by $Cu(SbF_6)_2$/**4g** was faster than the rate of the analogous reaction promoted by the homologous triflate catalyst in both, CH_2Cl_2 or $MeNO_2$ solvents. However, in $MeNO_2$, the ee obtained with $Cu(SbF_6)_2$/**4g** (93%) was lower than that obtained with $Cu(OTf)_2$/**4g** (> 97%) [93]. The different behavior of 'identical' cations has been explained assuming different degrees of interaction between the bis(solvated) cation and the corresponding anion. In particular, in the case of the triflate anion, it has been speculated that a less highly organized one-point catalyst–dienophile complex such as **B** may form [92]. In this context, the crystal structure determined by diffractometric means of the [Cu(OTf)(**4g**)($(H_2O)_2$](OTf) catalyst revealed that one of the triflate anions is weakly bound to the copper centre in the apical position of a distorted square pyramidal geometry. The remaining four basal positions are occupied by the two nitrogens of the bis(oxazoline) ligand and by the two oxygen atoms of two water molecules [65] (Scheme 68).

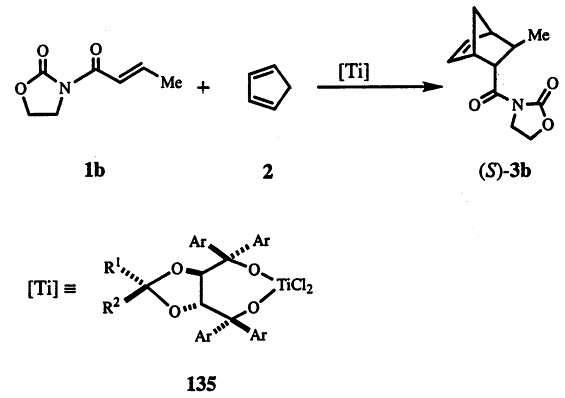
Jørgensen and coworkers [67] have investigated by semiempirical calculations using the AM1 method, the relative stability of the zinc intermediates $[Zn\{bis(oxazoline)\}(methyl\ glyoxylate)]^{2+}$ (compounds **A**–**C**, Scheme 69). In the calculations it was assumed that the two triflate anions are dissociated from the metal and that both the bis(oxazoline) and the glyoxylate ligands are chelating the metal through the two nitrogens and through the two carbonyl oxygen atoms, respectively. The tetrahedral and square-planar geometries at zinc were compared. For compounds **B** and **C** the tetrahedral geometry was calculated to be 18 and 75 kJ more stable than the planar one, this findings accounting for the absolute stereochemistry obtained for the hetero Diels–Alder product of the reaction between ethyl glyoxylate and 1,3-cyclohexadiene (1*R*,3*S*,4*S*) or 2,3-dimethyl-1,3-butadiene (*S*), in CH_2Cl_2. For compound **A** the tetrahedral geometry was calculated to be 158 kJ also more stable than the related planar one. In the tetrahedral intermediate the diene can approach the carbonyl from the *Re*-face to give *R* as the absolute stereochemistry at the former carbonyl carbon in the hetero Diels–Alder product, which is the reverse of the experimentally observed stereochemistry [67]. No satisfactory explanation for this fact has been put forward.

Davies, Deeth, and coworkers have developed the Cellular Ligand Field Stabilization Energy/Molecular Mechanics (CLFSE/MM) approach for modeling bis(oxazoline) and pyridine-bis(oxazoline)–copper(II) complexes [94]. Good agreement between theory and six experimentally determined crystal structures was achieved. Then, the structures of six Cu(II)-bis(oxazoline)–$(aqua)_2$ complexes were calculated. A tetrahedral twist was defined as the angle between the normals of Cu–N–N and Cu–O–O planes. The calculations revealed a substantial difference in tetrahedral twist depending on the nature of the oxazoline C4 substituent. For example the tertbutyl bis(oxazoline) (**4g**) complex has a larger twist (30°) than either the indanyl (**4ab**, 9°) or phenyl (**4e**, 4°) ligands. The authors concluded that this twist may be crucial in understanding the sense of induction and that a simple rationale of tetrahedral versus square-planar geometry no longer seems appropriate in the discussion of reactions involving Cu(II)–bis(oxazoline) complexes [94].

