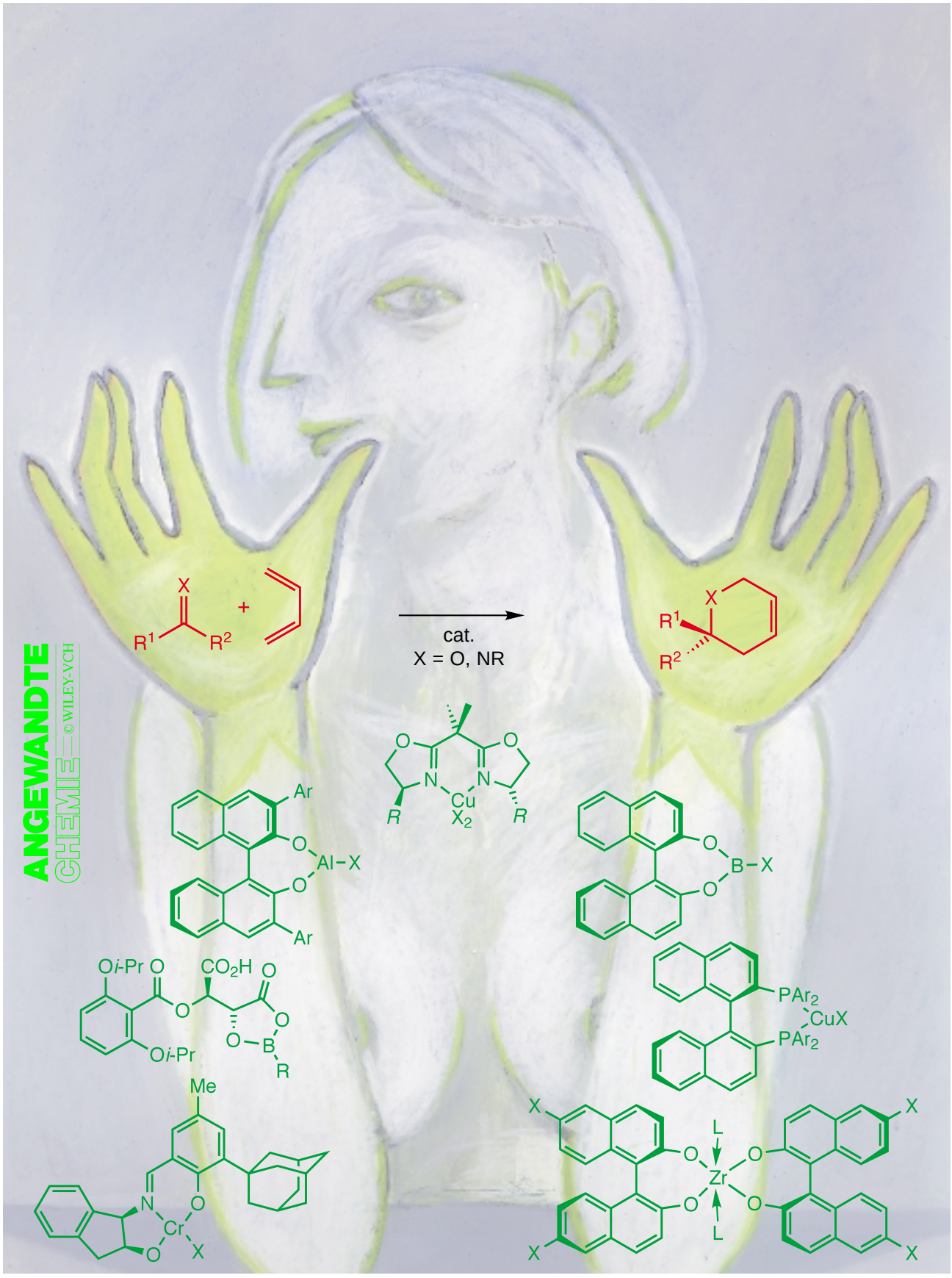


Enantioselective hetero-Diels–Alder reactions of carbonyl compounds and imines catalyzed by chiral Lewis acids. A painting by the Danish female artist Jo Dam Kærgaard provides the background for an overview of the described reactions and their catalysts.

Catalytic Asymmetric Hetero-Diels–Alder Reactions of Carbonyl Compounds and Imines

Karl Anker Jørgensen*

Asymmetric catalysis is a challenge for chemists: How can we design catalysts to achieve the goal of forming optically active compounds? This review provides the reader with an overview of the development of catalytic asymmetric hetero-Diels–Alder reactions of carbonyl compounds and imines. Since its discovery, the Diels–Alder reaction has undergone intensive development and is of fundamental importance for synthetic, physical, and theoretical chemists. The Diels–Alder reaction has been through different stages of development, and at the beginning of the 21st century catalytic Diels–Alder reactions are one of the main areas of focus. The preparation of numerous compounds of importance for our society is based on cycloaddition reactions to carbonyl compounds and imines. There are several parallels between the reactions of carbonyl compounds and those of imines, which, however, begin to vanish on entering the field of catalytic reactions. Why? From a mechanistic point of view some similarities can be drawn, but the synthetic development of catalytic enantioselective hetero-Diels–Alder reactions of imines are several years behind those of the carbonyl compounds. For hetero-Diels–Alder reactions of carbonyl compounds there a number of different chiral catalysts, and great progress has been achieved in developing enantioselective reactions for unactivated and activated carbonyl compounds. In contrast the development of catalytic enantioselective hetero-Diels–Alder reactions of imines is in its infancy and only few catalytic reactions have been published. This review will focus on the most important developments, and discuss the synthetic and mechanistic aspects of enantioselective hetero-Diels–Alder reactions of carbonyl compounds catalyzed by chiral Lewis acids. For the hetero-Diels–Alder reactions of imines, the diastereoselective reactions of optically substrates catalyzed by Lewis acids will be presented first, followed by the catalytic enantioselective reactions.

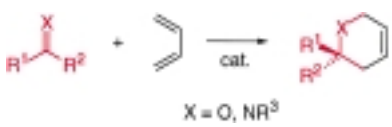
Keywords: asymmetric catalysis · carbonyl compounds · Diels–Alder reactions · imines · reaction mechanisms · synthetic methods

1. Introduction

The Diels–Alder (DA) reaction has, since its discovery in 1928 by Otto Diels and Karl Alder,[1] been one of the cornerstone reactions in organic chemistry for the construction of six-membered rings. The various types of DA reactions have contiuned to further developed and their spectrum of application in chemistry is enormous. The use of DA reactions covers compounds of academic and industrial interest and several compounds of importance for our society are synthesized based on this approach.

Two major developments have taken place with regard to DA reactions over the last 50 years. With the introduction of the theory of conservation of orbital symmetry by Woodward and Hoffmann, a lot of attention focused on the synthetic and mechanistic aspects of DA reactions—based on the Woodward–Hoffmann rules—in the 1960s and 1970s.[2] In the last two decades the focus has changed to the development and application of DA reactions leading to optically active compounds. The reason for the interest in obtaining optically active compounds using the DA methodology is that the reactions normally are easy to perform and proceed generally in a highly regio- and diastereoselective manner. Furthermore, the DA reaction can give up to four new chiral centers. The enantioselective version, especially when promoted by chiral Lewis acid complexes has further enhanced its power in the synthesis of optically active compounds.[3]

This review focuses on the development of catalytic asymmetric hetero-Diels–Alder (HDA) reactions of carbonyl compounds and imines with conjugated dienes [Eq. (1)].



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There are two basic strategies for asymmetric HDA reactions in order to control the absolute configuration of the product: 1) the use of a diene and/or a dienophile with a chiral auxiliary, and 2) the use of a chiral catalyst. The most efficient and economic way to effect an enantioselective reaction is probably the use of a chiral catalyst. This approach allows the direct formation of chiral compounds from achiral substrates under mild conditions and requires a substoichiometric amount of chiral material. To achieve catalytic enantioselective HDA reactions of carbonyl compounds and imines, coordination of a chiral Lewis acid to the carbonyl and imine functionalities is necessary. This coordination activates the substrate and provides the chiral environment that forces the approach of a diene to the substrate from the less sterically hindered face, introducing enantioselectivity in the reaction.

When a chiral Lewis acid catalyst is designed for a reaction, many parameters must be taken into account. The substrate should have a certain reactivity and be able to coordinate to a metal. The choice of the metal in combination with a chiral ligand is of particular importance. Furthermore, the Lewis acidity, the structural properties of the metal complex, and the electronic and structural properties of the chiral ligand all need to be considered.

The main group metals such as aluminum, boron, the hard early transition metals titanium and zirconium, and some lanthanide elements are all oxophilic metals which have been widely used in combination with chiral ligands containing oxygen as the coordinating atoms. Among the most commonly used chiral ligands of this type are the 1,1′-binaphthol (BINOL)- and $\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol (TADDOL)-based ligands. However, problems such as aggregation may arise due to the high oxophilicity of these metals which can lead to a deactivation of the catalyst. Designing a ligand in such a way that catalyst aggregation is prevented has become a topic of current interest and includes the introduction of sterically demanding groups around the oxygen atoms, attachment of monomeric catalysts to a polymer, and synthesis of rigid polymeric chiral catalysts. Chiral ligands containing nitrogen as the coordinating atoms show a broad flexibility towards both hard and soft metals. Ligands containing phosphorus as the coordinating atoms, for example, the 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) ligands, are soft ligands, and great success has been achieved by applying these ligands in combination with soft metals, such as copper(I).

The discovery and development of a highly efficient catalyst system rely on the knowledge of the possible reactive intermediates and, not least, on extensive screening. The conformational preferences of the complex between the substrate and the Lewis acid are responsible for the stereochemical outcome of a given reaction. The understanding of asymmetric induction requires a knowledge of the structure and the relative reactivity of the substrate–Lewis acid complex(es) formed in the reaction solution. In some cases, solvents and/or additives may also play an important role in the stereochemical outcome since they can also coordinate to the Lewis acid leading to a change of the geometrical structure of the catalyst. All these factors must be kept in mind during the interpretation and prediction of the stereochemical outcome of a reaction promoted by a chiral Lewis acid catalyst.

Catalytic asymmetric HDA reactions have been intensively developed in recent years with the main focus on the synthetic aspects, while the number of mechanistic studies has been limited. In this review, the main attention will be on the development and understanding of HDA reactions in which Lewis acid catalysts are used for preparing optically active six-membered ring systems. For the HDA reactions of carbonyl compounds the focus will be on enantioselective reactions catalyzed by chiral Lewis acids. The section dealing with imines will be devoted to reactions leading to optically active HDA adducts obtained from Lewis acid catalyzed reactions starting from either optically active imines or dienes. Finally, catalytic enantioselective reactions of imines will be described. The reason for including the HDA reactions of optically active imines and dienes is that the use of these substrates has been intensively studied recently, while the development of catalytic enantioselective reactions is still in its infancy.

1.1. The Mechanistic Aspects and Concepts of Activation by Lewis Acids

One cannot discuss HDA reactions in the present context without trying to understand the reaction course from a mechanistic point of view. The majority of the reactions discussed can be classified into two types of [$_\pi$2s+$_\pi$4s]

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cycloadditions, the normal and inverse electron demand HDA reactions, based on the relative energies of the frontier molecular orbitals (FMOs) of the diene and the dienophile (Figure 1).[2, 4]

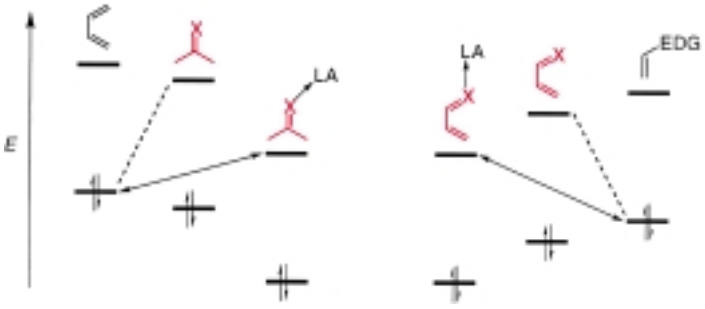


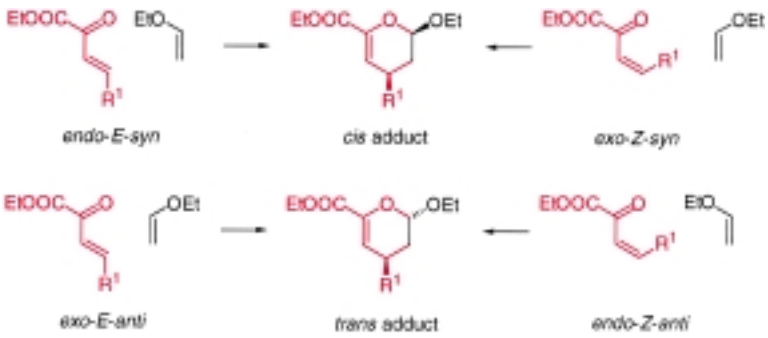
Figure 1. A FMO diagram of the normal (left; $HOMO_{diene}-LUMO_{dienophile}$-controlled) and inverse electron demand HDA reaction (right; $LUMO_{diene}-HOMO_{dienophile}$-controlled) in the absence and the presence of a Lewis acid. X = O, NR; LA = Lewis acid; EDG = electron-donating group.

The normal electron demand reaction is a $HOMO_{diene}-LUMO_{dienophile}$-controlled HDA reaction which predominantly occurs between electron-rich dienes and electron-deficient dienophiles (Figure 1, left, dashed line). The inverse electron demand HDA reaction is primarily controlled by a $LUMO_{diene}-HOMO_{dienophile}$ interaction which can be found, for example, in reactions of enones and heteroanalogues with alkenes having electron-donating groups (Figure 1, right, dashed line).

The basic concept of activation in HDA reactions is to utilize the lone pair of electrons of the carbonyl and imine functionality for coordination to the Lewis acid. The coordination of the dienophile to the Lewis acid changes the FMOs of the dienophile and for the normal electron demand reactions a decrease of the LUMO and HOMO energies is observed leading to a better interaction with the dienophile (Figure 1, left, solid line). The energy difference between the $HOMO_{diene}$ and the $LUMO_{dienophile}$ is thus reduced compared with that for the absence of a Lewis acid, and can therefore account for the activating effect of the Lewis acid. The catalytic properties of the Lewis acid for the inverse electron demand HDA reaction is due to the coordination of the Lewis acid to a heteroatom of the 1,3-diene, leading to a decrease of the $LUMO_{diene}$ and $HOMO_{dienophile}$ energies, and thus, based on a FMO way of reasoning, a more favorable interaction with the electron-rich alkene takes place (Figure 1, right, solid line). Furthermore, the coordination to the Lewis acid alters also, to some extent, the distribution of the atomic orbital coefficients of the dienophile and the 1,3-diene. For a carbonyl compound an increase in the magnitude of the LUMO atomic orbital coefficient at the carbonyl carbon atom is observed making it more susceptible to the diene. However, this polarization may also influence the reaction mechanism.

The stereochemistry of a product formed in the HDA reaction depends on the approach of the substrate; the HDA reaction can proceed *endo* or *exo*. For the HDA reaction of, for example, an β,γ-unsaturated α-keto ester with ethyl vinyl ether there are four possible approaches leading to four diastereomers, as the β,γ-unsaturated α-keto ester can be both *E*- and *Z*-configured. These four possibilities are outlined in Scheme 1 and it appears that the *cis* adduct can be formed by either an *endo-E-syn* or *exo-Z-syn* orientation, whereas the *trans* adduct is obtained by either an *exo-E-anti* or *endo-Z-anti* orientation.

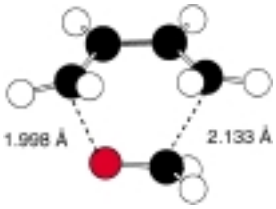
The diastereoselectivity of the HDA reaction of, for example, carbonyl compounds is affected by the presence of Lewis acids. The uncatalyzed reaction of aldehydes usually show *endo*-selectivity for the carbonyl substituent.[5] In the presence of Lewis acids as catalysts, it has been proposed that the Lewis acid is oriented *trans* to the carbonyl substituent and that the modest *endo*-selectivity observed in most cases is due to a preference for the solvated Lewis acid being *exo* because of its size.[6] However, when discussing the stereochemical course of HDA reactions, it is important to note that the configuration of the diene in the ground state does not necessarily have to be the same as that of the reacting diene.[7]



Scheme 1. The four different approaches for the HDA reaction of an β,γ-unsaturated α-keto ester with ethyl vinyl ether.

Compared to the numerous theoretical calculations on the normal DA reaction, only very few theoretical studies of HDA reactions have been performed,[8] and even fewer on Lewis acid catalyzed HDA reactions. It has been pointed out that the HDA reaction can change from a concerted non-synchronous mechanism to a stepwise mechanism depending on the substituents on the reacting species and on the reaction conditions.

The transition state of the HDA reaction is generally found to be unsymmetrical. For the reaction of formaldehyde with 1,3-butadiene, Houk et al. have calculated the C–C and C–O bond lengths to be 2.133 and 1.998 Å, respectively, in the transition state **1** by using ab initio calculations (Scheme 2).[8b] The reaction of formaldimine follows the same trend for the transition-state structure.



Scheme 2. The transition state **1** (ab initio calculations) of the HDA reaction of formaldehyde with 1,3-butadiene is unsymmetrical.

An investigation of the HDA reaction of formaldehyde with 1,3-butadiene, in which the oxygen atom of the aldehyde was coordinated to BH_3 as a model for a Lewis acid,[8b] gave two

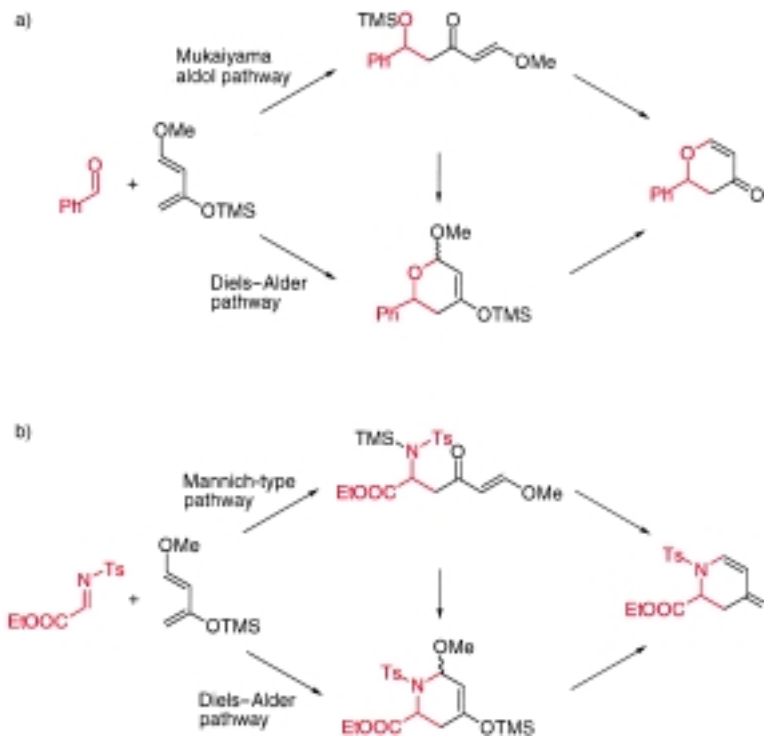
transition states, in which BH_3 adopts either an *exo* or an *endo* position relative to the diene. The transition state with the BH_3 in the *exo* position has the lowest energy and the calculated transition-state structure is much less symmetrical than **1**; the C–C bond length is calculated to be 0.42 Å longer, while the C–O bond length is 0.23 Å shorter than in **1**. The transition state of the Lewis acid catalyzed reaction has significant zwitterionic character, with a partial positive charge of 0.37 on the diene and a negative charge on the formaldehyde oxygen atom of -0.65 and -0.28 on BH_3. The coordination of the carbonyl oxygen atom to BH_3 makes the carbonyl group an acceptor of negative charge, and the O–B bond length in the transition state is 0.12 Å shorter than that in the BH_3–formaldehyde complex, indicating a tighter complexation in the transition state.

By coordination of the formaldehyde oxygen atom to BH_3 the activation energy of the reaction with 1,3-butadiene drops considerably. This is in agreement with the experimental results, since Lewis acid catalysis in general are required for reactions of carbonyl dienophiles to proceed[9] and/or are found to enhance the reaction rate. Houk et al. have found that at the highest level of calculations (MP2/6-31G*), the activation energy is 8.9 kcal mol^{-1}, which is 12.0 kcal mol^{-1} lower in energy than the uncatalyzed reaction.[8b] The calculations indicate that the *exo* position is favored due to the greater electrostatic repulsion between BH_3 and the butadiene fragment in the *endo* transition-state structure.

