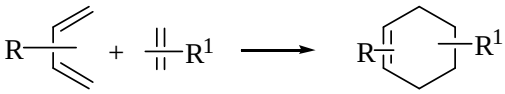
Chapter-1

Hetero-Diels-Alder reaction of carbonyl compounds: A Review

1.1 Introduction

The Diels-Alder reaction (DA) involves [4+2] cycloaddition of a conjugated diene (**1**) with dienophile (**2**) (Figure 1.1). It turned out to be an unparalled synthetic method for the construction of a six-membered ringand provided a new ground for the synthesis of many complex organic molecules.[1-3]



1 **2** **3**

Figure 1.1DA reaction of conjugated dienes with dienophiles.

The utility of the DA reaction has been further expanded by the incorporation of heteroatoms in both, the diene and the dienophile and such reactions are known as hetero-Diels-Alder (HDA) reactions.[4] The HDA reaction is one of the most used synthetic strategies for the construction of six- membered heterocyclic compounds[5] having the basic skeleton of several drugs and natural products.[6] Various heterodienes and heterodienophiles having oxygen, nitrogen, phosphorous and sulphur atom(s) are capable to undergo HDA reactions.

HDA reactions involving carbonyl compounds as hetero-dienes and/or hetero-dienophiles have made a number of substituted six-membered oxygen containing heterocycles, namely dihydropyrans accessible. This ring occurs as structural pattern in many biologically active natural products.[7] Present review places main emphasis on oxa-HDA reactions.

There are two types of the HDA reactions of the carbonyl compounds, namely the normal electron demand (NED) and the inverse electron demand (IED) cycloadditions (Figure 1.2).[8]

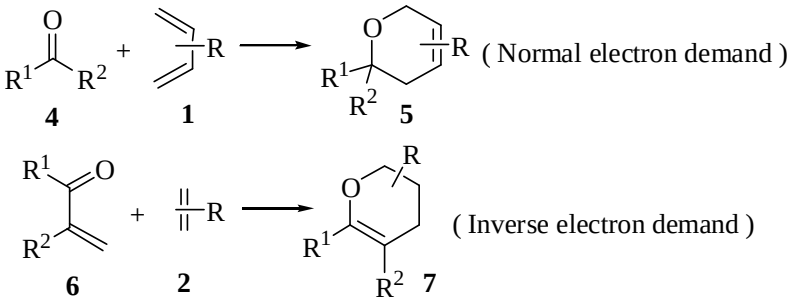


Figure 1.2NED and IED HDA reactions involving carbonyl functionality.

For the NED HDA reaction, the carbonyl functionality **(4)** reacts with the conjugated diene **(1)** as the hetero-dienophile. FMO analysis reveals that for this type of reaction, the Highest Occupied Molecular Orbital (HOMO) of the diene interacts with the Lowest Unoccupied Molecular Orbital (LUMO) of the carbonyl heterodienophile (Figure. 1.3). However, the NED HDA reaction of the carbonyl compounds proceeds poorly with the aliphatic and aromatic aldehydes and ketones unless highly reactive dienes and/or Lewis acid catalysts are used.[5a] The activation of the carbonyl group occurs by co-ordinating the lone-pair electrons of the oxygen atom with a Lewis acid. The coordination of the lone-pair electrons to the Lewis acid decreases energy of the LUMO of dienophile; thus the energy difference between the $HOMO_{diene}$ and $LUMO_{dienophile}$ is reduced as compared to the reactions taking place in the absence of theLewis acid. This effect of Lewis acid enhances the reactivity of the carbonyl functionality leading to a facile reaction between the dienophile and the diene.

Similarly, in IED cycloaddition reactions, the Lewis acid co-ordinates with the oxygen atom of the 1,3-heterodiene and leads to decrease in the energies of the FMOs

resulting in the reduction of the energy gap of LUMO of heterodiene and HOMO of alkene which results in favourable reaction conditions.

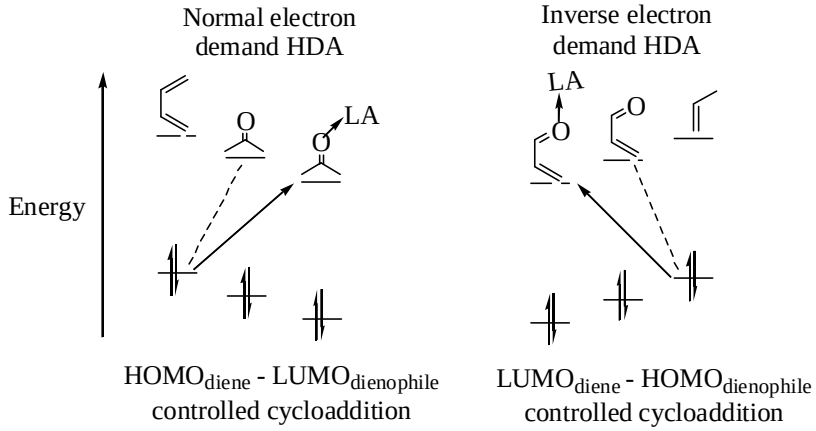


Figure 1.3 FMO presentation showing the effect of Lewis acids on carbonyl groups**.**

1.2 Mechanistic pathways for the HDA reaction of the carbonyl compounds

The oxa-HDA reaction may follows one of the two courses:

a) a traditional DA cycloaddition, or

b) Mukaiyama-aldol reaction followed by a cyclization step.

The traditional DA cycloaddition reaction pathway can take place either as a concerted reaction with an asynchronous transition state or a stepwise mechanism. On the other hand, the Mukaiyama-aldol reaction pathway occurs via a stepwise mechanism with an acyclic intermediate**(8)**, which undergoes ring-closure leading to the final HDA adduct **(9)** (Figure 1.4).

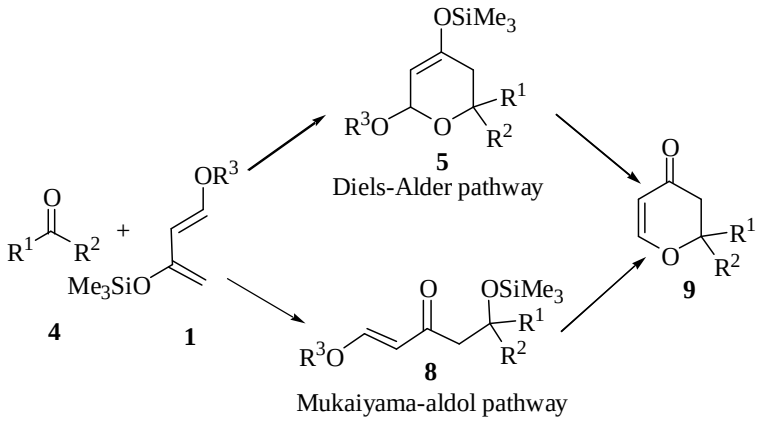


Figure 1.4 Possible pathways for the HDA reaction of carbonyl compound.

The mechanism of the HDA reaction has been investigated theoretically and results indicate that depending on the reaction conditions, it may occurs concertedly or through a step-wise mechanism (Figure 1.5).[9-11] The HDA reactions between aldehydes and 1,3-butadiene were found to follow a concerted mechanism with asynchronous transition state with high activation energy barrier.[9a,b] Similar results were obtained for the other uncatalyzed oxa-HDA reactions. However, course of the catalytic cycloaddition reactions depends on the Lewis acid used as catalyst. For example, the HDA reaction of benzaldehyde with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) was found to follow a concerted mechanism in the presence of $ZnCl_2$[10b] or α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) catalyst,[10d] while in the of presence of BF_3[10b] and aluminium complexes,[10f] the reaction occurred via a stepwise mechanism.

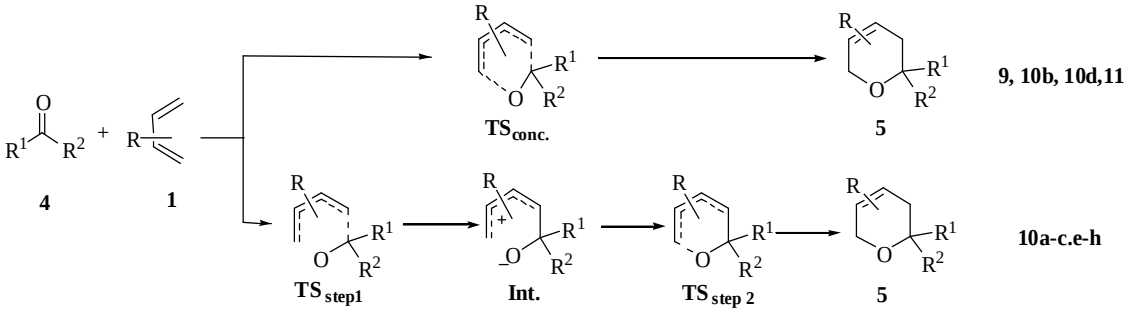


Figure 1.5 Concerted and stepwise cycloaddition mechanisms for the HDA reaction of carbonyl compounds.

In this review, HDA reactions involving carbonyl functionality have been discussed underthe following sub-sections.

1.3 HDA reactions of the carbonyl functionality as dienophile.

1.3.1 HDA reactions of the carbonyl functionality as dienophile without catalyst.

1.3.1.1 HDA reactions of the unactivated carbonyl compounds.

1.3.1.2 HDA reactions of the activated carbonyl compounds.

1.3.2 HDA reactions of the carbonyl functionality as dienophile in the presence of catalyst.

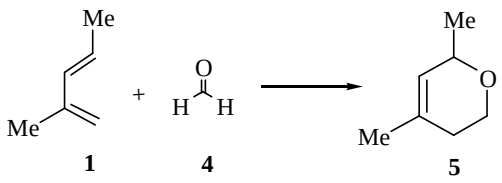
1.3 HDA reactions of the carbonyl functionality as dienophile

1.3.1 HDA reactions ofthe carbonyl functionality as dienophile without catalyst

1.3.1.1 HDA reaction of the unactivated carbonyl compound

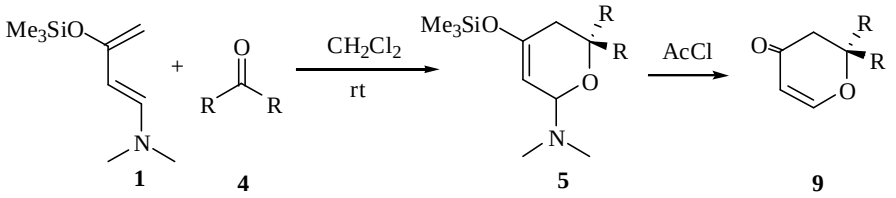
Carbonyl compounds as dienophile are much less reactive; thus, only a limited number of HDA reactions between the unactivated carbonyl compounds and simple dienes have been reported.These reactions need long reaction time, high pressure and high temperature. In view of this, the majority of these reactions are restricted either to the reaction of highly electron-rich dienes with simple carbonyl compound or the reaction of highly activated carbonyl compound with simple dienes.

Qresham and Steadman reported HDA reaction of formaldehyde **(4)** with methylpentadiene **(1)**(Scheme 1.1).[12]



Scheme 1.1

Rawal et al.[13] reported the DA reactions of the carbonyl compounds **(4)** with 1-dimethylamino-3-siloxy-1,3-butadiene (Rawal's diene) **(1)**; the [4+2] cycloadducts **(5)** after workup with acetylchloride afforded the corresponding dihydropyrones **(9)** (Scheme 1.2).

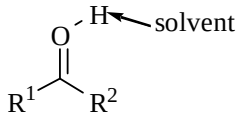


1 **4** **5** **9**

R= Alkyl, Aryl, Acyl, H

Scheme 1.2

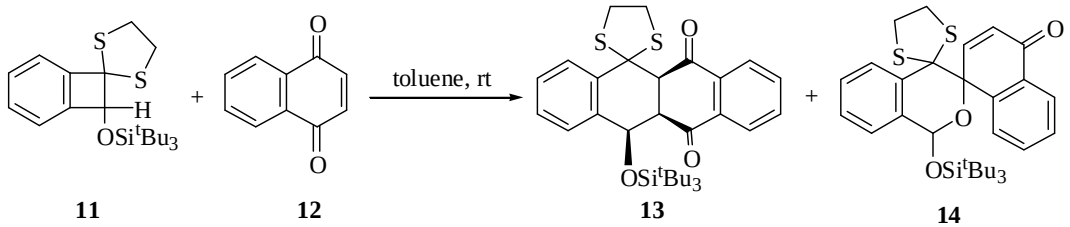
They investigated effect of the solvent and concluded that the higher reactivity in chloroform was due to a C-H---O=C hydrogen bond interaction between $CHCl_3$ and the carbonyl oxygen atom (Figure 1.6).[14]



10

Figure 1.6 Activation of carbonyl group by a hydrogen bond interaction with a protic organic solvent**.**

Adiwidjaja et al. carried out the HDA reaction of 1,4-naphthoquinone **(12)** with benzocyclobuteneprecursors **(11)** having 1-silyloxy group to give the corresponding cycloadduct, isochromane **(14)** as the major product (Scheme 1.3).[15]

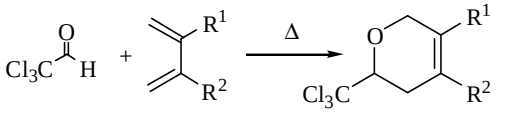


11 **12** **13** minor **14** major

Scheme 1.3

1.3.1.2 HDA reactions of the activated carbonyl compounds

Dale and Sisti accomplished the HDA reaction of chloral **(4)** with various 1,3-dienes**(1)** by heating in a sealed tube to give 5,6-dihydro-1,2-pyrans **(5)** in good yields (Scheme 1.4).[16]

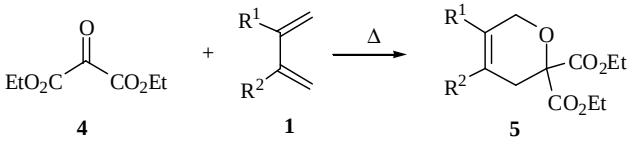


4 **1** **5**

5	R^1	R^2	% yield
a	H	Me	30
b	Me	Me	53

Scheme 1.4

Fong[17a] and Ruden and Bonjouklian[17b] reported the reaction between diethyl ketomalonate **(4)** (synthetic equivalent of carbondioxide) and simple dienes **(1)** to afford [4+2] cycloadducts **(5)** in good yields (Scheme 1.5).

