Hetero-Diels–Alder Reactions of Ketones — A Challenge for Chemists

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Keywords: Asymmetric catalysis / Cycloaddition / Ketones / Alkenes / Synthesis design

The recent developments of mainly catalytic and enantioselective hetero-Diels–Alder reactions of ketones are presented. First, direct reactions of unactivated ketones are presented, focusing on the recent hydrogen bond-promoted hetero-Diels–Alder reactions with activated conjugated dienes. Then, direct catalytic enantioselective hetero-Diels–Alder reactions of activated ketones with conjugated dienes are outlined. The use of different chiral copper(II) and zinc(II) catalysts are shown and the use of the hetero-Diels–Alder adducts in organic synthesis presented. Finally, the inverse-electron demand hetero-Diels–Alder reactions of α,β-unsaturated ketone functionalities are discussed. The different chiral Lewis-acid complexes and chiral amines used for catalytic asymmetric hetero-Diels–Alder reactions are presented and the scope of these reactions in the synthesis of optically active α-hydroxy lactones, formyl esters and carbohydrates are demonstrated. The mechanistic aspects of the catalytic enantioselective hetero-Diels–Alder reactions are also discussed.

Introduction

Carbonyl compounds can undergo various cycloadditions, such as the hetero-Diels–Alder reaction. This class of reaction provides one of the most direct methods for the formation of six-membered oxygen-containing heterocycles and has been studied very intensively[1] because of the importance of the oxygen-heterocycle adducts formed. However, the scope of these reactions has some limitations: nearly all the hetero-Diels–Alder reactions of carbonyl compounds reported use aldehydes as the dienophile and even then special reaction conditions such as Lewis acid activation is required.[1,2] Ketones are much less reactive than aldehydes in hetero-Diels–Alder reactions due to both steric and electronic reasons, and until recently only a very few examples of hetero-Diels–Alder reactions of ketones had been reported. An important aspect of hetero-Diels–Alder reactions of ketones is the construction of oxygen heterocycles having a quaternary carbon atom center and a challenge is to have stereocontrol over the formation of these quaternary carbon atom centers.[3]

In this microreview the recent developments of hetero-Diels–Alder reactions of ketones will be presented with the focus on catalysis. There are two main types of hetero-Diels–Alder reactions which ketones can undergo: the direct normal-electron and the inverse-electron demand cycloaddition reactions, and both reaction types will be covered. The starting point will be the "simplest" catalyst of them all — the proton — by presenting the hydrogen bond-promoted hetero-Diels–Alder reactions and finishing with chiral Lewis acid complexes as catalysts for hetero-Diels–Alder reactions with both normal- and inverse-electron demand.

The two concepts for hetero-Diels–Alder reactions of ketones are outlined in Figure 1. For the direct-electron demand hetero-Diels–Alder reaction, a ketone reacts with a conjugated diene and in order to promote the reaction either pressure[4] or catalysis is required. The frontier molec-

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

ular orbital responsible for this type of reaction is the ketone LUMO interacting with the diene HOMO. Activation of the ketone by coordination of a Lewis acid to the ketone oxygen atom will lower the energy of the ketone LUMO and thus a more favourable interaction with the diene HOMO will be possible. Another approach for activating the hetero-Diels–Alder reaction of ketones with conjugated dienes is to use ketones having electron-withdrawing groups (R^1 and/or R^2) such as esters, as these substituents will also 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.

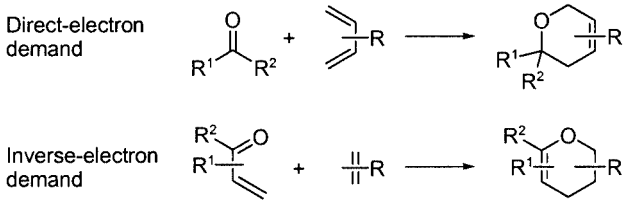


Figure 1. The direct- and inverse-electron demand hetero-Diels–Alder principle for reactions of ketones

For the inverse-electron demand hetero-Diels–Alder reactions, the ketone functionality is now a part of an α,β-unsaturated system that reacts in a cycloaddition reaction with electron-rich alkenes (Figure 1). The reaction is controlled by the LUMO of the α,β-unsaturated ketone interacting with the HOMO of the alkene. This reaction can also be catalyzed by Lewis acids which coordinate to the ketone functionality of the α,β-unsaturated acyl system, thereby lowering the LUMO energy of the enophile. For these inverse-electron demand hetero-Diels–Alder reactions, the ketone carbon atom is converted into a prochiral sp^2-hybridized carbon atom where the chiral center(s) in the molecule is introduced in the reaction.

Direct Hetero-Diels–Alder Reactions of Unactivated Ketones

A simple and elegant process for accelerating hetero-Diels–Alder reactions of ketones was presented recently by Rawal et al.[5] During an investigation of solvent effects on the hetero-Diels–Alder reaction of aldehydes with 1-dimethylamino-3-silyloxybutadiene a significantly higher reaction rate was found in $CHCl_3$ than in other aprotic organic solvents. It was concluded that this increased reactivity was due to a C–H···O=C hydrogen bond interaction between $CHCl_3$ and the carbonyl oxygen atom, making the carbonyl group a stronger hetero-dienophile (Figure 2).

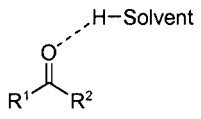
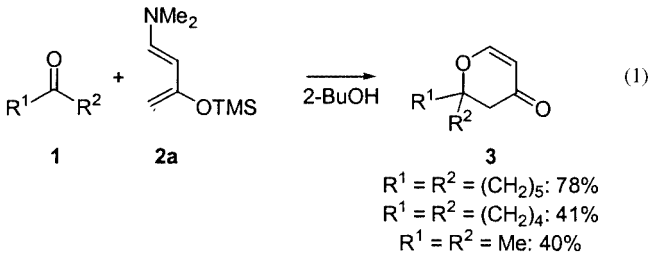


Figure 2. Activation of a ketone by hydrogen bonding with a solvent

Solvent studies showed that unactivated ketones, which generally are considered to be unreactive,[1] could be activated by hydrogen-bonding solvents and underwent hetero-Diels–Alder reactions with activated dienes. An investigation of various solvents revealed that a smooth [2+4] cycloaddition of ketones **1** with 1-dimethylamino-3-silyloxybutadiene **2a** took place in 2-butanol at room temperature, giving the hetero-Diels–Alder product **3** after hydrolysis [Equation (1)].[5]



