1
Asymmetric Catalysis of Diels–Alder Reaction

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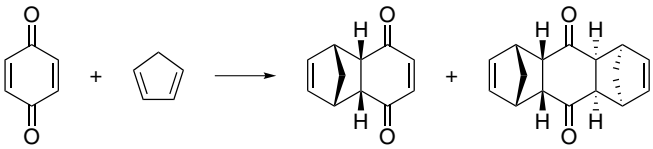
1.1
Introduction

The Diels–Alder (DA) reaction (or "diene synthesis") between a diene and a dienophile generates two σ bonds stereoselectively and up to four chiral centers in a single step to afford six-membered cyclic compounds. This cycloaddition reaction named after Professor Otto Paul Hermann Diels (1876–1954) and his student Kurt Alder (1902–1958) was discovered in 1928 during studies on the reaction of benzoquinone with cyclopentadiene (Scheme 1.1) [1, 2], and has become an extremely useful and classic methodology in organic synthesis. For their discovery, Diels and Alder received the Nobel Prize in chemistry in 1950. Since this landmark discovery, great progress in the area has been achieved and the historical development for the past 80 years can be divided into three periods: (i) from the discovery to the 1950s, the studies mainly focused on the substrate scope and mechanism research, and one of the representative works was the Alder endo rule; (ii) from the 1950s to the 1970s, the DA reaction was successfully applied to the total synthesis of many complex molecules, and two important theories [molecular orbital theory (Woodward-Hoffmann rule) and frontier orbital theory (Kenichi Fukui)] were applied to explain the mechanism; (iii) from the 1980s to the present day, the exploration and application of an enantioselective version of DA reactions have attracted tremendous interest from chemists [3].



Scheme 1.1 The discovery of DA reaction.

Different types of DA reactions have been extensively reviewed, such as intramolecular DA reactions [4], dehydro-DA reactions [5], enzymatic catalysis of DA

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reactions [6], Lewis acid catalyzed enantioselective DA and the hetero Diels-–Alder (HDA) reaction [7], organocatalysis of the DA and HDA reactions [8], DA reaction in aqueous media and so on [9]. For enantioselective DA reactions, chiral catalysts play a key role in the reactivity and enantioselectivity. In this chapter we will mainly discuss the development of chiral catalysts, including metal-based chiral Lewis acids and organocatalysts for DA and oxa HDA reactions, as well as their applications in the synthesis of natural products and biologically important compounds. The catalytic asymmetric aza Diels–Alder reaction is comprehensively reviewed in the following chapter by Kobayashi and will not be included here.

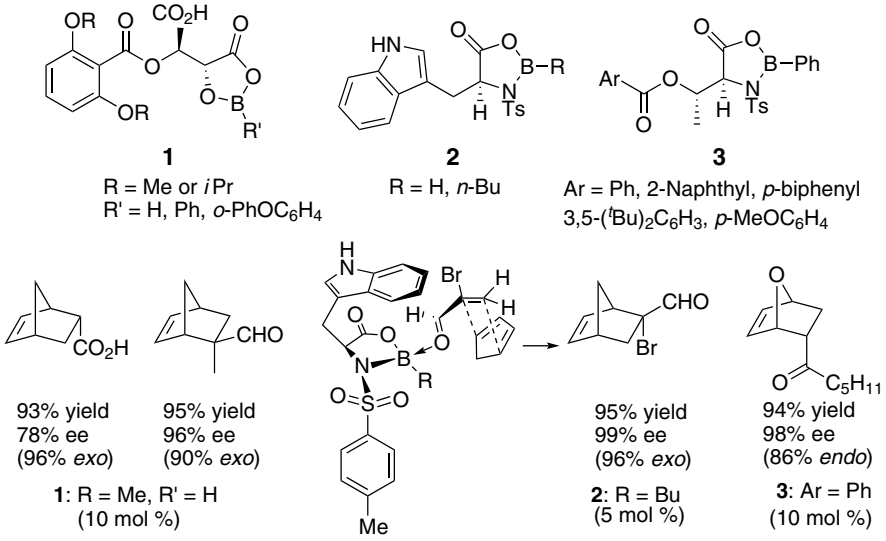
1.2
Asymmetric Diels–Alder Reaction

1.2.1
Lewis Acid Catalyzed Asymmetric Diels–Alder Reaction

Chiral Lewis acid catalyzed asymmetric reactions represent the most powerful methods to afford optically active compounds. For DA reactions, many excellent results have been achieved by applying various chiral Lewis acids as catalysts. In the following section, the development of catalytic asymmetric DA reactions will be highlighted, based on the category of Lewis acid catalyst.

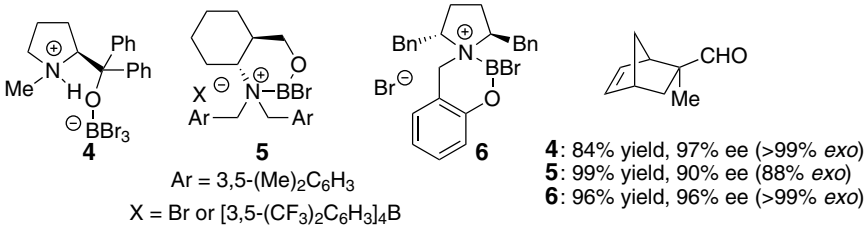
1.2.1.1 Chiral Boron, Aluminum, and Indium Complexes

Chiral Boron Complexes In the field of asymmetric DA reactions, chiral boron complexes are among the most effective catalysts and have been thoroughly investigated [10]. In 1988, Yamamoto's group reported an efficient chiral (acyloxy) boron catalyst **1** (CAB) for the DA reaction between acrylic acid and cyclopentadiene to give the corresponding adduct in 93% yield and 78% ee (Scheme 1.2), which demonstrated for the first time the possibility of achieving useful enantioselectivities for DA reactions of simple dienophiles with a simple chiral controller ligand [11a]. Further expanding the substrate scope to α,β-unsaturated aldehydes and cyclic or acyclic dienes [11b] and studies on the mechanism [11c] make this catalyst more practical. In 1991, Corey and coworkers envisaged the possibility that the (*S*)-tryptophan-derived chiral oxazaborolindione **2** would facilitate the Diels–Alder pathway represented by the transition-state assembly (Scheme 1.2) through attractive interaction as well as the usual steric repulsion, and this surmise was confirmed by the reaction of cyclopentadiene and 2-bromoacrolein, affording the corresponding cycloadduct in 95% yield and 99% ee with the desired absolute configuration (Scheme 1.2) [12]. *Allo*-Threonine derived catalysts **3** were recently reported by Harada's group to catalyze the DA reactions of a variety of enone dienophiles with dienes, including cyclic, acyclic dienes or furan, in high yields, good diastereoselectivities and excellent enantioselectivities (Scheme 1.2) [13].



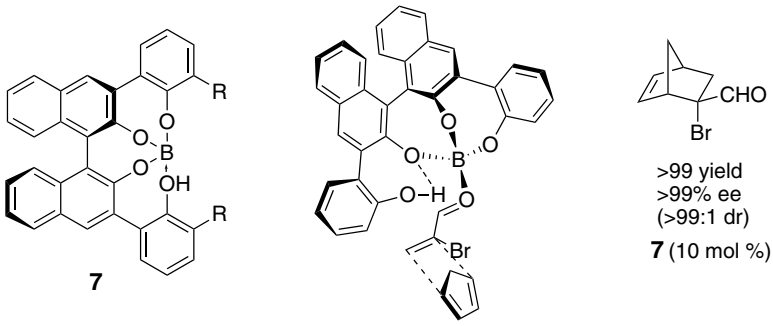
Scheme 1.2 Selected examples for enantioselective DA reactions catalyzed by **1–3**.

Cationic boron catalyst was found to be very effective for the asymmetric DA reaction due to its strong acidic property. Kobayashi's group and Aggarwal's group independently employed the chiral boron complex **4** (20 mol%) containing Lewis acid and Brønsted acid units as catalyst for the cycloaddition reaction between methacrolein and cyclopentadiene, up to 97% ee of the adduct was obtained (Scheme 1.3) [14]. In 1996, Corey's group developed a chiral super-Lewis acidic catalyst, excellent results (up to 98% ee) were obtained for the reaction of both active and inactive 1,3-dienes under the catalysis of **5** (10 mol%) [15a], and a similar catalyst **6** was developed in 2003 [15b].



Scheme 1.3 Selected examples for enantioselective DA reactions catalyzed by **4–6**.

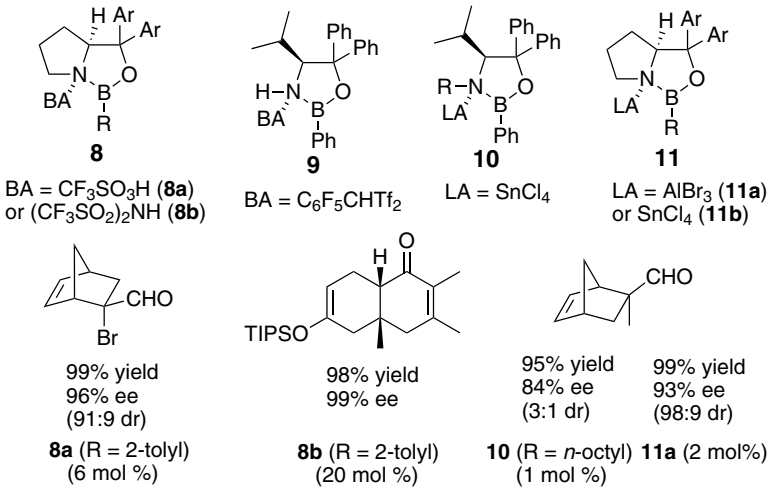
Great progress for catalytic asymmetric DA reactions has been achieved using boron complexes by introducing a Brønsted acid or Lewis acid to assist or activate chiral boron complexes (Scheme 1.4). Yamamoto's group made pioneering contributions to this field [16]. In 1994, Yamamoto designed a chiral boron catalyst **7** via intramolecular Brønsted acid activation, and excellent reactivities and enantioselectivities were afforded for the reactions between α,β-unsaturated aldehydes and dienes (Scheme 1.4) [16a]. Later, a series of Brønsted-assisted Lewis acid (BLA)



Scheme 1.4 Enantioselective DA reaction catalyzed by BLA catalyst.

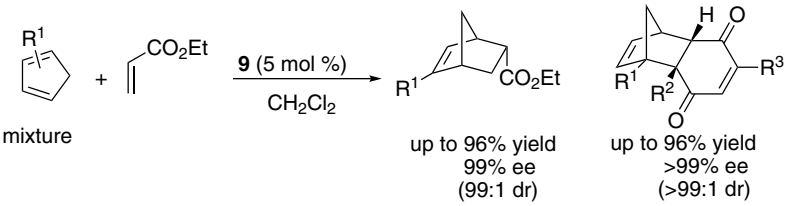
catalysts were further synthesized and subjected to the asymmetric DA reactions. Intramolecular Brønsted acid was found to play an important role in accelerating the rate of DA reactions and in achieving a high level of enantioselectivity, due to intramolecular hydrogen bonding interaction and attractive π–π donor–acceptor interaction in the transition-state assembled by hydroxy aromatic groups in a chiral BLA catalyst (Scheme 1.4) [16b, c].

In 2002, Corey and coworkers developed a powerful chiral Lewis superacid **8a** which was easily generated from commercially available amino alcohol by condensation with an aryboroxine to afford an oxazaborolidine, followed by subsequent activation with triflic acid. Complex **8a** was found to be highly effective for the DA reactions of a variety of α,β-unsaturated aldehydes, ketones, and esters (Scheme 1.5). In order to avoid the decomposition of catalyst **8a**, triflimide was employed to generate a more stable catalyst **8b**. Under the catalysis of **8b**, DA reaction of a wide range of dienophiles, including diethyl fumarates, acrylate, enones and quinones, with cyclic or acyclic dienes gave the corresponding products in very high yields and ees (Scheme 1.5) [18].



Scheme 1.5 Selective results for DA reactions catalyzed by **8–11**.

Yamamoto and coworkers reported the first regio- and enantioselective DA reactions of 1- and 2-substituted cyclopentadienes using Brønsted acid activated chiral oxazaborolindine **9** as catalysts. In the reactions of 1- and 2-substituted cyclopentadiene mixtures with ethyl acrylate, only 2-subsitituted cyclopentadienes were found to be reactive, giving the corresponding products in high yields and ees (Scheme 1.6). A one-pot procedure for the preparation of the cycloadduct containing adjacent all-carbon quaternary stereocenters was also successfully achieved, whereby excess ethyl acrylate was employed to consume all the 2-substituted cyclopentadiene, and a more active dienophile (quinone) was added subsequently to react with the remaining 1-substituted cyclopentadiene [19].

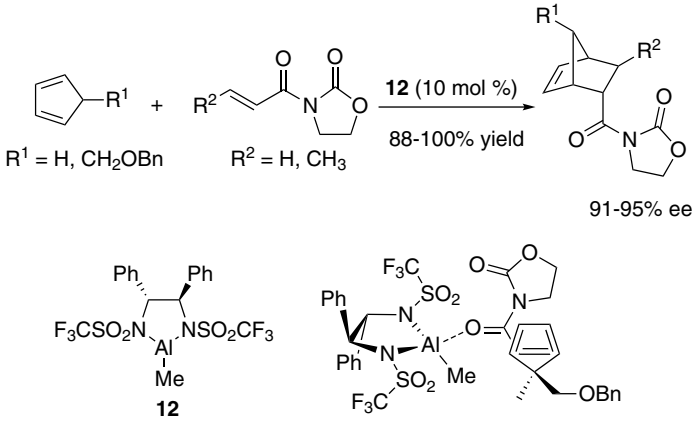


Scheme 1.6 Enantioselelective DA reactions catalyzed by **9**.

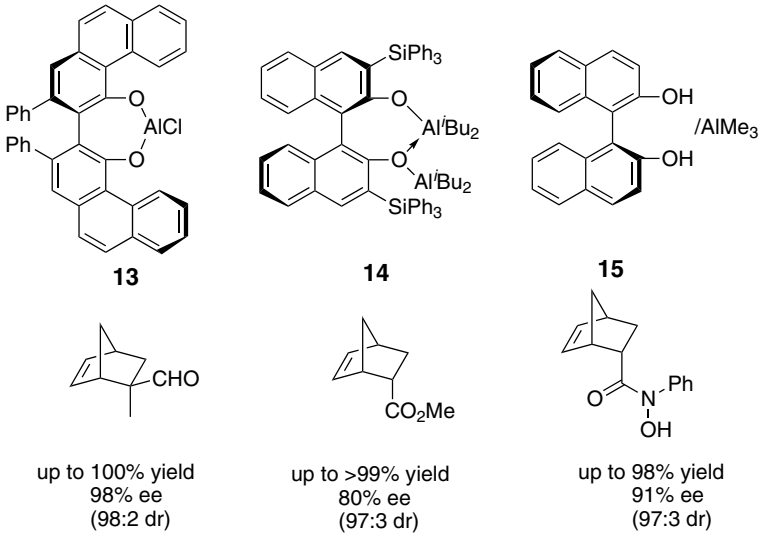
In 2005, Yamamoto and coworkers utilized a Lewis acid to activate chiral oxazaborolidine for asymmetric DA reactions and a type of moisture-tolerant catalysts **10** was developed. This catalyst system was effective for the reactions of a variety of dienophiles, including α,β-unsaturated aldehydes, esters, enones and quinones, affording the corresponding cycloadducts with a high level of reactivities and enantioselectivities (Scheme 1.5) [20a]. Corey's group also found that $AlBr_3$ could activate oxazaborolidine to generate useful catalysts **11a** for DA reactions of a very wide range of dienophiles and dienes (Scheme 1.5) [20b]. Very recently, Paddon-Row and coworkers reported the first computational investigations for oxazaborolidine catalyzed asymmetric DA reactions, which is very helpful for understanding the mechanistic aspects for the boron catalysts and the related transition state [20c].

Chiral Aluminum and Indium Complexes Corey's group reported a highly enantioselective DA reaction using a chiral aluminum complex **12** (10–20 mol%) derived from diamide ligand as catalyst, up to 95% ee of the adducts was obtained. Transition-state assembly was proposed and the absolute stereopreference in this DA reaction was believed to be the result of catalyst **12** binding to the acrylyl carbonyl of the dienophile at the lone pair anti to nitrogen, fixing the acrylyl group in the s-*trans* conformation (Scheme 1.7) [21]. Chiral aluminum complexes of biaryl ligands have also been exploited in asymmetric DA reactions. Wulff and coworkers developed catalyst **13** (0.5–10 mol%) derived from VAPOL, which was highly efficient for the reactions of cyclopentadiene and 2-methacrolein to give the *exo* cycloadduct in up to 100% yield with 98% ee (Scheme 1.8) [22]. In 2001, Yamamoto's group employed multinuclear chiral aluminum Lewis acids **14** (5–10 mol%), easily generated from the reaction of organoaluminum reagents with optically pure binaphthol derivatives, for DA reactions of cyclopentadiene and methyl acrylate, moderate to good enantios-

electivies (Scheme 1.8) were attained [23]. Recently, Renaud and coworkers utilized hydroxamic acids as templates for chiral aluminum promoted enantioselective DA reactions, a stoichiometric amount of complex **15** was required in order to get high yields and enantiomeric excess of the adduct (Scheme 1.8). Facile coversion of the products to the corresponding alcohols or aldehydes makes the hydroxamic acid intermediates particularly useful [24].



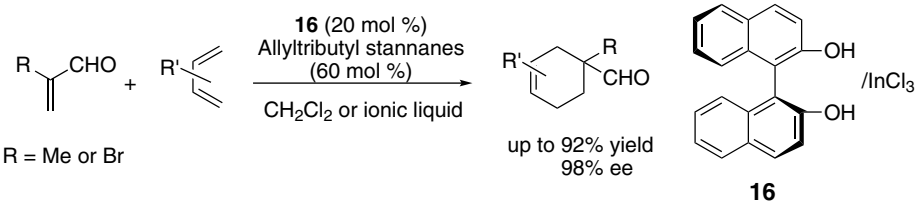
Scheme 1.7 Enantioselective DA reactions catalyzed by chiral aluminum complex **12**.



Scheme 1.8 Chiral aluminum complexes for DA reactions.

In 2005, Loh's group reported the first chiral indium complex **16** catalyzed asymmetric DA reactions [25a], in which allyltributylstannane was added to regenerate active chiral BINOL-In-allyl catalyst. The cycloaddition of a wide variety of cyclic or acyclic dienes with 2-methacrolein or 2-bromoacrolein gave the corresponding adducts in good yields and excellent enantioselectivities (Scheme 1.9).

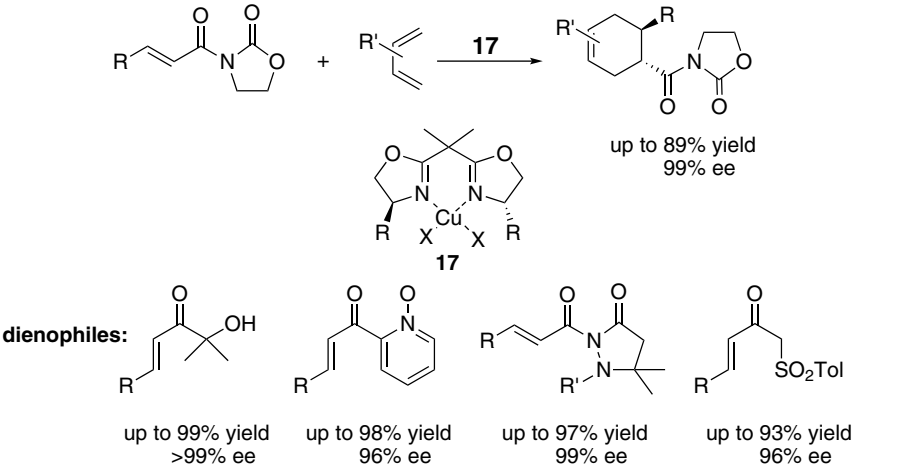
In particular, the procedure is operationally simple and the catalyst can be easily prepared from commercially available chemicals at ambient temperature. This chiral indium catalyzed enantioselective DA reaction was also performed in ionic liquid, and catalysts could be recycled and reused for seven times without significant loss of reactivities and enantioselectivities [25b].



