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Asymmetric hetero-Diels–Alder reactions of carbonyl compounds

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Abbreviations: Ac, acetyl; Adam, adamantanyl; Ar, aryl; BAMOL, 1,1′-biaryl-2,2′-dimethanol; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; BINOL, 1,1′-bi-2-naphthol; BIPHEP, 2,2′-bis(diphenylphosphino)-1,1′-biphenyl; Bmim, 1-butyl-3-methylimidazolium; Bn, benzyl; BNP, 1,1′-binaphthyl-2,2′-diylphosphate; Boc, *tert*-butoxycarbonyl; Box, bisoxazoline; BPTPI, 3-(benzene-fused-phthalimido)-2-piperidinonate; BQd, benzoylquinidine; Bu, butyl; Bz, benzoyl; cat, catalyst; Cbz, benzyloxycarbonyl; Cy, cyclohexyl; de, diastereomeric excess; DIANANE, *endo*,*endo*-2,5-diaminonorbornane; DIPEA, diisopropylethylamine; DPE, diphenylethane; ee, enantiomeric excess; EM, energy minimisation; Et, ethyl; Fmoc, 9-fluorenylmethoxycarbonyl; fod, 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate; Fu, furyl; HDA, hetero-Diels–Alder; Hept, heptyl; Hex, hexyl; hfc, 2-{[3-chloro-4-fluoro-phenylimino]methyl}phenol; HMDSA, bis(trimethylsilyl)amide; L, ligand; LA, Lewis acid; Me, methyl; MEOX, methyl 1-oxo-(2-oxazolidine)-4-carboxylate; MEPY, methyl 2-oxopyrrolidine-5-carboxylate; Mes, methanesulfonyl (mesyl); MOM, methoxymethyl; MPPIM, 4-methoxycarbonyl-1-(3-phenylpropanoyl)-2-oxoimidazolidinate; MS, molecular sieves; MTBE, methyl *tert*-butyl ether; Naph, naphthyl; Nf, nonaflate; NOBIN, 2-amino-2′-hydroxy-1,1′-binaphthyl; Non, nonyl; NUPHOS, 1,4-bis(diphenylphosphino)-1,3-butadiene bridged diphosphine; Oct, octyl; ONIOM, our own *n*-layered integrated molecular orbital and molecular mechanics method; PCC, pyridine chlorochromate; PDC, pyridinium dichromate; PEG, poly(ethylene glycol); Pent, pentyl; Ph, phenyl; PHEBox, 2,6-bis(oxazolinyl)phenyl; PhthN, phthalimido; Piv, pivaloyl; PMB, *p*-methoxybenzoyl; Pr, propyl; PS, polystyrene; PT, phenyltetrazolyl; Py, pyridyl; PYBOX, 2,6-bis(2-oxazolyl)pyridine; Salen, 1,2-bis(salicylidenamino)ethane; TADDOL, α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; TBAF, tetra-*n*-butylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TEA, triethylamine; TES, triethylsilyl; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Thio, thiophene; TIPS, triisopropylsilyl; TMS, trimethylsilyl; Tol, tolyl; Tr, triphenylmethyl (trityl); Ts, 4-toluenesulfonyl (tosyl); TS, transition state.

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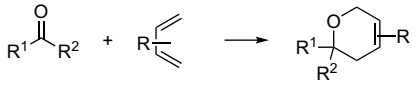
1. Introduction

Since its discovery in 1928 by Diels and Alder,[1] the Diels–Alder reaction has become one of the cornerstone reactions in organic chemistry for the construction of six-membered rings.[2] The high regio- and stereoselectivity typically displayed by this cycloaddition, the ease of its execution and the feature that, during its course, up to four new stereocentres may be created simultaneously have resulted in innumerable applications of this transformation in the construction of highly complex targets. Indeed, this reaction has undergone intensive development, becoming of fundamental importance for synthetic, physical and theoretical chemists. Today, this powerful reaction is one of the most examined and well appreciated reactions, having an enormous spectrum of application in chemistry. The preparation of numerous compounds of academic and industrial interest is widely based on cycloaddition reactions to carbonyl compounds. There are many variants of the Diels–Alder reaction, such as the intramolecular [4+2] cycloaddition or the hetero-Diels–Alder (HDA) reaction (Scheme 1).[3] Indeed, the pivotal role that the carbo Diels–Alder reaction often plays in the construction of carbocycles can be taken over by the HDA reaction in the regio- and stereoselective synthesis of heterocycles.[4]

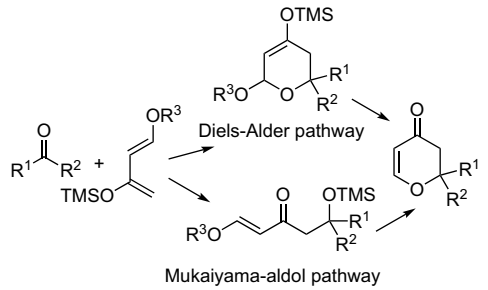


Scheme 1. HDA reaction of carbonyl compounds.

Moreover, the Diels–Alder reaction has been found to be an excellent tool to build up chiral cyclic systems.[5] The reason for the interest in obtaining optically active compounds using the Diels–Alder methodology is that these reactions normally are easy to perform and proceed generally in a highly regio- and diastereoselective manner. Furthermore, the Diels–Alder reaction can give up to four new chiral centres. In particular, the asymmetric HDA reaction is among the most powerful available methodologies for the construction of optically active six-membered heterocycles, with extensive synthetic applications in natural or unnatural products with a wide range of biological activity.[6] Indeed, the asymmetric HDA reaction, involving carbonyl compounds as the heterodienophiles or the heterodienes, has allowed the preparation of numerous chiral six-membered oxygen-containing heterocycles.[3a,7] The most typical products are substituted tetrahydropyran rings, which are frequently occurring structural motifs in biologically active natural products. Among the various carbon–carbon bond-forming reactions, the enantioselective HDA reaction of carbonyl compounds has emerged as an important method in synthetic organic chemistry, because carbon–carbon and carbon–oxygen bonds are both formed to stereoselectively afford six-membered pyran derivatives. Heterocyclic synthesis by using the Diels–Alder methodology is particularly useful, because of the highly stereoselective nature of the reaction, which often results in the formation of only one isomer, a remarkable selectivity considering the fact that as many as four diastereoisomers can, in principle, be formed in the reaction of a diene with an aldehyde. There are two basic strategies for asymmetric HDA reactions of carbonyl compounds in order to control the absolute configuration of the product. The first strategy involves the use of a diene and/or a dienophile with a chiral auxiliary, while the second involves the generally more economical use of a chiral catalyst. This approach allows the direct formation of chiral compounds from achiral substrates under mild conditions. To achieve catalytic enantioselective HDA reactions of carbonyl compounds, coordination of a chiral Lewis acid to the carbonyl functionality is necessary. This coordination activates the substrate and provides the chiral environment that forces the approach of a diene to the substrate from the less sterically hindered face, introducing enantioselectivity in the reaction. In recent years, an intensive effort has been developed to achieve asymmetric HDA reactions of carbonyl compounds, and the synthetic development of catalytic enantioselective HDA reactions has especially been in focus, while the number of mechanistic studies is limited. The basic idea in performing these reactions in a catalytic enantioselective manner is to use the Lewis-acid properties for coordination to the carbonyl compound, leading to its activation, and the chiral ligand, which is coordinated to the Lewis acid, to direct the three-dimensional approach of the diene to one of the faces of the carbonyl compound. A large variety of chiral Lewis-acid complexes can catalyse the HDA reaction of carbonyl compounds with dienes. On the other hand, a number of asymmetric HDA reactions, involving either chiral dienophiles or chiral dienes, have been recently successfully developed. At the same time, numerous novel chiral HDA catalysts have been developed, attempting to control the stereochemical outcome of the cycloaddition. Thus, a number of novel chiral Lewis-acid catalysts based on chromium, copper, titanium, aluminium, rhodium and other metals have provided new opportunities for enantioselective cycloadditions, allowing the use of both activated and unactivated aldehydes as well as ketones. Furthermore, hydrogen bonding of a simple chiral alcohol or amine to a carbonyl group can also be exploited as a mode of activation for HDA chemistry and complements alternative asymmetric catalytic strategies.[8] Indeed, a number of asymmetric catalytic HDA reactions have been recently performed in the presence of chiral organocatalysts. The first enantioselective catalytic HDA reaction of carbonyl compounds was attempted by Danishefsky et al., who employed a chiral lanthanide β-diketonato complex $Eu(hfc)_3$ as a Lewis acid to achieve 58% ee in the HDA reaction of benzaldehyde with 1-*tert*-butoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene.[9] Ever since this work, the growing importance of asymmetric HDA reactions of carbonyl compounds can be attributed to the development of a number of very effective chiral catalysts, such as chiral Cr–salen complexes discovered by Jacobsen et al., in 1998, and widely employed for asymmetric HDA reactions of Danishefsky's diene with aldehydes to give the corresponding dihydropyranones in good enantioselectivities.[10]

In the area of mechanistic aspects of the HDA reaction, Danishefsky et al. have demonstrated that the product could be formed by two different modes of cyclisation, depending, essentially, on the Lewis-acid catalyst employed.[9c,11] Indeed, two mechanistic pathways have generally been taken into account for the HDA reaction when Lewis-acid-catalysed reactions are considered. The intermediates of the two pathways were identified, and these two pathways were formulated as a Mukaiyama-aldol reaction followed by a cyclisation step, and a traditional Diels–Alder cycloaddition, as outlined in Scheme 2. In some cases, the Mukaiyama-aldol intermediate has been isolated and characterised and shown to undergo a ring-closure reaction, leading to the final HDA adduct. On

the other hand, the traditional HDA-cycloaddition reaction pathway can also take different reaction courses, either as a concerted reaction with an unsymmetrical transition state or as a stepwise mechanism.[12] The different reaction paths are dependent, in particular, on the employed Lewis-acid properties, although only a very limited insight into the mechanism of catalytic enantioselective HDA reactions of carbonyl compounds is available. Indeed, compared to the numerous theoretical calculations on the normal Diels–Alder reaction, very few theoretical studies of HDA reactions of carbonyl compounds have been performed.[12] On the other hand, the uncatalysed reaction is likely to proceed in a concerted fashion with an unsymmetrical transition state.



Scheme 2. Two possible pathways for HDA reaction of carbonyl compounds.

This review updates the asymmetric HDA reactions of carbonyl compounds, such as aldehydes and ketones, covering the literature from 2000 to 2008. Unlike its predecessor reported by Jorgensen in 2000 and dealing with catalytic cycloadditions involving both carbonyl compounds and imines,[13] this review includes the asymmetric HDA reactions of carbonyl compounds based on the use of chiral auxiliaries in addition to chiral catalysts. It should be noted that the same author reported, in 2004, a personal microreview focussing on catalytic HDA reactions of ketones.[14] On the other hand, another personal account, covering the asymmetric catalytic HDA reactions of Danishefsky's and Brassard's dienes with aldehydes, was reported, in 2007, by Feng et al.[15] The application of the general asymmetric HDA reaction for synthesising carbohydrate derivatives and glycosidase inhibitors was reviewed, in 2004, by Osborn and Coisson.[16] In a different context, Gouverneur and Reiter have reviewed the biocatalytic approaches to HDA adducts of carbonyl compounds,[17] since Nature's repertoire of biosynthetic transformations has recently been recognised to include the Diels–Alder cycloaddition reaction. Indeed, evidence now exists that there are enzymes that mediate the Diels–Alder reaction and, in particular, the HDA reaction in secondary metabolic biosynthetic pathways. Today, there is unambiguous proof that natural enzymes are capable of catalysing HDA reactions and an increasing number of publications have reported elegant biomimetic approaches to HDA-type intermediates or products.[18]

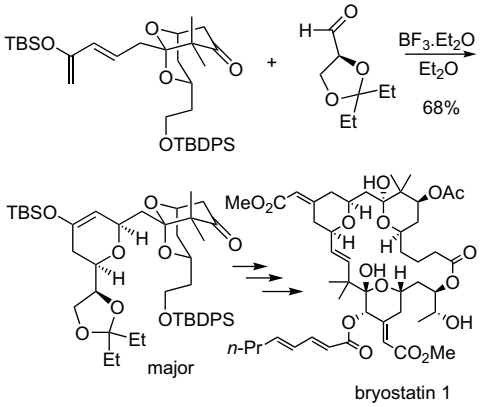
The present review demonstrates that the most important achievements are the spectacular expansion of novel chiral catalysts, including the especially attractive chiral organocatalysts, which enable a large number of asymmetric HDA reactions to be performed under very mild conditions with generally 1–10 mol % of catalyst loadings. Indeed, a collection of new chiral Lewis-acid catalysts and organocatalysts have provided new opportunities for these enantioselective cycloadditions, allowing the use of both activated and unactivated aldehydes as well as ketones. In addition, a number of powerful asymmetric HDA reactions using chiral dienophiles or chiral dienes have been developed recently. This review is divided into four subsections, according to the different types of carbonyl compounds involved in the HDA reactions, namely unactivated aldehydes, activated aldehydes and activated ketones, as well as α,β-unsaturated ketones and α,β-unsaturated aldehydes for the inverse HDA reactions.

2. Reactions of unactivated aldehydes

Unactivated aldehydes have been the most employed dienophiles in asymmetric HDA reactions, providing a convenient access to a wide range of partly unsaturated chiral six-membered heterocycles.

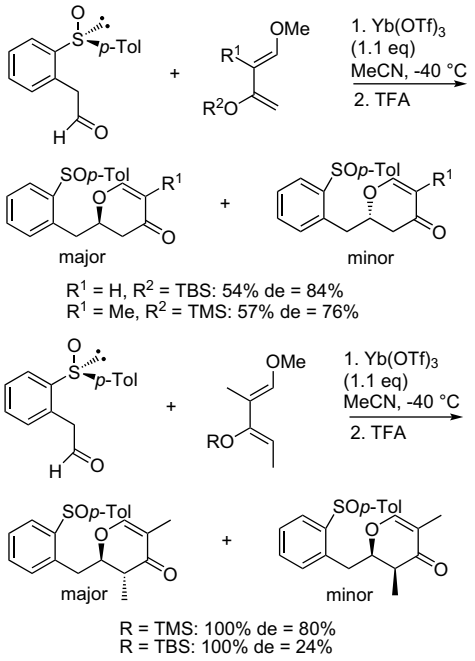
2.1. Chiral auxiliaries

A series of chiral aldehydes have recently been involved in asymmetric HDA reactions in order to construct chiral 2,3-dihydro-4-pyranone moieties, widely used in the preparation of specific carbohydrates, as well as in the total synthesis of natural products. As an example, Burke et al. have involved this methodology as the key step in the total synthesis of the northern hemisphere (C1–C16) of bryostatin 1, a potent anticancer agent.[19] Thus, the B-ring of the expected product could be derived from a chiral pentylidene-protected glyceraldehyde and a siloxydiene via a Lewis-acid-catalysed HDA reaction, as depicted in Scheme 3. When the reaction was performed in the presence of $BF_3 \cdot Et_2O$, it gave a mixture of three diastereomers in 91% yield and in a 75:20:5 ratio, from which the major isomer was easily separated and further converted into the final expected product.



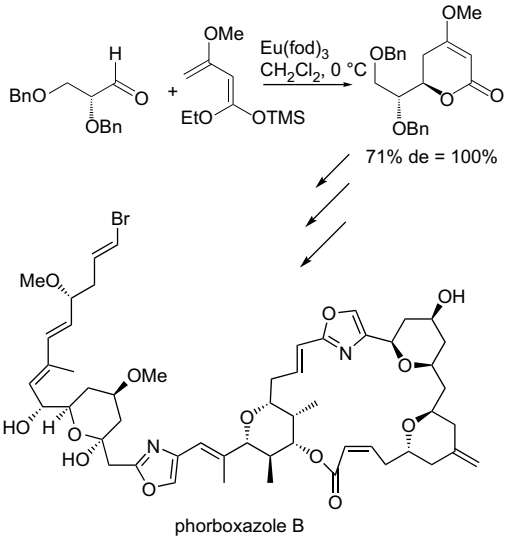
Scheme 3. Synthesis of bryostatin 1 northern hemisphere (C1–C16).

In 2006, Garcia Ruano et al. reported the asymmetric HDA reactions of (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetaldehyde with Danishefsky's and related dienes in the presence of $Yb(OTf)_3$.[20] These reactions took place in a completely stereoselective manner, mediated by a remote sulfinyl group (1,5-asymmetric induction), to afford the corresponding 2,3-dihydro-4*H*-pyran-4-ones (Scheme 4). The results indicated that any decrease in the size of the silyloxy group had minimal influence on the stereoselectivity control in the reactions of 1,3-disubstituted dienes, but produced a large and negative effect for 1,2,3,4-tetrasubstituted dienes. In addition, it could be stated that the presence of a methyl group at C2 did not affect significantly the stereoselectivity of the reaction. The formation of the trans isomers as the major isomers in these reactions suggested that they were stepwise processes, involving a Mukaiyama-aldol condensation followed by intramolecular cyclisation of the resulting intermediates, which was corroborated by the isolation of these intermediates.



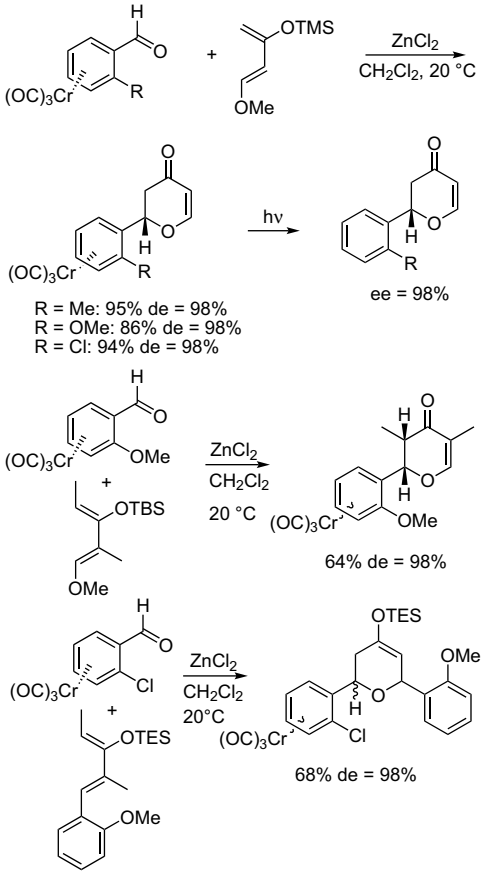
Scheme 4. HDA reactions of (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetaldehyde with Danishefsky-type dienes.

In 2007, a total synthesis of the potent antitumour agent, phorboxazole B, bearing 15 asymmetric centres, was developed by Burke et al. on the basis of a catalytic diastereoselective HDA reaction of a mannitol-derived aldehyde with Brassard's diene, as shown in Scheme 5.[21]



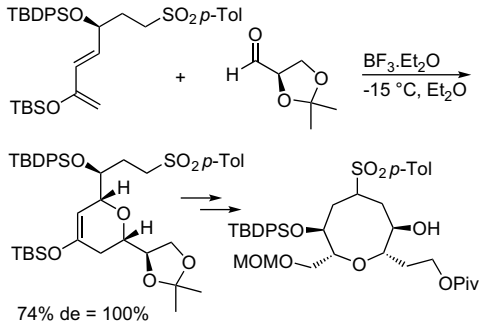
Scheme 5. Synthesis of phorboxazole B.

On the other hand, the potential of benzaldehyde–chromium tricarbonyl complexes as efficient chiral dienophiles in asymmetric HDA reactions was demonstrated, in 2001, by Baldoli et al.[22] Therefore, the $ZnCl_2$-promoted cycloaddition of a series of enantiopure *ortho*-substituted benzaldehyde–$Cr(CO)_3$ complexes with Danishefsky's diene gave the corresponding 2-aryl-pyranones in good yields and complete enantiospecificity (Scheme 6). The scope of this new methodology was successfully extended to two other dienes, affording, in each case, the corresponding cycloadduct as a single diastereomer.



Scheme 6. HDA reactions of chiral benzaldehyde–chromium tricarbonyl complexes.

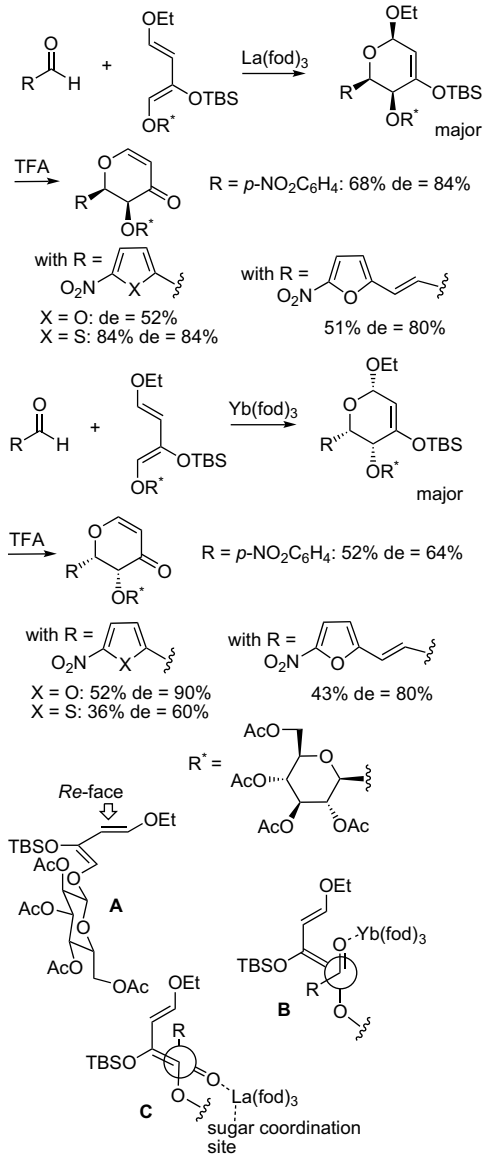
In some cases, both the diene and the dienophile involved in the asymmetric HDA cycloaddition are chiral. As an example, a double diastereoselective HDA reaction between a chiral aldehyde and a diene bearing an allylic chiral centre was developed by Palenzuela et al., in 2001, giving rise to only one cycloadduct when the reaction was carried out in the presence of $BF_3 \cdot Et_2O$ at −15 °C, as shown in Scheme 7.[23] This chiral cycloadduct was further transformed into the corresponding linear ether, which was then converted into a tetrasubstituted oxocane.



Scheme 7. Double diastereoselective HDA reaction.

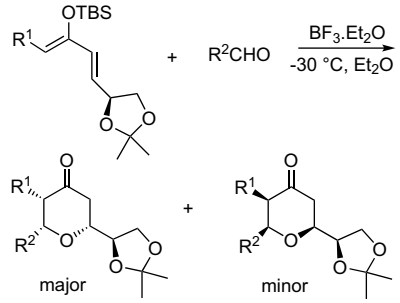
Several chiral dienes have been employed as chiral auxiliaries in asymmetric HDA reactions with achiral dienophiles. As an example, Stoodley et al. have developed the asymmetric cyloaddition of a 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl diene with electron-deficient aldehydes promoted by $Ln(fod)_3$.[24] These reactions provided the corresponding glycals as a mixture of two diastereomers with high diastereoselectivities. In each case, a switch in selectivity was observed when the Lewis acid was

changed from La(fod)$_3$ to Yb(fod)$_3$, as outlined in Scheme 8. According to these striking results, it was concluded that pericyclic-like pathways were not involved in these reactions, and that aldol-like pathways had occurred. It was proposed that Yb(fod)$_3$ formed a monodentate complex with the aldehyde, making the *Re*-face of the complexed aldehyde react with the less-hindered *Re*-face of the diene conformer **A** via an aldol-like pathway, e.g., **B**. In the case of La(fod)$_3$, a bidentate complex was required involving the aldehyde (complexed as before) and a coordination site on the sugar. As a consequence of this steering effect, the *Si*-face of the complexed aldehyde reacted with the *Si*-face of the diene conformer **B**, again via an aldol-like pathway, e.g., **C**. In both reactions, the aldol-like intermediates were postulated to collapse to the observed *endo* cycloadducts (Scheme 8).



Scheme 8. HDA reactions of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl diene.

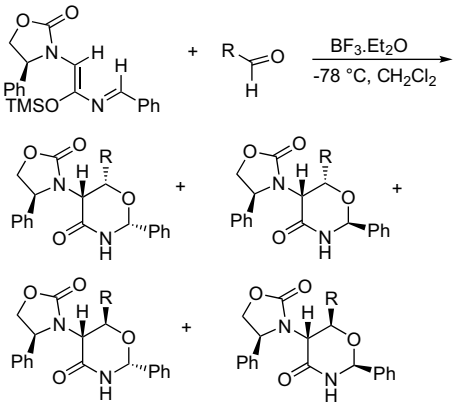
In 2005, Wessjohann et al. reported the use of chiral dienes bearing a chiral moiety at position 5 to control the stereoselectivity of the HDA cycloaddition of a range of α,β-unsaturated aldehydes.[25] In spite of the low reactivity of the α,β-unsaturated aldehydes, this methodology allowed a combinatorial library of highly substituted tetrahydropyrones to be synthesised with full chemo- and regioselectivity combined with good-to-excellent diastereoselectivity, as shown in Scheme 9.



R^1 = H, R^2 = MeCH=CH: 78% de = 34%
R^1 = H, R^2 = PhCH=CH: 85% de = 24%
R^1 = Me, R^2 = MeCH=CH: 84% de = 60%
R^1 = Me, R^2 = PhCH=CH: 85% de = 82%
R^1 = Et, R^2 = MeCH=CH: 84% de = 74%
R^1 = Et, R^2 = PhCH=CH: 72% de = 78%
R^1 = *i*-Pr, R^2 = MeCH=CH: 77% de = 74%
R^1 = *i*-Pr, R^2 = PhCH=CH: 69% de = 60%

Scheme 9. HDA reaction of chiral dienes with α,β-unsaturated aldehydes.

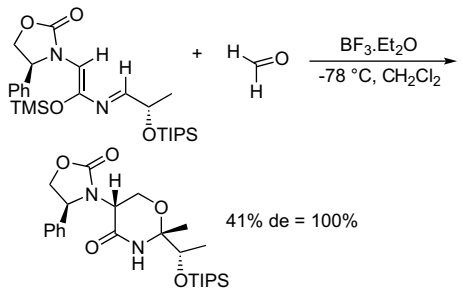
In addition, Panunzio et al. have studied the asymmetric HDA reaction of aldehydes with a series of chiral azadienes, such as chiral 2-aza-3-trimethylsilyloxy-1,3-dienes, providing the corresponding perhydro-oxazin-4-ones in good yields and diastereoselectivities of up to 74% de (Scheme 10).[26] These heterocyclic cycloadducts have proved to be useful intermediates in the synthesis of enantiopure α-amino-β-hydroxy acids.



R = *n*-Pr: 65% (78/0/3/19)
R = *i*-Pr: 54% (0/30/16/54)
R = *n*-Hept: 59% (75/0/4/21)
R = Ph: 52% (0/0/43/57)
R = *p*-MeOC$_6$H$_4$: 30% (0/0/83/17)
R = *p*-NO$_2$C$_6$H$_4$: 45% (0/0/87/13)
R = 2-Naph: 57% (0/0/84/16)
R = 3-(*N*-Boc)-Indolenyl: 62% (0/0/82/18)

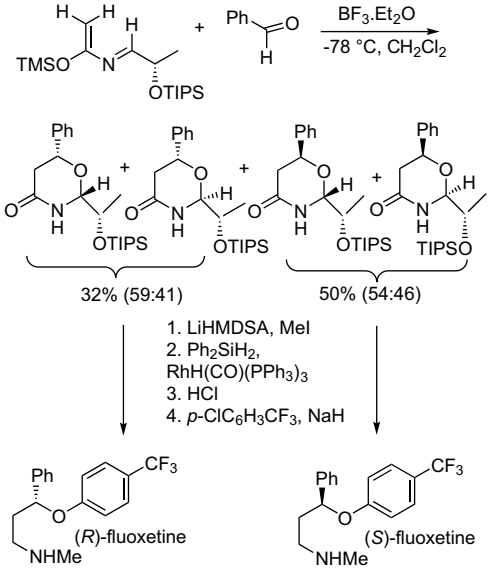
Scheme 10. HDA reaction of chiral 2-aza-3-trimethylsilyloxy-1,3-diene.