(1)

It was found that solvents with less-shielded hydroxy groups were more effective in accelerating the reaction. The reaction proceeded well, with ketones such as cyclohexanone, cyclopentanone and acetone giving a variety of spirodihydropyrones in moderate to good yields [Equation (1)]. The hetero-Diels–Alder reactions promoted by hydrogen bonding are sensitive to steric and electronic variations in the ketone; for example the reaction of cyclohexanone was completed in 5 h, while the reaction of 2-methylcyclohexanone was only 50% complete after four days.[5]

To understand these solvent-assisted reactions, a computational investigation was performed to assess how hydrogen-bond interactions with $CHCl_3$ influence the chemical reactivity of the ketone in the hetero-Diels–Alder reaction of acetone with 1-dimethylamino-3-silyloxybutadiene.[6] These calculations showed that in the gas phase, the hydrogen-bond activation of acetone by one and two $CHCl_3$ molecules reduces the activation energy for the hetero-Diels–Alder reaction from 19.3 to 13.6 and 8.5 kcal/mol, respectively.

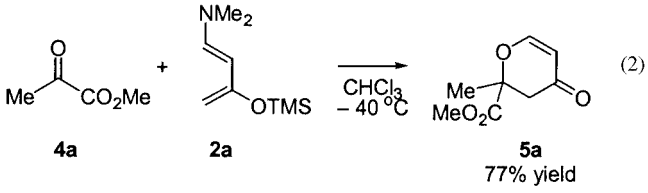
Rawal et al. contributed with an important extension of the hydrogen-bonding-promoted hetero-Diels–Alder reactions as they showed that chiral diols, such as TADDOL α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol), could catalyze the [2+4] cycloaddition of aromatic aldehydes with 1-dimethylamino-3-silyloxybutadiene to give dihydropyrones with excellent enantioselectivity.[7] This result showed that hydrogen bonding activation of a simple chiral alcohol to a carbonyl compound can be compared to enzymes.

The number of other hetero-Diels–Alder reactions of unactivated ketones with dienes is limited. Strong Lewis acids such as Me_2AlCl used in equimolar amounts were found to promote the hetero-Diels–Alder reaction of a Danishefsky-type diene grafted onto a modified Merrifield resin with different ketones in moderate yields.[8] The reaction of, for example, cyclohexanone, acetophenone and benzophenone gave the hetero-Diels–Alder adducts in moderate yields

(55%, 24% and 39%, respectively) after removing the resin by standard procedures. Similar dienes, not attached to a solid phase, have previously been reacted with the same ketones, catalyzed by $ZnCl_2$, and good yields of the corresponding dihydropyrones were obtained.[9]

Direct Hetero-Diels–Alder Reactions of Activated Ketones

Prior to the development of the hydrogen-bonding-catalyzed hetero-Diels–Alder reaction of unactivated ketones, based upon a C–H···O=C hydrogen-bond interaction between $CHCl_3$ and the carbonyl oxygen atom, Rawal et al. showed that the activated ketone, methyl pyruvate **4a**, reacted with 1-dimethylamino-3-silyloxybutadiene **2a** in $CHCl_3$ at −40 °C. After acetyl chloride workup (removal of the TMS and NMe_2 groups) the carboxylated dihydropyranone **5a** was isolated in 77% yield [Equation (2)].[10]



(2)

The majority of the recent work dealing with hetero-Diels–Alder reactions of activated ketones has been concentrated on asymmetric catalysis. The substrate in these reactions, such as an α-keto ester, is set up for bidentate coordination to a chiral Lewis acid as outlined in Figure 3. The bidentate coordination of the α-keto ester to the chiral Lewis acid has two purposes: (*i*) to activate the keto functionality for reaction, and (*ii*) for the chiral ligand to discriminate one of the faces of the ketone functionality. In Figure 3 the *Re*-face of the ketone is shielded by a C_2-symmetric chiral ligand.

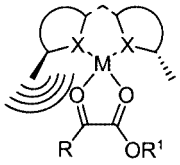
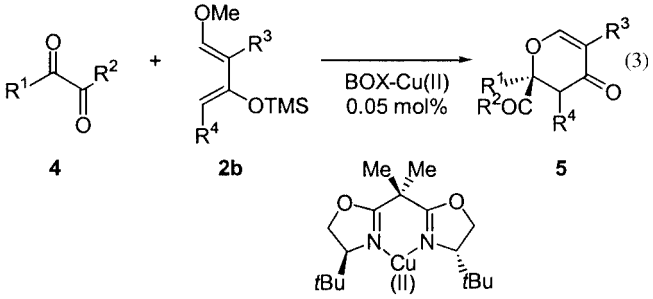


Figure 3. Coordination of a an α-keto ester to a chiral C_2-symmetric metal complex

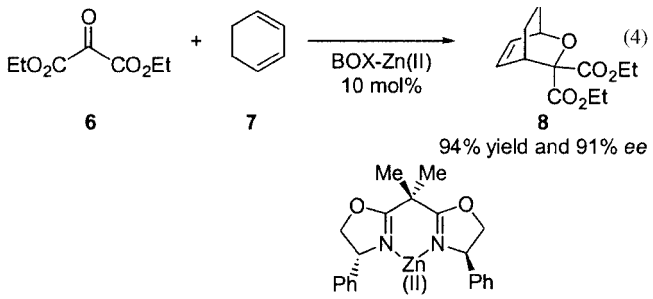
α-Keto esters **4** and α-diketones **4** react with activated dienes of the Danishefsky type **2b** in the presence of chiral copper(II) complexes. The first catalytic highly enantioselective version of the hetero-Diels–Alder reactions was catalyzed by C_2-symmetric bis(oxazoline)[11]-copper(II) complexes [Equation (3)].[12]