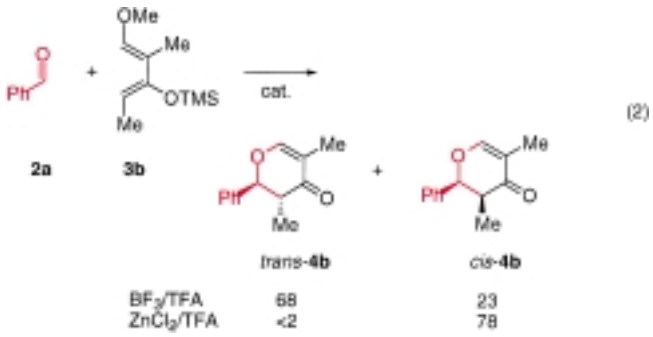
Two mechanistic pathways have generally been taken into account for the HDA reaction when Lewis acid catalyzed reactions are considered. The two pathways are formulated as 1) a traditional DA cycloaddition or 2) formation of the HDA adduct by a Mukaiyama-aldol reaction pathway in the case of a carbonyl compound, or a Mannich-type reaction for an imine (Scheme 3).

There are only few mechanistic studies of Lewis acid catalyzed HDA reactions with carbonyl compounds and imines. Danishefsky et al. concluded that the reaction of benzaldehyde **2** with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene (**3b**) in the presence of BF_3 as the catalyst proceeds by a stepwise mechanism, whereas a concerted reaction takes place when $ZnCl_2$ or lanthanides are the catalysts.[10] The evidence of a change in the diastereomeric outcome of the reaction is that *trans*-**4b** is the major HDA adduct in the BF_3-catalyzed reaction, while *cis*-**4b** is the major adduct, for example, for the $ZnCl_2$-catalyzed reaction—the latter resulting from an *exo* addition [Eq. (2)].

The influence of Lewis acids on the reaction pathway is also dependent on the reactant structure. The HDA reaction of monosubstituted dienes have shown that, for example, BF_3 catalysis can give the HDA adduct by a mechanism in which the Mukaiyama aldol and Michael cyclization pathway does not seems to operate.[11]



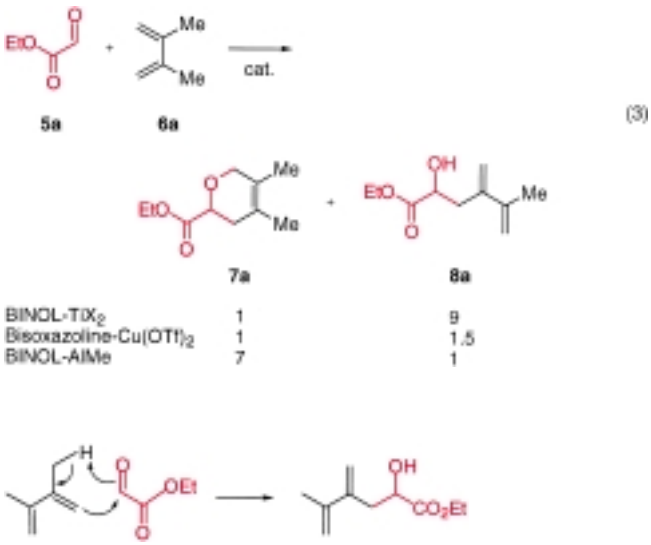
Scheme 3. The two different reactions pathways for the reaction of a) a carbonyl (benzaldehyde) and b) an imine (*N*-tosyl α-imino ester) with an activated diene (Danishefsky's diene). The HDA adduct can be formed by a traditional DA pathway as well as by a Mukaiyama-aldol pathway in the case of the carbonyl compound and by a Mannich-type reaction for the imine. TMS = Me_3Si; Ts = $SO_2C_6H_4CH_3$.



(2)

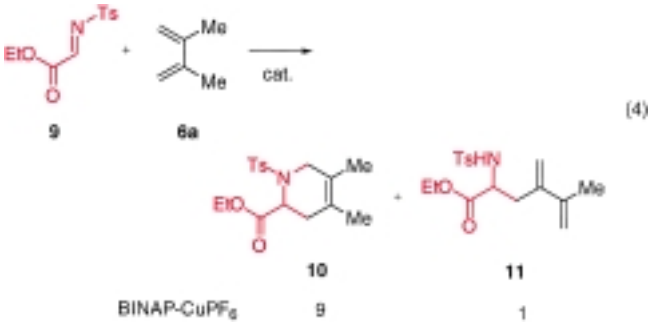
The reaction course of the HDA reaction can also be dependent on the Lewis acid complex used as the catalyst. When the substrate contains an allylic C–H bond, both a HDA and an ene reaction can take place. For the reaction of glyoxylate **5a** with 2,3-dimethyl-1,3-butadiene (**6a**) both the HDA adduct **7a** and ene adduct **8a** can be obtained [Eq. (3)]. In the presence of BINOL–titanium(IV) complexes as the catalyst, the ene adduct **8a** is the major product with a **7a**:**8a** ratio of up to 1:9,[12] while using bisoxazoline–copper(II) as the catalyst, a nearly 1:1 ratio of **7a**:**8a**[13] is obtained. However, the HDA adduct **7a** is the major product when a BINOL–aluminum(III) catalyst is applied.[14] The mechanism of the reaction of **5a** with **6a** leading to the ene adduct **8** is outlined in Scheme 4.

For the HDA reaction of imines a similar observation has been made. The reaction of the *N*-tosyl α-imino ester **9** with



Scheme 4. The mechanism for the ene reaction of ethyl glyoxylate with a diene having an allylic C–H bond.

6a catalyzed by a BINAP–copper(I) complex gives the HDA and ene adducts **10** and **11**, respectively, in a 9:1 ratio [Eq. (4)].[15]



The mechanistic picture of the HDA reactions which appears after this brief description of the aspects and concepts of activation of the substrate by Lewis acids indicates that many parameters have influence on reaction course.

2. Hetero-Diels–Alder Reactions of Carbonyl Compounds

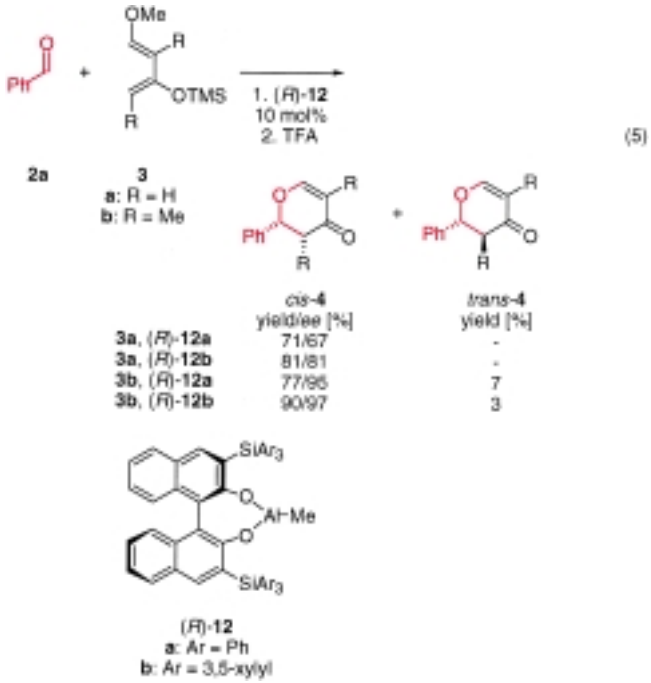
The HDA [π2 + π4] cycloaddition reaction of aldehydes and ketones with 1,3-dienes is a well-established synthetic procedure for the preparation of dihydropyrans, which are attractive substrates for the synthesis of carbohydrates and other natural products.[3] Carbonyl compounds are in general of limited reactivity in HDA reactions with dienes since only electron-deficient carbonyl groups as in glyoxylates, chloral, ketomalonate, 1,2,3-triketones, and related types of compounds, react with dienes having electron-donating groups. However, the use of Lewis acids or high-pressure conditions have led to a new era for HDA reactions. In particular, the application of chiral Lewis acid catalysts has provided new opportunities for enantioselective cycloadditions. The first part of this section will be devoted exclusively to the development of enantioselective HDA reactions of carbonyl compounds catalyzed by chiral Lewis acids.

2.1. Reactions of Unactivated Aldehydes

Some of the developments of catalytic enantioselective HDA reactions have their origin in the DA chemistry where many of the catalysts have been applied. This is valid for catalysts which allow a monodentate coordination of the carbonyl functionality, such as the chiral aluminum and boron complexes. However, new chiral catalysts for HDA reactions have also been developed.

2.1.1. Chiral Aluminum and Boron Complexes

The first reliable and highly efficient chiral aluminum(III) catalyst for HDA reactions of aldehydes was reported by Yamamoto et al.[16] The use of the chiral BINOL-AlMe complexes (*R*)-**12** was found to be highly effective for the HDA reaction of various aldehydes with activated Danishefsky-type dienes. For example, the reaction of benzaldehyde **2a** with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) and *trans*-1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-pentadiene **3a** and **3b**, respectively, affords *cis*-dihydropyrones *cis*-**4** as the major product in high yield with up to 97% *ee* [Eq. (5)]. The reaction proceeds well



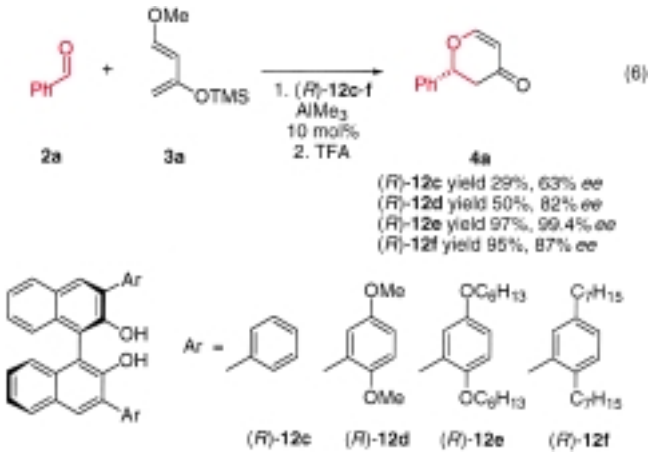
in nonpolar solvents such as toluene, where higher enantiofacial selectivity is observed compared to polar solvents such as CH_2Cl_2, where a significant retarded reaction rate is found.

The choice of the bulky triarylsilyl moiety in catalyst (*R*)-**12b** is crucial for the success of the reaction, and in contrast to this, the catalysts derived from $AlMe_3$ and (*R*)-3,3′-disubsti-

tuted binaphthol (substituent = H, Me, Ph) were only effective in stoichiometric amounts and gave fewer satisfactory results with regard to reactivity and enantioselectivity. The reason for this change might be that the catalyst bearing the sterically hindered auxiliary forms a complex with the aldehyde which is readily liberated from the catalyst after reaction with the diene to release steric repulsion, resulting in the regeneration of catalyst.

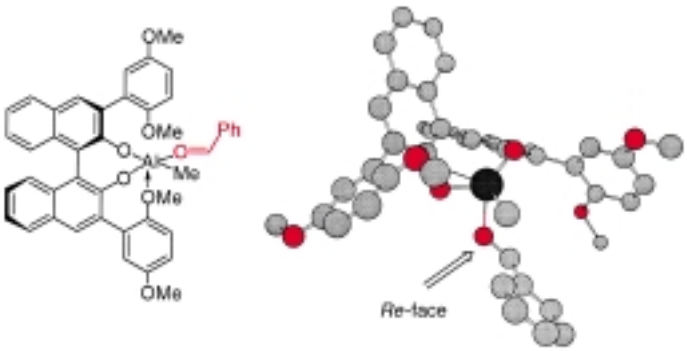
For the HDA reaction in Equation (5), it was found that chiral ketones such as 3-bromocamphor can bind selectively to one enantiomer of the complex.[17] Thus, if the HDA reaction is performed in the presence of the racemic catalyst **12** and 3-bromocamphor (0.3 molar equivalents each), *cis*-**4** is isolated with up to 80% *ee* compared to 95% *ee* for the reaction catalyzed by (*R*)-**12b**.

The use of the chiral BINOL–AlMe catalysts for the HDA reactions has also included ligands which have the possibility to form hypercoordinated aluminum complexes.[18, 19] Performing the reaction of benzaldehyde **2a** with Danishefsky's diene **3a** leads to the formation of the HDA adduct **4a** in the presence (*R*)-**12c–f** in up to 97% yield and 99.4% *ee* using (*R*)-**12e** as the catalyst [Eq. (6)]. A clear trend appears: ligand (*R*)-**12c**, which has neither the steric bulk, nor the coordinating ether oxygen atoms characteristic of (*R*)-**12e**,



catalyzes the reaction, but only modest chemical and optical yields of **4a** are obtained. Ligand (*R*)-**12d**, having methoxy groups, is almost as efficient as (*R*)-**12e**, but with a modest chemical yield. Ligand (*R*)-**12f**, which should be expected to have steric properties similar to those of (*R*)-**12e**, proved to fall somewhere in between (*R*)-**12c** and (*R*)-**12e** with 87% *ee* for **4a**. The lack of the ether oxygen atoms in **12c**, which are capable of coordinating to the metal, significantly affects the enantioselectivity compared to (*R*)-**12e** and (*R*)-**12d**. These results indicate that hypercoordination can be an important factor for the design of HDA catalysts for carbonyl compounds.[19]

Based on the absolute configuration of the HDA adduct **4a**, formed in the reaction which was catalyzed by (*R*)-**12e**, model calculations using (*R*)-**12d** show that the preferred geometry for the intermediate is one in which the two oxygen atoms from the BINOL ligand and the methyl substituent are located in the equatorial plane with one of the ligand hypercoordinating ether oxygen atoms and the benzaldehyde oxygen atom as the two axial ligands (Scheme 5).[19] The 2,5-dimethoxyphenyl substituent which is not coordinating to



Scheme 5. A model for the intermediate in the HDA reaction of benzaldehyde with activated dienes catalyzed by chiral BINOL–aluminum(III) complexes that are able to form hypercoordinating aluminum complexes.

aluminum is oriented perpendicular to the BINOL ligand, while the 2,5-dimethoxyphenyl substituent which hypercoordinates aluminum is twisted towards the metal. This twisting creates a chiral environment as the nonhypercoordinated 2,5-dimethoxyphenyl substituent shields the *Si* face of benzaldehyde, while the *Re* face is available for approach by the diene.

The mechanism for the HDA reaction of benzaldehyde **2a** with Danishefsky's diene **3a** catalyzed by aluminum complexes was investigated from a theoretical point of view using semiempirical calculations.[20] The reaction was studied in the absence, and presence, of $(MeO)_2AlMe$ as a model catalyst for the BINOL–AlMe system. The change in energy for the concerted HDA reaction, and formation of the HDA adduct by a Mukaiyama-aldol reaction, is shown in Figure 2. The conclusion of the study was that in the absence of a catalyst the concerted reaction is the most likely one with a transition-state energy of 27 kcal mol^{-1}, while for the reaction catalyzed by $(MeO)_2AlMe$, a two-step mechanism is found with a transition-state energy of 10 kcal mol^{-1} for the first step (the C–C bond being formed) leading to the Mukaiyama-aldol intermediate, followed by a 3 kcal mol^{-1} transition-state energy for the ring-closure step. The aldol intermediate seems to be stabilized by an interaction of the cation with the oxygen atom of the Lewis acid.

With regard to the asymmetric aluminum-catalyzed HDA reactions it should finally be mentioned that small *ee* values have been obtained in reactions with menthoxydichloroaluminum as the chiral catalyst.[21]

Chiral boron(III) Lewis acid catalysts have been successfully applied for enantioselective HDA reactions of carbonyl compounds.[22] The chiral acyloxylborane catalysts (CAB I) **13a–d**, were the first class of efficient chiral boron catalysts for asymmetric DA reactions.[22, 23] The arylboron catalysts **13b** and **13c** which are air and moisture stable have been shown by Yamamoto et al. to induce excellent chiral induction in the HDA reaction between aldehydes such as **2a** and

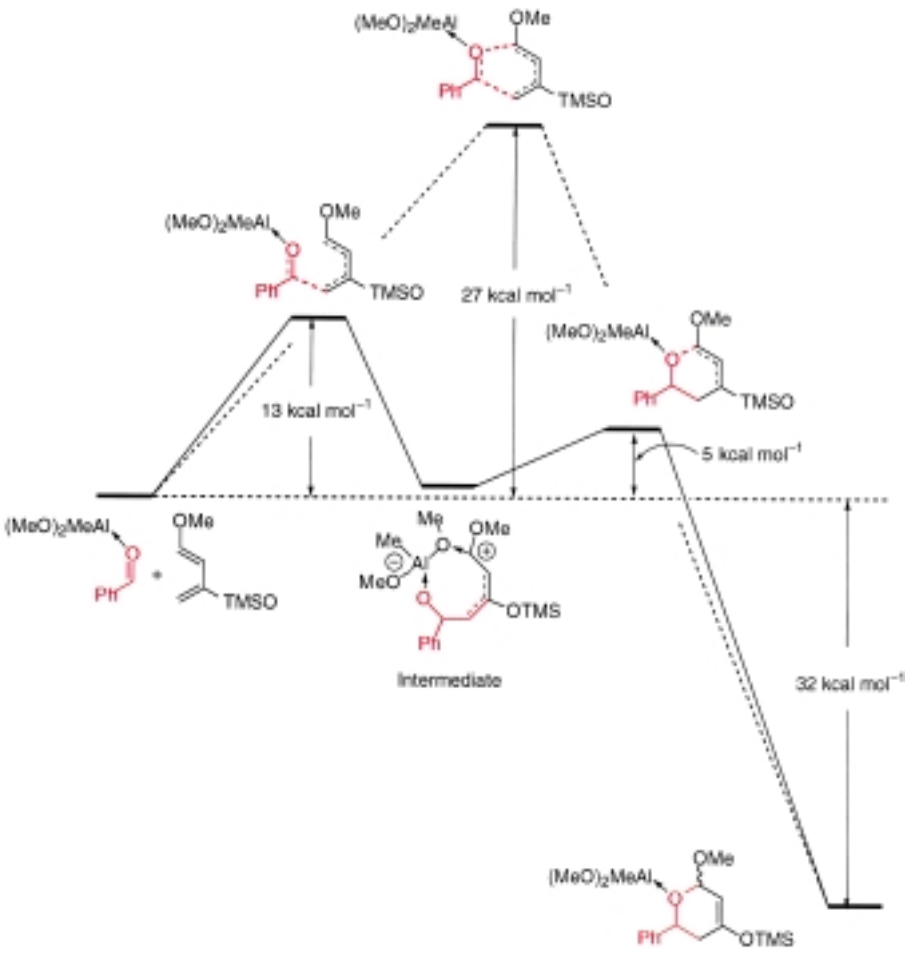
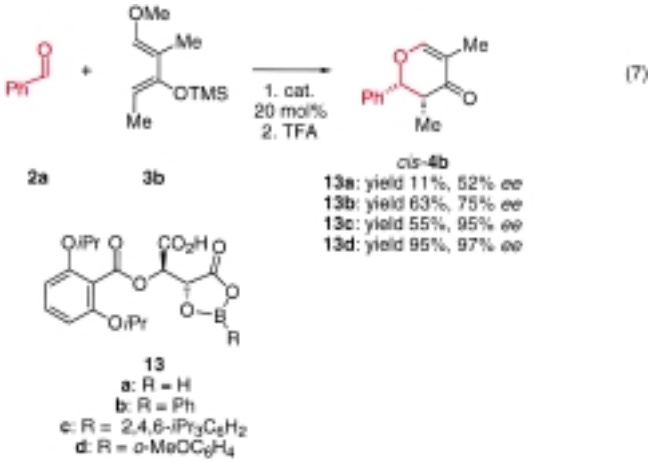


Figure 2. A schematic presentation of the energies of the transition states in the concerted reaction of benzaldehyde with Danishefsky's diene and the $(MeO)_2AlMe$ catalyzed Mukaiyama-aldol like pathway.

Danishefsky's dienes such as **3a** with up to 95% yield and 97% *ee* of the HDA adduct *cis*-**4b** [Eq. (7)].[22]



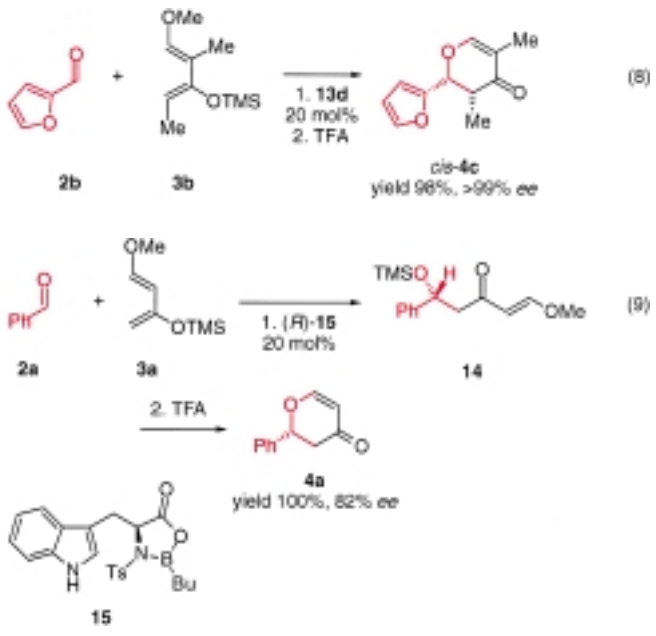
The HDA reaction catalyzed by complex **13d** proceeds well for several aromatic and α,β-unsaturated aldehydes and has, for example, been used for an enantioselective route to the carbon-branched pyranose derivative *cis*-**4c** [Eq. (8)].[22]

The characteristic structural feature of the CAB I catalysts is a dioxaborolidinone formed with a tartaric acid derivative and a borane reagent. Following this concept, catalysts were prepared from, for example, *N*-sulfonyl α-amino acids.[23] The chiral (*S*)-tryptophan-derived oxazaborolidine catalyst **15** developed by Corey et al. has been applied for the conversion of aldehydes to the HDA adduct **4a** by reaction with Danishefsky's diene **3a**.[23h] The reaction of benzaldehyde **2a** affords mainly the Mukaiyama-aldol product **14** which after isolation was converted to **4a** by treatment with trifluoroacetic acid (TFA) [Eq. (9)]. It was observed that no HDA adduct was produced in the initial step providing evidence for the two-step process.