In the same area, these workers have obtained optimal results by using an azadiene bearing two chiral moieties, such as that depicted in Scheme 11. Therefore, under these conditions, the reaction took place with a complete control of the diastereoselectivity, since it afforded the corresponding tetrahydro-1,3-oxazin-4-one as a single diastereomer.[27]



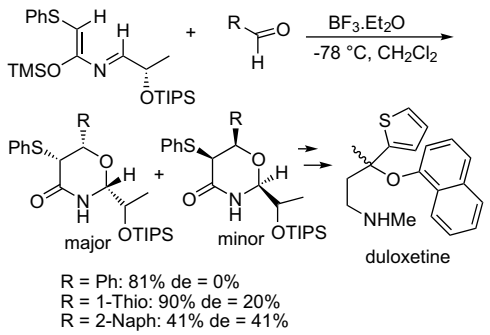
Scheme 11. HDA reaction of 2-aza-3-trimethylsilyloxy-1,3-diene bearing two chiral moieties.

The preceding methodology was applied by the same authors to the syntheses of enantiomerically pure (*S*)- and (*R*)-fluoxetine, marketed as a racemate under the trade name Prozac®, a potent and highly selective inhibitor of serotonin reuptake, as shown in Scheme 12.[28]



Scheme 12. Syntheses of (*S*)- and (*R*)-fluoxetine.

In the same field, these workers reported, in 2006, the synthesis of chiral 5-phenylthio-1,3-oxazinan-4-ones through the HDA reaction of the corresponding chiral azadienes with a range of aldehydes.[29] As shown in Scheme 13, all the reactions were completely regioselective and no traces of azetidinones, arising from a 4π-conrotatory electrocyclisation, were detected. After desulfurisation, these cycloadducts were further converted into (*R*)- and (*S*)-fluoxetine, and (*R*)- and (*S*)-duloxetine.

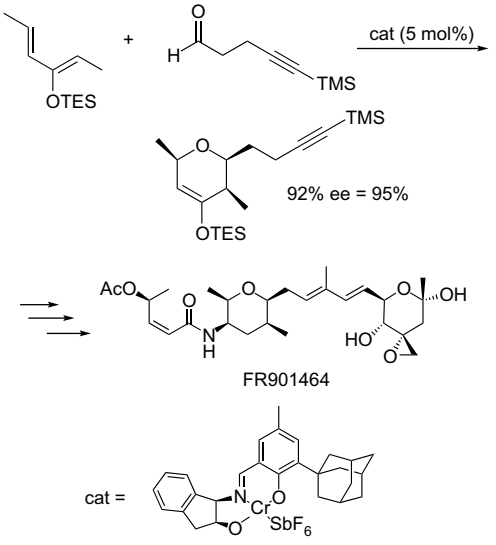


Scheme 13. Syntheses of 5-phenylthio-1,3-oxazinan-4-ones and duloxetine.

2.2. Chiral catalysts

2.2.1. Chiral chromium catalysts

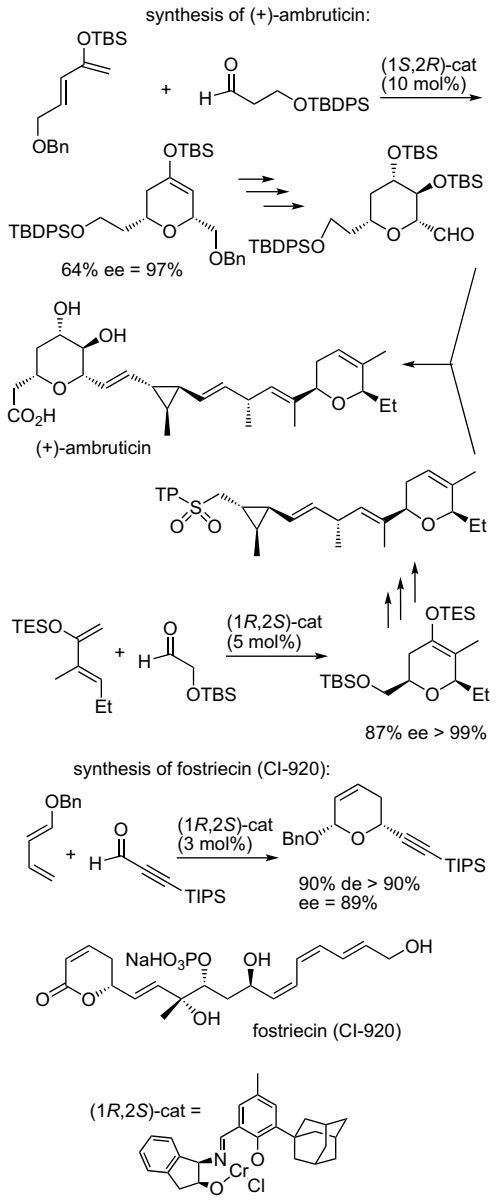
In recent years, many different types of chiral catalysts have been developed to promote the very challenging HDA reaction of unactivated aldehydes with dienes. These various catalysts include chiral chromium, titanium, rhodium, aluminium, zirconium, cobalt, manganese, zinc, copper, magnesium and ytterbium complexes. In the last 10 years, chiral chromium complexes have been the most frequently applied Lewis-acid catalysts to the asymmetric HDA reaction of unactivated aldehydes and, in particular, the chiral salen–Cr(III) complexes discovered by Jacobsen et al. in 1998,[10] and those reported in 1999.[30] The use of these catalysts for this type of reaction has allowed the total syntheses of a large number of natural biologically active products to be successfully developed.[31] In 2000, Jacobsen et al. elaborated the total synthesis of FR901464, which was the most potent member of a new series of bacterially produced antitumour antibiotics.[32] The key step for the synthesis was the highly enantio- and diastereoselective HDA cycloaddition between a hexadiene and a ynal catalysed by Jacobsen's tridentate Cr(III) catalyst, as depicted in Scheme 14.



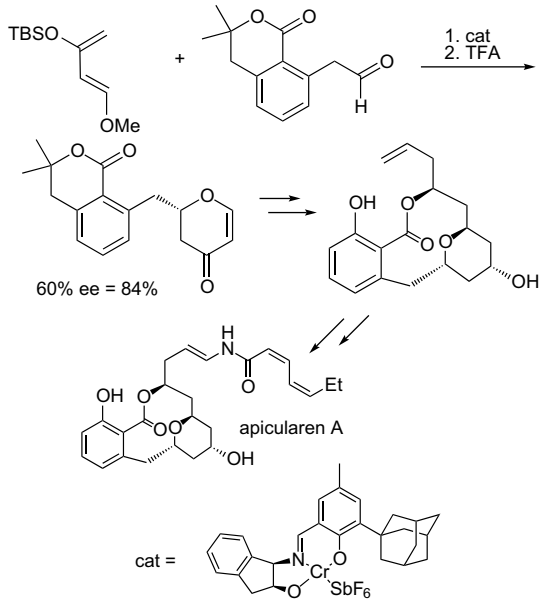
Scheme 14. Synthesis of FR901464.

The scope of this methodology was extended by these workers to the total syntheses of two other important natural products, (+)-ambruticin,[33] an antifungal agent, and fostriecin (CI-920), an antitumour agent.[34] As shown in Scheme 15, the synthesis of fostriecin (CI-920) was based on the diastereo- and enantioselective HDA reaction of an alkoxybutadiene with an ynal catalysed by chlorinated Jacobsen's complex, while the synthesis of (+)-ambruticin involved two cycloadditions of this type. Thereby, this synthesis was initiated with an HDA reaction between a pentadiene and a β-alkoxy aldehyde, providing the corresponding dihydropyran in high enantioselectivity (Scheme 15). The carbon framework of the right-hand dihydropyran was accessed through a second asymmetric HDA reaction occurring between another pentadiene and a α-alkoxy aldehyde with high yield and enantioselectivity (>99% ee) (Scheme 15).

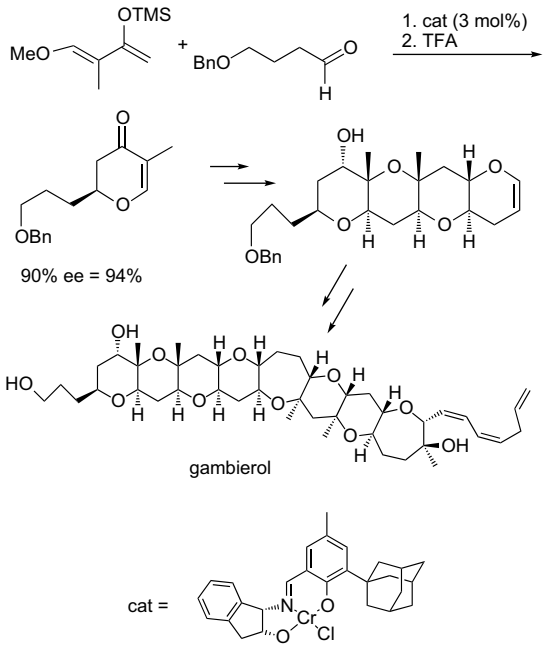
In 2000, De Brabander and Bhattacharjee reported a truncated version of apicularen A, which belongs to a growing class of macrocyclic salicylates with unique biological properties.[35] The key intermediate of the synthesis was a chiral dihydropyranone derived from the HDA cycloaddition of the polyfunctionalised aldehyde, depicted in Scheme 16, with Danishefsky's diene catalysed by



Scheme 15. Syntheses of (+)-ambruticin and fostriecin (CI-920).



Scheme 16. Synthesis of side-chain truncated apicularen A.



Scheme 17. Synthesis of gambierol.

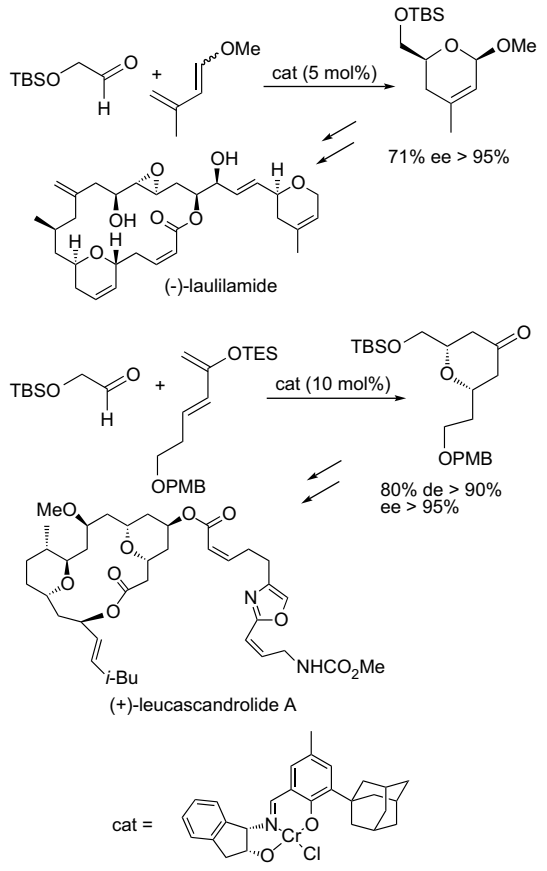
Jacobsen's chiral catalyst. After treatment of this cycloadduct with TFA, the corresponding dihydropyranone was obtained in good yield and enantioselectivity and then converted into the expected macrocyclic portion of apicularen A.

Jacobsen's tridentate Cr(III) catalyst was also employed to catalyse the asymmetric HDA cycloaddition of a Danishefsky-type diene with a χ-alkoxy aldehyde, providing the corresponding cycloadduct in both high yield and enantiomeric purity, as shown in Scheme 17.[36] This product was further converted into the A–D-ring system of the marine ladder toxin, gambierol, and then into gambierol, itself.

In 2001, Paterson et al. reported the total synthesis of the potent microtubule-stabilising anticancer agent, (−)-laulimalide, using Jacobsen's HDA methodology for the enantioselective construction of the side-chain dihydropyran (Scheme 18).[37] The cycloadduct obtained in good yield and with up to 95% ee was further converted into (−)-laulimalide, which was finally obtained in 27 steps and 2.9% overall yield. In 2003, the same workers applied a similar methodology to develop the total synthesis of (+)-leucascandrolide A, a cytotoxic 18-membered macrolide.[38] Indeed, the key feature of the sequence included Jacobsen's asymmetric HDA reaction between an aldehyde and a 2-siloxydiene, occurring with high yield, and diastereo- and enantioselectivity, as shown in Scheme 18.

A more potent and structurally simplified analogue of laulimalide, 11-desmethyllaulimalide, was synthesised by Wender et al., in 2006, offering a cost- and step-economical advantage over the synthesis of laulimalide.[39] The key optically active allylsilane of the synthesis was prepared through Jacobsen's HDA cycloaddition of a readily available aldehyde with Danishefsky's diene, yielding the corresponding pyranone in high yield and enantioselectivity (Scheme 19).

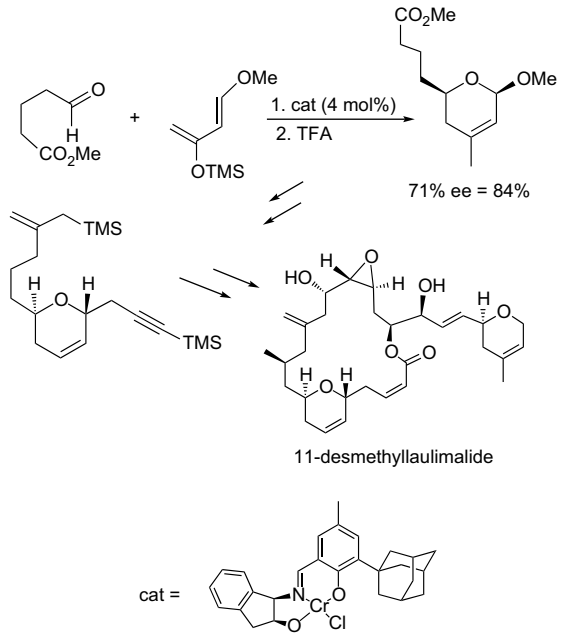
In 2005, a catalytic enantioselective HDA approach to the C20–C32 segment of the phorboxazoles was reported by Burke et al.[40] A Danishefsky diene reacted with a β-alkoxy aldehyde to give the corresponding cycloadduct bearing four stereogenic centres in high



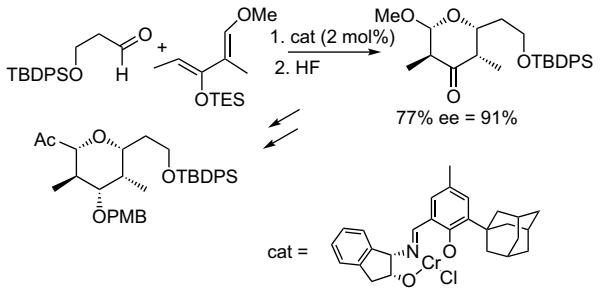
Scheme 18. Syntheses of (−)-laulimalide and (+)-leucascandrolide A.

yield and enantioselectivity. This product was further converted in five steps into the C20–C32 phorboxazole subunit (Scheme 20).

Another application of Jacobsen's methodology was the development, in 2006, of an enantioselective total synthesis of (−)-dactylolide, an antitumour agent, achieved in 21 steps.[41] The intermediate tetrahydropyran was formed in high yield and enantioselectivity (≤99% ee) (Scheme 21). The same catalyst was also

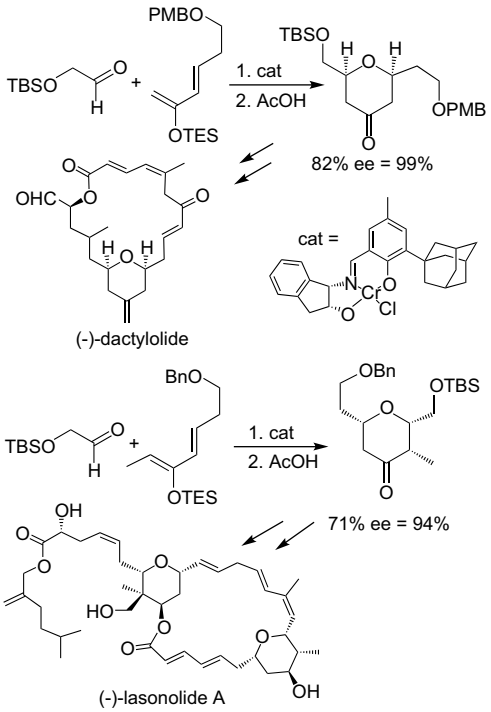


Scheme 19. Synthesis of 11-desmethyllaulimalide.



Scheme 20. Synthesis of C20–C32 phorboxazole subunit.

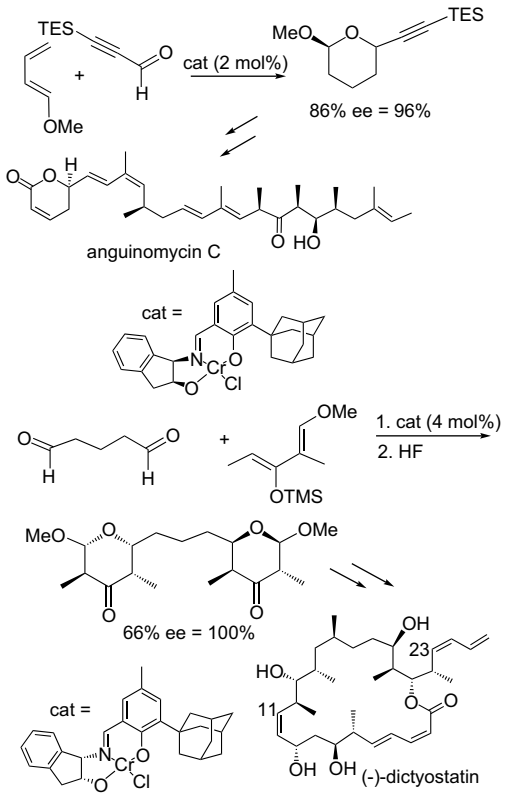
successfully applied by Ghosh and Gong, in 2007, to the total synthesis of (−)-lasonolide A, a macrolide antitumour agent, as shown in Scheme 21.[42]



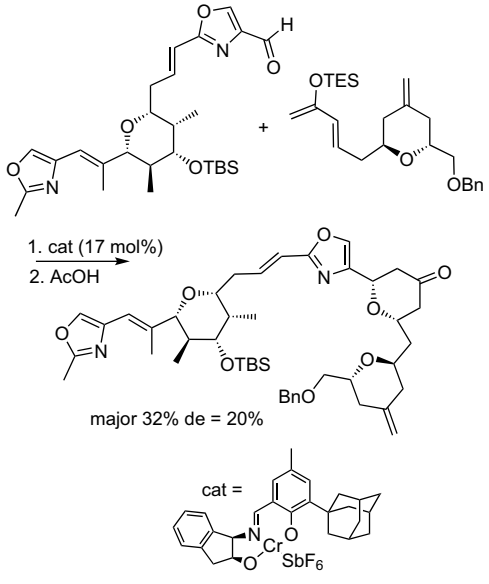
Scheme 21. Syntheses of (−)-dactylolide and (−)-lasonolide A.

Other extremely potent natural antitumour agents, such as anguinomycin C,[43] and also the C11–C23 segment of (−)-dictyostatin,[44] could be synthesised by employing Jacobsen's asymmetric HDA reactions as the key steps. Thereby, the total synthesis of anguinomycin C began with the preparation of a chiral dihydropyran by a cycloaddition between methoxybutadiene and a protected propargylic aldehyde in high yield and enantioselectivity of up to 96% ee (Scheme 22). In the case of the synthesis of the C11–C23 segment of (−)-dictyostatin, a double enantioselective HDA reaction constituted the key step of the synthesis, providing the corresponding enantiomerically pure diketone in good yield (Scheme 22).

In the course of developing total syntheses of phorboxazoles A and B, the scope of Jacobsen's HDA methodology was examined by Paterson and Luckhurst in more complex situations. In 2003, these authors demonstrated that this methodology could be applied with some success to the coupling of complex highly functionalised substrates, in the context of a convergent approach to assemble the phorboxazole ring system (Scheme 23).[45] A possible explanation for this modest result (32% yield, 20% de) was a competitive ligation between the oxazole nitrogen atom of the



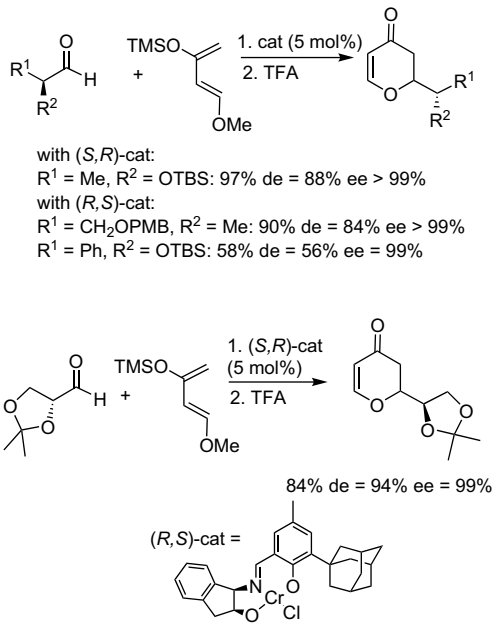
Scheme 22. Syntheses of anguinomycin C and (−)-dictyostatin C11–C23 segment.



Scheme 23. Synthesis of phorboxazole A C4–C32 segment.

aldehyde and the salen ligand heteroatoms for the Cr(III) atom of the catalyst. A study of the HDA reactions between 2-silyloxydienes and a variety of oxazole-containing aldehydes demonstrated, however, that diastereoselectivities of up to 94% de could be obtained for the corresponding products.[46]

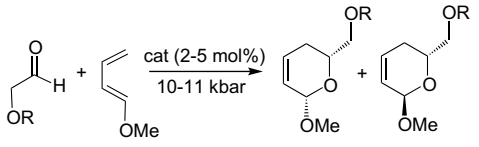
In addition, a few Jacobsen catalyst-controlled doubly diastereoselective HDA reactions have been studied, involving both a chiral aldehyde and a Jacobsen's catalyst. As an example, this type of reaction was employed by Wender et al., in 2002, in order to develop



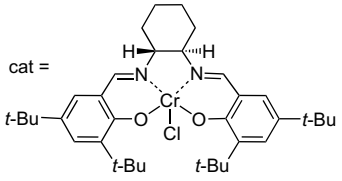
Scheme 24. Jacobsen catalyst-controlled HDA reactions of chiral aldehydes.

a total synthesis of (−)-laulimalide in 25 steps and in 3.5% overall yield.[47] The key step involved a Jacobsen catalyst-controlled doubly diastereoselective HDA reaction between Danishefsky's diene and a chiral aldehyde derived from (*R*)-citronellic acid, which produced the corresponding chiral pyranone in 87% yield and 82% de. In the same context, these authors have developed a practical synthesis of a novel and highly potent analogue of the anticancer agent, bryostatin.[48] In this case, the key HDA reaction involved a diastereomerically enriched aldehyde derived from (−)-menthone (24% de), which gave, through a cycloaddition with Danishefsky's diene in the presence of Jacobsen's catalyst, 88% yield of the expected pyranone in high diastereoselectivity (94% de). In 2002, Jacobsen and Joly studied the stereoselectivity of the HDA reaction between Danishefsky's diene and a variety of chiral aldehydes, since this strategy would provide selective access to stereochemically elaborated dihydropyranone derivatives, which were not readily accessible using simple enantioselective reactions of achiral substrates.[49] As shown in Scheme 24, excellent levels of both diastereo- and enantioselectivity were obtained, combined with high yields, for a series of chiral aldehydes in the presence of Jacobsen's catalyst.

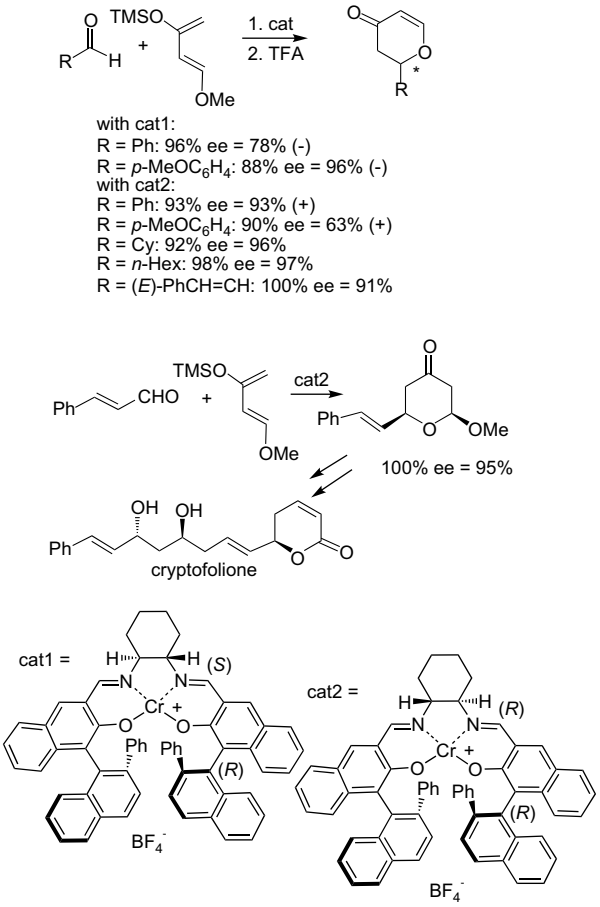
A series of other chiral chromium complexes have been involved in asymmetric HDA reactions,[50] such as the (salen)Cr(III)Cl complex depicted in Scheme 25, which was developed, in 1998, by Jacobsen



R = TBS: 84% de = 92% ee (*cis*) = 87% ee (*trans*) = 78%
R = TBDPS: 55% de = 94% ee (*cis*) = 56% ee (*trans*) = 32%
R = $SiPh_3$: 49% de = 92% ee (*cis*) = 52% ee (*trans*) = 31%



Scheme 25. High-pressure HDA reaction of *O*-protected glycolaldehydes catalysed by (salen)Cr(III)Cl complex.

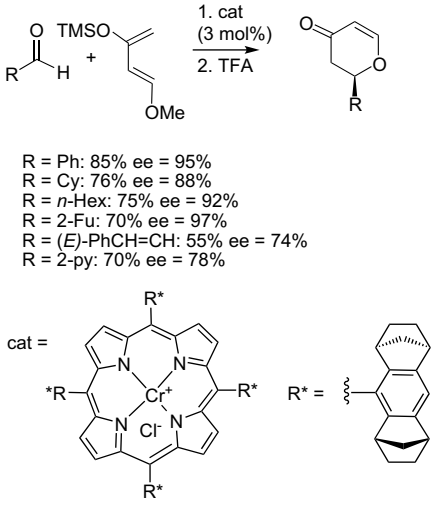


Scheme 26. HDA reactions of aldehydes catalysed by cationic (salen)Cr(III) complexes and synthesis of cryptofolione.

et al.[10] This complex was applied by Jurczak et al. to catalyse the enantioselective high-pressure HDA reaction of 1-methoxybuta-1,3-diene with variously *O*-protected glycolaldehydes.[51] The best results were obtained with *tert*-butyldimethylsilyloxyacetaldehyde, affording the corresponding cycloadduct in good yield, and diastereo- and enantioselectivity of up to 92% de and 87% ee, respectively (Scheme 25).

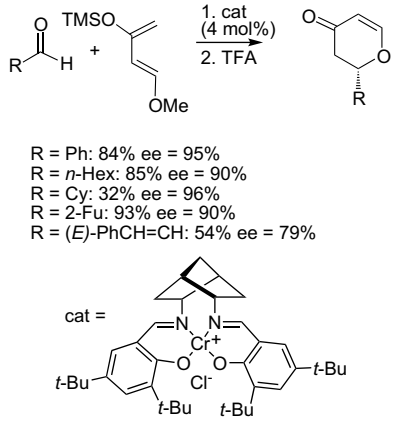
In 2001, Katsuki et al. reported the use of other chiral cationic (salen)Cr(III) complexes for the HDA reaction of a large variety of aldehydes with Danishefsky's diene, providing the corresponding cycloadducts in high yield and enantioselectivity of up to 97% ee, as shown in Scheme 26.[52] It is worthwhile noting that, in all the reactions examined, (*R*,*S*)- and (*R*,*R*)-complexes showed an opposite sense of enantioselectivity, suggesting that the ligand conformation of the complexes, which was dictated by the chirality of the ethylenediamine unit, played an important role in the asymmetric induction by the complexes. In 2005, this methodology was applied to the total synthesis of cryptofolione by the same authors, as depicted in Scheme 26.[53]

On the other hand, Berkessel et al. demonstrated, in 2006, that chiral chromium(III) porphyrins were efficient and highly enantioselective catalysts for the HDA reaction of aliphatic, aromatic and heteroaromatic aldehydes with dienes of varying electron density.[54] In a number of cases, the corresponding cycloadducts were obtained with enantioselectivities of more than 90% ee, as shown in Scheme 27. It was particularly noteworthy that coordinating aldehydes, such as pyridine-2-carbaldehyde, could be reacted without any sign of catalyst inactivation.