Scheme 1.9 Chiral indium catalyzed enantioselective DA reaction.

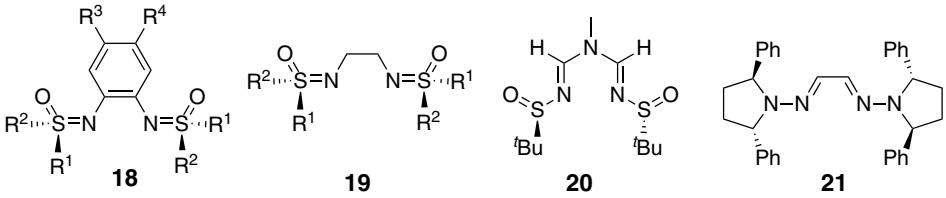
1.2.1.2 Chiral Copper, Magnesium, and Zinc Complexes

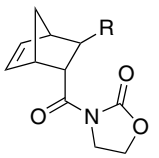
Chiral Copper Complexes Fruitful and excellent results for asymmetric DA reactions have been achieved under the catalysis of copper(II) complexes, and nitrogen-containing ligands are the most often used ligands [26]. Evans and coworkers demonstrated for the first time that bis(oxazoline)-copper(II) complex **17** could act as a Lewis acid to promote the enantioselective DA reaction of acryloyl-2-oxazolidinones and cyclopentadiene. Systematic investigation of the counterion effect, substrate scope, transition state model and synthetic applications was also carried out. It was disclosed that counterion structure and chelating dienophiles are critically important for this reaction [27]. The asymmetric DA reactions for substrates bearing other chelating templates (Scheme 1.10) catalyzed by **17** (1–16 mol%) have also been successfully achieved recently [28].



Scheme 1.10 Chiral oxazoline copper catalyzed DA reaction.

Bolm's group reported that C_2-symmetric bissulfoximines **18**, **19**/Cu(OTf)$_2$ complexes (10 mol%) catalyzed enantioselective DA reactions between cyclopentadiene and acryloyl-2-oxazolidinones, up to 93% ee of the adduct was obtained (Scheme 1.11) [29]. Further spectroscopic investigation of bissulfoximine copper (II) complexes indicated that the chiral ligand and the dienophile form a tetragonally distorted complex in CH_2Cl_2. The ligand binds to the Cu(II) center via the imine nitrogens, whereas the dieophile interacts via the carbonyl oxygen atoms [29b]. Ellman and coworkers developed analogous bis(sulfinyl)imidoamidine ligands **20** through a modular synthesis from readily available building blocks for Cu(II) catalyzed enantioselective DA reactions, providing a high level of asymmetric induction with 10 mol% of **20**/Cu(SbF$_6$)$_2$ (Scheme 1.11). Notably, the Cu(II) ligand complex exists as a unique M_2L_4 helicate in the solid state, and predominately coordinates via the sulfin oxygen in a solution of **20** [30a]. In 2004, Lassaletta *et al.* utilized chiral bis-hydrazones **21** as the ligands for Cu(OTf)$_2$-catalyzed DA reactions, the corresponding cycloadducts were obtained in good yields and enantioselectivities (Scheme 1.11) [30b].



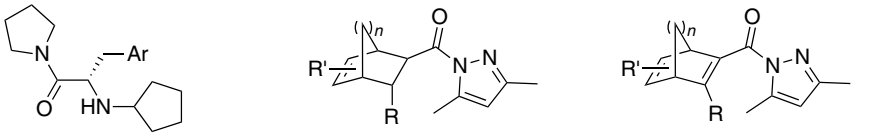


18: up to 98% yield, 93% ee (85:15 dr)
19: up to 98% yield, 83% ee (94:6 dr)
20: up to 96% yield, >98% ee (>99:1 dr)
21: up to 90% yield, 95% ee (98:2 dr)

Scheme 1.11 Enantioselective DA reaction catalyzed by **18–21**/Cu(II).

Ishihara's group designed a small-molecule artificial metalloenzyme which was prepared *in situ* from L-DOPA derived monopeptide **22** (2.2–11 mmol%) and Cu(OTf)$_2$ or Cu(NTf$_2$)$_2$ (2–10 mol%) for the enantioselective DA reactions between α,β-unsaturated 1-acyl-3,5-dimethylpyrazoles and cyclopentadienes. This biomimetic catalytic system provided the corresponding cycloadducts in good yields with excellent enantioselectivities. The authors suggested that the existence of intramolecular cation–π interaction in [**22a**·Cu(II)](OTf)$_2$ might be very important for controlling the conformation of sidearms in chiral ligands (Scheme 1.12) [31a]. Very recently, asymmetric DA reactions of propiolamide derivatives and cyclopentadienes catalyzed by **22b**/Cu(NTf$_2$)$_2$ (10 mol%) have been successfully realized in excellent yields and enantioselectivities [31b]. In the field of Cu(II)-catalyzed DA reactions, DNA-based Cu(II) catalysts (5–30 mol%) have also been successfully developed

by Feringa *et al.*, and excellent enantioselectivities (up to 98%) were attained [32]. The asymmetric induction in this catalytic system arises completely from the chirality of the DNA template.



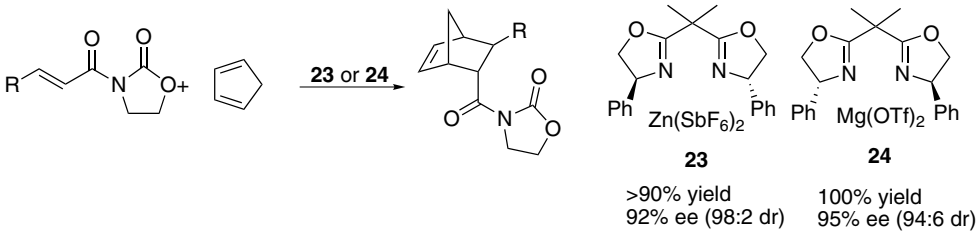
22a: Ar = 3,4-$(MeO)_2C_6H_3$, **22b:** 2-naphthyl

22a/$Cu(OTf)_2$ or $Cu(NTf_2)_2$: 76->99%yield (87-98% ee) (88->99% *endo*)

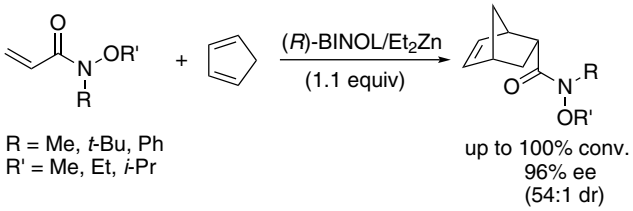
22b/$Cu(NTf_2)_2$: 22-91% yield (89-96% ee)

Scheme 1.12 Chiral monopeptide ligand for Cu(II)-catalyzed DA reactions.

Chiral Zinc and Magnesium Complexes In 1996, Evans and coworkers discovered that chiral bis(oxazoline)-Zn(II) complex was an effective catalyst for the enantioselective DA reaction and the counterion was found to be critical for this reaction, 92% ee of the adduct was achieved using **23** (10 mol%) as catalyst (Scheme 1.13) [27c,33a]. Chiral bis(oxazoline)-Mg(II) complex **24** (10 mol%) with 2 equiv of H_2O or tetramethylurea as auxiliary ligands has also proven to be an effective catalyst for the DA reaction with good yields and excellent enantioselectivities (Scheme 1.13) [33b,c,d]. In 2002, Renaud's group reported enantioselective DA reactions of cyclopentadiene and *N*-alkoxyacrylamides using a stoichiometric amount of BINOL-Zn complex prepared from BINOL and Et_2Zn, the corresponding adducts was obtained in up to 96% ee (Scheme 1.14) [33e].



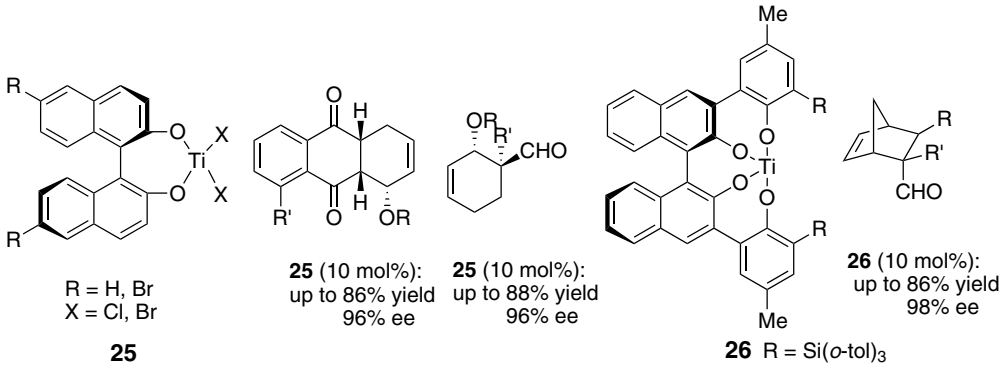
Scheme 1.13 Chiral bis(oxazoline)/Cu(II)-catalyzed DA reaction.



Scheme 1.14 BINOLate zinc catalyzed DA reaction.

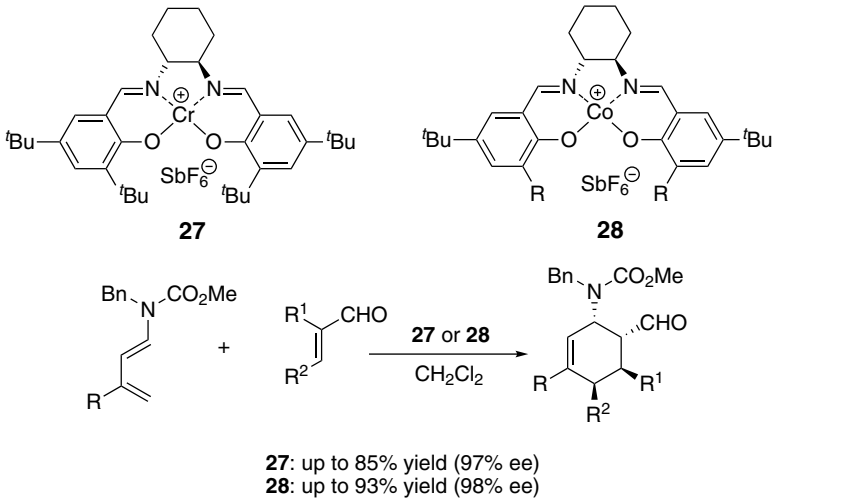
1.2.1.3 Chiral Transition Metal Complexes

Chiral Titanium Complexes Mikami and coworkers reported an asymmetric DA reaction between naphthoquinone and 1-methoxylbutadiene catalyzed by chiral titanium complexes **25** (R = H, X = Cl, 10 mol%) (Scheme 1.15) generated from BINOL and $Ti(O^iPr)_2Cl_2$ in the presence of molecular sieves (MS), affording a single endo stereoisomer in 85% ee. This approach has provided a potential entry to the asymmetric synthesis of anthracycline antibiotics [34a]. Further studies showed the DA reactions of 5-hydroxynaphthoquinone (juglone) with butadienyl acetate using a MS-free catalyst **25** afforded the corresponding cycloadduct in up to 96% ee (Scheme 1.15). However, only 9% ee was obtained in the presence of MS [34b]. Employing the same catalysts for enantioselective cycloaddition of methacrolein to alkoxyadiene gave the corresponding products in good yields and ees (Scheme 1.15) [34b,c]. Yamamoto's group developed an alternative chiral helical titanium complex (**26**, Scheme 1.15) and applied this type of catalyst in enantioselective DA reactions of cyclopentadienes with methacrolein derivatives, affording the corresponding products in up to 86% yield with 98% ee (Scheme 1.15) [34d].



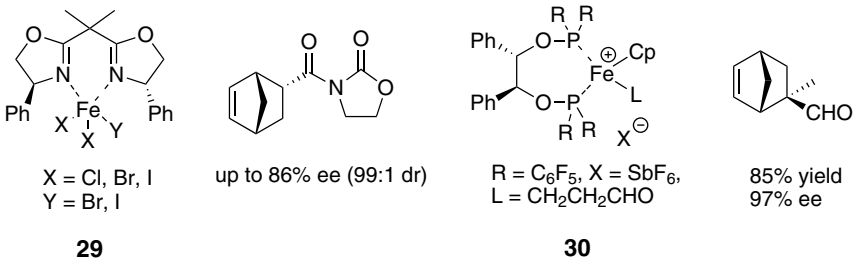
Scheme 1.15 Chiral titanium complex catalyzed DA reaction.

Chiral Chromium and Cobalt Complexes Rawal's group achieved a highly enantioselective DA reaction of substituted 1-amino-1,3-butadienes and methacrolein by the catalysis of Jacobsen's salen-Cr(III) complex **27** (5 mol%) in the presence of 4 Å MS in CH_2Cl_2, affording the corresponding highly functionalized cyclohexene derivatives having a quaternary chiral center with excellent yields and ees (Scheme 1.16). The high endo-selectivity of the DA reaction and the substituents at the 1-position of the diene were found to be very important for the success of this process [35]. Salen-Co(III) complexes **28** have also proven to be highly efficient for the same reaction, and as low as 0.05 mol% catalyst loading was enough to achieve high yield (93%) and enantioselectivity (98%) of the reaction (Scheme 1.16). Importantly, the reactions are conveniently carried out at room temperature, under an air atmosphere, and with minimal solvent. These conditions are highly desirable for industrial applications [36].



Scheme 1.16 Salen-chromium and Salen-cobalt catalyzed DA reaction.

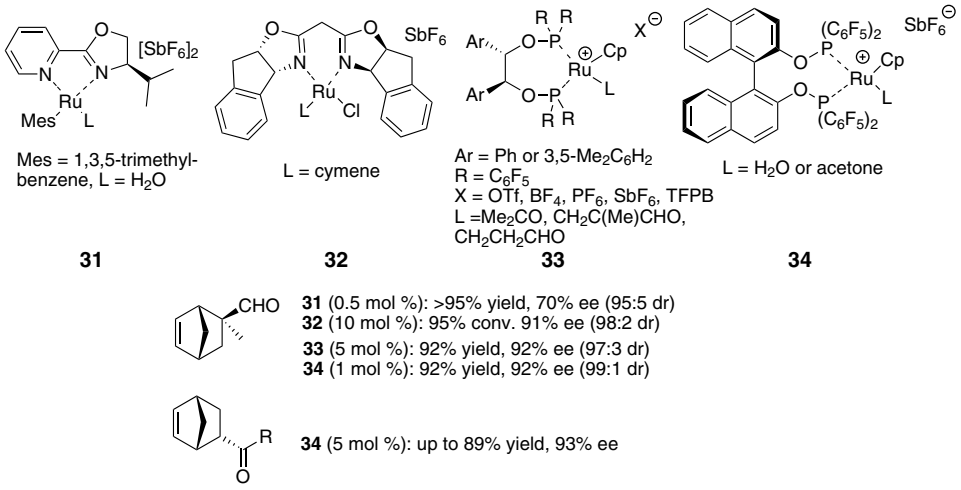
Chiral Iron Complexes In 1991, Corey and coworkers employed chiral bis(oxazoline)/Iron(III) complexes **29** (10 mol%) (Scheme 1.17) as the catalysts for enantioselective DA reactions of cyclopentadiene and 3-acryloxyl-1,3-oxazolindin-2-one, the corresponding cycloadduct was obtained in 86% ee with 99 : 1 endo/exo selectivity. The chiral ligand was readily and efficiently recoverable from the reactions for reuse. The ready availablility of chiral ligand combined with the low cost of iron salts make this methodology potentially useful for practical application [37a]. Kündig's group developed chiral cyclopentadienyl-iron(III) complexes **30** bearing electron-poor phosphine ligands as catalysts (5 mol%) for cycloaddition of 2-methacrolein and cyclopentadiene in CH_2Cl_2, the corresponding product was afforded in 85% yield and 97% ee (Scheme 1.17) [37b].



Scheme 1.17 Chiral iron(III) complex catalyzed DA reaction.

Chiral Ruthenium Complexes Davies and coworkers discovered that chiral arene ruthenium complexes **31** were highly efficient for the DA reaction between methacrolein and cyclopentadiene with only 0.5 mol% catalyst loading. The reaction proceeded rapidly at room temperature (0.25 h) to give the corresponding cycload-

duct in high yield and ee value with good *exo* selectivity (Scheme 1.18) [38]. Faller's group prepared chiral bis(oxazoline) ligand modified ruthenium(II) complexes **32** and subjected this type of complex to the reaction of methacrolein and cyclopentadiene, up to 91% ee value and 98% *exo* selectivity were achieved (Scheme 1.18) [39a]. The same group also reported enantioselective DA reactions with the racemic Ru/BINAP-monoxide complex using proline or prolinamide as a chiral poisoning agent [39b]. Since 2001, Kündig's group has developed a series of chiral ruthenium catalysts (**33** and **34**) containing bidentate phosphine ligands and systematically investigated their application in enantioselective DA reactions of cyclopentadiene derivatives with methacrolein or α,β-unsaturated ketone. The corresponding adducts have been obtained in good yields with excellent diastereoselectivities and enantioselectivities (Scheme 1.18). Notably, this group reported the first example of a one-point binding transition metal Lewis acid catalyst capable of coordinating and activating an α,β-unsaturated ketone for enantioselective DA reactions [37b, 40]. Other transition metal complexes such as rhodium [41a], palladium [41b], and iridium [41c] have also been applied to asymmetric DA reactions.

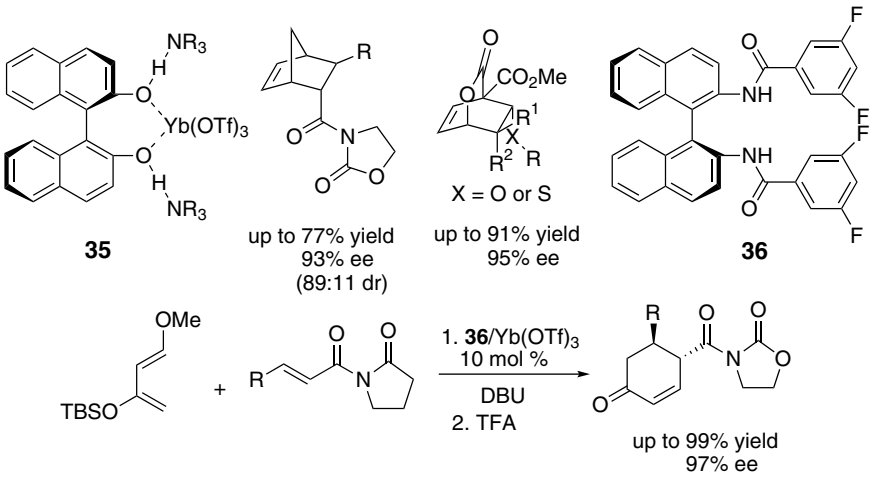


Scheme 1.18 Enantioselective DA reaction catalyzed by chiral ruthenium complexes.