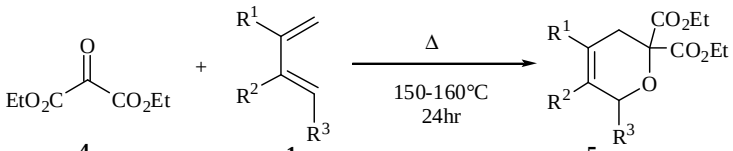


4 **1** **5**

5	R^1	R^2
a	H	H
b	Me	H
c	Me	Me

Scheme 1.5

A similar reaction was accomplished with trimethyl-silyloxy-1,3-diene **(1)** (Scheme 1.6).[18]

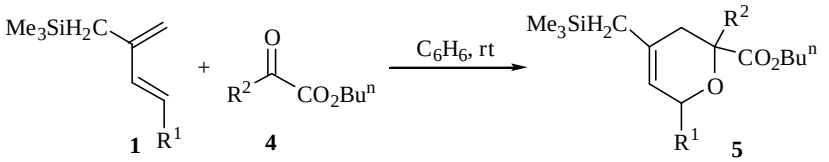


4 **1** **5**

5	R^1	R^2	R^3
a	$OSiMe_3$	H	OMe
b	H	H	$OSiMe_3$
c	$OSiMe_3$	H	H
d	$OSIMe_3$	H	Me

Scheme 1.6

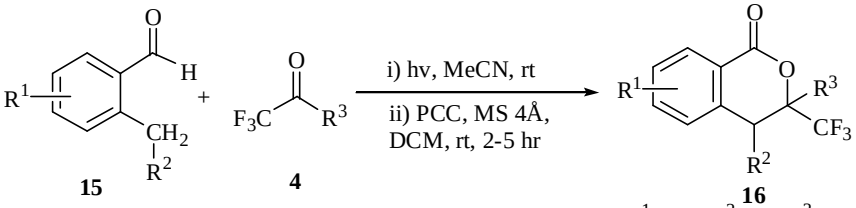
Hosomi et al. found that n-butyl glyoxylate and ketomalonate reacted with silylsubstituted 1,3-dienes to afford dihydropyrans in good yields (Scheme 1.7).[19]



5	R^1	R^2	%yield
a	H	H	74
b	OMe	H	93
c	H	CO_2Et	71
d	OMe	CO_2Et	100

Scheme 1.7

Tokaki et al. achieved the HDA reaction of α-hydroxyl-*o*-quinodimethanes, generated photochemically from *o*-tolualdehydes **(15)** with trifluoromethyl ketones which after subsequent oxidation with PCC gave 1-isochromanones **(16)** as a formal oxidative [4+2] cycloaddition adduct (Scheme 1.8).[20]



16	R^1	R^2	R^3	%yield
a	4,6-$(Me)_2$	H	Ph	75
b	4-Me	H	Ph	57
c	H	H	Ph	68
d	4-F	H	Ph	54
e	H	Ph	Ph	44
f	H	*n*-Hx	Ph	61
g	4,6-$(Me)_2$	H	Me	30
h	4,6-$(Me)_2$	H	Bn	39
i	4,6-$(Me)_2$	H	C≡C-^{n}Bu	75

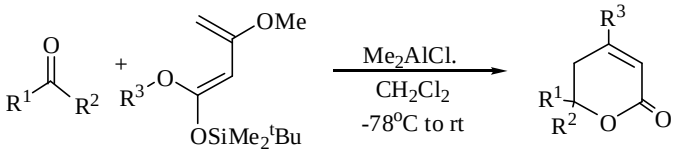
Scheme 1.8

1.3.2 HDA reactions of the carbonyl functionality as dienophile in the presence of catalyst

As the HDA reaction of the carbonyl compounds occurs sluggishly, it is often catalyzed with a Lewis acid or organocatalyst. The complexation of the carbonyl oxygen with a catalyst activates its dienophilic activity by lowering the LUMO energy, as discussed earlier.

1.3.2.1 Using Lewis acid as catalyst

In 1982, Broekhof et al. for the first time carried out successfully the HDA reaction of the non-activated aldehydes with simple dienes using a mixture of $AlCl_3$ or $SnCl_4$ and nitroalkane as catalyst with good yields; but this catalyst system turned out to be explosive and difficult to handle.[21] Mann et al. reported the synthesis of 6-substituted-5,6-dihydropyrones**(17)** from the HDA reaction of 1,3-dialkoxy-1-trialkoxy-1,3-butadiene (Brassard's diene) **(1)** analogoues grafted on a modified Merrifield resin with various aldehydes and ketones using an equivalent amount of Me_2AlCl as catalyst (Scheme 1.9).[22]

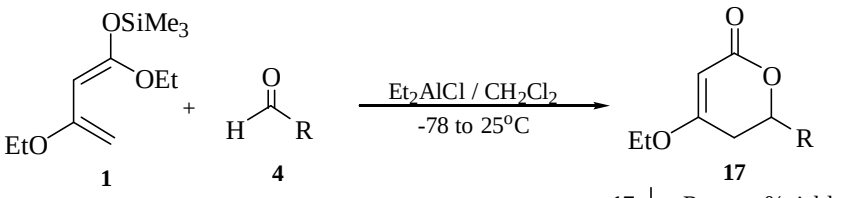


4 **1** **17**

17	ketone	R^3	%yield
a	Cyclohexanone	Me	55
b	Acetophenone	Me	24
c	Benzophenone	Me	39

Scheme 1.9

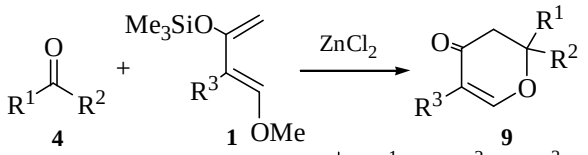
Winkler and Oh used various Lewis acids for the HDA reaction of Brassard's diene **(1)** with aldehydes **(4)** and found that diethylaluminium chloride (Et_2AlCl) gave the best results (Scheme 1.10).[23]



17	R	%yield
a	*n*-Hx	68
b	Ph	79
c	*Cy*	83
d	*t*-Bu	96
e	$(CH_2)_2OBn$	33
f	*n*-Pe	97

Scheme 1.10

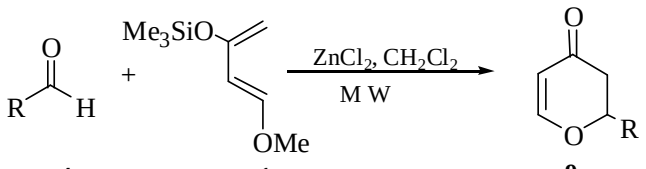
Danishefsky's group instead used $ZnCl_2$ as catalyst.[24] It was found that benzaldehyde reacted with Danishefsky's diene to give the *trans*-substituted dihydropyranone preferentially in the presence of BF_3 as the Lewis acid catalyst, while a *cis*-substituted dihydropyranone was obtained on using $ZnCl_2$ as catalyst.[24d] Similarly, Page et al. prepared 2,2-disubstituted-2,3-dihydropyran-4-ones **(9)** from the $ZnCl_2$ catalyzed HDA reaction of substituted Danishefsky's diene **(1)** with activated ketones **(4)** (Scheme 1.11).[25]



9	R^1	R^2	R^3	% yield
a	Me	CO_2Et	H	72
b	Me	CO_2Me	H	69
c	Me	CN	H	78
d	Me	CO_2Me	H	75
e	CH_2Br	CO_2Et	H	81
f	CO_2Et	CO_2Et	H	88
g	Me	CO_2Me	OAc	74
h	CO_2Et	CO_2Et	OAc	86

Scheme 1.11

Osborn et al. accomplished the microwave irradiated HDA reaction between Danishefsky's diene **(1)** and unactivated aldehydes **(4)** in the presence of $ZnCl_2$ catalyst to afford 2,3-dihydro-4*H*-pyran-4-ones **(9)** in excellent yield (Scheme 1.12).[26]

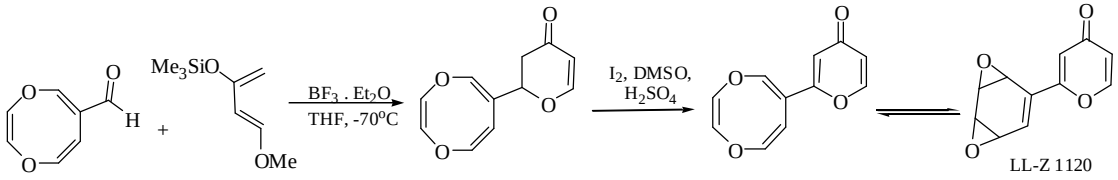


4 **1** **9**

9	R	%yield
a	*m*-F-C_6H_4	92
b	Ph	83
c	(*E*)-Me-CH=CH	94

Scheme 1.12

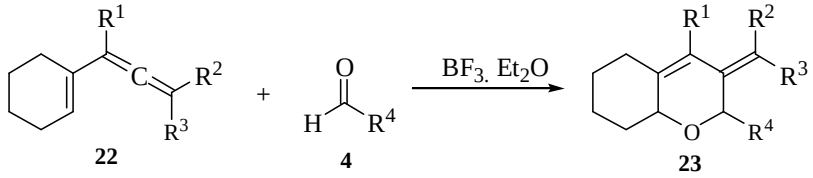
Doz et al. used boron trifluoride etherate ($BF_3.Et_2O$) as catalyst for the cycloaddition reaction of unsaturated aldehydes **(18)** with electron-rich Danishefsky's diene **(1)** for the simple synthesis of the antibiotic, LL-Z1120 **(21)** (Scheme 1.13).[27]



18 **1** **19** **20** **21**

Scheme 1.13

Regas and coworkers reported the HDA reaction of unactivated aldehydes **(4)** with vinylallenes **(22)** in the presence of $BF_3.Et_2O$ as catalyst and found the reaction highly regio- and facial-selective (1.14).[28] On computing the above reaction using DFT method, it was concluded that in the absence of the catalyst, reaction followed pericyclic mechanism, while in the presence of BF_3 as catalyst, the reaction occurred through a polar transition state.[10e,28]



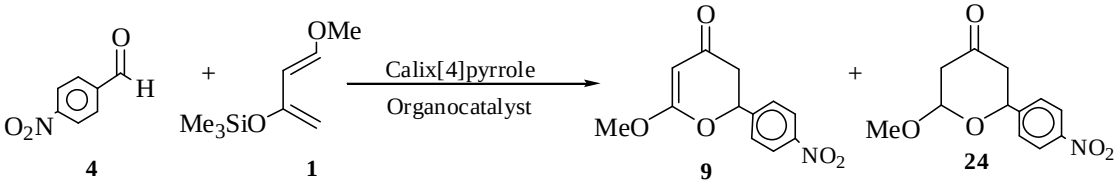
23	R^1	R^2	R^3	R^4	%yield
a	Me	Me	H	Et	63
b	Me	Me	H	*i*-Pr	26
c	Me	Me	H	Ph	76
d	Me	Ph	H	Et	49
e	Me	Ph	H	*i*-Pr	24
f	Me	Ph	H	Ph	74
g	Et	Me	H	Et	70
h	Et	Me	H	*i*-Pr	60
i	Et	Me	H	Ph	62
j	Et	Ph	H	Et	54
k	Et	Ph	H	*i*-Pr	36
l	Et	Ph	H	Ph	40
m	Et	Me	Me	Ph	39

Scheme 1.14

A number of other Lewis acids, such as Pd(II) bisphosphine,[29] montmorillonite clay,[30] cationic iron (III) porphyrin catalyst {[Fe(TPP)]BF_4},[31] lanthanide(III) salts (Yb or Sc) of superacids,[32] and others[33] have also been used.

1.3.2.2 Using organocatalysts

Cafro et al. reported the HDA reaction of *p*-nitrobenzaldehyde **(4)** with Danishefsky's diene **(1)** (5:1) using calix(4)pyrrole organocatalyst to obtain the products **9** and **24** in 33% and 50% yields respectively (Scheme 1.15).[34]



Scheme 1.15

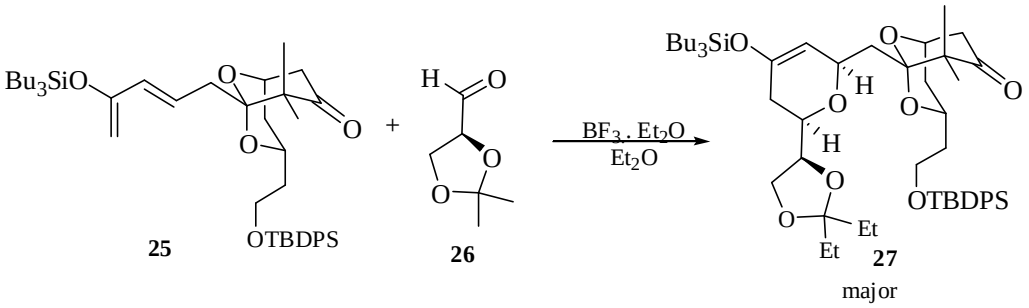
1.4 Asymmetric HDA reaction of the carbonyl functionality as dienophile:

It has been found that optically active six-membered heterocyclic ring can be constructed conventionally through an asymmetric HDA reaction. In this context the

HDA reaction with carbonyl compound is found to be a powerful method for the formation of both carbon-carbon and carbon-oxygen bonds to give pyran derivative stereoselectively. For this purpose two procedures have been developed namely using a chiral diene and/or a chiral dienophile or using a chiral catalyst as chiral auxillary.

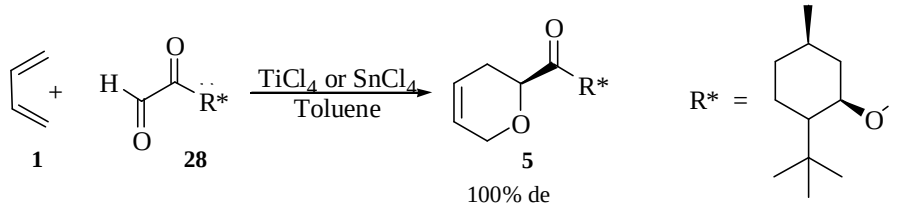
1.4.1 Using chiral carbonyl compounds as dienophile

Burke et al. described the total synthesis of the northern hemisphere (C1-C16) of bryostatin, which is a very important anticancer drug agent, from Lewis acid catalyzed HDA reaction of chiral pentylidene-protected glyceraldehydes **(26)** with siloxyldiene **(25)** in the presence of $BF_3.Et_2O$. On applying this methodology three diastereomers was obtained in high yield and the major isomer **(27)** could beeasily separated (Scheme 1.16).[35]



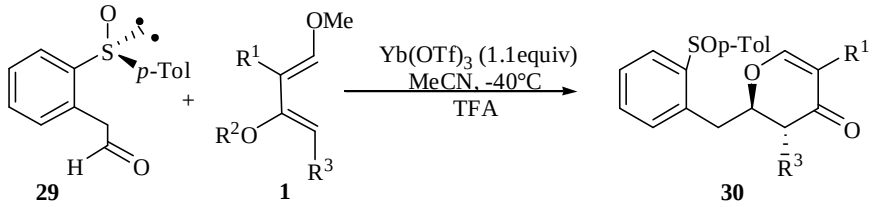
Scheme 1.16

Theasymmetric HDA reaction of (*R*)-8-phenylmenthyl glyoxylate (**28**) with 1,3-butadiene **(1)** was reported by Jurezak et al.in the presence of $SnCl_4$ or $TiCl_4$ as catalyst to afford a cycloadduct **(5)** as the only major stereoisomer (Scheme 1.17).[36]



Scheme 1.17

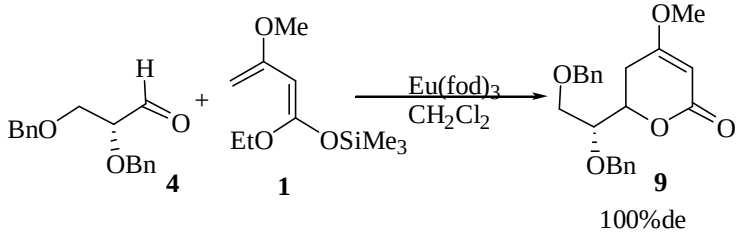
On the other hand, $Yb(OTf)_3$ catalyzed asymmetric HDA reactions of (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetaldehyde (**29**) with Danishefsky's and related dienes **(1)** gave 2,3-dihydro-4*H*-pyran-4-ones **(30)** with complete stereoselectivity (Scheme 1.18). The major isomer was *trans* which indicated the reaction to follow a stepwise mechanism involving a Mukaiyama-aldol condensation followed by intramolecular cyclization.[37]