Scheme 27. HDA reaction of aldehydes catalysed by Cr(III) porphyrins.

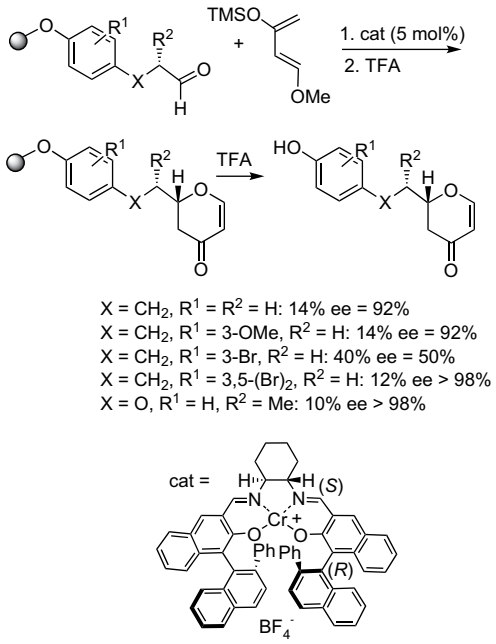
Another new type of chiral chromium–salen complex, bearing DIANANE (*endo*,*endo*-2,5-diaminonorbornane) as a chiral backbone, was synthesised by Berkessel and Vogl, in 2006, and then successfully applied to similar HDA reactions to those described above.[55] These reactions afforded the corresponding cycloadducts in high yields and enantioselectivities of up to 96% ee, as shown in Scheme 28.



Scheme 28. HDA reaction of aldehydes catalysed by DIANANE–Cr(III) salen complex.

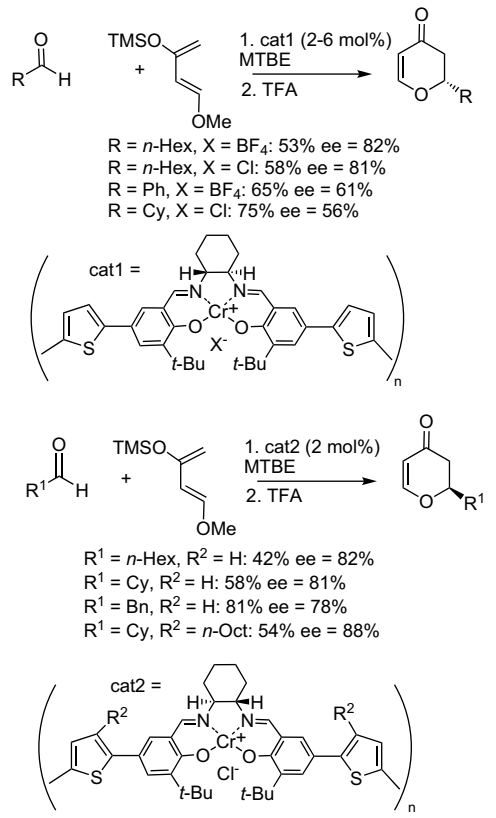
The preparation and application of polymer-supported reagents and catalysts is a rapidly growing field in modern synthetic chemistry.[56] In the area of asymmetric HDA reactions, however, future research will have to extend the methods available for performing these reactions on a solid support,[57] since this area remains relatively understudied.[58] In 2006, Waldmann et al. reported the first enantioselective version of the HDA cycloaddition employing a polymer-bound aldehyde.[59] Indeed, a series of aliphatic aldehydes were synthesised on a solid support and then subjected to enantioselective HDA reactions with Danishefsky's diene in the presence of Jacobsen's catalyst or Katsuki's catalyst, as depicted in Scheme 29. The latter catalyst allowed the best yields of up to 40% and enantioselectivities of up to 99% ee to be obtained for the formed tetrahydropyrans after cleavage from the solid support (Scheme 29).

In 2001, Seebach et al. demonstrated that salen ligands could be immobilised on polystyrene by copolymerisation of suitable crosslinking styryl derivatives with styrene.[60] In the course of this study, it was shown that these chiral polymer-bound Cr–salens presented a high catalytic activity in the HDA reaction of Danishefsky's diene with aldehydes, such as benzaldehyde,



Scheme 29. HDA reactions of polymer-bound aldehydes.

caproaldehyde and cyclohexane carboxaldehyde, affording the corresponding cycloadducts with selectivities similar to those obtained under homogeneous conditions (up to 70% ee). In 2002, better enantioselectivities of up to 84% ee were reported by the same group by employing chiral Cr–salen complexes immobilised on silica gel by radical grafting.[61] More recently, Schulz et al. have reported the successful use of new electropolymerised chiral salen–chromium complexes as heterogeneous catalysts for the HDA reaction of several aldehydes with Danishefsky's diene (Scheme 30).[62] This

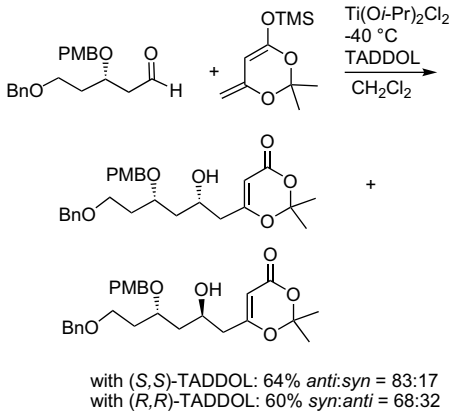


Scheme 30. Electropolymerised Cr–salen complexes for HDA reactions.

novel immobilisation procedure for the chiral salen-based chromium catalysts occurred by electropolymerisation of the corresponding monomeric thiophene complexes. These insoluble catalysts were re-used up to six times, affording the expected cycloadducts with unchanged enantioselectivity of up to 88% ee along with the recycling procedure.

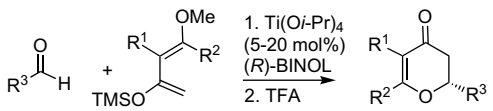
2.2.2. Chiral titanium catalysts

On the other hand, a number of chiral titanium catalysts have been successfully employed as chiral Lewis acids to catalyse HDA reactions. As an example, TADDOL–titanium complexes have been used to catalyse this type of reaction. Thereby, Jiang et al. have studied the HDA reaction of benzaldehyde with Danishefsky's diene in the presence of Ti(O*i*-Pr)$_4$ and TADDOL, which provided the corresponding cycloadduct in low yield (10%) and enantioselectivity (6% ee).[63] In the course of developing a novel synthesis of the spongistatin AB spiroketal, Crimmins and Smith have developed an HDA reaction of a functionalised chiral aldehyde with a silyl dienolate, giving rise, in the presence of TADDOL and Ti(O*i*-Pr)$_2$Cl$_2$, to the corresponding dioxinone.[64] It was shown that the use of (*S*,*S*)-TADDOL delivered an 83:17 mixture favouring the *anti* diastereomer, whereas the use of (*R*,*R*)-TADDOL gave a 68:32 preference for the *syn* diastereomer, as depicted in Scheme 31.

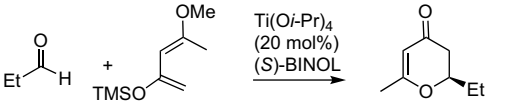


Scheme 31. HDA reactions of chiral aldehyde catalysed by TADDOL–titanium complexes.

Another asymmetric HDA reaction, involving both a chiral aldehyde and a chiral titanium catalyst, constituted the key step of a synthesis of the C1–C14 fragment of laulimalide reported, in 2001, by Davidson and Nadolski.[65] In spite of the usually observed high efficiency of a chiral ligand such as BINOL, the cycloaddition of a chiral aldehyde derived from L-(−)-citronellal with a Danishefsky-type diene yielded the corresponding dihydropyranone in 53% yield with a disappointing diastereoselectivity of 67% de. A number of highly enantioselective HDA reactions using BINOL or its derivatives as ligands of titanium have, however, been successfully reported in the last 8 years. As an example, Le Blanc et al. reported, in 2000, the HDA reaction of polyfluoroalkylaldehydes with Danishefsky's diene performed in the presence of a chiral Lewis acid prepared from BINOL and Ti(O*i*-Pr)$_4$, leading to the corresponding polyfluoroalkyl dihydropyrenones in moderate-to-good yields (≤60%) and high enantioselectivities of 92–99% ee.[66] Similar conditions have been extensively applied by Feng et al. to prepare a wide variety of optically active 2,6-[67] and 2,5-disubstituted dihydropyrones,[68] with generally high yields (up to 99%) and high enantioselectivities of up to 99% ee, as shown in Scheme 32. The scope of this methodology was extended to the synthesis of the important natural product, (+)-hepialone, in one step.

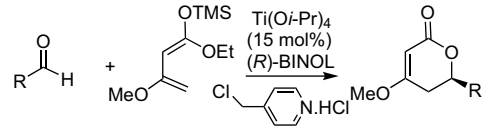


R^1 = H, R^2 = Me, R^3 = Ph: 70% ee = 98%
R^1 = H, R^2 = Me, R^3 = *p*-Tol: 93% ee = 98%
R^1 = H, R^2 = Me, R^3 = *m*-Tol: 73% ee = 99%
R^1 = H, R^2 = Me, R^3 = *p*-ClC_6H_4: 81% ee = 99%
R^1 = H, R^2 = Me, R^3 = *m*-ClC_6H_4: 83% ee = 98%
R^1 = H, R^2 = Me, R^3 = *o*-ClC_6H_4: 90% ee = 83%
R^1 = H, R^2 = Me, R^3 = *p*-$NO_2C_6H_4$: 99% ee = 99%
R^1 = Me, R^2 = H, R^3 = Ph: 86% ee = 99%
R^1 = Me, R^2 = H, R^3 = *o*-ClC_6H_4: 99% ee = 90%
R^1 = Me, R^2 = H, R^3 = *o*-$NO_2C_6H_4$: 99% ee = 91%
R^1 = Me, R^2 = H, R^3 = *p*-CNC_6H_4: 95% ee = 92%
R^1 = Me, R^2 = H, R^3 = *p*-FC_6H_4: 73% ee = 93%
R^1 = Me, R^2 = H, R^3 = 2-py: 98% ee = 96%
R^1 = Me, R^2 = H, R^3 = 2-Fu: 99% ee = 97%
R^1 = Me, R^2 = H, R^3 = *p*-$MeOC_6H_4$: 99% ee = 91%

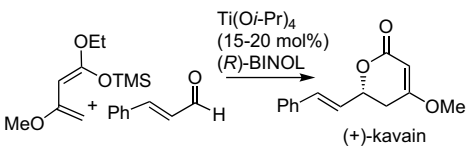


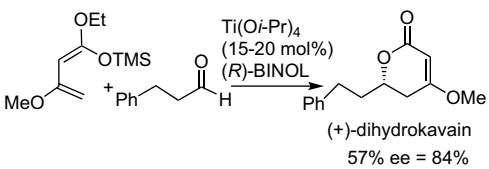
Scheme 32. HDA reactions catalysed by BINOL–titanium complex.

In 2008, the same workers extended the scope of this methodology to the enantioselective HDA reaction of Brassard's diene with a series of aliphatic aldehydes.[69] In this case, the catalyst was generated from (*R*)-BINOL, Ti(O*i*-Pr)$_4$ and 4-picolyl chloride hydrochloride, allowing the corresponding cycloadducts to be formed in moderate-to-good yields and with high enantioselectivities of up to 88% ee (Scheme 33). In addition, this procedure could be applied to the one-step syntheses of two natural products, (+)-kavain and (+)-dihydrokavain.



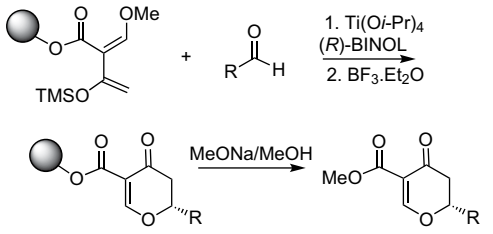
R = Ph: 56% ee = 87%
R = *n*-Bu: 46% ee = 82%
R = *n*-Pr: 79% ee = 84%
R = Et: 72% ee = 88%
R = *i*-Pr: 54% ee = 83%
R = Cy: 65% ee = 81%
R = (*E*)-MeCH=CH: 79% ee = 85%





Scheme 33. HDA reactions of Brassard's diene catalysed by BINOL–titanium complex.

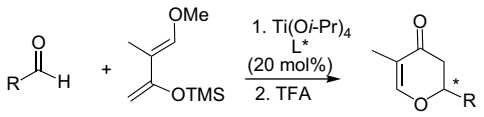
A BINOL–titanium complex has been successfully used by Wang et al. to catalyse the HDA reactions of various aldehydes with poly(ethylene glycol) (PEG)-bound Danishefsky's diene.[70] The excellent results obtained through this soluble polymer-supported methodology are summarised in Scheme 34.



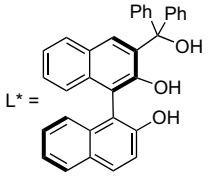
R = Ph: 92% ee = 96%
R = *p*-$NO_2C_6H_4$: 99% ee = 95%
R = *p*-Tol: 98% ee = 93%
R = *o*-Tol: 99% ee = 94%
R = *p*-ClC_6H_4: 73% ee = 93%
R = *o*-ClC_6H_4: 99% ee = 90%
R = *p*-FC_6H_4: 89% ee = 88%
R = 2-Naph: 88% ee = 90%
R = 3-Naph: 95% ee = 95%
R = 2-Fu: 99% ee = 99%
R = Cy: 78% ee = 89%

Scheme 34. HDA reactions using soluble polymer support.

In addition, the HDA reactions of aldehydes with dienes have been performed with high success in the presence of several BINOL derivatives. As a very recent and highly efficient example, Yu et al. reported, in 2008, that the Ti(IV) catalyst derived from a 3-monosubstituted (*R*)-BINOL could exhibit an enhanced catalytic activity for the HDA reaction of both aromatic and aliphatic aldehydes with the diene depicted in Scheme 35.[71] Excellent yields and enantioselectivities were obtained for almost all of the tested substrates, as shown in Scheme 35. When the corresponding 3,3′-bisubstituted BINOL–titanium complex was used as a catalyst for similar reactions, moderate yields (up to 72%) and lower enantioselectivities (up to 80% ee) were observed, in 2008, by the same group.[72]

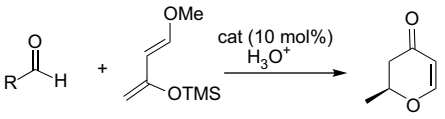


R = Ph: 98% ee = 94%
R = *p*-$NO_2C_6H_4$: 91% ee = 99%
R = *m*-$NO_2C_6H_4$: 86% ee = 96%
R = *o*-$NO_2C_6H_4$: 94% ee = 92%
R = *p*-ClC_6H_4: 99% ee = 93%
R = *m*-ClC_6H_4: 99% ee = 95%
R = *p*-Tol: 89% ee = 93%
R = 2-Naph: 99% ee = 93%
R = *p*-CNC_6H_4: 92% ee = 99%
R = *p*-BrC_6H_4: 98% ee = 92%
R = *n*-Pr: 91% ee = 99%
R = *i*-Pr: 75% ee = 92%
R = *n*-Hex: 92% ee = 97%
R = *(E)*-MeCH=CH: 86% ee = 91%



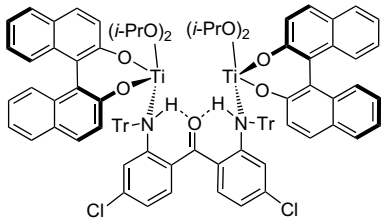
Scheme 35. HDA reactions catalysed by 3-substituted BINOL–titanium complex.

In 2002, a novel chiral bis-titanium(IV) catalyst derived from (*S*)-BINOL was successfully used for the enantioselective HDA reactions of a series of aldehydes with Danishefsky's diene, which allowed fairly high enantioselectivities combined with good yields to be obtained for the corresponding cycloadducts, as shown in Scheme 36.[73]



R = Ph: 64% ee = 71%
R = *n*-Pent: 57% ee = 95%
R = $Ph(CH_2)_2$: 77% ee = 97%
R = $Ph(CH_2)_6$: 66% ee = 92%
R = *i*-Pr: 60% ee = 64%
R = $Me(CH_2)_2C{\equiv}C$: 45% ee = 95%
R = $Me(CH_2)_2CH{=}CH$: 58% ee = 69%

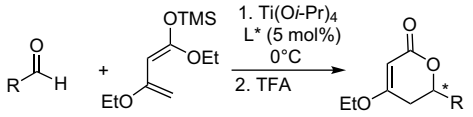
cat =



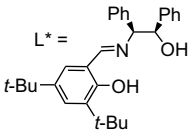
Scheme 36. HDA reactions catalysed by BINOL-derived bis-titanium catalyst.

5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-bi-2-naphthol (H_8-BINOL) is a new atropisomeric diol ligand, which possesses a unique structure, compared to conventional BINOL. Similar reactions to those depicted above were also performed by Jiang et al., in 2000, by using a chiral H_8-BINOL–Ti(IV) catalyst, affording the corresponding dihydropyrones in high yields (up to 92%) and with high levels of enantioselectivity with wide substrate generality (up to 99% ee).[63,74] In the same area, Ding et al. have developed these reactions in solvent-free conditions and in the presence of the corresponding H_4-BINOL–Ti(IV) catalyst.[75] This catalytic system provided an attractive protocol to various chiral dihydropyrones obtained in quantitative yield and enantioselectivity of 99% ee in almost all substrates. Moreover, an exceptionally low catalyst loading of 0.1–0.005 mol % was sufficient to achieve a high yield and optical purity of the products. Very recently, Li et al. have reported the synthesis of a novel chiral $H'4$-NOBIN ligand through partial hydrogenation of 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN).[76] This ligand was further evaluated in the enantioselective Ti-catalysed HDA reaction of Danishefsky's diene with aldehydes, providing the corresponding cycloadducts in moderate-to-high yields (up to 99%) and enantioselectivities of up to 84% ee. In addition, Ding et al. have devised a new type of dendritic titanium catalyst by the molecular assembly of chiral dendritic Schiff-base ligands, titanium(IV) ions and a chiral activator such as (*S*)-naproxen.[77] The catalytic system with dendritic NOBIN-derived Schiff-base ligands was applied to the Ti-catalysed HDA reaction of Danishefsky's diene with aldehydes, giving excellent enantioselectivities of up to 97% ee combined with very high catalytic activities (>99% yields).

Although BINOL and its derivatives are some of the most widely used ligands, a few other chiral ligands have been investigated as the ligands of titanium complexes in the HDA reaction of aldehydes with dienes. As an example, a new type of axially dissymmetric ligand, (*R*)-bis{(*R*)-2,2,2-trifluorohydroxyethyl}biphenyl, was found to function as a ligand for the HDA reaction of benzaldehyde with Danishefsky's diene, providing the corresponding cycloadduct in moderate yield (20%) and enantioselectivity (54% ee) in the presence of Ti(O*i*-Pr)$_4$.[78] In addition, Feng et al. have developed a highly enantioselective HDA reaction of Brassard's diene with aldehydes in the presence of Ti(IV) tridentate Schiff-base complexes.[79] Indeed, the corresponding chiral products were formed under mild conditions with high enantioselectivities of up to 99% ee, as shown in Scheme 37. Mechanistic studies indicated that the reaction pathway was influenced by the reaction temperature. Thus, at higher temperatures (0 °C), the reaction was



R = Ph: 71% ee = 93%
R = *o*-ClC_6H_4: 70% ee = 99%
R = *m*-ClC_6H_4: 70% ee = 90%
R = *p*-ClC_6H_4: 87% ee = 97%
R = *p*-FC_6H_4: 53% ee = 93%
R = *p*-CNC_6H_4: 61% ee = 90%
R = *p*-$NO_2C_6H_4$: 56% ee = 91%
R = 2-Naph: 61% ee = 96%

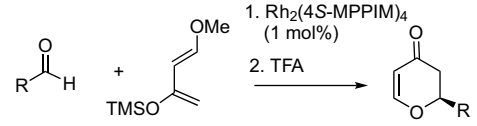


Scheme 37. HDA reactions catalysed by Ti(IV) tridentate Schiff-base complex.

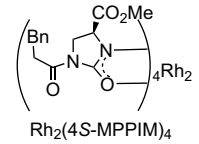
mostly a Diels–Alder process, whereas at lower temperatures (−78 °C), it was a Mukaiyama-aldol process.

2.2.3. Chiral rhodium catalysts

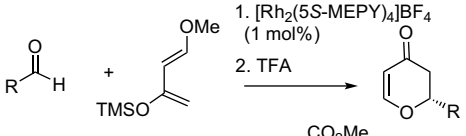
Over the last decade, the exceptional power of chiral dirhodium(II) carboxylate and carboxamidate catalysts has been demonstrated in a diverse array of enantioselective reactions.[80] In particular, highly enantioselective HDA reactions of aromatic aldehydes with Danishefsky's diene and its derivatives have been performed by Doyle et al., using chiral dirhodium(II) carboxamidates with uncommonly high turnover numbers of up to 10,000 and catalyst loadings as low as 0.01 mol %. In the case of using Danishefsky's diene, the best catalyst was shown to be Rh_2(4*S*-MPPIM)$_4$, displaying high levels of enantioselectivity, as summarised in Scheme 38.[81] In 2008, the same group used the corresponding cationic chiral dirhodium carboxamidates, such as [Rh_2(5*S*-MEPY)$_4$]BF_4, as catalysts to promote similar reactions, which allowed enantioselectivities of up to 93% ee to be obtained in place of 73% ee when using the corresponding non-cationic complex Rh_2(5*S*-MEPY)$_4$ (Scheme 38).[82]



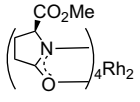
R = Ph: 93% ee = 91%
R = *p*-Tol: 90% ee = 82%
R = *p*-$NO_2C_6H_4$: 92% ee = 95%
R = *o*-$NO_2C_6H_4$: 84% ee = 87%
R = *p*-FC_6H_4: 96% ee = 82%
R = *p*-ClC_6H_4: 91% ee = 90%
R = *p*-$CF_3C_6H_4$: 92% ee = 88%
R = (*E*)-*p*-$NO_2C_6H_4CH{=}CH$: 41% ee = 89%
R = 5-NO_2-2-Fu: 48% ee = 93%
R = 5-NO_2-2-Thio: 81% ee = 94%
R = 2-Naph: 98% ee = 90%
R = 2-Fu: 84% ee = 88%



Rh_2(4*S*-MPPIM)$_4$



R = *p*-$NO_2C_6H_4$: 70% ee = 93%
R = Ph: 40% ee = 88%

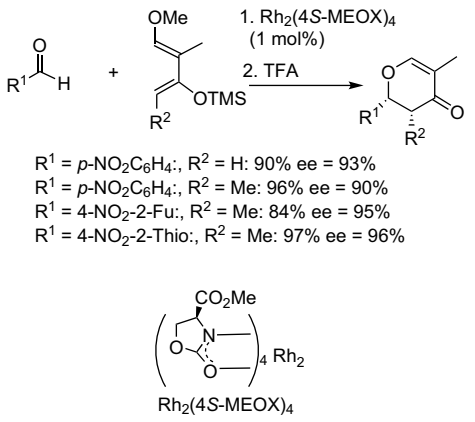


Rh_2(5*S*-MEPY)$_4$

Scheme 38. Rh_2(4*S*-MPPIM)$_4$- and [Rh_2(5*S*-MEPY)$_4$]BF_4-catalysed HDA reactions.

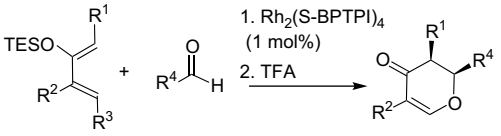
The scope of the preceding methodology was extended to the use of methyl and dimethyl-substituted Danishefsky's dienes, giving rise to the corresponding *cis* dihydropyrans.[81c,83] For this type

of diene, a chiral dirhodium(II) carboxamidate, Rh_2(4*S*-MEOX)$_4$, provided the best yields and enantioselectivities, as depicted in Scheme 39.



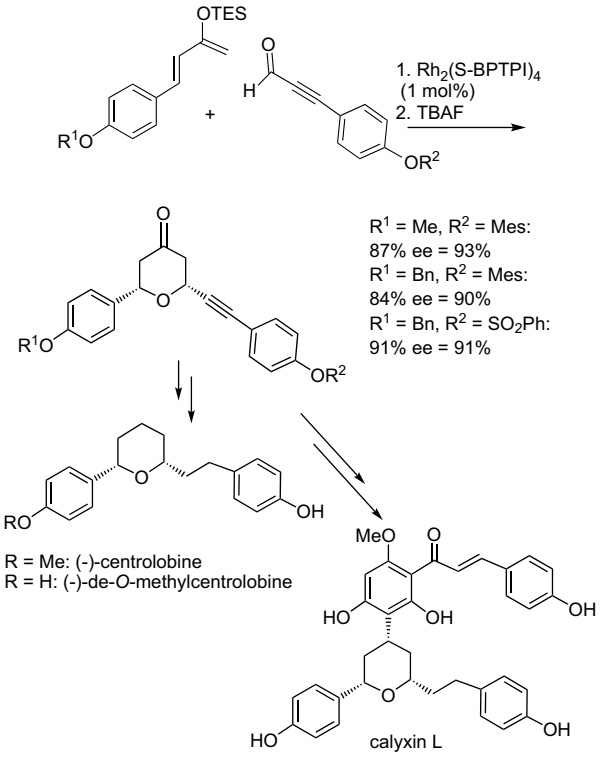
Scheme 39. Rh_2(4*S*-MEOX)$_4$-catalysed HDA reactions.

In the preceding study, it was shown that electron-withdrawing *p*-nitrobenzaldehyde reacted more than 700-fold faster than electron-donating *p*-anisaldehyde. In order to propose a more general and highly efficient catalyst for these HDA reactions, Hashimoto et al. have reported the involvement of Rh_2(*S*-BPTPI)$_4$, a new dirhodium(II) carboxamidate complex, incorporating (*S*)-3-(benzene-fused-phthalimido)-2-piperidinonate as a chiral bridging ligand.[84] As shown in Scheme 40, this novel catalyst has proved to be an exceptionally effective and general Lewis-acid catalyst for *endo* and enantioselective HDA reactions of various aldehydes with Danishefsky-type dienes, as well as with monooxygenated dienes, in which up to 99% ee and turnover numbers as high as 48,000 have been achieved.



Scheme 40. Rh_2(*S*-BPTPI)$_4$-catalysed HDA reactions.

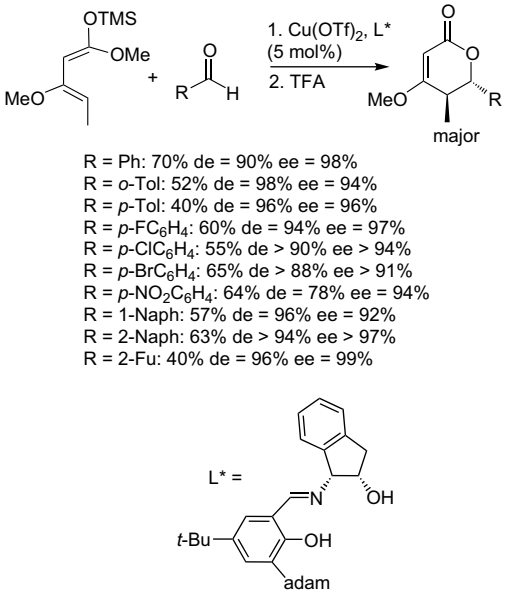
In 2007, this highly efficient methodology was exploited for the total syntheses of three natural products, the antitumour agent, calyxin L,[85] the antibiotic agent, (−)-centrolobine, and the antileishmanial agent, (−)-de-*O*-methylcentrolobine, as depicted in Scheme 41.[86]



Scheme 41. Syntheses of calyxin L, (−)-centrolobine and (−)-de-*O*-methylcentrolobine.

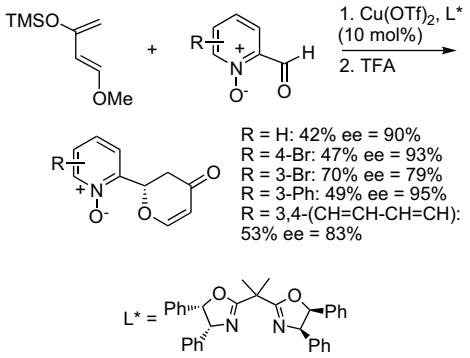
2.2.4. Other chiral metal catalysts

Since 2000, only a few examples of Cu-catalysed asymmetric HDA reactions of aldehydes have been described, such as that developed by Feng et al.[87] These reactions, involving a Brassard-type diene, were catalysed by a new chiral Cu(II) tridentate Schiff-base complex, affording the corresponding 5-methyl-containing α,β-unsaturated δ-lactone derivatives in moderate yields, high enantioselectivities of up to 99% ee and excellent diastereoselectivities of up to 99% de, as shown in Scheme 42.