1.2.1.4 **Chiral Rare Earth Metal Complexes**

In 1994, Kobayashi's group reported that enantioselective DA reaction of 3-acryl-1,3-oxazolindin-2-ones with cyclopentadienes using chiral ytterbium triflate catalyst (20 mol%) generated from BINOL, $Yb(OTf)_3$ and tertiary amine yielded endo adducts as the major isomers in up to 93% ee (Scheme 1.19). Other lanthanide (Lu, Tm, and Er) triflate complexes of BINOL were also found to be effective catalysts for the same reaction [42a]. Tertiary amines played a key role for both diastero and enantioselectivities, and *cis*-2,6-dimethyl-*N*-methylpiperidine proved to be the best additive. Most interestingly, both enantiomers are afforded with the same catalysts by addition or without addition of 1,3-diketones as achiral ligands [42a, b]. Markó

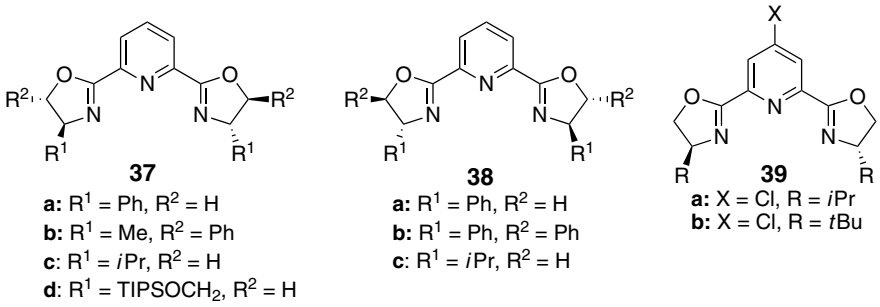
and coworkers successfully developed an asymmetric inverse electron-demand DA reaction of 3-carbomethoxy-2-pyrone derivatives and electron-rich dienophiles using **35** (20 mol%) as catalysts. The corresponding cycloadducts were obtained in up to 95% ee; they are key intermediates for the preparation of complex polycyclic compounds [43]. Very recently, Nishida and coworkers reported the first highly enantioselective DA reaction of electron-rich Danishefsky's diene with electron-deficient alkenes under the catalysis of complex **36**/$Yb(OTf)_3$ in the presence of DBU as the additive (Scheme 1.19). Remarkable (+)-nonlinear effects observed in this catalytic system suggested the possibility of the formation of a reservoir of nonreactive aggregates in the reaction system [44].



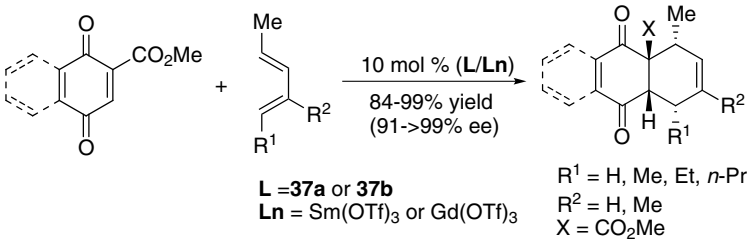
Scheme 1.19 Enantioselective DA reaction catalyzed by chiral lanthanide complexes.

Chiral 2,6-bis(oxazolidinyl) pyridines (pybox) were found to have a wide range application for lanthanide-catalyzed DA reactions (Scheme 1.20). In 2001, Furuzawa's group discovered that isopropyl-pybox (**37c**)/$Sc(OTf)_3$ complex (10 mol%) could catalyze the enantioselective DA reaction of acyl-1,3-oxazolidin-2-one with cyclic or acyclic dienes, yielding the corresponding products in good enantioselectivities (up to 90% ee). This reaction was also performed in less toxic benzotrifluoride and supercritical carbon dioxide, giving the products with good selectivity (65–75% ee) [45a]. Desimoni and coworkers also contributed a lot of effort on the pybox/lanthanide-catalyzed DA reactions [45b–f]. Under the catalysis of **38b**/$Eu(OTf)_3$ *exo* products were obtained for the reaction of acyl-1,3-oxazolidin-2-one with cyclopentadiene in 52% yield and >99% ee. The high enantioselectivity was attributed to the presence of a phenyl group at the 5-position of **38b** [45b]. Further studies showed that MS [45c], substitutents of pybox [45c–f], and lanthanide cations [45c–f] significantly affected both reactivities and enantioselectivities of the reaction. Xiao and coworkers investigated the impact of the electronic and steric properties of **38** on the enantioselectivity of the DA reaction of acyl-1,3-oxazolidin-2-one with cyclopentadiene, up to 96% ee of the corresponding cycloadduct was achieved under the catalysis of **39b**/$Sc(OTf)_3$

(5 mol%) [46]. In 2003, Evans and coworkers reported that chiral samarium and gadolinium complexes generated from pyridyl-bis(oxazoline) ligands (**37a** and **37b**) were able to catalyze enantioselective DA reaction of quinone with substituted 1,3-dienes, affording the corresponding products with excellent diastereoselectivities and enantioselectivities (Scheme 1.21). The absence of a nonlinear effect in this system suggested that neither catalyst aggregation nor dimer formation was occurring [47].



Scheme 1.20 Representative pybox Ligands for lanthanides-catalyzed DA Reactions.



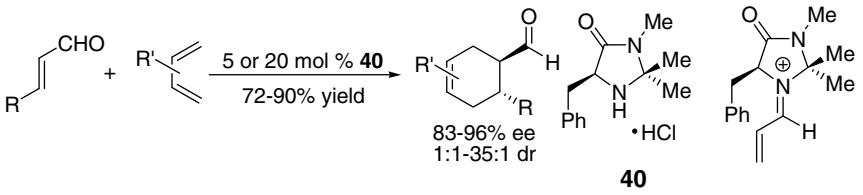
Scheme 1.21 Enantioselective DA reaction catalyzed by chiral lanthanide complexes.

1.2.2
Organocatalysis of Asymmetric Diels–Alder Reaction

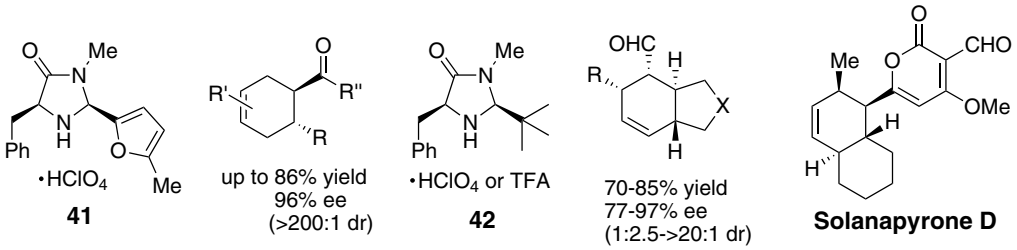
1.2.2.1 Chiral Secondary Amine Catalyzed Asymmetric Diels–Alder Reaction

Metal-based chiral Lewis acids have dominated the field of asymmetric catalysis for over 30 years, while organocatalysis emerging just in the last decade has been attracting extensive interest from chemists. In 2000, MacMillan's group reported the first highly enantioselective DA reaction of α,β-unsaturated aldehydes with 1,3-dienes under the catalysis of chiral secondary amine catalyst **40** (Scheme 1.22). The LUMO-lowering activation of aldehyde with amine to form reversible iminium ion intermediate (Scheme 1.22) provided great opportunities for exploring a novel asymmetric catalysis system [48]. Later, the chiral secondary amine catalyzed enantioselective DA reaction via iminium intermediate was thoroughly investigated by searching for new efficient catalysts and broadening the substrate scope. In 2002, MacMillan and coworkers successfully extended their work from α,β-unsaturated

aldehydes to ketones with a modified catalyst **41** (20 mol%) (Scheme 1.23) [49]. The same group also developed the first organocatalytic intramolecular DA reaction under the catalysis of **42** (20 mol%), and completed the total synthesis of marine metabolite solanapyrone D in six steps based on the developed methodology (Scheme 1.23) [50].

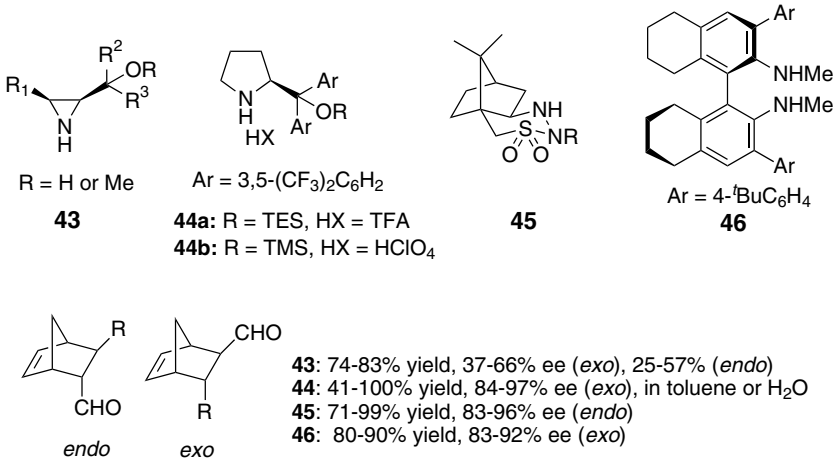


Scheme 1.22 The first organocatalysis of asymmetric DA reaction.



Scheme 1.23 Enantioselective DA reaction catalyzed by chiral secondary amine **41–42**.

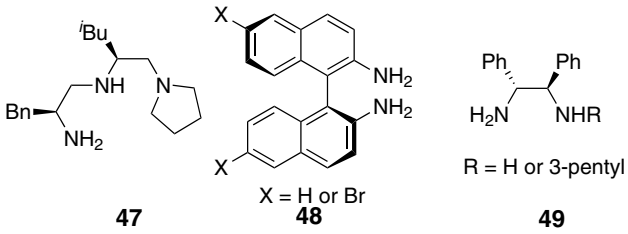
In 2001, Bonni's group developed the HCl or $HClO_4$ salt of chiral aziridine **43** for catalysis of asymmetric DA reactions, moderate enantioselectivities with almost 1 : 1 diastereoselectivities were obtained (Scheme 1.24) [51]. Hayashi and coworkers found that **44a**, a trifluoroacetic acid (TFA) salt of diarylprolinol silyl ether, was an efficient organocatalyst for *exo*-selective DA reactions of α,β-unsaturated aldehydes with cyclopentadiene in toluene, up to 97% ee was achieved [52a]. Very recently, the same group successfully developed a practical procedure for enantioselective DA reaction using water as a solvent under the catalysis of **44a**. It was interesting to find that water could significantly accelerate the reaction and obviously improve the enantioselectivity of the catalysis [52b]. In 2008, Lee and coworkers discovered that camphor-derived sulfonyl hydrazines **45** (20 mol%) in the presence of trichloroacetic acid (10 mol%) could promote the same reaction at 0 °C or room temperature in brine without any added organic solvent to give the endo cycloadducts as the major isomers in 71–99% yields with good to excellent ees (93–96%) (Scheme 1.24) [53]. A binaphthyl-based diamine **46** was synthesized by Maruoka and coworkers in 2006 [54]. The application of diamine **46** (12 mol%) in combination with $TsOH{\cdot}H_2O$ (10 mol%) for the enantioselective DA reaction of α,β-unsaturated aldehydes with cyclopentadiene afforded the *exo* product (13 : 1 dr) with up to 92% ee (Scheme 1.24).



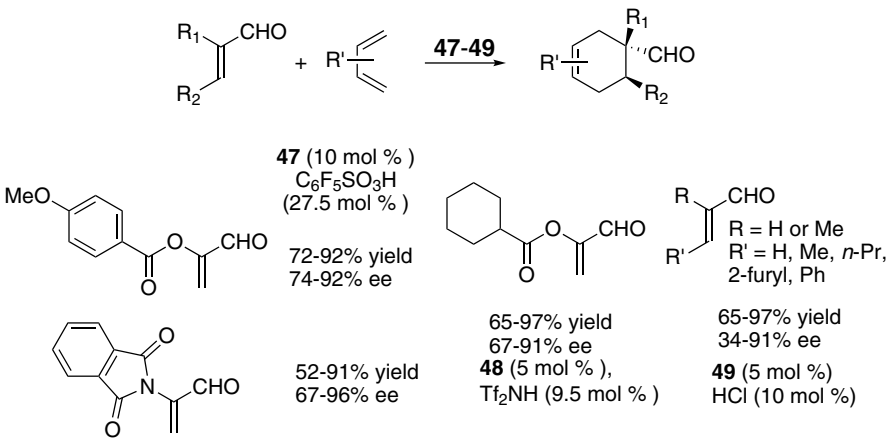
Scheme 1.24 Enantioselective DA reaction catalyzed by chiral secondary amine **43–46**.

1.2.2.2 Chiral Primary Amine Catalyzed Asymmetric Diels–Alder Reaction

Chiral secondary amines have proven not to be effective catalysts for the DA reaction of sterically hindered α-substituted acroleins due to their bulkiness of chiral and the difficulty in the formation of iminium ions with α-substituted acroleins. In 2005, Ishihara and coworkers realized the first organocatalyzed DA reaction of α-substituted acroleins with a series of cyclic and acyclic dienes using less bulky primary amine **47** (Scheme 1.25), and the corresponding *exo* cycloadducts were attained in excellent yields and ees (Scheme 1.26) [55]. In an effort to improve the catalytic activity and enantioselectivity of the primary amine catalyzed DA reaction of α-substituted acroleins, Ishihara utilized a weak basic aromatic amine **48** (5 mol%) in combination with the strong Brønsted acid Tf_2NH as catalyst, up to 97% yield and 91% ee of the corresponding cycloadduct were afforded (Scheme 1.26) [56]. At the same time, Ha's group reported that the HCl salt of 1,2-diamino-1,2-diphenylethane **49** also promoted the asymmetric DA reaction of cyclopentadiene with crotonaldehyde, giving the corresponding products in high yields with good to excellent enantiomeric excesses (Scheme 1.26) [57].

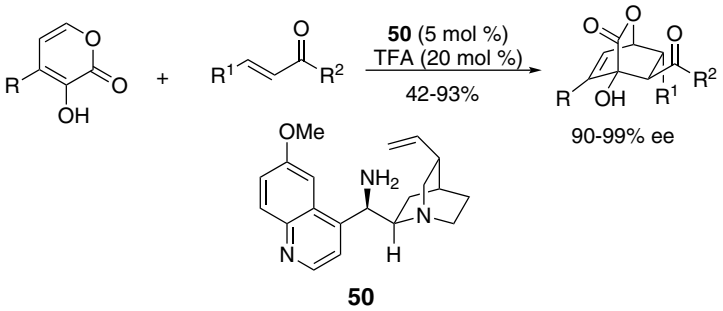


Scheme 1.25 Chiral primary amine catalysts.



Scheme 1.26 Enantioselective DA reaction catalyzed by chiral primary amine **47–49**.

Very recently, Deng and coworkers developed an efficient asymmetric DA reaction of 2-pyrone derivatives with a variety of α,β-unsaturated ketones, one type of more challenging substrates, under the catalysis of cinchona alkaloid **50**, the corresponding *exo* cycloadducts were obtained in moderate to excellent yields with 90–99% ees (Scheme 1.27) [58]. The corresponding cycloadduct could be transformed to one type of highly functionalized chiral intermediate by simple thermal decarboxylation without loss of enantioselectivity.



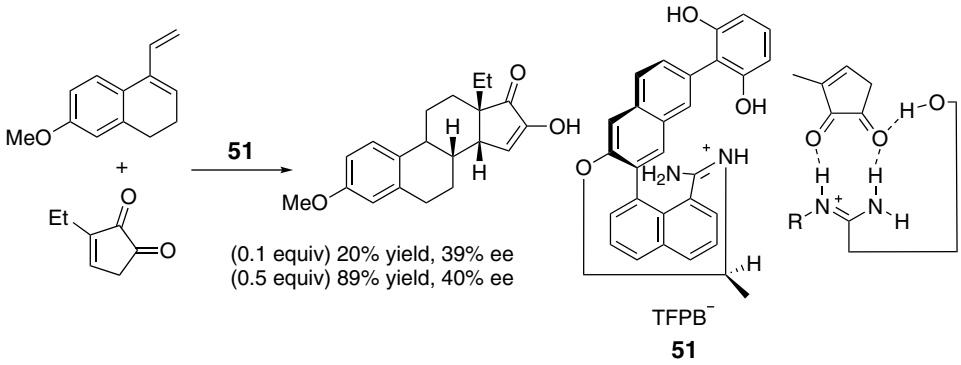
50

Scheme 1.27 Chiral primary amine **50** catalyzed DA reaction.

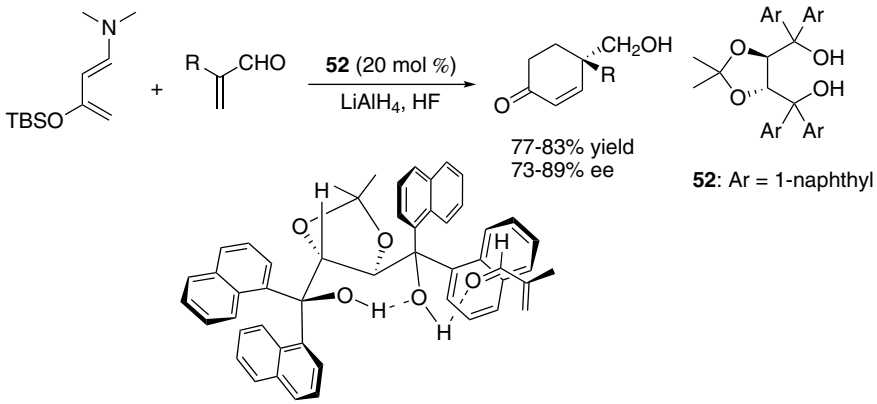
1.2.2.3 **Brønsted Acid Catalyzed Asymmetric Diels–Alder Reaction**

In the field of organocatalysis of DA reactions, the use of chiral Brønsted acid as catalyst [59a–c] has been less developed in comparison with chiral Lewis base. The first Brønsted acid catalyzed DA reactions were reported by Göbel's group by employing axially chiral amidinium ions **51** despite the fact that only 40% ee of the adduct was obtained with as high as 50 mol% catalyst loading (Scheme 1.28) [59d–e]. In this catalytic system, the diketone substrate was activated by chiral Brønsted acid via multiple hydrogen-bonding interaction. The first highly efficient and enantioselective DA reaction was realized by Rawal's group employing (α,α,α′,

α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) TADDOL **52** as a Brønsted acid catalyst [60]. Up to 92% ee of the corresponding cycloadduct was obtained for the reaction of aminosiloxydienes and substituted acroleins (Scheme 1.29). A possible asymmetric induction model was proposed, in which the dienophile was supposed to be activated by an intermolecular hydrogen bonding between carbonyl and hydroxy groups, and the intramolecular hydrogen bonding between two hydroxy groups of TADDOL catalyst can facilitate the intermolecular hydrogen-bonding activation for the catalysis [60].

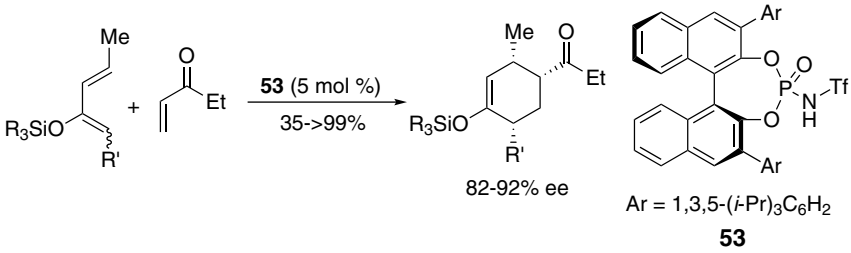


Scheme 1.28 Enantioselective DA reaction promoted by hydrogen bonding interaction.



Scheme 1.29 Hydrogen bonding promoted DA reaction by TADDOL **52**.

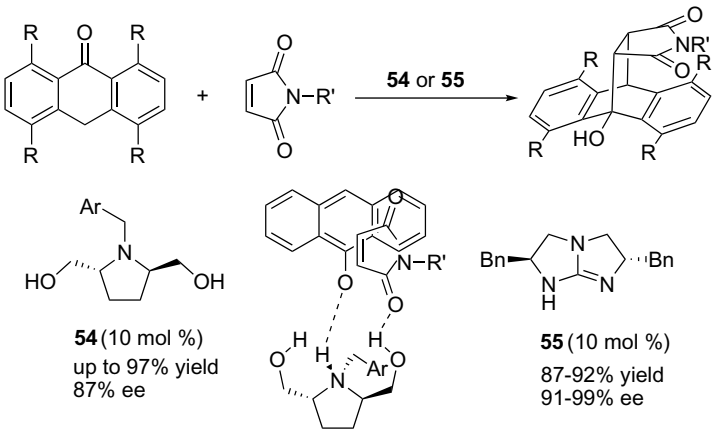
On the basis of hydrogen-bonding activation strategy, Yamamoto's group developed an alternative chiral Brønsted acid, *N*-triflyl phosphoramide **53** derived from optically pure 3,3′-Ar_2BINOL, for the enantioselective DA reaction of ethyl vinyl ketone with electron-rich silyloxydiene, and the corresponding products were achieved in moderate to excellent yields with high enantioselectivities (Scheme 1.30). The success of this catalytic system was attributed to the strong Brønsted acidity of *N*-triflyl phosphoramide [61].