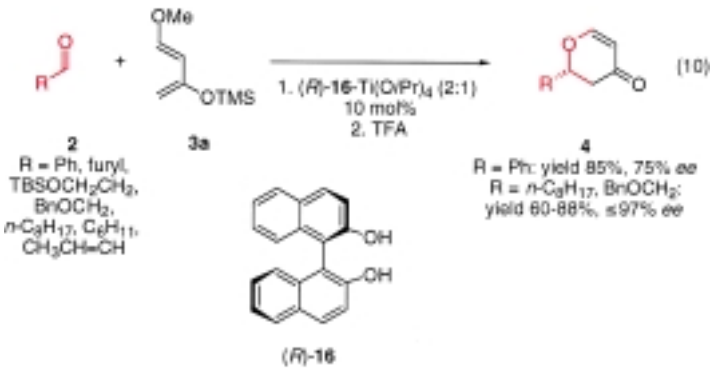
2.1.2. Chiral Transition and Lanthanide Metal Complexes

Different chiral transition- and lanthanide metal complexes can catalyze the HDA reaction of unactivated and activated (vide infra) aldehydes with especially activated dienes. For the chiral titanium catalysts the focus has been on the use of BINOL–titanium(IV) complexes for the HDA reactions. These catalysts have been widely used as chiral catalysts in enantioselective C–C bond-forming reactions of aldehydes.[12, 24]

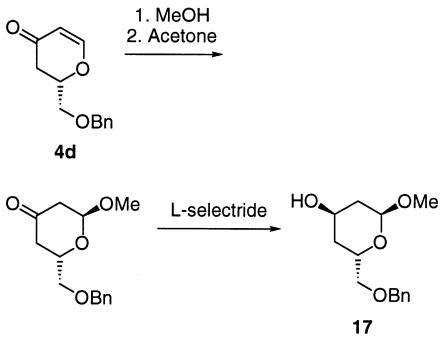
Keck et al. reported that a catalyst generated from (*S*)- or (*R*)-BINOL **16** and $Ti(OiPr)_4$ in a 2:1 ratio is more selective than the catalyst formed from a 1:1 mixture.[24f] The former



catalyst was shown to catalyze the HDA reaction of aldehydes **2** with Danishefsky's diene **3a** affording the dihydropyrones **4** with moderate to excellent *ee* values (up to 97% *ee*) [Eq. (10)].

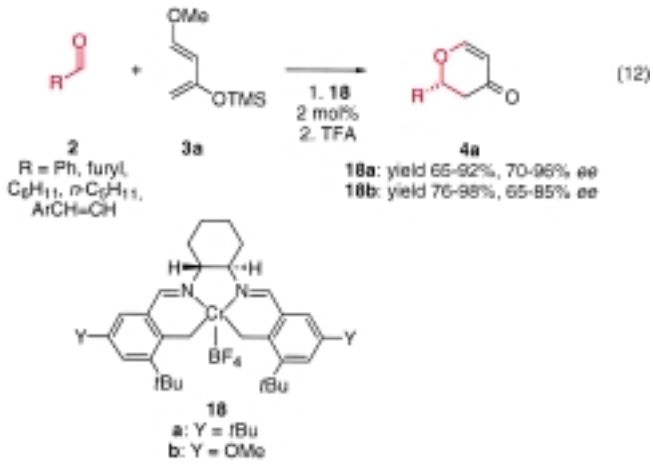


The dihydropyrones are not produced directly in the initial BINOL–titanium(IV) catalyzed reaction. The major product at this stage is the Mukaiyama-aldol product which subsequently was cyclized by treatment with TFA.[24f] The formal HDA adduct **4d** (97% *ee*) obtained from α-(benzyloxy)acetaldehyde is an important intermediate for compactin and mevinolin (lovastatin), whose structural subunit **17** is available in three steps by applying the HDA approach [Eq. (11)].[24f]



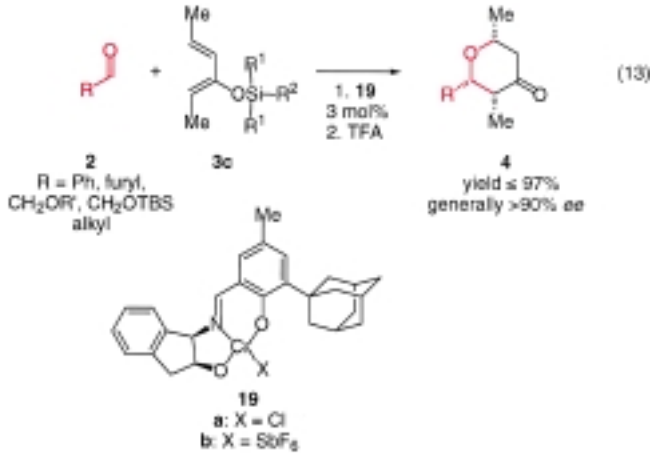
A bis[3-(heptafluorobuturyl)camphorato]oxovanadium(IV) complex (5 mol%) was shown by Togni to catalyze the HDA reaction of mainly benzaldehyde with dienes of the Danishefsky type.[25] Moderate to good enantioselectivities were observed if the reactions were carried out at low temperature. A thorough investigation was performed with benzaldehyde and various activated dienes, and reactions involving double stereodifferentiation using a chiral aldehyde.

The salen ligand has been used in catalytic enantioselective HDA reactions of carbonyl compounds with dienes in combination with metal salts such as chromium and cobalt (H_2salen = bis(salicyliden)ethylenediamine). Jacobsen et al.[26] have shown that the chiral salen–chromium(III) complexes **18a**, and **18b** can catalyze the HDA reaction of different aldehydes **2** containing aromatic, aliphatic, and conjugated substituents with Danishefsky's diene **3a** [Eq. (12)]. The reaction proceeds in good yield (up to 98%) and 62–93% *ee*. It was found that the presence of oven-dried powdered 4 Å



molecular sieves (MS) led to an increased yield and enantioselectivity. The lowest enantioselectivity (62% *ee*, catalyst **18b**) was obtained for hexanal, while the highest (93% *ee*, catalyst **18a**) was obtained for cyclohexylaldehyde. The mechanism of the HDA reaction was investigated in terms of a traditional HDA-type cycloaddition, or formation of the HDA-adduct by a Mukaiyama-aldol-reaction path (Scheme 3a]. In the presence of the chiral salen–chromium(III) catalyst system, ^{1}H NMR spectroscopy of the crude reaction mixture of the reaction of benzaldehyde with **3a** revealed the exclusive presence of the HDA-pathway adduct. The Mukaiyama-aldol condensation adduct was prepared independently and subjected to the conditions of the chiral salen–chromium(III) catalyzed reactions. No detectable HDA adduct could be observed and these results point towards a [2+4] cycloaddition mechanism.

An important step in the development of a more general catalytic enantioselective HDA reaction has also been achieved by Jacobsen et al. by the introduction of chiral tridentate Schiff base chromium(III) complexes **19** [Eq. (13)].[27] These complexes, which are highly diastereo- and enantioselective catalysts for the reaction of unactivated



aldehydes, can catalyze the reaction of less nucleophilic dienes bearing fewer than two oxygen substituents. The adamantyl-substituted catalysts **19a** and **19b** gave the best

results, and both aliphatic and aromatic aldehydes underwent HDA reactions. It was found that use of the hexafluoroantimonate chromium catalyst **19b** resulted in a faster and more enantioselective reaction and that the reaction can proceed without solvent. The reaction was tested for various dienes, for example 1-methoxy-1,3-butadiene reacts with $TBSOCH_2$-CHO (TBS = tBuMe$_2$Si) in the presence of only 0.5 mol% catalyst **19a** to give the corresponding HDA adduct in >99% *ee*. This latter reaction provides, after hydrolysis and oxidation to the corresponding lactone, an efficient access to interesting natural product structures.

Danishefsky et al. were probably the first to observe that lanthanide complexes can catalyze the HDA reaction of aldehydes with activated dienes.[28] The reaction of benzaldehyde **2a** with activated conjugated dienes such as **3d** was found to be catalyzed by [Eu(hfc)$_3$] (**20**) (hfc = 3-(heptafluoropropylhydroxymethylene)camphorate) giving up to 58% *ee* [Eq. (14)]. For other substrates the HDA adducts were

(14)

obtained with 20–40% *ee* when the reaction was performed in $CHCl_3$ at room temperature with 1 mol% of **20**. A significant improvement was obtained when the reaction was performed in the absence of a solvent and at reduced temperature. Catalyst **20** has also been applied for diastereoselective HDA reactions using chiral *O*-menthoxy-activated dienes, derived from (−)-menthol, giving up to 84% *de*[28b,c] and has been used for the synthesis of optically pure saccharides.

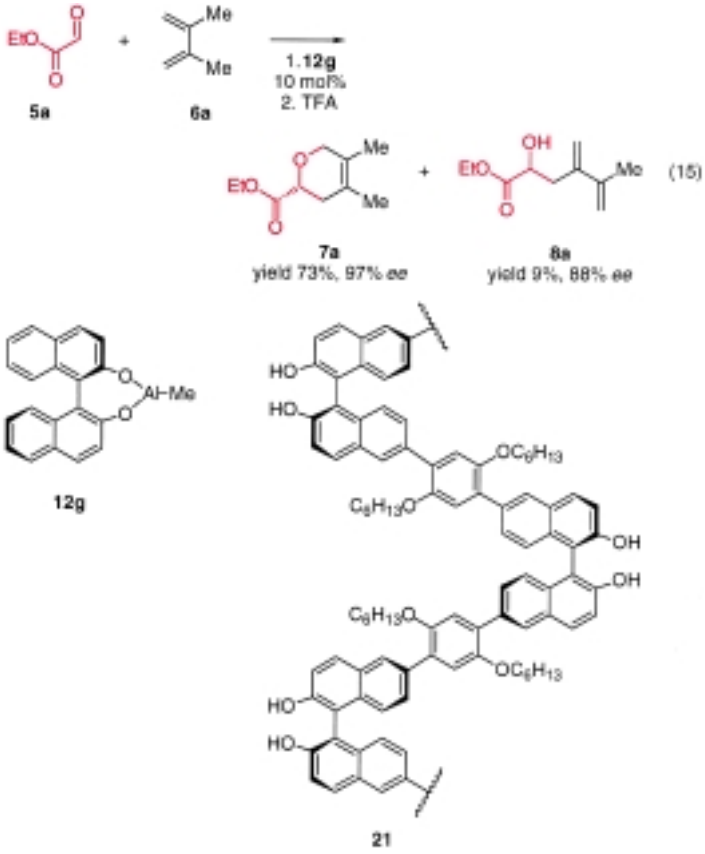
More recently, Inanaga et al. have shown that ytterbium tris[(*R*)-(−)-1,1′-binaphtyl-2,2′-diyl]phosphonate can catalyze the HDA reaction of aromatic aldehydes with Danishefsky's diene to give the HDA adduct in good yield and with up to 93% *ee* at room temperature.[29] The addition of 2,6-lutidine improved the catalytic properties of the complex.

2.2. Reactions of Activated Aldehydes

Different main group, transition, and lanthanide metal complexes can catalyze the HDA reaction of activated aldehydes with activated and nonactivated dienes. The chiral metal complexes which can catalyze these reactions include complexes that allow substrates to coordinate in a mono- or bidentate fashion.

2.2.1. Chiral Aluminum and Boron Complexes

Chiral BINOL–AlMe complexes can catalyze a highly chemo- and enantioselective HDA reactions of activated aldehydes with conjugated dienes.[14] The reaction of ethyl glyoxylate (**5a**) with simple dienes, such as 2,3-dimethyl-1,3-butadiene (**6a**), in the presence of (*R*)-BINOL–AlMe **12g** as the catalyst gives the HDA **7a** adduct as the major product in 73% yield with up to 97% *ee* and with only 7% of the ene adduct **8a** [Eq. (15)]. This is a significant change in chemoselectivity towards the HDA reaction pathway compared with the use of chiral titanium(IV) as well as chiral copper(II) and zinc(II) complexes, which give mainly the ene adduct, and a mixture of HDA and ene adducts, respectively (vide infra).



(15)

The reaction in Equation (15) was further developed to be the first catalytic enantioselective HDA reaction catalyzed by a chiral polymeric Lewis acid complex.[30, 31] The use of the chiral polybinaphthyl polymer **21** in combination with $AlMe_3$ in the reaction of **5a** with **6a** gave the HDA adduct **7a** in 67% yield and up to 95% *ee*, and a **7a**:**8a** ratio of 5:1. The most important aspect of the using **21** is that it can easily be recovered by simple filtration with MeOH and reused without significant change in yield, chemo-, and enantioselectivity.

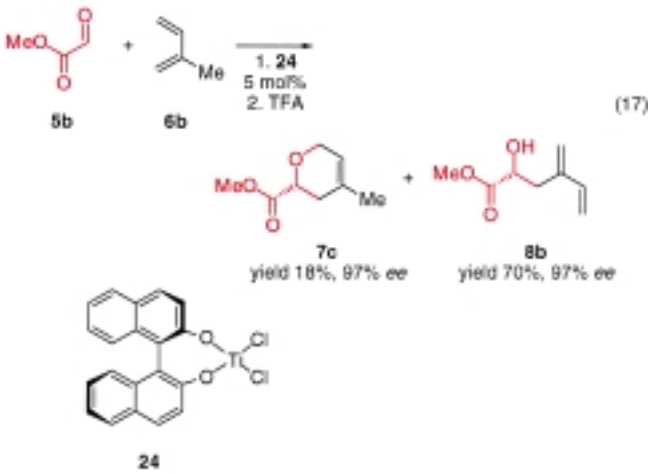
Mikami et al. have shown that chiral boron(III) complexes can catalyze the HDA reaction of glyoxylates with Danishefsky's diene [Eq. (16)].[32] Two classes of chiral boron catalysts were tested, the β-amino alcohol derived complex **22** (Tf = SO_2CF_3) and bis-sulfonamide complexes. The former catalyst gave the best results for the reaction of methyl glyoxylate (**5b**)

with diene **3a**, where the HDA adduct **7b** was isolated in 69% yield and 94% *ee*, while the chiral bis-sulfonamide boron complex gave only 62% *ee*.

Based on the absolute configuration of **7b** [Eq. (16)], it was postulated that **5b** coordinates in a monodentate fashion to the chiral catalyst **22** as outlined in **23** by which the *Re*-face of the activated carbonyl functionality is shielded by the triflate group allowing the diene to approach in an *endo*-fashion to the *Si*-face of the carbonyl functionality.[32]

2.2.2. Chiral Transition Metal and Lanthanide Complexes

The interest in chiral titanium(IV) complexes as catalysts for reactions of carbonyl compounds has, for example, been the application of BINOL–titanium(IV) complexes for ene reactions.[12, 24] When isoprene **6b** was employed as the diene for reaction with methyl glyoxylate **5b** in the presence of catalyst **24** prepared in situ from $[Ti(OiPr)_2X_2]$ and an optically pure BINOL, both the HDA and ene products **7c** and **8b**, respectively, [**7c**:**8b** ratio 1:4] were obtained with excellent enantioselectivity (97% *ee*) [Eq. (17)].[33]



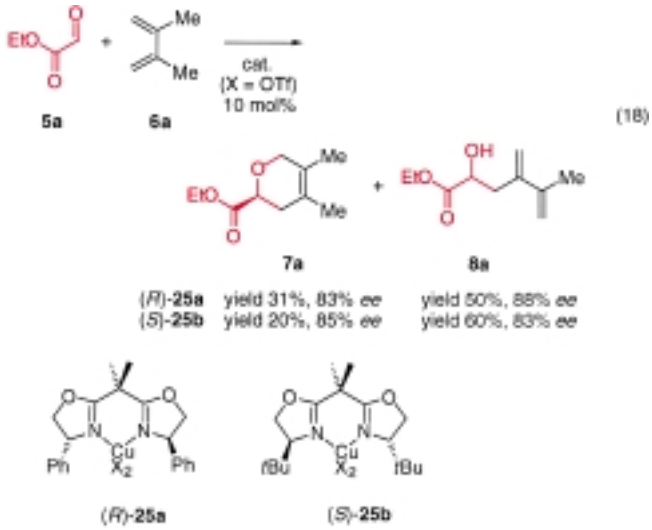
Mikami et al. have also shown that a BINOL–titanium(IV) complex in which the 6 and the 6′-position of the BINOL ligand is substituted with bromine catalyzes a selective HDA reaction of methyl glyoxylate with 1-methoxy-1,3-diene in up to 81% yield and 97% *ee*.[33c]

The remarkable change in reaction course is notable when changing the metal from aluminum to titanium for HDA reactions using BINOL as the chiral ligand. When the chiral aluminum(III) catalyst is applied the HDA adduct is the major product, while for the chiral titanium(IV) catalyst, the ene adduct is the major product. The reason for this significant change in reaction course is not fully understood. Maybe the glyoxylate coordinates to the former Lewis acid complex in a monodentate fashion, while in the latter case, the glyoxylate coordinates in a bidentate fashion and these two coordination modes promote the two different reaction courses.

Chiral salen–cobalt(III) complexes can also catalyze the reaction of glyoxylates with activated dienes to give the HDA adduct in moderate yield and enantiomeric excess.[34]

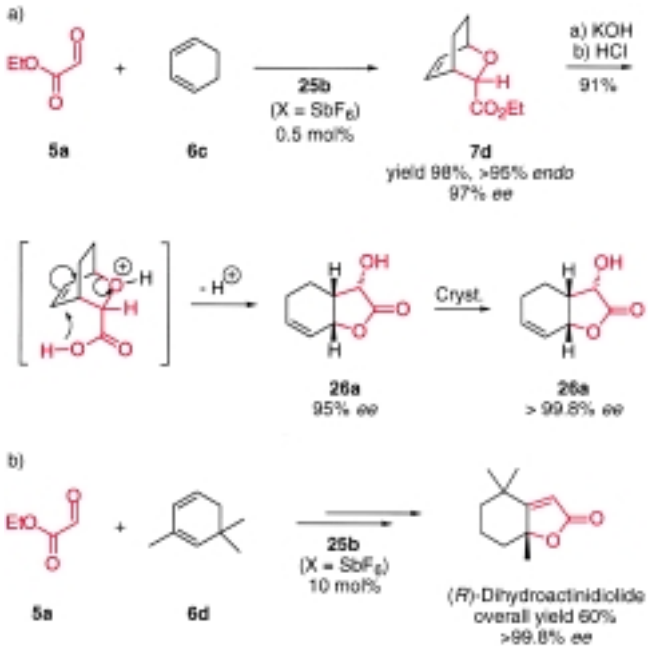
In 1995, it was demonstrated that chiral C_2-symmetric bisoxazoline–copper(II) complexes[35–43] are efficient catalysts for HDA and ene reactions of glyoxylates with simple dienes[13] leading to an intense activity in the use of these catalyst for different HDA reactions.

For the reaction of ethyl glyoxylate (**5a**) with, for example, 2,3-dimethyl-1,3-butadiene (**6a**) in the presence of Ph-BOX-CuX_2 (*R*)-**25a** or *t*Bu-BOX-CuX_2 (*S*)-**25b** (BOX = bisoxazoline) catalysts, ratios of 1:0.6 to 1:1.8 of the HDA adduct **7a** relative to the ene adduct **8a** were obtained [Eq. (18)]. These



results show that the chiral BOX–copper(II) system gives a higher ratio of HDA products than the chiral BINOL–titanium (IV) catalyst. The absolute configuration of the product in these HDA reactions catalyzed by the chiral BOX–copper(II) complexes led, according to the best of our knowledge, to the first report with the interesting observation that the 4-*tert*-butyl-BOX ligand and the 4-phenyl-BOX ligand in combination with copper(II) salts give opposite asymmetric induction in the product. Using the copper catalysts derived from the *R* enantiomer of the phenyl-BOX ligand and the *S* enantiomer of the *tert*-butyl-BOX ligand in combination with copper(II) afforded the same *S* enantiomer of the cycloaddition product.

