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Chalcones, a Privileged Scaffold: Highly Versatile Molecules in [4+2] Cycloadditions

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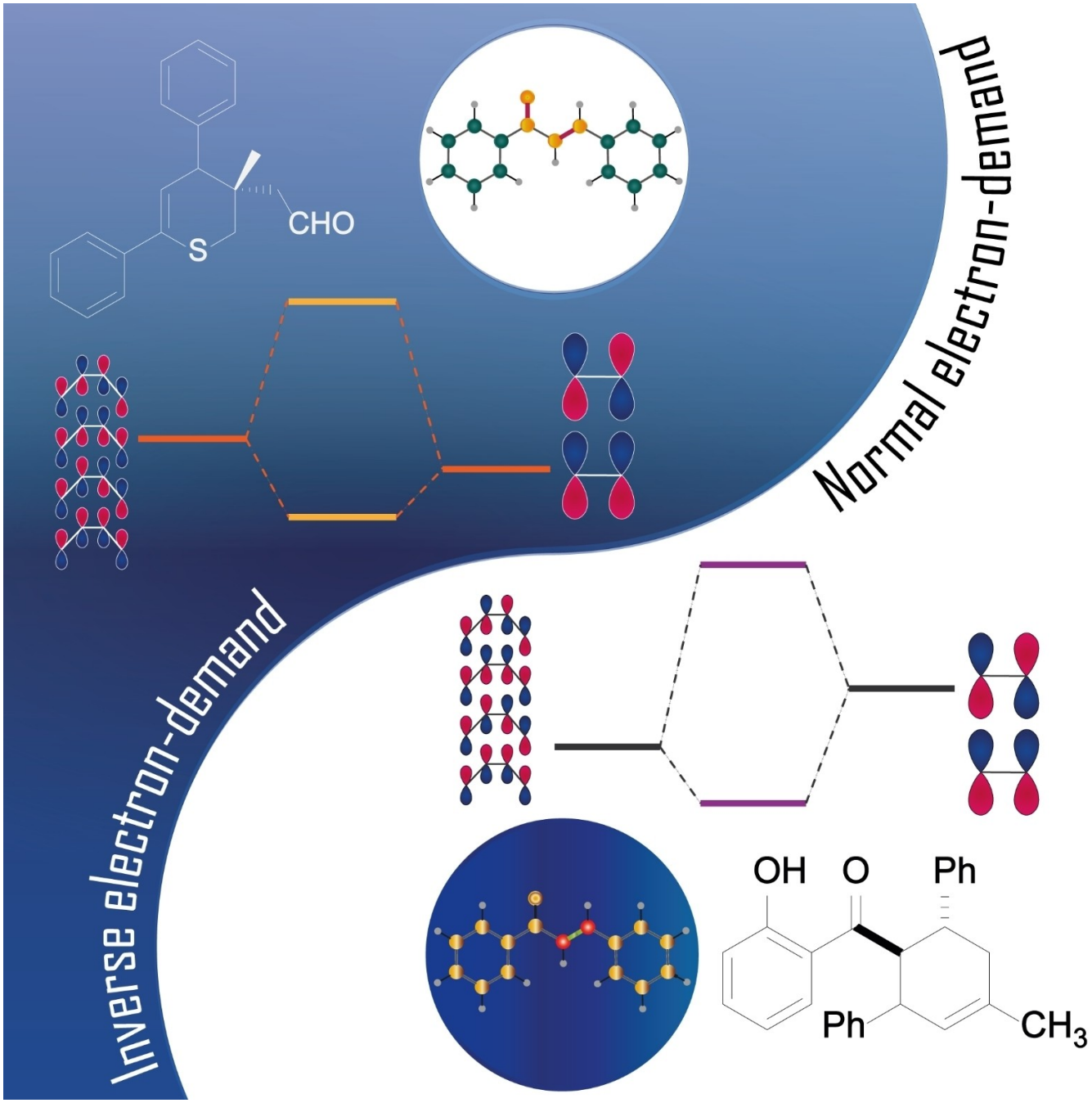

Abstract: Chalcones are aromatic ketones found in nature as the central core of many biological compounds. They have a wide range of biological activity and are biogenetic precursors of other important molecules such as flavonoids. Their pharmacological relevance makes them a privileged scaffold, advantageous for seeking alternative therapies in medicinal chemistry. Due to their structural diversity and ease of synthesis, they are often employed as building blocks for chemical transformations. Chalcones have a carbonyl conjugated system with two electrophilic centers that are commonly used for nucleophilic additions, as described in numerous articles. They can also participate in Diels-Alder reactions, which are [4+2] cycloadditions between a diene and a dienophile. This microreview presents a chronological survey of studies on chalcones as dienes and dienophiles in Diels-Alder cycloadditions. Although these reactions occur in nature, isolation of chalcones from plants yields very small quantities. Contrarily, synthesis leads to large quantities at a low cost. Hence, novel methodologies have been developed for [4+2] cycloadditions, with chalcones serving as a 2π or 4π electron system.

1. Introduction

The name chalcone is derived from "chalcos", the Greek word for "bronze". This owes itself to the color of most natural chalcones. These classic aromatic ketones are biogenetic precursors of many biological compounds such as flavonoids and isoflavonoids.[1] Since chalcones have been biosynthesized with several variations, they are believed to be the product of different biopathways, depending on the plant of origin. Nevertheless, the most reliable synthetic approach is described by Andersen and Markham.[2]

Generally, their structure is characterized by two aromatic rings linked by a three-carbon α,β-unsaturated carbonyl moiety. The ring closer to the carbonyl group is usually denominated the A ring and the vinyl aromatic group the B ring. The simplest chalcones have a 1,3-diphenyl-2-propen-1-one structure (Figure 1). Several derivatives of this scaffold are found in vegetables, fruits, and other plants.[3] Both isomers of chalcones occur in nature, but greater stability is found for the *trans* (E) versus *cis* (Z) isomer due to the steric effects of the A ring on the carbonyl group. Chalcones isolated from plants display a variety of substituents, including hydroxyls, methoxyls, prenyls, and glycosides.[1,3–9]

The chalcone structure is considered a privileged scaffold because it has several important biological properties, including antioxidant, antibiotic, anti-inflammatory, anticancer, and antiviral.[3,5,6,10–17] Such a wide range of biological activity is mainly attributed to its Michael acceptor capability, which facilitates interaction with the sulfhydryl group of cysteine residues and other thiols that exist in many vital biological molecules, including enzymes.[3,18] Moreover, chalcones have interesting optical properties, absorbing light near the UV and visible range, which widens their applications to the fields of imaging, optical technology, biomarkers, materials science, and microelectronics.[19,20]

According to the Web of Science,[21] chalcone molecules were reviewed in 137 articles in the last decade. These are essential molecules in chemistry and medicine, as shown by the distribution of the articles in different fields of knowledge (some contain information belonging to more than one field; Figure 2). The reports mainly focus on the synthesis, organic transformation, and pharmacological properties of natural or synthetic derivatives. However, none of them have made an analysis of the duality of chalcones in a [4+2] cycloaddition reaction. The latter reaction presents one of the key methods for constructing carbocycles and takes place between a 4π and a 2π electron system, commonly known as a diene and dienophile.

The current contribution concentrates on the ability of chalcones to act as a diene or dienophile under the right conditions. This chemical behavior has led to the development

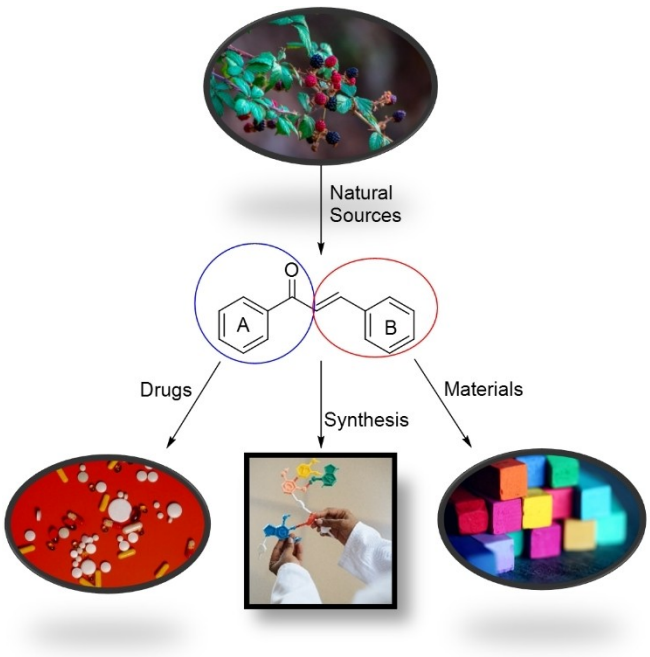

Figure 1. Basic structure of chalcones and their applications.

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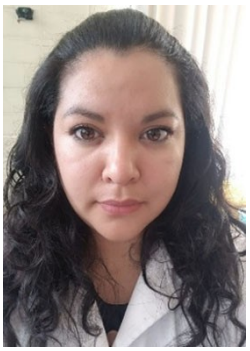
of novel synthetic protocols for [4+2] cycloadditions used to prepare more complex structures.

1.1. Chemical synthesis of chalcones

The isolation of chalcones from natural sources is a long and complicated process involving different techniques that must be standardized for every plant. Since plants do not produce large quantities of these compounds, the yield per kilogram of organic material tends to be in the mg order (sometimes less). Therefore, the most efficient way to obtain chalcone molecules is through organic synthesis. Due to the design of new analogs considered chalcones, their structural diversity has broadened. For instance, the basic structure of **1** has been modified with heteroaryl scaffolds and that of bis-chalcones **3** with three aryl groups. Moreover, bis-chalcones **2** have been derived from acetone, bis-chalcones **4** from cyclic ketones, and bis-chalcones **5** from tetrahydrohexa heterocyclic ketones. Other chalcones (**6**, **7**) are analogs of cinnamaldehyde and aza/thioketones (Figure 3A).[17,20,22–24] Some synthetic chalcones have been approved as drugs for various treatments, including metochalcone (a choleretic), hesperidin methyl chalcone (a vascular protector), and sofalcone (an antiulcer and mucoprotective agent) (Figure 3B).[1]

Salvador Mastachi Loza received his PhD in Chemical Sciences from the Universidad Autónoma del Estado de México while working with Diels-Alder reactions between chalcones and exo-heterocyclic dienes. He did a research stay at the Universidad de Granada in the group of Prof. Juan A. Tamayo under the supervision of Dr. Francisco Franco. In 2021, he joined the group of Dr. Miguel A. Vazquez as a postdoctoral researcher.