1, 30	R^1	R^2	R^3	%yield
a	H	Si^tBu_3	H	54
b	Me	$SiMe_3$	H	57
c	Me	$SiMe_3$	Me	100
d	Me	Si^tBu_3	Me	100

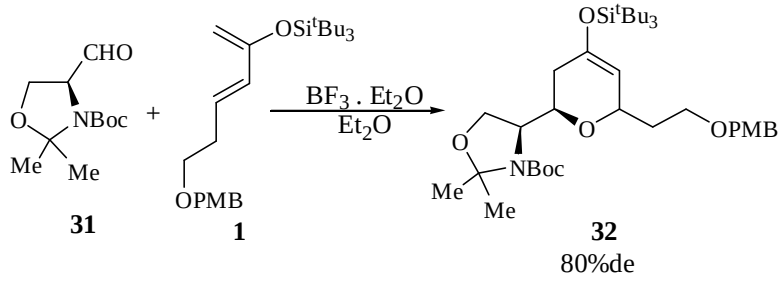
Scheme 1.18

In the context of the total synthesis of the phorboxazole B, potent antitumour agent, HDA reaction of a mannitol-derived aldehyde (**4**) was accomplished with Brassard's diene (**1**) catalyzed by $Eu(fod)_3$ (Scheme 1.19).[38]



Scheme 1.19

Fontana et al. in 2010, carried out BF_3 mediated HDA reaction between Danishefsky's diene **(1)** and Garner aldehyde (**31**) to give *trans*-2,6-disubstituted tetrahydropyranone **(32)** with excellent diastereoselectivity towards the *exo-syn* adduct (Scheme 1.20).[39]

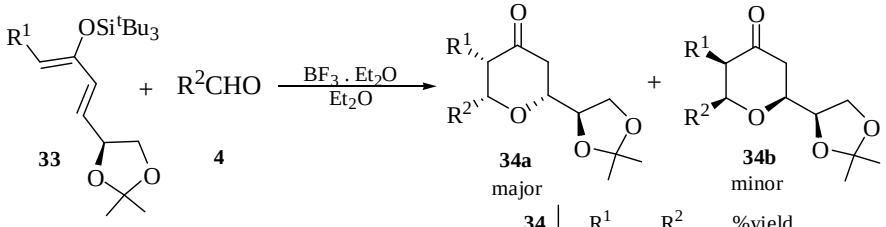


31 **1** **32**
80%de

Scheme 1.20

1.4.2 Using chiral dienes

A series of chiral dienes have been used as chiral auxiliaries in asymmetric HDA reactions. Stoodley et al. accomplished asymmetric HDA reaction of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyldiene with activated aldehydes catalyzed by Ln(fod)$_3$ to give the corresponding glycals with high diastereoselectivities.[40] Similarly, Wessjohann et al. reported asymmetric HDA reaction of α,β-unsaturated aldehydes with dienes **(33)** having a chiral moiety at position 5in the presence of $BF_3.Et_2O$ to give highly substituted tetrahydropyrones **(34)** with full chemo- and regio-selectivity (Scheme 1.21).[41]



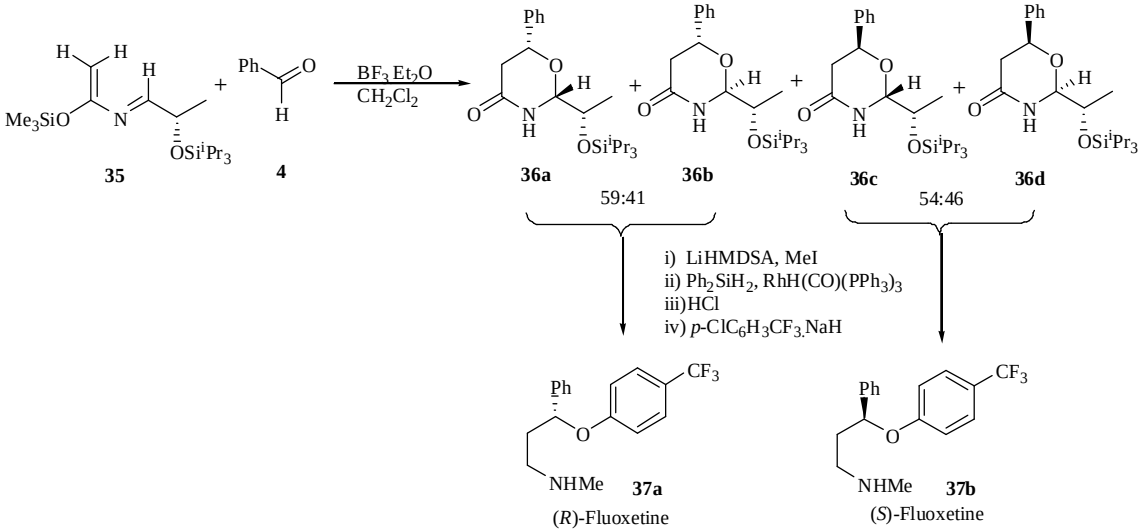
33 **4** **34a** major **34b** minor

34	R^1	R^2	%yield
a	H	Me-CH=CH	78
b	H	Ph-CH=CH	85
c	Me	Me-CH=CH	84
d	Me	Ph-CH=CH	85
e	Et	Me-CH=CH	84
f	Et	Ph-CH=CH	72
g	*i*-Pr	Me-CH=CH	77
h	*i*-Pr	Me-CH=CH	69

Scheme 1.21

Panunzio and co-workers reported a stereoselective HDA reaction of asymmetric azadiene derivatives with aldehydes to give the corresponding perhydrooxazin-4-ones, the intermediates used in the synthesis of enantiopure α-amino-β-hydroxy

acids.[42a]. On using azadienes bearing two chiral moieties, the reaction proceed with complete control of diastereoselectivity to afford a single diastereomer of the tetrahydro-1,3-oxazin-4-one.[42b] In 2006, they reported asymmetric cycloaddition of the chiral azadiene **(35)** with benzaldehyde **(4)** for the synthesis of chiral 5-phenylthio-1,3-oxazin-4-ones **(36)**. On desulfurization, which synthesized *(R)*- and *(S)*- fluoxetine **(37)** (Scheme 1.22),[42c,d] and *(R)*- and *(S)*- duloxetine.[42d]



Scheme 1.22

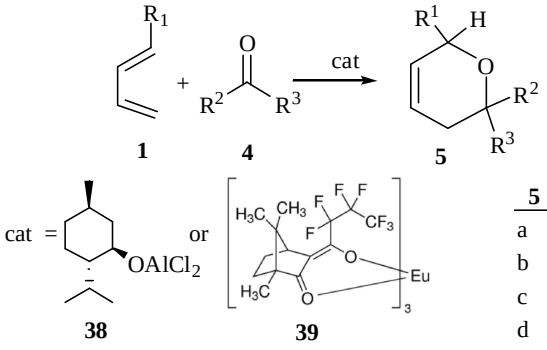
1.4.3 Using chiral catalysts

Using Lewis acid as catalyst

A number of chiral catalysts based on aluminium, copper, chromium, zinc, titanium, rhodium, magnesium, cobalt, ytterbium, manganese and zirconium complexes have been employed as chiral auxiliaries for the HDA reactions of the carbonyl compounds.

In 1987, Quimpere and Jankowshi used menthoxyaluminium dichloride **(38)** and lanthanide chiral catalysts for the HDA reaction of diethyl ketomalonate and n-butyl glyoxylates with 1-methoxybuta-1,3-diene and penta-1,3-diene. They found up

to 16% *ee* with **38** and up to 64% on using lanthanide catalyst ($Eu(hfc)_3$) **(39)** for the HDA reaction of diethyl mesoxalate and 1-methoxybuta-1,3-diene (Scheme 1.23).[43]

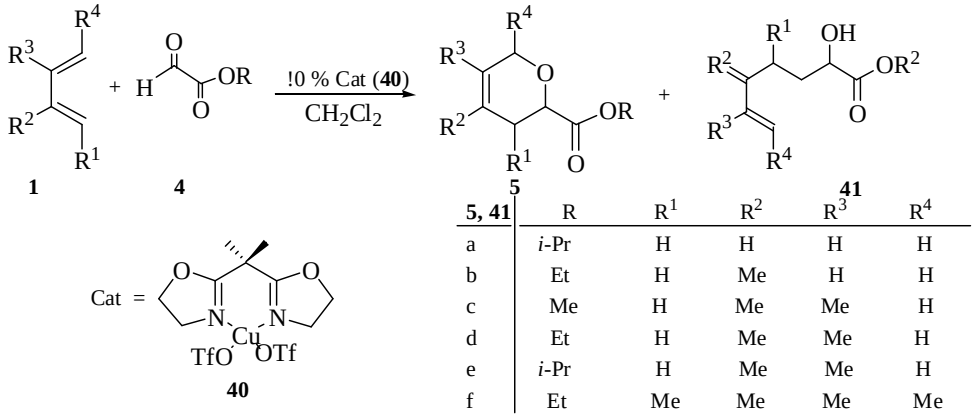


5	R^1	R^2	R^3
a	OMe	CO_2Et	CO_2Et
b	Me	CO_2Et	CO_2Et
c	OMe	H	CO_2Bu
d	Me	H	CO_2Bu

Scheme 1.23

Likewise, other aluminium based chiral catalysts have been used successfully.[9f, 44, 45]

Johannson and Jorgenson reported the use of a new copper(II)bisoxazoline **(40)** chiral catalyst for the highly enantioselective HDA reaction of glyoxylate esters **(4)** with dienes **(1)** (Scheme 1.24).[46a] They also studied the solvent effect by the use of polar solvent such as nitroethane or 2-nitropropane and observed a significant improvement of the HDA product **(5)**: ene product ratio **(41)**.[46b]

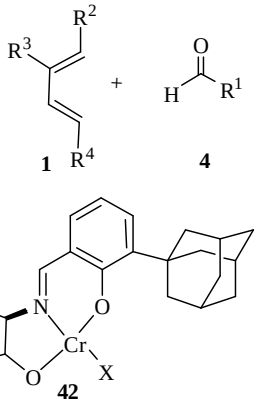


5, 41	R	R^1	R^2	R^3	R^4
a	*i*-Pr	H	H	H	H
b	Et	H	Me	H	H
c	Me	H	Me	Me	H
d	Et	H	Me	Me	H
e	*i*-Pr	H	Me	Me	H
f	Et	Me	Me	Me	Me

Scheme 1.24

The Cu-based chiral catalysts have been used successfully in many other HDA reactions.[47-52]

From the last 10 years, chiral chromium complexes have been used widely for the asymmetric HDA reaction of the carbonyl compounds. Chavez and Jacobsen discovered highly enantio- and diastereo-selective Jacobsen's tridentate Cr(III) catalyst **(42)** for the asymmetric HDA reaction between aldehydes **(4)** and dienes **(1)** bearing a single oxygen substitutent (Scheme 1.25).[53] These catalysts have been used extensively for the total synthesis of numberous natural biologically active compounds.



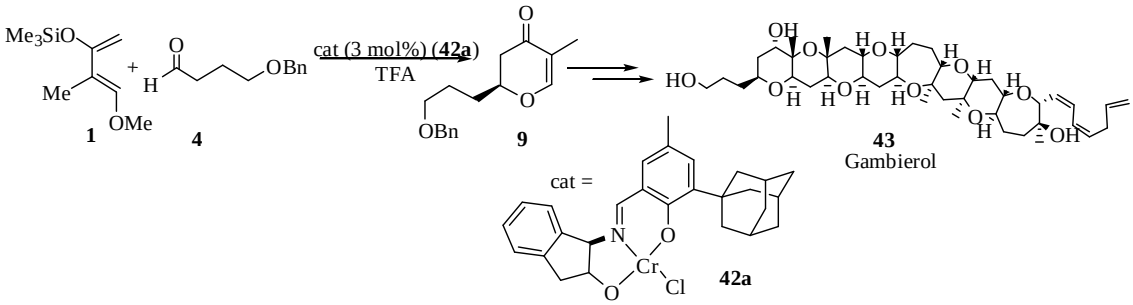
Cr(III) complex

42	X
a	Cl
b	SbF_6

5	R^1	R^2	R^3	R^4	42	%yield
a	CH_2OSiBu_3	Me	$OSiEt_3$	Me	a	90
b	CH_2OSiBu_3	Me	$OSiEt_3$	Me	b	97
c	Ph	Me	$OSiEt_3$	Me	b	72
d	*n*-Pe	Me	$OSiEt_3$	Me	b	85
e	$(CH_2)_4CH=CH_2$	Me	$OSiEt_3$	Me	a	85
f	2-Furyl	Me	$OSiEt_3$	Me	a	77
g	$(CH_2)_2C\equiv C\text{-}SiMe_3$	Me	$OSiEt_3$	Me	a	92
h	CH_2OSiBu_3	H	$OSiEt_3$	$C\equiv CH$	b	61
i	CH_2OSiBu_3	H	$OSiEt_3$	Me	b	78
j	CH_2OSiBu_3	H	Me	OMe	b	71

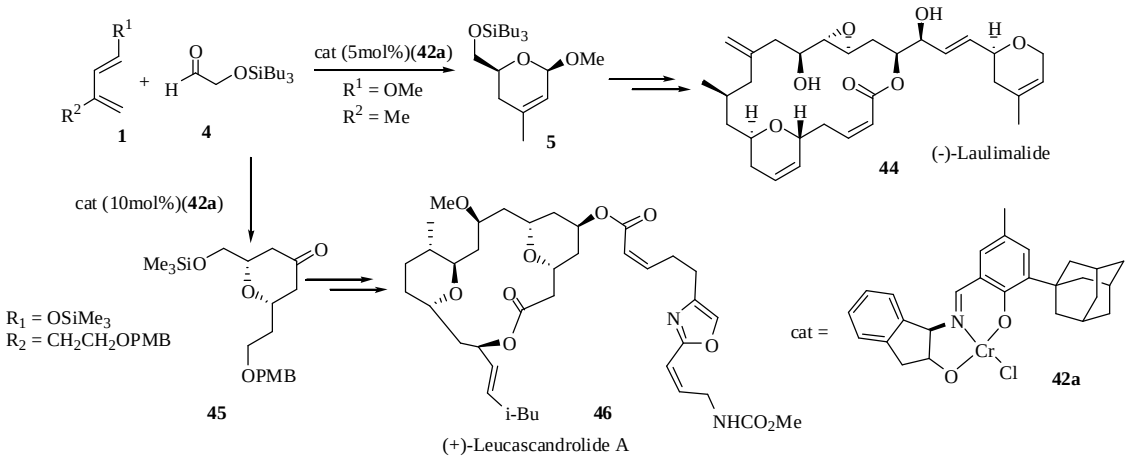
Scheme 1.25

Likewise, Cr(III) catalyst **(42a)** known as Jacobsen's catalyst has been advantageously used for accomplishing HDA reaction of Danishefsky-type diene **(1)** with γ-alkoxy aldehydes **(4);** the cycloadduct **(9)** was obtained in good yield with high enantiomeric purity. This product was used as the precursor for the A–D-ring system of the marine ladder toxin, gambierol **(43)** (Scheme 1.26).[54]