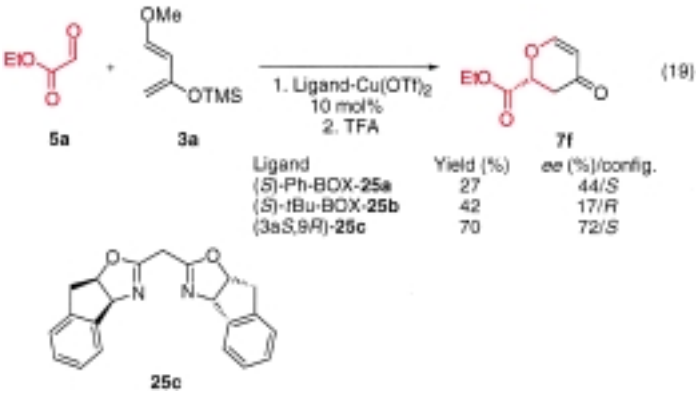
The enantioselective HDA reaction catalyzed by chiral BOX–copper(II) complexes can be used for conjugated cyclic dienes, such as 1,3-cyclohexadiene (**6c**) (Scheme 6a).[13, 44]



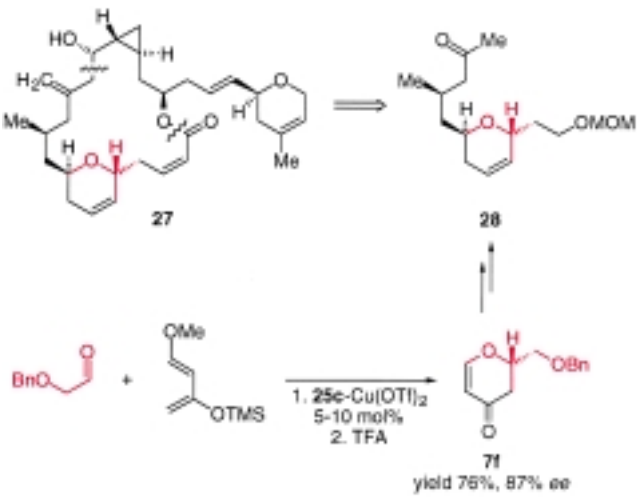
Scheme 6. a) Catalytic enantioselective HDA reaction of ethyl glyoxylate (**5b**) with 1,3-cyclohexadiene (**6c**) leading to a synthetic approach for the formation of the optically active bicyclic lactone **26a**. b) The catalytic enantioselective HDA approach for the formation of the optically active sex phereomone (*R*)-dihydroactinidiolide.

The HDA reaction of glyoxylates with conjugated dienes is dependent on solvent, and counterions have significant effects on the rate and enantioselectivity of this reaction.[44] The reaction of **6c** was much faster when less coordinating SF_6^- was used instead of $F_3CSO_2O^-$ (OTf^-, triflate) as the counterion, and the reaction was carried out in a more polar solvent such as $MeNO_2$ instead of CH_2Cl_2; in this way the HDA adduct **7d** was isolated in 98% yield with >97% *ee*. It was rationalized that the reactive BOX–copper(II) catalyst is the dicationic species. Therefore, the dissociation of the two counterions from copper is important in order to activate the catalyst, and the more polar solvents will stabilize the dissociated ligand–copper cations. The potential of this reaction is illustrated by the enantioselective synthesis of a bicyclic lactone **26a** by treatment with base followed by a rearrangement reaction under acidic conditions (Scheme 6a). This approach has been used for the synthesis of (*R*)-dihydroactinidiolide (Scheme 6b),[45] which is one of the main components of the pheromone for the queen recognition of the workers of the red fire ant, *Soleneopsis invicta*. The total synthesis, which starts from ethyl glyoxylate (**5a**) and 2,6,6-trimethyl-1,3-cyclohexadiene (**6d**) shows for the HDA reaction the highly regio, diastereo- and enantioselective catalytic properties of the (*S*)-*t*Bu-BOX-CuX_2 ($X = SbF_6$) complex **25b**. The catalytic enantioselective approach to the formation of the bicyclic lactones outlined in Scheme 6 seems to work only for 1,3-cyclohexadiene derivatives. However, the corresponding optically active bicyclic lactone containing a cyclopentene ring can easily be prepared by a catalytic enantioselective ene reaction catalyzed by chiral BOX–copper(II) complexes of glyoxylate with cyclopentene, followed by an iodolactonization reaction.[43c]

Ghosh et al. have also investigated the HDA reaction catalyzed by chiral BOX–copper(II) complexes between ethyl glyoxylate (**5a**) and Danishefsky's diene **3a** by applying catalyst systems derived from $Cu(OTf)_2$ and ligands (*S*)-Ph-BOX (*S*)-**25a**, (*S*)-*t*Bu-BOX (*S*)-**25b**, and the conformationally constrained BOX ligand **25c** in order to compare the properties of the latter ligand with the two others [Eq. (19)][46]. The HDA adduct **7f** was obtained in 70% yield and 72% *ee* by using **25c** and $Cu(OTf)_2$, which for this particular reaction was a significant improvement compared with the two other catalysts.



The methodology in Equation (19) has been used for the synthesis of the C_3-C_{14} segment **28** of the antitumor agent laulimalide **27** (Scheme 7).[47] The constrained chiral BOX ligand **25c** in combination with $Cu(OTf)_2$ afforded dihydropyrane **7f** by a HDA reaction in good yield and high enantiomeric excess, which was, converted to the C_3-C_{14} segment **28** by a Ferrier type of rearrangement in several steps.



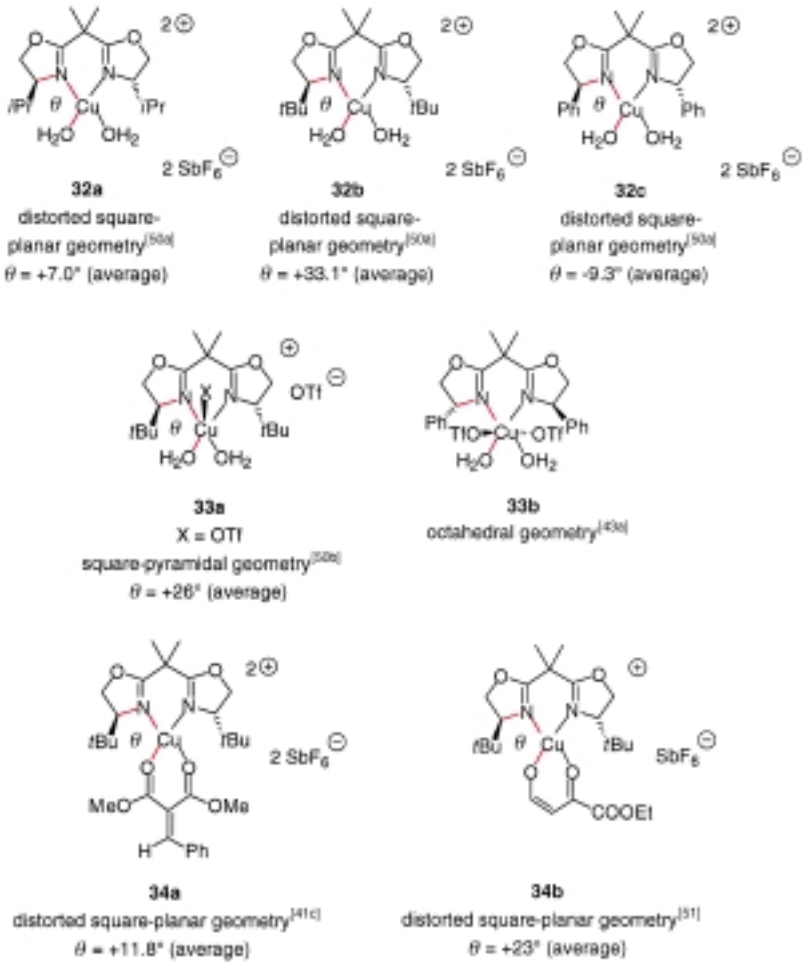
Scheme 7. The catalytic enantioselective HDA approach developed by Ghosh et al.[47] for the formation of the optically active C_3-C_{14} segment **28** of the antitumor agent laulimalide **27**. MOM = CH_2OMe.

Chiral BOX–zinc(II) complexes can also catalyze the HDA reaction of glyoxylates with conjugated dienes such as 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene.[48] The reaction gave for the former diene a higher HDA:ene ratio than with the corresponding chiral copper(II) complexes, however,

the enantiomeric excess was slightly reduced. For the reaction of 1,3-cyclohexadiene slightly lower yield and enantiomeric excess were also found.

Desimoni et al. have found that chiral BOX–manganese(II) complexes can catalyze intramolecular HDA and ene reactions with the latter as the major product.[49]

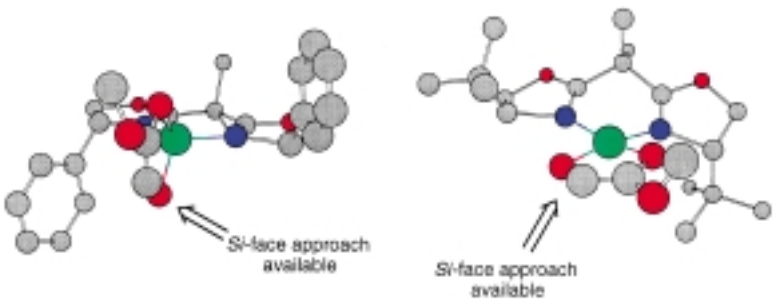
The mechanism and especially the intermediates of the HDA reactions catalyzed by the chiral BOX–copper(II) complexes deserve a separate discussion due to the peculiar ligand effect on the asymmetric induction. Based on the absolute configuration of the HDA adducts it was initially proposed that two different intermediates were operating in the reactions depending on the substituent attached to the chiral center in the BOX ligand.[13] These two intermediates were a tetrahedral intermediate (**30**) for the reactions in which glyoxylate is coordinated to (*S*)-Ph-BOX-Cu^{II} in a bidentate fashion, while a square-planar intermediate (**31**) could account for the absolute configuration of the HDA adduct obtained in the reaction catalyzed by (*S*)-*t*Bu-BOX-Cu^{II}. The two different structural intermediates, **30** and **31**, allow the diene to approach the same face of the carbonyl functionality leading to the same absolute configuration in the product, although the absolute configuration of the chiral ligand is opposite (Scheme 8).



Scheme 9. The structures of some chiral BOX-copper(II)-ligand complexes characterized by X-ray crystallography. The bonds in red define the distortion angle θ.

Several chiral BOX–copper(II) catalysts **32a–c**,[50a] as well as **33a**[50b] and **33b**,[43a] and chiral BOX–copper(II) substrate/hydrolyzed enone complexes **34a**, **b**[41c, 51] have been characterized by X-ray structure analysis (Scheme 9).

Chiral BOX–copper(II) coordinated complexes can have different coordination geometries. When the coordination number is four, copper(II) exhibits a distorted square-planar geometry with a dihedral angle θ in the range from $\theta = +7.0^\circ$ for the *i*Pr-BOX-Cu$(OH_2)_2$ complex **32a** to $\theta = +33.3^\circ$ for *t*Bu-BOX-Cu$(OH_2)_2$ **32b** and $\theta = -9.3^\circ$ for Ph-BOX-Cu$(OH_2)_2$ **32c**.[50a] When the coordination number is five, the complex has a square-pyrimidal geometry **33a** with the water molecules distorted 26° out of the plane.[50b] For the (*S*)-Ph-BOX-Cu$(OTf)_2(OH_2)_2$ complex, an octahedral complex is found **33b**.[43a] A chiral BOX–copper(II)–alkylidene malonate complex has a distorted square-planar geometry with an average distortion of 118° (**34a**).[41c] In the inverse electron demand HDA reaction catalyzed by (*S*)-**25b** as the catalyst a failed reaction with an enone gave a crystal of the anion of the hydrolyzed enone bound to the chiral BOX–copper(II) **34b**, in which an average distortion of 23° of the two oxygen atoms was formed.[51] If one assumes that glyoxylate replaces the two water molecules in **32b**, a chiral BOX–copper(II)–substrate intermediate **31** is formed which can account for the experimentally observed stereochemical outcome of the reactions catalyzed by the *t*Bu-BOX-Cu^{II} and *i*Pr-BOX-Cu^{II} complexes. Furthermore, the structure of the complexes **34a**, **b** supports also the distorted square-planar intermediate **31** for the reactions catalyzed by the *t*Bu-BOX-Cu^{II} complexes. However, the X-ray structure of the (*S*)-Ph-BOX-Cu$(H_2O)_2 \cdot 2SbF_6$ complex **32c** can not account for the absolute configuration of the HDA adducts obtained by this catalyst, while the tetrahedral intermediate **31** does.

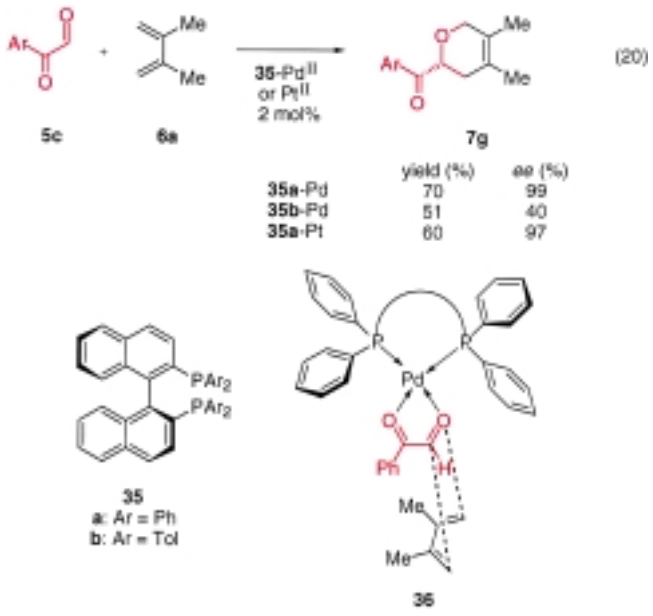


Scheme 8. Structures of intermediates **30** (left) and **31** (right).

The above described X-ray structures were mainly obtained by Evans et al. However, they did not propose any model that rationalizes the asymmetric induction by the Ph-BOX-Cu^{II} catalyst

in the original paper dealing with DA reactions.[52] Recently, a paper was published by the same group concerning the opposite asymmetric induction of the catalysts Ph-BOX-Cu^{II} and *t*Bu-BOX-Cu^{II}.[50a] Although they could not offer an explanation for this phenomenon yet, it was indicated that a tetrahedral copper(II) center was unlikely. The major arguments for this conclusion were the high *endo*-selectivity observed from the HDA and ene reactions catalyzed by Ph-BOX-Cu^{II} and the lack of the obvious electronic effects from *para*-X-Ph-BOX ligands in combination with copper(II) salts. The enantiomeric excesses of the adduct obtained in HDA reactions using *para*-X-Ph-BOX ligands and copper(II) salts were 89 (X = Cl) 93 (X = H), 93% (X = OMe). The unambiguous electronic effect of the *para*-substituents on X-Ph-BOX ligands can not exclude possible attractive catalyst–substrate (π-donor–π-acceptor) interactions.[35c, 53] To account for the enantioselective induction in reactions catalyzed by *para*-X-Ph-BOX-Cu^{II} Evans et al. have proposed a square-pyrimidal configuration.[50a]

Cationic BINAP–palladium and –platinum complexes **35a**, **b** can catalyze highly enantioselective HDA reactions of arylglyoxals with acyclic and cyclic dienes [Eq. (20)].[54] The HDA reaction proceeds well for reaction of phenylglyoxal **5c** with 2,3-dimethyl-1,3-butadiene (**6a**) in the presence of the



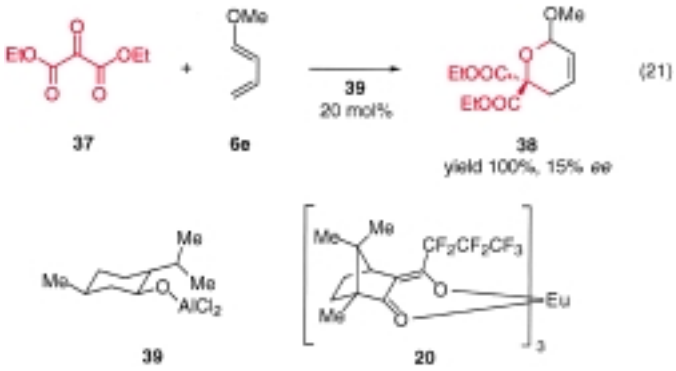
BINAP ligand and palladium(II) and platinum(II) salts giving 70 and 60% yield, and 99 and 97% *ee*, respectively, for the two Lewis acids. It is important that molecular sieves (3 Å) are added to the reaction to achieve the high enantiomeric excess, especially for the chiral palladium(II)-catalyzed reactions. The enantioselective reactions catalyzed by **35a**, **b** proceed with no ene adduct formation for *para*-substituted arylglyoxyals and lead to good yields and high enatiomeric excesses for acyclic and cyclic dienes, such as 1,3-cyclohexadiene which gives 69 and 74% yield and >99% *ee* of the *endo* diastereomer as the only product for the two catalysts.

When glyoxylate esters are used as the dienophile, the reaction with, for example, 2,3-dimethyl-1,3-butadiene (**6a**) in the presence of **35a**–Pd^{II} as the catalyst gave an almost equal amount of the HDA and ene adducts.[54b] The enantioselectivity for the HDA adduct was excellent with up to 98% *ee*. Based on the X-ray structure analysis of the cationic palladium species coordinated with an (*S*)-BINAP ligand having a slightly distorted square-planar geometry, it was proposed that the two carbonyl atoms of the phenyl glyoxal coordinate to the metal in a bidentate fashion as shown for **36**. Because the approach of the diene to the *Si*-face of the formyl group is blocked by the equatorial phenyl group of the ligand, the diene attacks the *Re*-face to favor the observed (*R*)-cycloadduct.[54b]

Only few investigations have included chiral lanthanide complexes as catalysts for HDA reactions of activated aldehydes.[55] The reaction of *tert*-butyl glyoxylate with Danishefsky's diene gave the expected HDA adduct in up to 88% yield and 66% *ee* when a chiral yttrium bis-trifluoromethanesulfonylamide complex was used as the catalyst.

2.3. Reactions of Ketones

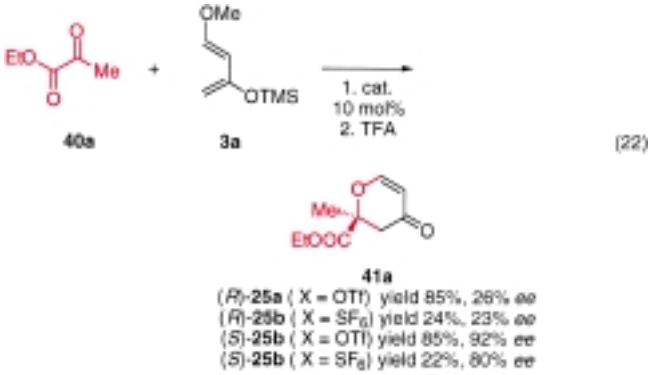
Ketones are generally less reactive than aldehydes. Therefore, the HDA reaction of ketones should be expected to be more difficult to achieve. This is well reflected in the few reported catalytic enantioselective HDA reactions of ketones compared with the many successful examples on the enantioselective reaction of aldehydes. Before we started our investigations of catalytic enantioselective HDA reactions of activated ketones[56] there was, to the best of our knowledge, only one example reported of such a reaction by Jankowski et al. using the menthoxyaluminum catalyst **39** and chiral lanthanide catalysts **20**. The highest enantioselectivity of 15% *ee* for the HDA adduct **38** was achieved for the reaction of ketomalonate **37** with 1-methoxy-1,3-butadiene (**6e**) using **39** as the catalyst [Eq. (21)].[21]



The C_2-symmetric BOX–copper(II) complexes can also catalyze highly enantioselective HDA reactions of α-keto esters and α-diketones with conjugated dienes.[56] These HDA reactions produce a chiral quaternary carbon center and the preparation of such a center is a demanding task in organic synthesis.[57]

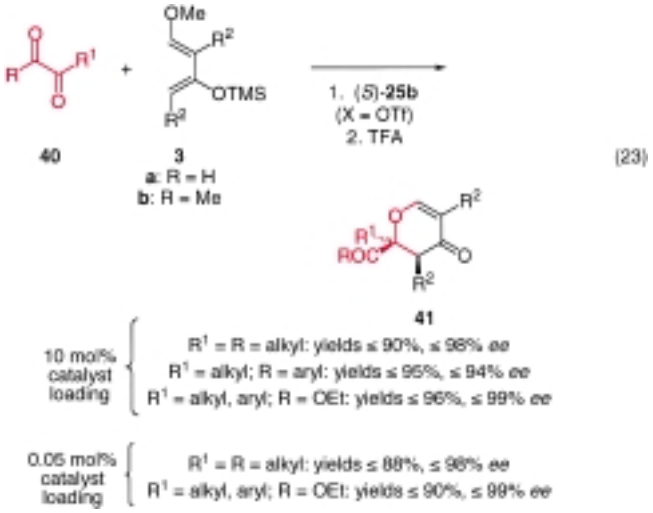
Simple dienes, such as 2,3-dimethyl butadiene or 1,3-cyclohexadiene, do not react in a HDA reaction with, for

example, ethyl pyruvate (**40a**) in the presence of chiral BOX–copper(II) complexes. However, the use of activated dienes, such as Danishefsky's diene **3a**, afforded the HDA reaction [Eq. (22)].[56] Many different chiral BOX ligands



were tested and it was found that the *t*Bu-BOX-CuX_2 **25b** catalyst is the best for the reaction shown in Equation (22). The reaction is highly dependent on the counterions which have a significant effect on the yield and enantiomeric excess of the HDA adduct **41a**; the triflate ion is superior to the hexafluoroantimonate ion for this reaction as it led to higher yield and enantiomeric excess for all cases studied. This is opposite to the previous observations,[44, 58] but the better results using triflate in the present reaction could be attributed to the fact that that the triflate provides the suitable Lewis acidity for activating the present dienophile, and/or the fluoride atoms contained in the antimonate might destroy, or interfere, with the silyloxy-containing diene **3a**.