Tania I. Ramirez Candelero, a PhD student in chemical sciences at the Universidad Autónoma del Estado de México, is working on obtaining spirocyclic compounds through Diels-Alder reactions. She did a research stay at the Universidad de Granada in the group of Prof. Juan A. Tamayo under the supervision of Dr. Jose Antonio Vidal. Her research interests include spirocyclic compounds, cycloadditions, and the use of chalcones and exocyclic dienes in cycloaddition reactions.



Luis J. Benítez Puebla received his PhD in chemical sciences in 2022 while working in the field of organometallic chemistry at the University of Guanajuato. His research interests include organometallic chemistry, Fischer carbenes, and catalysis.

Aydeé Fuentes Benítes received her PhD in Chemical-Biological Sciences in 2006 at the Escuela Nacional de Ciencias Biológicas-IPN while working in the field of organic synthesis. Currently, she is a full-time professor at the Universidad Autónoma del Estado de México. Her research line is focused on the cycloaddition reactions to synthesize novel organic compounds with possible biological activity.

Carlos González Romero got his PhD in Chemical Biological Sciences in 2006 at the Escuela Nacional de Ciencias Biológicas and has been a full-time professor at the Universidad Autónoma del Estado de México since 1993. He worked in the Research Division of Syntex Corporation (1980–1993) as a Sr Chemist in the development of new molecules with biological activity. His interests are in the synthesis of triazoles through cycloaddition reactions and their biological evaluation.

Miguel A. Vazquez has been a full-time professor at the University of Guanajuato since 2007. He got his PhD in Organometallic Chemistry in 2004 from the Instituto Politécnico Nacional (IPN-Mexico City). In the same year he started with Polaquimia Company as a leading researcher in the R&D department (2004–2007). He has carried out research stays at the University of the Basque Country in the group of Prof. Fernando Cossio and at the University of Houston under the supervision of Dr. Olafs Daugulis. His research focuses on the chemistry of Fischer carbene complexes with special emphasis on the development of new methodologies to generate carbo- and heterocycles and study their application to different areas of science.

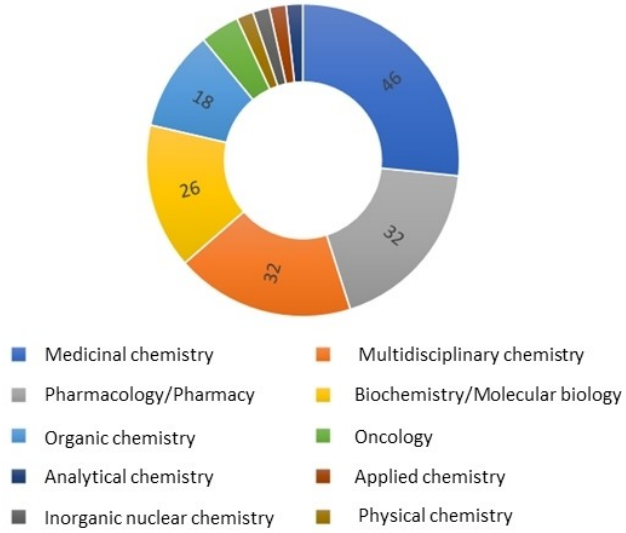


Figure 2. Recently reviewed topics in relation to chalcones.

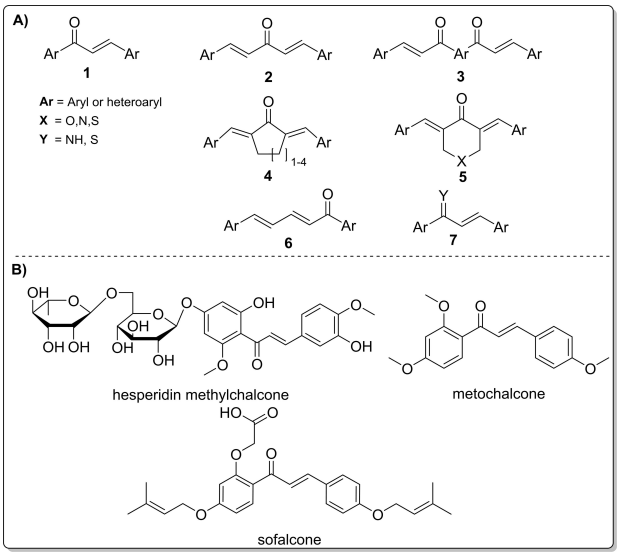


Figure 3. A) Structural diversity of synthetic chalcones. B) Some chalcone approved as drugs.

1.1.1. The Claisen-Schmidt condensation

The most common method for the synthesis of chalcones and their analogs is the Claisen-Schmidt condensation (Scheme 1), which involves the condensation of a ketone **9** with α hydrogens and an aromatic aldehyde **8** under basic or acid catalysis.

R^1= R^3=Aryl or HeteroAryl; **R^2**=H, alkyl, CN, SO_2R; **n**= 0,1,2.....

Scheme 1. Synthesis of chalcones with the Claisen Schmidt condensation.

The formation of the desired α,β-unsaturated ketone is directly dependent on the substrates and the catalyst. Whereas catalysis with a strong base yields chalcones in a matter of hours or even minutes, with an acid the process lasts for days. A wide range of basic and acid catalysts effectively generate chalcones in high yields. Numerous reports describe chalcone synthesis with inorganic or organic bases, while acid conditions (varying from Brønsted to Lewis acids) are less frequently employed.[1] These syntheses can be carried out with unconventional methods such as microwave heating,[25,26] ultrasound,[27] and grinding.[28,29]

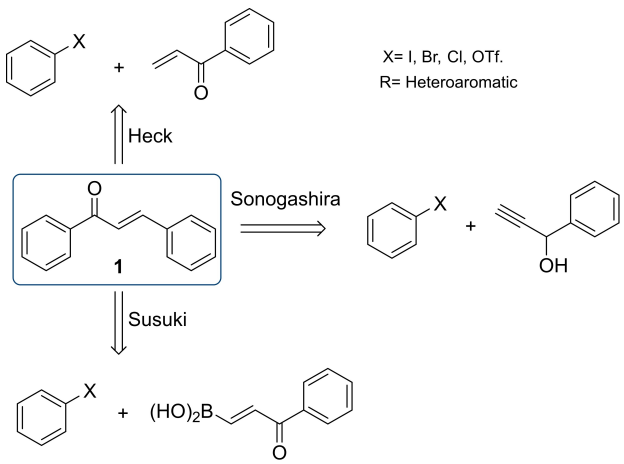
1.1.2. Coupling reactions

Chalcone synthesis has also been accomplished through Heck, Sonogashira, and Suzuki coupling reactions (Scheme 2).[5–7] Such reactions have advantages over the Claisen-Schmidt condensation in the event that the substrates have susceptible or complex functional groups. These coupling reactions represent a viable alternative for the preparation of the desired compounds **1**.[30]

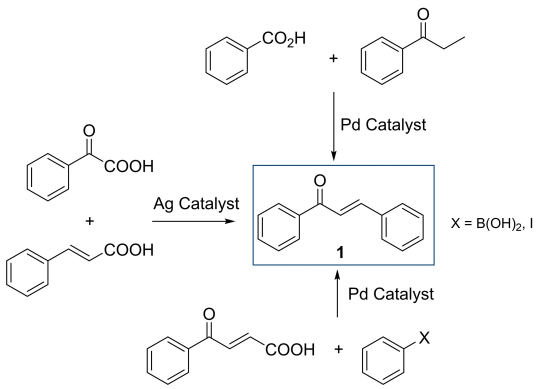
Other less common coupling reactions involve the use of silver or palladium for direct cross coupling or carboxylic acids as the starting material (Scheme 3).[31]

1.1.3. Additional strategies

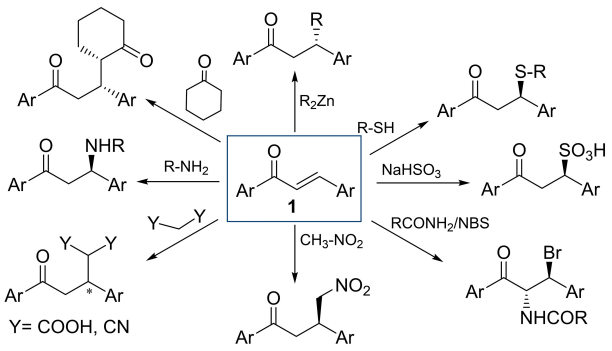
There are other reactions for the synthesis of chalcones, such as the Friedel-Craft acylation and the Wittig reaction. Moreover, 2-hydroxychalcones have been prepared through a photo Fries rearrangement of phenyl cinnamates under UV irradiation. Recently, different conditions (**I**–**IV**) were utilized for a one-pot reaction between benzyl alcohols and ketones. Accordingly, the alcohol was oxidized to the corresponding aldehyde, which underwent condensation with the arylketone (Scheme 5).[1,5–7]



Scheme 2. Commonly known coupling reactions leading to the synthesis of chalcones.



Scheme 3. Other coupling reactions employed for the synthesis of chalcones.



Scheme 4. Example of Michael addition reactions with chalcones.

1.2. Reactivity of chalcones

Chalcones are considered versatile synthons for developing new drugs. Pharmacological activity can be increased by linking distinct functional groups to the aromatic rings.[32–36] As building blocks, however, the most important transformations of chalcones occur within the α,β-unsaturated ketone moiety, which bears two electrophilic carbons due to delocalization of the electron density in the C=C–C=O system. The conjugated system of chalcones allows for facile nucleophilic additions at the carbonyl group (1,2-addition) or the β-carbon (1,4-addition/Michael addition).