The *t*Bu-(bisoxazoline)(BOX)-Cu$(OTf)_2$ complex turned out to be a general catalyst for the catalytic enantioselective hetero-Diels–Alder reaction of different α-keto esters **4** and α-diketones **4** with the Danishefsky-type of dienes **2b**. The hetero-Diels–Alder adducts **5** were obtained after hydrolysis with TFA and the most remarkable feature of the catalytic system is that the reactions proceed with excellent enantioselectivities and yields using only 0.05 mol % of the catalyst. The yield and enantiomeric excess of the hetero-Diels–Alder adducts obtained for reaction with Danishefsky's diene ($R^3 = R^4 = H$) were, for example, 90% yield and 98.4% *ee* for methyl pyruvate, 88% yield and 93.9% *ee* for 2,3-butadione, and 76% yield and 97.8% *ee* for 2,3-pentadione. The absolute configuration of **5** using the (*S*)-enantiomer of the *t*Bu-BOX ligand was consistent with an intermediate of the type shown in Figure 3 in which the *tert*-butyl group of the chiral ligand shields the *Re*-face of the ketone allowing the diene to approach the *Si*-face of the ketone. The catalytic enantioselective hetero-Diels–Alder reaction of α-keto esters and α-diketones is a simple procedure for the synthesis of optically active dihydropyrones having a chiral quaternary carbon atom, as well as several chemical handles/functionalities which can easily be manipulated using standard chemical techniques. Methyl pyruvate has also been reacted with Danishefsky's diene in the presence of a chiral catalyst prepared from chiral diamines, carbonyl compounds and copper(II).[13] The chiral catalysts were formed by reaction of, for example, (1*S*,2*S*)-diphenylethylene diamine with ketones and Cu^{II} salts; the highest enantiomeric excess obtained of the hetero-Diels–Alder adduct **5a**, isolated in 85% yield, was 94% *ee* using the catalyst obtained from cyclobutanone.



(3)

Simple dienes, such as cyclohexadiene and cyclopentadiene, do not react with α-keto esters and α-diketones in the presence of C_2-symmetric BOX-Lewis-acid complexes as catalysts. In order for these less-activated dienes to react with ketones the carbonyl function has to be even more activated. It has been found that, for example, ketomalonate **6** reacts with cyclohexadiene **7** using chiral Lewis-acid catalysis [Equation (4)].[14] Screening investigations revealed that the chiral Ph-BOX-Zn^{II} complex was a convenient catalyst for the reaction of **6** with **7** and the hetero-



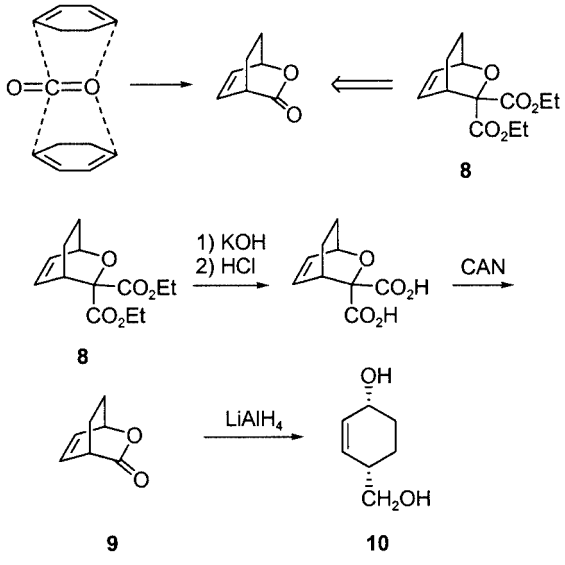
(4)

Diels–Alder adduct **8** could be obtained in high yields and with up to 91% *ee*.

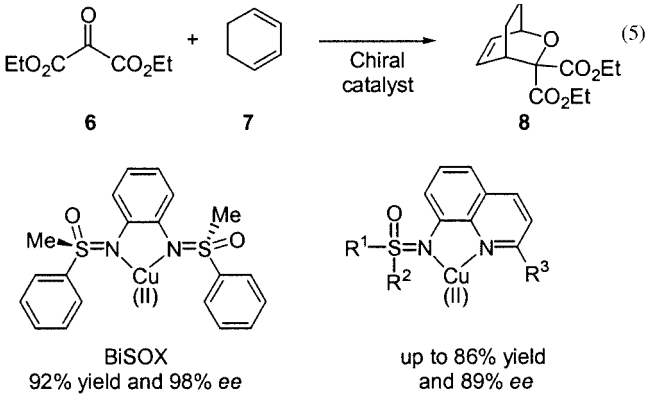
The Ph-BOX-Zn^{II} complex can also catalyze the hetero-Diels–Alder reaction of ketomalonate **6** with other conjugated dienes.[14] Cyclopentadiene reacts smoothly with **6**, however, the hetero-Diels–Alder adduct is unstable above −30 °C, while the Danishefsky-type dienes reacted with **6** catalyzed by Ph-BOX-Zn^{II} to give the corresponding hetero-Diels–Alder adducts in good yields and enantioselectivity. The reaction course of **6** with Danishefsky's diene is metal-ion dependent: the use of zinc(II) gives the desired hetero-Diels–Alder adduct, while the copper(II)-catalyzed reaction gives a mixture of the hetero-Diels–Alder and Mukaiyama aldol adducts.

The hetero-Diels–Alder adduct **8** obtained from the catalytic enantioselective reaction of ketomalonate **6** with cyclohexadiene **7** is equivalent to the adduct obtained from an enantioselective addition of cyclohexadiene to CO_2 as outlined at the top of Scheme 1. Indeed, saponification of the hetero-Diels–Alder diester **8** followed by addition of acid results in the dicarboxylic acid, which by treatment with CAN gives the chiral CO_2 synthon — lactone **9** — in 42% overall yield from **8**. Reduction of **9** with $LiAlH_4$ gives the diol **10** in 94% yield and 83% *ee* (Scheme 1). The outcome (**10**) of the catalytic enantioselective hetero-Diels–Alder reaction of the ketomalonate **6** with cyclohexadiene **7** as shown in Scheme 1 is, in principle, a stereoselective 1,4-addition of a hydroxy group and a hydroxymethyl group to 1,3-cyclohexadiene.[14]