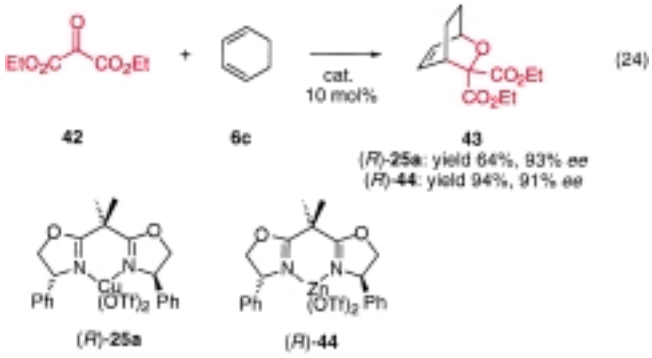
The HDA reaction of activated dienes catalyzed by *t*Bu-BOX-Cu^{II} (*S*)-**25b** is a reaction which can be used for different α-dicarbonyl compounds **40**. The results outlined in Equation (23) show the scope of the catalytic enantioselective reaction using 10 mol% of the catalyst. High yields and excellent enatiomeric excesses of the HDA adducts **41** were obtained in the reactions of **40** with the activated dienes **3a**, **b**. The results also show that the reaction proceeds well with good yield and very high enantiomeric excess for α-diketones and α-keto esters containing alkyl and phenyl



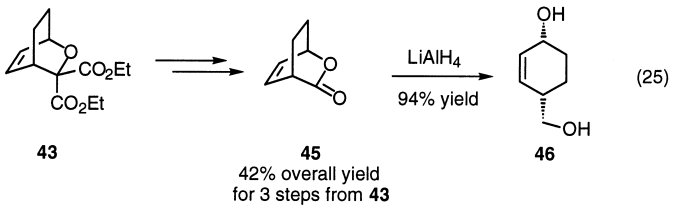
substituents. These HDA reactions of ketones can proceed to complete conversion using only 0.05 mol% of the catalyst (*S*)-**25b** (X = OTf) with only one enantiomer detected by chiral GC of the crude product.[56b] The very low catalyst loading was found to be quite general for different α-dicarbonyl substrates and some representative results are also given in Equation (23). The turnover number for the reaction of methyl pyruvate with Danishefsky's diene is 1800 per mol catalyst (based on 90% yield using 0.05 mol% of the catalyst) for 20 h, or 90 $mol^{-1}\,h^{-1}$.[56b] This is probably one of the lowest catalyst loadings, in addition to providing one of the highest turnover numbers in Lewis acid catalyzed asymmetric reactions. Wulff et al. have, for example, found a turnover number of 200 per mol catalyst in 4 h (50 $mol^{-1}\,h^{-1}$) reported by employing 0.5 mol% the VAPOL–aluminum(III) catalyst (VAPOL = vaulted biphenanthrol (2,2′-diphenyl-3,3′-biphenanthrene-4,4′-diol)) for enantioselective DA reactions,[59] while Mikami et al. have reported the use of 0.2 mol% of a BINOL–titanium(IV) catalyst for glyoxylate–ene reactions[33c] and Evans et al. haved used 0.1 mol% BOX–copper(II) catalyst for the ene reaction of ethyl glyoxylate with methylenecyclohexane (0 °C, 24 h, = 90% yield, 94% *ee*).[43b]

The absolute configuration of the HDA adduct obtained by the reaction of ketones with activated dienes catalyzed by (*S*)-**25b** points also to an intermediate in which the geometry around the central copper atom is square-planar similar to that in **31**, and that the diene approaches the carbonyl functionality in an *endo*-fashion.

The chiral BOX–metal(II) complexes can also catalyze HDA reactions of other ketonic substrates.[60] The reaction of ethyl ketomalonate (**42**) with 1,3-conjugated dienes such as 1,3-cyclohexadiene (**6c**) can proceed with chiral BOX–copper(II) and –zinc(II) complexes, Ph-BOX-$Cu(OTf)_2$ (*R*)-**25a** and Ph-BOX-$Zn(OTf)_2$ (*R*)-**44**, respectively, as the catalysts [Eq. (24)]. The reaction proceeds with good yield and



enantioselectivity using (*R*)-**44** as the catalyst. Compared to the copper(II)-derived catalyst which affects a much faster reaction, the use of the zinc(II)-derived catalyst is more convenient as the reaction could be conducted at room temperature to achieve 94% yield and 94% *ee* of the HDA adduct **43**. The HDA adduct **43** formed in Equation (24) can be transformed into the optically active CO_2-synthon **45** which might have potential in organic synthesis as it can be converted into diol **46** [Eq. (25)],[61] a key intermediate for



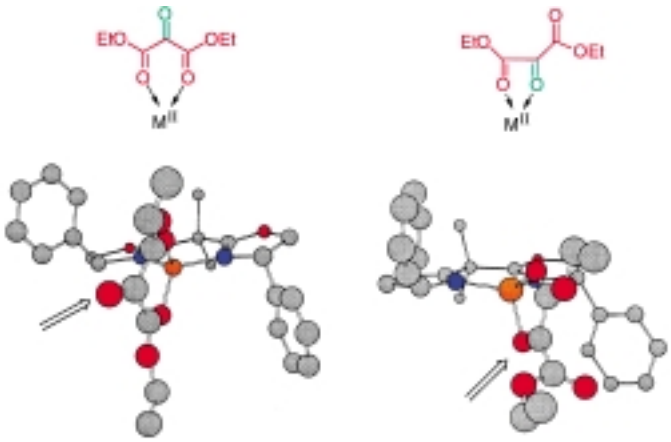
43 **45** 42% overall yield for 3 steps from **43** **46** (25)

the synthesis of, for example, cyclohexenyl carbinols[62] and anticapsin.[63]

Notably the reaction of ketomalonate **42** with cyclopentadiene in the presence of *t*Bu-BOX-Cu(OTf)$_2$ betweeen room temperature and $-78\,^{\circ}C$ showed some unexpected behavior:[60] When the reaction was performed at room temperature no HDA adduct was observed. However, when the reaction temperature was lowered to -40 to $-78\,^{\circ}C$ ^1H NMR spectroscopy showed that the HDA adduct was formed with high conversion, but when the temperature was increased to above $-30\,^{\circ}C$ a retro-HDA took place.

Ketomalonate reacts also with other types of conjugated dienes with formation of HDA adducts in moderate to good enantioselectivity. For the Danishefsky-type dienes, good enantioselectivities and yield of the HDA adducts can also be achieved with chiral BOX–zinc(II) catalysts, while the copper(II)-derived catalysts gave the formal HDA and Mukaiyama-aldol products.[60]

Calculations on the coordination of ketomalonate **42** to copper(II) and zinc(II) have revealed that the six-membered ring system is slightly more stable than the five-membered ring system (Scheme 10). The coordination of **42** to the Ph-BOX-Zn(OTf)$_2$ (*R*)-**44** catalyst shows that the six-membered



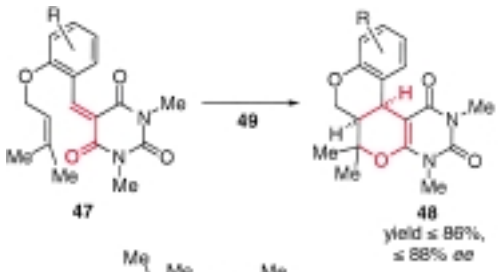
Scheme 10. The two different coordination modes, a five- and six-membered intermediate, for ethyl ketomalonate **42** to a Lewis acid (the reacting carbonyl functionality is green) and the proposed intermediate in which **42** is coordinated to the Ph-BOX-Zn^{II} (*R*)-**44** catalyst in the different coordination modes. In the C_2-symmetric intermediate (left) neither of the sides is protected, in the asymmetric intermediate (right) one of the two sides is protected.

intermediate is C_2-symmetric with no obvious face-shielding of the carbonyl functionality (left), while for the five-membered intermediate (right) the carbonyl is shielded by the phenyl substituent. Calculations of the transition-state energy for the reaction of the two intermediates with 1,3-cyclohexadiene leads to the lowest energy for the five-membered intermediate and this approach is in agreement with the experimental results.[60]

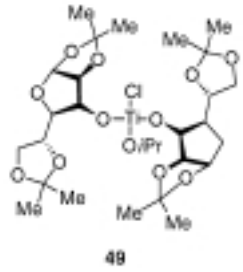
2.4. Inverse Electron demand Reactions

The catalytic enantioselective HDA reaction of α,β-unsaturated carbonyl compounds with electron-rich alkenes is a simple approach for the formation of 2-substituted 3,4-dihydro-*2H*-pyrans, which are useful precursors for natural products such as carbohydrates. This is an inverse electron demand controlled reaction with a dominant interaction between the LUMO of the 1-oxa-1,3-butadiene and the HOMO of the alkene (see Figure 1, right). This reaction is usually a concerted nonsynchronous transformation with retention of the configuration of the dienophile and shows normally high regioselectivity, which in the presence of Lewis acids is improved and, furthermore, also increases the reaction rate.

The inverse electron demand catalytic enantioselective HDA reaction has not been investigated to a very high extent. The first example of this class of reactions was published by Tietze et al. in 1992 where an intramolecular cycloaddition of the heterodiene **47** catalyzed by a diacetoneglucose-derived titanium(IV) Lewis acid **49** gave exclusively the *cis* product **48** in good yield and up to 88 % *ee* [Eq. (26)].[64] The reaction is



47 **48** yield ≤ 88%, ≤ 88% *ee* (26)



49

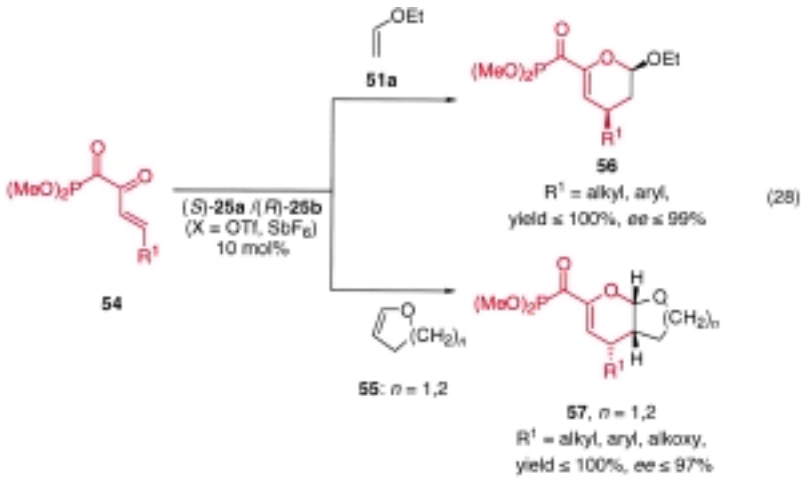
dependent on the solvent, and a racemate was obtained in $CHCl_3$, while the highest enantioselectivity was found in 1,2,3,5-tetramethylbenzene. The catalytic enantioselective intramolecular HDA reaction of **47** catalyzed by **49** shows an interesting temperature effect as **48** is formed in 88 % *ee* at 25 °C, while a racemic mixture is formed at 0 °C and 100 °C.

A chiral titanium(IV) complex was also applied by Wada et al. for the intermolecular HDA reaction of (*E*)-2-oxo-1-phenylsulfonyl-3-alkenes **50** with enol ethers **51** [Eq. (27)].[65] The TADDOL–TiX$_2$ (X = Cl, Br) complexes **53** were found to catalyze an enantioselective reaction giving the dihydro-

pyrans **52**. The reaction is dependent on the anion of the catalyst; the best yield and enantioselectivity were found for the TADDOL–$TiBr_2$ complex. The dihydropyrans **52** were obtained in good yields and up to 97% *ee*.

The chiral BOX–copper(II) complexes are also effective catalysts for highly enantioselective HDA reactions of α,β-unsaturated acyl phosphonates[66] and α,β-unsaturated keto esters.[50b, 67]

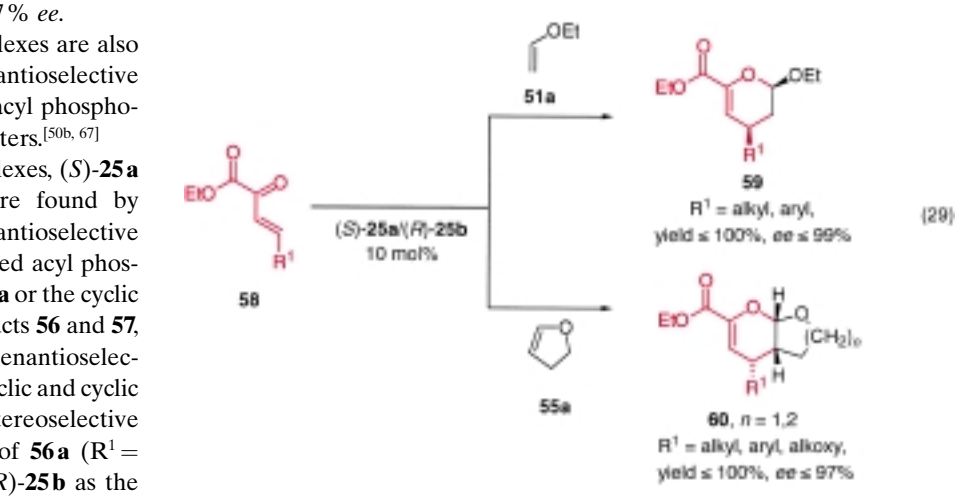
The chiral BOX–copper(II) complexes, (*S*)-**25a** and (*R*)-**25b** (X = OTf, SbF_6), were found by Evans et al. to catalyze the enantioselective HDA reactions of the α,β-unsaturated acyl phosphonates **54** with ethyl vinyl ether **51a** or the cyclic enol ethers **55**, giving the HDA adducts **56** and **57**, respectively, in very high yields and enantioselectivities [Eq. (28)].[66] Notably the acyclic and cyclic enol ethers react in a highly stereoselective manner and the same enantiomer of **56a** (R^1 = Me) is formed using (*S*)-**25a** and (*R*)-**25b** as the

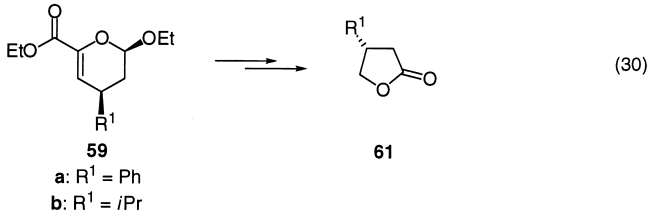


catalyst for the reaction in Equation (28). Furthermore, it is of practical importance that the HDA reaction can proceed in the presence of only 0.2 mol% of (*R*)-**25a** (X = SbF_6) with minimal reduction in the yield of the HDA adduct and no loss of enantioselectivity (93% *ee*).

More recently, further developments have shown that the reaction outlined in Equation (28) can also proceed for other alkenes; for example, the reaction of the silyl enol ether of acetophenone[66b] gives the *endo* diastereomer in up to 99% *ee*. Furthermore, it was shown that β-ethyl-β-methyl-substituted acyl phosphonate also can undergo a diastereo- and enantioselective HDA reaction with ethyl vinyl ether catalyzed by the chiral Ph-BOX-copper(II) catalyst. The preparative use of the HDA reaction was demonstrated by performing reactions in gram scale and by showing that no special measures are required for the reaction and that the dihydropyrans can be obtained in high yield and with very high diastereo- and enantioselectivities.

Our development of the catalytic enantioselective inverse electron demand HDA reaction,[67] which was followed by related papers by Evans et al.[50b, 66b] focused in the initial phase on the reaction of mainly β,γ-unsaturated-α-keto esters **58** with ethyl vinyl ether (**51a**) and 2,3-dihydrofuran (**55a**) [Eq. (29)]. Under catalysis by **25b** (X = OTf_2) or the aqua complex **32b** (Scheme 9) this reaction proceeds in high yield, diastereo-, and enantioselectivity.[50b, 66b, 67] The reaction tolerates a broad range of substituents at R^1, such as alkyl, aryl, alkoxy, and thiobenzyl. The reaction can proceed with only 0.5 mol% of catalyst **32b** with only a slight decrease in enantioselectivity and diastereoselectivity.[50b, 66b] Furthermore, preliminary studies have indicated that the catalyst **32b** can be reused in multiple reaction cycles without significant loss in yield and stereoselectivity, and that the β,γ-unsaturated-α-keto esters were somewhat more reactive than α,β-unsaturated-acyl phosphonates in catalytic HDA reactions.[50b, 66b] The absolute configuration of the HDA adducts **59a**, **b** was assigned by transformation to the lactones **61a**, **b** with known configuration [Eq. (30)].[50b, 66b]

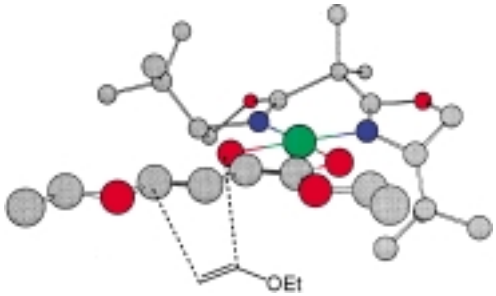




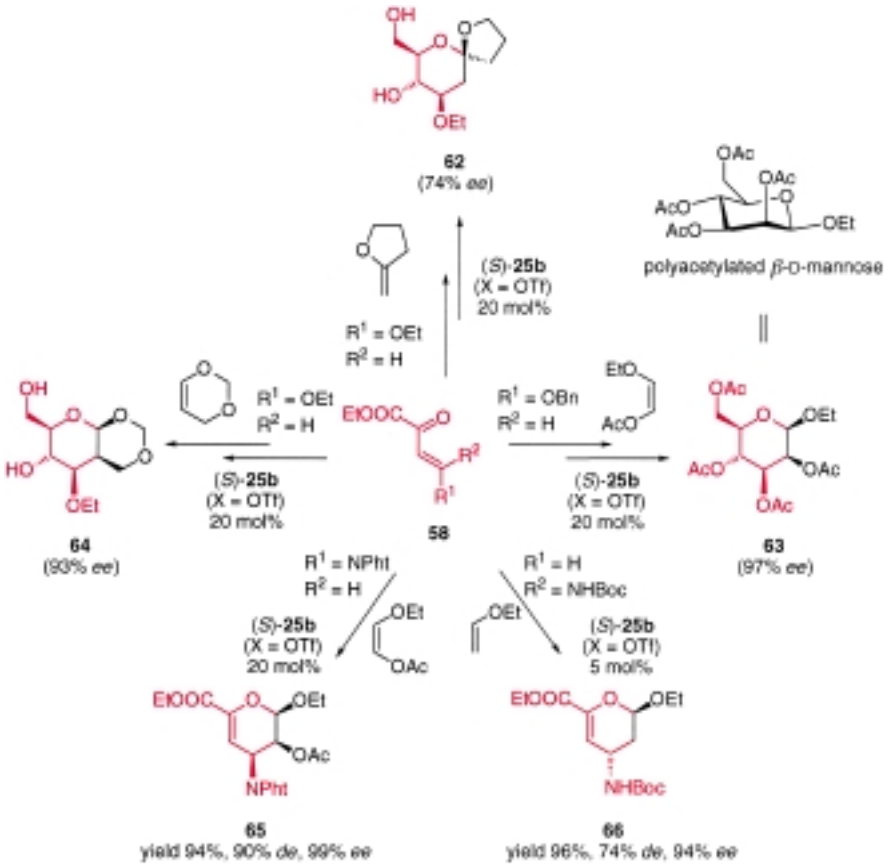
Further developments of this inverse electron demand catalytic enantioselective HDA reaction using β-substituted β,γ-unsaturated-α-keto esters **58** have resulted in simple

approaches for the synthesis of optically active carbohydrates[51] including amino sugars[68] (Scheme 11). The reaction can be used for the preparation of optically active spiro carbohydrates **62**, which is an important functionality found in natural products such as pheromones, steroidal compounds, antiparasitic agents, and polyether antibiotics.[69] *cis*-Alkenes are also useful substrates for inverse electron demand catalytic enantioselective HDA reactions of β,γ-unsaturated-α-keto esters, which lead to the HDA adduct in good yield and with very high diastereo- and enatioselectivities. This reaction has been used for the synthesis of the ethyl β-D-manonose tetraacetate (**63**). Interestingly, the β-glycoside linkage at C-1 of this monosaccharide is difficult to synthesize by standard carbohydrate chemistry, because it is neither possible to use the neighboring group effect at C-2, nor the anomeric effect. The HDA approach can also be used as a synthetic procedure for the preparation of the nonnaturally occurring acetal-protected C-2-branched carbohydrate **64**. The formation of amino sugars by this catalytic enantioselective reaction has shown that diastereomers **65** and **66** with different protecting groups can be formed in high yield, diastereo-, and enantioselectivities. Amino sugars can be applied as pharmaceuticals, for example, for the treatment of diabetes and as promising drugs against influenza.[70]

The absolute configuration of products obtained in the highly stereoselective HDA reactions with inverse electron demand catalyzed by the *t*Bu-BOX-Cu^{II} complex can also be accounted for by a square-planar geometry at the copper(II) center. Support for a square-planar intermediate is provided by the X-ray structure analysis of the hydrolyzed enone bound to the chiral BOX-copper(II) catalyst (see **34b** in Scheme 9). It has been assumed that the γ-substituted β,γ-unsaturated α-keto ester **58** coordinates in a bidentate fashion through the carbonyl oxygen atoms to the (*S*)-*t*Bu-BOX-Cu^{II} catalyst leading to intermediate **67** (Scheme 12). The approach of, for example, ethyl vinyl ether to the γ-substituted β,γ-unsaturated α-keto esters will thus take place from the *Si*-face of the reacting carbonyl functionality, as the *Re*-face is shielded by the *tert*-butyl substituent of the chiral ligand.