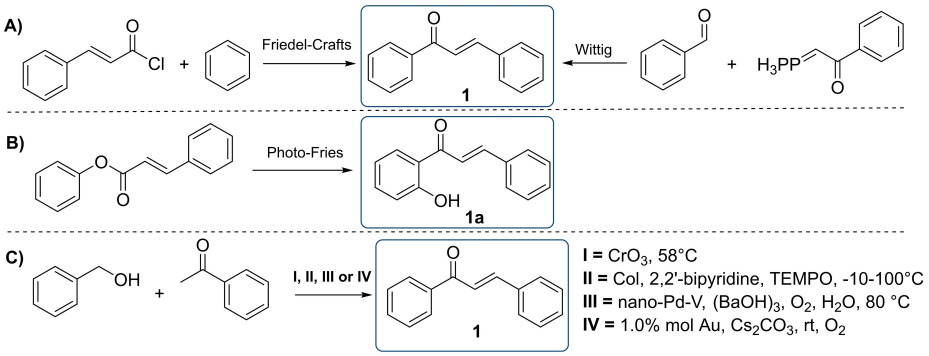
By utilizing Michael-type reactions, it is possible to introduce a plethora of functional groups with high stereoselectivity. Nucleophilic 1,4-addition is another pharmacokinetic mechanism of action described in the literature, as aforementioned. Research has been conducted to mimic this sulfa-Michael addition with high enantioselectivity. For instance, chalcones have been reacted with thiols to form thioethers or sodium bisulfite, involved in the synthesis of sulfonic acids.[37–40] Other examples of 1,4-additions include the aminohalogenation of the olefin with amides and N-bromosuccinimide,[41] as well as the addition of alkanes,[42] nitroalkanes,[43] malonates,[44] malonitrile,[45] ketones,[46] or amines[47] by employing chiral catalysts (Scheme 4). The interaction with chiral catalysts shows the relevance of chalcones in the development of novel stereoselective reactions.[48] *Dear Author, Scheme 4 comes after Scheme 5. Please check it and correct it if necessary.*

Apart from Michael additions, chalcones have been extensively used for the synthesis of biologically active 5- and 6-membered azaheterocycles, including pyrrole,[49] isoxazole,[50] pyrazole,[51] benzodiazepine,[52] triazole,[53] and pyrimidine.[54] The most common reactants, illustrated in Scheme 6, are among the many that exist for achieving such transformations.

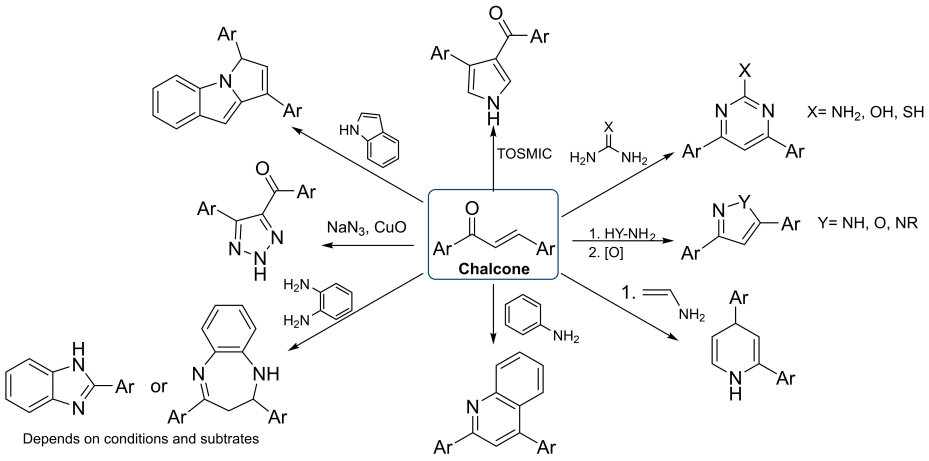
Some reviews offer an overview of these cycloadditions and their conditions, with a very detailed comparison between the distinct substrates employed for synthetizing azaheterocycles from chalcones.[55–57]

2. Chalcones in Diels-Alder cycloadditions

Although the Diels-Alder (DA) reaction was reported in the 1920s, it was not discovered as a natural biosynthetic pathway to generate different types of adducts with medicinal properties until the investigation by Taro Nomura and Yaro Hano[58] in the 1980s. These researchers worked with an ancient Chinese remedy named "Sang-Bai-Pi", which is the root bark of *Morus alba*, a plant that produces white mulberries. Sang-Bai-Pi has been used in traditional Chinese medicine in various preparations elaborated from the leaves, branches, fruit, or root bark of this plant. Through a series of extractions, Nomura and Hano



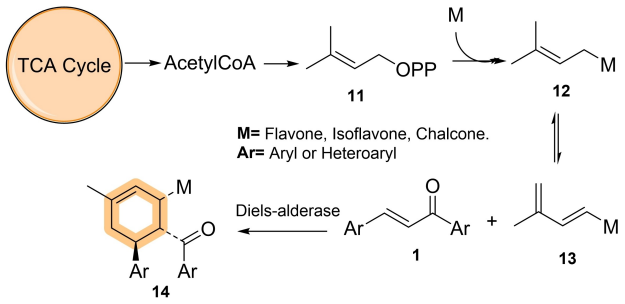
Scheme 5. A) The Friedel-Crafts and Wittig reactions used for the synthesis of chalcones. B) Photo Fries rearrangement leading to the formation of 2-hydrocychalcones. C) One-pot synthesis of chalcones from benzyl alcohol.



Scheme 6. Transformation of chalcones into relevant azole heterocycles.

isolated two compounds designated as kuwanons G and H, which were provided by a Diels-Alder cycloaddition between two chalcone derivatives and a dehydroflavone.[58] Nomura carried out cell culture and ^{13}C labeling studies and proposed a biosynthetic pathway for the adducts. It was found that isoprenyl pyrophosphate **11** derived from the tricarboxylic cycle could be attached to different secondary metabolites, such as chalcones, flavones, and isoflavones. If the plant has the necessary enzyme for the prenylation process, the prenylated compound **12** is furnished. Then dehydrogenation of the isoprenyl fraction of **12** gives rise to the corresponding diene **13**. Subsequently, a Diels-Alderase enzyme catalyzes the cycloaddition with a chalcone analog of **1** and completes the formation of the DA adduct **14** (Scheme 7).[59–61] Further transformations can afford additional compounds, also considered DA adducts because the aforementioned metabolic pathway is always the first step.

After this study, many other DA adducts were derived from chalcones isolated from different Morus *spp.* plants found around the globe, and the biological activity of such adducts was evaluated with positive results.[59,60,62–71] As of 2019, 80 mulberry DA type adducts had been isolated from the Moraceae family of plants. These can be divided into four categories based on their structure: (I) Adducts of chalcones and prenylated flavonoids (kuwanon G); (II) Adducts of chalcones and prenylstilbenes (kuwanol E); (III) Adducts of chalcones and prenylated 2-arylbenzofurans (chalcomoracin); and (IV) Adducts of another type (bromosin A, mulberrofuran G, or sanggenon S).[67,72,73] Almost 46% of the known mulberry DA adducts are of type I, while types II and III are sometimes specific to a particular species of the mulberry plant. Type IV adducts are dimers from prenylated chalcones or compounds with further transformations (Figure 4). Some type IV adducts have lost the cyclohexene cycle, but it has been established through ^{13}C cell culture that they follow the mulberry DA metabolic pathway. For a better understanding of the variety of structures, extraction methods, mulberry plant species, chalcone substrates, and biological activity of type I–IV compounds, see the US patent 2014/0004215A1.[71]



Scheme 7. Metabolic pathway for the formation of Diels-Alder adducts from Morus *spp.*

Many isolated compounds are still being investigated to determine whether they are mulberry DA adducts, or at least DA adducts when they are not isolated from a mulberry species. An example of a DA adduct is calyxin Y, isolated from *Alpinia katsumadai*, which is another Chinese plant employed in medicinal treatments. Others such as Palodesangretins (I–II) and Palodesangrens (A–E) are isolated from *Brosimum rubescens*, a Peruvian plant (called "palo de sangre") utilized as a tonic.[74–76]

A survey in 2010 described at least 200 molecules isolated from various plants and microorganisms that might be biosynthesized from DA reactions catalyzed by Diels-Alderase enzymes (Scheme 8).[77–84] Interestingly, chalcones as dienophiles appear to be used as substrates by moraceous plants only.

Such discoveries inspired researchers to perform assays with chalcones in DA reactions to synthesize novel molecules and develop stereoselective protocols that mimic the biosynthesis of mulberry DA adducts. With that in mind an extensive literature search was conducted in academic databases based on several keywords: chalcone [4+2] cycloaddition formal cycloaddition and Diels-Alder. Only the studies in which the chalcone enone moiety participated in [4+2] cycloadditions were selected for the current review. In the following sections the relevant reports are discussed in chronological order with the aim of placing each one in a historical context thus showing

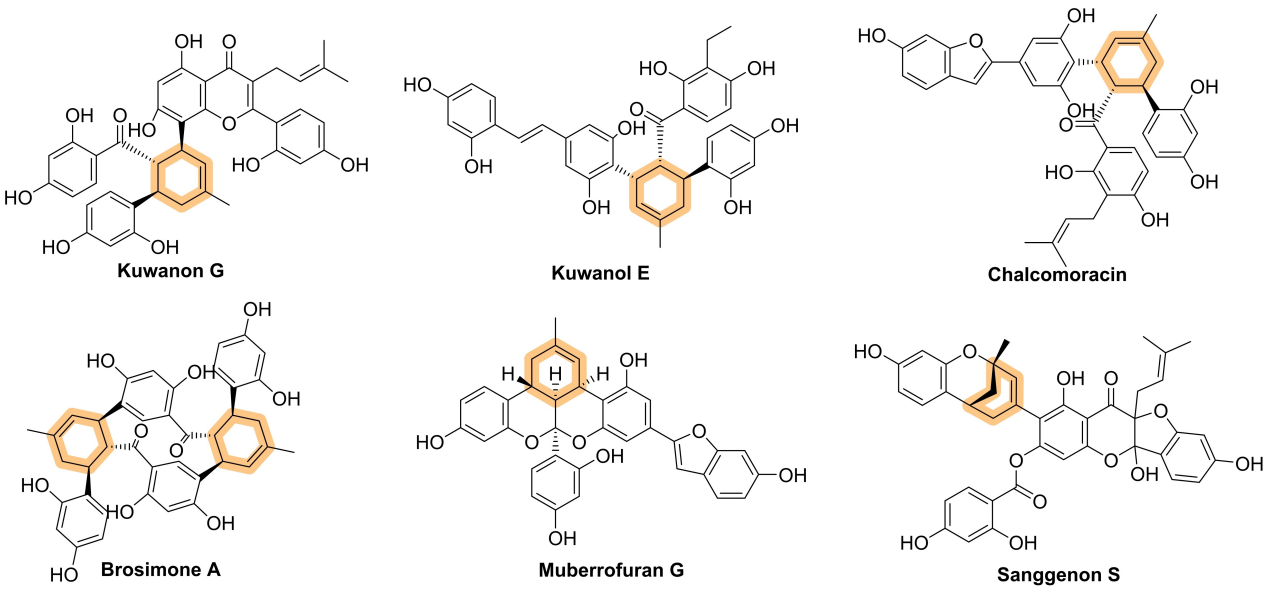
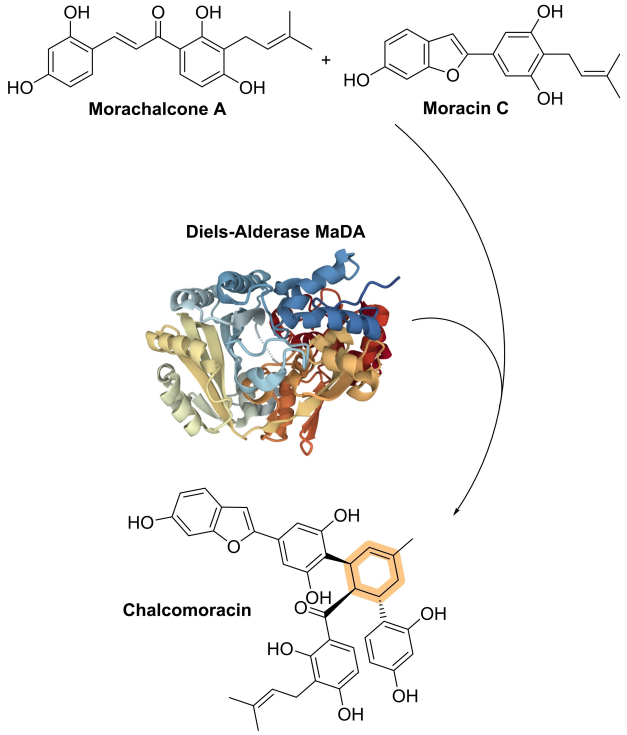