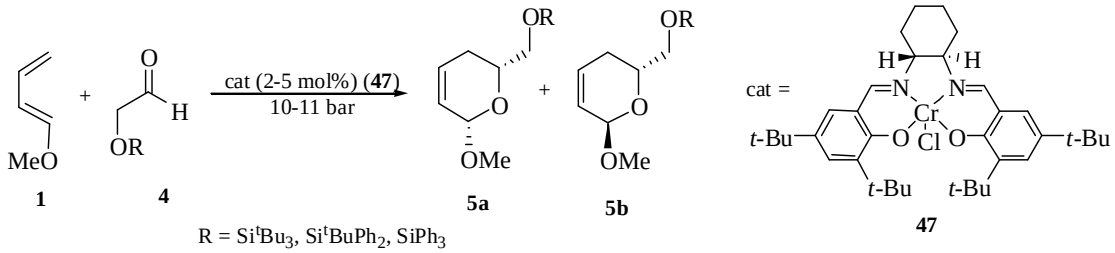
Scheme 1.26

Paterson et al. extended the above methodology for the synthesis of(-)-laulimalide **(44),** apotent microtubule-stabilising anticancer agent(Scheme 1.27).[55a] Furthermore, this methodology was extended to the diastereo- and enantioselective total synthesis of (+)-leucascandrolide A **(46)**, a cytotoxic 18-membered macrolide with high yield (Scheme 1.27).[55b] Other reported uses of Jacobsen's catalyst include synthesis of 11-desmethyllaulimalide, laulimalide,[56] segments of the phorboxazoles,[57,58] and antitumor agents (-)-dactylolide[59], (-)-lasonolide A[60], anguicnomycin C[61] and (-)-dictyostatin.[62]



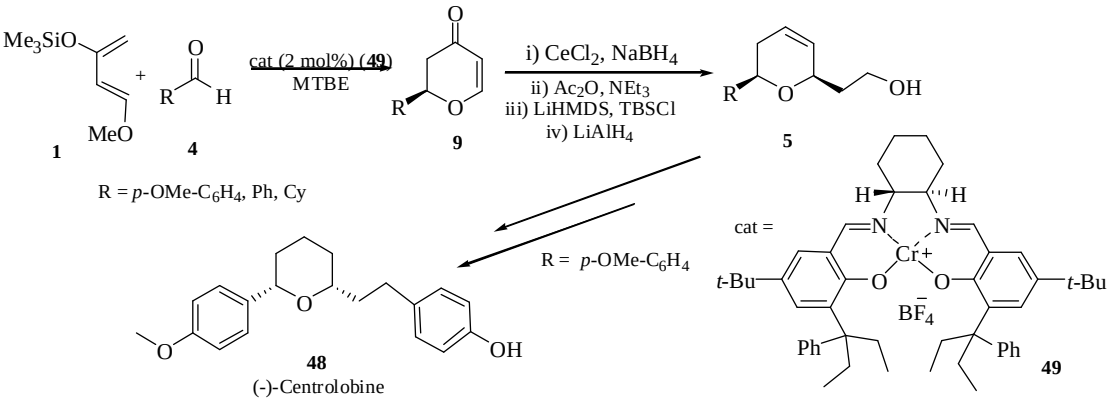
Scheme 1.27

Jurczak et al. used (salen)Cr(III)Cl complex **(47)**, developed by Jacobsen et al. for the high-pressure enantioselective HDA reaction of various O-protected glycolaldehydes **(4)** with 1-methoxybuta-1,3-diene **(1)** to afford the corresponding cycloadducts **(5a and 5b)** in good yields (Scheme 1.28).[63]



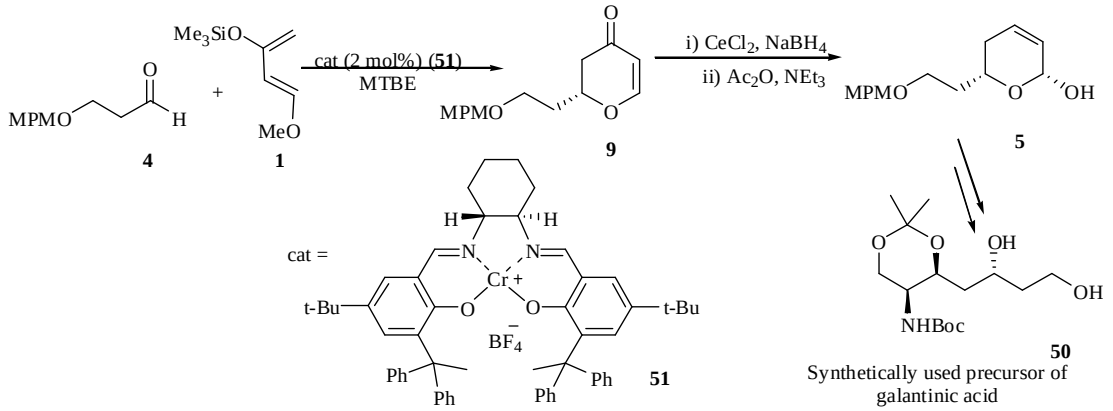
Scheme 1.28

Furthermore in 2010, they applied this methodology for the synthesis of *cis*-6-substituted 2-(2-hydroxyethyl)-5,6-dihydro-2*H*-pyrans **(5)** from HDA reaction of aldehyde **(4)** with Danishefsky's diene **(1)** followed by Luche reduction and Ireland Claisen rearrangement. This strategy was utilized for the synthesis of (-)-centrolobine **(48)** (Scheme 1.29).[64]



Scheme 1.29

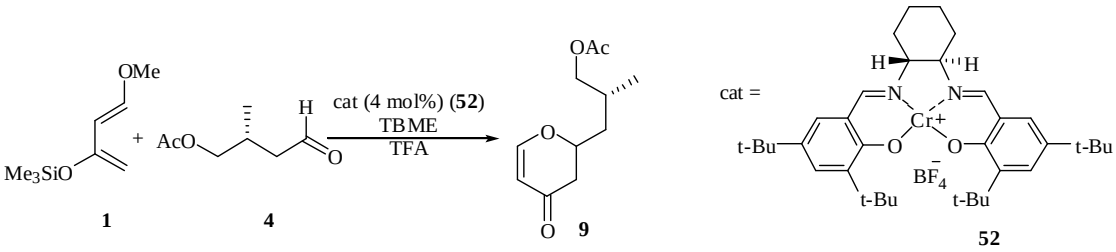
In 2011, they reported the synthesis of the precursor ofgalantinic acid **(50)** from the reaction of 3-(4-methoxybenzyloxy)propanal **(4)** with Danishefsky's diene **(1)** using new (salen)Cr(III) complex **(51)** as catalyst bearing a 1,1-diphenylethyl substituent at the 3-position of the salicyliden moiety (Scheme 1.30).[65]



Scheme 1.30

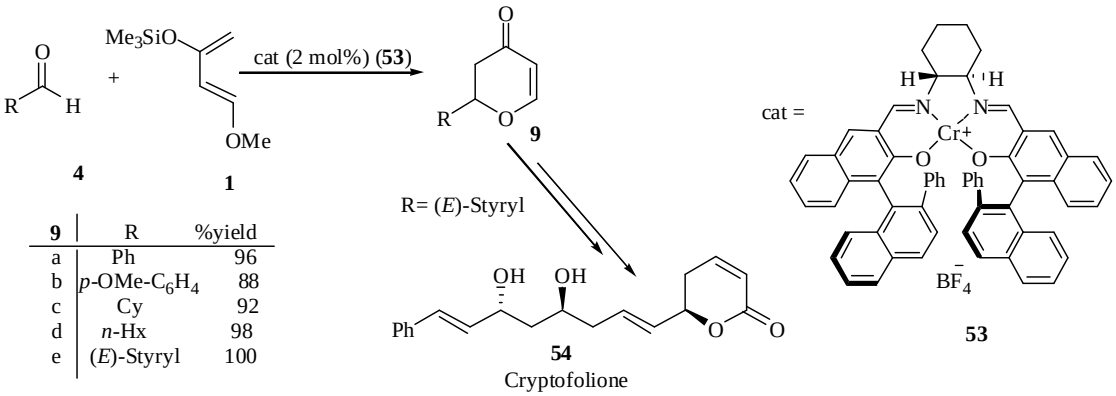
The use of chiral(salen)Cr(III) complexes catalyst was subsequently extended to the cycloaddition of 1,3-cyclohexadiene with alkyl glyoxylates.[66] Recently, Raghavan and Samanta reported the synthesis of C3-C12 subunit of the tumor growth

inhibitors, laulimalide, wherein the key step included stereoselective HDA reaction using (*S*,*S*)-Cr-salen-BF_4 **(52)** (Scheme 1.31).[67]



Scheme 1.31

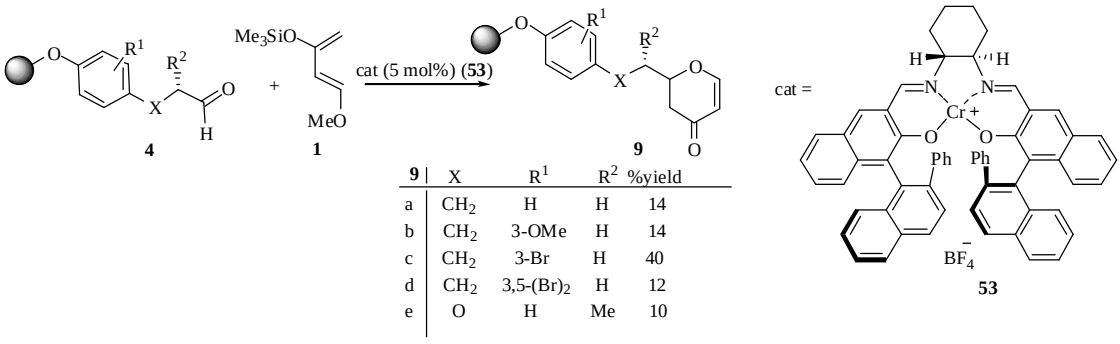
The chiral cationic (salen)Cr(III) complexes **(53)** have been used for the total synthesis of cryptofolione **(54)** (Scheme 1.32).[68]



9	R	%yield
a	Ph	96
b	*p*-OMe-C_6H_4	88
c	Cy	92
d	*n*-Hx	98
e	(*E*)-Styryl	100

Scheme 1.32

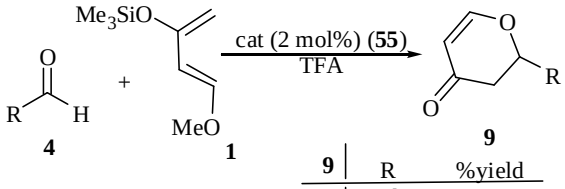
In 2006, Waldmann et al. described the enantioselective HDA reaction of polymer-bound aldehydes **(4)** with Danishefsky's diene **(1)** by employing 5 mol% of **53** (Scheme 1.33). The target compounds constituted the core structure of a class of natural products having biological activity.[69]



9	X	R^1	R^2	%yield
a	CH_2	H	H	14
b	CH_2	3-OMe	H	14
c	CH_2	3-Br	H	40
d	CH_2	3,5-$(Br)_2$	H	12
e	O	H	Me	10

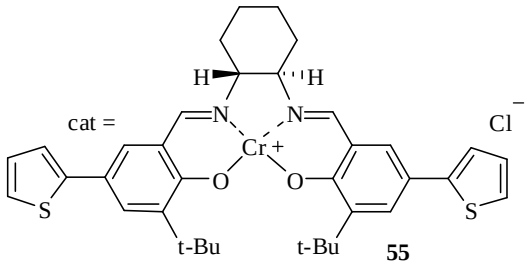
Scheme 1.33

In 2007, Schulz et al. carried out the HDA reaction of aldehydes with Danishefsky's diene using electro-polymerised chiral salen–chromium heterogeneous catalyst to obtain the expected cycloadducts successfully. These insoluble catalysts were able to be re-used several times.[70a] Furthermore, in 2008, they synthesized a new chiral thiophene-salen-chromium complex **(55)** to promote similar HDA reactions (Scheme 1.34).[70b]



4 **1** **9**

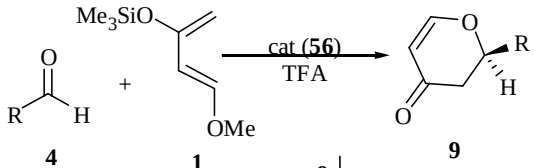
9	R	%yield
a	Ph	56
b	*o*-OMe-C_6H_4	60
c	*o*-Cl-C_6H_4	60
d	*p*-CN-C_6H_4	69
e	2-Thiophenyl	56
f	2-Furyl	14
g	Bn	60
h	(*E*)-Styryl	45
i	n-Hx	72
j	Cy	72



55

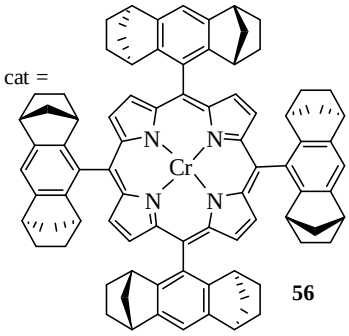
Scheme 1.34

In 2006, Berkessel et al. developed chiral chromium(III) porphyrin **(56)** catalysts for the highly enantioselective HDA reaction of various aldehydes **(4)** with a variety of dienes **(1)** (Scheme 1.35).[71]



4 **1** **9**

9	R	%yield
a	Ph	85
b	Cy	76
c	*n*-Hx	75
d	(*E*)-Styryl	55
e	2-Furyl	70
f	2-Py	70

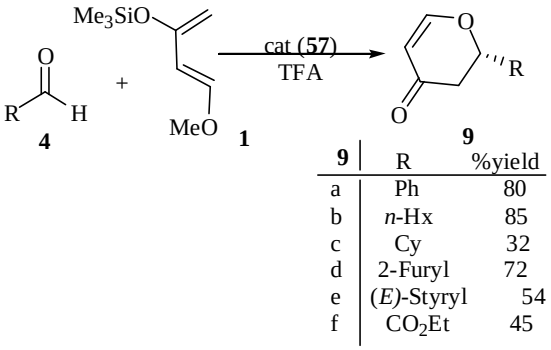


56

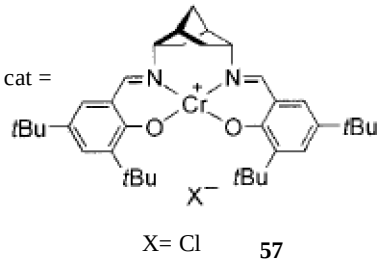
Scheme 1.35

Furthermore, in 2006, they discovered a newly chiral chromium–salen complex **(57)**, containing *endo*,*endo*-2,5-diaminonorbornane (DIANANE) moiety for

the successful HDA reactions of Danishefsky's diene **(1)** with various aldehydes **(4)** to afford the corresponding cycloadducts **(9)** in good yield with high enantioselectivity (Scheme 1.36).[72]