Taking all the above results together, it seems clear that to account for the observed features in Diels–Alder reactions promoted by bis(oxazoline)-based catalytic systems adequately it is necessary to consider several factors: the metal, the bis(oxazoline), the solvent, the counteranion, the presence of coordinating additives, and the conformation of the coordinated dienophile. All of these factors may



Scheme 69.



1b **2** **(*S*)-3b**

135

Scheme 70.

affect the geometry of the intermediate catalyst–dienophile complex. Important distorsions from square planar to tetrahedral geometry and coordination of the counteranion can not always be discarded and, consequently, to focus the discussion on tetrahedral versus square-planar geometries results in oversimplification. Moreover, to date most of the discussions have focused on steric effects. Possible contributions from electronic factors have not yet been addressed.

In summary, the coordination chemistry of the metal/bis(oxazoline)/counteranion/dienophile/solvent system is far from fully understood. In order to ascertain the actual structure of the metal-bis(oxazoline) and/or the related metal-bis(oxazoline)–dienophile complexes (or appropriate models) further experimental and theoretical studies are required.

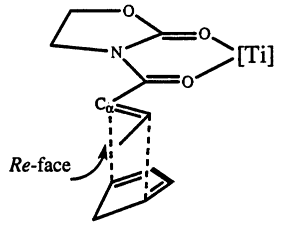
4.2. Ti–TADDOLate-catalyzed reactions

Since Narasaka and colleagues reported on the enantioselective Diels–Alder reaction of *N*-acyloxazolidinones with cyclopentadiene [95] (Scheme 70) catalized by chiral titanium complexes **135**, derived from α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs) [96], systems of this type have been extensively studied and considerable efforts have been devoted to elucidate its mechanistic aspects.

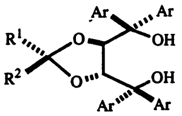
In general, with (*R*,*R*)-Ti–TADDOLates, the *endo* adducts are obtained preferentially, with the *S* at C(2) *endo* enantiomer being the major product [97]. Assuming the previous coordination of the *N*-acyloxazolidinone, in a bidentate manner and in the preferred *s-cis* conformation [98], the observed stereochemical outcome of the reaction is the result of the cyclopentadiene attack from the *Re* face of the α-carbon of the double bond, as depicted in Scheme 71. However, the sense of the enantioselectivity reverses with catalysts **135** derived from TADDOLs with 1-naphthyl groups on the dimethanol unit [97] and the *R* at C(2) *endo* enantiomer was also the major adduct when the C_1-symmetric TADDOLates with 3,5-dimethylphenyl substituents, represented in Scheme 72, were used as catalysts [99].

Assuming the formation of hexacoordinate, octahedral, neutral complexes of titanium(IV), five different adducts of stoichiometry [$TiCl_2$(TADDOL)(*N*-acyloxazolidinone)] (**A**–**E**, Scheme 73) are predicted for the reaction of the titanium catalysts [$TiCl_2$(TADDOL)] (**135**) with *N*-acyloxazolidinones **1**. The TADDOL and the *N*-acyloxazolidinones act as bidentate chelate ligands.