Figure 4. Mulberry Diels-Alder adducts of types I–IV. The six-membered ring obtained from a Diels-Alder reaction is portrayed in orange.



Scheme 8. Biosynthesis of chalcomoracin through Diels-Alderase catalysis. (Protein PBD ID: 6JQH).[61,88,89]

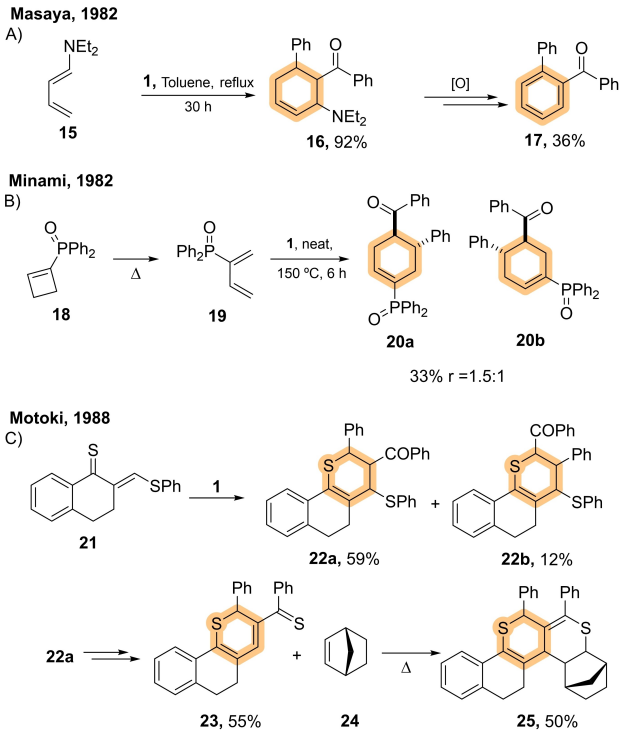
the familiarity of the authors with the state-of-the-art developments at a given point in time. The explanation of the historical advance of scientific knowledge can also help to identify the likely directions for future research on chalcones as versatile synthons for [4+2] cycloadditions. The compilation of the information herein reviewed reveals that chalcones not only can behave as dienophiles Diels-Alder Chalcone Inverse electron demand Catalysis Cycloaddition but also as heterodienes in [4+2] cycloadditions. This duality is presented in two sections. Most of the studies focused on developing stereoselective protocols in which chalcones were the selected reactants.

2.1. Chalcones as dienophiles

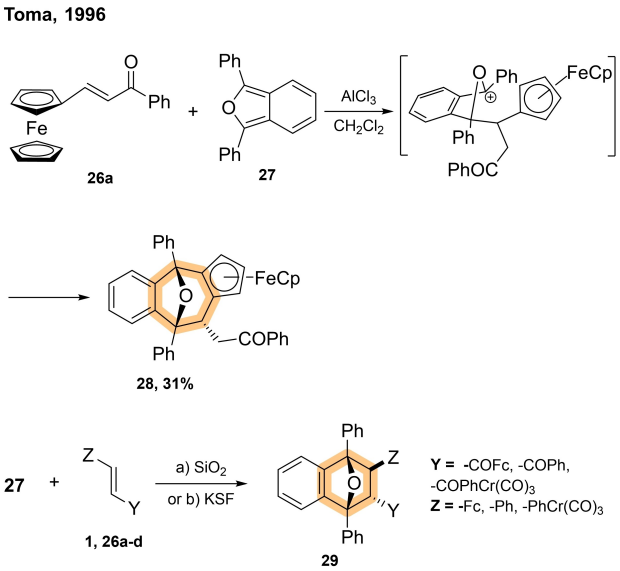
One of the first examples of chalcones used as dienophiles was a report on the synthesis of 2-substituted biphenyls. N,N-diethyl-1,3-butadienylamine (**15**) reacts with different β-substituted styrene compounds such as chalcone **1** to achieve DA reactions in good yields under thermal conditions. Surprisingly, the other regioisomer is not found as a byproduct of the reaction. Subsequent oxidation of the amine fraction and aromatization is an efficient method for the preparation of compounds **17** (Scheme 9A).[85] Chalcones are highly regioselective compared to other olefins, making them interesting substrates for DA reactions due to the simplification of adduct isolation.

Experiments were carried out in the 1980s with functionalized dienes (a 4π electron system) bearing amines and other functional groups. 1-Ciclobutenylphosphine oxide (**18**) proved to be efficient as a starting reactant for DA reactions. Thus, a thermal electrocyclic ring opening of **18** affords diene **19**, which undergoes cycloaddition with chalcone **1**. The reaction was replicated at different temperatures, finding no reaction at 100 °C and better results at higher temperatures (150 °C). As a dienophile, however, the chalcone is not as good as diethyl acrylate (86% yield) under these conditions. Although this methodology tended to generate a mixture of regioisomers **20a,b** with low selectivity (Scheme 9B), it successfully synthesized triphenylphosphine oxide derivatives.[86]

Heterodienes are exceptional reactants for the preparation of new six-membered heterocycles by DA cycloaddition.



Scheme 9. The first reports on chalcones in Diels-Alder reactions with functionalized dienes.



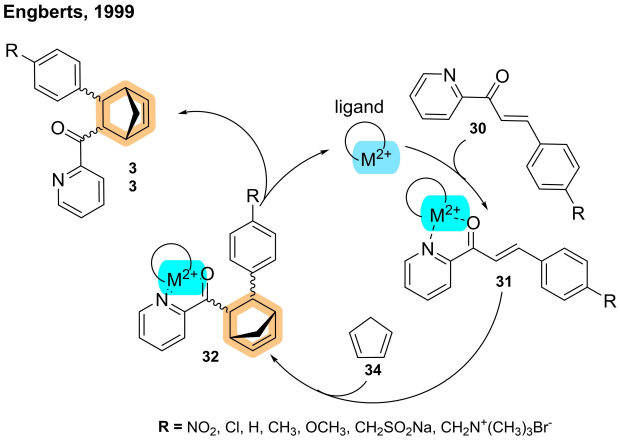
Scheme 10. Diels-Alder reaction involving chalcones bearing aromatic rings with a metal complex, carried out under different Lewis acid conditions.

Conjugated thioketones are a good example, as shown by the thermal reaction of thioketone **21** with chalcone **1**. The reaction proceeds with good yields and excellent regioselectivity for **22 a** and **22 b**. Further reaction with the major isomer **22 a** allows for a second DA reaction of the heterodiene **23** with norbornene to obtain compound **25** in good yield (Scheme 9C).[87] Thioketones are extraordinary nucleophiles, possibly indicating a stepwise reaction rather than a concerted mechanism, which would make this a formal [4 + 2] cycloaddition.

Substitution in the chalcone aromatic rings leads to improved reactivity under selected conditions, especially for the compounds synthesized with ferrocene and phenyltricarbonylchromium as aromatic moieties. Thus, the Lewis-acid-catalyzed reaction of chalcone **26 a** with isobenzofuran **27** undergoes a Michael addition followed by a Friedel-Crafts alkylation, delivering compound **28** as the major product. Further experimentation included solventless conditions in which the reactants were supported on SiO_2 or acidic montmorillonite clay KSF. Under both these conditions, a DA reaction occurs between **1**,**26 a**–**e** and **27** without Friedel-Crafts alkylation. For the preparation of **29**, better yields were generally provided by reactions mediated by SiO_2 versus KSF when chalcones contained ferrocene or chromium complexes. However, no substantial difference in yield was found for the more common chalcone (**1**). Also relevant was the generation of the *exo* isomer as a single product, a result confirmed by X-ray diffraction spectroscopy (Scheme 10).[90]

Chalcones are exceptional dienophiles due to their electron-deficient olefin moiety and their facile synthesis. They have been utilized to develop novel catalysts for DA reactions. At first, these catalysts were based on Cu(II) or Ni(II) coordinated with chiral ligands to increase the selectivity and water solubility of the products, something that was difficult with other Lewis acid catalysts at the time. Water solubility is important because water accelerates the rate of certain reactions, including DA cycloaddition, and is environmentally friendly (among other benefits).[91] One of the first successful attempts to accomplish a DA reaction with chalcones was with 1-(2-pyridiyl) chalcone **30** and cyclopentadiene **34**. The catalytic cycle is initiated by the coordination of the catalyst with the chalcone, followed by the DA reaction and the formation of intermediate **32**. Finally, the catalyst and the DA adduct **33** dissociate and the catalyst goes back into the cycle (Scheme 11).

The catalytic cycle generates four isomers, consisting of the *endo* (S,S) and (R,R) as well as the *exo* (S,S) and (R,R). Higher



Scheme 11. Catalytic cycle for the Lewis-acid-catalyzed Diels-Alder reaction in water.

yields were given by the *endo* isomers (>90%). Initially, diamino ligands were employed to enhance the enantioselectivity of the major isomer. However, the rate of formation of **31** diminished with Cu (II) and even more so with Ni(II) as the catalyst because each of these caused a very low binding energy. Alternatively, L-amino acids were able to make the catalysts more water-soluble. This change improved the enantiomeric excess (*ee*) with aromatic amino acids as ligands, especially L-tyrosine, N-methyl-L-tyrosine, N-methyl-*p*-methoxy-L-phenylalanine, and L-abrine at pH 4.6–5.2. Cu (II) was selected due to the greater stability it showed in the formation of **31**. Thus, **33** could be obtained with an *ee* > 67% for the *endo* isomer when R=H.