Bolm et al. have successfully applied a chiral bis(sulfoximine) (BiSOX)-$Cu(OTf)_2$ as catalyst for the hetero-Diels–Alder reaction of ketomalonate **6** with cyclohexadiene (**7**) [Equation (5)].[15] The reaction afforded the hetero-Diels–Alder adduct **8** in excellent yield and enantioselectivity and thus afforded an improved synthetic procedure towards anticapsine. The absolute configuration of **8** was determined to be (1*S*,4*R*) when using the (*S*,*S*)-BiSOX-Cu-$(OTf)_2$ catalyst. Later developments by the same group led to the introduction of a new class of quinoline-based C_1-symmetric monosulfoximine ligands [Equation (5)].[16] The use of these new ligands in combination with $Cu(OTf)_2$ as the Lewis acid also afforded the enantioselective hetero-Diels–Alder reaction of **6** with **7**. Based on an X-ray structure of one of the chiral quinoline-based C_1-symmetric monosulfoximine ligands and $CuCl_2$, in which the two nitrogen atoms of the chiral ligand coordinate to the copper(II) center, an intermediate was proposed in which the ketone oxygen atom and one ester carbonyl atom coordinate to the copper(II) center in a bidentate fashion with a distorted tetrahedral geometry.[16]



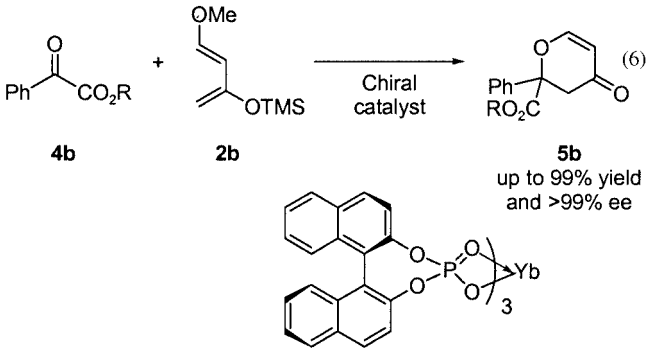
Scheme 1. Top: The principle for the formation of a chiral CO_2 synthon; bottom: synthesis of the chiral CO_2 synthon **9** and the formation of the optically active 1,4-disubstituted 2-cyclohexene **10**

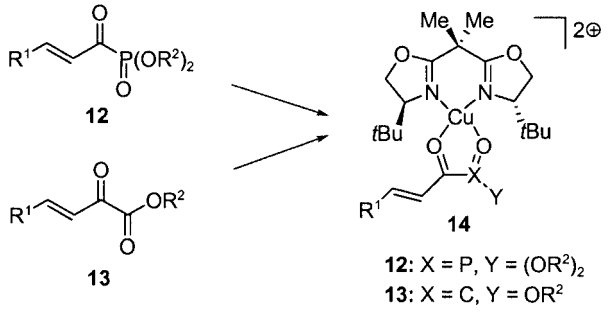


Only a few other examples of catalytic enantioselective hetero-Diels–Alder reactions of activated ketones with dienes have been published over the last couple of years. A chiral 1,1′-binaphthyl-2,2′-diyl phosphonate-Yb^{III} complex proved to be an excellent catalyst for the hetero-Diels–Alder reaction of phenylglyoxylate **4b** with Danishefsky's diene **2b** as up to 99% yield and >99% *ee* of the hetero-Diels–Alder adduct **5b** was isolated after treatment with TFA [Equation (6)].[17] It would be very interesting to follow the application of this catalyst for the hetero-Diels–Alder reaction of other ketones as it has also been shown to be an effective catalyst for the hetero-Diels–Alder reaction of aldehydes.[17]

Inverse Hetero-Diels–Alder Reactions of α,β-Unsaturated Ketones

Compared to the hetero-Diels–Alder reactions of ketones with dienes discussed above, where only a limited number catalytic and enantioselective reactions have been reported, the number of hetero-Diels–Alder reactions in which the ketone functionality is part of a heterodiene is

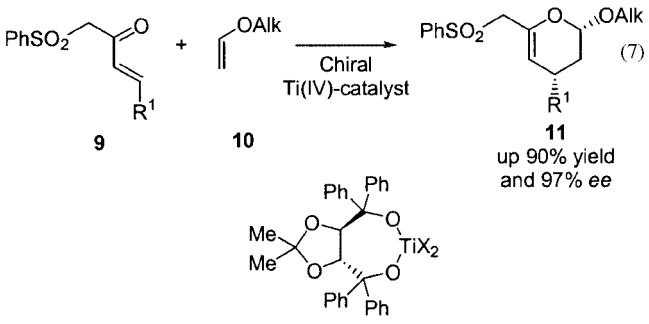




Scheme 2. Bidentate coordination of activated α,β-unsaturated acyl phosphonates and esters, **12** and **13**, respectively, to the chiral *t*Bu-BOX-copper(II) catalyst **14**

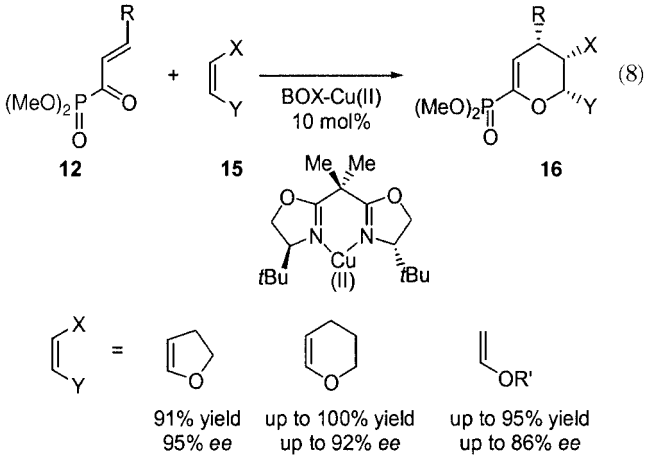
much higher. The first catalytic inverse-electron demand enantioselective hetero-Diels–Alder reactions were published about 10 years ago. The first version was an intramolecular cycloaddition of a heterodiene catalyzed by a diacetoneglucose-derived titanium(IV) complex.[18]

In a series of papers Wada et al. initiated the first intermolecular catalytic enantioselective hetero-Diels–Alder reactions of ketones.[19] The reaction proceeds well for enones **9** having both alkyl and aryl substituents (R^1), which react with various vinyl ethers **10** to give only one diastereomer of the hetero-Diels–Alder adduct **11** in very high yields and enantiomeric excesses [Equation (7)]. The enantioselectivity of the reaction was dependent on the bulkiness of the alkoxy substituent of the vinyl ether, with *tert*-butyl vinyl ether giving the best enantioselectivity. Various synthetic transformations of **11** were also presented.[19c]