Scheme 1.30 Chiral phosphoramide catalyzed enantioselective DA reaction.

1.2.2.4 Bifunctional Organocatalysis of Asymmetric Diels–Alder Reaction via Hydrogen Bonding

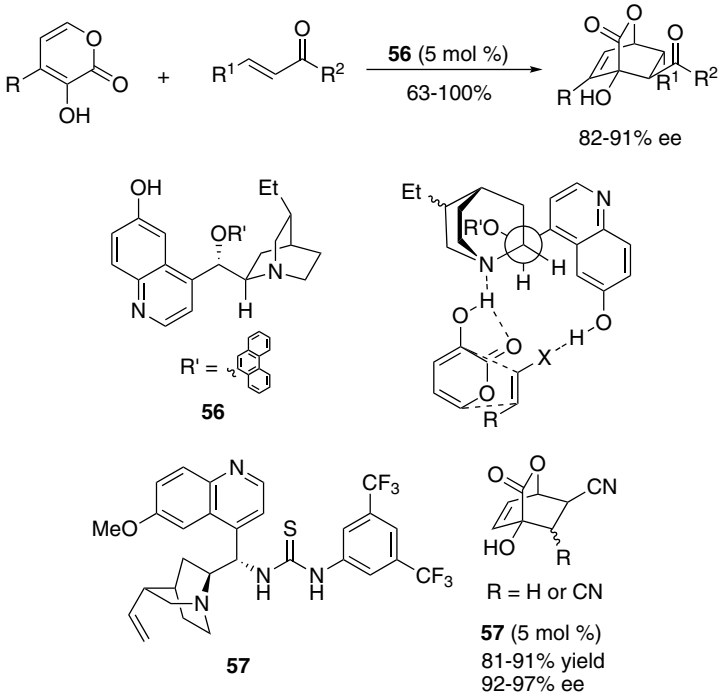
In 2001, Yamamoto and coworkers realized the catalytic asymmetric DA reaction of anthrone and maleimide derivatives using chiral pyrrolidine **54** as a bifunctional catalyst, up to 97% yield and 87% ee of the corresponding adduct were obtained (Scheme 1.31) [62]. A possible transition state model for this [4 + 2] cycloaddition was proposed, in which two hydrogen bonds are believed to exist between the catalyst and the substrates. One is between the protonated pyrrolidine catalyst and anthrone enolate, and the other is between the hydroxy group of pyrrolidine and the carbonyl group of maleimide [62]. Such kinds of double hydrogen-bonding interactions allow the substrate activation and stereochemistry control to occur simultaneously. In 2006, Tan and coworkers successfully realized similar reactions using a chiral bicyclic guanidine **55** as catalyst, excellent yields and enantioselectivities of the reaction were afforded (Scheme 1.31) [63].



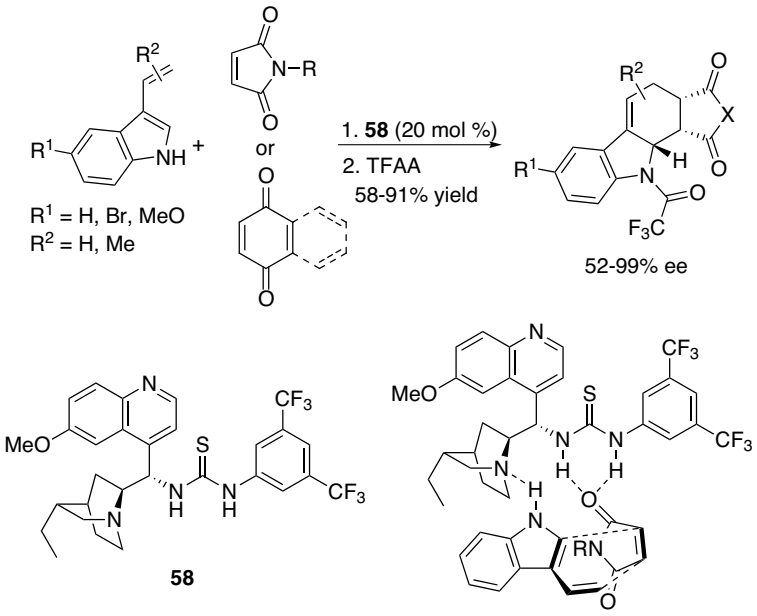
Scheme 1.31 Bifunctional organocatalysis of asymmetric DA reaction.

Deng's group developed an alternative asymmetric DA reaction of 2-pyrones with a variety of α,β-unsaturated ketones or esters using 5 mol% of bifunctional cinchona alkaloids catalysts **56**, the corresponding adducts were obtained in 60–100% yields

with 82–91% ees (Scheme 1.32) [58]. Catalyst **56** has both hydrogen bond donor and acceptor motifs, and mechanistic studies suggest there are multiple hydrogen bonding interaction networks between catalyst and substrates which simultaneously raise the energy of the HOMO of the diene and lower the energy of the LUMO of the dienophile [64]. Deng and coworkers have also developed the asymmetric DA reaction between 2-pyrones and conjugated nitriles under the catalysis of cinchona-based thiourea **57** (5 mol%), good *exo* diastereoselectivity (up to 97 : 3) and enantioselectivity (up to 97% ee) of the catalysis were afforded (Scheme 1.32). In this reaction system, catalyst **57** was again considered as a bifunctional organocatalyst which could activate both dienes and dienophiles via hydrogen bonding interaction [64]. In 2008, Bernardi and coworker achieved the first asymmetric DA reactions between 3-vinylindoles and maleinides or quinones using a modified bifunctional thiourea catalyst **58**. The corresponding fused heterocycle could be readily obtained in good to excellent yields with very high ees (Scheme 1.33). It was suggested that the interaction between the basic moiety of the catalyst and the N−H group of the diene and the hydrogen bonding activation of the dienophile by the thiourea moiety might be responsible for the catalysis [65]. The resultant cycloadducts are potentially useful for the synthesis of a variety of biologically important natural or unnatural alkaloids.



Scheme 1.32 Bifunctionalized catalysts promoted enantioselective DA reaction.



Scheme 1.33 Enantioselective DA reaction promoted by **58**.

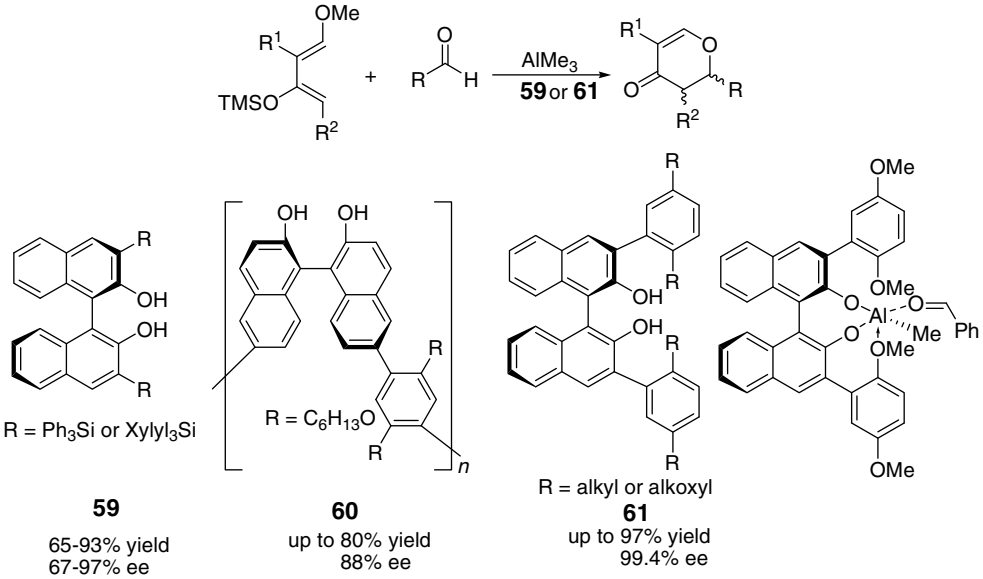
1.3
Asymmetric Oxa-Diels–Alder Reaction

1.3.1
Lewis Acid Catalyzed Asymmetric Oxa-Diels-Alder Reaction

1.3.1.1 Chiral Aluminum, Boron, and Indium Complexes

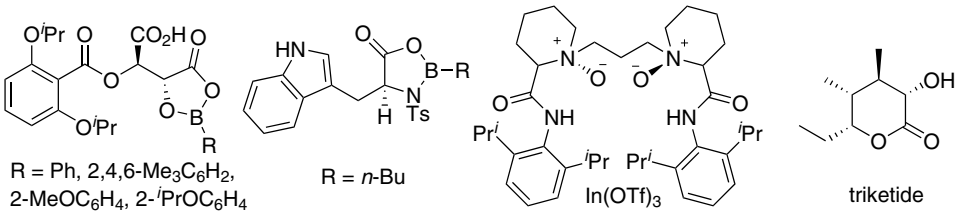
Asymmetric hetero Diels–Alder (HDA) reaction of carbonyl compounds with various dienes can afford dihydropyranone derivatives, one type of important synthons for natural or unnatural product synthesis. In 1988, Yamamoto's group reported the first HDA reactions of aldehydes and Danishefsky's dienes under the catalysis of 10 mol% of Al(III) complexes of **59** with good yields and up to 97% ee (Scheme 1.34). The steric hindrance on the 3,3′-position of binaphthyl was found to be crucial for the high reactivity and enantioselectivity. The chiral organoaluminum reagent derived from Me_3Al and 3,3′-dialkylbinaphthol (alkyl = H, Me or Ph) was employable only as a stoichiometric promoter and less satisfactory results were obtained in terms of both reactivity and enantioselectivity [66a]. Yamamoto and coworkers further applied an asymmetric poisoning strategy employing chiral ketone (3-bromocamphor) as an antagonist to enantioselectively deactivate one enantiomer of racemic BINOL-Al complex and the less deactivated enantiomer catalyzed the reaction to give the product in up to 82% ee [66b]. Jørgensen and Pu developed a type of chiral polymer aluminum catalyst **60**/Al for enantioselective HDA reaction of

2,3-dimethyl-1,3-butadiene with ethyl glyoxylate, and chiral polymer ligand **60** could be easily recycled and reused without lose of reactivity and enantioselectivity [67a]. In 2000, Jørgensen's group systematically investigated the effect of the steric and electronic environment of chiral Al complexes of **61** (10 mol%) for the asymmetric HDA reactions of benzaldehyde with Danishefsky's diene in *tert*-butyl methyl ether, up to 97% yield and 99.4% ee were achieved. It was found that bulkiness and hypercoordination of 3,3-substituents played a key role in this highly efficient and enantioselective reaction, and a possible hypercoordination model was also postulated to explain the asymmetric induction pathway. In this model, in addition to the coordination of benzaldehyde, one of the ether oxgen atoms of the chiral ligands was believed to coordinate to aluminum and form a trigonal-bipyrimidal structure at the aluminum center which accounted for the stereochemistry outcome of the reaction [67b].



Scheme 1.34 Enantioselective HDA reaction catalyzed by chiral aluminum complexes.

Chiral boron complexes have also been successfully applied in asymmetric HDA reactions. In 1992, Yamamoto employed **1** (CAB) for the enantioselective HDA reaction of aldehydes with Danishefsky's diene, up to 95% ee of the corresponding adduct was obtained (Scheme 1.35) [68]. Complex **2** developed by Corey and coworkers was also an efficient catalyst, up to 82% ee of the product was obtained for the reaction of benzaldehyde with Danishefsky's diene via the Mukaiyama aldol reaction pathway [69]. Very recently, Feng's group developed a novel aromatic amide derived chiral *N,N*-dioxide/$In(OTf)_3$ complex **62** (Scheme 1.35) for the same type of HDA reaction. This catalyst system was applicable for a broad range of aromatic, aliphatic and heterocyclic aldehyde substrates [70]. This protocol was further employed to the sub-gram scale synthesis of triketide in 21% overall yield.



1 (20 mol %)
47-95% yield
75-95% ee

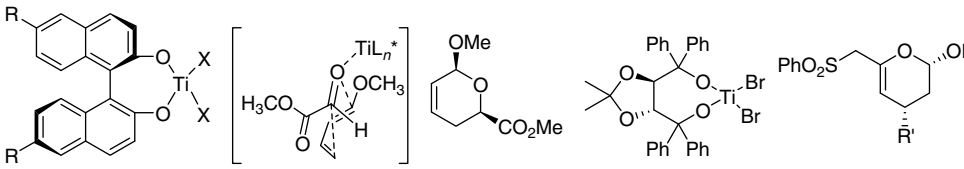
2
100% yield
82% ee

62 (5 mol %)
20-98% yield
78-99% ee

Scheme 1.35 Enantioselective HDA reactions catalyzed by boron and indium complexes.

1.3.1.2 Chiral Titanium and Zirconium Complexes

Chiral titanium (IV) complexes have been widely used as catalysts for asymmetric HDA reactions. In 1991, Mikami and coworkers reported an enantioselective HDA reaction between methyl glyoxylate and 1-methoxyldienes using BINOL-TiX_2 complexes **25** (10 mol%) as catalysts, cis cycloadducts were obtained as major products in high yields and excellent ees (Scheme 1.36). The observed cis-selectivity suggested the titanium catalyst **25** should be complexed in an *anti*-fashion and then the HDA reaction proceeded through an endo-orientation [71a, 34c]. Wada's group found that TADDOL-$TiBr_2$ (**63**, 5–10 mol%) could catalyze an inverse-electron demand HDA reaction of vinyl ether with α,β-unsaturated ketones, giving dihydropyranes in good to excellent yields and up to 97% ee (Scheme 1.36) [71b].



R = H, Br
X = Cl, Br
25

anti-endo

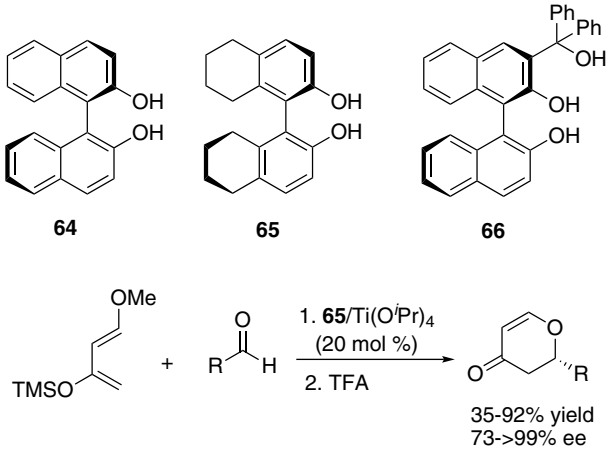
86% yield
97% ee

63

77-96 yield
59-97% ee

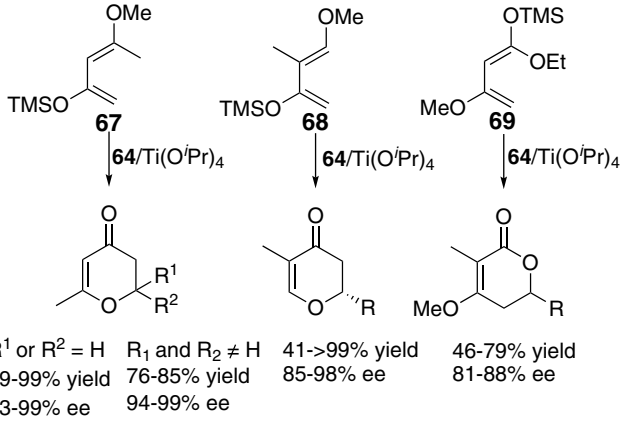
Scheme 1.36 Enantioselective HDA reactions catalyzed by chiral titanium complexes.

In 1995, Keck and coworkers reported the asymmetric HDA reaction of Danishefsky's diene with a variety of aldehydes using the catalyst (10 mol%) generated from BINOL **64** and $Ti(O^iPr)_4$ in the ratio of 2 : 1 in the presence of 4 Å MS and TFA (0.3 mol%), the corresponding dihydropyrones were obtained in 75–97% ees [72]. Feng's group contributed a lot of effort on the chiral titanium-catalyzed HDA reaction of aldehydes and electron-rich dienes. A systematic investigation on the ligand screening, the effects of temperature, solvent, catalyst concentration and loading, ratio of ligand and $Ti(O^iPr)_4$, as well as MS additive, disclosed that a titanium catalyst (20 mol%) prepared *in situ* by mixing a 1 : 1 ratio of H_8-BINOL **65** and $Ti(O^iPr)_4$ could promote the HDA reaction between Danishefsky's diene and a wide variety of aldehydes efficiently via the Mukaiyama aldol pathway. High levels of enantioselectivities have been obtained in this catalytic system (Scheme 1.37) [73].



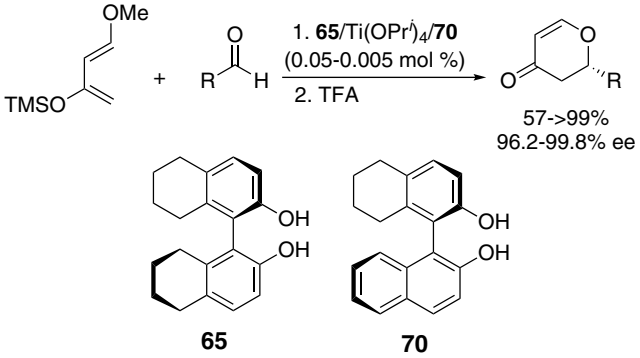
Scheme 1.37 Chiral BINOL-Ti complexes for HDA reaction.

Feng and coworkers have also expanded BINOL-Ti(IV) catalysts to the HDA reactions of substituted Danishefsky-type dienes (**67**, **68**) with aldehydes. Optically active 2,6-disubstituted, 2,2,6-trisubstituted, and 2,5-disubstituted dihydropyrones could be obtained in high yields with good to excellent enantioselectivities [74]. Yu and coworkers developed 3-diphenylhydroxymethyl-substituted BINOL (**66**)-titanium(IV) catalyst (20 mol%) for the same reaction via the DA pathway, affording 2,5-disubstituted dihydropyrones with up to 99% yield and 99% ee [75]. In 2008, an efficient asymmetric HDA reaction of Brassard's diene and aliphatic aldehydes was reported by Feng and coworkers using BINOL-Ti(IV) catalyst (10–20 mol%) in the presence of 4-picolyl hydrochloride as an additive, the corresponding α,β-unsaturated δ-lactones were afforded in 46–79% yields and 81–88% ees (Scheme 1.38) [76]. This methodology has also been successfully applied to a one-step synthesis of (*R*)-(+)-kavain and (*S*)-(+)-dihydrokavain.



Scheme 1.38 Enantioselective HDA reactions catalyzed by BINOL-Ti complexes.