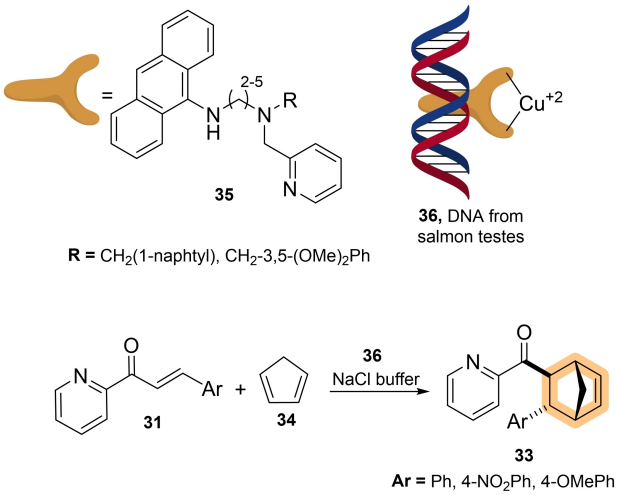
The substituents in chalcone **30** had no effect on the reaction yield or the *ee*, yet the solvent displayed an interesting variation. The reaction of L-abrine in water led to 74% *ee* in 3 days. In contrast, other common solvents for Lewis-acid-catalyzed DA reactions, including chloroform, dichloromethane (DCM), and ethanol, resulted in an *ee* that was still <44% after five days.[92]

Chiral biocatalysis used to be almost exclusively carried out with enzymes until the aforementioned report. By demonstrating good enantioselectivity with biomolecules such as amino acids, the study initiated the search for other molecules frequently found in living organisms. Although DNA is an excellent example of chirality in nature, pure DNA does not provide good results. To overcome this obstacle, DNA was prepared with a fixed sequence of nucleotides aimed at enhancing functionality. Since it efficiently transferred chirality, synthetic DNA-based catalysis of DA reactions was born. In 2005, the interaction of a copper (II) complex with a DNA construct, derived from salmon testes, created a deoxyribozyme (DNAzyme). These synthetic enzymes can catalyze reactions that require high enantioselectivity.

Rather than displacing the ligand, DNA interacts with the complex to transfer chirality to the active site of the catalyst.[93,94] For instance, ligand **35** promotes the *in situ* formation of the DNAzyme **36**, which is utilized for the DA reaction between chalcones **31** and diene **34** (Scheme 12). The reaction is analogous to the catalytic cycle illustrated in Scheme 11, but the DNA template is the chiral inductor. The reaction proceeded with yields of over 80% and *endo* selectivity above 90%. The *endo* selectivity was better when R=1-methylnaphtyl. Apparently, the spacer produced improved enantioselectivity. The shorter chain length of the *endo* versus *exo* isomer led to a better *ee* (33–48% *vs.* 16–37%, respectively). Contrarily, the *ee* was greater for the *exo* than *endo* isomer (90–80% vs. 53–34%, respectively) when R=1-methyl-3,5-dimethoxy benzene. The use of different Ar substituents in chalcones had no significant effect on the results.[95] As another approach, a DA reaction was performed between chalcone **31** and diene **34** with ten distinct oligomers in the presence of copper nitrate, attaining yields over 95% and an *ee* >96%. The 3′-GTGGCAT-FAFTACGA sequence turned out to be the most effective.[96]

With the discovery of the ability of ligands to bind to biological compounds and the observation of transferred chirality, additional molecules such as proteins became extremely interesting for enantioselective hybrid catalysis.[97]

Roelfes, 2005



Scheme 12. Novel copper DNAzyme for the enantioselective catalysis of Diels-Alder reactions.

Accordingly, a study in 2006 employed a water-soluble amphiphilic phthalocyanine-copper complex **37** (Figure 5A) with a set of serum albumin proteins as binding agents. Bovine serum albumin (BSA) was the best binding agent for the DA reaction between chalcone **31** (R=H) and diene **34** (Figure 5B). The reaction was carried out in a formate buffer solution at 3 °C to give a 74% yield. The *endo/exo* selectivity was 96:4. A very similar selectivity (95:5) was detected when the reaction was

Reetz, 2006

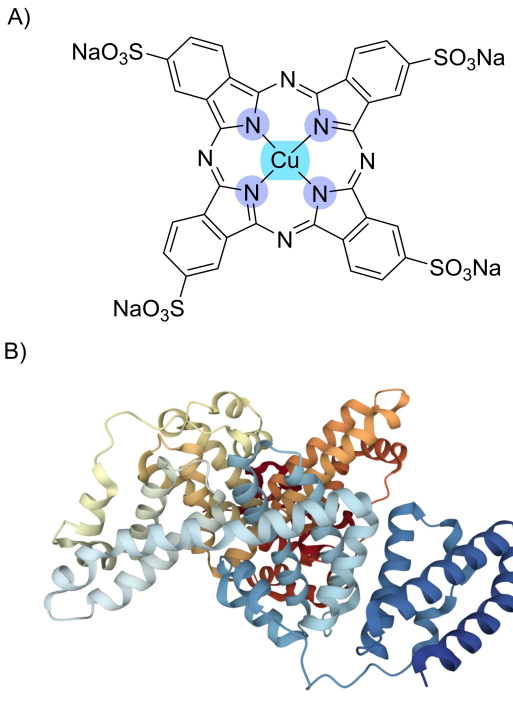


Figure 5. A) Amphiphilic phthalocyanine-copper complex. B) 3D representation of BSA (Protein PDB ID: 4F5S).[88,89,100]

performed only with complex **37**, indicating that BSA had no impact on this parameter. Nevertheless, BSA did indeed increase the *ee* to 93%, evidencing the successful transfer of chirality. The application of other hybrid complexes such as BSA-Cu$(NO)_3$ and BSA-Cu$(OTf)_2$ led to racemic mixtures.

Chalcones with distinct substituents each provided very similar results (with little variation) in experiments with human, porcine, rabbit, sheep, and chicken serum albumin. Under optimized conditions, a substantial *ee* was only observed with HSA, PSA, and SSA, but in none of these cases was it higher than that found for BSA. The catalytic cycle might be different from the one previously discussed (Scheme 11), as complex **37** has a particular configuration. Indeed, the authors propose the mono-coordination of copper with the carbonyl function.[98] These artificial Diels-Alderases later proved to be effective, such as the one based on the transmembrane protein FhuA.[99]

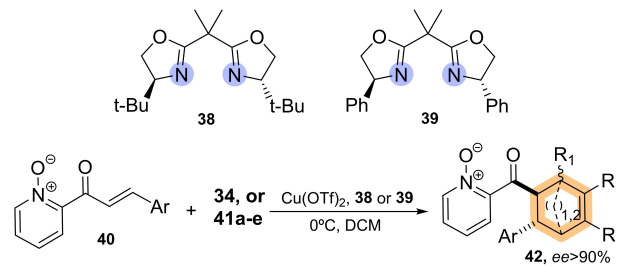
Bisoxazolinones (BOX), when forming metal complexes as bidentate ligands, have been successful in various enantioselective reactions.[101] Hence, they were evaluated in a DA reaction between chalcone **31** and diene **34**, with either a Cu (II) or Zn (II) triflate and BOX **38** or **39**. The outcome was low diastereo- and enantioselectivity (41–11%) for the *endo* and *exo* isomers. In additional reactions carried out with BOX ligands, the N-oxides of the pyridyl chalcones (**40**) showed very high selectivity for the *endo* adduct (98–92%), with an *ee* $>$86% for both diastereoisomers of **42**. The reaction was faster in DCM at 0 °C than at −40 °C, but there was no effect on selectivity. Meanwhile, ligand **38** furnished the inverse *ee* in relation to **39**. Finally, these results were extended to other dienes, which also afforded the *endo* isomer as the major product and an *ee* $>$90% (Scheme 13). N-pyridyl oxide was easily reduced with aqueous ammonium chloride. Therefore, the enantioselective DA reaction was accomplished with synthetic chiral organic ligands.[102]

The bidentate ligands **43, 44, 45**, and **46** in Cu (II) complexes served as DNAzymes, evidenced by their capacity to efficiently bind a DNA oligomer from salmon testes. Compound **43** not only improved the enantioselectivity of the DA reaction between pyridyl chalcone **31** (Ar=Ph) and diene **34** but also generated a 58-fold increase in the reaction rate. In contrast, the increase exhibited by the other ligands was ~2-fold. The best findings were in relation to the different fractions of DNA oligonucleotides tested, with the double stranded fractions demonstrating the greatest enantioselectivity. A larger number of consecutive guanine fractions at the center of the oligonucleotide gave a greater rate and improved selectivity of the reaction. The G-trimer **47** was the most effective of the stDNA fractions, displaying a 100-fold increase in the reaction rate and 99% *ee* for the *endo* adduct (Figure 6).[103]

Another approach for achieving [4+2] cycloadditions is to initiate the DA reaction with a single-electron transfer (SET) process. For this purpose, 2′-hydroxychalcone **48** was essential due to the electronic properties of these compounds. Thus, chalcone **48** could react with diene **41b** when catalyzed by a mixture of CoI_2 /Bu_4NBH_4/1,10-phenantroline/ZnI_2 in a 10:10:10:60 mol proportion. The corresponding cycloadduct was obtained in 95% yield. With other dienes, the yield of the DA adduct varied in accordance with its substituents. Even asymmetric dienes produced a single regioisomer with *endo* selectivity. Whereas the yields were high in the presence of the 2′-hydroxyphenyl moiety, they were less than 55% without it, thus proving its importance. Adding electron donating groups on the chalcone 2′-hydroxyphenyl ring required a 20/20/40/120 mol percentage proportion to give yields from 33–84%. The proposed mechanism indicates coordination of ZnI_2 to the hydroxy and carbonyl groups of chalcone **48**. Subsequently, either Co(I) or BH_4^- acts as an electron donor to provide radical anion **49** through SET. Afterwards, the reaction with diene **50** delivers a stabilized allylic radical **51b**, which cyclizes to form the ketyl radical **52**. Loss of ZnI_2 furnishes **53** and **49** to repeat the cycle (Scheme 14A).[104]