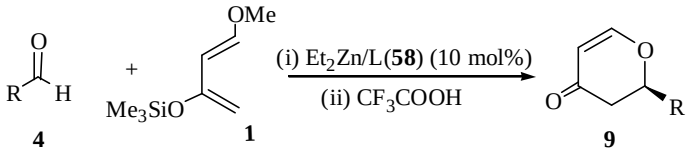


9	R	%yield
a	Ph	80
b	*n*-Hx	85
c	Cy	32
d	2-Furyl	72
e	(*E*)-Styryl	54
f	CO_2Et	45

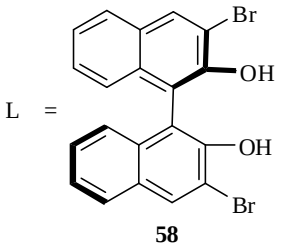


Scheme 1.36

In 2002, Ding et al. carried out enantioselective HDA reaction of Danishefsky's diene **(1)** with aldehyde **(4)** catalyzed by 1,1′-bi-2-naphthol (BINOL) zinc complex, prepared from Et_2Zn and 3,3′-Br_2-BINOL**(58)** in situ to give 2-substituted 2,3-dihydro-4*H*-pyran-4-one **(9)** (Scheme 1.37).[73]

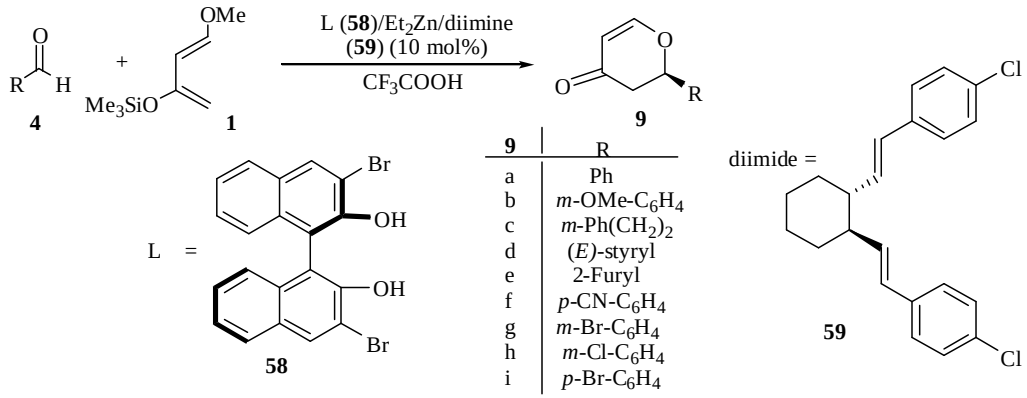


9	R	%yield
a	Ph	> 99
b	*m*-OMe-C_6H_4	> 99
c	Ph-$(CH_2)_2$	40
d	(*E*)-Styryl	34
e	2-Furyl	> 99
f	*p*-CN-C_6H_4	> 99
g	*m*-Br-C_6H_4	> 99
h	*m*-Cl-C_6H_4	92
i	*p*-Br-C_6H_4	> 99



Scheme 1.37

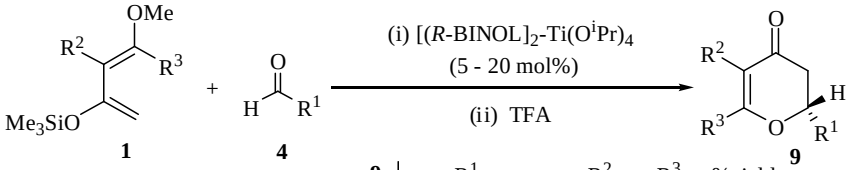
Furthermore, a new chiral zinc catalyst, bearing **58** and a diimine activator **(59)** was developed and applied for the HDA reaction (Scheme 1.38).[74]



9	R
a	Ph
b	*m*-OMe-C_6H_4
c	*m*-Ph$(CH_2)_2$
d	(*E*)-styryl
e	2-Furyl
f	*p*-CN-C_6H_4
g	*m*-Br-C_6H_4
h	*m*-Cl-C_6H_4
i	*p*-Br-C_6H_4

Scheme 1.38

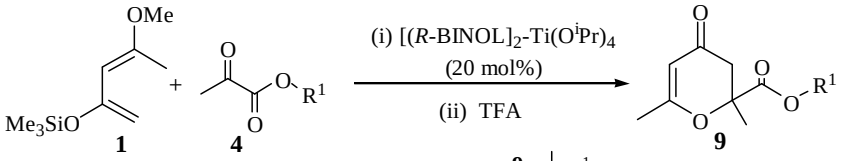
Numberous chiral titanium catalysts have been successfully employed to catalyse HDA reactions. Feng and co-worker applied the BINOL-Ti(O^iPr)$_4$ catalyst for the HDA reactions between Danishefsky's diene **(1)** and aldehydes **(4)** to prepare optically active 2,5-disubstituted and 2,6-disubstituted dihydropyrones **(9)** with up to 99% yield and 99% *ee*. On the basis of the isolated intermediate, they proposed the mechanism as Mukaiyama aldol pathway. The above methodology was employed for the synthesis of (*R*)-(+)-hepialone, an important natural product in single step (Scheme 1.39).[75]



9	R^1	R^2	R^3	%yield
a	Ph	H	Me	70
b	*m*-Cl-C_6H_4	H	Me	83
d	*p*-NO_2-C_6H_4	H	Me	99
e	*m*-OMe-C_6H_4	H	Me	61
f	*p*-OMe-C_6H_4	H	Me	83
g	2-Naphthyl	H	Me	82
h	*p*-F-C_6H_4	H	Me	89
i	*p*-CN-C_6H_4	H	Me	86
j	*n*-Pe	H	Me	77
k	Ph	Me	H	86
l	*o*-Cl-C_6H_4	Me	H	99
m	*o*-NO_2-C_6H_4	Me	H	99
n	*p*-OMe-C_6H_4	Me	H	99
o	2-Py	Me	H	98

Scheme 1.39

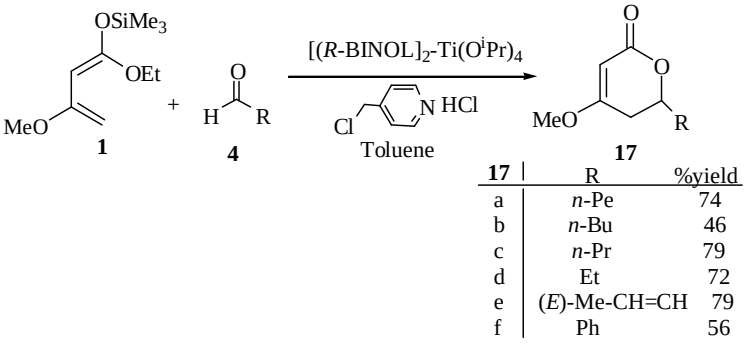
Similarly, these workers also reported HDA reactions of 4-methoxy-2-trimethylsiloxy-penta-1,3-diene **(1)** with pyruvates **(4)** using (*R*)-BINOL-Ti(O^iPr)$_4$ catalyst (Scheme 1.40).[75c,d]



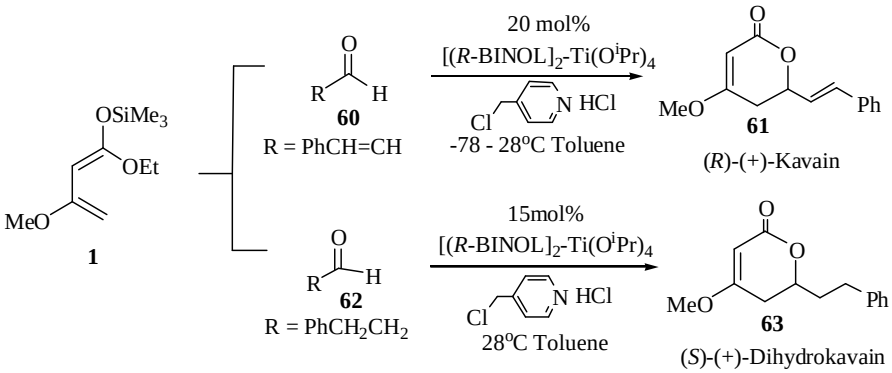
9	R^1	%yield
a	Et	85
b	Me	82
c	*i*-Pr	76

Scheme 1.40

Furthermore in 2008, the same workers extended this methodology to the asymmetric HDA reaction of the aldehydes **(4)** with Brassard's diene **(1)** using (*R*)-BINOL-Ti(O^iPr)$_4$ and 4-picolyl chloride hydrochloride system as catalyst to afford δ-lactone derivatives **(17)** (Scheme 1.41). By using this procedure, they also synthesized (*R*)-(+)-kavain **(61)** and (*S*)-(+)-dihydrokavain **(63)** natural products in one step from cinnamaldehyde **(60)** and 3-phenylpropionaldehyde **(62)** respectively.[76]

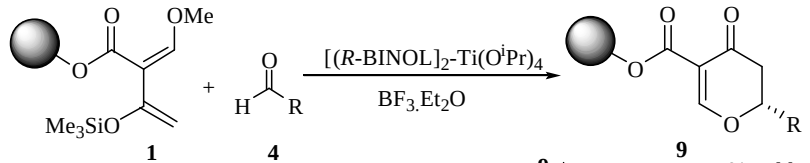


17	R	%yield
a	*n*-Pe	74
b	*n*-Bu	46
c	*n*-Pr	79
d	Et	72
e	(*E*)-Me-CH=CH	79
f	Ph	56



Scheme 1.41

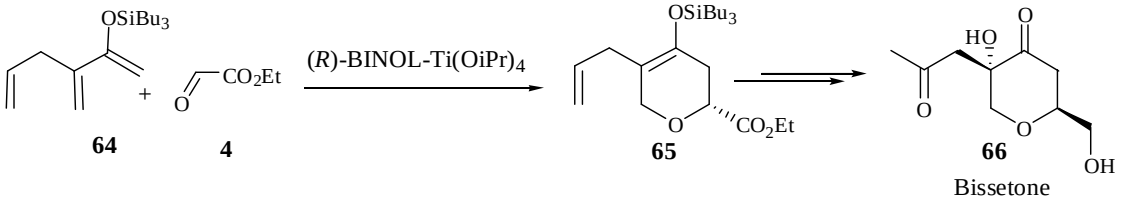
Wang et al. employed BINOL-titanium complex successfully to catalyse the HDA reactions of variety of aldehydes **(4)** with polyethylene glycol (PEG)-bound Danishefsky's diene **(1)** (Scheme 1.42).[77]



9	R	%yield
a	Ph	92
b	*o*-NO_2-C_6H_4	99
c	*p*-Me-C_6H_4	98
d	*o*-Me-C_6H_4	99
e	*o*-Cl-C_6H_4	99
f	*p*-Cl-C_6H_4	73
g	*m*-Cl-C_6H_4	90
h	*p*-F-C_6H_4	89
i	2-Naphthyl	88
j	3-Naphthyl	95
k	2-Furyl	99
l	Cy	79

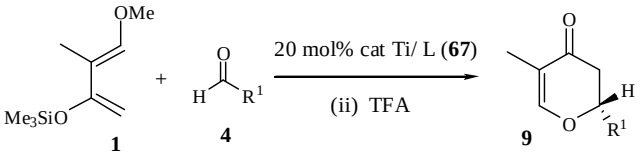
Scheme 1.42

Jurczak and coworker demonstrated a new approach for the asymmetric synthesis of bissetone **(66)**, metabolities of 1,5-anhydrous υ-fructose having an antimicrobial activity through the HDA cycloaddition of 2,3-substituted diene **(64)** with glyoxylate **(4)** in the presence of BINOL-Ti catalyst (Scheme 1.43).[78]

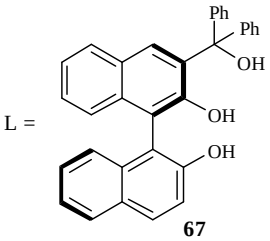


Scheme 1.43

Several other BINOL derivatives have also been used for the successful HDA reactions of aldehydes with dienes. Yu et al. demonstrated successful HDA reaction of both aliphatic and aromatic aldehydes **(4)** with *trans*-1-methoxy-2-methyl-3-trimethylsiloxy-buta-1,3-diene **(1)** using titanium(IV) catalysts derived from substituted (*R*)-BINOL (Scheme 1.44). Especially with Ti(IV) complex of 3-diphenylhydroxymethyl-subtituted BINOL **(67)** ligand, they obtained the desired product in highest yield with highest enantioselectivity.[79]

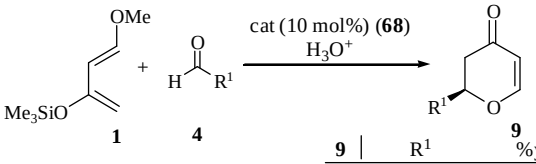


9	R^1	%yield
a	Ph	98
b	*p*-NO_2-C_6H_4	91
d	*o*-NO_2-C_6H_4	94
f	*p*-Cl-C_6H_4	99
g	*m*-Cl-C_6H_4	99
1	*p*-Me-C_6H_4	89
j	*m*-Me-C_6H_4	98
k	2-Naphthyl	99
l	*p*-CN-C_6H_4	92
m	*p*-CF_3-C_6H_4	98
n	*p*-Br-C_6H_4	98
o	2-Furyl	98
q	Pr	91
r	*n*-Pe	94

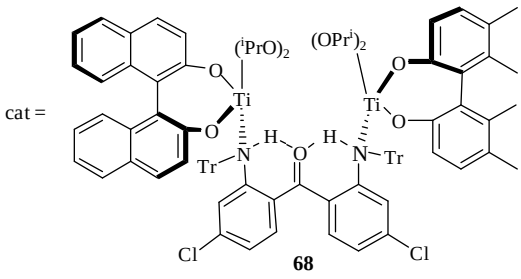


Scheme 1.44

In 2002, Maruoka et al. employed chiral bis-titanium(IV) catalyst **(68)** from (*S*)-BINOL for the HDA reactions of different aldehydes **(4)** with Danishefsky's diene **(1)** (Scheme 1.45) to obtain the corresponding cycloadducts **(9)** with high enantioselectivities and good yields.[80]

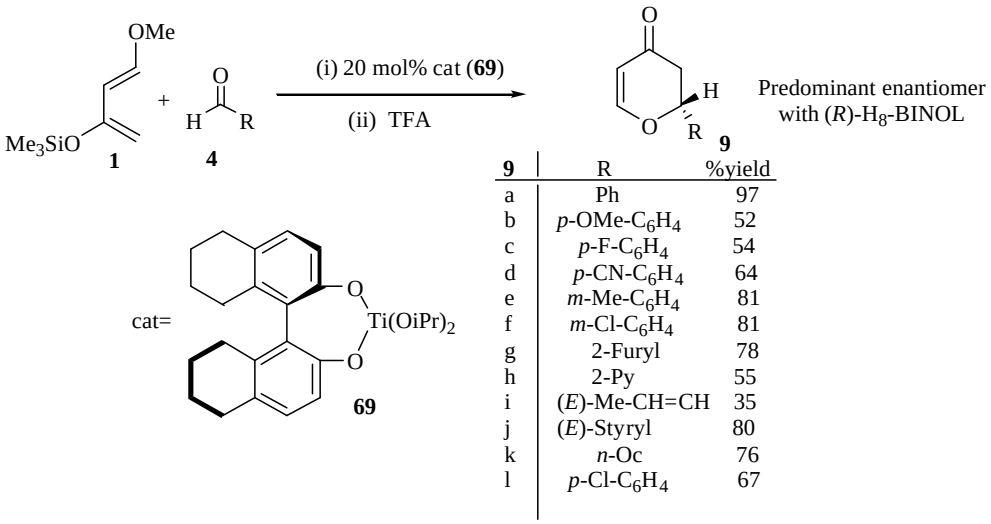


9	R^1	%yield
a	Ph	64
b	*n*-Pe	57
c	$Ph(CH_2)_2$	77
d	$Ph(CH_2)_6$	66
f	*i*-Pr	64
g	$Me(CH_2)_2C{\equiv}C$	45
h	$Me(CH_2)_2CH{=}CH$	58