Scheme 42. HDA reactions catalysed by Cu(II)–tridentate Schiff base complex.

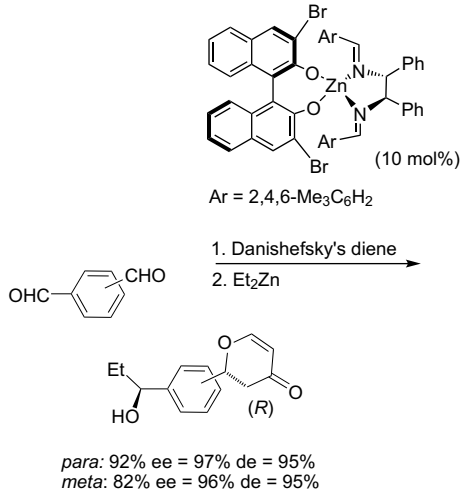
In 2007, another Cu-catalysed HDA reaction of aldehydes was reported by Jorgensen et al., using chiral bisoxazoline ligands.[88] The reactions were performed between *N*-oxy-pyridine-2-carbaldehydes and Danishefsky's diene, providing the corresponding chiral heterocycles in moderate yields and good enantioselectivities of up to 93% ee (Scheme 43).



Scheme 43. Cu(II)-catalysed HDA reactions of *N*-oxy-pyridine-2-carbaldehydes.

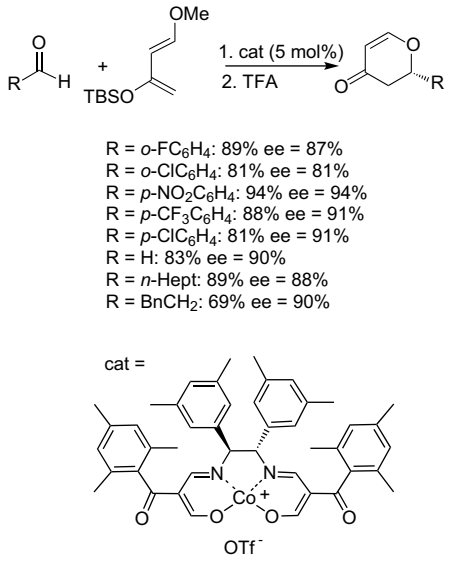
The use of chiral zinc catalysts for the enantioselective HDA reaction has generally been hardly explored. In this area, the chiral zinc catalyst prepared from (*R*)-3,3′-Br_2-BINOL and $ZnEt_2$ has been demonstrated by Ding et al. to be highly efficient and enantioselective for the HDA reaction of Danishefsky's diene with aldehydes, affording the corresponding cycloadducts in excellent yields (34–99%) and enantioselectivities of up to 98% ee (58–98%).[89] In this study, a new type of chiral zinc catalyst, containing an (*R*)-3,3′-Br_2-BINOL ligand and a diimine activator (depicted in Scheme 44), has also been found to be an excellent catalyst for the HDA reaction. Moreover, the application, by the same workers, of this type of catalyst was extended to the diethylzinc addition to benzaldehyde, affording the corresponding secondary alcohol with up to 95% ee. On the basis of these observations, the integration of the enantioselective HDA and the diethylzinc addition reactions has been achieved in one pot with the promotion of a single chiral zinc catalyst in a sequential manner. Indeed, these authors have achieved the integration of two asymmetric reactions in one pot with the promotion utilising a single catalyst for the HDA reaction of Danishefsky's diene and the diethylzinc addition to aldehydes (Scheme 44).[90]

In 2000, Yamada et al. reported the synthesis of novel optically active Co(III) complexes and investigated these catalysts for the



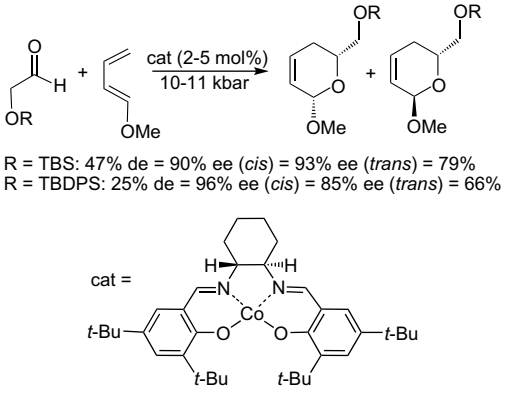
Scheme 44. Asymmetric domino HDA/diethylzinc addition reactions.

enantioselective HDA reactions of aliphatic and aromatic aldehydes with Danishefsky's diene.[91] In the presence of a cationic Co(III) triflate complex derived from chiral 1,2-bis(3,5-dimethylphenyl)-1,2-ethylenediamine, the reaction proceeded in high yield and enantioselectivity of up to 94% ee (Scheme 45).



Scheme 45. Co(III)-catalysed HDA reactions.

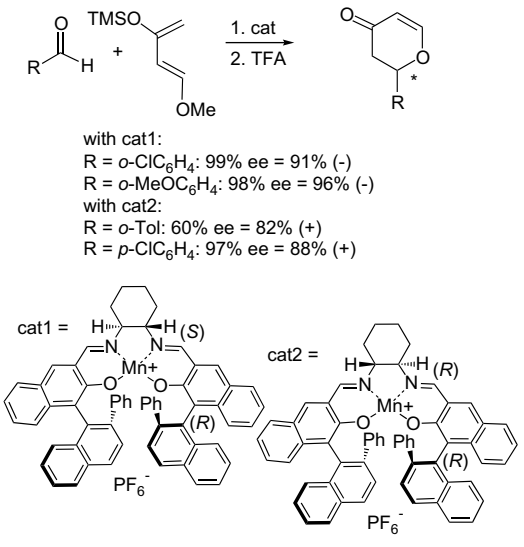
In the same context, Jurczak et al. have studied the HDA reactions of 1-methoxybuta-1,3-diene with *O*-protected glycolaldehydes under high pressure and in the presence of chiral (salen)Co(II) complexes, which yielded the corresponding cycloadducts in moderate yields and enantioselectivities of up to 93% ee (Scheme 46).[51]



Scheme 46. Co(II)-catalysed HDA reactions.

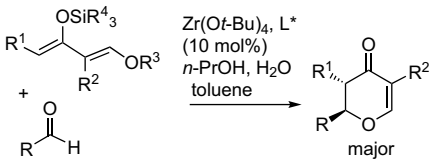
Chiral cationic (salen)Mn(III) complexes have also served as catalysts for the HDA reaction of Danishefsky's diene with aldehydes, achieving, in some cases, high enantioselectivity (up to 96% ee), as shown in Scheme 47.[52a]

In 2000, Jorgensen et al. studied the Al-catalysed HDA reaction of benzaldehyde with Danishefsky's diene, performed in the presence of various chiral ligands derived from BINOL.[92] With a catalyst generated from (*R*)-3,3′-bis(2,5-dihexyloxyphenyl)-BINOL and $AlMe_3$, the corresponding cycloadduct was obtained with 97% yield and 99% ee. This study demonstrated that hypercoordination of the chiral ligand to the aluminium Lewis-acid centre was of importance for the reaction. Many chiral catalysts, in particular chiral Lewis acids, are often unstable in air or in the presence of water. Consequently, many catalysts are often prepared in situ in an appropriate

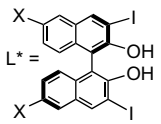


Scheme 47. Mn(III)-catalysed HDA reactions.

solvent immediately before use, and cannot be stored for extended periods. In this context, Kobayashi et al. have developed air-stable, storable and highly efficient chiral zirconium Lewis acids to promote asymmetric HDA reactions.[93] These new catalysts were prepared from $Zr(Ot\text{-}Bu)_4$ and (*R*)-3,3′-diiodobinaphthol, or its derivatives, propanol and a small amount of water. The reaction of various aldehydes with Danishefsky's dienes proceeded smoothly to afford the corresponding *trans* pyranones in high yields and with high diastereo- and enantioselectivity, as depicted in Scheme 48. This methodology has been applied to the synthesis of important natural products such as (+)-prelactone C and (+)-9-deoxygoniopypyrone.[93b]

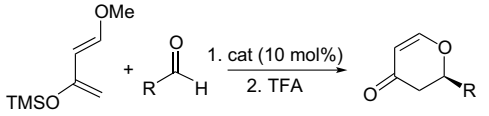


R = Ph, $R^1 = R^2 = X = H$, R^3 = Me, R^4 = TMS:
80% ee = 97%
R = *p*-Tol, $R^1 = R^2 = X = H$, R^3 = *t*-Bu, R^4 = TMS:
58% ee = 93%
R = *p*-ClC_6H_4, $R^1 = R^2 = X = H$, R^3 = *t*-Bu, R^4 = TMS:
65% ee = 84%
R = Ph, $R^1 = R^2 = X = H$, R^3 = *t*-Bu, $R^4 = SiEtMe_2$:
84% ee = 90%
R = *n*-Pent, $R^1 = R^2 = X = H$, R^3 = *t*-Bu, $R^4 = SiEtMe_2$:
69% ee = 91%
R = Ph, $R^1 = R^2$ = H, R^3 = *t*-Bu, R^4 = TMS, $X = C_2F_5$:
100% de = 84% ee = 98%
R = *p*-Tol, $R^1 = R^2$ = H, R^3 = *t*-Bu, R^4 = TMS, $X = C_2F_5$:
93% de = 76% ee = 90%
R = *p*-ClC_6H_4, $R^1 = R^2$ = H, R^3 = *t*-Bu, R^4 = TMS, $X = C_2F_5$:
99% de = 80% ee = 97%
R = *(E)*-PhCH=CH, $R^1 = R^2$ = H, R^3 = *t*-Bu, R^4 = TMS
$X = C_2F_5$: 78% de = 80% ee = 87%
R = $BnCH_2$, $R^1 = R^2$ = H, R^3 = *t*-Bu, R^4 = TMS, X = I:
68% de = 80% ee = 87%

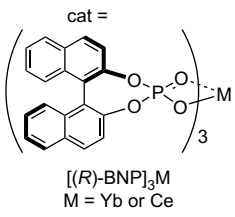


Scheme 48. Zr(IV)-catalysed HDA reactions.

Recent intensive studies on chiral rare-earth complexes as catalysts are frequently reporting various successful examples of highly efficient asymmetric reactions.[94] As an example, Inanaga et al. have synthesised novel rare-earth metal complexes with chiral phosphate ligands, which acted as isolable and storable Lewis-acid catalysts for the asymmetric HDA reaction of aldehydes with Danishefsky's diene under homogeneous conditions.[95] Thereby, the ytterbium complex of (*R*)-1,1′-binaphthyl-2,2′-diylphosphate ((*R*)-BNP) effectively promoted these reactions in the presence of 2,6-lutidine as an additive, providing the corresponding cycloadducts in high yields and enantioselectivities of up to 93% ee (Scheme 49). In addition, the use of another chiral catalyst of the same type, such as $Y[(R)\text{-}H_8\text{-}BNP]_3$, allowed up to 99% ee and 81% yield to be obtained for the cycloaddition occurring between benzaldehyde and Danishefsky's diene.[95c] The scope of the preceding methodology was extended by the same group to the use of cerium, another rare-earth metal. Indeed, the corresponding novel chiral cerium complex has been found to be an excellent storable catalyst for similar reactions, since high yields and enantioselectivities (up to 94% ee) were observed, as shown in Scheme 49.[96]



with cat = $[(R)\text{-}BNP]_3Yb$ and 2,6-lutidine:
R = Ph: 94% ee = 89%
R = *p*-$MeOC_6H_4$: 86% ee = 93%
R = *p*-ClC_6H_4: 70% ee = 88%
R = *p*-Tol: 79% ee = 89%
R = 2-Naph: 79% ee = 84%
R = 2-Fu: 83% ee = 76%
with cat = $[(R)\text{-}BNP]_3Ce$:
R = Ph: 91% ee = 80%
R = *p*-Tol: 96% ee = 88%
R = *p*-EtC_6H_4: 95% ee = 93%
R = *p*-(*i*-Bu)C_6H_4: 61% ee = 93%
R = *p*-(*t*-Bu)C_6H_4: 75% ee = 94%
R = *p*-FC_6H_4: 91% ee = 85%
R = *p*-BrC_6H_4: 80% ee = 92%

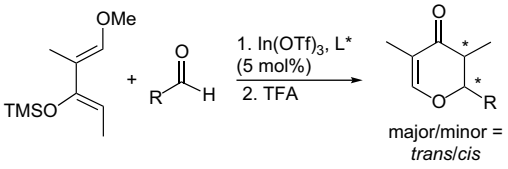


$[(R)\text{-}BNP]_3M$
M = Yb or Ce

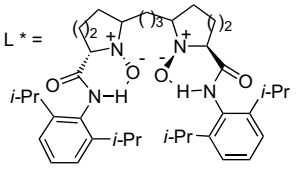
Scheme 49. Yb(III)- and Ce(III)-catalysed HDA reactions.

In spite of In(III) being a strong activator of carbonyl compounds, In(III) complexes have rarely been employed as chiral catalysts. In this context, Feng et al. developed, in 2008, a novel and efficient chiral catalyst system based on *N*,*N*′-dioxide/$In(OTf)_3$ complexes and its application in the enantioselective HDA reaction.[97] As shown in Scheme 50, the reaction of an extremely broad range of aldehydes with a Danishefsky's diene allowed the corresponding chiral pyranones to be produced in good yields and with up to 99% ee.

In 2008, Peters and Tiseni demonstrated that a complex formed in situ from $Er(OTf)_3$ and a simple commercially available norephedrine ligand promoted an unprecedented HDA reaction of α,β-unsaturated acid chlorides with a broad range of aromatic and heteroaromatic aldehydes.[98] The corresponding δ-lactone building blocks were obtained with generally excellent enantioselectivity, as shown in Scheme 51. In order to explain these results, the authors proposed the catalytic cycle depicted in Scheme 51. They assumed that the ligand and both substrates all bound to the same centre, since Er(III) is known to prefer high coordination numbers, typically 7–10. The results were in accordance with a mechanism in which the reversibly binding Lewis-basic site formed a nucleophilic dienolate, which strongly bound to the metal ion, resulting in a highly organised transition state for a vinylogous aldol addition reaction. The turnover was achieved by an intramolecular acylation.

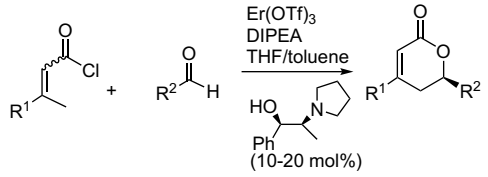


R = Ph: 96% de = 90% ee = 98%
R = *m*-ClC_6H_4: 98% de = 90% ee = 99%
R = 3,4-$Cl_2C_6H_3$: 93% de = 88% ee = 99%
R = *p*-Tol: 96% de = 90% ee = 98%
R = *p*-FC_6H_4: 96% de = 90% ee = 99%
R = *m*-BrC_6H_4: 96% de = 90% ee = 97%
R = *m*-$NO_2C_6H_4$: 90% de = 90% ee = 97%
R = *m*-$PhOC_6H_4$: 95% de = 90% ee = 98%
R = *m*-HOC_6H_4: 96% de = 90% ee = 96%
R = *n*-Pent: 52% de = 84% ee = 97%
R = *n*-Hex: 52% de = 84% ee = 98%
R = (*E*)-PhCH=CH: 92% de = 90% ee = 98%

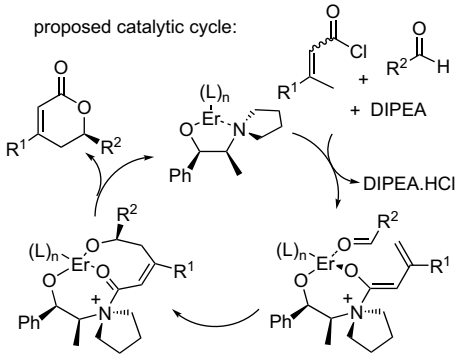


Scheme 50. In(III)-catalysed HDA reaction.

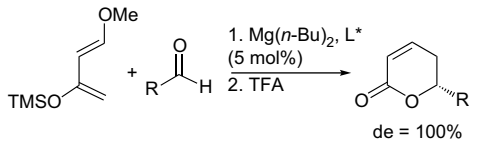
In addition, the first asymmetric Mg-catalysed HDA reactions of aldehydes have been very recently reported by Ding et al.[99] Among a collection of BINOL and TADDOL derivatives, a chiral BINOL-derived ligand, depicted in Scheme 52, was selected as the most efficient to give the best enantioselectivities of up to 99% ee for the



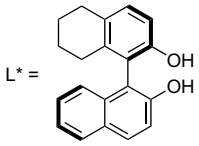
R^1 = *i*-Pr, R^2 = Ph: 56% ee = 95%
R^1 = Et, R^2 = Ph: 62% ee = 95%
R^1 = *i*-Bu, R^2 = Ph: 54% ee = 98%
R^1 = Cy, R^2 = Ph: 65% ee = 96%
R^1 = R^2 = Ph: 64% ee = 94%
R^1 = Ph, R^2 = 2-Naph: 55% ee = 95%
R^1 = Ph, R^2 = *o*-ClC_6H_4: 77% ee = 88%
R^1 = Ph, R^2 = *m*-ClC_6H_4: 78% ee = 93%
R^1 = Ph, R^2 = *p*-ClC_6H_4: 71% ee = 92%
R^1 = Ph, R^2 = *m*-BrC_6H_4: 77% ee = 95%
R^1 = Ph, R^2 = *p*-BrC_6H_4: 70% ee = 93%
R^1 = Ph, R^2 = *o*-$NO_2C_6H_4$: 91% ee = 91%
R^1 = Ph, R^2 = *p*-$NO_2C_6H_4$: 72% ee = 88%
R^1 = Ph, R^2 = *m*-$CF_3C_6H_4$: 87% ee = 93%
R^1 = Ph, R^2 = *p*-$NO_2C_6H_4CH$=CH: 62% ee = 92%
R^1 = Ph, R^2 = 2-Thio: 40% ee = 95%



Scheme 51. Er(III)-catalysed HDA reactions.



R = Ph: 99% ee = 99%
R = *p*-$MeOC_6H_4$: 99% ee = 97%
R = $BnCH_2$: 99% ee = 80%
R = (*E*)-PhCH=CH: 99% ee = 97%
R = 2-Fu: 99% ee = 93%
R = *p*-Tol: 99% ee = 97%
R = *m*-ClC_6H_4: 99% ee = 94%
R = *p*-BrC_6H_4: 99% ee = 95%
R = *p*-ClC_6H_4: 99% ee = 91%
R = *o*-BrC_6H_4: 99% ee = 88%
R = *o*-Tol: 99% ee = 96%
R = 2,6-$Cl_2C_6H_4$: 91% ee = 94%

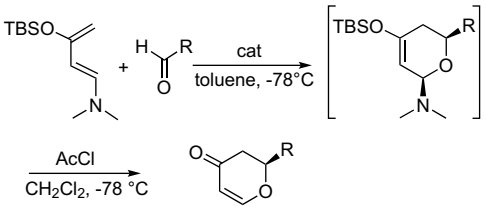


Scheme 52. Mg(II)-catalysed HDA reactions.

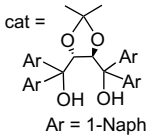
cycloadducts arising from the reactions of a variety of aldehydes with Danishefsky's diene (Scheme 52).

2.2.5. Chiral organocatalysts

For a long time, it was not known that organocatalysts could be used to catalyse the Diels–Alder reactions and, in particular, base-catalysed Diels–Alder reactions were regarded as uncommon. In recent years, however, several different organocatalysts have been developed.[100] Indeed, a number of organocatalytic enantioselective HDA reactions have recently been developed, and these have become a topic of interest in asymmetric organocatalysis. Among these reactions, one of the most exciting developments was the 1-naphthyl-TADDOL-promoted reaction of 1-amino-3-siloxybutadiene with aldehydes, which was reported, in 2003, by Rawal et al.[8] Thus, this cycloaddition proceeded smoothly to furnish the cycloadducts highly enantioselectively after treatment with AcCl, as depicted in Scheme 53.



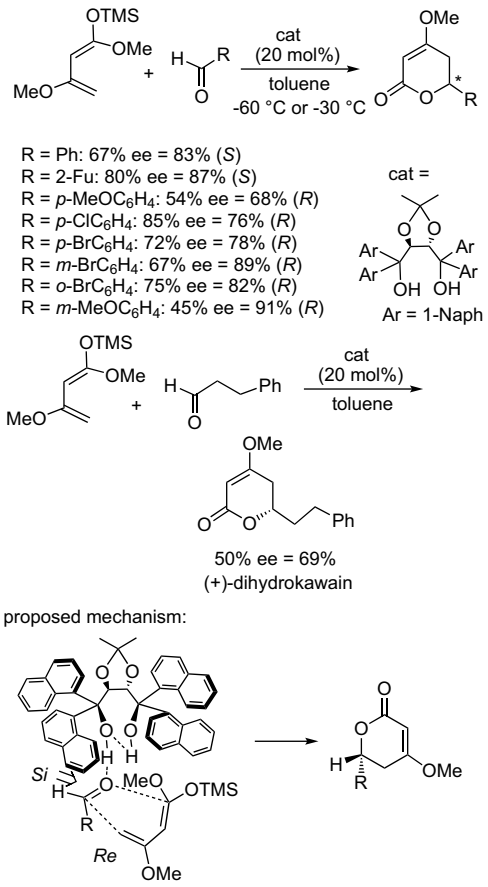
R = Ph: 70% ee > 98%
R = *p*-$MeOC_6H_4$: 68% ee = 94%
R = 1-Naph: 69% ee > 98%
R = 2-Naph: 97% ee = 94%
R = *p*-$CF_3C_6H_4$: 68% ee = 94%
R = 2-Fu: 67% ee = 92%
R = Cy: 64% ee = 86%
R = (*E*)-CH=CHPh: 52% ee = 94%



Scheme 53. Organocatalytic HDA reactions of aminosiloxydiene.

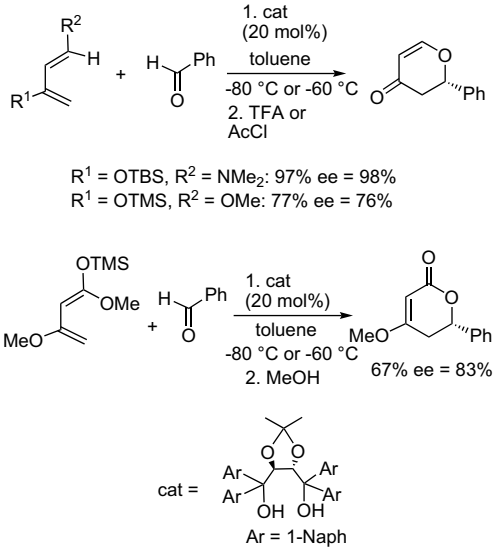
In 2004, the same TADDOL derivative was employed by Ding et al. to induce the HDA reactions of aldehydes with Brassard's diene, affording the corresponding δ-lactone derivatives highly enantioselectively (Scheme 54).[101] The usefulness of this methodology was demonstrated in the total synthesis of the natural product, (+)-dihydrokawain. In order to explain the asymmetric induction of the reaction, these workers have proposed a possible mechanism, as outlined in Scheme 54. In this (*S*,*S*)-catalytic system, the steric hindrance of the naphthyl moiety shielded the *Si*-face of the aldehyde, while the *Re*-face was available to accept the attacking diene, to give the product with the *R* configuration, as expected. It was evident that the strength of the intermolecular

hydrogen bonding between the catalyst and the substrate, the greater steric hindrance of the 1-naphthyl group and the π–π interaction between the naphthyl ring and the carbonyl group of the substrate all played important roles in the control of the enantioselectivity of the catalytic reactions.



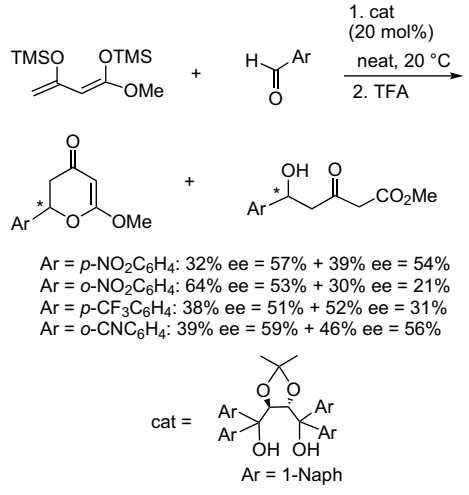
Scheme 54. Organocatalytic HDA reactions of Brassard's diene.

In the same context, Ding et al. have investigated enantioselective HDA reactions of Danishefsky's diene and its analogues with various aldehydes in the presence of a range of TADDOL derivatives.[102] An interesting phenomenon, namely that naphtha-1-yl-TADDOL exhibited a remarkably superior performance, compared to that of its analogues, such as simple phenyl-TADDOL or naphtha-2-yl-TADDOL, was found in several HDA reactions in terms of both activity and enantioselectivity. Indeed, the α,α′-aryl substituents in the TADDOL molecules were found to exert a significant impact on both the activity and the enantioselectivity of the catalysis. Thus, the use of naphtha-1-yl-TADDOL as the organocatalyst allowed high enantioselectivities of up to 98% ee to be obtained, as shown in Scheme 55. In addition, the mechanism of the reaction was studied theoretically, using the ONIOM (B3LYP/6-31G*:PM3) method with *trans*-1,3-dimethoxy-1,3-butadiene as the model for Danishefsky's diene, indicating that the reaction evolved via a concerted mechanism through an asynchronous and zwitterionic transition structure, as depicted in Scheme 54. The carbonyl group of the aldehyde was activated by forming an intermolecular hydrogen bond with one of the hydroxy groups of TADDOL. Meanwhile, the intramolecular hydrogen bond between the two hydroxyl groups in TADDOL was found to facilitate the intermolecular hydrogen bonding with the aldehyde. The involvement of highly polarised transition states was confirmed by a computational study of the diol-catalysed HDA reactions of Rawal-type dienes reported, in 2007, by Houk et al.[103] It was shown that the 1,4-butanediol model systems for catalysis by TADDOLs were consistent with a cooperative hydrogen-bonding arrangement.



Scheme 55. Organocatalytic HDA reactions of Danishefsky's diene and analogues.

In the course of investigating the viability of the enantioselective vinylogous aldol reaction of Chan's diene in the presence of naphtha-1-yl-TADDOL as organocatalyst, Villano et al. have found that the involvement of electron-poor aromatic aldehydes in this reaction enhanced the reactivity and enabled a competing asymmetric HDA reaction to take place in comparable (or higher) yields and enantioselectivities under solvent-free conditions (Scheme 56).[104]

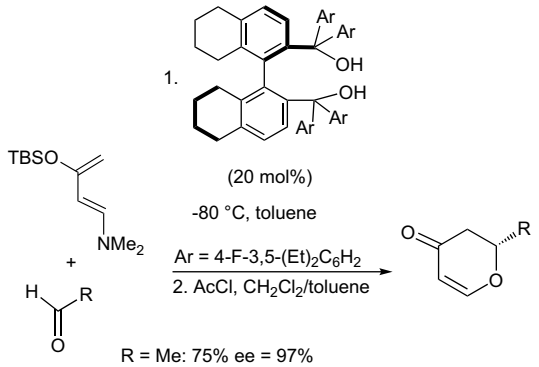


Scheme 56. Organocatalytic HDA reactions of Chan's diene.

Some recent publications have outlined the development of a novel computational procedure, reverse docking, which has proved to be a useful tool for studying the enantioselectivity of several organocatalysed reactions.[105] In this procedure, a large flexible organocatalyst is docked around rigid-transition-state models of catalyst-free reactions generated by ab initio transition-state optimisation calculations. The resulting reverse-docking positions represent simplified models for the transition states of the

organocatalysed HDA reaction. Therefore, Deslongchamps et al. described, in 2007, the reverse docking of a TADDOL catalyst to rigid-state models of catalyst-free reactions (TS-models) for an asymmetric HDA reaction.[106] In previous reports, the reverse docking of similar organocatalysts to rigid TS-models has shown promise for generating TS-models for the catalysed reaction, and revealed clear energetic trends favouring the experimentally preferred product enantiomers. Although the results indicated a mode of catalysis consistent with the experimental data, the relative docking energies between TS-model enantiomers were too great to allow an in silico correlation with experimentally observed ees. Thus, several changes were made to the reverse-docking algorithm, EM-Dock, allowing the first reported correlation with experimentally reported ee values, based solely on reverse docking and molecular mechanics energies.