Scheme 12. Structure of the intermediate **67** formed in the reaction of **58** with **51a** in the presence of (*S*)-**25b**.



Scheme 11. The use of the BOX-copper(II) complex *t*Bu-BOX-Cu^{II} (*S*)-**25b** for the synthesis of optically active carbohydrates and amino sugars using catalytic inverse electron demand HDA reactions. NPht = phthalimidyl; Boc = *t*BuOCO.

3. Hetero-Diels–Alder Reactions of Imines

Nitrogen-containing compounds such as amino acids, peptides, and alkaloids are abundant in nature. They are of fundamental importance to our society and are, for example, particularly attractive for medicinal chemistry due to the pronounced biological and physiological properties of these compounds. The HDA, ene, and alkylation reactions of imines are powerful methodologies for the construction of nitrogen-containing compounds.[3, 71, 72] With the increasing demands for producing optically active compounds in both enantiomeric forms, asymmetric synthesis of these compounds is a formidable challenge to the synthetic organic chemists. Not surprisingly, considerable attention has been paid to the development of asymmetric addition reactions to imines.

3.1. Diastereoselective Reactions

Great progress has been achieved in diastereoselective HDA and ene reactions, as well as the 1,2-nucleophilic

addition reactions of organometallic compounds to imines. However, many challenges remain and they need to be addressed, particularly with respect to the use of chiral Lewis acid catalysis for controlling the stereochemistry of reactions between achiral substrates.

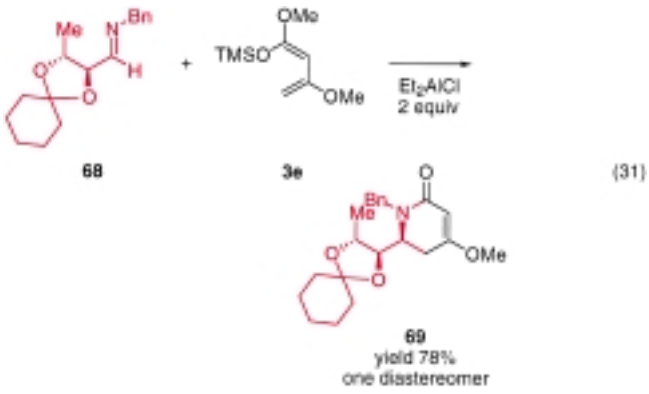
Compared to the great achievements during the last decade concerning enantioselective reactions of carbonyl compounds using chiral Lewis acid catalysts, the analogous enantioselective HDA reactions remained unavailable for a long time. Only very recently advances appeared for catalytic and catalytic enantioselective HDA reactions of imines. Some common problems related to the use of imines as substrates in catalytic enantioselective reactions can be summarized as follows: 1) the nitrogen atom of imines is more Lewis basic than the oxygen atom of carbonyl compounds. As a consequence, the coordination of the imine, or the product, to the chiral Lewis acid catalyst is stronger, leading to deactivation or inhibition of the catalyst. Therefore, stoichiometric amounts of chiral Lewis acids are often needed to achieve conversion and high asymmetric induction; 2) the flexible *E/Z* conformations of imines allow more possible structures to exist in solution; 3) the low reactivity and poor electrophilicity of the imine double bond; 4) the tendency towards deprotonation of the α-acidic proton of enolizable imines to form enamines; 5) some imines are unstable and difficult to isolate which can lead to additional difficulties.

The addition reactions of organometallic reagents, including the addition of allyl–metal reagents to C=N bonds, have been reviewed several times.[73] In the present context an overview focusing on the catalyzed enantioselective HDA reactions of imines will be presented for the formation of optically active aza-DA compounds. First, the HDA reactions of chiral substrates catalyzed/mediated by Lewis acids will be discussed followed by catalytic enantioselective HDA reactions of achiral imines.

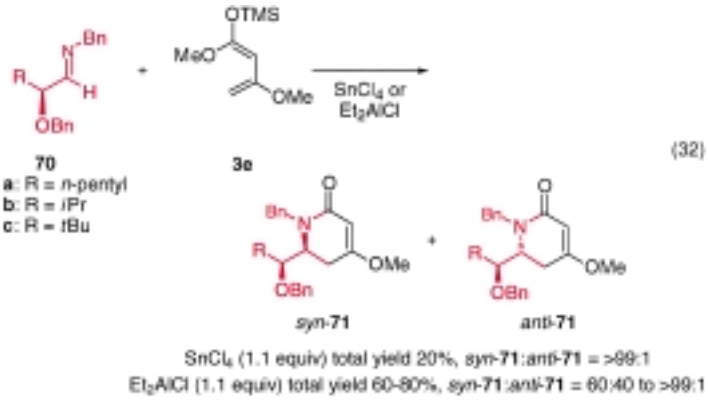
3.1.1. Reactions of Chiral Imines Derived from Chiral Carbonyl Compounds

Unactivated imines are normally not reactive enough to be used as dienophiles for HDA reactions. Exceptions are intramolecular additions[74] or the use of iminium salts.[75] In 1982, Danishefsky et al. reported the first cycloaddition involving imines with an activated diene in the presence of $ZnCl_2$ as the Lewis acid.[76] It was later reported by Ojima et al. that $TiCl_4$ is an efficient catalyst for the reaction,[77] and more recently, Kobayashi et al. described the use of only 10 mol% of lanthanide triflates as catalysts for an imino-DA reaction.[78]

One of the first examples of an asymmetric cycloaddition of an unactivated imine was reported by Midland et al. in 1988.[79] The cyclohexylidene-protected α,β-dialkoxy imine **68**, which is prepared from L-threonine, reacts with Brassard diene **3e** in the presence of a strong Lewis acid, such as Et_2AlCl, to afford a single isomer of lactam **69** in high yield [Eq. (31)]. The *syn*-configuration of the adduct was proposed to be in agreement with a "chelation-controlled" addition mechanism.



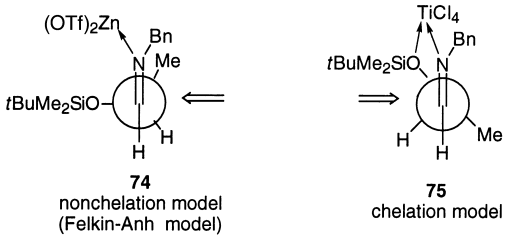
In order to investigate the effect of the nature of substrates and Lewis acids on the diastereoselectivity, Midland et al. prepared a series of α-alkoxy imines **70a–c** and studied the reaction with diene **3e** [Eq. (32)].[80] The use of $SnCl_4$ gave the



chelation-controlled diastereomers *syn*-**71** in low yields for all three substrates, while a higher *syn*-selectivity was observed when the steric bulk of the side chain was increased. When Et_2AlCl was used as the catalyst, both the "small" substrate **70a** and the "large" substrate **70c** led to a high degree of the "chelation-controlled" products *syn*-**71**, while for substrate **70b**, containing a medium-sized side chain, only poor diastereoselectivity was observed. The diastereoselectivity is also dependent on the stoichiometry of Et_2AlCl as an increase in the number of equivalents of Lewis acids from less than one equivalent to two equivalents resulted in an improvement of the *syn*-selectivity. It was concluded that in the case of Et_2AlCl as the catalyst, the mechanism may be more complicated than either a "chelation" or "nonchelation" rationale. In a real chelation-controlled process, a moderate diastereoselectivity should be expected in the case of a medium-sized substrate.

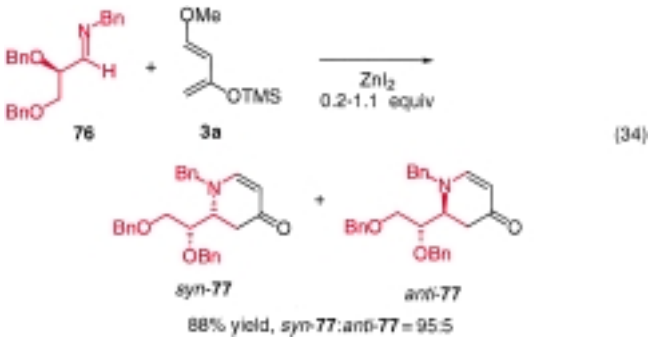
The HDA reaction of chiral α-silyloxy aldimines with activated 2-silyloxy-1,3-dienes has been investigated by Akiba et al.[81] Only the diastereomers *anti*- and *syn*-**73** were obtained from the reaction of imine **72** with diene **3f** [Eq. (33)]. The diastereoselectivity is dependent on the Lewis acid, solvent, and temperature. Notably, using $Zn(OTf)_2$ and $TiCl_4$ as the catalysts led to the formation of opposite diastereomers as the major products.

The nonchelation model **74** was proposed to account for the formation of *anti*-**73** as the major product using $Zn(OTf)_2$ as the catalyst, while chelation model **75** can account for the formation of *syn*-**73** using $TiCl_4$ as the catalyst (Scheme 13). The formation of the nonchelation product *anti*-**73** in the presence of $Zn(OTf)_2$ was explained by the insolubility of $Zn(OTf)_2$ in the solvent for the reaction (CH_2Cl_2). Thus, the reaction took place before the chelation complex of $Zn(OTf)_2$–imine was formed.



Scheme 13. Chelation and nonchelation models proposed by Akiba et al.[81] to account for the formation of the opposite induction in the presence of $Zn(OTf)_2$ and $TiCl_4$.

Recently, Díaz-de-Villegas et al. reported an asymmetric reaction of imine **76**, derived from (*R*)-2,3-*di*-*O*-benzylglyceraldehyde and benzylamine, with Danishefsky's diene **3a** [Eq. (34)].[82] Among various Lewis acids such as $MgBr_2$, ZnI_2, [Eu(fod)$_3$] fod = 7,7-dimethyl-1,1,1,2,2,3,3-heptafluoro-



4,6-octaedioate), $SnCl_4$, $TiCl_4$, Et_2AlCl, and BF_3, the catalyst ZnI_2 was the best in terms of yield and diastereoselectivity of the HDA adduct **77**. It was observed that in aprotic solvents, an increase in the solvent polarity led to an improvement of the selectivity with *syn*-**77** as the major diastereomer (toluene: 50% *de*; CH_2Cl_2: 82% *de*; CH_3CN or CH_3NO_2: 90% *de*).

The stereochemical outcome of the reaction was not affected by the complexing properties of the Lewis acids as observed by Midland et al. Both the chelating Lewis acid and the aluminum or boron catalysts, which usually prefer tetracoordination, gave the same diastereomer *syn*-**77** (chelation product) in excess. A chelation model and an anti-Felkin–Anh model[83] were proposed for the chelating Lewis acid ZnI_2, and nonchelating Lewis acids, Et_2AlCl and BF_3, respectively. The double asymmetric induction was investigated by employing imines bearing two chiral centers.[82] The reaction of an imine derived from (*S*)-α-methylbenzylamine, with Danishefsky's diene gave only a single diastereomer, while the reaction of other imines afforded a mixture of enaminones with modest diastereoselectivity.

The Lewis acid catalyzed HDA reaction of chiral imines with dienes has been applied for the preparation of natural products. Herczegh et al. reported the synthesis of analogues of the natural product swainsonine by using an asymmetric HDA reaction of a Schiff base, formed in situ from the D- or L-arabinose aldehyde and benzylamine, with Danishefsky's diene in the presence of $ZnCl_2$ as the Lewis acid catalyst.[84] Recently, Wang et al. reported the synthesis of azasugars by lanthanide-promoted HDA reactions in aqueous solution.[85] In the presence of 10 mol% [Nd(OTf)$_3$] the reaction of a chiral aldehyde, prepared from D-glycosamine hydrochloride, and cyclopentadiene produced only one diastereomer in a moderate yield which could be converted into azasugars.

The HDA adduct azabicyclo[2.2.1]-heptene **78** might be a key compound for the synthesis of products of interest such as the pharmaceutically important compounds (−)-aristeromycin, carbovir, 1592U89, and (1*R*,3*S*)-amidinomycin.[86] Several examples are available for the synthesis of optically active **78** starting from chiral or achiral substrates in the absence[86] and presence of a Lewis acid, as well as the presence of chiral Lewis acids, as catalysts.

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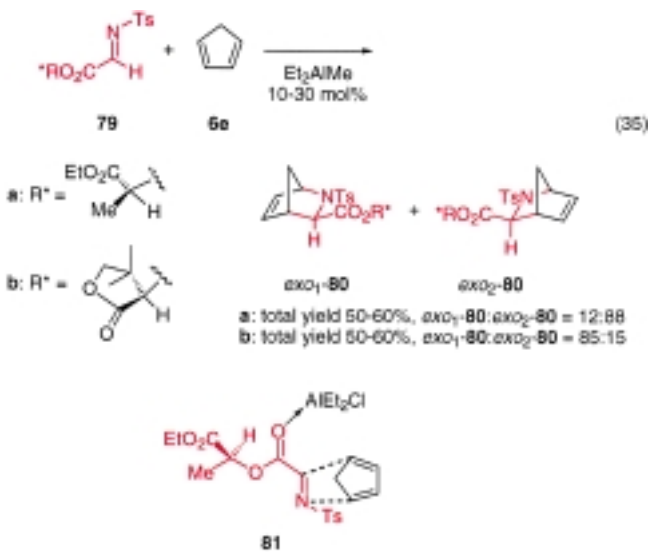
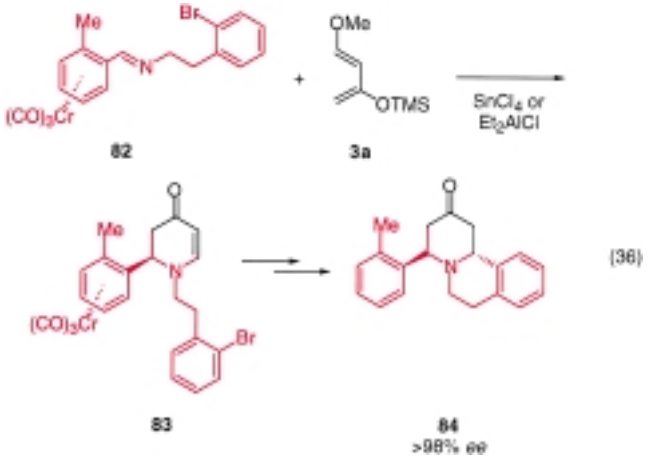
Holmes et al. have applied the (*S*)-lactate-derived *N*-tosyl imino acetate **79a** and (*R*)-panto-lactone derived imino acetate **79b** for reaction with cyclopentadiene **6e** [Eq. (35)][87] in various solvents, and in the absence and presence of different Lewis acids. In all cases, only the *exo*-diastereomers were obtained. The use of Et_2AlCl as catalyst resulted in 50–60% yield and 76% *de* for the lactate adduct *exo*$_2$-**80a**. In order to account for the formation of *exo*$_2$-**80a**, an approach of the cyclopentadiene to **79a** was proposed as outlined in **81**. In **81**, imine **79a** adopts an *E* conformation and the monodentate Et_2AlCl coordinates to the carbonyl oxygen atom *anti* to the bulky chiral auxiliary. This forces the approach of the cyclopentadiene to the less hindered face resulting in *Si*-attack.

The reaction outlined in Equation (35) has also been performed for imines with aromatic substituents on the nitrogen atom and the same chiral auxiliaries. This affords substituted tetrahydroquinolines in moderate to high yields with total regio- and stereoselectivity.[88] However, high diastereoselectivity (up to 92%) was only obtained by using



an imine with 8-phenylmenthyl as the chiral auxiliary, while imines substituted with bornyl and menthyl auxiliaries gave almost no asymmetric induction (0–10% *de*).

Recently, tricarbonylchromium complexes have been introduced as novel chiral auxiliaries for HDA reactions.[89] The reaction between the planar chiral *ortho*-substituted benzaldehyde imines **82** and Danishefsky's diene **3a** in the presence of 1.2 equivalents of Lewis acid, $SnCl_4$ or Et_2AlCl, gave single diastereomers, such as **83**, in most cases [Eq. (36)].[89] The major diastereomer is presumably formed by the approach of a diene from the side opposite to the $Cr(CO)_3$ group and addition to the imine face of the preferred *E* conformation. Subsequent cyclization of the cycloadduct, and oxidative metal removal gave the quinolizidine derivative **84** with >98% *ee*.

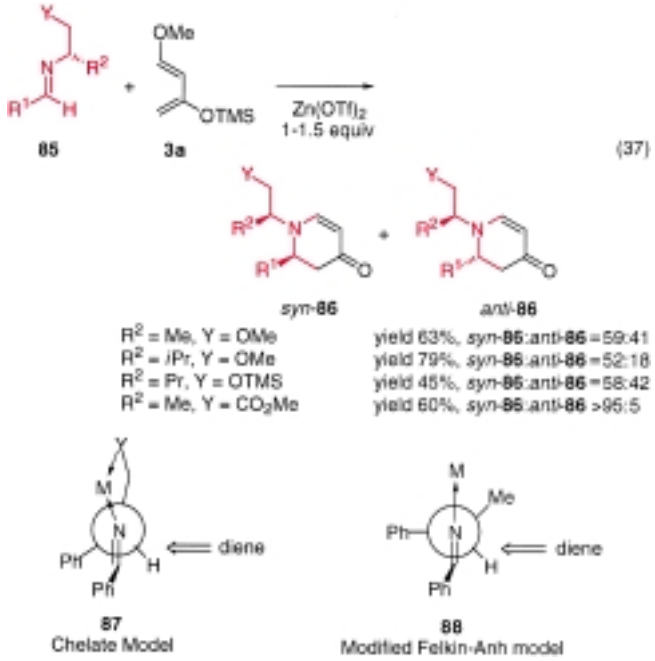


3.1.2. Chiral Imines Derived from Chiral Amines

Asymmetric HDA reactions employing chiral imines derived from chiral amines have been intensively investigated due to the easy access of both enantiomers. The most frequently used chiral amines are α-phenylethylamine, α-amino acids, β-amino alcohols, and their derivatives.[90]

The use of camphoryl as the chiral auxiliary on the nitrogen atom of the *N*-sulfonyl glyoxylate imine (similar to **79**) was introduced by Whiting et al.[91] This imine reacts with Danishefsky's diene **3a** affording up to 40% *de* in the presence of 0.25 equivalents of $Ti(OiPr)_4$.