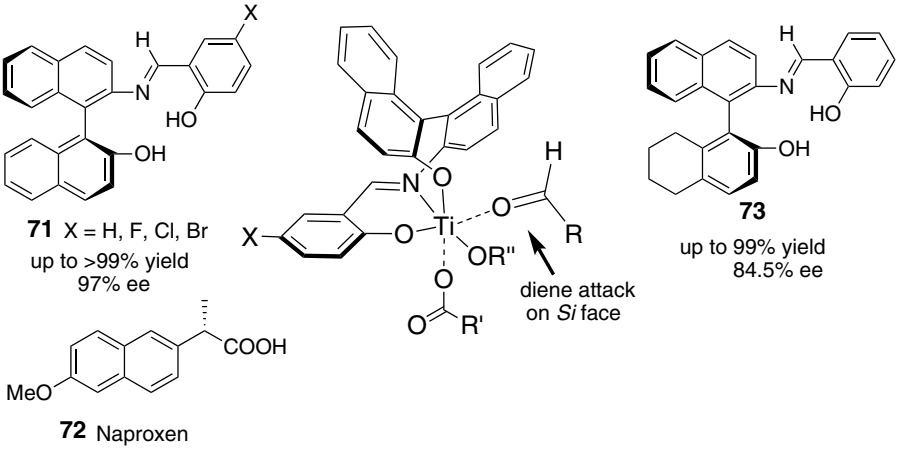
In 2002, Ding's group successfully discovered some exceptionally efficient enantioselective catalysts for the solvent-free HDA reactions of Danishefsky's diene with aldehydes using high-throughput screening of dynamic combinatorial catalyst libraries (104 members) of titanium complexes generated *in situ* from a series of chiral diols with $Ti(O^iPr)_4$. It was found that catalysts **65**/Ti/**70** and **70**/Ti/**70** could promote the HDA reactions with only 0.5–0.05 mol% catalyst loading to give dihydropyranones in up to quantitative yield and >99% ee (Scheme 1.39). In particular, only 0.005 mol% of **65**/Ti/**70** was effective enough to promote the reaction between furfural and Danishefsky's diene, affording the corresponding cycloadducts in 63% yield and 96% ee, which represents one of the lowest catalyst loadings for Lewis acid catalysis in the HDA reaction [77].



Scheme 1.39 Enantioselective HDA reaction catalyzed by complex **65**/Ti/**70**.

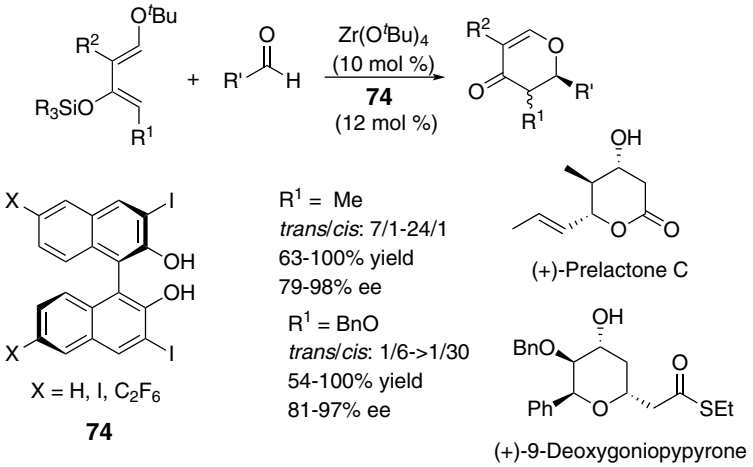
Ding and coworkers have also discovered a series of highly efficient chiral tridentate Schiff base **71** modified titanium catalysts for HDA reactions of Danishefsky's diene and aldehydes via a concerted [4 + 2] cycloaddition process (Scheme 1.40). A variety of 2-substituted dihydropyranones were afforded in up to 97% ee and >99% yield with 10 mol% of **71**/Ti/**71** as catalyst precursor in the presence of Naproxen **72** as an activator and 4 Å MS [78a, b]. Based on this type of catalyst system, some dendritic catalysts were designed and synthesized for the catalysis of the same reaction, affording the products in comparable enantiomeric excesses to those obtained with their homogeneous counterparts [78c, d]. The dendritic titanium catalyst could be recycled and reused at least three times without significant loss of activity and enantioselectivity. Very recently, Li and coworkers synthesized H_4-NOBIN derived tridentate Schiff base ligand **73**, which was then employed in the titanium-catalyzed HDA reaction with 2-naphthoic acid as additive. However, only moderate enantioselectivity was obtained [79].

BINOL-Zr(IV) complexes have also been applied to the catalytic asymmetric HDA reaction. In 2002, Kobayashi's group reported the first catalytic 2,3-trans-selective enantioselective HDA reaction between Danishefsky's dienes ($R^1 = Me$) and aldehydes in the presence of chiral zirconium complexes formed *in situ* with 3,3′-diiodobinaphthol derivatives **74**, $Zr(O^tBu)_4$, a primary alcohol and a small



Scheme 1.40 Chiral Schiff base ligand for titanium catalyzed HDA reaction.

amount of water, the corresponding cycloadducts were afforded in up to quantitative yield and 98% ee (Scheme 1.41). This reaction was found to proceed in a stepwise cycloaddition process. For the diene substrates with $R^1 = BnO$, 2,3-*cis*-dihydropyranones were achieved efficiently and enantioselectively (Scheme 1.41) [80]. (+)-Prelactone C and (+)-9-deoxygoniopypyrone have been concisely synthesized ultilizing this methodology.

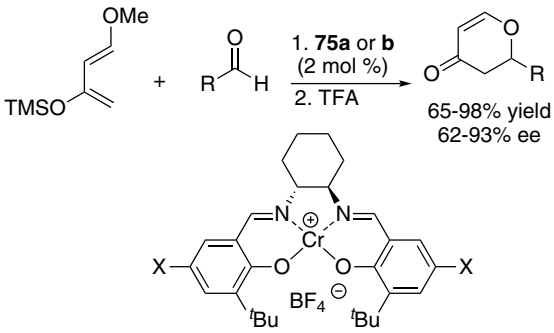


Scheme 1.41 Enantioselective HDA reaction catalyzed chiral zirconium complexes.

1.3.1.3 Chiral Chromium Complexes

Jacobsen and coworkers discovered that Salen-Cr(III) complex **75** (2 mol%) was an efficient catalyst for the enantioselective HDA of Danishefsky's diene and a variety

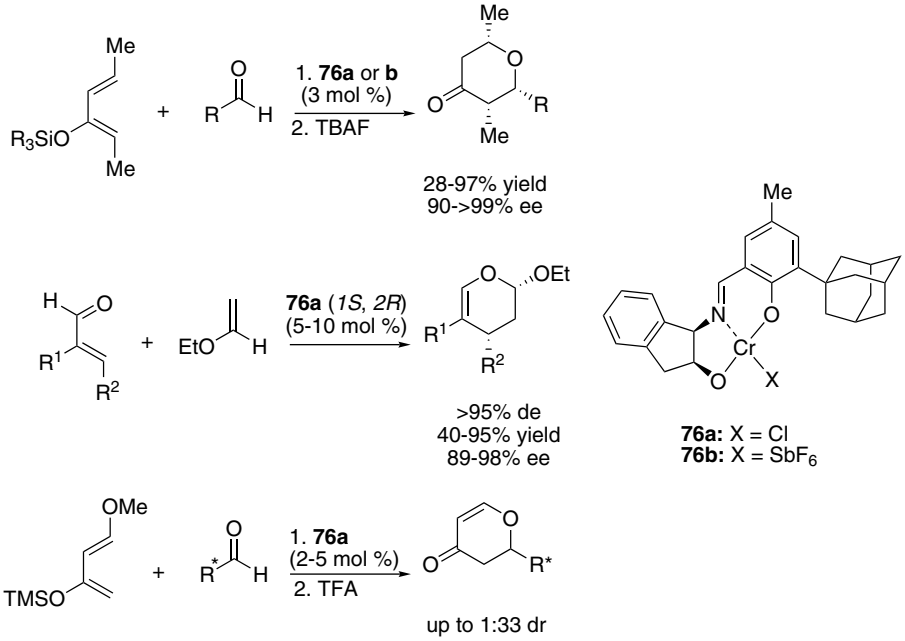
of aldehydes in the presence of 4 Å MS, the corresponding cycloadducts were obtained in 65–98% yields and 62–93% ees (Scheme 1.42). The reaction was confirmed to proceed via a concerted [4 + 2] cycloaddition pathway [81]. In 2005, complex **75** was used as catalyst for a high-pressure HDA of 1,3-butadiene and glyoxylates by Jurczak's group. However, only moderate enantioselectivity was afforded (44–71% ee) [82].



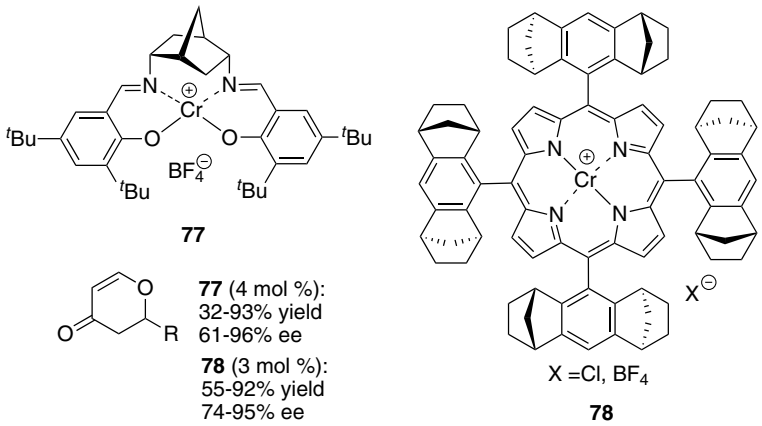
Scheme 1.42 Enantioselective HDA reaction catalyzed by Salen chromium complex.

Jacobsen and coworkers also developed chiral tridentate Schiff base chromium complexes **76** for enantioselective HDA reactions of trisilyloxy-2,4-hexadiene and a variety of aldehydes to afford *cis*-tetrahydropyranones in 28–97% yields and 90–99% ees (Scheme 1.43) [83a]. The catalyst loading could be reduced to 0.5 mol% for the reaction of 1-methoxyl-1,3-diene with $TBSOCH_2CHO$ without decrease in selectivity (91% yield, >99% ee). Complex **76a** was also found to be a highly efficient catalyst for inverse-demand HDA reactions of α,β-unsaturated aldehydes with ethyl vinyl ether to give for an electron-inverse-demand HDA *cis*-dihydropyranes with a high level of enantioselectivities (Scheme 1.43) [83b]. The use of complex **76a** in the HDA reaction of Danishefsky's diene with chiral aldehydes showed very high diastereoselectivity (up to 1 : 33). This methodology provides selective access to any of four possible stereoisomers of the dihydropyranone products by judicious use of aldehyde and catalyst enantiomers, while achiral tridentated Schiff base chromium complex only led to low diastereoselectivities [83c].

In 2006, Berkessel's group developed two chiral chromium catalysts, **77** with chiral 2,5-diaminonorborane backbone Salen ligand and **78** bearing chiral porphyrin ligand, for enantioselective HDA reactions of Danishefsky's diene with aldehydes, up to 92–93% yields and 95–96% ees of the products have been obtained (Scheme 1.44) [84]. Moreover, chiral cobalt (**79**) [85a], vanadium (**80**) [85b], and manganese (**81**) [85c] complexes have also been successfully applied in the same HDA reaction (Scheme 1.45).



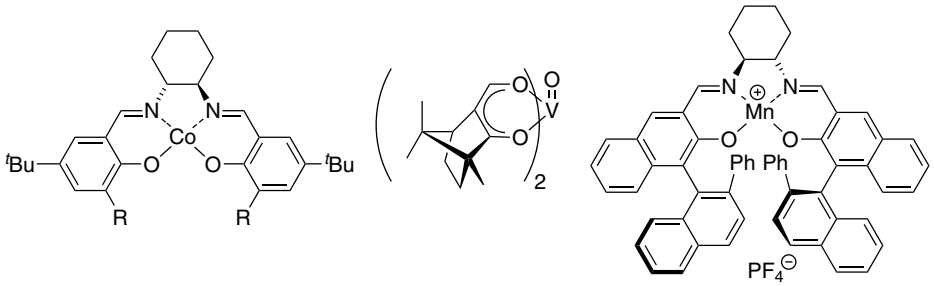
Scheme 1.43 Enantioselective HDA reactions catalyzed by chiral chromium complexes **76**.



Scheme 1.44 Chiral chromium complexes.

1.3.1.4 Chiral Copper and Zinc Complexes

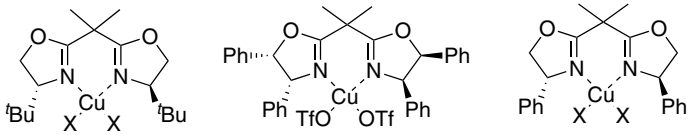
Chiral bis(oxazoline)-Cu(II) complexes (Scheme 1.46) represent one type of most efficient catalysts for asymmetric HDA reactions and have been intensively studied. In 1997, Jørgensen and coworkers reported the first highly enantioselective HDA reaction of Danishefsky's diene (Scheme 1.47, $R_3 = R_4 = H$) with various ketones including α-keto ester and α-diketone under the catalysis of **82a** (10 mol%), the corresponding cycloadducts have been achieved in 77–95% yields with up to 99% ee



79 **80** **81**

Scheme 1.45 Chiral cobalt, vanadium, and manganese complexes.

[86a]. Further research on this system led to a more general catalytic process for the HDA reaction of diketones with broad substrate scope, low catalyst loading, and excellent reactivity, diastereoselectivity, and enantioselectivity. For example, only 0.05 mol% of **82a** can catalyze the reaction of 2,3-pentanedinone with Danishefsky's diene (Scheme 1.47, $R^3 = R^4 = H$) efficiently, the reaction occurred at the methyl ketone fragment in 76% yield with 97.8% ee [86b].

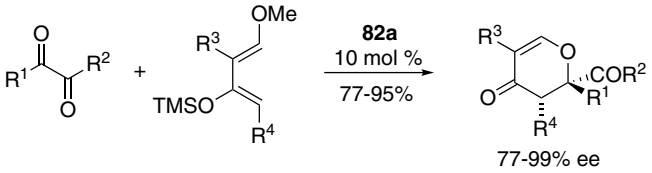


82a: X = OTf
82b: X = SbF_5

83

84a: X = OTf
84b: X = SbF_5

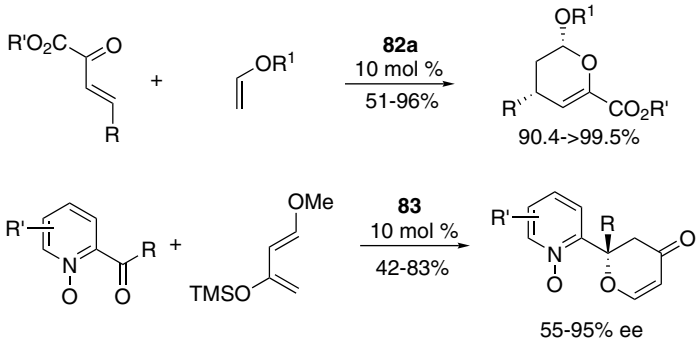
Scheme 1.46 Chiral copper complexes.



Scheme 1.47 Enantioselective HDA reactions catalyzed by copper complex **82a**.

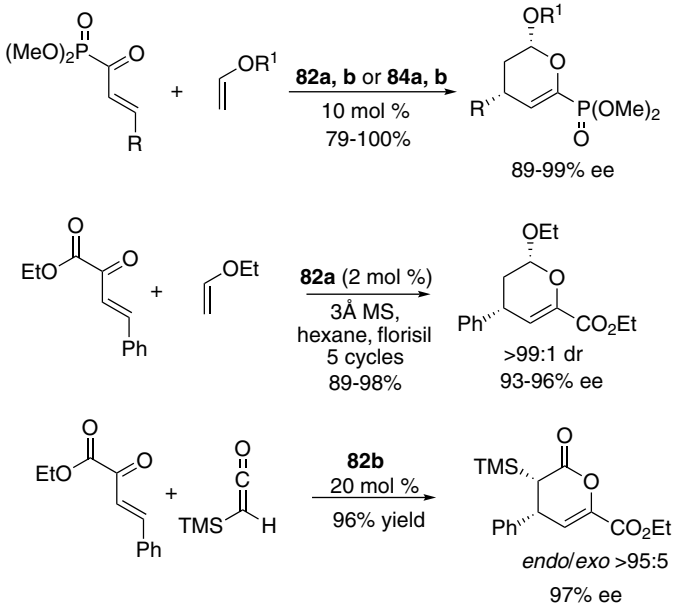
In 1998, Jørgensen's group developed a highly diastereo- (>95% de) and enantioselective inverse-electron-demand HDA reaction of β,γ-unsaturated α-keto esters bearing alkyl, ary and alkyoxy substitutents at the γ position with vinyl ether using **82a** as catalyst (Scheme 1.48), the corresponding cycloadducts were obtained in 51–96% yields with 90.4–99.5% ees [87a]. The substrate can be further expanded to γ-amino-protected β,γ-unsaturated α-keto esters and optically active amino sugar derivatives [87b,c]. Further experimental and theoretical investigations on the mechanism in chiral bis-oxazoline-Cu(II)-catalyzed HDA reactions have also been carried out [87d]. In 2007, Jørgensen and coworkers realized an enantioselective HDA reaction of *N*-oxy-pyridine aldehydes and ketone derivatives with Danishefsky's

diene under the catalysis of **83** (10 mol%), the corresponding cycloadducts were afforded in moderate yields and good enantioselectivities (Scheme 1.48). For the reaction of Brassard's diene, only the Mukaiyama aldol adduct was obtained in 84% yield and 99% ee [88].



Scheme 1.48 Enantioselective HDA reactions catalyzed by copper complexes **82**–**83**.

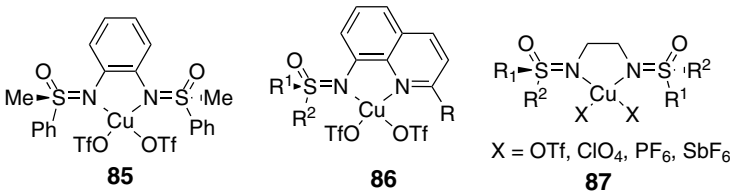
Evans and coworkers reported a diastereo- and enantioselective HDA reaction of α,β-unsaturated acryl phosphonates with cyclic or acyclic enol ethers in the presence of chiral bis-oxazoline-Cu(II) (**82** or **84**) (2 mol%) to give the corresponding cyclic enol phosphonates in excellent yields (79–100%) and ees (88–99%) (Scheme 1.49). These cycloadducts are useful chiral synthons and can be conve-



Scheme 1.49 Enantioselective HDA reactions catalyzed by copper complexes.

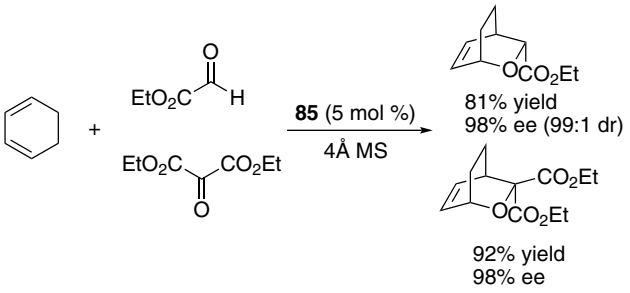
niently transformed to lactones, aldehydic ester and lactol methyl ether [89a]. Evans' group further extended these catalysts to the HDA reaction of β,γ-unsaturated α-keto esters and amides, affording the corresponding dihydropranes in excellent yields (87–99%), diastereo- (16 : 1 → 99 : 1), enantioselectivities (95–99%). Cycloadditions can be conducted with as low as 0.2 mol% of the chiral catalyst loading and are readily run on a multigram scale. When the reactions were conducted in hexane in the presence of absordent (florisil), complexes **82** can be recycled and reused four times without loss of activity (Scheme 1.49) [89b,c]. In 2001, an enantioselective HDA reaction of β,γ-unsaturated α-keto esters with trimethylketene was realized to afford δ-lactone in 96% yield with 97% ee (Scheme 1.49) [89d]. Other chiral bis(oxazoline)-Cu(II)-catalyzed HDA reactions have also been reported recently [90].

Chiral sulfoximine ligands (Scheme 1.50) developed by Bolm's group are also effective for the Cu(II)-catalyzed HDA reaction [91]. In 2002, Bolm and coworkers reported enantioselective HDA reactions of 1,3-cyclohexadiene with ethyl glyoxylate or activated ketone under the catalysis of **85** (5 mol%), affording the corresponding cycloadducts in excellent yields and ees (Scheme 1.51) [91a]. Later, Bolm's group found that quinoline-based C_1-symmetric monosulfoximine-Cu(II) complexes **86** could promote the same HDA reaction efficiently, giving the products in up to 96% ee [91b]. Recently, ethylene-bridged chiral bissulfoximines have also been applied to Cu(II)-catalyzed HDA reaction. Up to 99% ee of the product was obtained in the presence of 5 mol% of catalyst **87** [91c].