In 2008, some type **1** chalcones were used to synthesize DA adduct **54**, which then underwent a ring opening metathesis polymerization (ROMP) to furnish polymer **56**. The study tested distinct substituents on the aromatic rings of chalcones. The resulting compounds participated in DA reactions with cyclopentadiene (**34**) under microwave irradiation and catalytic amounts of $AlCl_3$. Yields for the reaction were moderate and the

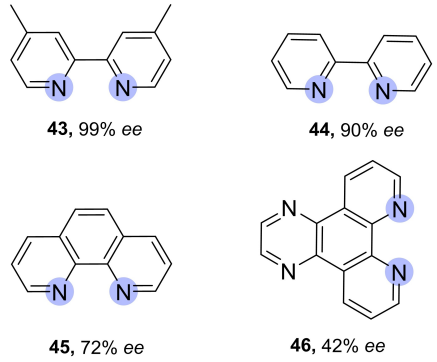
Pedro, 2007



41a = cyclohexadiene; **41b** = 2,3-dimethylbutadiene; **41c** = 2-methylbutadiene;
41d = 1-phenyl-butadiene
Ar = Ph, 4-OMePh, 4-NO_2Ph

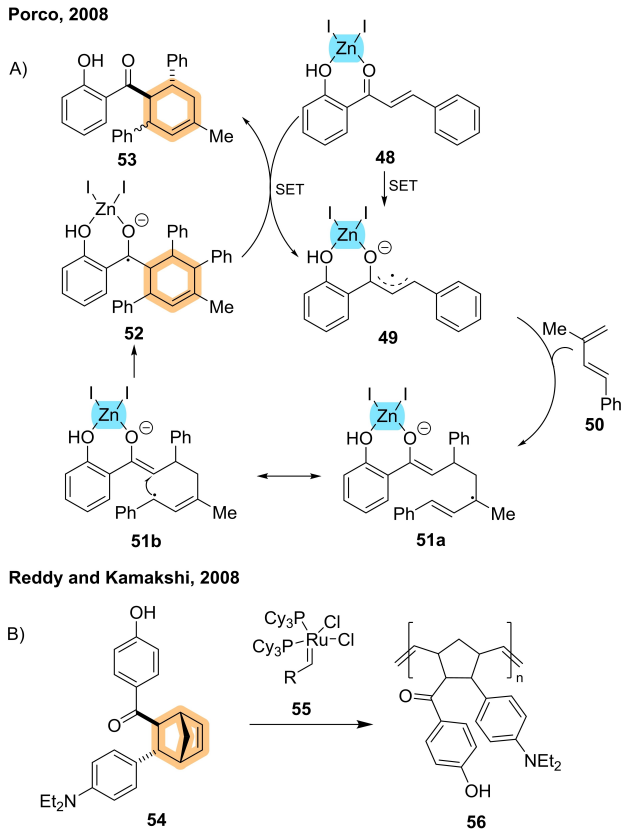
Scheme 13. Enantioselective Diels-Alder reaction with selected chalcones, catalyzed with distinct Cu(II) bisoxazolinone complexes.

Roelfes, 2008



Oligomer= d(TCAGGGCCCTGA)$_2$
47, 99.4% *ee*

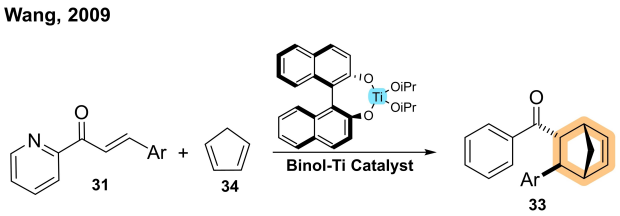
Figure 6. Bidentate ligands employed to form DNAzymes, which were used in enantioselective Diels-Alder reactions of chalcones.



Scheme 14. A) Mechanism for the Diels-Alder reaction initiated by single-electron transfer. B) ROMP of the Diels-Alder adducts produced from a chalcone.

endo adduct was usually the major isomer. However, ROMP was only observed with the *exo* isomer due to steric interactions of the growing polymer with the incoming monomer. Fortunately, DA adduct **54** displayed *exo* isomer selectivity (80:20), probably because of the formation of metal complexes with oxygen and nitrogen atoms on the chalcone. Compound **54** was then subjected to Grubb's catalyst **55** to afford polymer **56** (Scheme 14B), which exhibited intensive emission at 364 and 435 nm. This double fluorescence behavior stems from the different oxidation states of the two aromatic rings, serving as a special example of the fluorescent properties of chalcones. Hence, polymer **56** would be an interesting probe for the investigation of microenvironments.[105]

In 2009, the binaphthol-titanium complex prepared from (S)-Binol and $Ti(OiPr)_4$ (2:1) proved to be an excellent catalyst for generating DA adducts from chalcones **31** and dienes **34** (Scheme 15). Reaction conditions were optimized with a reaction temperature of 30 °C and HMPA as the base in acetone. In general, the *endo* isomer was obtained in ratios >80%, while the *ee* for most of the adducts was moderate (79–40%). Substituents at the 2-, 3-, and 4-positions had no discernible effect, except when the 2-aryl position contained an electron donating group or an electron withdrawing group in the 3-aryl position. The former case gave a better *ee* (>85%) and the latter a lower yield (e.g., the 11% yield found with Ar = 3-NO_2Ph).[106]

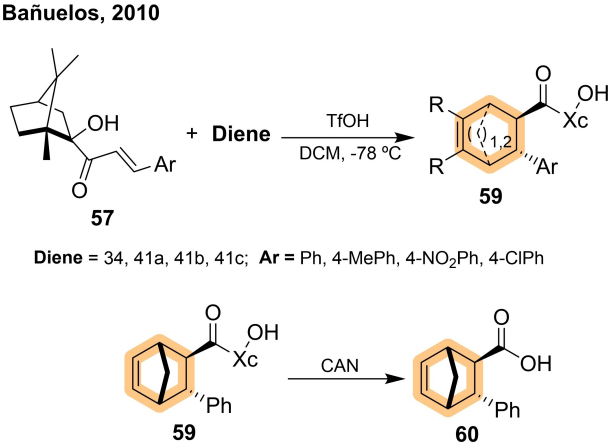


Ar = Ph, 4-NO_2Ph, 4-OMePh, 4-MePh, 4-ClPh, 2-ClPh, 3-ClPh, 3-NO_2Ph, 2-MePh, 2-NO_2Ph,2-BrPh, 2-OMePh, 1-Naphthyl, 2-Furanyl

Scheme 15. Enantioselective Diels-Alder reaction of chalcones catalyzed by the Binol-Ti complex.

Although chirality is normally induced by the catalyst, the substitution of the chalcone aromatic ring by a chiral inductor can also effectively promote DA cycloaddition, leading to high diastereo- and enantioselectivity. Thus, chalcones **57** with the 1(R)-(+)-hydroxycamphor moiety (Xc) were applied to enantioselective DA reactions with an achiral catalyst. Brønsted acids such as triflic acid (TfOH) and trifluoroacetic acid (TFA), for instance, provided great diastereomeric selectivity and excellent yields. Optimized conditions included the use of TfOH in DCM at −78 °C. The scope of the reaction encompassed cyclic and open-chain dienes. Furthermore, the *endo/exo* ratio was in all cases ≥150:1 and the *dr* ≥98:2 for compounds **59**. The camphor chalcone transfers chirality with outstanding results, and then the removal of the chiral inductor by oxidation produces carboxylic acids **60** with an *ee* >98% and yields over 90% (Scheme 16).[107]

As previously discussed, silver nanoparticles (AgNP) are able to promote SET-initiated DA reactions with 2'-hydroxychalcones **53** (see Scheme 14A). Thus, AgNPs generated from the combination of $AgBF_4$ and Bu_4NBH_4 achieved quantitative yields from the DA annulation between hydroxychalcone **53** and diene **61**, resulting in an *endo/exo* ratio of 78:22 for compound **62**. Subsequently, an attempt was made to develop a reusable catalyst by supporting the AgNPs in silica gel under solvent-free conditions. Even though **62** was furnished with lower *endo* selectivity (66:34), the yields were excellent (95%). The



Diene = 34, 41a, 41b, 41c; **Ar =** Ph, 4-MePh, 4-NO_2Ph, 4-ClPh

Scheme 16. Camphor chalcones serve as chiral inductors for stereoselective Diels-Alder reactions and then are oxidized to carboxylic acids.

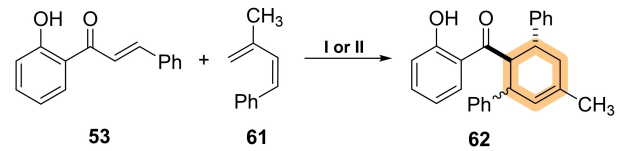
recovered catalyst was still in good condition after being stored for months. After three cycles, the yield of **62** had only decreased from 95 to 85% (Scheme 17).[108] Despite the low diastereoselectivity, the ability to recycle the catalyst is a remarkable advantage of this methodology.

As previously mentioned, chalcone cycloaddition was improved by including Cu(II) complexes that can bind to biological macromolecules. Hence, scientists were encouraged to focus on modifying the sequence proteins to enhance their binding strength. Accordingly, DA cycloaddition of chalcone **31** and diene **34** (see Scheme 15) was successfully catalyzed with the synthase subunit of the imidazole glycerol phosphate enzyme from *Thermotoga maritima* (tHisF). The change in this enzyme began by inserting a 2-His-1-carboxylate motif at the top, followed by the introduction of a Cys9Ala mutation at the ninth amino acid position to render the tHisF mutant Cys9Ala/Leu50His/Ile52His. The modified protein catalyzed the synthesis of cycloadduct **33** with an *ee* of 35% for the *endo* adduct (*dr* = 14:1), compared to the *ee* of 3% for normal tHisF. Apparently, the introduction of histidine on other positions led to competitive binding sites, thus completely changing the catalyzed reaction. Other mutants were prepared by substituting these sites with different amino acids: HHD-4xala, NC-4xala, and HHA-4xala. When utilizing $CuSO_4$ as the copper (II) source, the Cu(II)/HHD-4xala mutant metalloenzyme provided a better *ee* (46%) with *endo* selectivity (13:1). In contrast, a maximum *ee* of 4% and lower yields were generated with the remaining mutants (Table 1).[109] The study opened a new line of investigation, that of exploring which modifications to enzymes are able to improve the binding of Cu (II) and therefore allow for the formation of metalloenzymes capable of acting as stereoselective catalysts.