Detailed NMR investigations of the solution structures present in the **1e** + **135a**–**f** system (Scheme 74) have been carried out by DiMare and coworkers [100]. They observed that only three of the five possible titanium complexes are present in solution and that they are in different proportions. Thus, for example, the three adducts for the **1e** + **135a** reaction were in a 70:24:6 ratio. From NMR and molecular modeling, they concluded:

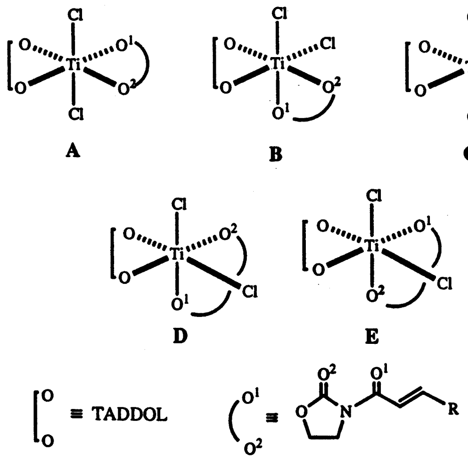


Scheme 71.

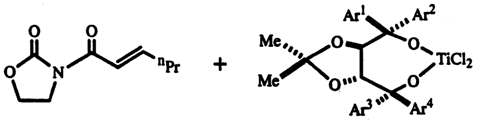


R¹	R²	Ar
3-BnOC_6H_4	H	3,5-Me_2-C_6H_3
Ph	H	3,5-Me_2-C_6H_3
Ph	Me	3,5-Me_2-C_6H_3

Scheme 72.



Scheme 73.



1e

135a: $Ar^1=Ar^2=Ar^3=Ar^4=Ph$
135b: $Ar^1=Ar^2=Ar^3=Ar^4=3,5\text{-}Me_2\text{-}C_6H_3$
135c: $Ar^1=Ar^4=Ph$, $Ar^2=Ar^3=p\text{-}F\text{-}C_6H_4$
135d: $Ar^1=Ar^4=p\text{-}FC_6H_4$, $Ar^2=Ar^3=Ph$
135e: $Ar^1=Ar^4=Ph$, $Ar^2=Ar^3=3,5\text{-}Me_2\text{-}C_6H_3$
135f: $Ar^1=Ar^4=3,5\text{-}Me_2\text{-}C_6H_3$, $Ar^2=Ar^3=Ph$

Scheme 74.

1. Both the rate- and stereochemistry-determining step is the reaction of the diene with the involved intermediate(s) **A**–**E**.
2. The major component of the mixture has structure **A** and is not responsible for the observed enantioselectivity in the Diels–Alder reaction with HCp because (i) there is no obvious biasing of the dienophile face, necessary to achieve enantioselection and (ii) the carbonyl oxygens of the *N*-acyloxazolidinone are *trans* to the strongly electron-releasing TADDOL oxygens and, consequently, the activation experienced by the dienophile is relatively low.
3. All the four remaining structures, **B**–**E**, could account for the observed enantioselection in the aforementioned Diels–Alder reaction because they present a stacked arrangement between one of the aryl residues of the TADDOL ligand and the oxazolidinone that differentiates between the two faces of the oxazolidinone moiety [101]. This stacking explains: (i) the strong shielding observed for several oxazolidinone protons of the second most abundant adduct and (ii) the high barrier to rotation for the pseudoaxial residue of the TADDOL ligand. Furthermore, as one of the carbonyl oxygens of the oxazolidinone is *trans* to a chloride ligand, these adducts may experience a higher degree of Lewis acid activation than adduct **A**, compensating for their lower concentrations.

Seebach et al. also proposed a reactive intermediate having a *cis* arrangement of the two chloride ligands at the titanium atom, based upon structural features found in the crystals of TADDOL derivatives [97].