85 **86** **87**

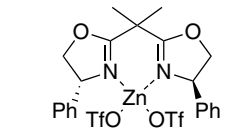
Scheme 1.50 Chiral sulfoximine-Cu(II) complexes.



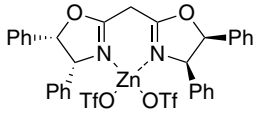
Scheme 1.51 Enantioselective HDA reactions catalyzed by chiral sulfoximine-Cu(II) complexes.

In comparison with chiral Cu(II) complexes, chiral bis(oxazoline)-Zn(II) complexes have received less successful application in the asymmetric HDA reaction. Jørgensen's group employed complexes **88** and **89** as catalysts for enantioselective

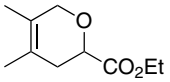
HDA reactions of ethyl glyoxylate with 2,3-dimethyl-1,3-butadiene or 1,3-cyclohexadiene, affording the corresponding adducts in only moderate ees (Scheme 1.52) [92]. For the HDA reaction of γ-amino-protected β,γ-unsaturated α-keto esters with ethyl vinyl ether, amino sugar derivative was obtained in 99% yield with 70% ee (Scheme 1.52) [87b].

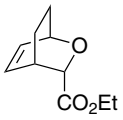


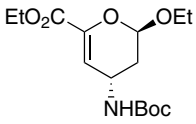
88



89







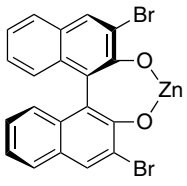
88: 26% yield, 87% ee
89: 42% yield, 79% ee

88: 84% yield, 27% ee
89: 84% yield, 65% ee

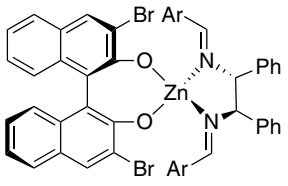
88: 99% yield
70% ee (70% de)

Scheme 1.52 Enantioselective HDA reaction catalyzed by chiral bis(oxazoline) copper complexes.

In 2002, Ding's group developed a highly efficient 3,3′-Br_2-BINOL-Zn(II) catalyst (Scheme 1.53) for the enantioselective HDA reaction of Danishefsky's diene with a variety of aldehydes [93]. Optically active 2-substituted dihydropyranones were afforded in up to 98% ee with excellent yields in the presence of 10 mol% of complex **89** which was generated *in situ* from the reaction of Et_2Zn with 3,3′-Br_2BINOL (Scheme 1.54) [93a]. Further studies showed that a series of chiral diimines activated BINOLate zinc complexes were also effective in promoting the HDA reaction in excellent enantioselectivities [93c]. In particular, two distinct asymmetric reactions including HDA of Danishefsky's diene and diethylzinc addition to aldehyde have been successfully integrated in one pot in the presence of a single catalyst (**90**, 10 mol%), up to 97.4% ee and 95.0% de of the products were obtained (Scheme 1.54) [93b,c]. In 2008, Ding and coworkers discovered that chiral BINOLate magnesium complexes were also highly efficient catalysts for the same HDA reaction to afford the products in up to 99% ees [94].



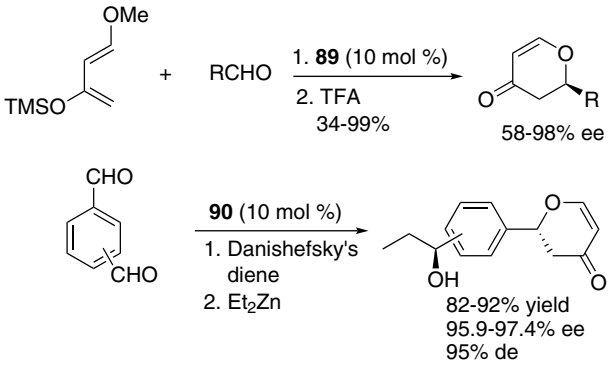
89



Ar = 2,4,6-$Me_3C_6H_2$

90

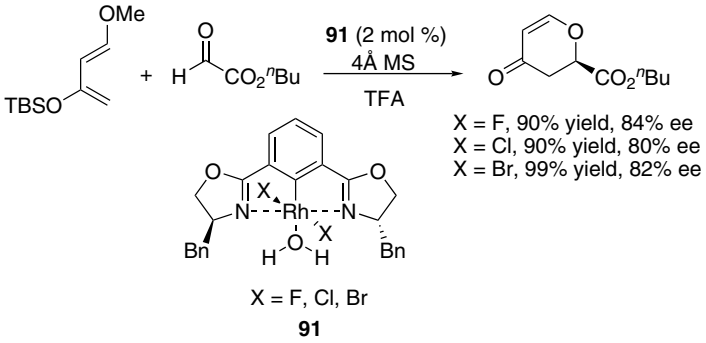
Scheme 1.53 Chiral zinc complexes.



Scheme 1.54 Enantioselective HDA reactions catalyzed by chiral zinc complexes.

1.3.1.5 Chiral Rhodium, Palladium, and Platinum Complexes

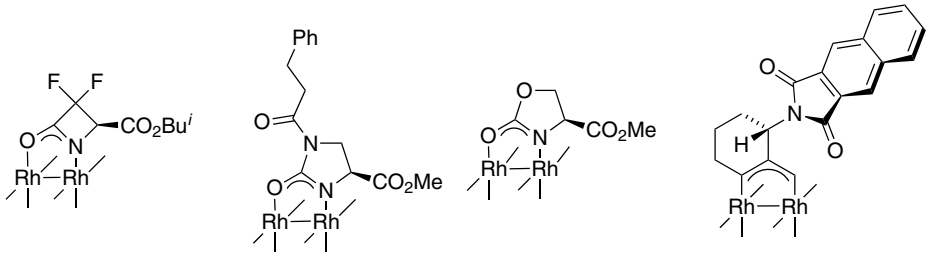
Chiral rhodium complexes have been rapidly developed and successfully applied to asymmetric HDA reactions for the last decade. In 2001, Nishiyama and coworkers reported an enantioselective HDA reactions of Danishefsky's diene with n-butyl glyoxylate promoted by chiral 2,6-bis(oxazolinyl)$RhCl_2(H_2O)$ complexes **91** as the catalysts (2 mol%), up to 84% ee of the corresponding adduct was obtained (Scheme 1.55). This reaction was confirmed to proceed via the concerted [4 + 2] cycloaddition pathway [95].



Scheme 1.55 Enantioselective HDA reaction catalyzed by chiral rhodium complexes **91**.

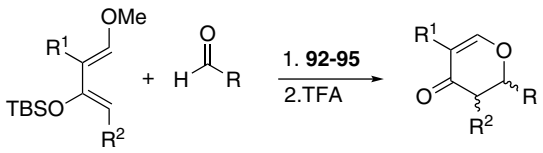
Chiral dirhodium(II) carboxamidate complexes (Scheme 1.56) have shown exceptional power for the catalysis of the asymmetric HDA reaction of diene with aldehydes. Doyle and coworkers have developed a variety of dirhodium complexes (**92–94** are the best) for promoting HDA reactions [96]. In 2001, Doyle's group discovered that complexes **92** and **93** are able to catalyze the addition of a variety of aldehydes to Danishefsky's diene (Scheme 1.57, $R^1 = R^2 = H$), affording the corresponding dihydropyranones in excellent yields and good ee values. When the catalyst loading was decreased to 0.01 mol% for the electron-poor aldehydes, cycloadducts could still be obtained in 71–81% yields with 61–73% ees, although

a longer time was required (4–10 days) [96a, c, d]. Complex **93** (1 mol%) was also effective for the reaction of 2,3-dimethyl Danishefsky's diene with aldehydes to give cis-selective cycloadducts in up to 96% yield and 97% ee [96d]. In 2004, Hashimoto's group developed an alternative dirhodium(II) carboxamidate complex **95** which demonstrated exceptional efficiency in the catalysis of the HDA reaction between Danishefsky's diene and a wide range of aldehydes. Particularly, when the loading of catalyst **95** was reduced to as low as 0.002 mol%, up to 96% yield and 91% ee of cycloadduct could be obtained in the reaction of phenylacetylenyl aldehyde with Danishefsky's dine. The turnover number in this case reaches 48 000 which is among the highest values for Lewis acid catalyzed asymmetric HDA reaction [97].



Rh_2(*4R*-dFIBAZ)$_4$ **92** | Rh_2(*4S*-MPPIM)$_4$ **93** | Rh_2(*4S*-MEOX)$_4$ **94** | Rh_2(*S*-BPTP)$_4$ **95**

Scheme 1.56 Chiral dirhodium complexes.

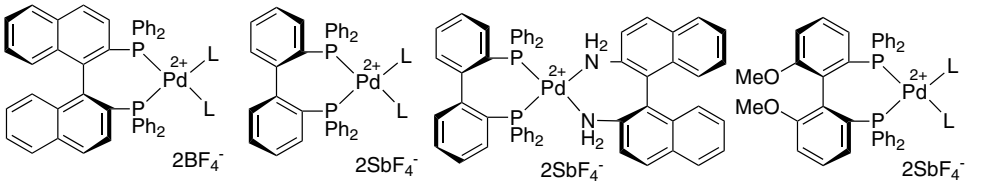


92	**93**	**94**	**95**
(0.01-1 mol %)	(0.01-1 mol %)	R = *p*-$NO_2C_6H_4$ (1 mol%)	(0.002-1 mol %)
33-98% yield 18-85% ee	41-95% yield 10-96% ee	65% yield 95% ee	81-97% yield 91-99% ee

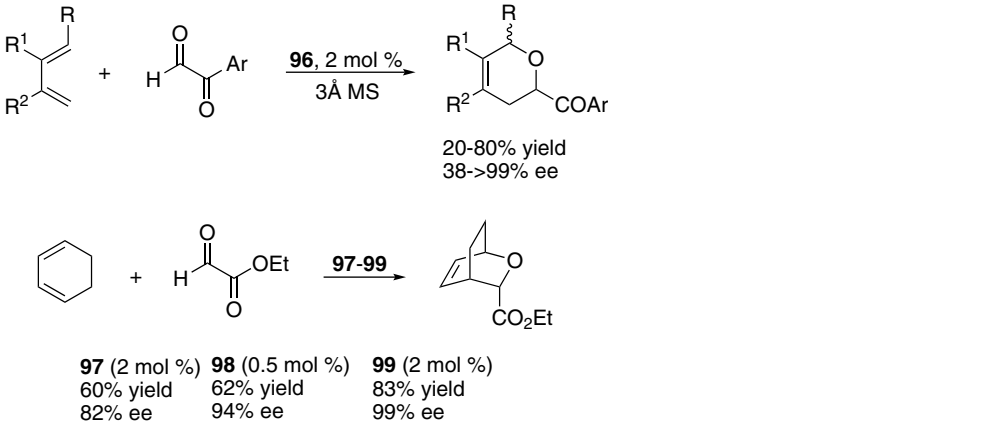
Scheme 1.57 Enantioselective HDA reaction catalyzed by dirhodium complexes.

Cationic Pd(II) complexes (Scheme 1.58) can also act as one type of chiral Lewis acid catalyst to promote the enantioselective HDA reaction of diene with aldehydes. Oi and coworkers reported that BINAP-Pd(II) **96** complex is highly enantioselective for the HDA reaction of aryglyoxylals with cyclic or acyclic substituted 1,3-butadiene, giving the corresponding cycloadducts in 20–88% yields and 38–99% ees (Scheme 1.59) with 2 mol% catalyst loading. The molecular sieve (3 Å) additive was found to be critically important for the enantioselectivity of the reaction. When glyoxylate ester was employed as the substrate, the ene adducts were also obtained in addition to HDA adducts [98]. In 2002, Mikami's group developed an enantiopure biphenylphosphine(BIPHEP)-Pd complex (*R*)-**97** by asymmetric activation of the

corresponding chirally flexible ligand-based racemic Pd complex (±)-**97** using enantiopure (*R*)-3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl (DM-DABN) as the chiral activator followed by *tropo*-inversion into the single Pd(II) diastereomer (*R*, *R*)-**98**) at 80 °C and protonation at 0 °C. HDA reaction of 1,3-cyclohexadiene with ethyl glyoxylate in the presence of (*R*,*R*)-**97** led to the corresponding cycloadducts in 60% yield with 82% ee (Scheme 1.59) [99a]. (*R*,*R*)-**98** was also an efficient catalyst for the reaction, giving the cycloadducts in 62% yield with 94% ee [99b]. Complex **99** developed by Gagné and coworkers catalyzed the same reaction efficiently to afford the product in 83% yield and 99% ee (Scheme 1.59) [100].

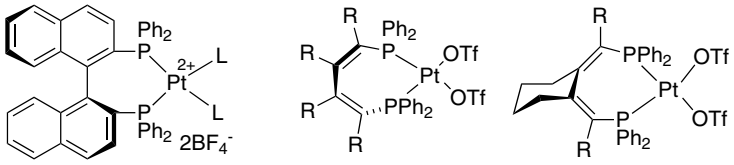


Scheme 1.58 Chiral palladium complexes.

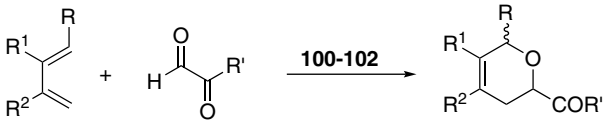


Scheme 1.59 Enantioselective HDA reaction catalyzed by chiral palladium complexes.

Oi's group also reported the use of BINAP-Pt(II) complex **100** as a chiral Lewis acid catalyst for the enantioselective HDA reaction of aryglyoxyal with acyclic or cyclic 1,3-dienes. The enantioselectivity of the catalysis could be up to 99% using 2 mol% of **100** (Scheme 1.60) [98]. Enantiopure flexible NUPHOS-Pt(II) complexes (**101** and **102**) were prepared by Doherty and coworkers using the similar strategy reported by Mikami [99a] using (*S*)-BINOL as the chiral template and trifluoromethanesulfonic acid as the protonation reagent to remove chiral auxiliary. The use of complexes **101** and **102** (2 mol%) in the catalysis of the HDA reaction of substituted 1,3-dienes with aryl glyoxals or glyoxylate esters showed that the enantioselectivity of the reaction could be as high as 99% with 60–99% of the substrate conversions (Scheme 1.61) [101].



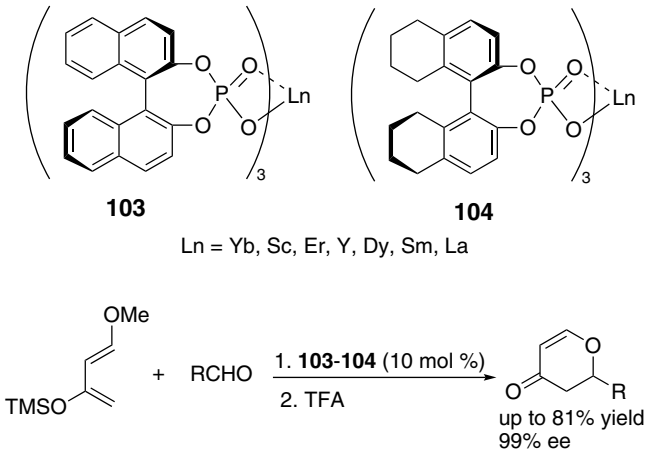
Scheme 1.60 Chiral platinum complexes.



Scheme 1.61 Enantioselective HDA reaction catalyzed by chiral platinum complexes.

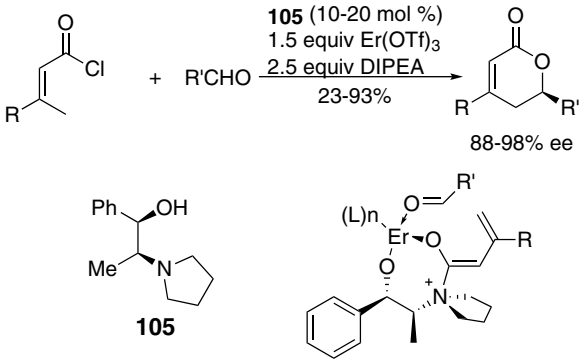
1.3.1.6 **Chiral Rare Earth Metal Complexes**

Although chiral lanthanide complexes were among the earliest catalysts developed for the HDA reaction of Danishefsky's diene with aldehydes [102], only very few chiral lanthanide complexes have been reported for their catalytic asymmetric version. Inanaga's group developed a type of chiral lanthanide phosphate complexes **103** and **104** (Scheme 1.62) which were demonstrated to be applicable for the enantioselective HDA of Danishefsky's diene with a variety of aldehydes, affording the corresponding cycloadducts in up to 81% yield and 99% ee [103]. It was found that



Scheme 1.62 Enantioselective HDA reaction catalyzed by lanthanide complexes **103–104**.

the additive 2,6-lutidine was beneficial to enantioselectivity and the use of heavy lanthanides afforded higher ees than did the lighter ones [103b]. This type of catalyst is also effective for the reaction of Danishefsky's diene with phenylglyoxylates, affording the corresponding products in up to 99% ee [103e]. Very recently, Peters and coworkers discovered that the chiral complex generated *in situ* from norephedrine **105** (10–20 mol%) and $Er(OTf)_3$ (1.5 equiv) in the presence of diisopropylethyl amine can promote the HDA reaction of α,β-unsaturated acid chlorides with a variety of aromatic aldehydes to afford δ-lactone efficiently with up to 98% ee (Scheme 1.63) [104]. In this catalytic system, chiral Er complex acts as a bifunctional catalyst to bind both substrates with the same metal center. This formal HDA reaction is actually via an aldol reaction pathway followed by an intramolecular acylation [104].

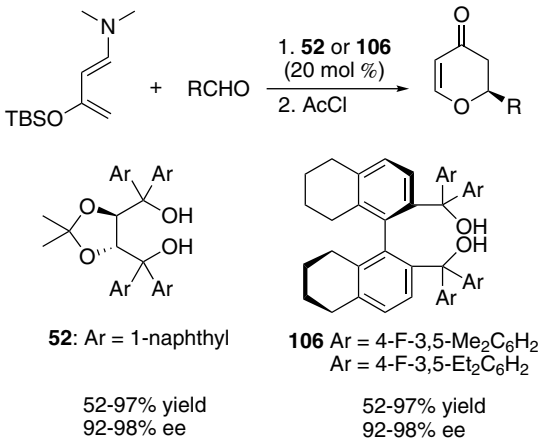


Scheme 1.63 Enantioselective HDA reaction catalyzed by Er complex.

1.3.2
Organocatalysis of Asymmetric Oxa-Diels–Alder Reaction

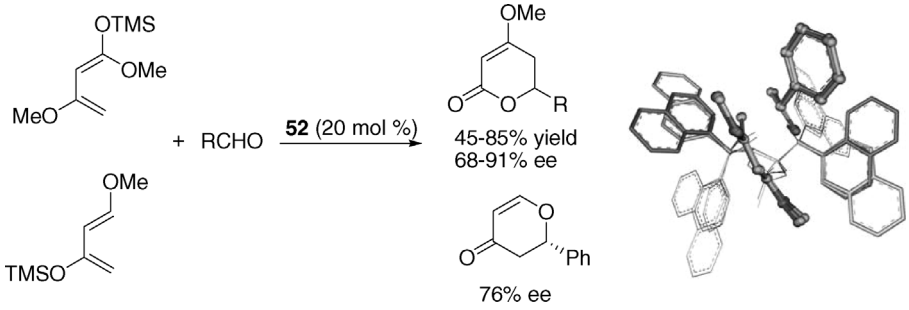
1.3.2.1 Hydrogen Bonding Promoted Asymmetric Oxa-Diels–Alder Reaction

Hydrogen bonding widely presents in nature, particularly in various large biomolecules such as proteins and nucleic acids, however, the use of this weak interaction with a small chiral molecule as hydrogen bonding donor (Brønsted acid) to promote enantioselective reactions was only a recent event [59a–c]. In 2003, Rawal's group reported the first highly efficient and enantioselective HDA reaction of aldehyde with electron-rich 1,3-diene through hydrogen bonding activation. The reaction of 1-amino-3-siloxy diene with a variety of aldehydes in the presence of a very simple hydrogen bonding donor TADDOL **52** proceeded smoothly to give the corresponding dihydropyranones after treatment with acetyl chloride in 52–97% yields and 92–98% ees (Scheme 1.64) [105a]. This pioneering work attracted a lot of interest in the area of asymmetric catalysis using hydrogen bonding activation [59a–c]. In 2005, Rawal and Yamamoto developed an alternative chiral Brønsted acid catalyst **106** bearing a partly reduced chiral binaphthyl backbone for the same HDA reaction, the corresponding products were obtained in 52–97% yields and 92–98% ee values (Scheme 1.64) [105b].