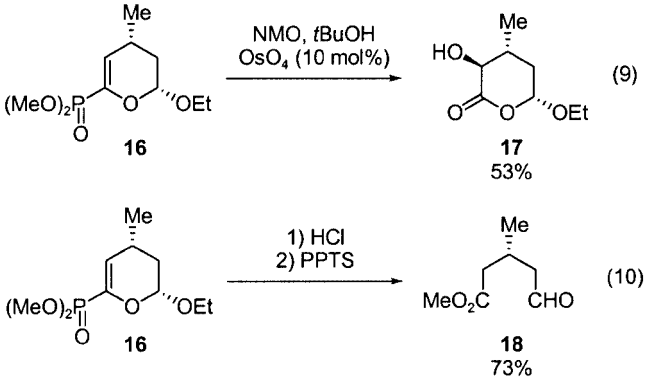


In a series of papers staring in 1998, the use of chiral BOX-copper(II) complexes as catalysts for the synthesis of optically active dihydropyrans by the hetero-Diels–Alder methodology of α,β-unsaturated ketone derivatives was presented, as well as the development and scope of these reactions. The use of activated α,β-unsaturated acyl phosphonates **12** was introduced by Evans et al.[20] and, independently, our group introduced the activated α,β-unsaturated α-keto esters **13**.[21] The underlying premise for the use of **12** and **13** was that good levels of diastereo- and enantioinduction might be anticipated by coordination of the substrate to the chiral *t*Bu-BOX-copper(II) catalyst giving the activated chiral complex **14** (Scheme 2).

The hetero-Diels–Alder reaction of α,β-unsaturated acyl phosphonates **12** with electron-rich hetero-dienophiles **15** catalyzed by chiral *t*Bu-BOX-Cu^{II} complexes was intensively investigated and the cycloaddition reaction with enols gave the optically active dihydropyrans **16** in high yields and with excellent stereoselectivities; some results are provided in Equation (8).[20d] Other hetero-dienophiles were also investigated, and for silyl enol ethers the stereochemical outcome of the reaction was dependent on the silyl group. The hetero-Diels–Alder reactions proceeded with excellent enantioselectivity, however the diastereoselectivity was found to be dependent on the silyl groups and it was postulated that these cycloaddition reactions proceed in a non-concerted manner.[20c]

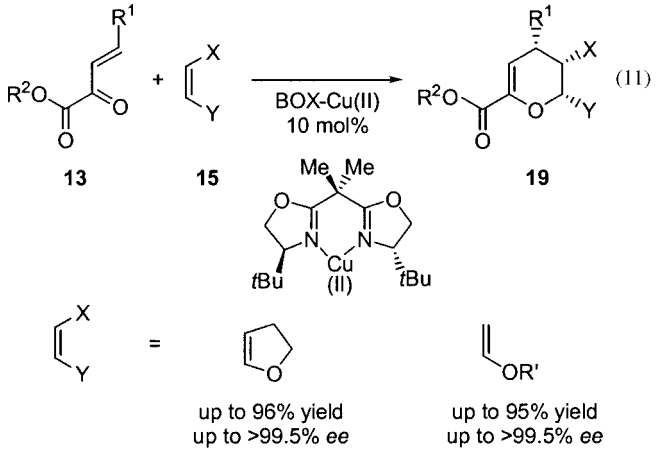


The scope of the hetero-Diels–Alder reaction of the α,β-unsaturated acyl phosphonates was assessed by a series of product syntheses of which two are presented in Scheme 3. Oxidation of the hetero-Diels–Alder adduct **16** using standard dihydroxylation conditions gave the α-hydroxy lactone **17** in 53% yield [Scheme 3, Equation (9)]. Treatment of the optically active dihydropyran **16** with dry HCl in MeOH afforded the corresponding acetal ester by cleavage of the acetal bond and solvolysis of the enol phosphonate, followed by treatment with a catalytic amount of pyridinium *p*-toluenesulfonate to give the formyl ester **18** (Scheme 3, Equation (10)].[20d]



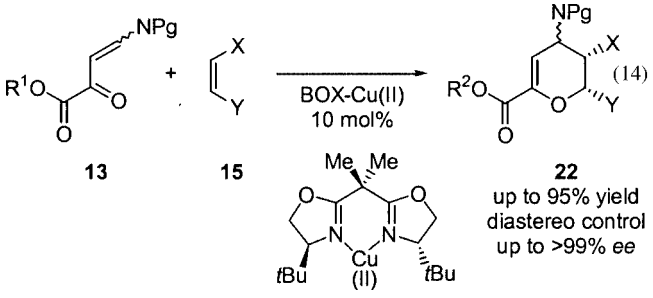
Scheme 3. Synthetic transformation of hetero-Diels–Alder adduct **16**; the formation of the optically active α-hydroxy lactone **17** is presented in Equation (9) and Equation (10) shows the synthesis of an optically active formyl ester **18**

The same catalytic system was applied to hetero-Diels–Alder reactions of α,β-unsaturated acyl esters **13** with different electron-rich hetero-dienophiles **15**.[20b,20d,21] The chiral *t*Bu-BOX-Cu^{II} complex was found to be an effective catalyst for this reaction, and gave the corresponding dihydropyrans **19** in high yields and with excellent stereoselectivity [Equation (11)].[20b,20d,21]



The utility of the optically active dihydropyrans **19** obtained in these hetero-Diels–Alder reactions was demonstrated by their transformation into various optically active carbohydrates (Scheme 4).[22] The formation of the optically active spiro-carbohydrate **20** was achieved by the catalytic enantioselective cycloaddition reaction of the corresponding α,β-unsaturated acyl esters with α-methylenetetrahydrofuran; the hetero-Diels–Alder adduct **19a** was obtained as the major diastereomer in up to 76% *ee* [Scheme 4, Equation (12)]. Standard chemical manipulations afforded **20**, which is related to compounds found in a variety of natural products such as pheromones, steroid derivatives, antiparasitic agents or polyether antibiotics.[23] In Scheme 4, Equation (13), the formation of an ethyl β-D-mannoside tetraacetate **21** from the hetero-Diels–Alder adduct **19b** is presented also using standard procedures. This synthesis, using the hetero-Diels–Alder approach, is an alternative to the use of carbohydrates for the synthesis of these types of compounds.