Scheme 1.45

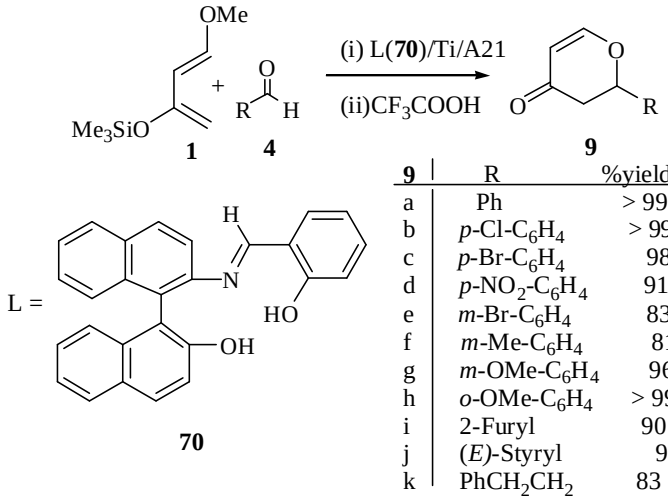
Jiang et al. reported chiral H_8-BINOL-Ti(IV) complex catalyzed highly enantioselective HDA reaction of Danishefsky's diene **(1)** and aldehydes **(4)** to synthesise optically active 2-substituted-2,3-dihydro-4*H*-pyran-4-one **(9)** with up to 99% *ee* (Scheme 1.46).[81] Ding et al. reported the above reactions in the solvent-free and molecular sieves free conditions by using H_4-BINOL/Ti /H_4-BINOL or H_4-BINOL/Ti /H_8-BINOL catalysts.[82]



9	R	%yield
a	Ph	97
b	*p*-OMe-C_6H_4	52
c	*p*-F-C_6H_4	54
d	*p*-CN-C_6H_4	64
e	*m*-Me-C_6H_4	81
f	*m*-Cl-C_6H_4	81
g	2-Furyl	78
h	2-Py	55
i	(*E*)-Me-CH=CH	35
j	(*E*)-Styryl	80
k	*n*-Oc	76
l	*p*-Cl-C_6H_4	67

Scheme 1.46

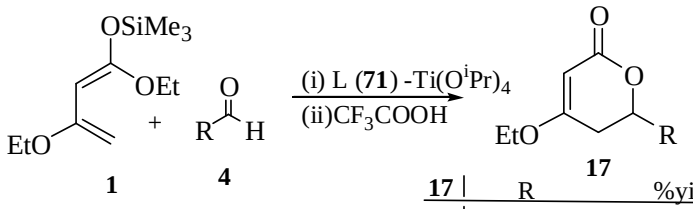
Li et al.[83] discovered a new chiral H′4-NOBIN ligand from partial hydrogenation of 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) for the HDA reaction. In 2002, Ding and group synthesized a new dendritic titanium catalyst from molecular assembly of chiral dendritic Schiff-base ligands **(70)**, titanium(IV) ions, and a chiral activator ((*S*)-naproxen) for the HDA reaction of Danishefsky's diene **(1)** with aldehydes **(4)** (Scheme 1.47). They found that the disposition of the dendritic wedges and the dendron size in the ligands have significant impact on the enantioselectivity of the reaction.[84]

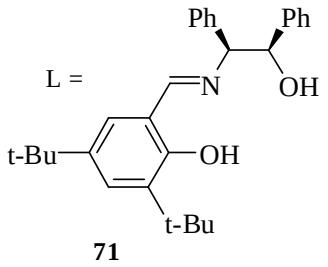


9	R	%yield
a	Ph	> 99
b	*p*-Cl-C_6H_4	> 99
c	*p*-Br-C_6H_4	98
d	*p*-NO_2-C_6H_4	91
e	*m*-Br-C_6H_4	83
f	*m*-Me-C_6H_4	81
g	*m*-OMe-C_6H_4	96
h	*o*-OMe-C_6H_4	> 99
i	2-Furyl	90
j	(*E*)-Styryl	96
k	$PhCH_2CH_2$	83

Scheme 1.47

In addition to the above reaction, Feng et al. achieved highly enantioselective HDA reaction of Brassard's diene **(1)** with aldehydes **(4)** in the presence of Ti(IV) tridentate Schiff base complexes to obtain chiral cycloadducts **(17)** (Scheme 1.48).[85]

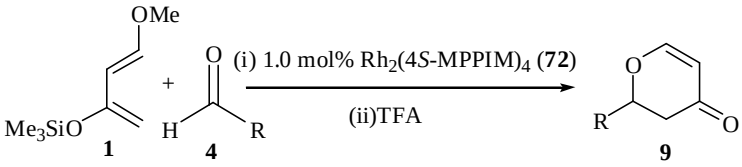


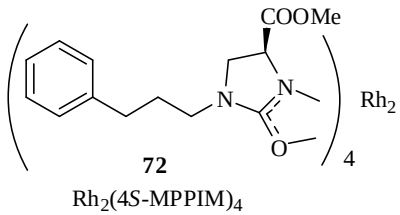


17	R	%yield
a	Ph	71
b	*m*-OMe-C_6H_4	45
c	*m*-Me-C_6H_4	53
d	*p*-Me-C_6H_4	36
e	*m*-Cl-C_6H_4	70
f	*p*-Cl-C_6H_4	87
g	*p*-F-C_6H_4	53
h	*p*-CN-C_6H_4	61
i	*p*-NO_2-C_6H_4	56
j	2-Naphthyl	61
k	*n*-Pe	26

Scheme 1.48

Doyle et al. reported dirhodium(II) carboxamidates **(72)** catalyzed stereoselective HDA reaction of aromatic aldehyde **(4)** and Danishefsky's diene **(1)** with high turnover and low catalyst loadings of ~0.01 mol% (Scheme 1.49).[86]

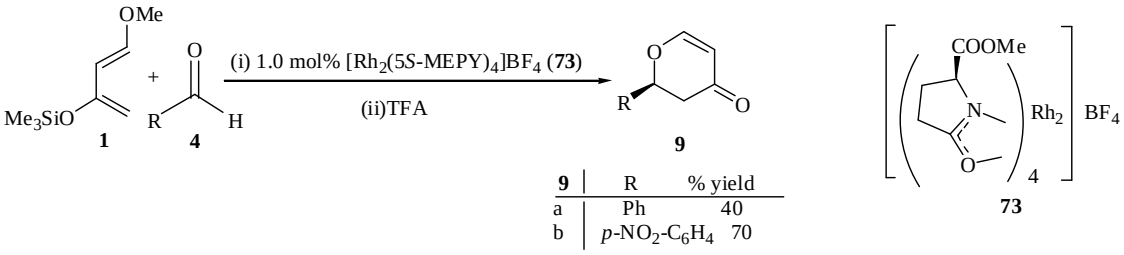




9	R	% yield
a	*p*-OMe-C_6H_4	90
b	*p*-Me-C_6H_4	90
c	Ph	93
d	*p*-Cl-C_6H_4	91
e	*p*-CF_3-C_6H_4	92
f	*p*-F-C_6H_4	96
g	*o*-NO_2-C_6H_4	84
h	*p*-NO_2-C_6H_4	92
i	2-Naphthyl	98
j	2-Furyl	88

Scheme 1.49

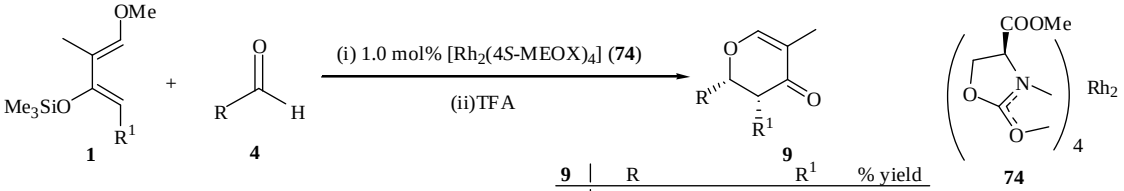
The above HDA reactions (Scheme 1.50) could be accomplished successfully in the presence cationic chiral dirhodium carboxamidates, such as $[Rh_2(5S\text{-MEPY})_4]BF_4$ **(73)**, as catalysts with high ee (93%)[87]



9	R	% yield
a	Ph	40
b	*p*-NO_2-C_6H_4	70

Scheme 1.50

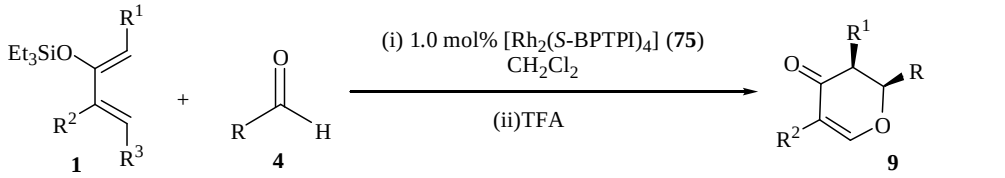
The previous methodology was further extended by the use of methyl and dimethyl-substituted Danishefsky's dienes **(1)** during the HDA reaction with aromatic aldehydes **(4)** to give the corresponding *cis*-dihydropyranones **(9)** (Scheme 1.51). The best results were achieved on using a chiral dirhodium(II) carboxamidate, $Rh_2(4S\text{-MEOX})_4$ **(74)** as catalyst.[87,88]



9	R	R^1	% yield
a	*p*-NO_2-C_6H_4	H	90
b	*p*-NO_2-C_6H_4	Me	98
c	4-NO_2-2-furyl	Me	84
d	4-NO_2-2-thiophenyl	Me	97

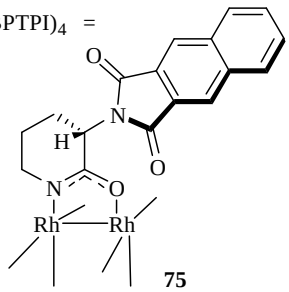
Scheme 1.51

Hashimoto et al. demonstrated a novel dirhodium(II) carboxamidate complex ($Rh_2(S\text{-BPTPI})_4$) **(75)**, bearing chiral (*S*)-3-(benzene-fused-phthalimido)-2-piperidinonate bridging ligand to catalyse enantio-selective HDA reactions of various aldehydes **(4)** with Danishefsky-type dienes **(1)** (Scheme 1.52).[89] Several natural products could be synthesized in similar manner.[90]



1 **4** **9**

Rh_2(*S*-BPTPI)$_4$ =

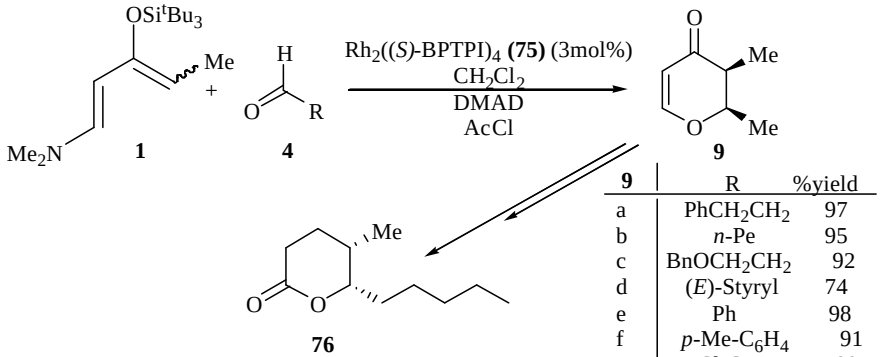


75

9	R	R^1	R^2	R^3	% yield
a	*p*-Me-C_6H_4	H	H	OMe	97
b	*p*-NO_2-C_6H_4	H	H	OMe	96
c	*p*-Cl-C_6H_4	H	H	OMe	95
d	*p*-CN-C_6H_4	H	H	OMe	93
e	*p*-CF_3-C_6H_4	H	H	OMe	93
f	(*E*)-Styryl	H	H	OMe	86
g	$BnCH_2$	H	H	OMe	89
h	$BnOCH_2$	H	H	OMe	83
j	*p*-NO_2-C_6H_4	Me	Me	OMe	92
j	(*E*)-Styryl	H	H	Me	87
k	(*E*)-Styryl	Me	Me	H	81

Scheme 1.52

Furthermore, in 2009, these workers reported the HDA reaction between Rawal's diene **(1)** and aldehydes **(4)** using the same dirhodium (II) carboxamidate,**75** as catalyst. Recently, in 2014, this methodology was used for an asymmetric synthesis of (-)-*cis*-aerangis lactone **(76)** (Scheme 1.53).[91]



1 **4** **9**

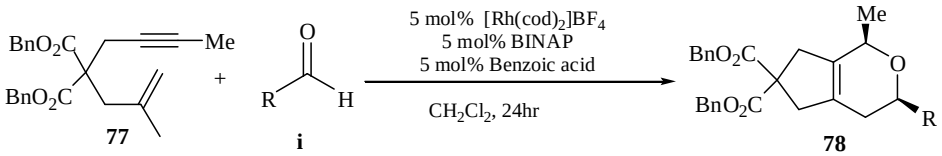
76

(-)-*cis*-Aerangis lactone

9	R	%yield
a	$PhCH_2CH_2$	97
b	*n*-Pe	95
c	$BnOCH_2CH_2$	92
d	(*E*)-Styryl	74
e	Ph	98
f	*p*-Me-C_6H_4	91
g	*p*-Cl-C_6H_4	89
h	*p*-NO_2-C_6H_4	93
i	2-Furyl	83
j	$BnOCH_2$	81
k	Ph-C≡C	82
l	*n*-Pe-C≡C	85
m	Cy	63

Scheme 1.53

Ishida and Tanaka in 2013, established one pot HDA reaction of 1,6-enyne **(77)** using cationic Rh(I)/BINAP complex and benzoic acid as catalyst, to afford single regio-isomer of annulated dihydropyran **(78)** (Scheme 1.54).[92]



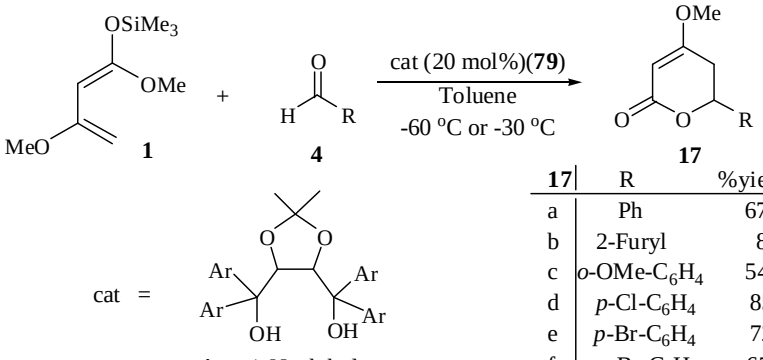
77	R	%yield
a	Ph	90
b	2-Naphthyl	87
c	*o*-Me-C_6H_4	85
d	*p*-OMe-C_6H_4	79
e	*p*-CF_3-C_6H_4	75
f	2-Furyl	70
g	*n*-Pr	80
h	*n*-Hp	74
i	Bn	75
j	Cy	72
k	$BnO(CH_2)_2$	60
l	$BnO(CH_2)_3$	61

Scheme 1.54

Besides, some other Lewis acid catalysts, such as chiral In(III) complexes,[10g,93] chiral Mg(II) complexes,[94] catalysts from $Zr(O^tBu)_4$ and (*R*)-3,3′-diiodobinaphthol or its derivatives,[95] catalyst system from $Er(OTf)_3$ and norephedrinse ligands,[96] rare earth metal complexes with chiral phosphate ligands, scandium catalyst,[97] chiral Co(III) complexes[98], enantiopure Pd(II) complexes[99] and Pt(II) metal complexes[100] have been used successfully.