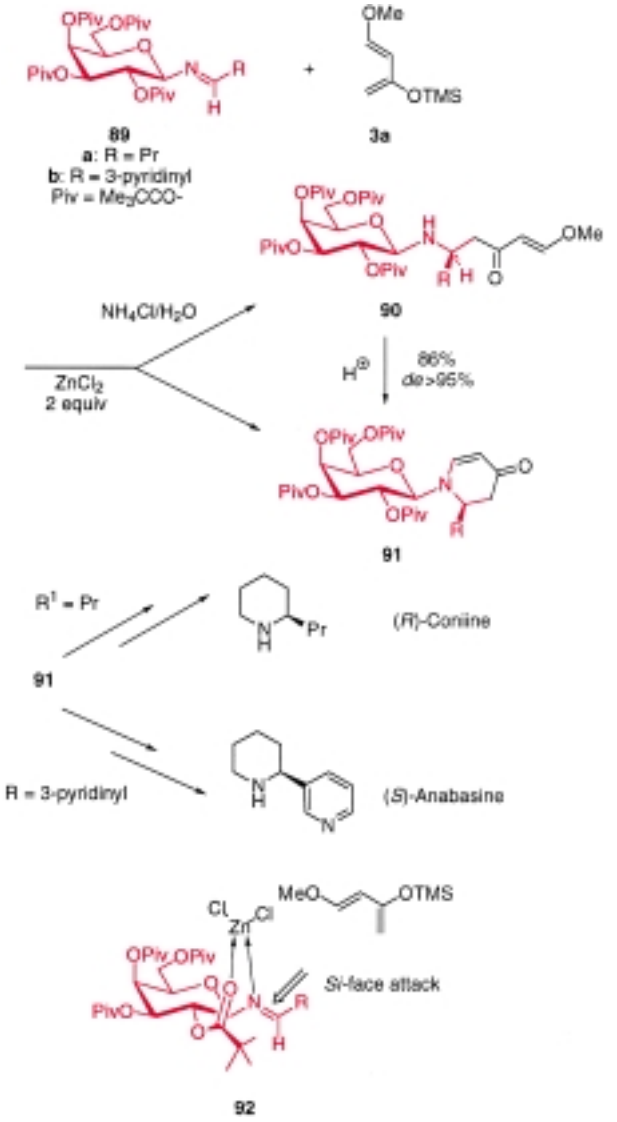
In 1993, Oh et al. reported excellent results using imines as the dienophiles for asymmetric HDA reactions which have the capacity to form a chelate.[92] The imines **85**, synthesized from α-amino alcohols, react with Danishefsky's diene **3a** and show some distinctive and instructive trends [Eq. (37)]. The



size of the stereodirecting group R^2 directly influences the stereoselectivity. As the bulk of R^2 increased, the diastereoselectivity was enhanced. In contrast, the substituents on the aldehyde part had little influence, except that there was no reaction with the bulky *tert*-butyl group. Imines which can form a cyclic chelate gave almost similar diastereoselectivities for the HDA adduct *syn*-**86** as those which did not have a second chelating site. Furthermore, the imines with a more Lewis basic second chelating group (Y = CO_2Me, OH) gave higher diastereoselectivity than imines with a less Lewis basic site (Y = OTMS). When imines derived from α-amino esters and β-amino alcohols were used, only single diastereomers were formed. To account for the stereoselectivity, the cyclic chelate model **87** was used, and a modified Felkin–Anh model **88** for those which can only form a monodentate coordination to the Lewis acid.

The use of imines with a carbohydrate template as the dienophile in diastereoselective HDA reactions has been investigated by Kunz et al.[93] The reaction of imines **89** with, for example, 2,3-dimethyl-1,3-butadiene or isoprene in the presence of $ZnCl_2$ as the catalyst proceeded well but afforded a mixture of three diastereomers (one from the α-anomer) with moderate diastereoselectivities. However, excellent selectivities could be achieved by reaction of **89** with Danishefsky's diene **3a** affording **91** in high yield and

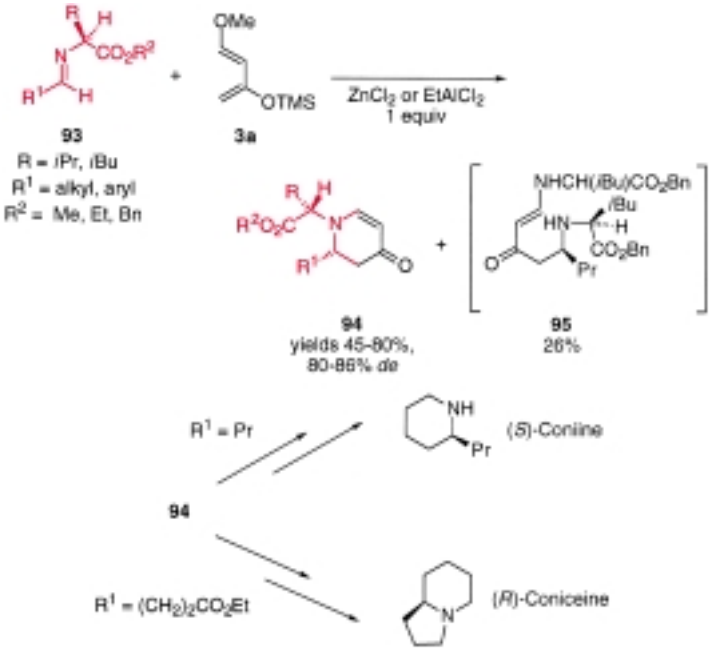
diastereoselectivity (Scheme 14). Compounds **91** were converted into (*R*)-coniine and (*S*)-anabasine, by subsequent reduction, decarbonylation, and removal of the carbohydrate template. It was believed that the reaction of **89** with isoprene was a concerted HDA process,[93] whereas the reaction with Danishefsky's diene proceeded by a Mannich-type process as the corresponding Mannich-addition products **90** were isolated if the reaction was quenched with NH_4Cl/H_2O.



Scheme 14. Synthesis of (*R*)-coniine and (*S*)-anabasine by $ZnCl_2$-catalyzed diastereoselective HDA reactions of carbohydrate-substituted imines as dienophile.[93]

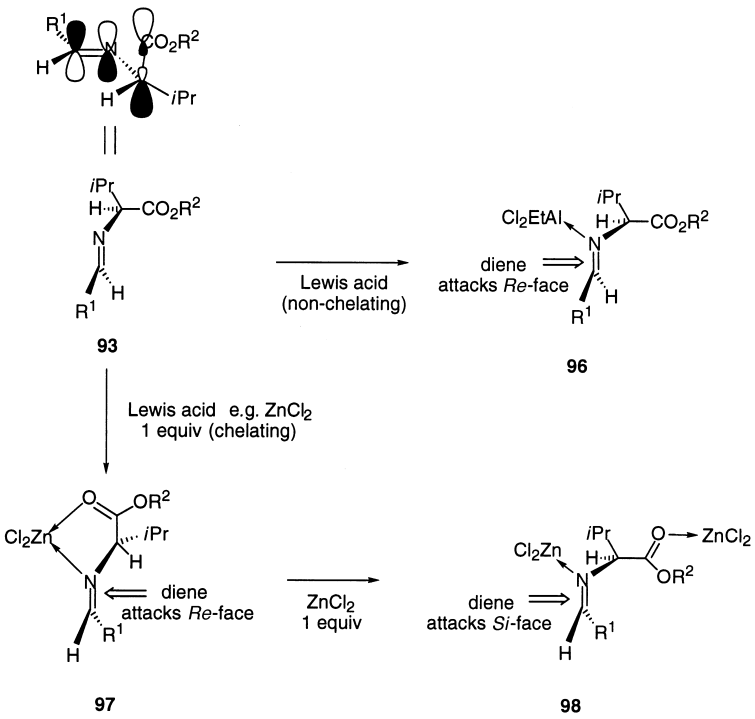
It has been proposed that Danishefsky's diene approach the sterically less shielded *Si*-face of the galactosyl imine-Lewis acid complex as outlined in **92** in Scheme 14.[93b,c]

Asymmetric Mannich-type reactions between imines derived from α-amino acid esters with activated dienes, leading to the HDA adducts **94** have been reported by Waldmann et al.[94] The reaction was found to be quite general as imines from aromatic and aliphatic aldehydes were good substrates. Excellent diastereoselectivities were obtained when valine and isoleucine esters were employed as the auxiliaries (Scheme 15). For the reactions of imines **93** with Danishefsky's diene **3a**, neither the presumed HDA intermediate nor a stepwise Mannich-type intermediate were detected. The enaminone **94** was obtained directly after aqueous work-up, except in one case where compound **95** was isolated in 26% yield as a by-product. The occurrence of **95** suggests that the reaction probably proceeds by a Mannich-type sequence. The removal of the chiral auxiliaries from the products required the cleavage of the chemically stable α-bond of the amino acid and the nitrogen atom. This was achieved for **94** and further reactions demonstrated that this HDA approach could be used for the synthesis of (*S*)-coniine and (*R*)-coniceine.



Scheme 15. Synthesis of (*S*)-coniine and (*R*)-coniceine by using catalytic diastereoselective HDA reactions of chiral imines with Danishefsky's diene.[94]

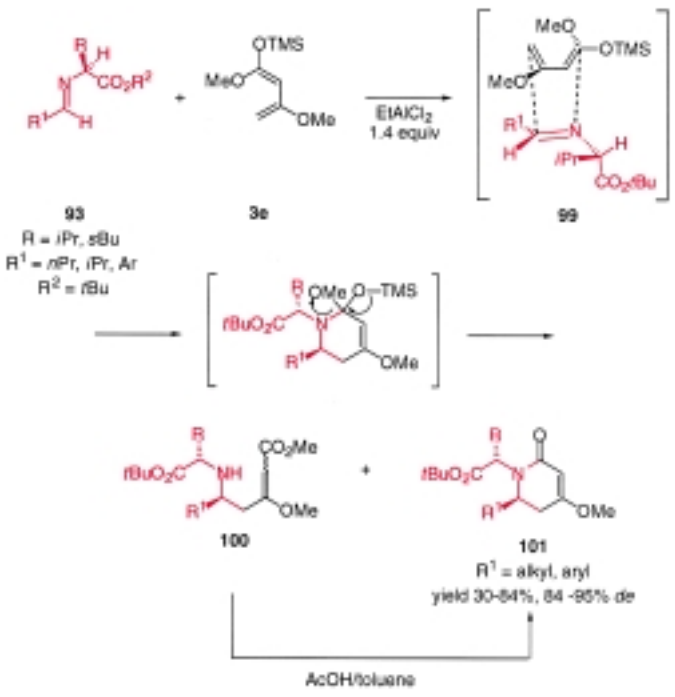
The sense of the stereoselectivity was found to be independent of the Lewis acids, as the same major isomer **94** was obtained by using either the chelating Lewis acids $ZnCl_2$ and $TiCl_4$, or the nonchelating Lewis acids BF_3 and Et_2AlCl. The stereochemical outcome of the reaction with nonchelating Lewis acids can be explained by assuming the modified Felkin–Anh type of intermediate **96** in which the Lewis acid coordinates to the nitrogen atom of the imine, and where the α-C–COOR substituent at the nitrogen atom simultaneously is oriented perpendicular to the imine. From a FMO point of view this leads to a parallel orientation of the $\sigma^*(\alpha\text{-C–COOR})$ orbital and the π^*(C=N) orbital (Scheme 16). To account for the lack of reversal of the stereochemical outcome by changing from a nonchelating to a chelating Lewis acid, it was suggested that an equilibrium between the *cis*- and *trans*-imine in the presence of $ZnCl_2$ exists and that the *cis*-imine probably reacts faster. This explanation was also based on the observation of different ^{1}H NMR chemical shifts of the aldimine proton and the amino acid α-H with and without the presence of one equivalent of $ZnCl_2$. The existence of the chelation intermediate **97** using one equivalent of $ZnCl_2$ was supported by the observation that the sense of the asymmetric induction was reversed by



Scheme 16. Models for the coordination of imine **93** to nonchelating and chelating Lewis acids.

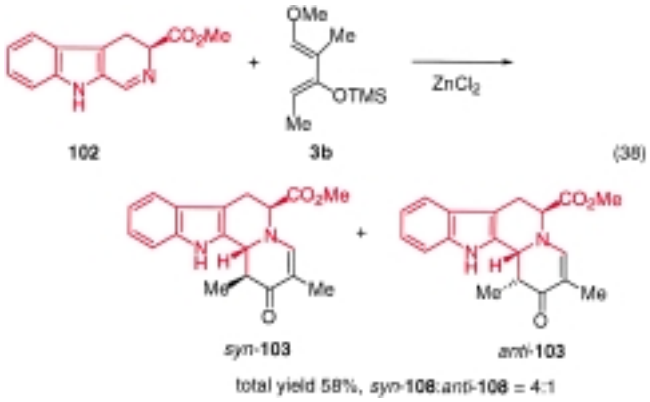
using two equivalents of $ZnCl_2$. The latter observation can be rationalized by the separate coordination of one equivalent of $ZnCl_2$ to the imine nitrogen atom and the second equivalent of $ZnCl_2$ to the ester carbonyl atom as outlined in **98**.

When the Brassard diene **3e** was treated with imine **93** in the presence of $EtAlCl_2$ as the catalyst, only the open-chain esters **100**, or a mixture of **100** and the HDA adduct **101** were isolated in high yields (Scheme 17).[94c] Compound **100** can be transformed into **101** by heating in the presence of acetic acid. The steric course of the reaction between **93** and **3e** was rationalized by assuming an *anti*-Felkin – Anh transition state **99** in which the interaction between the bulky TMS group of the diene and the sterically demanding group of the amino acid side chain is minimized.



Scheme 17. The catalytic diastereoselective HDA reaction of imine **93** with diene **3e**.

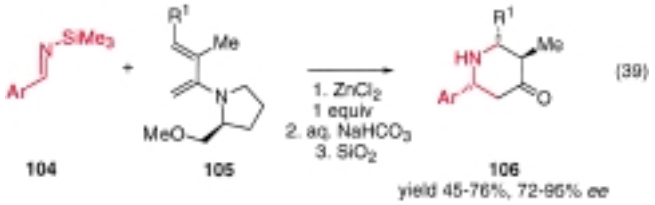
The principle that simple imines can participate in HDA reactions with activated dienes has been applied for the asymmetric synthesis of alkaloids. In 1985, Danishefsky et al. demonstrated the use of cycloadditions of chiral α-amino ester dienophiles for the synthesis of yohimbine congeners [Eq. (38)].[95] The reaction of the optically active tricyclic imine **102** with diene **3b** catalyzed by $ZnCl_2$ gave *syn*-**103** and *anti*-**103** in 58 % combined yield and with a *syn*:*anti* ratio of 4:1.



As an extension and application of the reaction between amino acid ester imines and dienes outlined in Equation (38), Waldmann et al. demonstrated the asymmetric synthesis of indolo[2,3-*a*]quinolinzidin-2-ones using related imines.[96] This diastereoselective synthesis of, for example, a tetracyclic amino ketone led to a new procedure for the preparation of optically active alkaloids of the yohimbine-type.

3.1.3. Chiral Dienes

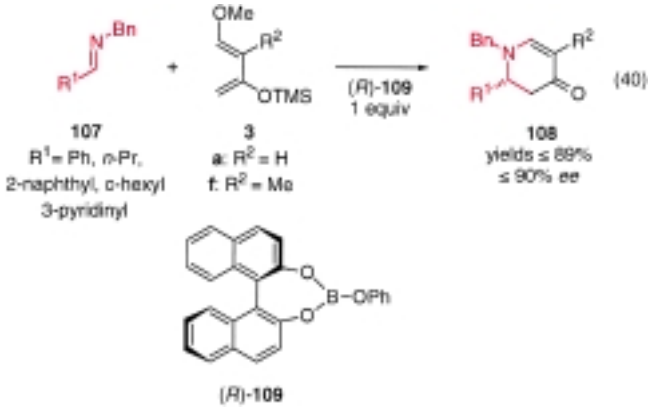
There are only very few examples dealing with the HDA reaction employing chiral dienes, and of these, the use of Lewis acid catalysis is even more limited. Barluenga et al. reported the synthesis and application of the chiral diene **105**, having a chiral pyrrolidine auxiliary. The reaction of the *N*-silylimines **104** with diene **105** catalyzed by $ZnCl_2$ afforded the piperidones **106** in moderate to good yields with good to excellent enantioselectivities [Eq. (39)].[97] The application of



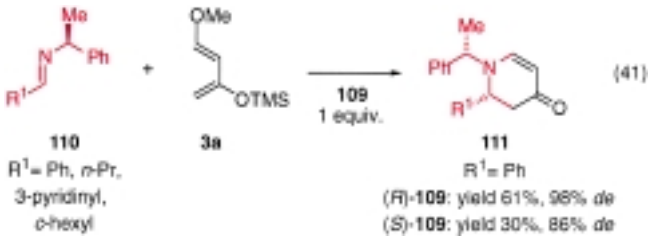
this methodology for the diastereo- and enantioselective synthesis of a pipeconic acid derivatives has also been described recently.[97c]

3.2. Diastereoselective Reactions with Chiral Catalysts

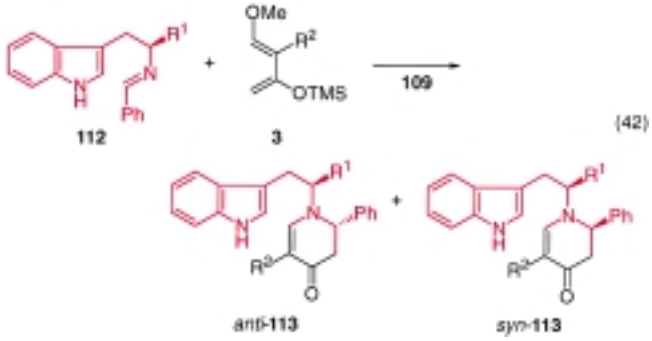
Lewis acid catalyzed diastereoselective HDA reactions using chiral imines and dienes have been investigated intensively. Excellent diastereoselectivities have been achieved in some cases, providing new synthetic procedures to optically active heterocycles. Despite the obvious advantages in the use of chiral catalysts, the development of chiral Lewis acid catalysts for the HDA reaction has only been carried out successfully over the last few years. In 1992, Yamamoto et al. showed that the chiral boron(III) reagent **109** could catalyze the HDA reaction of aldimines with Danishefsky-type dienes **3a** and **3f**.[98] In the presence of stoichiometric amounts of **109**, imines **107** reacted smoothly with dienes **3a**, **f** affording the HDA adduct **108** in good yields and with up to 90% *ee* [Eq. (40)].



The chiral boron catalyst **109** has also been applied for the reaction of chiral imines leading to double asymmetric induction. The imines **110** derived from α-methylbenzylamine and aldehydes reacted faster with diene **3a** in the matching case and nearly complete diastereoselectivity was observed [Eq. (41)]. The methodology was used for the synthesis of enantiomerically pure (+)-coniine and (−)-anabasine.[98b,c]

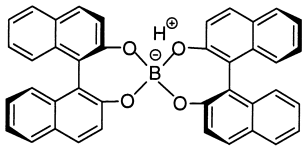


Waldmann et al. investigated the double asymmetric induction using catalyst **109** for the reaction of the chiral imines **112** with dienes **3** [Eq. (42)].[99] When the reaction between **112** and **3** was performed in the presence of (*R*)-**109** (the matched pair), a much higher ratio of dihydropiperidinone



anti-**113** to *syn*-**113** was obtained (de > 90%), compared to the use of $B(OPh)_3$ as the catalyst, while in the presence of (*S*)-**109** (mismatched case), only a slight enhancement was noted. The reaction of an achiral imine with an activated diene using the (*R*)-**109** as a catalyst gave the corresponding enaminones with low selectivity.

In a later investigation, Yamamoto et al. explored the use of another chiral boron catalyst, the Brønsted acid assisted Lewis acid **114**, for the HDA reactions in Equations (40) and (41).[100] The catalyst **114** was shown to be an efficient catalyst

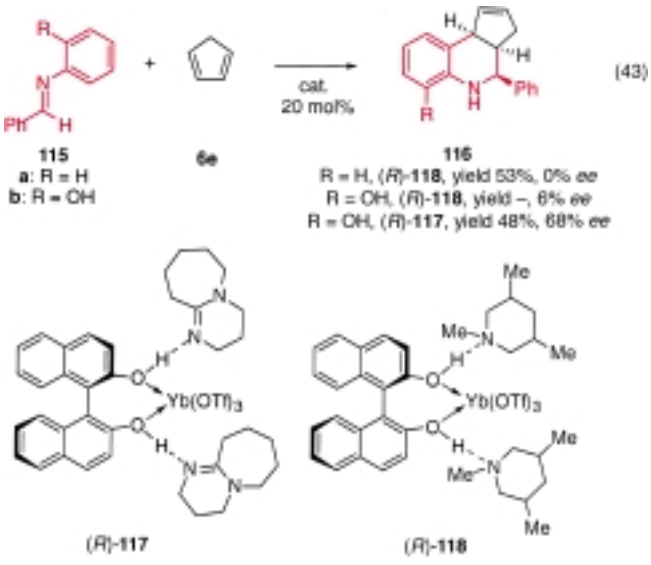


for the DA reaction between α-substituted α,β-enals and dienes.[101] However, for the HDA reactions, the use of one equivalent of **114** is necessary in order to achieve high asymmetric induction.

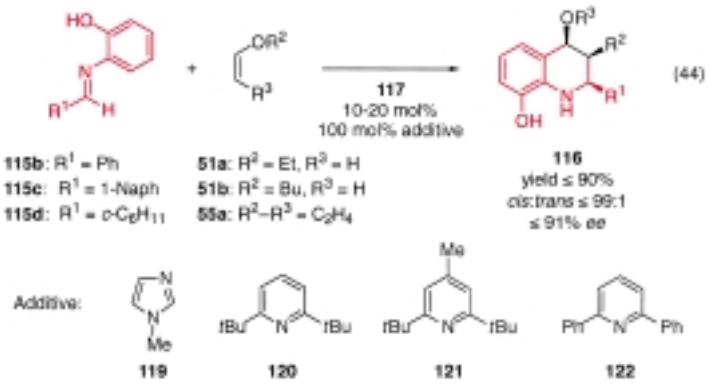
3.3. Catalytic Enantioselective Reactions

In 1996, Kobayashi et al. presented the first example of a catalytic enantioselective reaction of imines **115** (an azadiene) using chiral BINOL–ytterbium(III) complex **117** [Eq. (43)].[102] A similar catalyst **118** containing 1,3,5-trimethylpiperidine (TMP) as the amine component, which was previously found to catalyze efficiently the DA reactions of 3-acryloyl-1,3-oxazolidin-2-one with dienes,[103] catalyzed the reaction between **115a** and cyclopentadiene (**6e**). The tetrahydroquinoline derivative **116a** was isolated in 53% yield, but without chiral induction [Eq. (43)]. The use of imine **115b**, which is capable of coordinating in a bidentate fashion to the metal center, led to the formation of **116b** in high yield, but with only 6% *ee* in the presence of **118**. Changing TMP to diazabicyclo-[5.4.0]-undec-7-ene (DBU), however, led to an enantioselective reaction with 68% *ee*.