Jørgensen and coworkers obtained single crystals upon treating $[TiCl_2(O^iPr)_2]$ with the TADDOL of **135a** and the *N*-acyloxazolidinone **1c** ($R = Ph$). The structure, determined by X-ray diffraction, consists of the chiral diol and the oxazolidinone, in the expected *s*-*cis* conformation, in the equatorial plane and the two chloride ligands in the axial positions, *trans* to each other [102]. This structure corresponds to that the major isomer **A** detected in solution by NMR spectroscopy [100]. From the X-ray structural data, Jørgensen et al. assumed that isomer **A** probably represents the active catalyst in Diels–Alder reactions, in contrast to the Seebach et al. [97] and DiMare and coworkers [100] aforementioned proposal. Furthermore, Gothelf and Jørgensen have studied the reactions between (*E*)-3-butenoyl-1,3-oxazolidin-2-one and benzylidenephenylamine *N*-oxide, catalized by $[TiX(O^iPr)_3]$ and $TiX(O^iPr)$–TADDOLate ($X = Cl$, Br, OTf; $Tf = CF_3SO_2$) compounds, and they concluded that the intermediates having an axial chloride are more reactive [103]. They extrapolated this conclusion and proposed that intermediates **A** are probably the most reactive in Diels–Alder reactions [103].

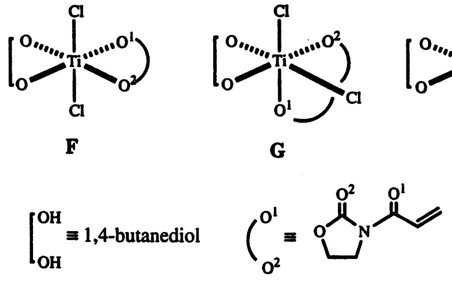
Recently, Mayoral and coworkers [104] have carried out Hartree–Fock and Density Functional Theory theoretical studies on the model complexes **F**–**H** [105] formed between 3-acryloyl-1,3-oxazolidin-2-one and [$TiCl_2$(1,4-butanediolate)] (Scheme 75). They concluded that the most stable isomer has structure **F**. Isomer **H** is the next most stable and **G** is the most unstable isomer, although it is close in energy to **H**. Furthermore, intermediate **G**, in which the carbonyl oxygen atom of the enolate moiety is *trans* with respect to a chloride, experiences the highest degree of Lewis acid activation and, therefore, it is the most reactive.

An additional point has to be considered when discussing a mechanistic model for the present reaction: the observation made by Seebach and coworkers that there is a nonlinear relationship between enantioselectivities of the catalysts and product [97]. This observation points to the participation of a second chiral ligand in the coordination sphere of the active center, probably through the formation of a dimeric complex [106]. This nonlinear relationship has not been considered at all in the mechanistic studies until now reported.

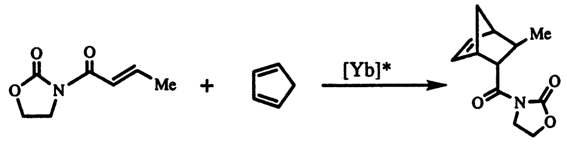
In summary, the actual nature of the active species in the enantioselective Diels–Alder reaction between *N*-acyloxazolidinones and cyclopentadiene catalyzed by Ti–TADDOLates remains unclear. Additional data on the nature of the least abundant detected intermediates, theoretical calculations on the possible transition states, extension to other metals which can furnish interesting further experimental results, as well as, rate data are needed before a definitive explanation can be made.

4.3. The Yb-BINOL catalytic system

Kobayashi and coworkers have developed a catalytic system based on $Yb(OTf)_3$ and (*R*)-(+)-binaphthol ((*R*)-BINOL). A mixture of the metallic triflate and the chiral ligand *R*-BINOL along with MS4Å and a tertiary amine, such as *cis*-1,2,6-trimethylpiperidine, effectively catalyze the Diels–Alder reaction between 3-(2-butenoyl)-1,3-oxazolidin-2-one and HCp the major product being the *endo* 2*S*,3*R* adduct [107–110] (Scheme 76).



Scheme 75.



1b **2** **(*S*)-3b**

$$[\mathrm{Yb(OTf)_3}] + (R)\text{-}(+)\text{-Binaphtol} + \text{amine} \xrightarrow[\mathrm{CH_2Cl_2}]{\text{MS 4Å}} [\mathrm{Yb}]^*$$

Scheme 76.