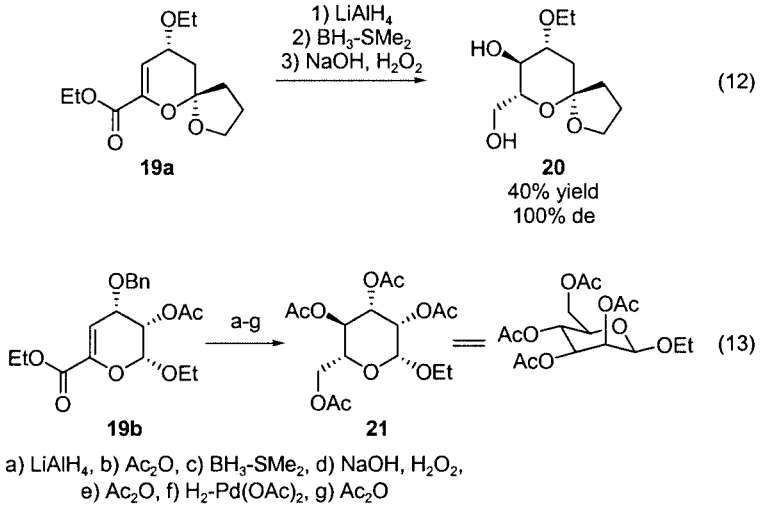
The hetero-Diels–Alder reaction of α,β-unsaturated acyl esters with electron-rich alkenes catalyzed by the chiral *t*Bu-BOX-Cu^{II} complex has also been used for the formation of optically active amino carbohydrates.[24] The reaction of γ-amino-protected β,γ-unsaturated α-keto esters **13** with alkenes **15** afforded the hetero-Diels–Alder adducts **22** in good yield and high diastereo- and enantioselectivity, and with full control of the stereocenter at the amino carbon atom [Equation (14)]. These carbohydrate precursors containing nitrogen atoms are interesting compounds in relation to the synthesis of carbohydrates as inhibitors of glucosidases for treatment of diabetes and drugs against influenza.[25]



The mechanism of the hetero-Diels–Alder reactions of α,β-unsaturated acyl phosphonates **12** and esters **13** with electron-rich hetero-dienophiles has also been investigated.[20–22] The diastereoselective preference for the *cis*-2,4-disubstituted dihydropyrans products is in agreement with an *endo* transition state. This is consistent with a secondary orbital interaction between the LUMO at the carbonyl atom of the α,β-unsaturated acyl system and the HOMO of the dienophile, as outlined in Figure 4.[20d]

The face selection of the reaction is determined by the absolute configuration of the chiral ligand. As outlined in Figure 3 and 4, the substrate in these reactions coordinates in a bidentate fashion to the copper(II) center. For this chiral *t*BuBOX-Cu^{II}-catalyzed reaction there is evidence supporting a substrate-chiral catalyst complex in which the angle of the plane of the coordinated 2-keto ester and the plane of the copper-bis(oxazoline) ligand is about 45°.[26] The use of the (*S*,*S*)-*t*Bu-BOX-Cu^{II} complex as catalyst will thus lead to a new complex in which the *tert*-butyl substituent shields the α-*Si*-face of the coordinated α,β-unsaturated acyl system similar to the face-shielding shown in Figure 3. The electron-rich hetero-dienophiles will thus approach the α,β-unsaturated acyl system from the α-*Re*-face, as outlined in Figure 4.

A change from vinyl ethers to ketene acetals, for example, in these hetero-Diels–Alder reactions catalyzed by chiral BOX-Cu^{II} complexes led to a different reaction course.[27]



Scheme 4. Synthetic transformations of hetero-Diels–Alder adduct **19**; the formation of an optically active spiro-carbohydrate **20** is presented in Equation (12) and Equation (13) shows the synthesis of an optically active ethyl β-D-mannoside **21**

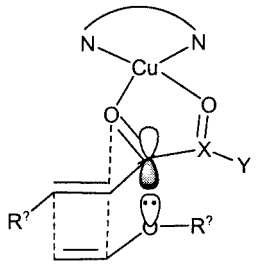
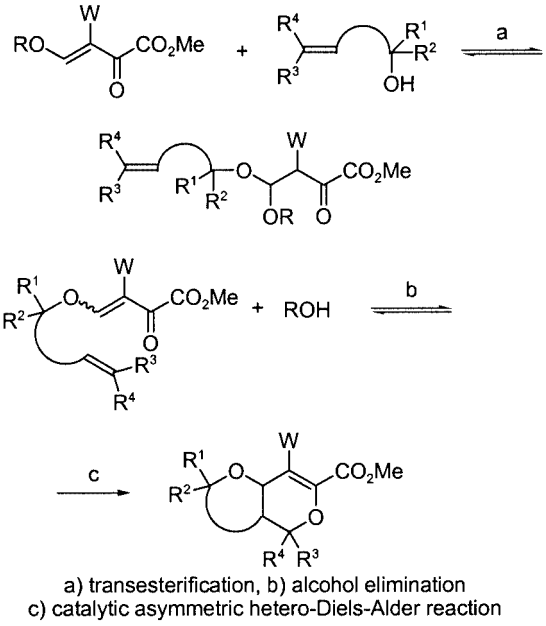


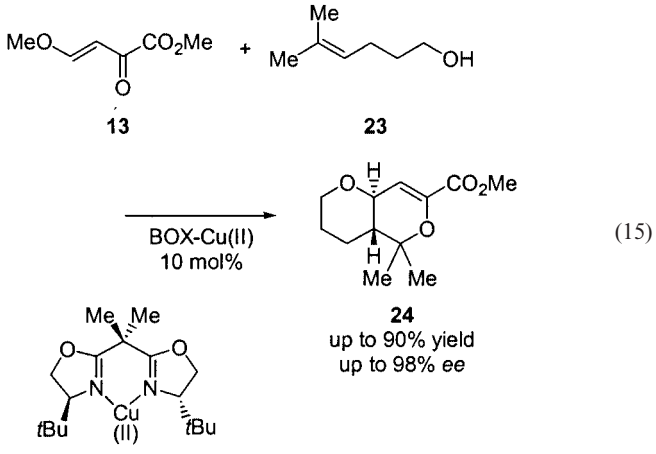
Figure 4. Secondary orbital interaction of the HOMO of the dienophile with the LUMO of the α,β-unsaturated acyl system

Under these reaction conditions two ketene acetal molecules added to α,β-unsaturated acyl esters, for example, and gave functionalized optically active δ-lactone acetals in good yields and with up to 95% *ee*.