Scheme 1.64 Hydrogen bonding promoted HDA reaction.

In 2004, Ding and coworkers developed the first catalytic enantioselective HDA reaction of Brassard's diene with aldehydes through hydrogen bonding activation using **52** as the catalyst, the corresponding optically active δ-lactones were afforded in moderate-to-good yields with up to 91% ee (Scheme 1.65). Using this methodology, (*S*)-(+)-dihydrokawain has been synthesized in one step from 3-phenylpropionaldehyde in 50% isolated yield and 69% enantiomeric excess [106]. TADDOL **52** can also catalyze the asymmetric HDA reaction of the less active Danishefsky's diene with aldehydes to afford the corresponding dihydropyranones in moderate yields and ee values [107].

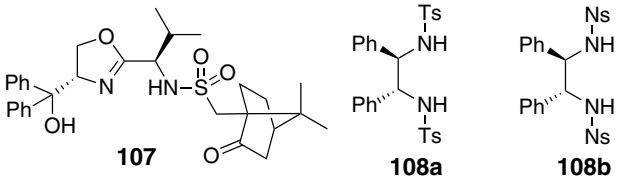


Scheme 1.65 Enantioselective HDA reactions catalyzed by TADDOL **52**.

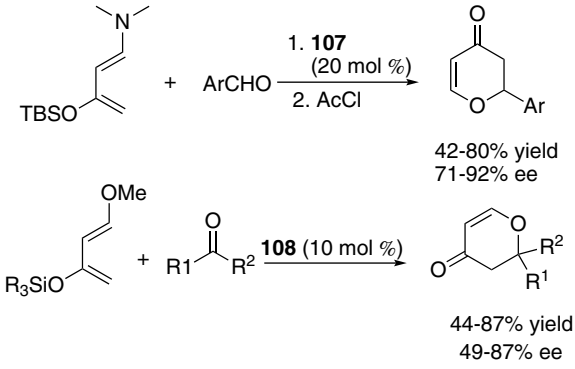
The hydrogen bonding interaction model and asymmetric induction pathway in this type of chiral Brønsted acid catalyzed HDA reaction were systematically studied by Ding and Wu [107], on the basis of X-ray crystal structures of TADDOL-DMF and **106**-benzaldehyde complexes [105b, 106] and theoretical calculations. In agreement with the experimental findings, the calculation results indicate that this TADDOL-catalyzed HDA reaction proceeds via a concerted mechanism through an asynchronous and zwitterionic transition structure. The carbonyl group of benzal-

dehyde is activated by forming an intermolecular hydrogen bond with one of the hydroxy groups of TADDOL. Meanwhile, the intramolecular hydrogen bond between the two hydroxy groups in TADDOL is found to facilitate the intermolecular hydrogen bonding with benzaldehyde [107]. The computational studies on hydrogen bond promoted HDA reactions from other groups also supported the mechanism proposed above [108]. Frejd and coworkers reported a cleft organocatalyst bearing a single hydroxy group for the same type of enantioselective HDA reaction, only low to moderate ees have been obtained [109].

Chiral Brønsted acid catalyst **107** (Scheme 1.66) bearing a chiral oxazoline backbone was synthesized and applied to the enantioselective HDA reaction of 1-amino-3-siloxyl-1,3-butadiene with aldehydes in Sigman's group, up to 92% ee of the adduct was achieved (Scheme 1.67) [110]. It was found that both hydrogen bonds in **107** are critically important for effective catalysis. In 2005, Jørgensen and Mikami independently reported the HDA reaction of Danishefsky's diene with glyoxylate or glyoxal under the catalysis of chiral bis-sulfonamides catalyst **108a–b** (Scheme 1.66) through double hydrogen bonding activation, moderate to good yields of the products with up to 87% ee could be obtained [111, 112].



Scheme 1.66 Chiral Brønsted acid catalysts.

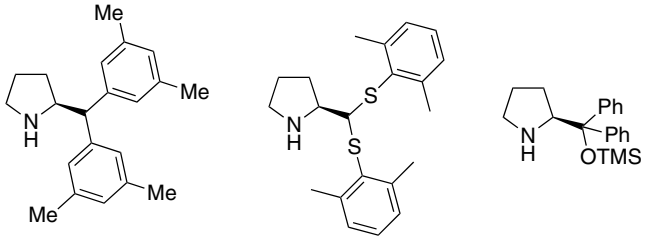


Scheme 1.67 Enantioselective HDA reactions through double hydrogen bonding activation.

1.3.2.2 Chiral Secondary Amine Catalyzed Asymmetric Oxa-Diels–Alder Reaction

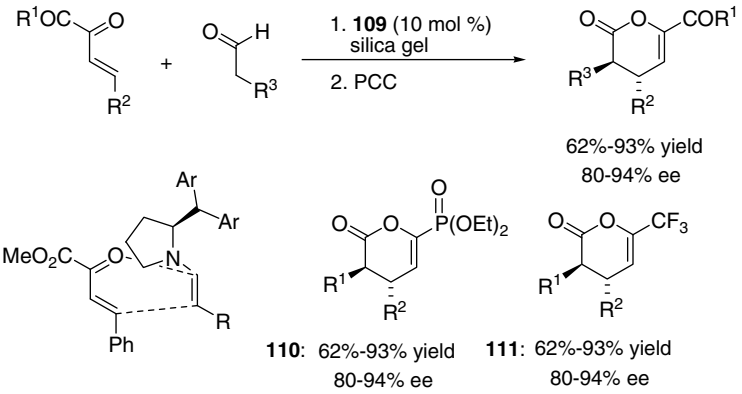
The use of chiral amines as catalysts for the asymmetric HDA reaction has been rarely reported. A limited number of successful catalytic systems have been achieved in inverse-electron-demand HDA reactions recently by using secondary amines

as the catalysts [113–116]. In 2003, Jørgensen and coworkers developed the first chiral amine **109** promoted HDA reactions of β,γ-unsaturated-α-ketones with aldehydes and *trans* lactones were afforded with good yields and up to 94% ee. The reaction proceeds through an active chiral enamine intermediate generated from chiral secondary amine and aldehyde, and silica gel is crucial for the regeneration of chiral amine catalyst (Scheme 1.68) [113]. Zhao and Liu reported the similar HDA reaction of β,γ-unsaturated-α-ketophosphonates and α,β-unsaturated trifluoromethyl ketones with catalysts **110** and **111**, respectively, and the corresponding cycloadducts were obtained in good yields and enantioselectivities (Scheme 1.69) [114, 115].



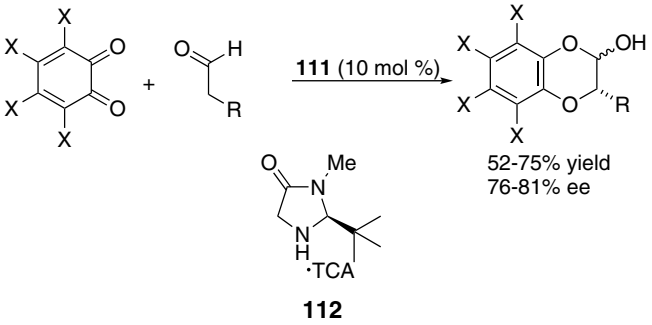
109 **110** **111**

Scheme 1.68 Chiral secondary amine catalysts.



Scheme 1.69 Inverse-electron-demand HDA reactions catalyzed by **109–111**.

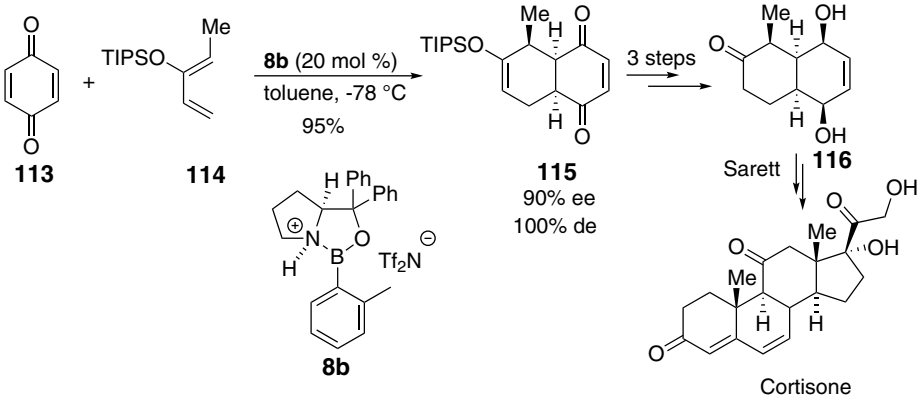
In 2007, an alternative enantioselective inverse-electron-demand HDA reaction of substituted quinones (X = H, Cl) and aldehydes was described by Dixon and coworkers using the secondary amine catalyst **111** (10 mol%) to afford the corresponding products with up to 81% ee. The resulting adduct could be further converted to optically active 2,3-dihydro-benzo[1, 4]dioxine compounds (Scheme 1.70) [116].



Scheme 1.70 Enantioselective HDA reaction catalyzed by chiral amine **112**.

1.4
Representative Applications in Total Synthesis

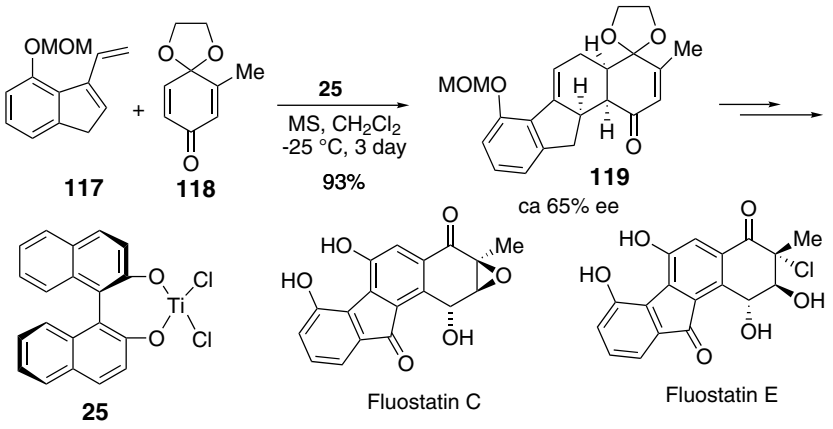
Chiral oxazaborolidine catalyzed enantioselective DA reactions have been applied to various organic syntheses of natural or unnatural products [7e]. A recent study reported by Corey *et al.* described the application of the catalytic asymmetric DA reaction as a key step for the synthesis of optically active intermediates of biologically important molecules, such as cortisone, dendrobine, or vitamin B12 and so on [117]. For example, the enantioselective DA reaction of benzoquinone **113** with diene **114** under the catalysis of **8b** (20 mol%), a chiral oxazaborolidine Lewis acid activated by Brønsted acid, in toluene at −78 °C to afford cycloadducts **115** in 95% yield with 90% ee and 100% de. The optically active **115** could be further transformed to **116** (>99% ee after recrystallization) in three steps, a key intermediate for the synthesis of cortisone (Scheme 1.71).



Scheme 1.71 Synthesis of optically active key intermediate of cortisone via catalytic asymmetric DA reaction.

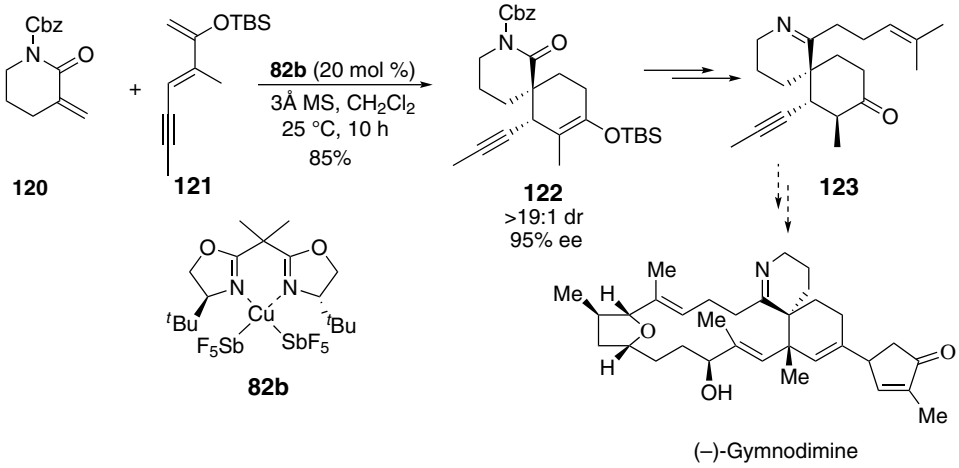
In 2008, Danishefsky and coworkers successfully realized the total synthesis of Fluostatin C, a biologically important compound with antibiotic and antitumor activities, utilizing an enantioselective DA reaction as a key step. The cycloaddition

reaction of diene **117** with methyl-substituted quinoneketal **118** under the catalysis of BINOL/Ti(IV) complex **25** afforded the corresponding adduct **119**, a key intermediate for the synthesis of Fluostatin C, in 93% yield with 65% ee (Scheme 1.72). Fluostatin C could be further converted to Fluostatin E after treatment with 1 M HCl [118]. The BINOL/Ti(IV) complex **25**-catalyzed enantioselective DA reaction was also used by Ward's group as a key step in the total synthesis of (−)-cyathin A_3 [119].



Scheme 1.72 Total synthesis of Fluostatin C and F.

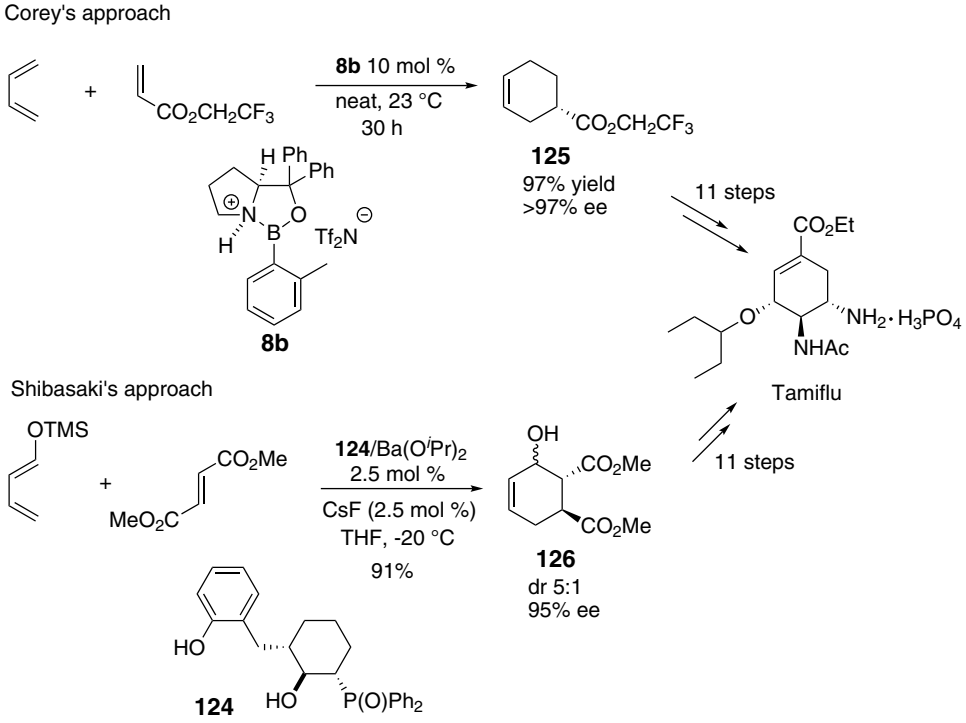
A key intermediate **123** for the total synthesis of marine toxin immunogen (−)-gymnodimine has been obtained by Romo and coworkers using a catalytic asymmetric DA reaction as a key step in the presence of Evan's bis(oxazoline)/Cu(II) complex **82**. The highly functionalized cycloadduct **122** was constructed in 85% yield with 95% ee and 90% de (Scheme 1.73) using 20 mol% of **82** in the presence of MS at room temperature [120]. Moreover, Evan's bis(oxazoline)/Cu(II) complex-catalyzed HDA reaction has also been successfully applied in the total synthesis of (*R*)-dihydroactinidiolide and (*R*)-actinidiolide by Jørgensen and coworkers [121].



Scheme 1.73 Total synthesis of (−)-gymnodimine.

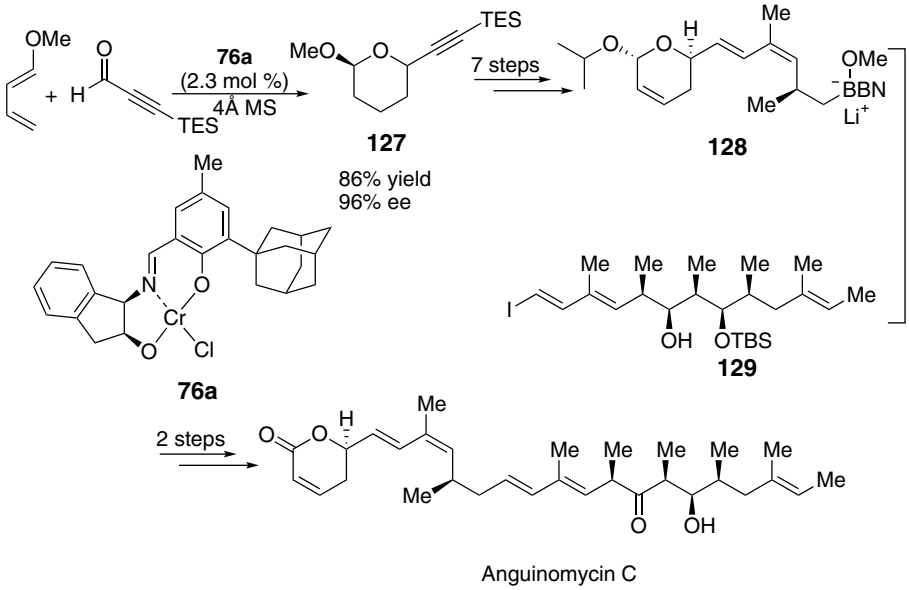
Tamiflu (oseltamivir phosphate) is a very important anti-influenza drug and several synthetic routes have been successfully developed with the approach for the drug production being from (−)-shikimic acid. In 2006, Corey and coworkers reported a facile approach to the total synthesis of Tamiflu employing the catalytic asymmetric DA reaction as a key step, avoiding the use of the relatively expensive and limited availability (−)-shikimic acid as starting material and the potentially hazardous and explosive azide-containing intermediates [122a]. The enantioselective DA reaction of 1,3-butadiene with trifluoroethyl acrylate in the presence of chiral boron complex **8b** (10 mol%) proceeded smoothly to give the corresponding cycloadduct **125** in 97% yield with >97%ee. Tamiflu was then efficiently synthesized in 11 steps from the cycloadduct intermediate **125** (Scheme 1.74) [122a].

In 2008, Shibasaki's group developed an alternative practical procedure for the synthesis of Tamiflu on the basis of the asymmetric DA reaction of 1-trimethylsiloxy-1,3-diene with dimethyl fumarate catalyzed by a chiral barium catalyst generated from chiral diol ligand **124** and $Ba(O^iPr)_2$ (Scheme 1.74) [123b]. The key intermediate **126** could be obtained in 91% yield and 95% ee on a scale of 58 g in the laboratory using 2.5 mol% of catalyst. CsF was found to be important for the removal of the TMS group of the diene to form the active barium dienolate via a transmetallation process. Starting from the key intermediate **126**, Shibashaki and coworkers have successfully developed a novel, efficient and easily handled route to the synthesis of Tamiflu [122b].