The precise structure of the catalyst and the reaction mechanism have not yet been clarified. From ^{13}C-NMR and IR spectrocopic measurements, a weak interaction between the nitrogen of the tertiary amine and the phenolic hydrogen of the coordinated *R*-BINOL was proposed and a direct interaction between the amine and the metal atom was excluded. Thus, it has been postulated that, in the chiral catalyst, the axial chirality of (*R*)-(+)-binaphthol is transferred via the hydrogen bonds to the amine parts of the molecule, which shield one side of the dienophile effectively [108,109]. Consistently, the amines employed in the preparation of the chiral catalyst strongly influenced the selectivities, bulkier amines giving better diastero- and enantioselectivities [109].

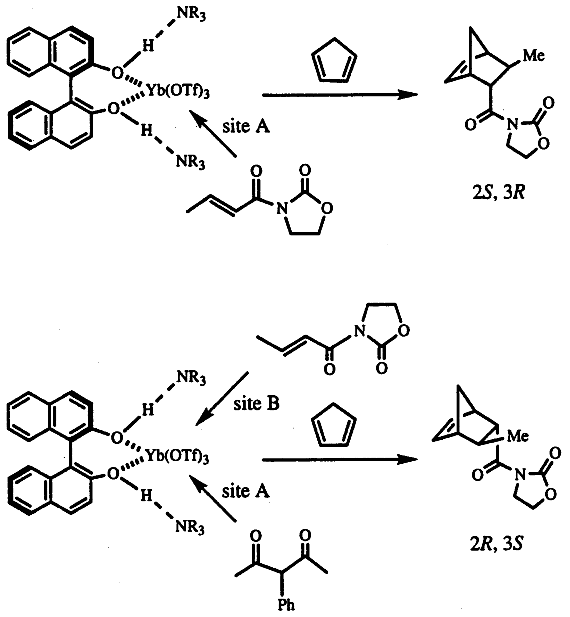
Aging of the catalyst was found to take place and the dienophile and several acetylacetonate derivatives, such as 3-phenylacetylacetonate, were found to be effective in preventing the catalyst from aging [111]. Interestingly, the enantioselectivities were controlled by the achiral ligands dienophile and acetylacetonate in such a way that, the addition of the acetylacetonates reverses the enantiofacial selectivity, the 2*R*,3*S* adduct being predominantly obtained. Thus, both enantiomers could be prepared by using the same chiral source i.e. (*R*)-(+)-binaphthol. This noticeable fact has been tentatively explained by assuming that there are two different sites in the coordination sphere of the ytterbium (Scheme 77); both the dienophile and substituted acetylacetone preferentially coordinate at site A, but when present, the stronger coordinating acetylacetone forces the dienophile to occupy site B. When the dienophile coordinates to the metal at site A, the cyclopentadienyl attack takes place preferably from the *si*-face of the dienophile, originating the *endo* 2*S*,3*R* adduct. Conversely, when the dienophile is forced to occupy site B, cyclopentadienyl attacks from the *re*-face and the 2*R*,3*S* enantiomer is formed [111]. Additionally, a negative nonlinear effect has been observed for both types of achiral additives [108,109].

Although the proposed model rationalize most of the experimental observations, it is still tentative and the correct structure of the active catalyst has to be unambiguously demonstrated. Thus, for example: (i) the geometry around the ytterbium remains unknown; (ii) the specific properties of the two coordination sites (A and B) are not defined; (iii) the potential displacement from the coordination sphere of the metal of one or more triflate ligands, generating the corresponding cationic complexes, has not been considered; (iv) the role of the molecular sieves in the catalyst mechanism has not been ascertained; and (v) the observed nonlinear effect has not been explained.