Using chiral organocatalysts

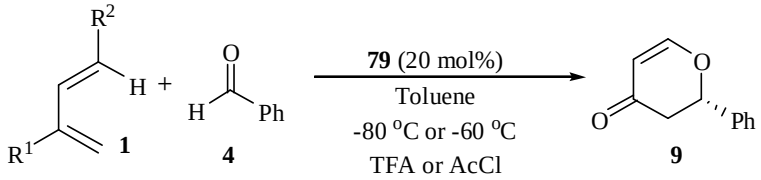
In 2004, Ding et al. investigated TADDOL derivatives **(79)** catalyzed enantioselective HDA reaction of aldehydes **(4)** with Brassard diene **(1)** successfully through hydrogen bonding activation (Scheme 1.55).[101]



17	R	%yield	ee
a	Ph	67	83
b	2-Furyl	80	87
c	*o*-OMe-C_6H_4	54	68
d	*p*-Cl-C_6H_4	85	76
e	*p*-Br-C_6H_4	72	78
f	*m*-Br-C_6H_4	67	89
g	*o*-Br-C_6H_4	75	82
h	*m*-OMe-C_6H_4	45	91

Scheme 1.55

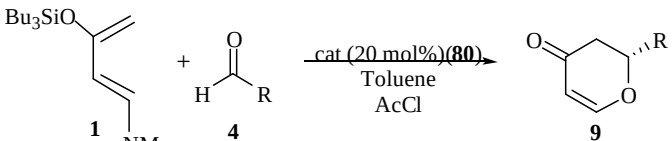
In 2006, they accomplished enantioselective HDA reaction of Danishefsky's diene **(1)** with benzaldehyde **(4)** in the presence of **79** to synthesise 2-phenyl-2,3-dihydro-4*H*-pyran-4-one **(9)** after workup with trifluoroacetic acid (Scheme 1.56)[10d]



9	R^1	R^2	% yield	ee
a	OSi^tBu_3	NMe_2	97	98
b	$OSiMe_3$	OMe	77	76

Scheme 1.56

Rawal et al. reported the enantio-selective HDA reactions of Rawal's diene and aldehyde by the use of **79** as catalyst.[102a,b] In 2005, they illustrated chiral 1,1′-biaryl-2,2′-dimethanol (BAMOL) **(80)** derivatives as highly effective catalyst for the enantioselective HDA reaction of Rawal's diene **(1)** with a variety of unactivated aldehydes **(4)** (Scheme 1.57).[102c]



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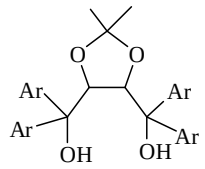


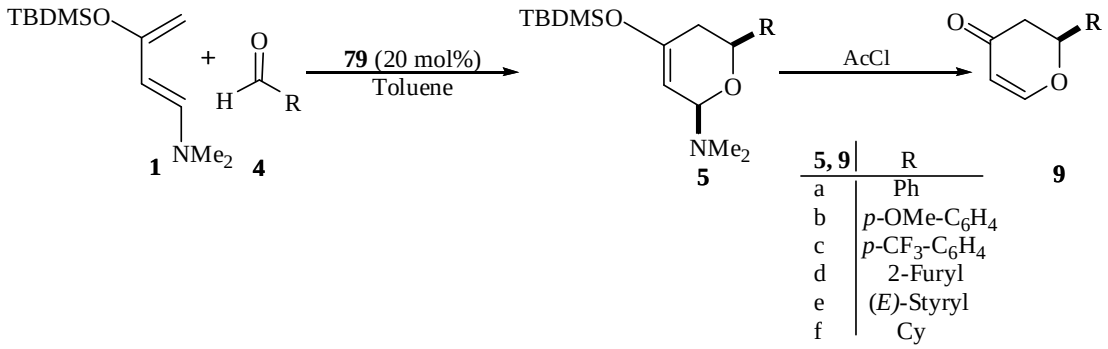
80	Ar
a	4-F-3,5-$Me_2C_6H_2$
b	4-F-3,5-$Et_2C_6H_2$

9	R	79	yield(%)	ee
a	Me	b	75	97
b	*n*-Pr	a	76	94
c	$Ph(CH_2)_2$	a	95	95
d	$PhS(CH_2)_2$	a	76	94
e	$PhS(CH_2)_3$	a	67	92
f	1-Propynyl	a	42	98
g	*t*-Bu	a	79	90
h	Cy	a	99	84
i	Ph	b	84	98
j	*m*-OMe-C_6H_4	b	86	98
k	*o*-NO_2-C_6H_4	b	93	98
l	1-Naphthyl	b	67	97
m	2-Furyl	b	96	99

Scheme 1.57

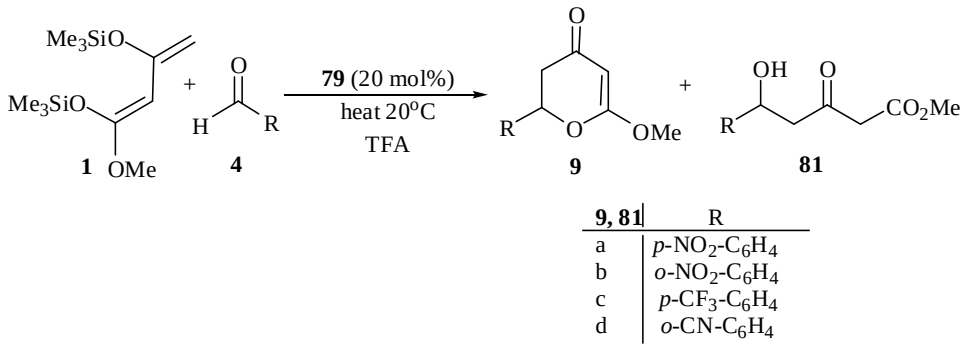
Anderson and co-workers investigated theoretically the asymmetric HDA reaction of benzaldehyde **(4)** with Rawal's diene **(1)** catalyzed by **79** through the

combined use of molecular mechanics and ONIOM calculations. The difference of activation energy between (*S)* and (*R)* products corresponds to 97% (*S)* at -40°C, which is the excellent correlation between experimental and theoretical results (Scheme 1.58).[103]



Scheme 1.58

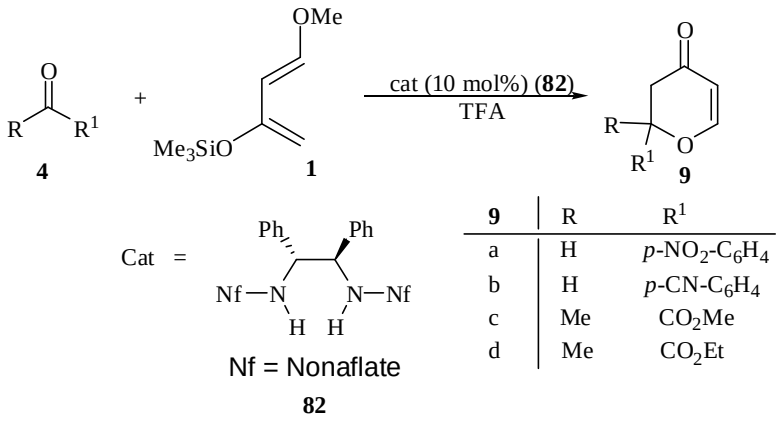
Villano et al. accompalished successfully the asymmetric HDA reaction of electron-poor aromatic aldehydes **(4)** with 1,3-bis-(trimethylsilyloxy)-1-methoxy-buta-1,3-diene (Chan's diene) **(1)** using **79** as promoter through hydrogen-bonding activation (Scheme 1.59).[104]



Scheme 1.59

Deslongchamps and co-workers investigated theoretically the reverse-docking of a TADDOL catalyst to the rigid transition-state (TS) representation of the catalyst-free asymmetric HDA reaction and found a clear energetic trend in favor of the experimentally preferred product enantiomers.[105]

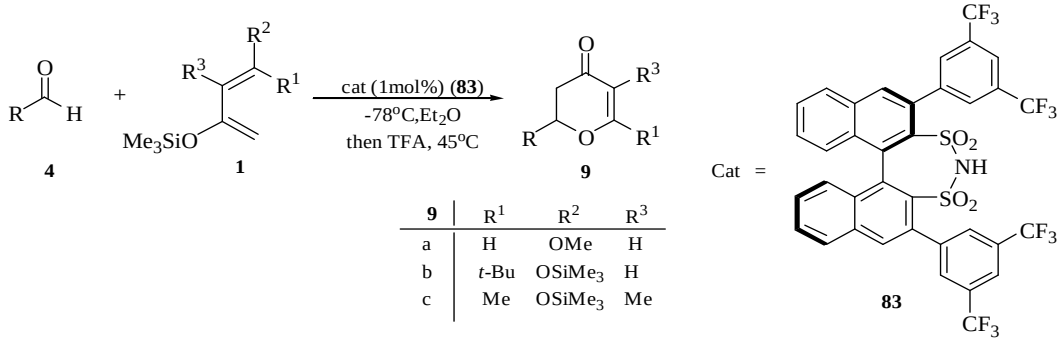
In 2005, Jorgensen et al. carried out successfully HDA reaction of aldehydes **(4)** with Danishefsky's diene **(1)** using chiral bis-sulfonamide derivatives of vicinal diamines **(82)** as organocatalysts (Scheme 1.60).[106]



9	R	R^1
a	H	*p*-NO_2-C_6H_4
b	H	*p*-CN-C_6H_4
c	Me	CO_2Me
d	Me	CO_2Et

Scheme 1.60

Tonoi and Mikami investigated HDA reaction between Danishefsky's diene and glyoxylate or phenylglyoxal using bis-trifluoromethanesulfonylamide (bis-triflylamide) catalyst.[107] Recently, in 2012, List and group presented an efficient catalytic enantioselective HDA reaction of Danishefsky's diene **(1)** with aldehydes **(4)** catalyzed by a chiral disulfonamide **(83)** (Scheme 1.61). The utility of this methodology was illustrated with the first enantioselective synthesis of potent aromatase inihibitor.[108]

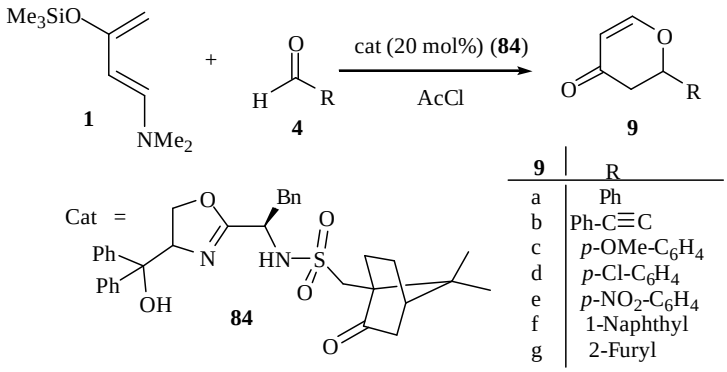


9	R^1	R^2	R^3
a	H	OMe	H
b	*t*-Bu	$OSiMe_3$	H
c	Me	$OSiMe_3$	Me

Scheme 1.61

Rajaram and Sigman developed anew chiral organocatalyst incorporating a rigid oxazoline backbone to catalyse the HDA reactions of aldehydes with Rawal's

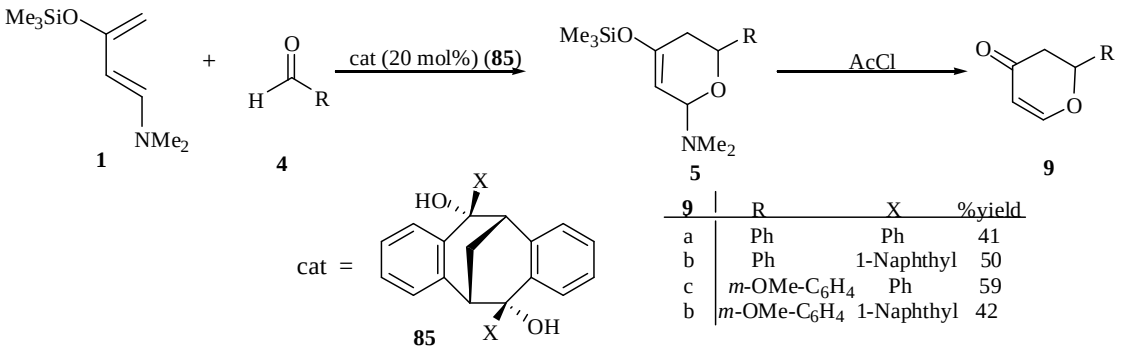
diene.[109a] In 2007, Sigman and Jensen studied the enantioselective HDA reaction of benzaldehyde **(4)** with Rawal's diene **(1)** performed in the presence of another organocatalyst **(84)**, containing an oxazoline core with a pendant amine and alcohol groups (Scheme 1.62). It was observed that both the enantioselectivity and the reaction rate could be correlated directly with the catalyst acidity.[109b]



9	R
a	Ph
b	Ph-C≡C
c	*p*-OMe-C_6H_4
d	*p*-Cl-C_6H_4
e	*p*-NO_2-C_6H_4
f	1-Naphthyl
g	2-Furyl

Scheme 1.62

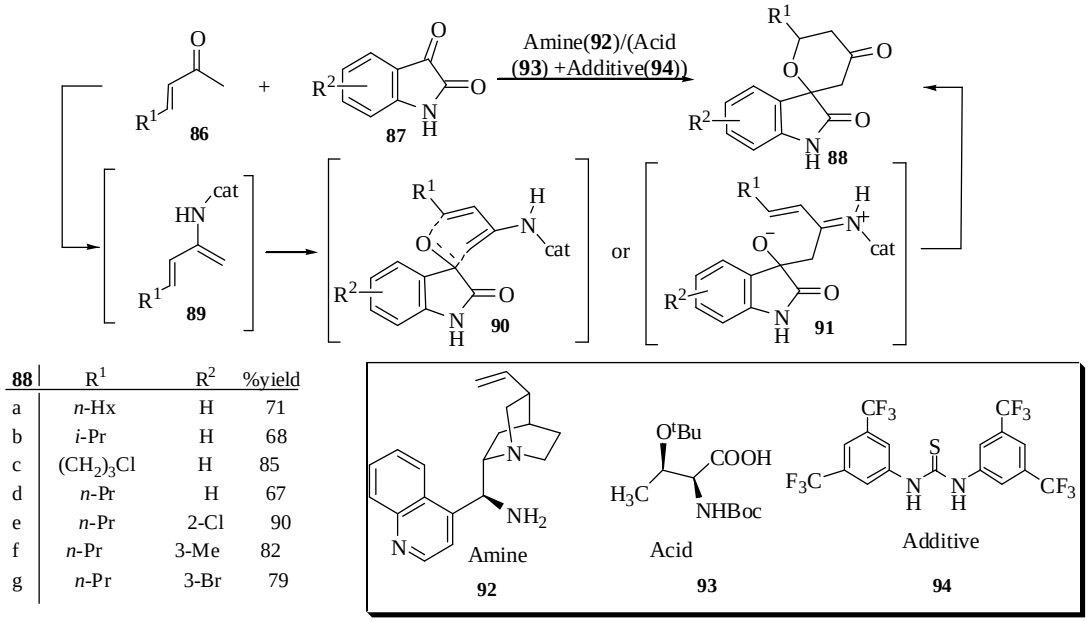
In 2007, Frejd et al. reported the new chiral carbocyclic cleft molecules **(85)** derived from 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione to catalyse the HDA reaction of benzaldehydes **(1)** and Rawal's diene **(4)** (Scheme 1.63).[110]