Wada et al. have also developed a novel catalytic asymmetric tandem-transesterification-intramolecular hetero-Diels–Alder reaction.[28] Their concept is outlined in Scheme 5. The process involves first the conjugate addition of unsaturated alcohols to β-alkoxy-substituted α,β-unsaturated esters and then a reversible elimination of alcohols, followed by the catalytic enantioselective hetero-Diels–Alder reaction.

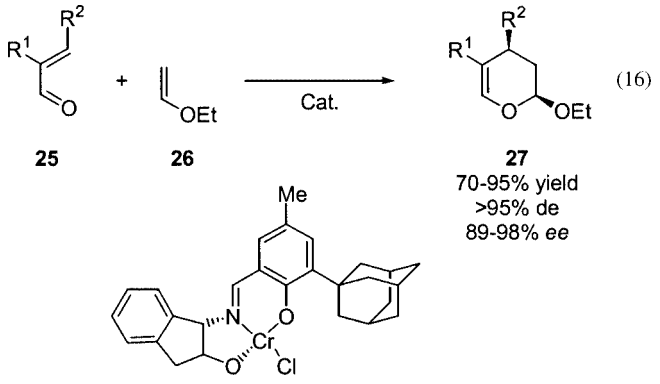


Scheme 5. Catalytic asymmetric tandem transesterification-intramolecular hetero-Diels–Alder reaction

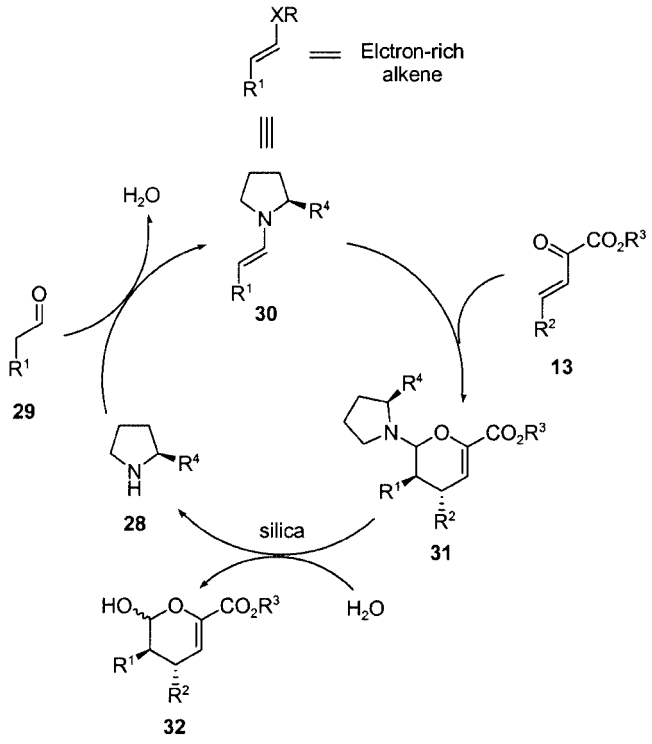


The catalytic asymmetric tandem transesterification-intramolecular hetero-Diels–Alder reaction was investigated for a series of catalysts such as the chiral TADDOL-Ti^{IV} and BOX-Cu^{II} complexes.[28b] Careful optimization revealed that the chiral BOX-$Cu(OTf)_2$ complex, in the presence of molecular sieves to avoid an acid-catalyzed reaction, afforded the *trans*-fused hydropyranopyran derivative **24** in high yield and excellent enantioselectivity [Equation (15)].

In relation to the reactions above for ketones, one example of a closely related catalytic enantioselective inverse-electron demand hetero-Diels–Alder reaction of α,β-unsaturated aldehydes should be mentioned briefly [Equation (16)].[29] Jacobsen et al. have shown that the chiral Schiff base-Cr^{II} complex is a highly diastereo- and enantioselective catalyst for the hetero-Diels–Alder reaction of different substituted α,β-unsaturated aldehydes **25** with ethyl vinyl ether **26** in particular. The scope of the reaction was demonstrated, and the use of the hetero-Diels–Alder adducts obtained was documented by various synthetic substitution reactions of one of the dihydropyran derivatives formed.

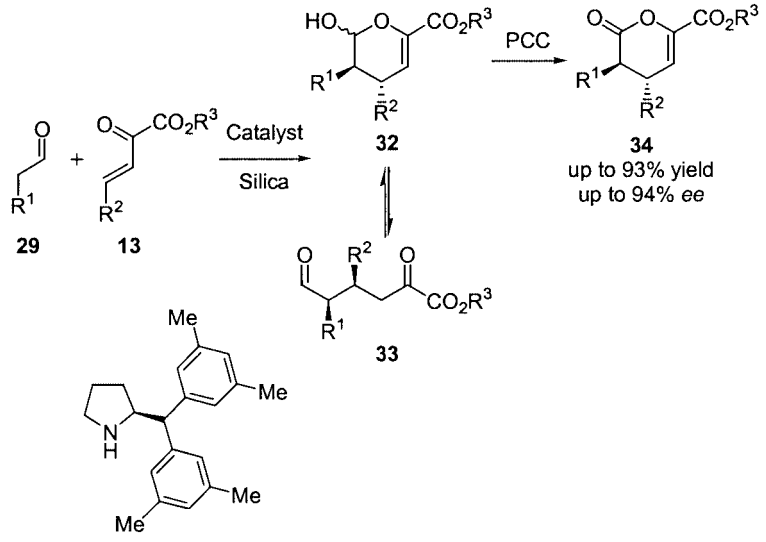


The concept of inverse-electron demand hetero-Diels–Alder reactions has been extended to organocatalytic asymmetric hetero-Diels–Alder reactions.[30] This concept is based on the consideration that the enamine **30** formed by reaction of a chiral amine **28** with an aldehyde **29** can be considered as an electron-rich alkene, which will react in a cycloaddition reaction with α,β-unsaturated acyl esters **13** to give the hetero-Diels–Alder adduct **31**, which, after cleavage of the aminal group in **31** by silica, gives the hemiacetal **32**, obtained as a mixture of the two anomers (Scheme 6).