Since the pioneering DNA-based asymmetric catalysis reported by Roelfes, there has been great interest in the search for a thermostable binding macromolecule. In 2010, synthetic oligomers denominated h-Tel and c-kit were used by Roe et al. for the DA reaction between pyridine chalcones **31** and cyclopentadiene (**34**) to synthesize **33** (see Scheme 15). Both oligomers were able to bind Cu (II) and lead the reaction to good yields and a dr >90:10. The *ee* was higher when employing h-Tel (up to 51%) in combination with analogs of the pyridine chalcones.[110] The importance of the study was the observation of stronger binding with Cu (II) in the event that the oligomers had a G-quadruplex versus duplex arrangement. The G-quadruplex arrangement has the possibility of varying the folding topology and thus of offering structural diversity and greater opportunities (Figure 7A). In 2012, Wang *et al.* utilized human telomeric G-quadruplex DNA as a binding agent, finding similar yield, stereoselectivity, and enantioselectivity (Figure 7B). Additionally, the absolute configuration of the adducts was reversed with the parallel versus antiparallel fragment.[111]

The following year, DNA was supported on silica and functionalized with ammonium salts, which could then interact with the phosphate fractions of DNA (Figure 8). This silica-supported **st-DNA/s1** structure was able to easily bind Cu (II) and catalyze DA reactions of chalcones **31** and cyclopentadiene (**34**). Supported DNA achieved 99% conversion, 99:1 *endo* selectivity, and 94% *ee*. Moreover, the catalyst was recovered 10 times, observing a maximum decrease in the *ee* to 85%, with conversion >97%.[112] Years later, DNA-Cu(II) was supported on $Si(OEt)_4$ with $Si(OEt)_3$-C_3H_6-$N(Me)_3^+$ to deliver quantitative yields and 99% *ee* with the same substrates.[113]

Cong, 2010



Conditions: **I,** AgNP,DCM 25 °C, 99% 78:22
II, SiO_2-AgNP 40 °C, 95% 66:34

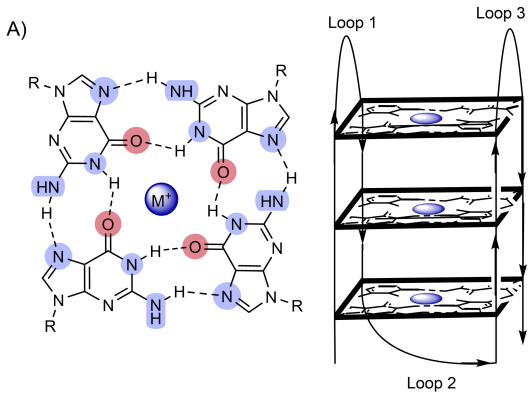
Recycle: 1st, 90%; 2nd, 88%; 3rd, 85%.

Scheme 17. Silica-supported AgNPs used for a Diels-Alder reaction of chalcones initiated by single-electron transfer.

Table 1. Artificial metalloenzymes used for a stereoselective Diels-Alder reaction.[a] (**Podtetenieff, 2010**)

Catalyst	Conversion (%)	ee (%)	Endo/Exo
CuII/HHD-4xala	73	46	13:1
CuII/NC-4xala	61	5	9:1
CuIIHHA-4xala	56	4	8:1

[a] The reaction was performed between chalcone **31** and cyclopentadiene (**34**) 1:5.



B)

Roe, 2010

h-Tel: 5'-AGGTTAGGTTAGGTTAGG
c-kit: 5'-AGGAGGGCGCTGGGAGGGAGGG

Wang, 2012

Antiparallel	Parallel
ODN-1: 5'-$G_3(TTAG_3)_3$	ODN-5: 5'-$G_3(TTAG_3)_3$
ODN-2: 5'-$G_3(ATAG_3)_3$	ODN-6: 5'-$G_3(TTAG_3)_3$
ODN-3 5'-$G_3(TATG_3)_3$	ODN-7: 5'-$G_3(TTAG_3)_3$
ODN-4 5'-$G_3(TTTG_3)_3$	ODN-8: 5'-$G_3(TTAG_3)_3$

Figure 7. A) An example of the G-quadruplex DNA arrangement. B) Oligomers employed in the Diels-Alder reaction of chalcones **31** involving metalloenzymes.

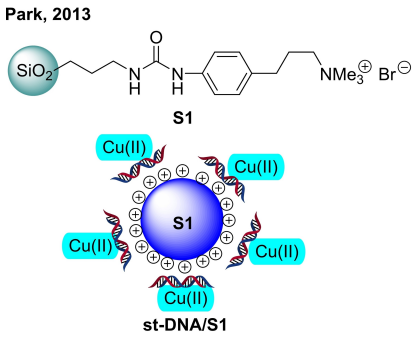
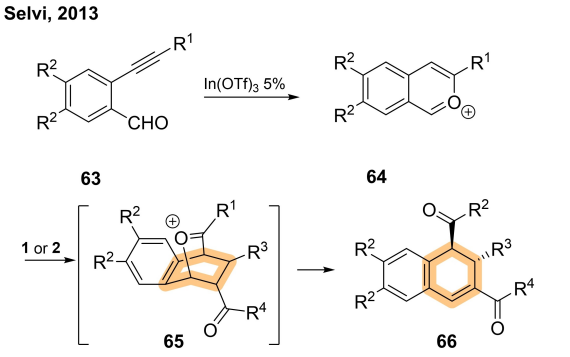


Figure 8. Structure of the silica-supported DNA catalyst used in the Diels-Alder reaction of chalcones **31**.

Oxa-dienes **64** are typically formed with *o*-alkenylarene aldehydes **63** and a metal-halogen salt. These compounds behave as electron-deficient dienes in reactions with electron-rich dienophiles. However, generating the oxa-diene with indium triflate allowed for DA cycloaddition with chalcones, which are electron-deficient dienophiles. Such reactivity was without precedent. The inclusion of chalcone **1** or bis-chalcone **2** gave intermediate **65**, the stabilization of which was tied to the elimination of the oxonium ion to afford the corresponding ketone **66** (Scheme 18). The products were delivered in moderate yields and the *trans* isomer was the only one isolated.[114] Changing the reactivity of the diene turned out to be a creative way to accomplish uncommon cycloadditions, although the role of the triflate group was not explained.

Asymmetric DA reactions are easily carried out with Lewis acid catalysts, especially the metal-based acids because of their capacity to harness the chirality of enantiopure ligands. It is possible to obtain interesting results with silicon-sulfur-stabilized cations, which are a group of Lewis acids capable of serving as chiral inductors. Chiral silicon-sulfur compounds bearing a binaphthyl backbone, developed over the course of 4 years (Figure 9), were able to catalyze a DA reaction between analogs of chalcone **1** and cyclohexadiene. In the first effort, there were low yields (< 60%) and an *ee* below that found with previous methods (< 7%). However, the *dr* was high enough to



R¹= Ph, 4-OMePh, nBu; **R²=** OMe, H; **R³=** Ph, 4-OMePh, 4-ClPh, 3,4-OMePh, 4-NO_2Ph, 4-MePh; **R⁴=** Ph, 4-OMePh, 4-BrPh, CH_2=CHPh

Scheme 18. Diels-Alder reaction of chalcones with indium triflate as the catalyst.

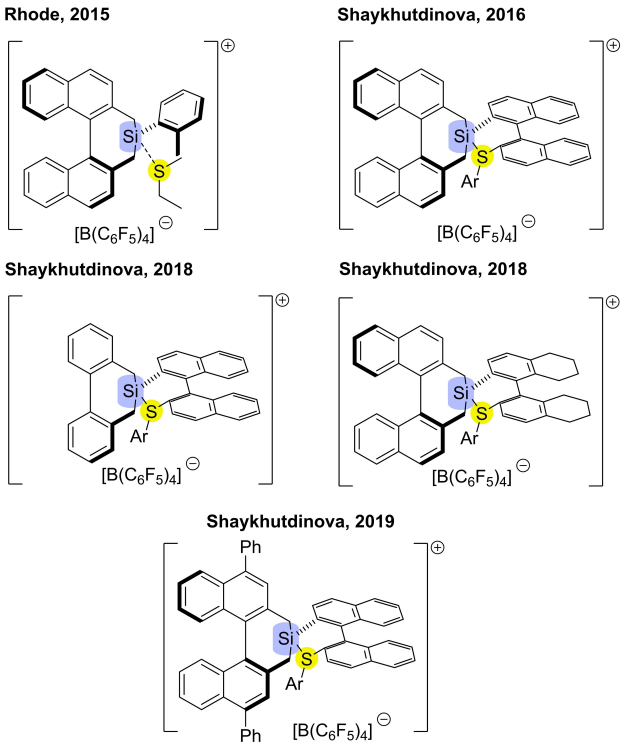


Figure 9. Structure of the silicon-sulfur-stabilized cations used as catalysts for the stereoselective Diels-Alder reaction of chalcones.

make this catalyst viable, as the *endo* adduct was furnished in a 95:1 ratio.[115] The incorporation of aryl groups at the sulfur moiety rendered a similar *dr* > 98:2, while yields reached over 60%. The *ee* varied from 7–59% with the different chalcone substituents.[116] The subsequent study on chiral silicon-sulfur compounds showed that the binaphtyl silepine backbone was not necessary, evidenced by the same level of *ee* with or without it. Whereas an *ortho-ortho* substitution at the aryl group decreased the *ee*, a catalyst with a sulfur H_8-naphtyl backbone provided a small (2–3%) increase. In accordance with prior reports, a marginal increment in *ee* was achieved with a 4,4'-diphenyl binaphtyl silepine backbone.[117–119]

At that time, the use of biological macromolecules as chiral inductors was the best way to attain high enantioselectivity in DA reactions with chalcones. Curcubit[8]uril (**67**) represents a unique option for the catalysis of DA reactions. It is able to bind Cu(II) cations and its closed structure can function as a nanoreactor (Figure 10). The DA reaction between chalcones **31** and diene **34** was accelerated up to 9.5 times with Cu (II), amino acids as ligands, and a small amount of **67**. The reaction with (versus without) **67** yielded an improved *dr* and *ee*. The authors explain that the complex is "trapped" at the center of the macromolecule, allowing the reaction to occur inside the established nanoreactor. The aromatic amino acids afforded the best outcome, with quantitative yields, the generation of the *endo* adduct at 97%, and 97% *ee*.[120]

Aluminum is also known to function as a Lewis acid in DA reactions. Asymmetric catalysis was carried out with bisiminoaryl NCN pincer ligands to synthesize complexes **68** and **69**

Zheng, 2015

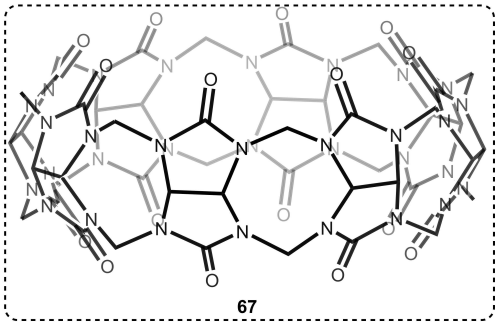


Figure 10. Structure of Curcubit[8]uril, a molecule that can bind cations to form a nanoreactor for catalysis of Diels-Alder reactions.