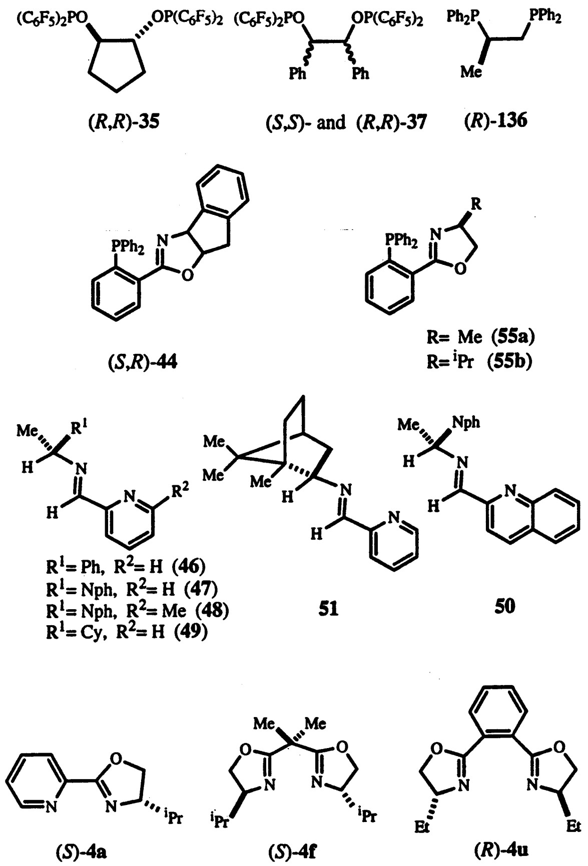
In conclusion, further additional work has to be done in order to advance in the knowledge of the actual nature of the catalysts or catalyst precursors.

4.4. One point binding half-sandwich catalysts

A few well-defined cationic half-sandwich complexes of general formula $[(\eta^n\text{-ring})M(L^1L^2)^*L^3]^{+x}$ have been used as chiral catalysts in enantioselective Diels–Alder reactions. In these compounds, the metal belongs to Group 8 or 9 (Fe, Ru, Os, Rh, Ir) and present a d_6 configuration, the chiral chelate ligand $(L^1L^2)^*$ possess C_1 or C_2-symmetry, and L^3 represents a good leaving group, usually a solvent molecule. Several types of $(L^1L^2)^*$ ligands with *P*,*P*-, *P*,*N*- or *N*,*N*- sets of donor atoms have been used. Thus, η^5-C_5H_5-iron [34,35] or -ruthenium [36] compounds with the diphosphines **35** [34] or **37** [35,36] and η^5-C_5Me_5–rhodium compounds with the (*R*)-(+)-1,2-bis(diphenylphosphino)propane ligand **136** [40], η^6-*p*-$MeC_6H_4^iPr$–ruthenium [37,112], or –osmium [112] and η^5-C_5Me_5–rhodium [112] or –iridium [112] complexes with the phosphino–oxazolines **44** [37,112] or **55** [112], η^5-C_5Me_5–iridium [42] or –rhodium [38] and η^6-*p*-$MeC_6H_4^iPr$–ruthenium [38] or -osmium [112] compounds containing the pyridin–imines **46**–**49** [38,42,112], **51** [38,42,112], or **50** [42], η^6-$Me_3C_6H_3$–ruthenium [39] or η^5-C_5Me_5–rhodium [41]



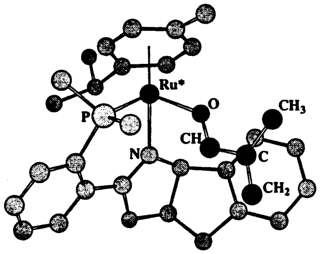
Scheme 77.



Scheme 78.

compounds with the pyridin–oxazoline (*S*)-**4a**, and η^5-C$_5$Me$_5$–rhodium [41] complexes with the bis(oxazolines) (*S*)-**4f** and (*R*)-**4u** have been tested as catalysts (Scheme 78).