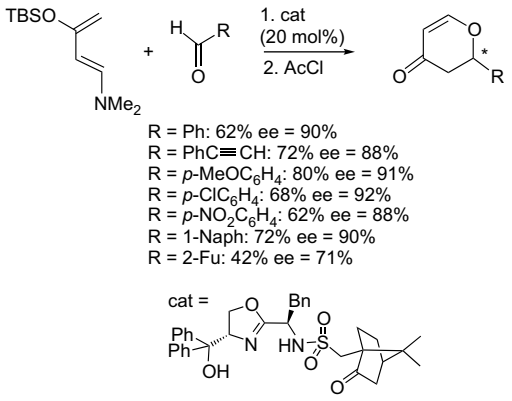
In 2005, Yamamoto et al. found that the axially chiral 1,1′-biaryl-2,2′-dimethanol (BAMOL) scaffold to be highly effective for the catalysis of the HDA reaction of a wide range of aliphatic and aromatic aldehydes.[107] This new scaffold shared with TADDOLs a bis-(diarylhydroxymethyl) functionality, in which the steric and electronic properties were readily tunable. Useful yields and excellent enantioselectivities were obtained for the HDA reaction between a 1-amino-3-siloxydiene and a wide variety of unactivated aldehydes (Scheme 57).



Scheme 57. BAMOL-catalysed HDA reactions.

In 2005, Jorgensen et al. reported the use of chiral bis-sulfonamide derivatives of vicinal diamines as organocatalysts for the HDA reaction of aldehydes with Danishefsky's diene.[108] The corresponding chiral tetrahydropyranones could be isolated in good yield with a moderate enantioselectivity of up to 50% ee. Another novel chiral organocatalyst with a rigid oxazoline backbone was developed by Sigman and Rajaram and applied to similar reactions, providing a high degree of enantioselectivity combined with moderate-to-good yields, as shown in Scheme 58.[109]

In 2007, Sigman and Jensen studied the effect of the organocatalyst acidity on the enantioselectivity of the HDA reaction performed in the presence of another organocatalyst, which had a unique design featuring an oxazoline core with a pendant amine and alcohol group.[110] By using this modular catalyst design, the effect of the catalyst acidity was systematically probed in the HDA reaction of benzaldehyde with the same aminodiene. Indeed, it was found that both the reaction rate and the enantioselectivity could be directly correlated with the catalyst acidity. In 2007, Frejd et al. reported the synthesis of a novel chiral organocatalyst system, based on the dibenzobicyclo[3.3.1]nona-2,6-diene framework.[111] These organocatalysts were further investigated for similar HDA

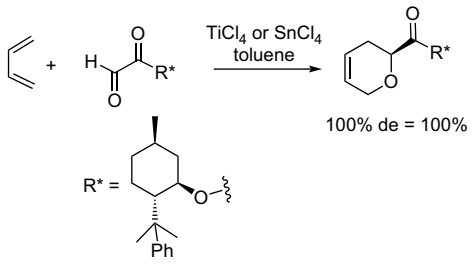


Scheme 58. HDA reactions catalysed by rigid oxazoline.

reactions, providing both moderate yields and enantioselectivities (≤52% ee).

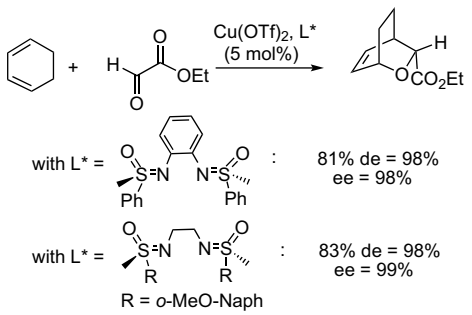
3. Reactions of activated aldehydes

Activated aldehydes, such as alkyl glyoxylates, have been successfully engaged in HDA reactions and could be combined with electron-rich Danishefsky-type or less nucleophilic dienes. These reactions are often high yielding, but can give rise to side products resulting from a competitive ene reaction. These activated dienophiles are set up for bidentate coordination and it is this structural feature that has been exploited for asymmetric catalysis. The HDA reaction of activated aldehydes, such as alkyl glyoxylates, with simple 1,3-dienes has not been intensively investigated. In recent years, only a few examples of using chiral activated aldehydes as chiral dienophiles have been reported. In 2004, Jurczak et al. developed the HDA reaction of (*R*)-8-phenylmenthyl glyoxylate with 1,3-butadiene in the presence of a Lewis acid, such as $SnCl_4$ or $TiCl_4$, which provided the corresponding cycloadduct as a single diastereoisomer and in quantitative yield (Scheme 59).[112]



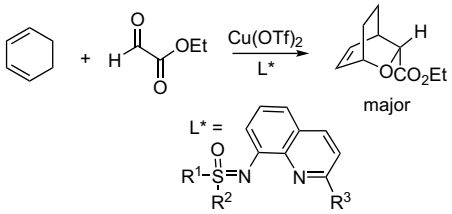
Scheme 59. HDA reaction of (*R*)-8-phenylmenthyl glyoxylate with 1,3-butadiene.

On the other hand, many chiral catalysts have been applied to catalyse enantioselective HDA reactions. Several types of chiral ligands have been used in recent years for the copper-catalysed HDA reaction. Bolm et al. have been interested in incorporating the chiral sulfoximine functionality into various structures for use as chiral ligands in HDA reactions.[113] Thereby, highly enantioselective HDA reactions were performed by Bolm et al. in the presence of a C_2-symmetric bis-sulfoximine copper complex as the chiral catalyst.[114] As shown in Scheme 60, the cycloaddition between ethyl glyoxylate and 1,3-cyclohexadiene in the presence of a chiral aryl-bridged bis-sulfoximine and $Cu(OTf)_2$ yielded the HDA adduct in high yield with an exceptionally high diastereo- and enantioselectivity. As an extension of this methodology, these workers have demonstrated that C_2-symmetrical ethylene-bridged bis-sulfoximines had the same potential to induce chirality for the same reaction (Scheme 60).[115]



Scheme 60. Cu(II)-catalysed HDA reactions with bis-sulfoximine ligands.

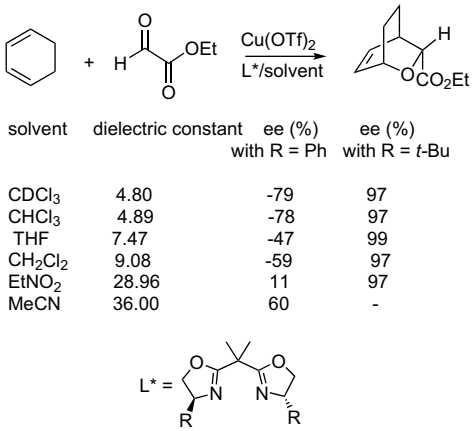
In order to ascertain whether the C_2-symmetry of the efficient bis-sulfoximine ligands was really essential, or if C_1-symmetric monosulfoximine derivatives could also be applied in asymmetric HDA reactions and lead to high enantioselectivities, the same group has developed the synthesis of various sulfoximines, in which the second donor atom was a quinolyl nitrogen.[116] The use of these novel ligands in the Cu(II)-catalysed HDA reaction between 1,3-cyclohexadiene and ethyl glyoxylate led to the corresponding cycloadduct in excellent yield and diastereoselectivity and with up to 91% ee (Scheme 61).



(*R*)-L*, R^1 = Me, R^2 = Ph, R^3 = H: 97% de = 94% ee = 75%
(*R*)-L*, R^1 = Me, R^2 = *o*-$MeOC_6H_4$, R^3 = H: 98% de = 96% ee = 91%
(*R*)-L*, R^1 = *n*-Pent, R^2 = *o*-$MeOC_6H_4$, R^3 = H: 93% de = 94% ee = 86%
(*S*)-L*, R^1 = Me, R^2 = *o*-$MeOC_6H_4$, R = R^3 = H: 88% de = 96% ee = 91%

Scheme 61. Cu(II)-catalysed HDA reactions with C_1-symmetric monosulfoximine ligands.

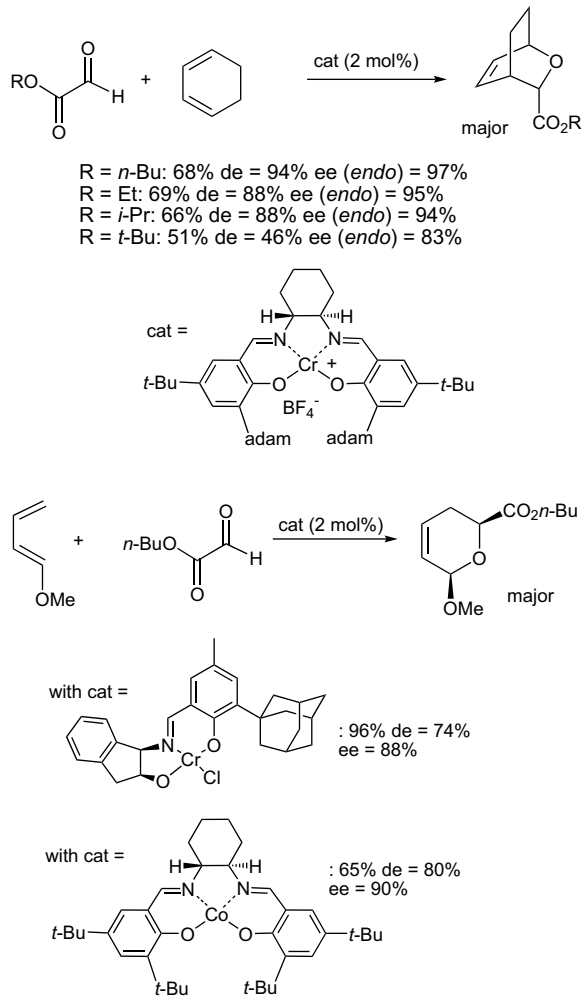
In 2002, Jorgensen et al. studied the Cu(II)-catalysed HDA reaction of ethyl glyoxylate with 1,3-cyclohexadiene in the presence of various chiral bisoxazolines as ligands.[117] Surprisingly, it was shown that the absolute configuration of the HDA adduct obtained in the presence of the chiral bis(phenyloxazoline)Cu(II) complex was dependent on the solvent. In this case, a linear relationship between the enantioselectivity and the dielectric constant of the solvent was observed (Scheme 62). The enantioselectivity for the adduct obtained with the chiral bis(*tert*-butyloxazoline)Cu(II) complex was, however, independent of the solvent (Scheme 62). On the basis of the X-ray structures and theoretical calculations, this observed reversal in the enantioselectivity when changing from the [Cu(II)(*t*-Bu-Box)] to the [Cu(II)(Ph-Box)] system was caused by a geometrical transformation, mainly of steric origin.



solvent	dielectric constant	ee (%) with R = Ph	ee (%) with R = *t*-Bu
$CDCl_3$	4.80	-79	97
$CHCl_3$	4.89	-78	97
THF	7.47	-47	99
CH_2Cl_2	9.08	-59	97
$EtNO_2$	28.96	11	97
MeCN	36.00	60	-

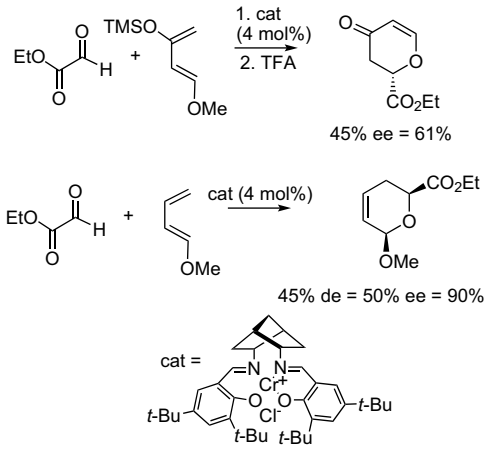
Scheme 62. Cu(II)-catalysed HDA reactions with bisoxazoline ligands.

Chiral (salen)Cr(III) complexes have been demonstrated by Jurczak et al. to be efficient catalysts for the HDA reactions of alkyl glyoxylates with various dienes.[118] As an example, the cycloaddition of 1,3-cyclohexadiene performed in the presence of a chiral (salen)Cr(III) complex, depicted in Scheme 63, led to the corresponding adducts in good yields and excellent diastereo- and enantioselectivity.[119] In addition, the use of Jacobsen's catalyst to promote the cycloaddition between 1-methoxybuta-1,3-diene and *n*-butyl glyoxylate allowed the corresponding cycloadduct to be obtained in good yield and cis-diastereoselectivity with up to 88% ee (Scheme 63).[120] In 2004, this reaction was also performed in the presence of a chiral (salen)Co(II) complex, providing up to 90% ee, as shown in Scheme 63.[121]



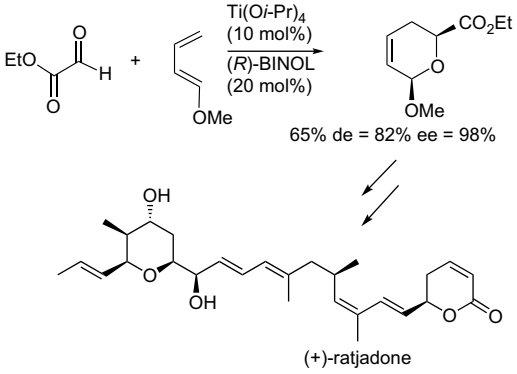
Scheme 63. HDA reactions catalysed by (salen)Cr(III) and (salen)Co(II) complexes.

Another type of chiral chromium–salen complex, bearing DIANANE (*endo*,*endo*-2,5-diaminonorbornane) as the chiral backbone, was successfully applied by Berkessel and Vogl, in 2006, to the HDA reactions of ethyl glyoxylate with Danishefsky's diene and less reactive 1-methoxybuta-1,3-diene.[55] These reactions afforded the corresponding cycloadducts in moderate yields and enantioselectivities of up to 90% ee, as shown in Scheme 64.



Scheme 64. HDA reactions catalysed by DIANANE–Cr(III) salen complex.

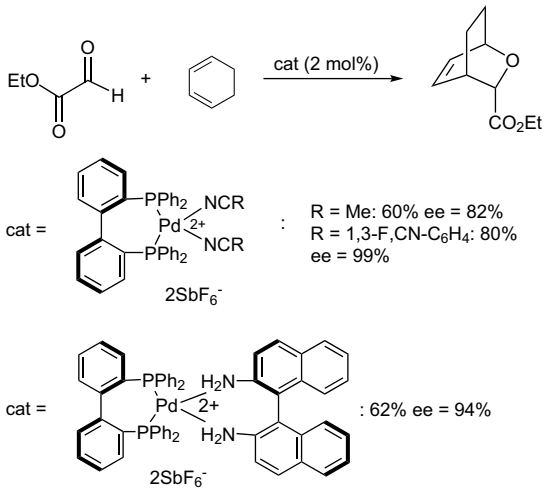
In 2000, Kalesse et al. reported the total synthesis of biologically active (+)-ratjadone, using as the key step, the HDA reaction of ethyl glyoxylate with 1-methoxybuta-1,3-diene catalysed by a BINOL–titanium complex.[122] This diastereo- and enantioselective reaction, depicted in Scheme 65, was also employed as the key step in the synthesis of other natural products, such as callystatin A and (+)-goniothalamin.[123] Moreover, chiral binaphthyl ligands containing sterically bulky 3,3′-substituents have been used by Pu and Gong in combination with $AlMe_3$ to catalyse the HDA reaction of enamide aldehydes with Danishefsky's diene, providing up to 78% ees along with moderate yields (20–60%).[124]



Scheme 65. Synthesis of (+)-ratjadone via Ti(IV)-catalysed HDA reaction.

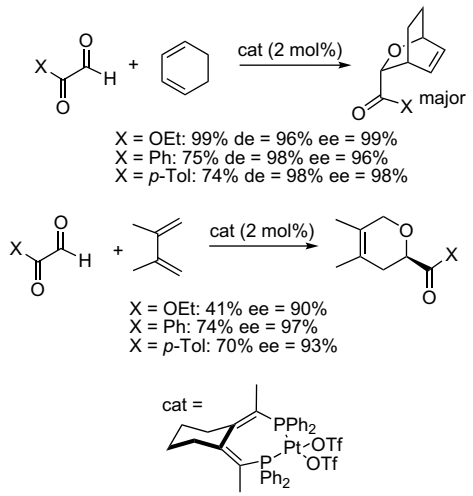
In 2002, the asymmetric HDA reaction of ethyl glyoxylate with 1,3-cyclohexadiene was successfully performed by Mikami et al. in the presence of enantiopure BIPHEP–Pd complexes, such as [Pd{(*R*)-BIPHEP}(MeCN)$_2$], which gave high enantioselectivity of up to 82% ee (Scheme 66).[125] When the BIPHEP–Pd catalyst was combined with chiral diaminobinaphthyl, an even better enantioselectivity of up to 94% ee was obtained for the same reaction (Scheme 66).[126] Other complexes of this type, such as [Pd{(*R*)-BIPHEP}(ArCN)$_2$], have been developed by Gagné et al. and investigated for the same reaction, providing enantioselectivity of up to 99% ee, as shown in Scheme 66.[127] Moreover, the application of these conditions to the reaction of phenyl glyoxal with 1,3-cyclohexadiene led to the corresponding cycloadduct with up to 99% ee, up to 96% de and 80% yield.[127]

On the other hand, enantiopure Lewis-acid platinum–metal complexes of conformationally flexible NUPHOS-type diphosphines have been demonstrated by Doherty et al. to be highly efficient catalysts for the HDA reaction between non-activated dienes and alkyl glyoxylates and aryl glyoxals.[128] As shown in



Scheme 66. HDA reactions catalysed by BIPHEP–Pd complexes.

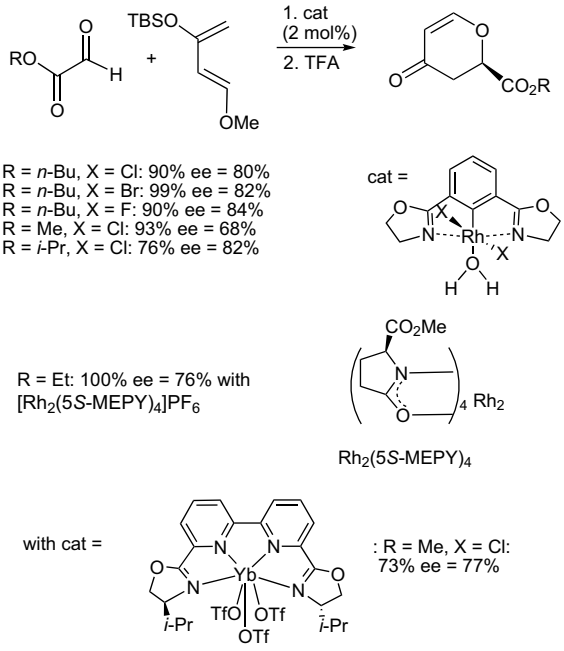
Scheme 67, enantioselectivities of up to 99% ee were obtained, rivalling those obtained using the corresponding platinum–BINAP complex.



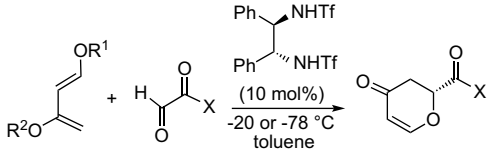
Scheme 67. HDA reactions catalysed by NUPHOS-type diphosphine–Pt complex.

In addition, chiral bis(oxazolinyl)phenylrhodium(III) aqua complexes have been involved to promote the HDA reaction of glyoxylates with Danishefsky's diene, giving enantioselectivities of up to 84% ee when the catalyst was chiral (PHEBox)*$RhF_2(H_2O)$.[129] Very recently, cationic chiral dirhodium carboxamidates, such as [Rh$_2$(5*S*-MEPY)$_4$]PF$_6$ or [Rh$_2$(5*S*-MEPY)$_4$]SbF$_6$, have been used to promote the HDA reaction of ethyl glyoxylate with Danishefsky's diene, providing the corresponding cycloadduct in quantitative yield and in 76% ee (Scheme 68).[82] Moreover, similar reactions were performed by Qian and Wang in the presence of various chiral bisoxazoline–lanthanide complexes.[130] Therefore, the HDA adduct resulting from the reaction between Danishefsky's diene and methyl glyoxylate was obtained in up to 77% ee and 73% yield in the presence of a chiral Yb complex, depicted in Scheme 68.

Finally, chiral bis-trifluoromethanesulfonylamides have been shown to work as efficient organocatalysts for the HDA reactions between Danishefsky's diene and glyoxylate or phenyl glyoxal, presumably through double hydrogen bonding (Scheme 69).[131] Among these bis-triflylamides, (*R*,*R*)-1,2-*N*,*N*′-bis-(trifluoromethanesulfonylamino)-1,2-diphenylethane (DPE-NTf) gave the highest enantioselectivity (87% ee). In addition, Jorgensen et al.



Scheme 68. HDA reactions catalysed by (PHEBox)$RhX_2(H_2O)$, $[Rh_2(5S\text{-MEPY})_4]PF_6$ and (Box)–Yb complex.



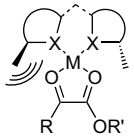
R^1 = *t*-Bu, R^2 = TMS, X = *n*-Bu: 23% ee = 23%
R^1 = Me, R^2 = TIPS, X = Ph: 67% ee = 87%
R^1 = Me, R^2 = TIPS, X = *p*-$F_3CC_6H_4$: 74% ee = 78%
R^1 = Me, R^2 = TIPS, X = *p*-$MeOC_6H_4$: 46% ee = 77%
R^1 = Me, R^2 = TIPS, X = *n*-Bu: 87% ee = 86%
R^1 = Me, R^2 = TBS, X = *n*-Bu: 55% ee = 58%
R^1 = Me, R^2 = TMS, X = *n*-Bu: 43% ee = 55%

Scheme 69. Bis-sulfonamide-catalysed HDA reactions.

have developed similar reactions catalysed by a bis-nonaflamide of the same chiral diamine, which gave enantioselectivities of up to 73% ee.[108]

4. Reactions of activated ketones

As shown in the preceding sections, aldehydes have frequently been employed as dienophiles in asymmetric HDA reactions, providing a convenient access to partly unsaturated six-membered heterocycles. In contrast, far fewer examples of enantioselective cycloadditions with ketones have been reported in the literature, because of their inherently low reactivity. Indeed, in comparison with the cycloaddition involving aldehydes as the heterodienophile, the HDA reaction of ketones is still today a challenge to chemists, since, until recently, only a very few examples of the asymmetric HDA reactions of ketones had been reported. An important aspect of the HDA reactions of ketones is the construction of oxygen heterocycles having a quaternary carbon atom centre and a concomitant challenge is to have stereocontrol over the formation of these quaternary carbon atom centres. Since ketones are less reactive than aldehydes on both steric and electronic grounds, special reaction conditions need to be applied for the cycloaddition to proceed. The direct catalytic enantioselective HDA reactions of activated ketones, presented in this section, make use of various Lewis-acid catalysts, whereas the cycloadditions involving unactivated ketones with dienes are very rare. The cycloaddition of dienes with ketones provides instant access to chiral dihydropyranones exhibiting a stereogenic quaternary carbon atom. The formed chiral dihydropyranones have been used as important building blocks in the natural product syntheses of carbohydrates, pheromones, insect toxins, antitumour agents, antibiotics and antiinflammatory sesquiterpenoids. The two main types of HDA reactions that ketones can undergo are the direct normal and the inverse electron-demand cycloaddition reactions. For the direct normal electron-demand HDA reaction, a ketone reacts with a conjugated diene and, in order to promote the reaction, either pressure or catalysis is required. The activation of the ketone can be performed by coordination of a Lewis acid to the ketone oxygen atom, which results in decreasing the energy of the ketone LUMO, thus making a more favourable interaction with the diene HOMO. To the best of author's knowledge, no example of an asymmetric HDA reaction involving an unactivated ketone has been reported in the literature in the last 8 years. Another approach for activating the HDA reaction of ketones with conjugated dienes is to use ketones having electron-withdrawing groups, such as esters, since these substituents are also able to lower the LUMO energy, leading to a more reactive substrate. A further activation of these activated ketones is to apply Lewis-acid catalysis, as this will lower the LUMO energy even more. The majority of the recent work dealing with asymmetric HDA reactions of activated ketones has been concentrated on asymmetric catalysis. In these reactions, the substrate, such as an α-keto ester, is set up for bidentate coordination to a chiral Lewis acid (or a chiral organocatalyst), as outlined in Scheme 70. The bidentate coordination of the α-keto ester to the chiral Lewis acid has two purposes, namely activation of the ketone functionality for the reaction, and discrimination of one of the faces of the ketone shielded by a chiral ligand, such as a C_2-symmetric chiral ligand, depicted in Scheme 70.

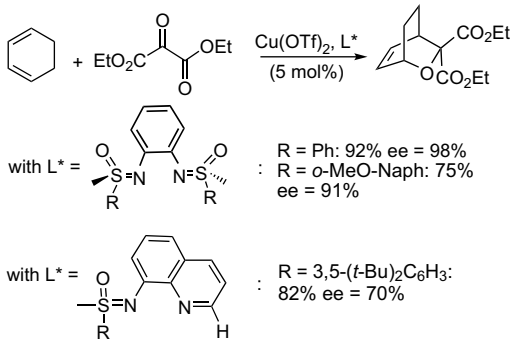


Scheme 70. Coordination of α-keto ester to chiral C_2-symmetric chiral ligand.

In the last 8 years, various chiral Lewis acids have been employed to catalyse enantioselective HDA reactions of activated ketones, with a particular preference for copper catalysts.

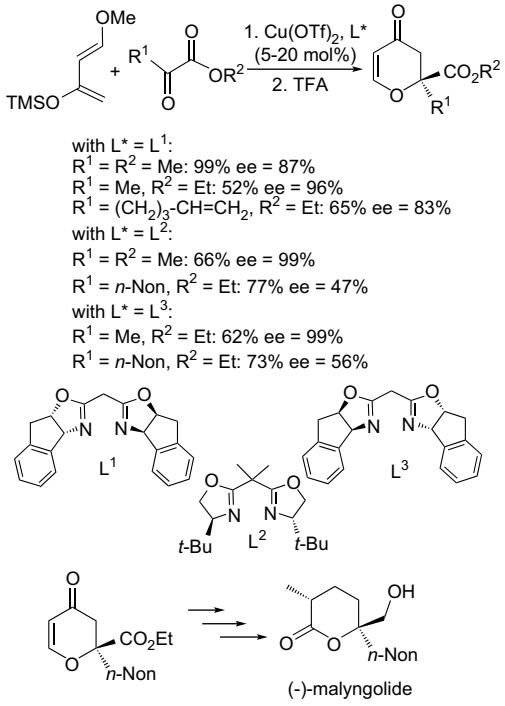
4.1. Chiral copper catalysts

A few types of chiral ligands have been used in recent years for the Cu-catalysed HDA reaction of activated ketones. In particular, Bolm et al. have developed several chiral ligands incorporating the chiral sulfoximine functionality. Highly enantioselective HDA reactions were performed by these workers in the presence of a C_2-symmetric bis-sulfoximine–copper complex as the chiral catalyst.[114a] As shown in Scheme 71, the cycloaddition between 1,3-cyclohexadiene and diethyl ketomalonate, performed in the presence of a chiral aryl-bridged bis-sulfoximine and $Cu(OTf)_2$, led to the corresponding cycloadduct in high yield and enantioselectivity.[115] The same authors also performed this reaction in the presence of C_1-symmetric monosulfoximine derivatives, in which the second donor atom was a quinolyl nitrogen. The use of these novel ligands in this Cu-catalysed HDA reaction led to the corresponding cycloadduct in good yield and enantioselectivity (Scheme 71).[116]



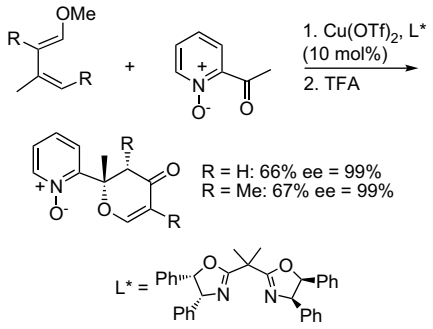
Scheme 71. Cu(II)-catalysed HDA reactions with bis- and monosulfoximine ligands.

In 2001, Ghosh and Shirai reported the asymmetric HDA reaction of Danishefsky's diene with a variety of α-keto esters performed in the presence of chiral *cis*-aminoindan-2-ol-derived conformationally constrained bisoxazoline ligands complexed with $Cu(OTf)_2$.[132] The resulting cycloadducts provided an important enantioselective access to quaternary carbon centres. The best enantioselectivity (99% ee) was obtained for α-keto esters containing a small alkyl group (Scheme 72). This methodology was applied to the synthesis of (−)-malyngolide.