9	R	X	%yield
a	Ph	Ph	41
b	Ph	1-Naphthyl	50
c	*m*-OMe-C_6H_4	Ph	59
b	*m*-OMe-C_6H_4	1-Naphthyl	42

Scheme 1.63

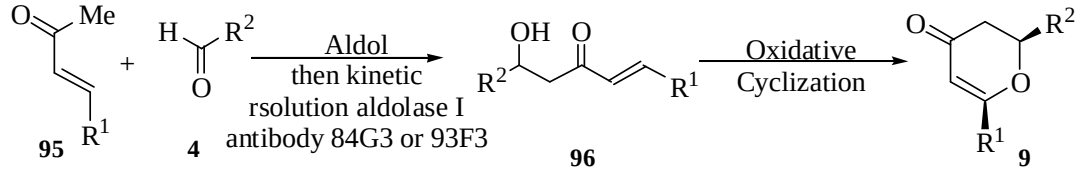
Cui and Tanaka achieved enantioselective organocatalytic HDA reaction of enones **(86)** with isatins **(87)** in the presence of amine-based catalyst to give substituted spiro-oxindolotetrahydropyranones **(88)** under mild conditions (Scheme 1.64).[111]



88	R^1	R^2	%yield
a	*n*-Hx	H	71
b	*i*-Pr	H	68
c	$(CH_2)_3Cl$	H	85
d	*n*-Pr	H	67
e	*n*-Pr	2-Cl	90
f	*n*-Pr	3-Me	82
g	*n*-Pr	3-Br	79

Scheme 1.64

Terada and group demonstrated completely enantioselective and *anti*-diastereoselective HDA reaction of ethyl glyoxylates with a series of silyloxy- and methoxydienes using chiral BINOL derived phosphoric acid as catalyst.[112] Govuerneur and Reiter investigated the bio-organic route for the HDA reaction of carbonyl compound to access dihydropyranones and found that on using biocatalyst, cycloaddition occurred through stepwise mechanism (Scheme 1.65).[113]

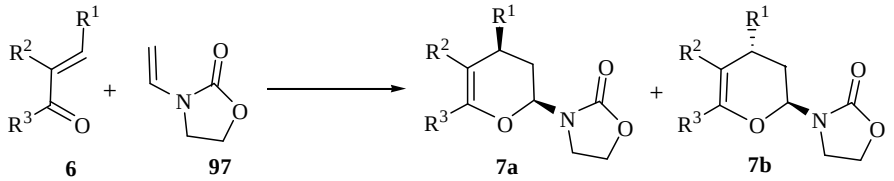


Scheme 1.65

1.5 HDA reactions of heterodienes incorporating carbonyl group

1.5.1 HDA reactions of heterodiene without catalyst

Aleksandra Pałasz reported the IED HDA reaction of α,β-unsaturated carbonyl compounds **(6)** with N-vinyl-2-oxazolidinone **(97)** to synthesise 3,4-dihydro-2*H*-pyran **(7)** regio- and diastereselectively (Scheme 1.66).[114]

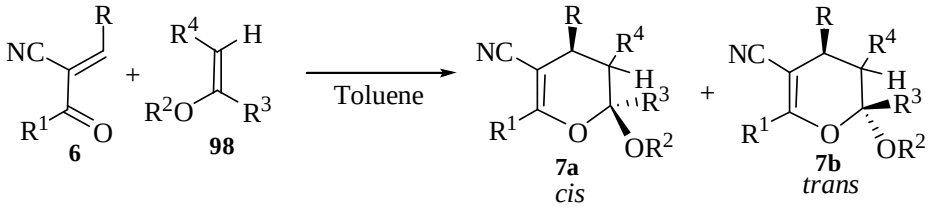


6 **97** **7a** *cis* **7b** *trans*

7	R^1	R^2	R^3
a	Ph	CN	Ph
b	*p*-NO_2-C_6H_4	CN	Ph
c	*p*-OMe-C_6H_4	CN	Ph
d	*p*-CN-C_6H_4	CN	Ph
e	*p*-NO_2-C_6H_4	$PhSO_2$	Me

Scheme 1.66

Pałasz and Szwed carried out the cycloaddition reaction of 1-oxa-1,3-butadienes **(6)** having cyano-functionality at C-3 position with enol ethers **(98)** (Scheme 1.67).[115]



6 **98** Toluene **7a** *cis* **7b** *trans*

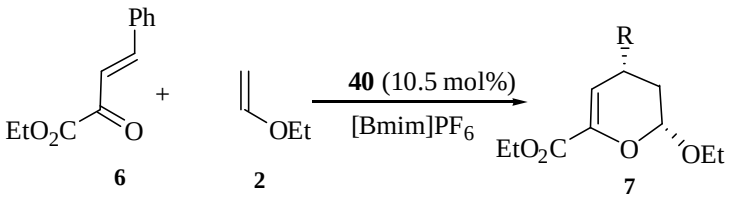
7	R	R^1	R^2	R^3	R^4	%yield
a	N(Ac)(CH_2Ph)	H	Et	H	H	70
b	N(Ac)(CH_2Ph)	H	*t*-Bu	H	H	48
c	N(Ac)(CH_2Ph)	H	Me	H	H	74
d	N(Ac)(CH_2Ph)	H	Et	Me	H	77
e	N(Ac)(CH_2Ph)	H	Et	H	Me	48
f	2-Thiophenyl	Ph	Et	H	H	79
b	2-Thiophenyl	Ph	*t*-Bu	H	H	81
c	2-Thiophenyl	Ph	Me	H	H	76
d	2-Thiophenyl	Ph	Et	Me	H	77
e	2-Thiophenyl	Ph	Et	H	Me	88

Scheme 1.67

1.5.2 HDA reactions of heterodiene in the presence of a catalyst

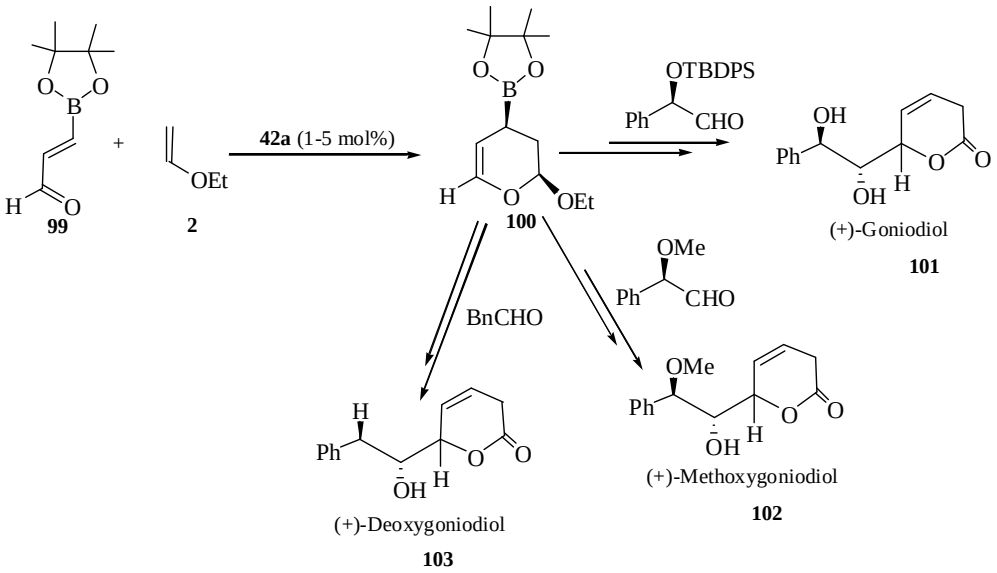
As in the case of other dienes, these reactions can also be catalyzed by Lewis acid or organocatalyst. In the last few years, the chiral bisoxazoline (Box) copper(II) complexes have been frequently employed as catalysts for the IED HDA reactions. Kurosu et al. developed Cu(II) catalysts bearing indane-derived bisoxazoline (Inda-Box) chiral ligand for the HDA reaction.[116a] Hutchings et al. used heterogenous

catalyst of chiral [(Ph-Box)Cu(OTf)$_2$] immobilized on zeolite Y and mesoporous materials for the HDA reaction of (*E*)-ethyl-2-oxa-3-pentenoate .[116b] In 2004, similar results were obtained by Klein Gebbink et al. by employing silica gel immobilized chiral [(*t*-Bu-Box)Cu(OTf)$_2$] catalyst for the same reaction.[116c] Kim et al. reported the use of [Bmim]PF_6 and [Bmim]SbF_6, hydrophobic ionic liquid ssuccessfully for the catalyst separation and recycling in bisoxazoline-copper **(40)** catalyzed asymmetric IED HDA reaction (Scheme 1.68).[116d]



Scheme 1.68

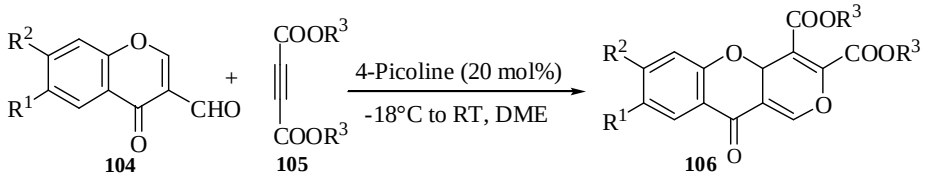
Numberous chromium catalysts have been successfully used for the catalysis of IED HDA reaction. Hall et al. and Carreaux et al. achieved HDA-cycloaddition/allylboration reaction of 3-boronoacrolein pinacolate, ethylvinyl ether and aldehydes in the presence of Jacobsen's catalyst **(42a)** leading to enantioselective construction of α-hydroxyalkyldihydropyrans.[117] This methodology was used for the total synthesis of (+)-goniodiol **(101)**,[118a] (+)-methoxygoniodiol **(102)** and (+)-deoxygoniodiol **(103)**[118b], natural antitumour products from (2*R*)-(tert-butyldiphenylsilyloxy)phenylacetaldehyde, (2*R*)-methoxy(phenyl)acetaldehyde and phenylacetaldehyde respectively as the aldehyde substrates (Scheme 1.69). The scope of this methodology was extended to acyclic 2-substituted enol ethers for the synthesis of potent natural thiomarinol antibiotic.[118c,d]



Scheme 1.69

A number of other Lewis acids, such as $Eu(fod)_3$,[1119] $SnCl_4$,[1119c] and chiral Sc(III)triflate[120] have also been used successfully.

Several examples of organocatalyst catalyzed IED HDA reactions have been described. Stephanatou et al. reported 4-picoline catalyzed HDA reaction between α,β-unsaturated aldehydes **(104)** and dialkyl acetylenedicarboxylate **(105)** to achieve pyrano[4,3-*c*]chromenes **(106)** (Scheme 1.70).[121]

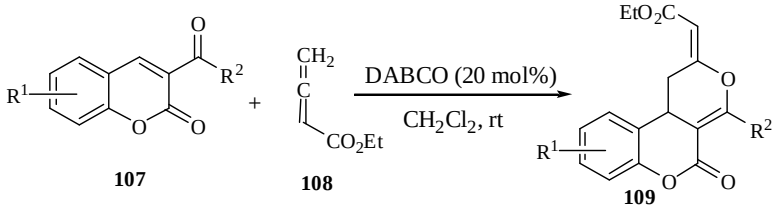


106	R^1	R^2	R^3	%yield
a	H	N	Me	42
b	$CH(Me)_2$	H	Me	48
c	Cl	H	Me	39
d	Cl	Me	Me	41
e	Me	H	Et	45
f	$CH(Me)_2$	H	Et	51
g	Cl	H	Et	38

Scheme 1.70

An enantioselective amino catalyzed IED HDA reaction of α,β-unsaturated acyl phosphonates has been reported by Jorgensen et al.[122] Wang et al. investigated

experimentally and theoretically [4+2]cycloaddition reaction of arylienoxindoles and allenoates catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) to access dihydropyran-fused indoles. On the basis of DFT studies, a stepwise mechanism was established.[123a] In 2012, Shi et al. used similar catalyst for the HDA reaction of 3-acyl-2*H*-chromenones **(107)** with ethyl2,3-butadienoate **(108)** to synthesise biologically active dihydropyran-fused chromenones **(109)** (Scheme 1.71).[123b]

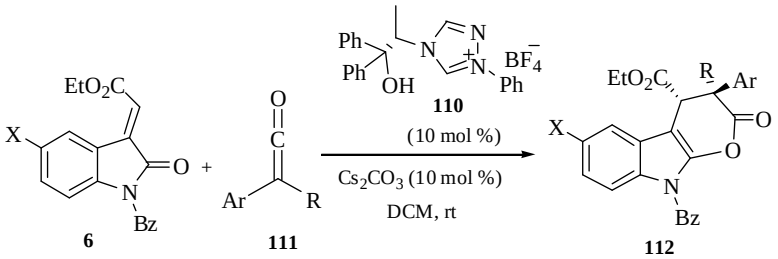


107 **108** **109**

109	R^1	R^2	%yield
a	H	Ph	92
b	6-Br	Ph	85
c	6-Cl	Ph	79
d	6-F	Ph	86
e	6,8-Cl_2	Ph	80
f	7-CF_3	Ph	92
g	6-Me	Ph	94
h	7-Me	Ph	88
i	H	Me	87
j	H	*p*-Cl-C_6H_4	89

Scheme 1.71

Feng et al. designed a C_2-symmetric chiral bisguanidine catalyst to catalyse the IED HDA reaction of chalcones and azlactones.[124] An enantioselective N-heterocyclic carbene (NHC) catalyzed HDA reactions of α-chloroaldehydes as enolate precursors with a wide range of enones have been developed by Bode et al.[125a,b] In 2010, they reported [4+2]cycloaddition of NHC bound enolates generated from α,β-unsaturated aldehydes with electron-deficient enones.[125c] Similarly, Lv et al. investigated chiral NHC **(110)** catalyzed formal HDA reaction of ketenes **(111)** with α,β-unsaturated carbonyl functionality (Scheme 1.72).[126a,b]



Scheme 1.72

Beside these, other organocatalysts, such as diphenylprolinol silyl ether,[127] prolinal dithioacetals,[128] dimethylaminopyridine (DMAP)[129] and phosphine[130] have been used.