All the complexes are saturated 18 e$^-$ species and present the so-called three-legged piano stool structure [34,36,37,40]. The coordination site occupied by the solvent molecule is the unique binding point accesible for incoming ligands. Consequently, the reaction between methacrolein, a one point binding dienophile, and cyclopentadiene has become the test for these chiral catalysts. The initial coordination of the dienophile has been proved to be the first step in the catalytic cycle in several cases [34,36,37,40]. In fact, the molecular structures of (S_{Ru})-[(η^6-*p*-MeC$_6$H$_4^i$Pr)Ru((*S*,*R*)-**44**)(methacrolein)][SbF$_6$]$_2$ (Scheme 79) and [(η^5-C$_5$H$_5$)-Ru((*S*,*S*-**37**)(methacrolein)][SbF$_6$], in which the dienophile is coordinated to the metal through its oxygen atom, have been solved by X-ray diffraction methods [36,37]. These structures also reveal that the dienophile adopts an *s-trans* conformation and NOESY measurements indicated that this conformation is retained in



Scheme 79.

solution [36]. The η^n-ring and the chiral ligand make up a chiral cavity, which is occupied by the dienophile. The chiral ligand, through one of its phenyl or pentafluorophenyl rings, shields one of the enantiotopic faces of the methacrolein. The diene approach from the other side of the dienophile rationalizes the observed sense of asymmetric induction. The obtained diastereoselectivity has been explained assuming the usually high *exo* selectivity found for α-substituted enals.

For [(η^5-C_5H_5)Ru((*S*,*S*)-**37**)(acetone)]Y species, the nature of the counterion has a large effect on the rate, but not on the enantioselectivity, of the reaction in the order $TfO^- < BF_4^- < PF_6^- < SbF_6^- < TFPB^-$ (TfO^- = trifluoromethanesulfonate, $TFPB^-$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate). The interpretation of a similar phenomenon in dicationic copper catalysts invoked competition of the anion and substrate for the Lewis acid site [92]. However, in this case, the molecular structure of the dienophile adduct [(η^5-C_5H_5)Ru((*S*,*S*)-**37**)(methacrolein)][SbF_6] reveals the existence of three fluorine atoms of the anion involved in hydrogen bond interactions: two with the cyclopentadienyl ring and one with the formyl hydrogen atom of the methacrolein moiety. It has been proposed that it is this interaction, which must be highly sensitive to the nature of the anion, which is responsible for the important changes in catalyst efficiency [36].

Finally, it seems interesting to point out that although in some of the [(η^n-ring)M(L^1L^2)*L^3]$^{+x}$ compounds the metal is a chiral center (when the (L^1L^2)* ligand has C_1 symmetry), no relationship between the configuration at the metal and the sense of the induced enantioselectivity has been observed.

5. Conclusions

Tremendous progress has been made in the field of transition-metal catalyzed enantioselective Diels–Alder reactions. By using transition metal based chiral Lewis acid catalysts, perfect selectivities and enzymatic rates and catalyst loading have been achieved for some Diels–Alder systems. However, several aspects remain unclear. Thus, for example, the way in which additives or counterion interact with the metallic fragment, affecting both conversion and selectivity, has not been clearly established. Similarly, the role of the molecular sieves, in some instances very important, has not been clarified. In the hetero version, only the interaction of C=O bonds has been relatively well studied. A few reports have been devoted to the corresponding aza reaction and the thia version is in its infancy. Other related systems involving Group 15 or 16 heteroatoms are waiting to be developed. The actual nature of the Lewis acid catalysts is still far from ascertained. In most cases, the structure of the chiral ligand transition metal Lewis acid moiety is not known and only in a few cases the geometry of the Lewis-acid catalyst–dienophile has been completely determined. Interesting chiral amplification phenomena that appeared in some systems have not been explained at all. We suspect that, most of these questions could be adequately answered with a better knowledge of the coordination chemistry of the metallic systems involved.

Acknowledgements

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