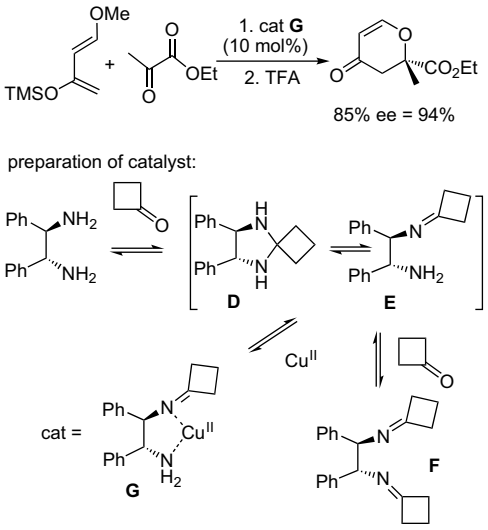
Scheme 72. Cu(II)-catalysed HDA reactions of α-keto esters in the presence of bisoxazoline ligands.

Various novel aryl-substituted bisoxazoline derivatives have been investigated by Rutjes et al. as chiral ligands for the asymmetric Cu-catalysed HDA reaction of methyl pyruvate with Danishefsky's diene.[133] The use of a 1-naphthyl-substituted ligand afforded the corresponding cycloadduct in almost quantitative yield, but with moderate enantioselectivity (≤35% ee). The application of the corresponding anthryl-substituted ligand did not, however, lead to any dramatic improvement, since only a slight enhancement of the enantioselectivity of up to 45% ee was observed, along with 82% yield. In 2007, Jorgensen et al. developed the HDA reaction of 1-pyridin-2-yl-ethanone with electron-rich dienes in the presence of chiral Cu(II)–bisoxazoline complexes, as depicted in Scheme 73.[88] Although moderate yields and good enantioselectivities were obtained when these conditions were applied to the corresponding aldehydes (see Scheme 43), the reactions of this ketone provided better yields and excellent enantioselectivities, as shown in Scheme 73.



Scheme 73. Cu(II)-catalysed HDA reactions of 1-pyridin-2-yl-ethanone.

In 2002, Dalko et al. investigated the HDA reaction of ethyl pyruvate with Danishefsky's diene in the presence of a new type of chiral copper catalyst.[134] The preparation of this catalyst was based on the condensation of a chiral 1,2-diamine with cyclobutanone, which afforded the corresponding imidazolidine **D** in solution in equilibrium with the corresponding open form **E**. The corresponding bisimine **F** and the starting diamine are often present with compounds **D** and **E** in the reaction mixture.[135] It was anticipated that chelating metals such as Cu(II) would shift this equilibrium towards the metallacyclic form **G** by forming a bidentate complex (Scheme 74). Thereby, the application of this catalyst to the HDA reaction of ethyl pyruvate provided the corresponding dihydropyrone with high enantioselectivity and yield, as shown in Scheme 74.



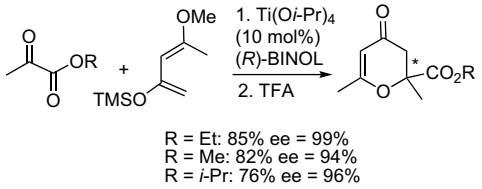
Scheme 74. Cu(II)-catalysed HDA reaction of ethyl pyruvate.

Finally, the HDA reaction between Danishefsky's diene and sterically hindered α-keto esters in the presence of a Lewis acid combined with various chiral bisoxazolines, such as 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], has been optimised by Wolf et al., using a validated high-throughput screening method.[136] The yields and enantioselectivities of three chiral dihydropyranones obtained by this multi-substrate one-pot screening approach were in excellent agreement with the individual screening results. The best enantioselectivities of up to 74%

ee and yields of up to 91% were obtained when $Cu(OTf)_2$ was used as the Lewis acid.

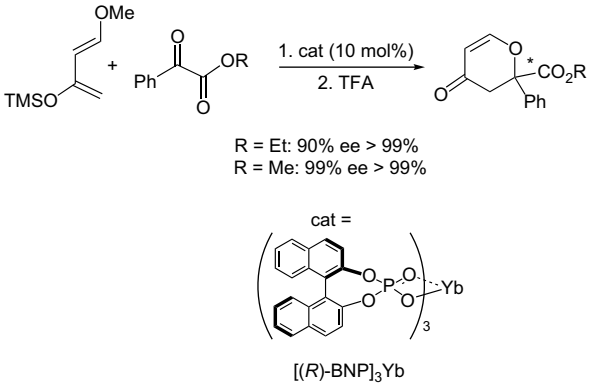
4.2. Other chiral catalysts

A chiral Lewis acid prepared from BINOL and $Ti(O\text{-}i\text{-}Pr)_4$ was applied to the HDA reactions of alkyl pyruvates with a Danishefsky-type diene, affording the corresponding 2,2,6-trisubstituted dihydropyrones in good yields and high enantioselectivities (Scheme 75).[67b]



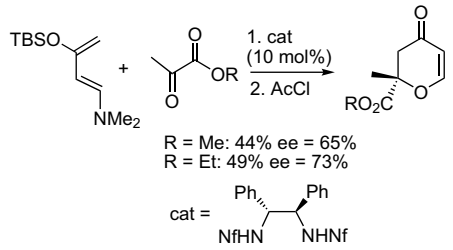
Scheme 75. Ti(IV)-catalysed HDA reactions of alkyl pyruvates.

In 2003, Inanaga et al. investigated novel rare-earth metal complexes with chiral phosphate ligands as Lewis-acid catalysts for the asymmetric HDA reaction of phenyl glyoxylates with Danishefsky's diene under homogeneous conditions.[95b] The ytterbium complex of (*R*)-1,1′-binaphthyl-2,2′-diylphosphate ((*R*)-BNP) was found to be particularly efficient for these reactions, since more than 99% ee was obtained in each case of substrate, as shown in Scheme 76.



Scheme 76. Yb(III)-catalysed HDA reactions of phenyl glyoxylates.

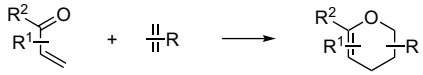
Asymmetric HDA reactions of activated ketones involving chiral organocatalysts are still very rare in the literature. In 2005, Jorgensen et al. reported the use of chiral bis-sulfonamide derivatives of vicinal diamines as organocatalysts for the HDA reaction of alkyl pyruvates with Danishefsky's diene.[108] The corresponding chiral cycloadducts could be isolated in good yields and enantioselectivities of up to 73% ee, as shown in Scheme 77.



Scheme 77. Organocatalysed HDA reactions of alkyl pyruvates.

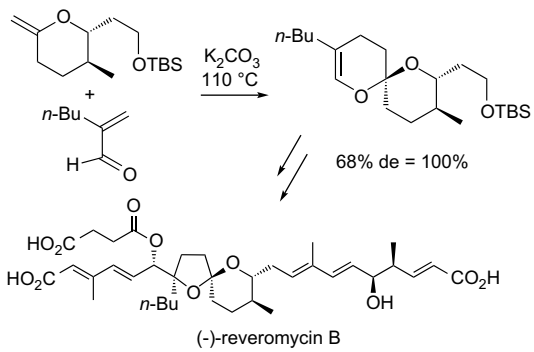
5. Inverse HDA reactions of α,β-unsaturated ketones and α,β-unsaturated aldehydes

Compared to the HDA reaction of ketones with dienes discussed above, where only a limited number of catalytic and enantioselective reactions have been reported, the number of asymmetric HDA reactions in which the ketone functionality is part of a heterodiene is much higher. In contrast, there are only a few examples of using α,β-unsaturated aldehydes in inverse HDA reactions. In the case of the inverse electron-demand HDA reaction, the ketone functionality is part of an α,β-unsaturated system, which reacts in a cycloaddition reaction with an electron-rich alkene (Scheme 78). The inverse electron-demand HDA reaction is primarily controlled by a $LUMO_{diene}$–$HOMO_{dienophile}$ interaction, which can be found, for example, in the reactions of enones and hetero analogues with alkenes having electron-donating groups, whereas the normal electron-demand reaction is a $LUMO_{dienophile}$–$HOMO_{diene}$-controlled HDA reaction, which predominantly occurs between electron-rich dienes and electron-deficient dienophiles.



Scheme 78. Inverse electron-demand HDA reactions of ketones.

Indeed, this reaction is controlled by the LUMO of the α,β-unsaturated ketone interacting with the HOMO of the alkene. This reaction can be catalysed by Lewis acids or organocatalysts, which coordinate to the ketone functionality of the α,β-unsaturated acyl system, thereby lowering the LUMO energy of the dienophile. For these inverse electron-demand HDA reactions, the ketone carbon atom is converted into a prochiral sp^2-hybridised carbon atom where the chiral centre(s) in the molecule is (are) introduced in the reaction.

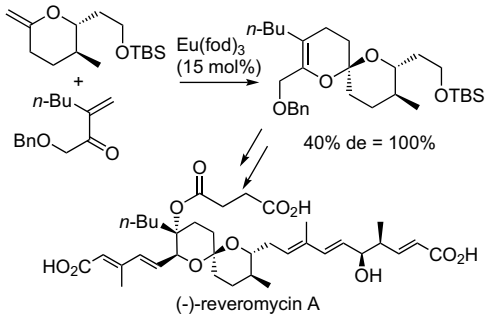


Scheme 79. Synthesis of (−)-reveromycin B.

5.1. Chiral auxiliaries

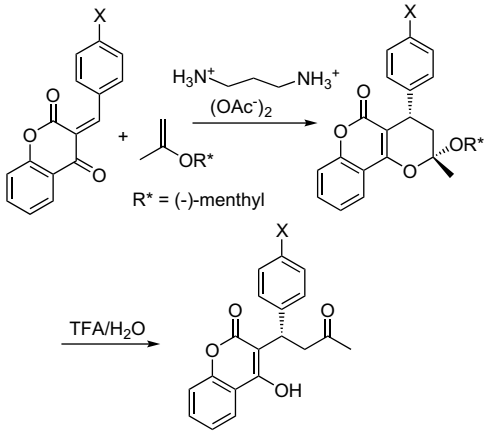
In recent years, important advances have been made in auxiliary-controlled inverse electron-demand HDA reactions. Indeed, a number of these asymmetric reactions have been developed on the basis of using chiral auxiliaries. As an example, Rizzacasa et al. have developed a total synthesis of the epidermal growth factor inhibitor, (−)-reveromycin B, in 25 linear steps from a chiral methylenepyran, which reacted with butylacrolein according to an asymmetric inverse electron-demand HDA reaction, as depicted in Scheme 79.[137] It was envisaged that the stereochemistry at the spiro centre of the resulting chiral 6,6-spiroketal would be controlled by an axial attack of the aldehyde oxygen atom, due to the anomeric effect. This enantiopure 6,6-spiroketal was further converted into the biologically active target, (−)-reveromycin B.

The scope of this methodology was extended by the same group, in 2004, to the total synthesis of (−)-reveromycin A, a potent anticancer agent.[138] In this case, the use of K_2CO_3 gave low yields of the expected spiroketal, because of the base lability of the starting tetrasubstituted diene (Scheme 80). Therefore, the Lewis-acid promotion of the cycloaddition was surveyed using this diene and the same chiral dienophile, providing, in the presence of $Eu(fod)_3$, the corresponding cycloadduct in moderate yield, but as a single diastereomer, which was further converted into the desired target, (−)-reveromycin A.



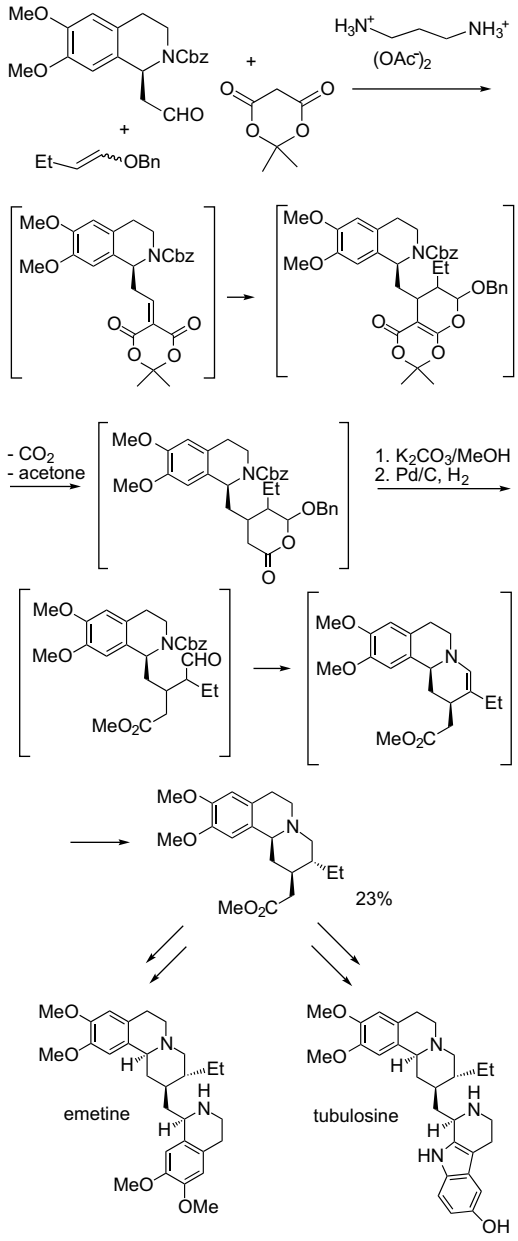
Scheme 80. Synthesis of (−)-reveromycin A.

A number of coumarin compounds, possessing anticoagulant activity, have been synthesised as potential drugs for the management of myocardial infarction. In order to design an enantioselective entry into this class of oral anticoagulants, Cravotto et al. have developed the asymmetric HDA reaction between in situ-generated 3-arylidene-2,4-chromanediones and the *iso*-propenyl ether derived from (−)-menthol.[139] Well-investigated and versatile anionic-pericyclic domino reactions that have been developed by Tietze's group are the domino Knoevenagel/HDA reactions.[140] In this type of reaction, a 1-oxa-1,3-butadiene is first formed in situ by the condensation of an aldehyde with a cyclic or highly reactive acyclic 1,3-dicarbonyl compound.[141] This oxabutadiene then undergoes a cycloaddition with a dienophile in the second step. The application of this methodology by Cravotto et al. has allowed chiral coumarin anticoagulants such as warfarin-like analogues to be prepared. After the release of the chiral cheap and recyclable auxiliary, the corresponding coumarin compounds, such as (*S*)-warfarin, (*S*)-coumachlor and (*S*)-acenocoumarol, were obtained in high enantioselectivity, as shown in Scheme 81.



Scheme 81. Syntheses of coumarin anticoagulants via domino Knoevenagel/HDA reactions.

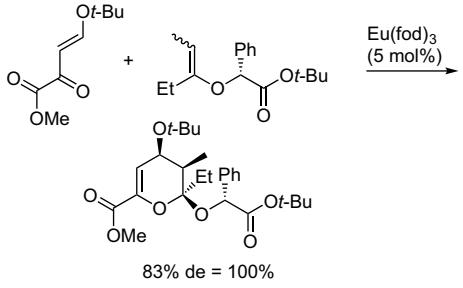
In the same area, Tietze et al. have reported the first enantioselective syntheses of the *Ipecacuanha* alkaloid, emetine, and the *Alangium* alkaloid, tubulosine, employing an asymmetric domino Knoevenagel/HDA reaction occurring between a chiral aldehyde, Meldrum's acid and an enol ether, as depicted in Scheme 82.[142] Under these reaction conditions, the cycloadduct was shown to lose CO_2 and acetone to give the corresponding lactone. In a second domino process, this lactone was treated with K_2CO_3 in methanol, followed by hydrogenation, to give, finally, the expected benzoquinolizidine, together with two other diastereomers in an overall yield of 66% (35:23:42). This chiral benzoquinolizidine was further converted into the enantiopure alkaloids, emetine and tubulosine.



Scheme 82. Syntheses of emetine and tubulosine.

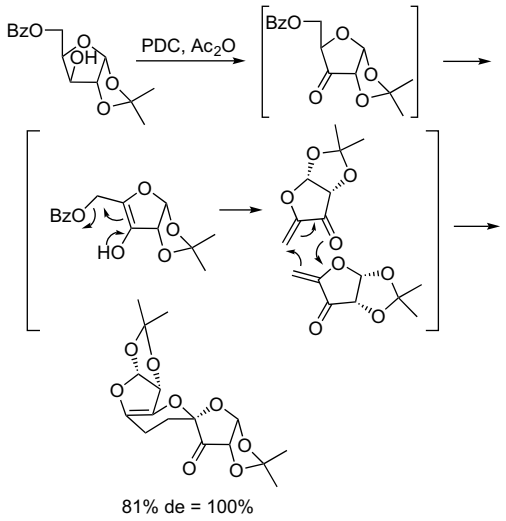
In 2003, Michelet et al. reported the synthesis of 1,2,3,5-substituted tetrahydropyrans on the basis of the $Eu(fod)_3$-catalysed HDA reaction of a trisubstituted chiral enol ether derived from (*R*)-mandelic acid and an activated heterodiene, promoting the creation of three stereogenic centres with remarkable and unprecedented

endo and facial stereocontrol, since a single diastereomer was isolated, as depicted in Scheme 83.[143]



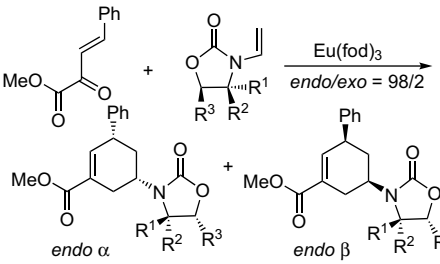
Scheme 83. HDA reaction of trisubstituted (*R*)-mandelic acid-derived enol ether.

Due to their prominent roles in biological processes, higher-carbon sugars have been receiving increasing attention in recent years. In this context, Liu et al. have developed a simple, one-pot multi-step route for the synthesis of a C10 higher-carbon sugar, based on the HDA reaction of an α,β-unsaturated ketone prepared in situ from protected D-xylose (Scheme 84).[144] In this reaction, a five-membered ring with an α,β-unsaturated ketone structure was formed in the presence of Ac_2O. Thus, the reaction of the starting protected D-xylose with PDC resulted in the initial formation of the corresponding 3-ketofuranose. A $PhCO_2H$ group was then lost from this 3-ketofuranose, forming an α,β-unsaturated ketone. Two molecules of this α,β-unsaturated ketone underwent the HDA reaction, affording the final cycloadduct in good yield as a single diastereomer.

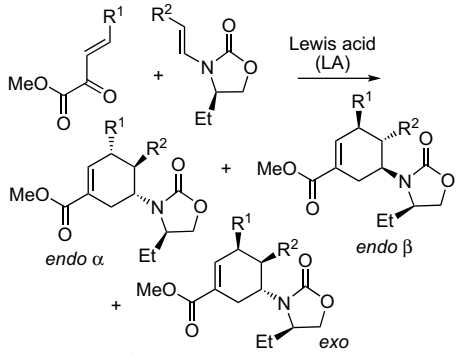


Scheme 84. Synthesis of higher-carbon sugar.

Aza-substituted dienophiles have rarely been used in asymmetric electron inverse demand cycloadditions. In this field, Dujardin et al. have developed such reactions involving enantiopure *N*-vinyl-2-oxazolidinones as new chiral dienophiles and β,γ-unsaturated α-keto esters under smooth $Eu(fod)_3$-catalysed conditions.[145] These reactions were achieved with high homogeneous *endo* and facial selectivities, weakly dependent on the substitution pattern of the chiral oxazolidinyl moiety (Scheme 85). An unequivocal relationship between the inducing stereogenic centre at C4′ of the oxazolidinyl ring and the two stereogenic centres created on the dihydropyranic ring was established. The *endo*-selective process proved to be facially controlled in favour of the (2*S*,4*S*)-adduct when starting from a (4*S*)-dienophile and in favour of the (2*R*,4*R*)-adduct when starting from a (4*R*)-dienophile. In 2007, an extension of this work was afforded by Dhal et al. by using β-substituted *N*-vinyloxazolidinones, providing the corresponding heteroadducts with high levels of *endo* and facial selectivities, as shown in Scheme 85.[146] In this study, the authors demonstrated that the choice of the Lewis acid proved to be critical, affording



R^1 = Et, R^2 = R^3 = H: 77% *endo* α/*endo* β = 96/4
R^1 = R^3 = H, R^2 = *i*-Bu: 92% *endo* α/*endo* β = 3/97
R^1 = Ph, R^2 = R^3 = H: 90% *endo* α/*endo* β = 96/4
R^1 = Bn, R^2 = R^3 = H: 93% *endo* α/*endo* β > 98/2
R^1 = H, R^2 = Me, R^3 = Ph: 80% *endo* α/*endo* β < 2/98
R^1 = H, R^2 = R^3 = Ph: 80% *endo* α/*endo* β < 2/98

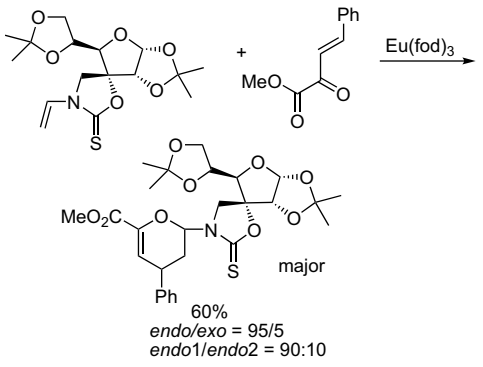


R^1 = Ph, R^2 = H, LA = $Eu(fod)_3$: 77%*:*
endo/exo = 98/2 *endo* α/*endo* β > 98/2
R^1 = R^2 = Ph, LA = $Eu(fod)_3$: 57%*:*
endo/exo = 98/2 *endo* α/*endo* β = 96/4
R^1 = R^2 = Ph, LA = $SnCl_4$: 72%*:*
endo/exo = 80/20 *endo* α/*endo* β < 2/98
R^1 = Ph, R^2 = Me, LA = $Eu(fod)_3$: 62%*:*
endo/exo > 98/2 *endo* α/*endo* β > 98/2
R^1 = Ph, R^2 = Me, LA = $SnCl_4$: 71%*:*
endo/exo > 98/2 *endo* α/*endo* β < 2/98
R^1 = 3,4,5-$(MeO)_3C_6H_2$, R^2 = Me, LA = $Eu(fod)_3$: 64%*:*
endo/exo > 98/2 *endo* α/*endo* β > 98/2
R^1 = 3,4,5-$(MeO)_3C_6H_2$, R^2 = Me, LA = $SnCl_4$: 67%*:*
endo/exo > 95/5 *endo* α/*endo* β < 2/98
R^1 = 3,4,5-$(MeO)_3C_6H_2$, R^2 = Ph, LA = $Eu(fod)_3$: 59%*:*
endo/exo = 98/2 *endo* α/*endo* β > 98/2
R^1 = 3,4,5-$(MeO)_3C_6H_2$, R^2 = Ph, LA = $SnCl_4$: 83%*:*
endo/exo = 93/7 *endo* α/*endo* β < 2/98

Scheme 85. HDA reactions of *N*-vinyl-2-oxazolidinones.

selectively either the *endo* α adduct using $Eu(fod)_3$ as the catalyst or the *endo* β adduct if the promoter was $SnCl_4$.

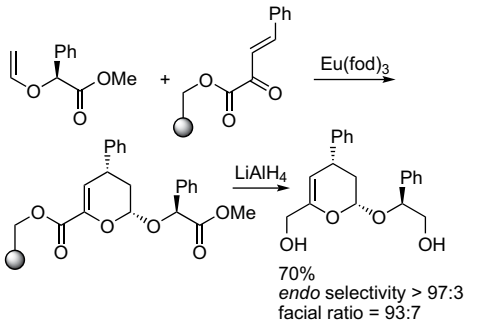
N-Vinyl-1,3-oxazolidine-2-thiones were also used as chiral new dienophiles in $Eu(fod)_3$-catalysed reverse HDA reactions involving benzylidene pyruvic acid methyl ester, but afforded only moderate *endo* and facial selectivities (*endo*/*exo* ≤89/11, facial *endo* selectivity ≤74/29), when compared to those obtained with the corresponding *N*-vinyl-1,3-oxazolidine-2-ones.[147] In contrast, a high diastereocontrol was observed with a sugar-derived *N*-vinyl-1,3-oxazolidine-2-thione, as depicted in Scheme 86. The efficient chiral transfer in this case could mainly be attributed to the specific



Scheme 86. HDA reaction of sugar-derived *N*-vinyl-1,3-oxazolidine-2-thione.

architecture of the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose moiety.

Resin-immobilised chiral reagents offer specific opportunities for the easy recovery and iterative use of expensive chiral sources.[148] A complementary approach, which avoids the prerequisite binding of the polymer to the chiral auxiliary, consists of supporting a prochiral substrate. In this context, Dujardin et al. have demonstrated the usefulness of a Wang resin-bound heterodiene for the stereoselective Eu(fod)$_3$-catalysed HDA reaction of a chiral vinyl ether.[149] As shown in Scheme 87, the *endo*-selective HDA reaction of (*S*)-(+)-*O*-vinyl mandelate with Wang-supported benzylidenepyruvate occurred with a high selectivity and yield, which compared well with those observed in solution. A further reductive cleavage by $LiAlH_4$ allowed the corresponding chiral dihydropyranic diol to be obtained as a mixture of two cis isomers in a 93/7 ratio. In addition, the solid-phase sequence allowed an unprecedented re-use of the catalyst in the presence of an excess of the dienophile in solution.

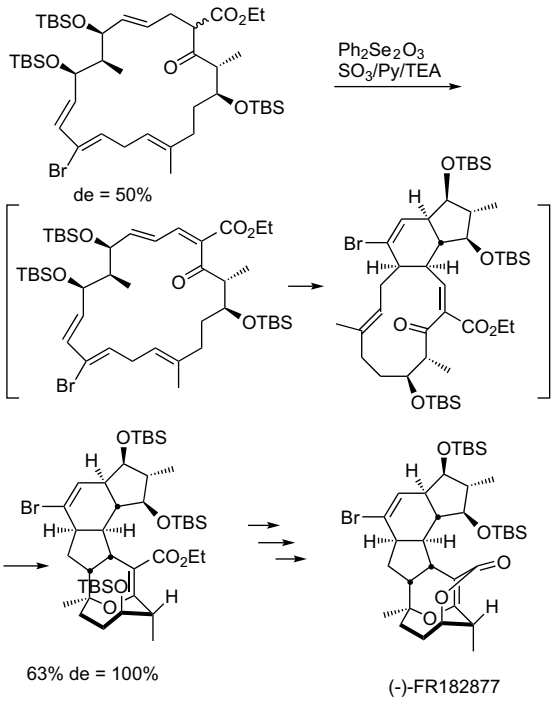


Scheme 87. HDA reaction of (*S*)-(+)-*O*-vinyl mandelate with Wang-supported benzylidenepyruvate.

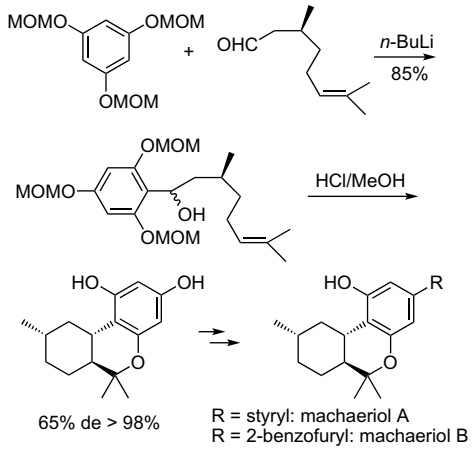
In addition, a few intramolecular HDA reactions involving a chiral starting material have been described in recent years. As an example, Evans and Starr have reported a cascade cycloaddition strategy leading to the total synthesis of the potent antitumour agent, (−)-FR182877.[150] The sequence of transannular cycloadditions, depicted in Scheme 88, culminated in the formation of a chiral pentacyclic product as a single diastereomer, which was further converted in four steps into the target, (−)-FR182877.