Scheme 1.74 Practical synthesis of Tamiflu based on catalytic asymmetric DA reactions.

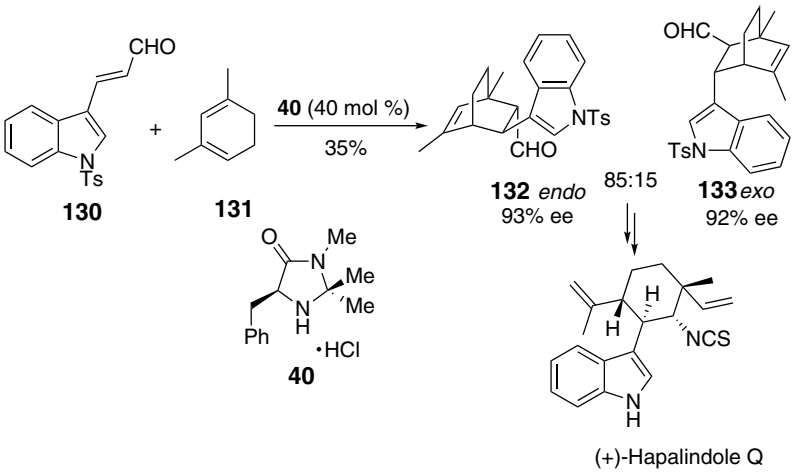
Enantioselective HDA reactions promoted by the chiral chromium (III) complex (Jacobsen catalyst) are often used as the key step in the total syntheses of natural products, for example, FR901464, (−)-colombiasin A, and Elisapterosin B by Jacobsen's group [123], (−)-Lasonolide (A) by Ghosh's group [124], (+)-neopeltolide by Paterson's group [125], and Platencin by Nicolaou's group [126]. In 2008, Gademann's group reported the first total synthesis of the antitumor polyketide Anguinomycin C, in which the dihydropyran key fragment **127** was constructed quickly by a **76a**-catalyzed enantioselective HDA reaction of 1-trimethylsiloxy-1,3-diene with TES-protected propargylic aldehyde. In the presence of 2.3 mol% of **76a**, this reaction gave the intermediate **127** in 86% yield with 96% ee, which was then transformed into **128** by a seven-step reaction sequence including a Negishi cross-coupling process. Finally, the cross coupling of **128** and **129** followed by deprotection accomplished the total synthesis of anguinomycin C (Scheme 1.75) [127].



Scheme 1.75 Total synthesis of anguinomycin C on the basis of a catalytic asymmetric HDA reaction.

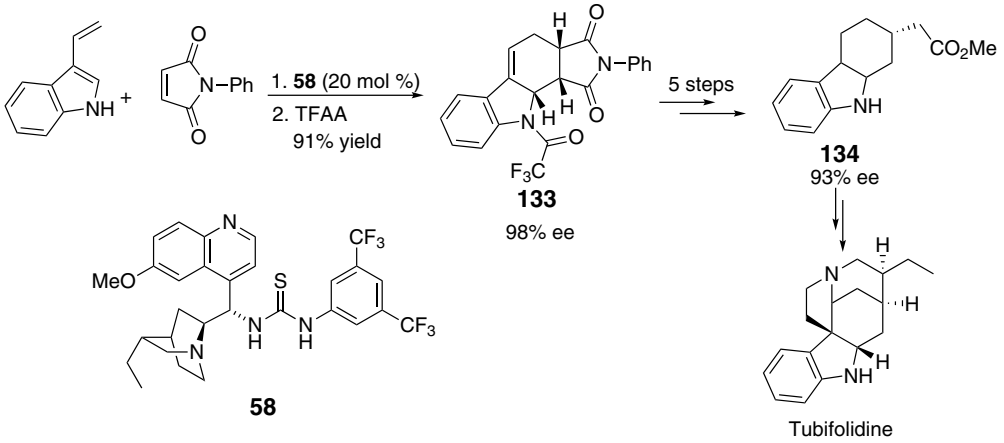
Organocatalysis of enantioselective DA reactions has also been used in the total synthesis of a variety of natural products. For example, the organocatalytic intramolecular DA reaction under the catalysis of **42** has been utilized in the total synthesis of marine metabolite solanapyrone D by the MacMillan group (Scheme 1.23) [50]. In 2003, the Kerr group achieved the first total synthesis of (+)-hapalindole Q with anti-algal and antimycotic activities, on the basis of an organocatalytic enantioselective DA reaction of diene **131** and dienophile **130** as the key step. A substoichiometric amount of **40** (40 mol%) promoted this reaction to give the key intermediate bearing four chiral centers including a quaternary center with

good diastereoselectivity (85 : 15) and 92–93% ee in moderate yield (35%) (Scheme 1.76) [128].



Scheme 1.76 Total synthesis of (+)-hapalindole on the basis of organocatalytic DA reaction.

In 2008, Bernardi and Ricci developed a hitherto elusive asymmetric DA reaction of 3-vinylindoles with maleinides or quinones using a bifunctional acid–base organocatalyst **58** (20 mol%), offering a direct approach to optically active tetrahydrocarbazole derivatives [65]. The cycloadduct **133** could be obtained in 91% yield with 98% ee, and was further converted to the intermediates **134** through a 5-step reaction sequence with only a slightly drop in enantioselectivity (93% ee) (Scheme 1.77). Optically active **134** can serve as a very important synthon for the total synthesis of tubifolidine [129].



Scheme 1.77 Total synthesis of tubifolidine based on organocatalytic DA reaction.

1.5 Conclusion

As described in this chapter, there have been great successes for both metal and organo-based catalysts in enantioselective Diels–Alder and hetero-Diels–Alder reactions in the last 30 years, providing optically active six-membered carbon cyclic or oxacyclic compounds conveniently. Although this area has reached some degree of maturity, with numerous highly efficient chiral catalyst systems with diverse substrate types and very excellent enantioselectivities, as well as many successful applications in the total syntheses of natural products and biologically important compounds, the high catalyst loading (1–20 mol%) is still one of the drawbacks or bottlenecks in the catalysis, especially for the organocatalysis of DA reactions. The future effort in this area will be continuously directed to the development of new DA or HDA reaction systems and novel catalyst systems with high chemo-, regio-, and enantio-selectivities at a low catalyst loading. The last criterion is particularly important for the practical application of DA or HDA reactions on an industrial scale.

1.6 Experimental: Selected Procedures

1.6.1 Procedure for the Preparation of Chiral Boron Complex 8b (R = o-tol, Ar = Ph) (Scheme 1.4) and Its Application in Asymmetric Diels–Alder Reactions (Scheme 1.5) [18b]

To a 2-necked round-bottom flask (100 mL) equipped with a stir bar, a glass stopper and a 50-mL pressure-equalizing addition funnel (containing a cotton plug and about 10 g of 4 Å molecular sieves, and functioning as a Soxhlet extractor) fitted on top with a reflux condenser and a nitrogen inlet adaptor were added (S)-(−)-α,α-diphenyl-2-pyrolindinemethanol (0.082 g, 0.324 mmol), tri-*o*-tolylboroxine (0.038 g, 0.107 mmol) and toluene (25 mL). The resulting solution was then heated to reflux for 3 h (bath temperature ∼145 °C) before cooling to about 60 °C when the addition funnel and condenser were quickly replaced with a short-path distillation head. The mixture was concentrated to about 5 mL by distillation. This distillation protocol was repeated three times by re-charging with 3 × 5 mL of toluene. The solution was then allowed to cool to room temperature and the distillation head was quickly replaced with a vacuum adaptor. Concentration *in vacuo* (about 0.1 mmHg, 1 h) afforded the corresponding oxazaborolidine as a clear oil, which can then be dissolved in CH_2Cl_2 and used in two Diels–Alder experiments. To an aliquot of the oxazaborolidine precursor (0.160 mmol, theoretical) in 1.0 mL of CH_2Cl_2 at −25 °C was added trifluoromethanesulfonimide (0.20 M solution in CH_2Cl_2, freshly prepared, 0.667 mL, 0.133 mmol) dropwise. After 10 min at −25 °C, a colorless homogeneous catalyst solution was ready for use in the Diels–Alder reactions. To the resulting **8b** solution were successively charged 2,2,3-trimethyl-1,4-benzoquinone (0.665 mmol) in CH_2Cl_2 (0.7–1.0 mL) and 2-triisopropylsilyloxy-1,3-butadiene at −78 °C. The reaction mixture was stirred at −78 °C for 12 h (monitored by TLC or

^{1}H NMR) before it was concentrated by rotary evaporation. Water (5 mL) and hexanes (3 mL) were added to this residue. The aqueous layer was extracted with hexanes (4×5 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the crude product. Further purification by chromatography on silica gel gave adducts in 98% yield with 99% ee.

1.6.2
Procedure for Chiral Secondary Amine 42 Catalyzed Asymmetric Diels–Alder Reaction of Cyclopentadiene with (E)-Cinnamaldehyde (Scheme 1.22) [50]

To a solution of catalyst **42** (0.64 g, 2.5 mmol) in MeOH/H_2O (95/5 v/v, 2.5 mL) was added (*E*)-cinnamaldehyde (6.36 mL, 50.4 mmol). The solution was stirred for 1–2 min before addition of cyclopentadiene (12.5 mL, 151 mmol). The resulting reaction mixture was stirred at 23 °C for 8 h then diluted with diethyl ether and washed successively with water and brine. The organic layer was dried over Na_2SO_4, and concentrated. Hydrolysis of the product dimethyl acetal was performed by stirring the crude product mixture in TFA : H_2O : $CHCl_3$ (1 : 1 : 2) for 2 h at room temperature, followed by neutralization with saturated aq. $NaHCO_3$ and extraction with Et_2O. Further purification by chromatography on silica gel with 10% EtOAc/hexanes as eluent to give adducts as a colorless oil in 99% yield (12.2 g, endo/exo = 1/1.3, 93% ee for both endo and exo).

1.6.3
Procedure for 65/Ti/70 Catalyzed Asymmetric Hetero Diels–Alder Reaction of Benzaldehyde with Danishefsky's Diene (Scheme 1.39) [77]

To a dried Schlenk tube under argon atmosphere was charged the catalyst **65**/Ti/**70** (0.008 mmol) generated *in situ* by mixing **65**, **70** and $Ti(O^iPr)_4$ in 1 : 1 : 1 molar ratio in toluene. Freshly distilled benzaldehyde (1.70 g, 16 mmol) and Danishefsky's diene (4.13 g, 24 mmol) were added sequentially to the catalyst. The reaction mixture was stirred for 48 h at 20 °C, diluted with diethyl ether (10 mL) and then treated with trifluoroacetic acid (3 mL). After the mixture was stirred for 0.5 h, saturated $NaHCO_3$ (20 mL) was added, the contents were stirred for 10 min, and the layers were separated. The aqueous layer was extracted with diethyl ether (3×50 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with hexanes/ethyl acetate (4 : 1), to afford 2.77 g (99.4% yield) of 2-phenyl-2,3-dihydro-*4H*-pyran-4-one as a colorless liquid with 99.4% ee.

1.6.4
Procedure for the Preparation of the Chiral Chromium Complex (1S, 2R)-76a and Its Application in the Asymmetric Hetero Diels–Alder Reaction of Ethyl Vinyl Ether with Crotonaldehyde (Scheme 1.43) [83b]

To a round-bottomed flask (200 mL) under a nitrogen atmosphere were added $CrCl_3$/THF (1 : 3) (2.80 g, 7.48 mmol), 3-(1-adamantyl)-2-hydroxy-5-methylbenzalde-

hyde-(1*S*, 2*R*)-1-aminoindanol imine (3.00 g, 7.48 mmol) and dry CH_2Cl_2 (60 mL) followed by dropwise addition of 2,6-lutidine (1.74 mL, 14.96 mmol). The solution was stirred for 3 h before dilution with CH_2Cl_2 (300 mL) and washing with water (3 × 180 mL) and brine (180 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The resulting solid was triturated with ice-cold acetone (10 mL), filtered, washed with an additional portion of cold acetone (10 mL), and air-dried to give the brown solid chromium complex (**76a**) as a dimer with a bridging water (2.3 g). To the filtrate (20 mL) was added water (2 mL) and the solution was allowed to stand, uncovered at 23 °C overnight. The resulting precipitate was filtered and washed with cold acetone to give an additional 0.6–0.8 g of the chromium complex ((1*S*, 2*R*)-**76a**) (combined yield 2.9–3.1 g, 75–80%). To an oven dried round-bottom flask (10 mL) were added freshly distilled ethyl vinyl ether (0.96 mL, 10.0 mmol) and (*E*)-crotonaldehyde (0.078 g, 1.0 mmol) followed by addition of freshly oven dried powdered 4 Å molecular sieves (0.150 g) and **76a** (0.024 g, 0.05 mmol). The resulting mixture was stirred at room temperature for 2 days then diluted with pentane and filtered through celite. The solvent was removed and the product was isolated by vacuum transfer to a flask cooled to −78 °C at 0.5 mmHg to give (*2S,4S*)-2-ethoxy-4-methyl-3,4-dihydro-2-*H*-pyran (0.106 g) as a clear oil in 75% yield with 94% ee.

1.6.5
Procedure for Chiral Copper Complex 82a (Scheme 1.46) Catalyzed Reaction of Asymmetric Hetero Ethyl Pyruvate with Danishefsky's Diene (Scheme 1.47) [86a]

82a was prepared by mixing $Cu(OTf)_2$ (0.036 g, 0.1 mmol) with 2,2′-isopropylidene-bis[(*4S*)-4-*tert*-butyl-2-oxazoline] (0.031 g, 0.105 mmol) in dry CH_2Cl_2 (2 mL) under an inert atmosphere with stirring for 2 h. The catalyst was cooled to −40 °C followed by addition of ethyl pyruvate (0.11 mL, 1 mmol) and Danishefsky's diene (0.25 mL, 1.2 mmol). The resulting solution was stirred for 30 h at −40 °C before quenched with TFA (0.1 mL dissolved in 20 mL of CH_2Cl_2). Then the mixture was stirred for an additional 1 h at 0 °C and neutralized with saturated aq. $NaHCO_3$. The solution was filtered through a plug of cotton, the organic phase was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic phase was dried, filtered and concentrated. Purification of the crude product using flash chromatography (EtOAc/light petroleum, 1 : 4) gave the corresponding product in 78% yield with 99% ee.

1.6.6
Procedure for the Preparation of Chiral Dirhodium Carboxamidate Complex 95 and Its Application in the Asymmetric Hetero Diels–Alder Reaction of Phenylpropargyl Aldehyde with Danishefsky's Diene (Scheme 1.57) [97]

To a round-bottomed flask was added a mixture of $Rh_2(OAc)_4 \cdot 2MeOH$ (0.76 g, 1.50 mmol) and (3*S*)-3-(1,3-dioxobenzo[f]isoindol-2-yl)-2-piperidinone (7.06 g, 24.0 mmol) in chlorobenzene (200 mL).The flask was fitted with a Soxhlet extraction

apparatus and the thimble in the Soxhlet extraction apparatus was charged with an oven-dried mixture (3 g) of two parts sodium carbonate and one part sand. The mixture was heated to reflux with vigorous stirring for 30 h before cooling to room temperature, the unreacted excess of ligand was precipitated, filtered, and concentrated *in vacuo* to afford the crude product (3.91 g). Further purification by chromatography on silica gel (150 g, EtOAc) followed by recrystallization from CH_2Cl_2–MeCN (4 : 1, 20 mL) provided the acetonitrile adduct of **95** (1.12 g, 53%) as red fine needles, which turned into the tris(hydrate) as red purple fine needles after standing. To an ice-cooled solution of **95** (0.0002 mmol, 0.40 mL, 0.5×10^{-3} M in CH_2Cl_2) and phenylpropargyl aldehyde (1.30 g, 10.0 mmol) in CH_2Cl_2 (17 mL) was added a solution of Danishefsky's diene (2.57 g, 12.0 mmol) in CH_2Cl_2 (2.6 mL). The resulting mixture was stirred at this temperature for 64 h before quenching with a 10% solution of trifluoroacetic acid in CH_2Cl_2 (about 0.5 mL) and then stirred at 23 °C for an additional 0.5 h. The whole was partitioned between EtOAc (100 mL) and saturated aq. $NaHCO_3$ (10 mL), and the separated organic layer was successively washed with water and brine, and dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography on silica gel (60 g, 2 : 1 hexane/EtOAc) afforded the corresponding product (1.46 g, 96%, 91% ee) as a pale yellow oil.

1.6.7
Procedure for TADDOL 52 Promoted Asymmetric Hetero Diels–Alder reaction of Benzaldehyde with 1-(N,N-Dimethylamino)-3-tert-butyldimethylsiloxy-1,3-Diene via Hydrogen Bonding Activation (Scheme 1.64) [105a]

To a solution of TADDOL **52** (0.1 mmol) and benzaldehyde (1.0 mmol) in toluene (0.5 mL) was added 1-(*N,N*-dimethylamino)-3-*tert*-butyldimethylsiloxy-1,3-diene (0.5 mmol) at −40 °C. The resulting solution was stirred for 24 h at this temperature before diluting with CH_2Cl_2 (2.0 mL). Acetyl chloride (1.0 mmol) was added dropwise at −78 °C, and the mixture was stirred for an additional 15 min then separated by chromatography on silica gel to afford 2-phenyl-2,3-dihydro-4*H*-pyran-4-one in 70% yield with 98% ee.

1.6.8
Procedure for Chiral Amine 109 Promoted Inverse Electron Demand Hetero Diels–Alder Reaction of Butyraldehyde and Enone (Scheme 1.69) [113]

To a solution of butyraldehyde (0.50 mmol) and enone (1.00 mmol) in CH_2Cl_2 (0.5 mL) was added catalyst **109** (0.05 mmol) followed by addition of silica gel (0.050 g) at −15 °C. The resulting mixture was allowed to warm to room temperature while stirring over night. The equilibrium mixture of intermediates was isolated by flash chromatography on silica gel (gradient CH_2Cl_2 to 15% Et_2O/CH_2Cl_2). Oxidation of the mixture of intermediates was performed in CH_2Cl_2 by addition of PCC (1.0 equiv) at room temperature. After 1 h, another equivalent of PCC was added, 5-ethyl-6-oxo-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester was

isolated in 69% yield with 84% ee by flash chromatography on silica gel with CH_2Cl_2 as the eluent.

Abbreviations

Ac	acetyl
Ar	aryl
BA	Brønsted acid
BINOL	1,1′-binaphth-2,2′-diol
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BIPHEP	2,2′-bis(diphenylphosphino)biphenyl
BLA	Brønsted acid assisted Lewis acid
Bn	benzyl
Bu	butyl
CAB	chiral (acyloxy) boron catalyst
Cp	cyclopentadienyl
DA reaction	Diels–Alder reaction
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
DM-DABN	3,3′-dimethyl-1,1′-binaphthyl-2,2′-diamine
dr	diastereomeric ratio
ee	enantiomeric excess
ees	enantiomeric excesses
Et	ethyl
HDA reaction	hetero Diels–Alder reaction
HOMO	highest occupied molecular orbital
LA	Lewis acid
LUMO	lowest unoccupied molecular orbital
Me	methyl
MOM	methoxymethyl
MS	molecular sieve
NOBIN	2-amino-2′-hydroxy-1,1′-binaphthyl
NUPHOS	(1*Z*,3*Z*)-1,4-bis(diphenylphosphino)buta-1,3-diene
Ns	*p*-nitrobenzenesulfonyl
PCC	pyridinium chlorochromate
Ph	phenyl
Pr	propyl
pybox	pyridyl-bis(oxazoline)
Salen	a ligand prepared by condensation of salicylic aldehyde and ethylene diamine
TADDOL	α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
TES	triethylsilyl

Tf	trifluoromethanesulfonyl (triflate)
TFPB	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
VAPOL	vaulted biphenanthrol

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