It was argued that the hydroxy group in **115b** could also interact with DBU to form a hydrogen bond with the hydroxy groups of the (*R*)-BINOL ligand, causing the decrease of the

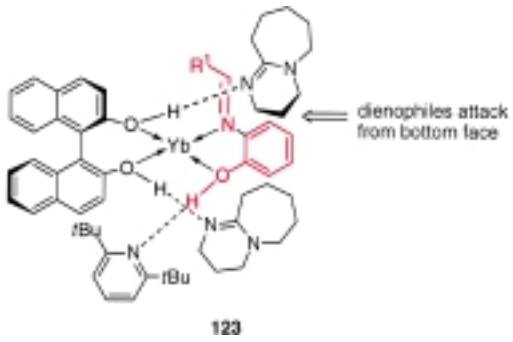


selectivity. Therefore, 20 mol% *N*-methylimidazole (NMI) **119** was added, and an improvement to 91% *ee* was obtained, however, the yield was only 21%. Different additives were then screened (**119**–**122**) and it was found that good yields and high enantioselectivities could be achieved if an appropriate additive was chosen for a particular substrate [Eq. (44)]. The reactions proceed in general with very high diastereoselectivity. The need for the different additives for different substrates in order to achieve the best results was explained by the slight difference in the asymmetric environment created by [$Yb(OTf)_3$], (*R*)-BINOL, and the additives. It should be noted that in the case of butyl vinyl ether **51b**, the *cis*/*trans* selectivity decreased significantly.



Kobayashi et al.[102] proposed a transition-state model **123** for the reaction in which the imine coordinates in a bidentate fashion to the metal, and in which the axial chirality of the (*R*)-BINOL is transferred through hydrogen bonds to the amine parts. The additive interacts with the phenolic hydrogen atom of the imines, which is fixed by the bidentate coordination to the metal. Since the top face of the imine is shielded by the amine, the dienophiles approach from the bottom face.

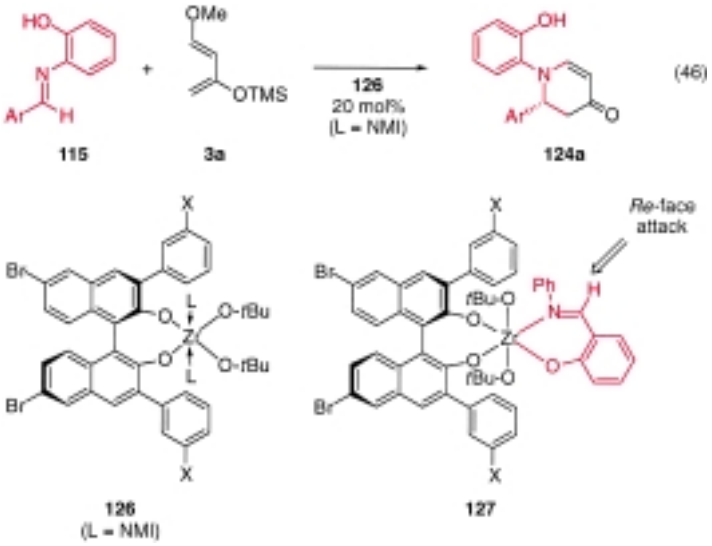
In 1998, the same authors reported the catalytic enantioselective HDA reaction using imines **115** promoted by a chiral



zirconium(IV) complex **125** [Eq. (45)].[104] The catalyst was prepared from $Zr(OtBu)_4$, (*R*)-Br-BINOL, and an amine ligand, for example NMI, in a ratio of 1:2:2–3. The reaction

between **115c** (Ar = 1-Naph = 1-naphthalinyl) and Danishefsky-type dienes **3** was found to be strongly influenced by both the ligands and the solvents. The best result (93% yield and 93% *ee*) was obtained from the reaction of **115c** and diene **3f** in toluene with NMI as the ligand in the presence of 10 mol% catalyst **125**. Furthermore, for a model reaction it was found that a chiral hafnium catalyst afforded slightly higher yield and enantioselectivity. Aldimines derived from aromatic and substituted aromatic aldehydes can be employed as the substrates for this reaction.

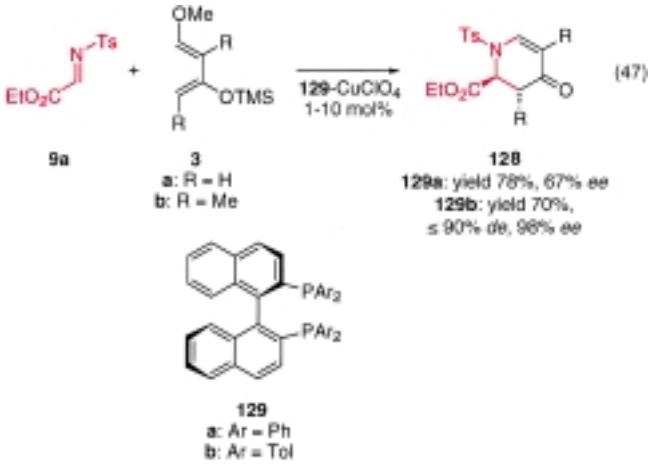
Generally, good enantioselectivities were achieved for *ortho*-substituted phenyl imines. However, for imine **115b** prepared from benzaldehyde, only 65% *ee* was achieved. The *ortho*-hydroxy group in the imines is found to be essential to achieve a high level of enantioselectivity, since even the imine prepared from 2-methoxyaniline gave low enantioselectivity. The absolute configuration of the products was assigned as *S* using catalyst **125** derived from the (*R*)-Br-BINOL ligand. However, no mechanism for the absolute asymmetric induction was discussed. For the same type of chiral catalysts a switch of enantioselectivity for this HDA reaction has been found using catalyst **126** [Eq. (46)].[105] The reaction of imine **115** with diene **3a** catalyzed by **126** (20 mol%) gave the corresponding piperidinone derivative in a slightly lower yield of 66%, but with a similar high enantiomeric excess of 84%. However, the absolute configuration of the product was found to be *R* which is opposite to the configuration obtained with



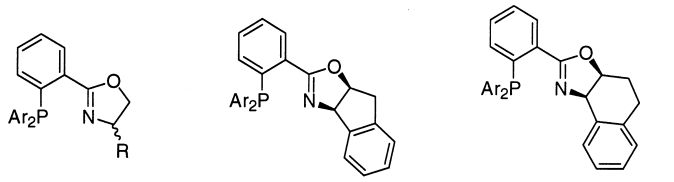
catalyst **125**. The results can be improved significantly by using molecular sieves. When the reaction was performed in the absence of molecular sieves at 0 °C, **124a** was isolated in only 45 % yield with 57 % *ee*; however, when molecular sieves (3 Å) were added the yield and enantioselectivity of **124a** improved to 80 % and 90 %, respectively.

The working model **127** was proposed[105] to account for the observed induction of enantioselective. The two bulky *tert*-butoxy groups are expected to occupy the two axial positions. One of the 3,3′-phenyl groups would effectively shield one face of the imine, and consequently, the diene attacks from the opposite side which is the *Re*-face when (*R*)-**126** was applied as the catalyst.

Our contribution to the development of catalytic enantioselective HDA reactions[106] of imines was initiated by the reaction of the *N*-tosyl α-imino ester **9a**[107] with the Danishefsky-type dienes **3a**, **b** in the presence of the chiral BINAP–copper(I) complexes **129** [Eq. (47)]. For the reaction of **9a** with **3b** catalyzed by **129b** (1 mol %), the *S* configuration of the *endo* diastereomer of the dimethyl-substituted HDA adduct **128** was obtained in 70 % yield, and up to 90 % *de* and 98 % *ee*.

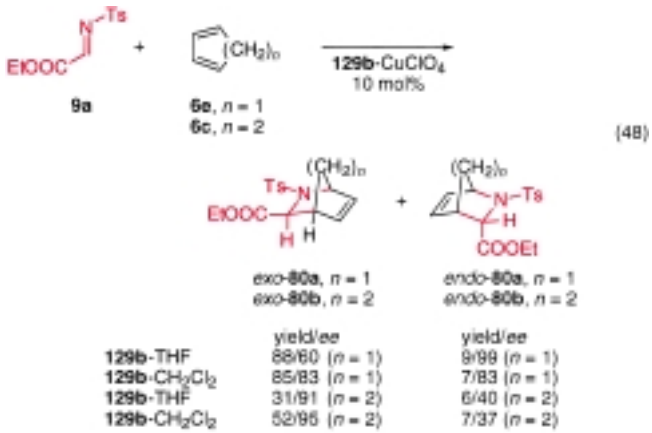


Further investigations of the reaction of the *N*-tosyl α-imino ester **9a** and other N-substituted α-imino esters **9b**–**e** have demonstrated that the metal complexes of the chiral phosphanyl-substituted oxazoline ligands **130a**–**j** are also good catalysts for especially the reaction of **9a** with Danishefsky's diene **3a**.[108] A combination of the chiral ligands **130a**–**j** and $CuClO_4$ (10 mol %) leads to the formation of **128** in high yield (up to 97 %) and with up to 86 % *ee*. This reaction is very tolerant to various solvents and proceeds well for nearly all the ligands.



a: Ar = Ph, R = Ph (*R*)
b: Ar = Ph, = *i*Pr (*S*)
c: Ar = Ph, R = *t*Bu (*S*)
d: Ar = *p*-Tol, R = *t*Bu (*S*)
e: (3a*R*,9b*S*), Ar = Ph
f: (3a*R*,9b*S*), Ar = *p*-Tol
g: (3a*R*,9b*S*), Ar = 2,4-xylyl
h: (3a*R*,9b*S*), Ar = Ph
i: (3a*R*,9b*S*), Ar = *p*-Tol
j: (3a*R*,9b*S*), Ar = 2,4-xylyl

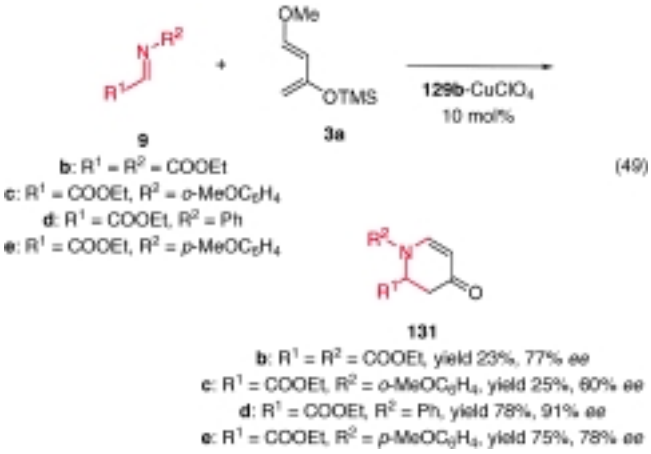
A significant improvement is that the reaction of the *N*-tosyl α-imino ester **9a** catalyzed by the chiral Tol-BINAP-Cu^I catalyst **129b** can proceed also with unactivated dienes.[108] The reaction of the cyclic dienes, cyclopentadiene (**6e**) and 1,3-cyclohexadiene (**6c**), in the presence of **129b** gave the useful HDA adducts *exo*-**80a** and *exo*-**80b** in good yield and enantioselectivity [Eq. (48)]. It was found that *exo*-**80a** is



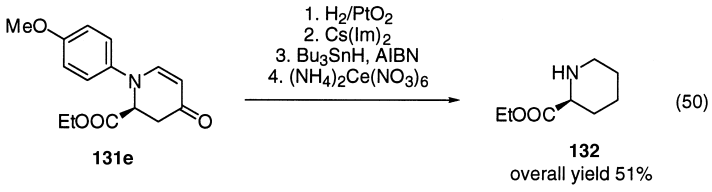
formed in 85 % yield and 83 % *ee*, while *exo*-**80b** is obtained by reaction with 1,3-cyclohexadiene in slightly lower yield, but with up to 95 % *ee*. This catalytic enantioselective approach opens up a new entry to the formation of the chiral fragment **78** which is a useful precursor for pharmaceutical important compounds (see Section 3.1.1.).

The catalytic enantioselective HDA reaction proceeds also for other types of dienes, and in several cases both HDA and ene adducts were formed. The catalytic ene reaction of the *N*-tosyl α-imino ester **9a** has been developed into a highly enantioselective reaction.[15]

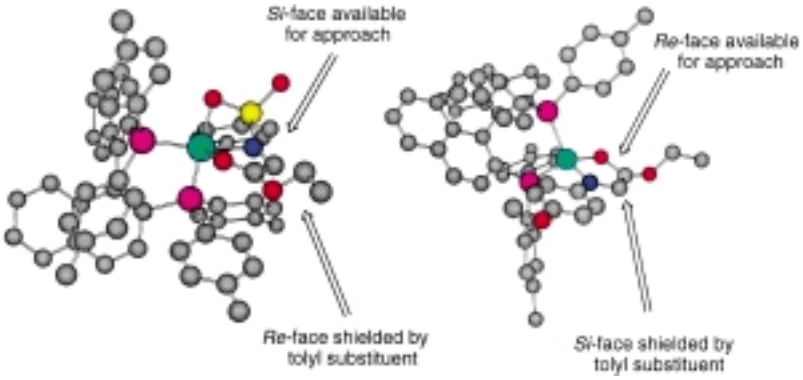
One of the drawbacks in using the *N*-tosyl α-imino ester **9a** is the removal of the *N*-tosyl substituent. This problem was solved by the introduction of other substituents which can be removed more easily.[108] The imines **9b–e** are substrates which react with Danishefsky's diene **3a** in the presence of the Tol-BINAP-Cu^{I} catalyst **129b**-Cu^{I} leading to the HDA adducts **131b–e** in moderate to good yields and enantioselectivities [Eq. (49)]. The imines **9a–c**, allow coordination to the catalyst by the *N*-substituent, while this is not possible for the **9d**, **e**. A by-product observed in some of the reactions is the Mannich-type product.



The HDA adduct **131e**, formed by using (*R*)-Tol-BINAP-$CuClO_4$ **129b**-Cu^{I} as the catalyst, can be applied for the formation of (*R*)-ethyl pipecolic ester **132** without loss of optical activity [Eq. (50); Im = imidazolide, AIBN = azobisisobutyronitrile].[108]



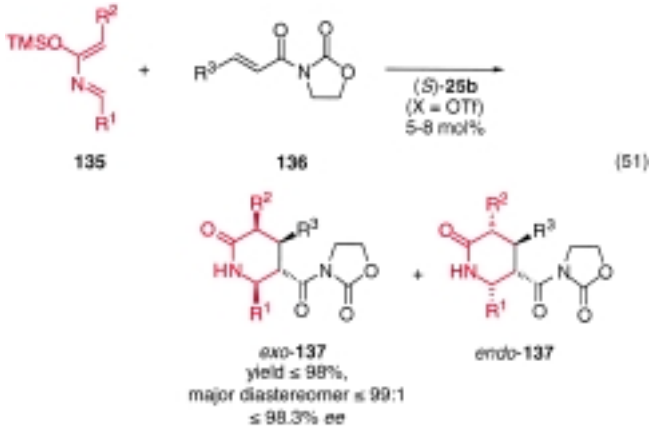
The HDA reaction of the imines **9a** and **9e** with the activated dienes catalyzed by the (*R*)-Tol-BINAP-$CuClO_4$ **129b**-Cu^{I} catalyst gave in the first case the *S* enantiomer and in the second case the *R* enantiomer, because the imines have two different binding modes to the catalyst. In the case of **9a**, the *N*-tosyl group can participate in the coordination to the chiral Lewis acid, while for **9e**, the *N*-*p*-methoxyphenyl substituent does not have this option. Based on the absolute configuration of the HDA adducts obtained in these reactions two different intermediates have been proposed.[108] For imine **9a** the glyoxylate carbonyl oxygen atom, the sulfonyl oxygen atom, and the imine nitrogen atom can coordinate to the catalyst leading to intermediate **133** (Scheme 18). For imine **9e**, a tetrahedral intermediate, **134**, in which the glyoxylate carbonyl oxygen atom and imine nitrogen atom coordinate to the catalyst, can account for the stereochemical outcome of the reaction.



Scheme 18. Structures of the intermediates **133** (left) and **134** (right).

It has also been demonstrated by Whiting et al.[109] that a variety of different combinations of chiral ligands and Lewis acids can catalyze the enantioselective HDA reaction of an imine similar to **9e** (methyl rather than ethyl) with Danishefsky's diene to give the corresponding HDA adduct. The highest enantiomeric excess being 97% using a combination of (1*S*,2*S*)-1,2-diphenylethylenediamine and MgI_2 as the catalyst.

The final catalytic enantioselective reaction to be discussed is the application of the BOX–copper(II) complex *t*Bu-BOX-CuX_2 (*S*)-**25b** (X = OTf) for the HDA reaction between 2-azadienes **135** and the dienophile **136** [Eq. (51)].[110] This



reaction, which was described by Jnoff and Ghosez, proceeds well for various substituted 2-azadienes to give *exo*-**137** as the major diastereomer in good yield and with up 98.3 % *ee*. This reaction affords a simple synthetic procedure for the formation of piperidones as the HDA adduct *exo*-**137a** can be converted to the piperidone **138** [Eq. (52)] in two steps (one-

pot process).[110] Based on the absolute configuration of the product obtained it was proposed that the reaction proceeds by a square-planar intermediate (see **31** for a related intermediate), in which the 2-azadiene approaches the less hindered face of the dienophile in an *exo*-fashion.

4. Summary and Outlook

The major developments of catalytic asymmetric HDA reactions of carbonyl compounds and imines have been presented. Various chiral catalysts are available for the different types of carbonyl compounds; for unactivated aldehydes chiral catalysts such as BINOL–aluminum(III), BINOL–titanium(IV), acyloxylborane(III), and tridentate Schiff base chromium(III) complexes can catalyze highly diastereo- and enantioselective HDA reactions. The mechanism of these reactions can be a stepwise pathway via a Mukaiyama-aldol intermediate or a concerted-like mechanism. For α-dicarbonyl compounds, which can coordinate to the chiral catalyst in a bidentate fashion, the chiral BOX–copper(II) complexes have shown very promising results. These complexes can catalyze HDA reactions of glyoxylates, α-keto esters, α-diketones, and ketomalonate with conjugated dienes leading to the HDA adducts in high yields and with very high diastereo- and enantioselectivities. In some cases it was possible to perform the reactions with very low catalyst loading. These normal electron demand reactions proceed via different structural intermediates depending on the chiral ligand. The chiral BOX–copper(II) complexes can also be used as catalysts for inverse electron demand HDA reactions of α,β-unsaturated carbonyl compounds with electron-rich alkenes, leading to a simple procedure for the formation 2-substituted 3,4-dihydro-*2H*-pyrans. These reactions proceed also in a highly selective manner and have been used for the synthesis of carbohydrates such as spiro carbohydrates, a β-D-manonose, and amino sugars.

For the corresponding HDA reactions of imines the main focus has been on diastereoselective reactions using imines derived from chiral carbonyl compounds, chiral amines, and chiral dienes. These reactions were catalyzed by different main group, transition, and lanthanide metal salts. In these reactions, the products are often formed in a highly diastereoselective manner and the use of these HDA reactions for the preparation of natural products has been presented. Furthermore, the mechanistic aspects of the reaction have been discussed, and diastereoselective reactions applying chiral catalysts have also been presented. A lot of effort has been devoted to the development of catalytic enantioselective HDA reactions of imines, but only a few successful reactions have been published. Chiral BINOL–ytterbium(III)-amine complexes can catalyze highly diastereo- and enantioselective reactions between *ortho*-hydroxy-substituted phenyl imines and activated dienes. BINAP- and phosphanyl-substituted oxazoline copper(I) complexes are useful as catalyst for an enantioselective HDA reaction of activated imines with activated and unactivated dienes. The chiral BOX–copper(II) complexes can also catalyze enantioselective HDA reactions of 2-azadienes.

What new developments will the beginning of this century bring us in the field of catalytic enantioselective HDA reactions of carbonyl compounds and imines? Hopefully, new catalysts leading to higher turnover numbers and higher selectivity. For the imines we are still in the beginning of the synthetic development and much work is required to reach the same level of selectivity as now available for carbonyl compounds.

We are only beginning to understand the fundamental role of the catalyst in these reactions—why are there such great differences in reaction course, selectivity, etc., when different metals containing the same chiral ligand are used for the same reaction? Mechanistic insight into these reactions will be of utmost importance in order to unveil the wonders and magic of catalysis that will allow us to take the next important steps in the fascinating world of the Diels–Alder chemistry.

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