Scheme 6. Catalytic principle of the organocatalytic hetero-Diels–Alder reaction

Chiral amines based on (2*S*)-pyrrolidines can catalyze the hetero-Diels–Alder reaction of aldehydes **29** with α,β-unsaturated acyl esters **13** giving the two anomers of **32**, which can also exist as the open form **33** (Scheme 7). Oxidation of **32** affords lactone **34** as a single diastereomer.[30] (*S*)-2-Bis(3,5-dimethylphenyl)pyrrolidine was found to be a useful catalyst for this organocatalytic hetero-Diels–Alder reac-



Scheme 7. The organocatalytic hetero-Diels–Alder reaction of aldehydes **29** with α,β-unsaturated acyl esters **13** catalyzed by a chiral pyrrolidine catalyst

tion and it was demonstrated that different aldehydes **29** reacted with **13** to give the optically active lactone **34** in good yield and enantiomeric excess.

The absolute configuration of the hetero-Diels–Alder adduct obtained by this organocatalytic reaction was used to determine the stereochemical outcome of the reaction. The proposed transition-state model is shown in Figure 5. The electronic properties of the enamine intermediate (**30** in Scheme 6) govern the regioselectivity, while the 2-diarylmethyl substituent on the pyrrolidine ring shields the *Si*-face of the enamine. Thus, the 2-diarylmethyl substituent of the enamine intermediate controls the *endo* addition of the α,β-unsaturated acyl ester to the *Re*-face of the alkene fragment.

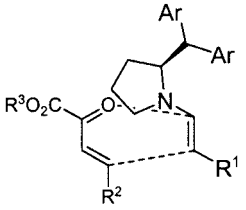
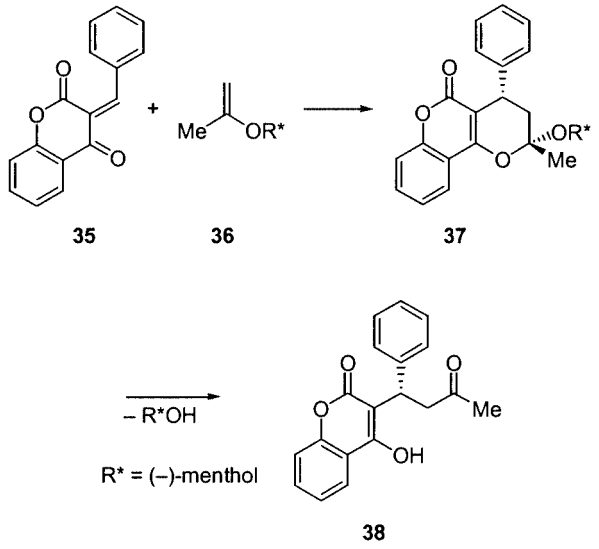


Figure 5. Proposed transition-state model for the diastereo- and enantioselective organocatalytic hetero-Diels–Alder reaction

The hetero-Diels–Alder approach to ketones has also been used more directly for the synthesis of pharmaceutically interesting compounds, such as the optically active anticoagulant warfarin.[31] The synthesis of optically active warfarin was based on a diastereoselective, one-pot, three-component Knoevenagel-hetero-Diels–Alder reaction between in situ generated 3-arylidene-3,4-chromandiones **35** and isopropenyl ether **36** derived from (−)-menthol as the chiral auxiliary, as outlined in Scheme 8.[32] Both warfarin **38** and other interesting compounds were prepared in high yields by the approach in Scheme 8 and among the different vinyl ethers used as dienophiles, the isopropyl ether derived



Scheme 8. Knoevenagel-hetero-Diels–Alder reaction for the formation of optically active warfarin

from (−)-(1*R*,2*S*,5*R*)-menthol gave the best results.[31] After removal of the chiral auxiliary from **37** and recrystallization, enriched warfarin was obtained with a 95% *ee*.

Finally, one more example of a diastereoselective inverse-electron demand hetero-Diels–Alder reaction should be mentioned. Chiral allenamides, based on, for example, chiral oxazolidinones, have been reacted with heterodynes, such as aryl vinyl ketones, to give highly functionalized 2-aryl-pyranyl heterocycles in moderate to high yields and with diastereomeric ratios >96:<4.[33]

Conclusion

The hetero-Diels–Alder reaction of ketones is a challenge to chemists as ketones are less reactive than aldehydes and therefore require special reaction conditions in order to undergo cycloaddition reactions. The oxygen-containing heterocycles obtained from hetero-Diels–Alder reactions of ketones are important compounds in chemistry as they, for example, contain a quaternary carbon atom, which might also be chiral.

Recent developments have shown that hydrogen-bonding solvents can activate ketones for hetero-Diels–Alder reactions with activated dienes. A chiral Lewis acid can catalyze the direct-electron demand hetero-Diels–Alder reactions of activated ketones and chiral copper(II) complexes are especially useful catalysts for these reactions. For the inverse-electron demand hetero-Diels–Alder reactions, chiral copper(II) complexes can catalyze the cycloaddition of α,β-unsaturated acyl compounds with electron-rich alkenes in high yield and excellent diastereo- and enantioselectivity. These reactions have also found use in the total synthesis of valuable compounds. Chiral amines can be used as catalysts as they generate an enamine, which can be considered as an electron-rich alkene, upon reaction with an aldehyde and therefore undergoes hetero-Diels–Alder reactions with α,β-unsaturated acyl compounds giving the hetero-Diels–Alder adduct with high stereoinduction.

The catalytic asymmetric hetero-Diels–Alder reaction of ketones is just beginning, and one of the challenges for chemists in the coming years is, for example, to develop a catalytic enantioselective reaction of simple unactivated ketones and α,β-unsaturated ketones.

Acknowledgments

This work was made possible by the enthusiastic and dedicated contribution to the development and understanding of catalytic asymmetric hetero-Diels–Alder reactions by the persons given in the reference list and the financial support of the Danish National Research Foundation.

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Received December 8, 2003
Early View Article
Published Online March 25, 2004