In 2004, Avery et al. developed the first synthesis of the naturally occurring antimalarials, machaeriols A and B, from (*S*)-citronellal on the basis of an intramolecular HDA reaction, producing a chiral tricyclic hexahydrodibenzopyran derivative in high diastereoselectivity as the key intermediate (Scheme 89).[151]

In addition, the *O*-prenyl derivative of a sugar aldehyde derived from D-glucose underwent a smooth intramolecular domino Knoevenagel/HDA reaction with 1,3-diones to afford a novel class of



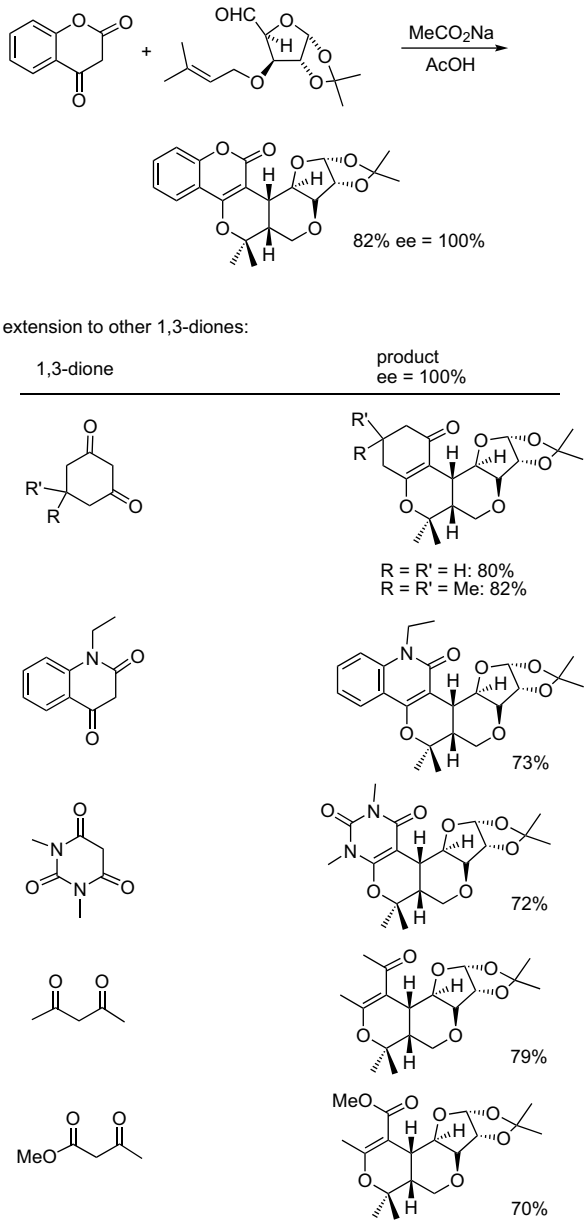
Scheme 88. Synthesis of (−)-FR182877 via intramolecular HDA reaction.



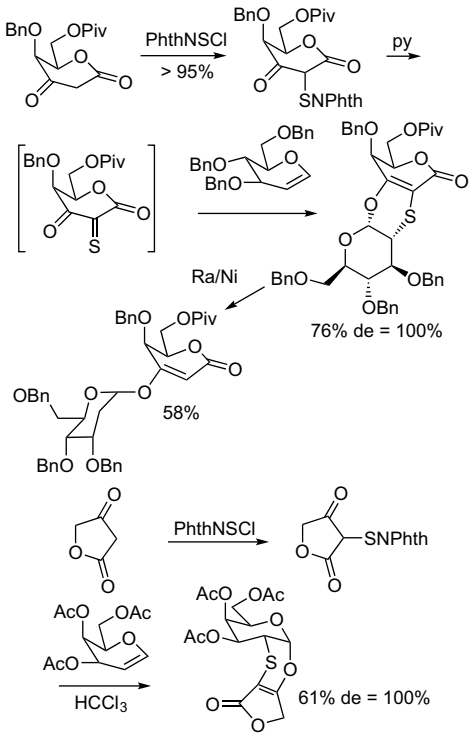
Scheme 89. Syntheses of machaeriols A and B via intramolecular HDA reaction.

carbohydrate analogues, the cis-fused furopyranopyrans (Scheme 90).[152] An extension of this study to spirocyclic 1,3-dicarbonyl compounds (spiro 1,3-dihydropyranones) was performed with the same aldehyde to furnish interesting chiral cis-annulated polycyclic heterocycles.[153]

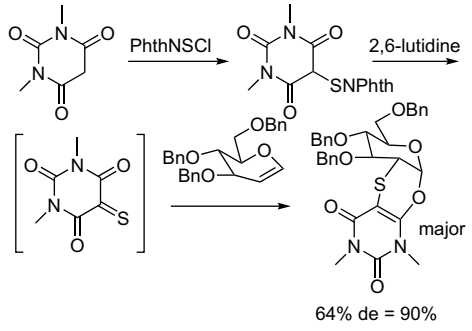
On the other hand, other α,β-unsaturated systems, such as hetero analogues of enones, have been involved in inverse electron-demand HDA reactions. Therefore, Capozzi et al. have reported a new procedure for the preparation of enantiopure β-keto-δ-lactones from glycals, which were easily transformed into the corresponding α,α′-dioxothiones, which, in turn, could be quantitatively trapped with dienophiles in inverse electron-demand HDA reactions.[154] As depicted in Scheme 91, a single regio- and stereoisomer was obtained for the cycloaddition of an oxothione with a tri-*O*-benzyl D-glucal, which was further subjected to desulfurisation, giving the corresponding enantiopure 2-deoxy disaccharide. In 2003, Franck et al. extended this methodology to other 2-thiono-3-ketolactones, which gave by cycloaddition with



Scheme 90. Domino Knoevenagel/HDA reactions with D-glucose derivative.



Scheme 91. HDA reactions of sugar-derived oxothiones.

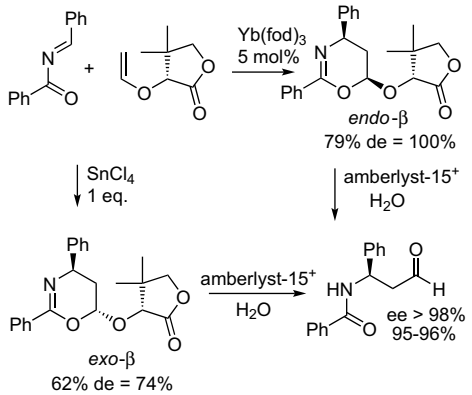


Scheme 92. HDA reaction of barbiturate-derived thionoimide.

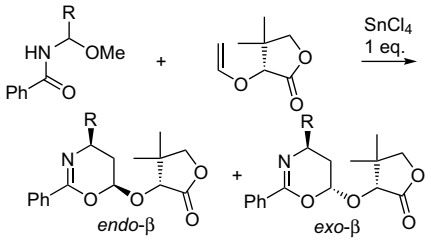
various carbohydrate glycals, other novel disaccharides bearing an *O*-glycosidic linkage at the anomeric centre and a thioether linking both C2 and C2′, thus creating a third heterocyclic ring.[155] As an example, the cycloaddition of phthalimidothiofuranolactone with tri-*O*-acetyl galactal afforded the corresponding bottom-faced cycloadduct in 61% yield and as a single stereomer (Scheme 91).

In the same area, novel chiral bridging nucleoside analogues have been prepared by Marzabadi et al. on the basis of cycloaddition reactions between glycals and barbiturate-derived reactive thionoimides in modest yields (Scheme 92).[156] In all the reactions conducted, the major cycloadducts obtained were the bottom-faced adducts resulting from the *endo* addition to the glycal. It was shown that the reactions were unaffected by changes in the sugar protecting groups or in the nature of the pyranose sugar.

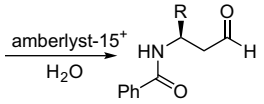
On the other hand, *N*-acylimines have been demonstrated by Dujardin et al. to be other potent hetero analogues of enones for HDA reactions with chiral vinyl ethers. In this context, these authors have disclosed a direct route to (*R*)-3-benzamido-3-phenylpropanal, produced by hydrolysis of a stable 6-alkoxy-5,6-dihydro-4*H*-1,3-oxazine, asymmetrically obtained from the HDA reaction between (*R*)-*O*-vinyl pantolactone and (*E*)-*N*-benzoyl benzaldimine, as depicted in Scheme 93.[157] This key cycloaddition gave high and divergent diastereoselectivities when performed in the presence of a catalytic amount of $Yb(fod)_3$ or a stoichiometric amount of $SnCl_4$.



Scheme 93. HDA reaction of *N*-acylimine.



R = Ph: 100% *exo*-β/*endo*-β = 82/18
R = *p*-FC_6H_4: 80% *exo*-β/*endo*-β = 87/13
R = *p*-$MeOC_6H_4$: 82% *exo*-β/*endo*-β = 86/14
R = *p*-$NO_2C_6H_4$: 36% *exo*-β/*endo*-β = 79/21
R = Bn: 71% *exo*-β/*endo*-β = 78/22
R = *t*-Bu: 69% *exo*-β/*endo*-β = 76/24



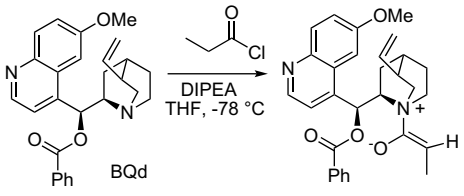
R = Ph: 63% ee = 96%
R = *p*-FC_6H_4: 62% ee = 96%
R = *p*-$MeOC_6H_4$: 62% ee = 93%
R = *p*-$NO_2C_6H_4$: 45% ee = 90%
R = Bn: 70% ee = 96%
R = *t*-Bu: 43% ee = 97%

Scheme 94. Syntheses of β-aryl and alkyl β-benzamido aldehydes from *N*,*O*-acetals.

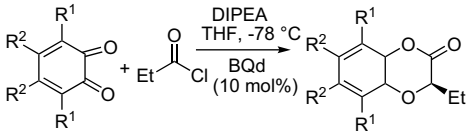
In the course of extending this procedure to other *N*-acylimines, these authors discovered that several compounds of this type lacked stability under the reaction conditions.[158] This lack of availability of unstabilised *N*-acylimines could be overcome by the use of the corresponding stable *N*,*O*-acetals acting as synthetic equivalents of *N*-acylimines in the Lewis-acid conditions used. In this context, the enantioselective syntheses of various β-aryl and alkyl β-benzamido aldehydes with ees ranging from 90 to 97% were achieved using a straightforward sequence that avoided any intermediate purification (Scheme 94).

In addition, Lectka et al. have developed HDA reactions between chiral ketene enolates, catalytically derived from acid chlorides and cinchona alkaloid nucleophilic catalysts in the presence of stoichiometric base, and heterodienes based on *o*-quinones.[159] These cycloadditions proceeded with excellent stereochemical control (up to >99% ee). For both the *o*-benzoquinone imide and the *o*-benzoquinone diimide manifolds, these reactions occurred with uniform enantioselectivity of >99% ee (see Scheme 96), whereas enantioselectivity

catalytic in situ generation of chiral ketene enolate:



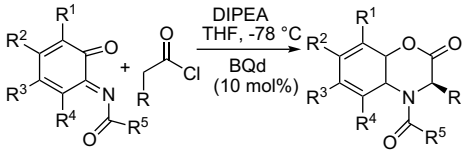
HDA reactions of *o*-quinones:



$R^1 = R^2$ = Cl: 91% ee = 99%
$R^1 = R^2$ = Br: 90% ee = 95%
$R^1 = R^2$ = CH=CH-CH=CH: 60% ee = 89%

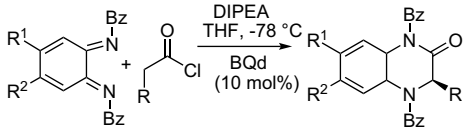
Scheme 95. HDA reactions of *o*-quinones.

HDA reactions of *o*-benzoquinone imides:



$R^1 = R^4$ = H, $R^2 = R^3$ = Cl, R^5 = *p*-$NO_2C_6H_4$
R = *i*-Bu: 65% ee > 99%
$R^1 = R^2 = R^4$ = H, $R^3 = CF_3$, R^5 = *p*-$NO_2C_6H_4$
R = Et: 62% ee > 99%
$R^1 = R^3$ = Cl, R^2 = Me, R^4 = H, R^5 = R = Bn:
63% ee > 99%
$R^1 = R^2 = R^4$ = H, R^3 = *t*-Bu, R^5 = R = *p*-$NO_2C_6H_4$:
61% ee > 99%

HDA reactions of *o*-benzoquinone diimides:



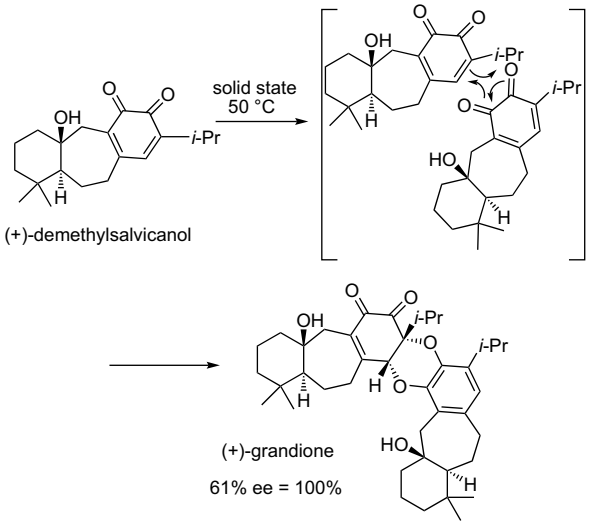
R^1 = H, R^2 = Bz, R = *i*-Bu: 84% ee > 99%
$R^1 = R^2$ = H, R = Bn: 83% ee > 99%
R^1 = H, $R^2 = CF_3$, R = *i*-Bu: 83% ee > 99%
R^1 = H, R^2 = Bz, R = $(CH_2)_3Cl$: 87% ee > 99%

Scheme 96. HDA reactions of *o*-benzoquinone imides and *o*-benzoquinone diimides.

ranging from 89 to 99% ee was obtained for *o*-quinones, as shown in Scheme 95.[160] The study of *o*-quinones is also presented in Section 5.2.4, dealing with organocatalysed inverse electron-demand HDA reactions. Although the cycloadditions of *o*-benzoquinone diimides do not concern the subject of this review, it was decided to include them, however, since this work is directly correlated with that concerning the cycloaddition of *o*-benzoquinone imides.

The wide scope of this methodology provided access to a diverse range of biologically and synthetically useful chiral products, including α-hydroxy esters, non-natural α-amino acids and quinoxalinones, all with remarkable, catalytic control of regio- and stereochemistry.

In 2005, Takeya et al. reported the synthesis of (+)-grandione, a unique isetexane diterpene dimer, on the basis of an unusual solid-state HDA-type dimerisation reaction of (+)-demethylsalvicanol.[161] The intramolecular HDA reaction of this chiral quinone, depicted in Scheme 97, provided one of the four possible cycloadducts in 61% yield. Very recently, Majetich and Zou have investigated an



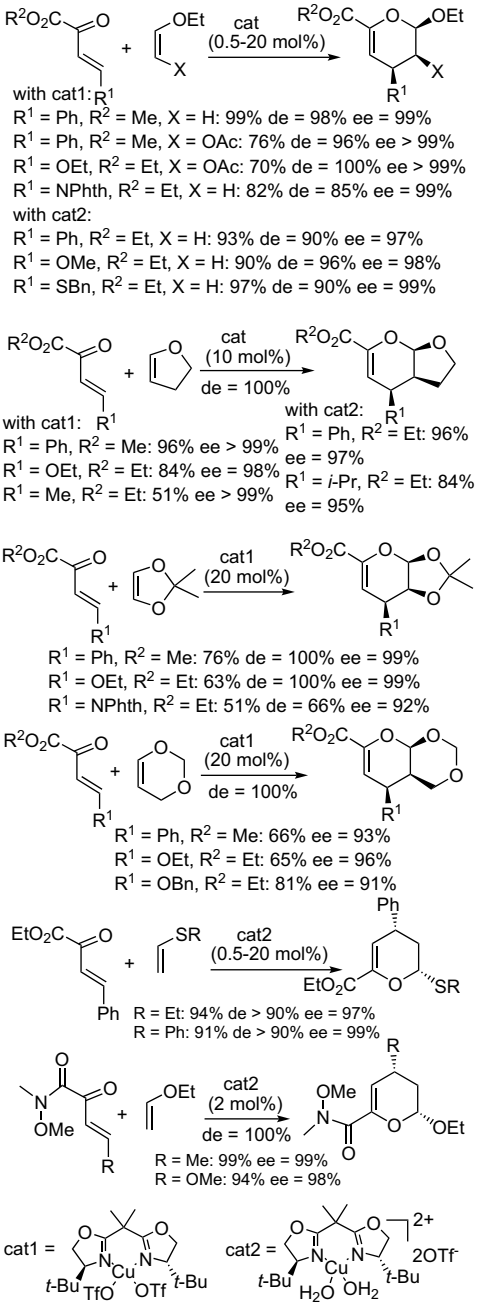
Scheme 97. Synthesis of (+)-grandione via solid-state HDA-type dimerisation reaction.

alternative strategy by using water as the solvent.[162] Therefore, when the reaction was carried out in water at 50 °C, (+)-grandione was isolated as a single stereomer in 52% yield.

5.2. Chiral catalysts

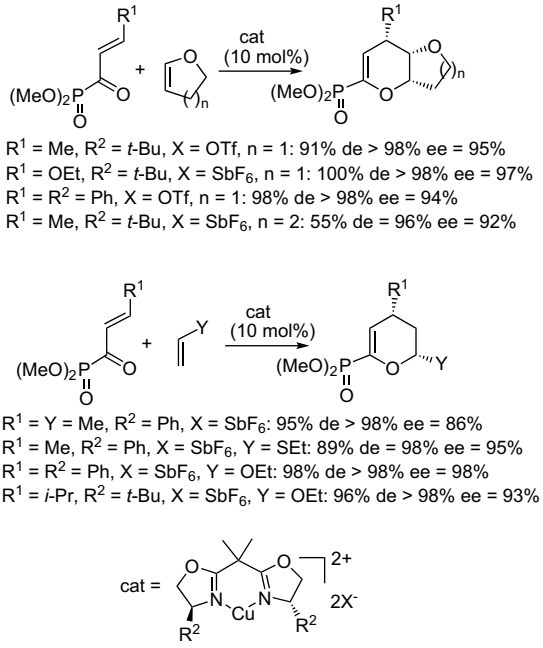
5.2.1. Chiral copper catalysts

Among the various chiral Lewis acids used as catalysts for the inverse electron-demand HDA reactions, the chiral bisoxazoline (Box) copper(II) complexes have been shown to be the most frequently employed in the last few years. In two independent reports from Evans et al. and from Jorgensen et al., it has been demonstrated that β,γ-unsaturated α-keto esters reacted with various vinyl ethers in the presence of these complexes and their hydrated counterparts.[163] Therefore, Jorgensen et al. have used a *tert*-butyl-substituted bisoxazoline Cu(II) complex, depicted in Scheme 98, to promote a number of successful HDA reactions of β,γ-unsaturated α-keto esters, including γ-amino-protected β,γ-unsaturated α-keto esters, with vinyl ethers and various types of cis-disubstituted alkenes, proceeding in good yield, high diastereoselectivity and excellent enantioselectivity. Comparable results were obtained by Evans et al. by using the corresponding hydrated complex, depicted in Scheme 98. The use of this complex was extended by Evans et al. to vinyl thioethers and β,γ-unsaturated α-keto amides, which gave the corresponding cycloadducts with similar excellent yields and stereoselectivities, as shown in Scheme 98. The potential of such reactions was demonstrated by the syntheses of various enantiopure carbohydrates such as spirosugars and *C*-branched sugars.



Scheme 98. HDA reactions of β,γ-unsaturated α-keto esters and amides with vinyl (thio)ethers.

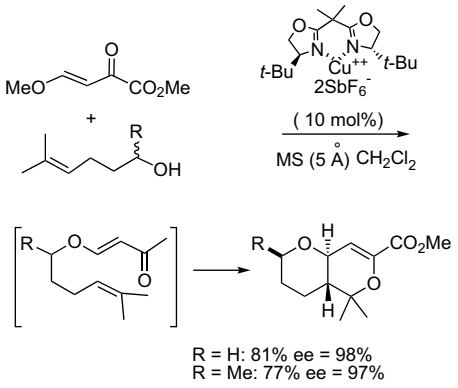
The scope of this methodology could be extended to α,β-unsaturated acyl phosphonates, which reacted with a series of vinyl (thio)ethers, providing the corresponding cycloadducts in high yield, and diastereo- and enantioselectivity. As shown in Scheme 99, a range of substitution patterns was possible on the heterodiene, since terminal alkyl, aryl and alkoxy substituents were all tolerated.[163d]



Scheme 99. HDA reactions of α,β-unsaturated acyl phosphonates with vinyl (thio)ethers.

An efficient catalytic double asymmetric induction during a new type of catalytic domino transetherification/intramolecular HDA reaction has been developed by Koga et al., leading to enantiomerically enriched trans-fused hydropyranopyran derivatives by using methyl (*E*)-4-methoxy-2-oxo-3-butenoate and δ,ε-unsaturated alcohols in the presence of (*S*,*S*)-*t*-Bu-Box-Cu(SbF_6)$_2$ and molecular sieves (5 Å) (Scheme 100).[164]

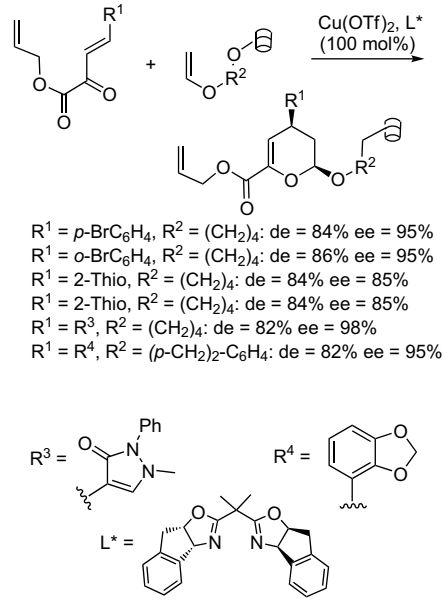
A number of the versatile catalytic systems described above suffer from considerable drawbacks, such as the requirement of a relatively large quantity of catalyst (generally 10 mol %), high cost and low turnover number. In an effort to find a solution to these problems, a number of heterogeneous systems have been developed in recent years. In general, homogeneous asymmetric catalysts have been anchored onto stationary supports such as organic cross-linked polymers or inorganic materials.[165] These methods offer several advantages such as easy separation of the products and recycling of the catalyst. The use of immobilised vinyl ethers has been applied to the asymmetric Cu-catalysed HDA reaction. Therefore, Schreiber and Stavenger could load a collection of vinyl ethers onto pools of polystyrene (PS) macrobeads.[166] These



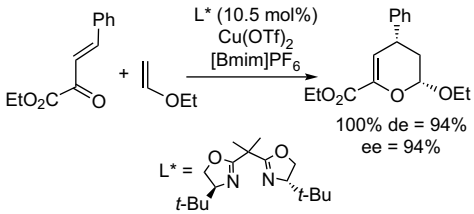
Scheme 100. Asymmetric domino transetherification/intramolecular HDA reaction.

support-bound vinyl ethers were then treated with a collection of β,γ-unsaturated keto esters in the presence of 20 mol % of a chiral [(*t*-Bu-Box)Cu(OTf)$_2$] complex to provide the corresponding resin-bound cycloadducts with up to 94% de and 96% ee. This methodology allowed the construction of a 4232-membered dihydropyrancarboxamide library to be made on 500-μm polystyrene beads. In the same area, Kurosu et al. have developed Cu-catalysed HDA reactions on polymer supports using indane-derived bisoxazoline (Inda-Box) as a novel chiral ligand.[167] Therefore, several vinyl ethers were loaded onto Lantern™,[168] a polystyrene-grafted surface, which is cylindrical in appearance. These polymer-supported vinyl ethers were further subjected to HDA reactions with structurally diverse heterodienes in the presence of chiral [(Inda-Box)Cu(OTf)$_2$] to give the corresponding cycloadducts with excellent diastereo- and enantioselectivity, as shown in Scheme 101. In addition, Hutchings et al. have immobilised chiral [(Ph-Box)Cu(OTf)$_2$] using mesoporous materials and zeolite Y, which was demonstrated to produce an effective heterogeneous catalyst for the HDA reaction between (*E*)-ethyl-2-oxo-3-pentenoate and vinyl ethyl ether, giving up to 41% ee.[169] In 2004, similar results (up to 41% ee) were obtained by Klein Gebbink et al. by using chiral [(*t*-Bu-Box)Cu(OTf)$_2$] immobilised on silica for the same reaction.[170]

In spite of the advantages presented by the heterogeneous systems, additional cumbersome modifications of the catalysts are often required and reduced catalytic activity and enantioselectivity



Scheme 101. HDA reactions of polymer-supported vinyl ethers.



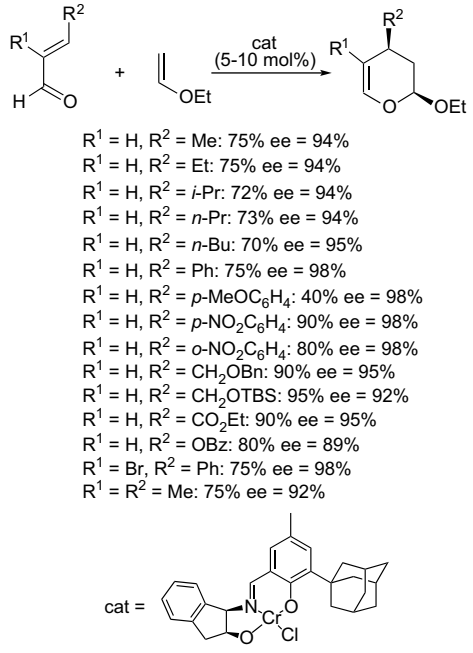
Scheme 102. HDA reaction in ionic liquid.

are often associated with these systems. Recently, a new approach involving ionic liquids[171] has been developed for catalyst separation and recycling.[172] In ionic liquids, a metal–ligand complex having an ionic nature could be solvated and immobilised without additional structural modification. The immobilised catalyst could be recycled by simple extraction of the ionic liquid with a relatively non-polar organic solvent after the reaction. In 2008, Kim et al. reported the successful use of hydrophobic ionic liquids, such as [Bmim]PF$_6$ and [Bmim]SbF$_6$, as powerful media for bisoxazoline–copper-catalysed asymmetric HDA reactions (Scheme 102).[173] Both the reactivity and the stereoselectivity were comparable to those of the corresponding homogeneous reactions. Moreover, in ionic liquids, the reaction was significantly faster than in dichloromethane and the metal–ligand complexes were recovered and recycled up to eightfold, exhibiting almost the same activity and stereoselectivity.

5.2.2. *Chiral chromium catalysts*

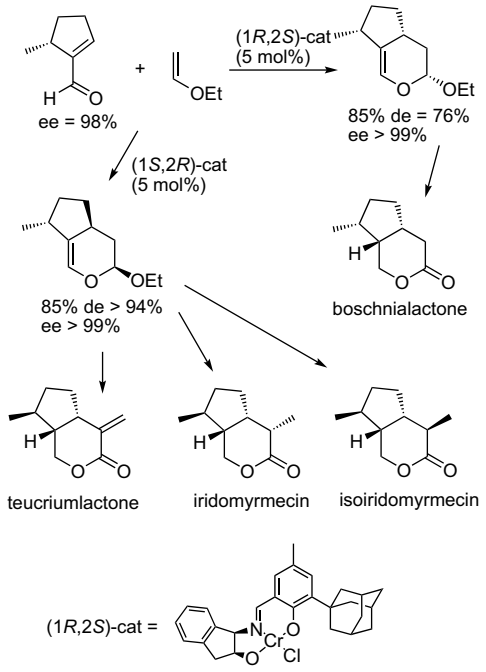
There are only a very few examples of asymmetric inverse electron-demand HDA reactions of oxabutadienes, which do not bear electron-withdrawing groups and, in particular, simple α,β-unsaturated aldehydes. In 2002, Jacobsen et al. reported the use of (1*R*,2*S*)-Jacobsen's catalyst to promote highly enantioselective inverse electron-demand HDA reactions of a range of α,β-unsaturated aldehydes with ethyl vinyl ether, providing the corresponding dihydropyran derivatives in a highly enantioenriched form (Scheme 103).[174]

In 2003, the same authors demonstrated the application of this methodology in the efficient and stereoselective synthesis of



Scheme 103. Jacobsen's catalyst-controlled HDA reactions of α,β-unsaturated aldehydes.

several iridoid natural products.[175] Therefore, the cycloaddition between ethyl vinyl ether and enantioenriched 5-methyl-1-cyclopentene-1-carboxaldehyde was performed in the presence of (1*R*,2*S*)-Jacobsen's catalyst or corresponding (1*S*,2*R*)-catalyst, affording the corresponding diastereomeric cycloadducts in excellent enantioselectivity (>99% ee in each case) and diastereoselectivities of 94 and 76% de, respectively. These cycloadducts were further converted into enantiopure boschnialactone, teucriumlactone, iridomyrmecin and isoiridomyrmecin (Scheme 104).

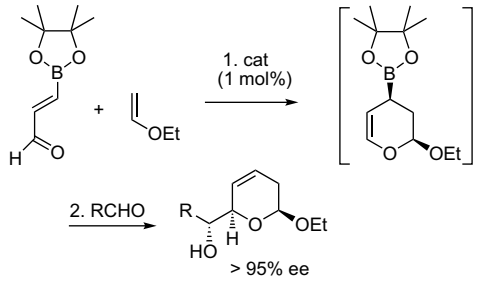


Scheme 104. Syntheses of iridoid natural products.

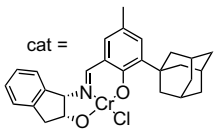
In 2003, Hall et al. and Carreaux et al. developed a catalytic enantioselective one-pot, three-component HDA-cycloaddition/allylboration reaction involving 3-boronoacrolein pinacolate, ethyl vinyl ether and aldehydes to afford α-hydroxyalkyl dihydropyrans.[176] The key substrate, 3-boronoacrolein pinacolate, was found to be an exceptionally reactive heterodiene in the HDA reaction with aldehydes catalysed by Jacobsen's catalyst. The corresponding α-hydroxyalkyl dihydropyrans were obtained from a wide variety of aldehydes, including unsaturated aldehydes and α-chiral aldehydes, with very high enantio- and diastereoselectivity, as shown in Scheme 105.

This methodology has been applied by Carreaux et al. to the syntheses of natural antitumour products, such as (+)-goniodiol,[177] (+)-methoxygoniodiol and its analogue, (+)-deoxygoniodiol,[178] by using (2*R*)-(*tert*-butyldiphenylsilyloxy)phenylacetaldehyde, (2*R*)-methoxy(phenyl)acetaldehyde and phenylacetaldehyde as the aldehyde substrates, respectively. As shown in Scheme 106, excellent diastereo- and enantioselectivity was obtained in all cases.

The scope of the preceding methodology could be extended to acyclic 2-substituted enol ethers, in spite of the presence of the added steric effect of the 2-substituent.[179] In this context, the first enantioselective total synthesis of a potent natural thiomarinol antibiotic was developed on the basis of a three-component HDA-cycloaddition/allylboration reaction between 3-boronoacrolein pinacolate, a diastereomeric mixture of a 2-substituted enol ether and an aldehyde depicted in Scheme 107.[180] It was shown that the reaction of this mixture of *Z*- and *E*-isomer only afforded the product consistent with a kinetically selective cycloaddition of the *Z*-isomer. The *Z*-isomer could be more reactive simply as a result of

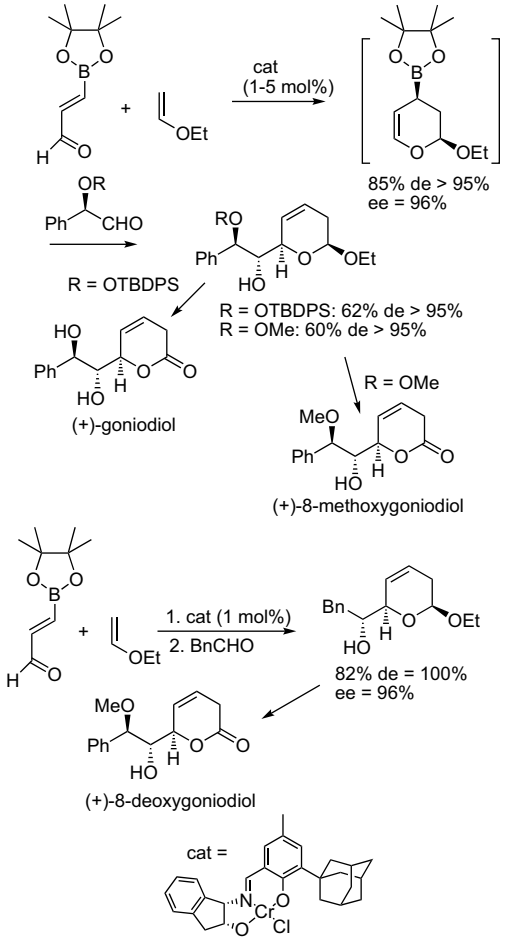


R = Ph: 85%
R = *p*-$NO_2C_6H_4$: 92%
R = *p*-$MeOC_6H_4$: 84%
R = *p*-ClC_6H_4: 77%
R = *p*-FC_6H_4: 80%
R = Bn: 82%
R = CH_2Bn: 87%
R = *i*-Bu: 81%
R = $TBSOCH_2$: 82%
R = *n*-Hex: 89%
R = *i*-Pr: 78%
R = (*E*)-*p*-$NO_2C_6H_4CH$=CH: 81%
R = (*E*)-MeCH=C(Me): 76%
R = (*E*)-EtO_2CCH=C(Me): 88%
R = CH_2=CH: 73%
(2*R*)-Ph-CH(OTBDPS): 78%

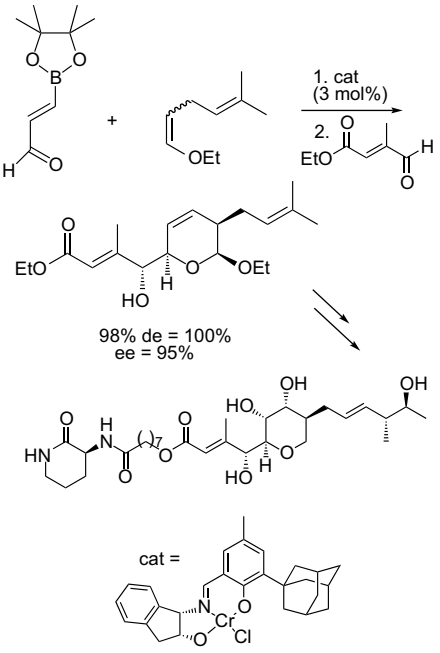


Scheme 105. Jacobsen's catalyst-controlled, three-component HDA-cycloaddition/allylboration reactions.

steric control by the very bulky catalyst, which led to the formation of a single cycloadduct in good yield, as depicted in Scheme 107. Indeed, this reaction featured an unusual, but fortuitous, kinetic



Scheme 106. Syntheses of (+)-goniodiol, (+)-8-methoxygoniodiol and (+)-8-deoxygoniodiol.

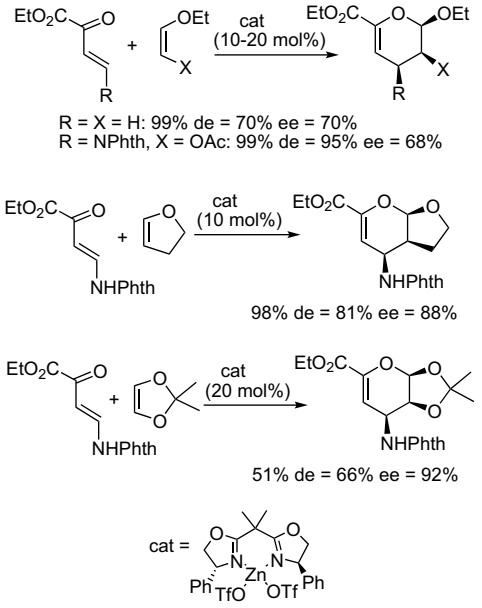


Scheme 107. Synthesis of thiomarinol derivative.

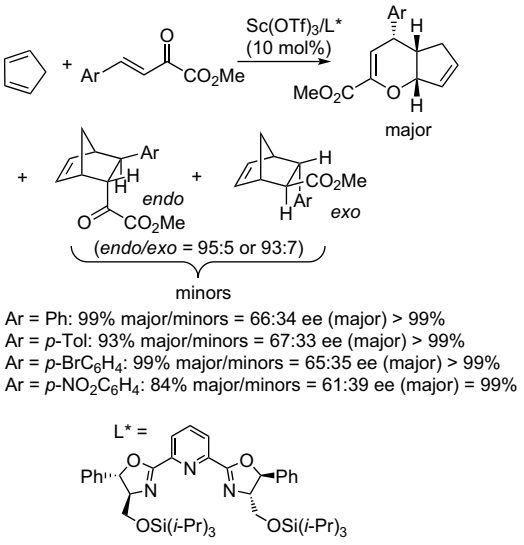
selection, favouring the requisite *Z*-dienophile from the mixture of isomers. This cycloadduct, enantio-, regio-, *E/Z*- and diastereoselectively obtained, was further converted into the desired thiomarinol derivative.

5.2.3. Other chiral metal catalysts

Among other chiral Lewis acids used as catalysts for the inverse electron-demand HDA reactions, a phenyl-substituted bisoxazoline zinc(II) complex, depicted in Scheme 108, has been successfully employed by Jorgensen et al.[163b] These authors have demonstrated that β,γ-unsaturated α-keto esters, including γ-amino-protected β,γ-unsaturated α-keto esters, reacted with various vinyl ethers in the presence of this complex, yielding the corresponding cycloadducts in good yield and diastereoselectivity, combined with excellent enantioselectivity.



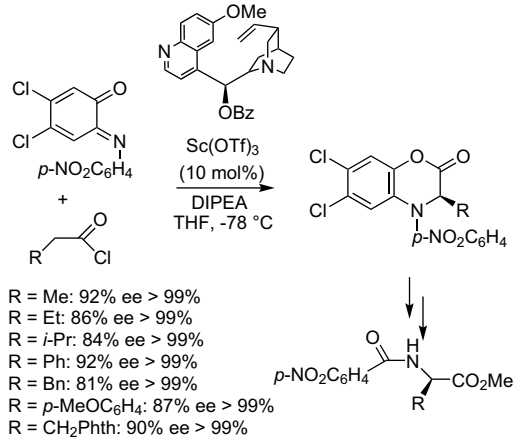
Scheme 108. Zn(II)-catalysed HDA reactions of β,γ-unsaturated α-keto esters with vinyl ethers.



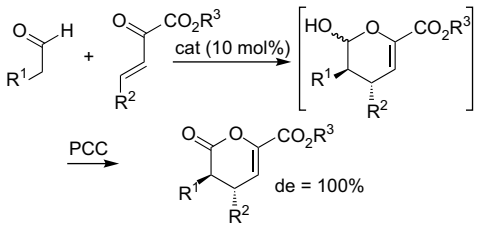
Scheme 109. Sc(III)-catalysed HDA reactions of methyl (*E*)-2-oxo-4-aryl-3-butenoates with cyclopentadiene.

In 2007, the cycloaddition between methyl (*E*)-2-oxo-4-aryl-3-butenoates and cyclopentadiene was studied by Desimoni et al.[181] These workers found that, in addition to the expected normal Diels–Alder adducts, the reaction gave the less-expected HDA cycloadducts. Therefore, when the reaction was performed in the presence of a catalytic amount of the chiral Sc(III) triflate complex of a PYBOX ligand, depicted in Scheme 109, the HDA cycloadducts became the main reaction products, obtained as single diastereomers and with excellent enantioselectivity of >99% ee. Surprisingly, the use of the corresponding chiral lanthanum complex furnished the opposite enantiomer in the reaction of methyl (*E*)-2-oxo-4-phenyl-3-butenoate, albeit with low enantioselectivity (11% ee).[182] Moreover, under these conditions, the Diels–Alder cycloadducts became largely predominant, since the ratio of the Diels–Alder cycloadduct to the HDA cycloadduct was estimated to be 81:19, combined to give 98% yield.

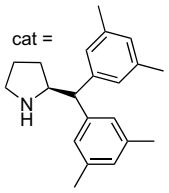
In addition, Lectka et al. reported, in 2007, an asymmetric bifunctional catalytic approach to non-natural α-amino acid derivatives on the basis of the HDA reaction between *o*-benzoquinone imides and ketene enolates in situ generated from the corresponding acyl chlorides.[183] Indeed, the combined use of a cinchona alkaloid-based catalyst and $Sc(OTf)_3$ allowed a remarkably high enantioselectivity to be obtained along with an excellent yield, as shown in Scheme 110. It was demonstrated that the presence of



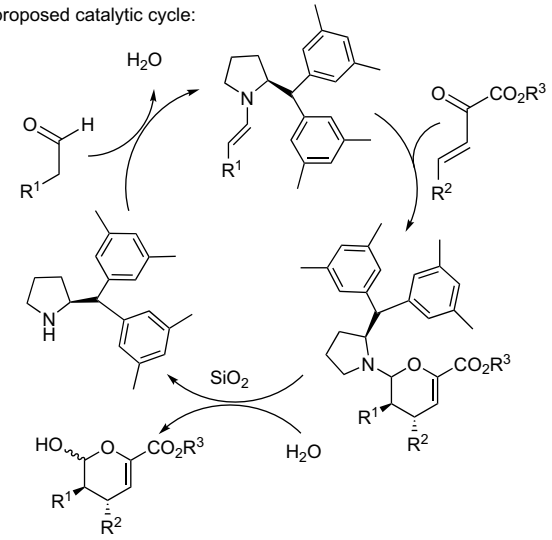
Scheme 110. Sc(III)-catalysed HDA reactions of *o*-benzoquinone imide with ketene enolates.



R^1 = Et, R^2 = Ph, R^3 = Me: 69% ee = 84%
R^1 = *i*-Pr, R^2 = Ph, R^3 = Me: 69% ee = 92%
R^1 = Bn, R^2 = Ph, R^3 = Me: 65% ee = 86%
R^1 = Et, R^2 = *p*-ClC_6H_4, R^3 = Me: 79% ee = 85%
R^1 = *i*-Pr, R^2 = *p*-ClC_6H_4, R^3 = Me: 70% ee = 90%
R^1 = Bn, R^2 = *p*-ClC_6H_4, R^3 = Me: 62% ee = 80%
R^1 = R^3 = Et, R^2 = Me: 81% ee = 86%
R^1 = *i*-Pr, R^2 = Me, R^3 = Et: 75% ee = 94%
R^1 = Bn, R^2 = Me, R^3 = Et: 72% ee = 89%



proposed catalytic cycle:



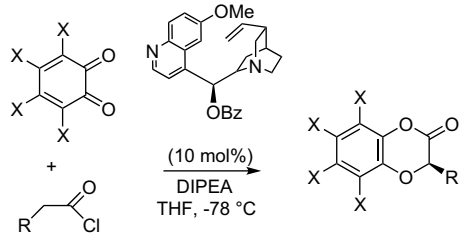
Scheme 111. Pyrrolidine-catalysed HDA reactions.

$Sc(OTf)_3$ in addition to the cinchona alkaloid-based catalyst reduced the reaction times and increased the chemical yields of the reactions. Effectively, these reactions were previously studied by the same authors in the presence of this cinchona alkaloid-based catalyst, but without $Sc(OTf)_3$ (see Scheme 113).[184]

5.2.4. Chiral organocatalysts

Only recently, several examples of organocatalysed inverse electron-demand HDA reactions have been described. Therefore, the concept of inverse electron-demand HDA reactions was extended, in 2003, to organocatalytic asymmetric HDA reactions by Jorgensen and Juhl.[185] This concept was based on the consideration that an enamine formed by the reaction of a chiral amine, such as a chiral pyrrolidine, with an aldehyde could be considered as an electron-rich alkene, which reacted in a cycloaddition reaction with an α,β-unsaturated acyl ester to give the corresponding HDA cycloadduct, which, after cleavage of the aminal group by silica, gave the corresponding hemiacetal, obtained as a mixture of the two anomers (Scheme 111). A further oxidation of this mixture with PCC yielded the corresponding lactone as a single diastereomer with good yield and high enantioselectivity, as shown in Scheme 111.

In 2006, a cinchona alkaloid-based catalyst was successfully employed by Lectka et al. to promote enantioselective HDA reactions between ketene enolates generated from the corresponding acyl chlorides and *o*-quinones, providing an efficient entry to chiral α-oxygenated carboxylic acid derivatives, which were obtained in good yield and excellent enantioselectivity of up to 99% ee (Scheme 112).[186]



R = Et, X = Cl: 91% ee = 99%
R = *i*-Pr, X = Cl: 75% ee = 93%
R = Ph, X = Cl: 90% ee = 90%
R = Bn, X = Cl: 72% ee = 99%
R = *p*-$MeOC_6H_4$, X = Cl: 58% ee = 99%
R = *p*-Tol, X = Cl: 75% ee = 93%
R = Et, X = Br: 90% ee = 95%

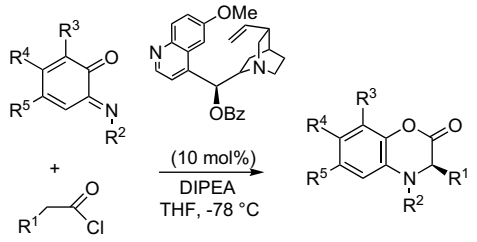
Scheme 112. HDA reactions of *o*-benzoquinones with ketene enolates catalysed by cinchona alkaloid.

The scope of the preceding methodology was successfully extended by the same group to *o*-benzoquinone imides, giving rise to the corresponding 1,4-benzoxazinone and 1,4-benzoxazine products in good yield and with uniformly excellent enantioselectivity, as shown in Scheme 113.[184]

In 2006, Bode et al. developed asymmetric *N*-heterocyclic carbene-catalysed highly enantioselective HDA reactions of α-chloroaldehydes as enolate precursors with a broad range of enones.[187] This process, involving a chiral triazolium salt as a precatalyst used in less than 1 mol%, afforded a diverse set of chiral 3,4,6-trisubstituted dihydropyran-2-ones under mild conditions, as shown in Scheme 114. Alternatively, β,γ-unsaturated α-keto esters proved to be highly reactive substrates and provided the corresponding cycloadducts in excellent yields and diastereo- and enantioselectivity (Scheme 114).

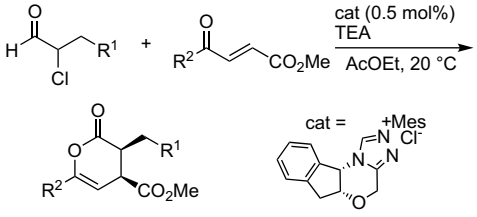
An enantioselective organocatalytic inverse electron-demand HDA reaction of in situ-generated enamines with *o*-benzoquinones was reported, in 2007, by Dixon et al.[188] A range of L-proline derivatives and imidazolidinones were investigated as organocatalysts for this reaction, allowing the selection of the *tert*-butyl-imidazolidinone depicted in Scheme 115 as the most potent organocatalyst, providing enantioselectivity of up to 80% ee. The stereochemical outcome of the reaction was consistent with a favoured attack of the *o*-benzoquinone at the less-hindered face of the in situ-generated enamine, as shown in Scheme 115. Accordingly, the *tert*-butyl group was responsible for fixing the conformation and providing the facial bias on the approach of the *o*-benzoquinone.

In 2007, Zhao et al. studied some novel prolinal dithioacetal derivatives as organocatalysts for the HDA reaction between β,γ-unsaturated α-ketophosphonates and aldehydes.[189] When the reaction was carried out in the presence of the more hindered catalyst depicted in Scheme 116, the corresponding 5,6-dihydro-4*H*-pyran-2-ylphosphonates were produced in good enantioselectivity of up to 94% ee. In all cases, only the trans stereoisomer was formed as a mixture of two corresponding anomeric diastereomers, which was further oxidised to the corresponding lactone derivative.

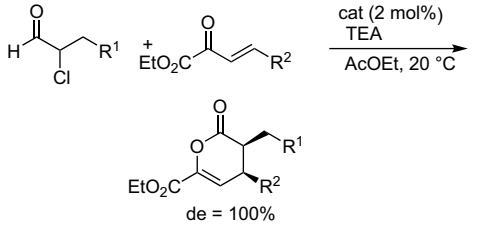


R^1 = Me, R^2 = *p*-$NO_2C_6H_4$, R^3 = H
R^4 = R^5 = Cl: 71% ee > 99%
R^1 = *i*-Pr, R^2 = *p*-$NO_2C_6H_4$, R^3 = H
R^4 = R^5 = Cl: 59% ee > 99%
R^1 = Ph, R^2 = *p*-$NO_2C_6H_4$, R^3 = H
R^4 = R^5 = Cl: 66% ee > 99%
R^1 = Bn, R^2 = *p*-$NO_2C_6H_4$, R^3 = H
R^4 = R^5 = Cl: 63% ee > 99%
R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-$NO_2C_6H_4$, R^3 = H
R^4 = R^5 = Cl: 83% ee > 99%
R^1 = CH_2Phth, R^2 = *p*-$NO_2C_6H_4$, R^3 = H
R^4 = R^5 = Cl: 86% ee > 99%
R^1 = *i*-Bu, R^2 = *p*-$NO_2C_6H_4$, R^3 = H
R^4 = R^5 = Cl: 65% ee > 99%
R^1 = Bn, R^2 = Fmoc, R^3 = R^5 = Cl
R^4 = Me: 63% ee > 99%
R^1 = Et, R^2 = *p*-$NO_2C_6H_4$, R^3 = H
R^4 = R^5 = Cl: 77% ee > 99%
R^1 = Et, R^2 = *p*-$NO_2C_6H_4$, R^3 = R^4 = H
R^5 = CF_3: 62% ee > 99%
R^1 = Bn, R^2 = *p*-$NO_2C_6H_4$, R^3 = R^4 = H
R^5 = *t*-Bu: 61% ee > 99%
R^1 = Et, R^2 = *p*-$NO_2C_6H_4$, R^3 = R^4 = H
R^5 = CF_3: 68% ee > 99%

Scheme 113. HDA reactions of *o*-benzoquinone imides with ketene enolates catalysed by cinchona alkaloid.

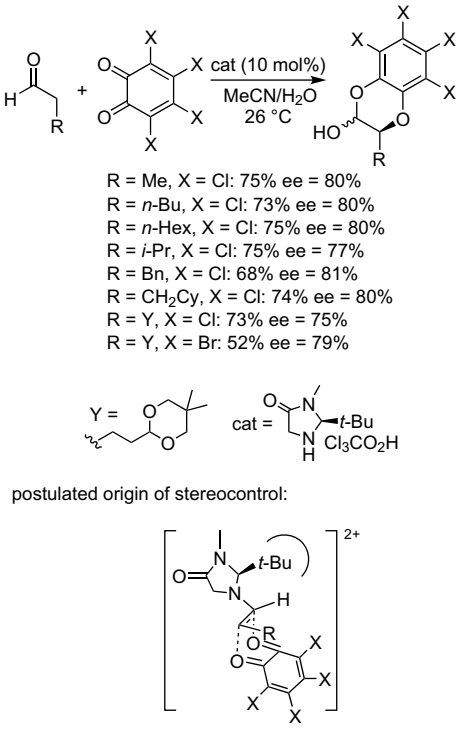


R^1 = Ph, R^2 = Me: 88% de > 90% ee = 99%
R^1 = R^2 = Ph: 98% de = 88% ee = 99%
R^1 = Ph, R^2 = *p*-BrC_6H_4: 80% de = 72% ee = 99%
R^1 = Ph, R^2 = Cy: 76% de > 90% ee = 86%
R^1 = Ph, R^2 = 2-Fu: 94% de = 78% ee = 99%
R^1 = *n*-Non, R^2 = Me: 71% de > 90% ee = 99%
R^1 = *n*-Non, R^2 = Ph: 90% de > 90% ee = 99%
R^1 = OTBS, R^2 = Ph: 80% de = 50% ee = 97%



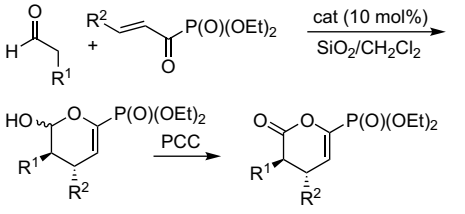
R^1 = Ph, R^2 = *p*-Tol: 74% ee = 97%
R^1 = Ph, R^2 = *n*-Pr: 84% ee = 98%
R^1 = Ph, R^2 = Cy: 85% ee = 95%
R^1 = *n*-Non, R^2 = *p*-Tol: 70% ee = 99%
R^1 = OTBS, R^2 = *p*-Tol: 83% ee = 95%

Scheme 114. *N*-Heterocyclic carbene-catalysed HDA reactions.



R = Me, X = Cl: 75% ee = 80%
R = *n*-Bu, X = Cl: 73% ee = 80%
R = *n*-Hex, X = Cl: 75% ee = 80%
R = *i*-Pr, X = Cl: 75% ee = 77%
R = Bn, X = Cl: 68% ee = 81%
R = CH_2Cy, X = Cl: 74% ee = 80%
R = Y, X = Cl: 73% ee = 75%
R = Y, X = Br: 52% ee = 79%

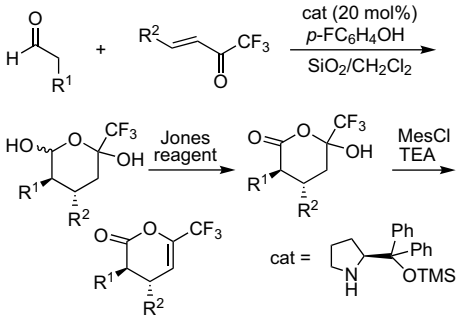
Scheme 115. Imidazolidinone-catalysed HDA reactions of *o*-benzoquinones with aldehydes.



R^1 = R^2 = Me: 79% ee = 87%
R^1 = Et, R^2 = Me: 87% ee = 82%
R^1 = *n*-Bu, R^2 = Me: 88% ee = 83%
R^1 = *n*-Pent, R^2 = Me: 87% ee = 89%
R^1 = *n*-Oct, R^2 = Me: 91% ee = 85%
R^1 = *i*-Pr, R^2 = Me: 69% ee = 89%
R^1 = Ph, R^2 = Me: 82% ee = 68%
R^1 = Bn, R^2 = Me: 69% ee = 94%
R^1 = Me, R^2 = Et: 72% ee = 80%
R^1 = R^2 = Et: 71% ee = 89%

Scheme 116. HDA reactions of β,γ-unsaturated α-ketophosphonates with aldehydes catalysed by L-prolinal dithioacetal.

In addition, Liu et al. have very recently developed unusual inverse electron-demand HDA reactions of aldehydes with α,β-unsaturated trifluoromethyl ketones, occurring under mild conditions and using chiral diphenylprolinol silyl ether as the organocatalyst.[190] This catalyst was used in combination with *p*-fluorophenol and gave rise to the corresponding cycloadducts, which were further oxidised to give the corresponding lactone derivatives. Due to their instability, these lactones were further dehydrated by treatment with methanesulfonyl chloride and triethylamine, leading, finally, to the corresponding dihydropyranones, obtained in moderate yields (for the three steps) with high diastereo- and enantioselectivity, as shown in Scheme 117.



R^1 = Me, R^2 = Ph: 63% de > 90% ee = 97%
R^1 = Me, R^2 = *p*-ClC_6H_4: 62% de > 90% ee = 97%
R^1 = Me, R^2 = *p*-BrC_6H_4: 63% de > 90% ee = 95%
R^1 = Me, R^2 = *m*-BrC_6H_4: 63% de = 92% ee = 92%
R^1 = Me, R^2 = *p*-Tol: 76% de = 92% ee = 94%
R^1 = Me, R^2 = *p*-$MeOC_6H_4$: 57% de > 90% ee = 93%
R^1 = Me, R^2 = *o*-$MeOC_6H_4$: 54% de = 96% ee = 83%
R^1 = Me, R^2 = 2-Naph: 50% de > 90% ee = 92%
R^1 = *i*-Pr, R^2 = Ph: 71% de = 92% ee = 93%
R^1 = Bn, R^2 = Ph: 51% de = 88% ee = 46%

Scheme 117. HDA reactions of α,β-unsaturated trifluoromethyl ketones with aldehydes catalysed by diphenylprolinol silyl ether.

6. Conclusions

This review updates the asymmetric HDA reactions of carbonyl compounds covering the literature from 2000 to 2008. It demonstrates that the most important achievements are the spectacular expansion of novel chiral catalysts, including the especially attractive chiral organocatalysts, which have been recently applied to this type of reaction, allowing a large number of asymmetric HDA reactions to be performed under very mild conditions with generally 1–10 mol % of catalyst loadings. Indeed, a collection of new chiral Lewis-acid catalysts and organocatalysts have provided new opportunities for these enantioselective cycloadditions, allowing the use of both activated and unactivated aldehydes as well as ketones. Moreover, numerous important developments of the asymmetric HDA reaction have dealt with the inverse electron-demand HDA concept. In addition, a number of asymmetric HDA reactions, involving either chiral dienophiles or chiral dienes, have been recently successfully developed. The development of a catalytic enantioselective reaction of simple unactivated ketones remains, however, a challenge for chemists in the coming years. The asymmetric HDA reaction is therefore well represented as an important tool for organic synthesis and is one of the most powerful available methodologies for the construction of optically active six-membered oxygen-containing heterocycles, with extensive synthetic applications in natural or unnatural products with a wide range of biological activity.

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Biographical sketch

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