(Figure 11). Reaction of chalcones **1** with 2,3-dimethylbutadiene and 1,3-ciclohexadiene produced the cycloaddition adduct in quantitative yields and a *dr* >99% with complex **69**. No

Liu, 2017

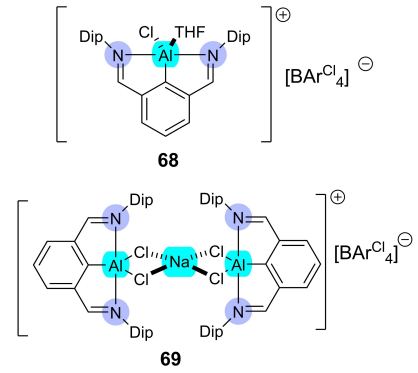
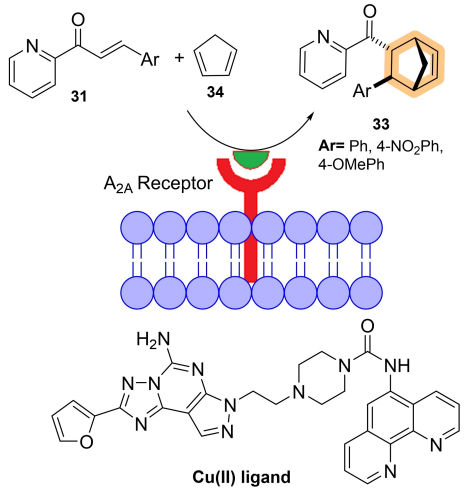


Figure 11. Aluminum-based complexes used as Lewis acid catalysts in Diels-Alder reactions of chalcones.

Ghattas, 2018



Scheme 19. Diels-Alder reaction catalyzed between human embryonic kidney cell receptors and a copper complex.

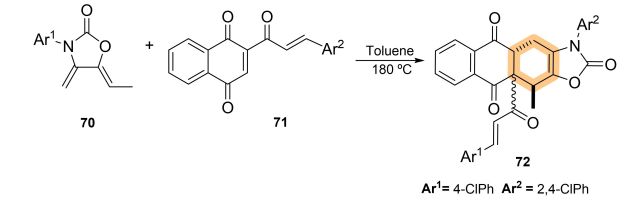
difference was detected between the *in situ* formation of the aluminum complex and its pre-synthesis.[121]

There was an interesting development in DA reactions with chalcones in 2018 that may lead to therapeutic applications. Enantioselective reactions were catalyzed by human cell receptors, utilizing Cu (II) as an antagonist. As a consequence, chalcones **31** generated the corresponding cycloadduct with cyclopentadiene when human embryonic kidney (HEK) cells, expressing adenosine receptors A_{2a}, were bound to a Cu (II) phenanthroline complex (Scheme 19). Under these conditions, reaction yields were low (<42%), but the *endo* adduct was obtained with 80% selectivity and an *ee* <28%.[122] This represents a preliminary effort to develop catalysts on the human cell surface, thus opening a new field for the application of metalloenzymes.

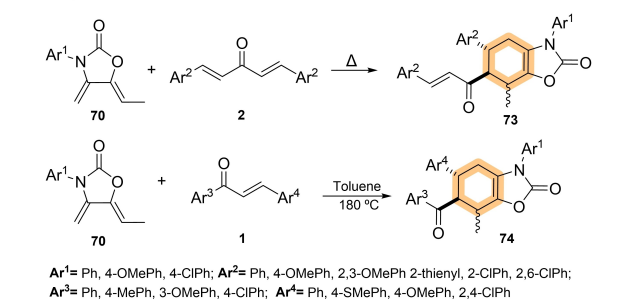
The expected behavior is sometimes not observed when another olefin is in the chalcone. For example, the development of novel naphthoquinone chalcones **71** and their use as dienophiles led to a new type of chalcone **72** through DA cycloaddition. Moreover, the reaction of chalcones with *exo*-heterocyclic dienes **70** gave rise to cycloaddition at the naphthalene moiety instead of the chalcone. These chalcone derivatives are relevant because of their naphthoquinone-benzoxazolone ring. The reaction yield was over 80% under conditions of conventional heating, with the *endo* adduct as the major diastereomer.[123] In yet another study, the reaction of chalcones **1** and bis-chalcones **2** provided DA adducts **73**/**74** with high regio- and stereoselectivity. *Exo* adduct preference existed with polar solvents and *endo* adduct preference with non-polar solvents. Greater temperatures furnished better yields and improved selectivity for the *endo/exo* mixture, although selectivity was affected by the Ar substituents (Scheme 20), especially at the *ortho* position.[124]

Nonmetallic phosphonium-stabilized cations have been employed in different reactions with good results. Chalcones **1**

Mastachi, 2018



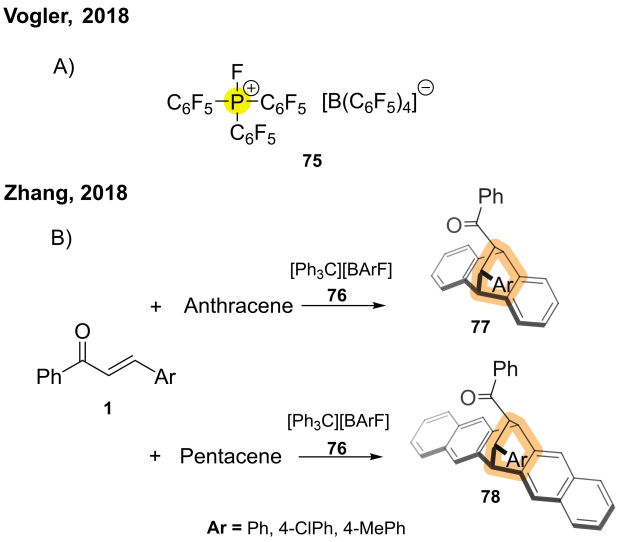
Mastachi, 2019



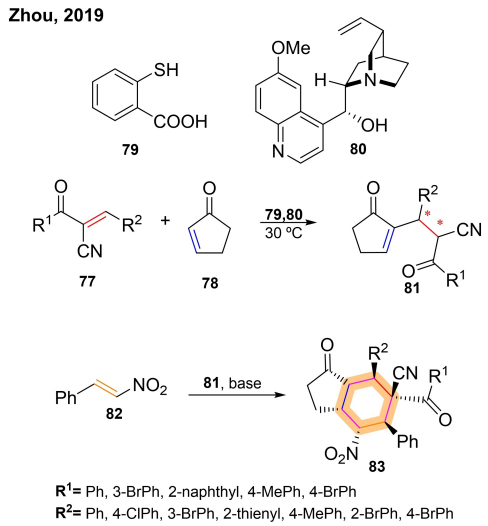
Scheme 20. Diels-Alder reactions of chalcones and bischalcones with exo-heterocyclic dienes.

and 1,3-ciclohexadiene underwent a DA reaction, rendering 100% conversion, yields above 90%, and *endo* selectivity >95% under optimized conditions, which included catalyst **75** (Scheme 21A).[125] Another nonmetallic Lewis-acid-stabilized cation, carbocation **76**, was instrumental for the reaction between chalcones **1** and anthracene/pentacene, affording cycloadducts **77** and **78** in good yields (>80%) (Scheme 21B).[126] This catalyst offers an interesting alternative for developing complex compounds with chalcones. Mechanistic studies are under way to explain the activation of the dienophile.

The α-substituted chalcones can also be a part of multicomponent [4+2] annulations with high stereo- and regioselectivity. For instance, a stepwise multicomponent cycloaddition was performed with cyanochalcones **77**, utilizing thiol carboxylates stabilized by chiral amines. This reaction requires cyano chalcones to accomplish the addition to the electron-deficient



Scheme 21. Phosphorus-stabilized cations used in Diels-Alder reactions of chalcones with fused aromatic compounds.



Scheme 22. Multicomponent [4+2] cycloaddition of chalcones catalyzed by a thiol-carboxylate stabilized with a chiral amine.

olefin **82** and carry out the annulation with great selectivity. The best results were found with thiol **79** and amine **80**, which generated yields >70% and an *ee* >90% (Scheme 22). Further functional group transformations were performed as well, including the reduction of the nitro group to an amine.[127] This reaction is important because of the formation of six chiral centers with excellent selectivity.

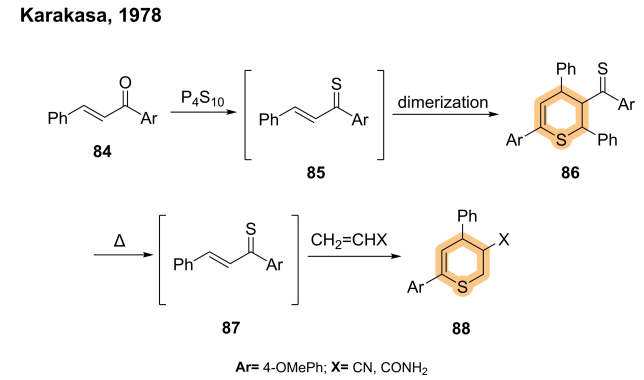
The examples herein discussed demonstrate the versatility of chalcones containing distinct substrates when they act as dienophiles in DA reactions. Since such reactions occur in nature, and the compounds are readily obtainable by synthesis or extraction, scientists have been able to develop novel catalysts capable in most cases of providing high regio-, diastereo-, and enantioselectivity. These developments are currently being applied to additional dienophiles not as readily available as chalcones but important for the synthesis of other novel compounds that require high stereoselectivity.

Although the total synthesis of natural compounds is not covered in the present review, many of the procedures described have been utilized to prepare natural DA adducts and analogs.[128–136]

2.2. Chalcones as dienes

The reports on chalcones as dienes in DA reactions, though scarce, have shown another advantage of these compounds as building blocks. In this role, chalcones undergo hetero-Diels-Alder reactions (HDA) with an inverse-electron-demand addition. The diene tends to be equally or less electron rich than the dienophile, accomplished by varying the substituents of both these molecules. Moreover, catalysts can be used to lower the LUMO of dienes or raise the HOMO of dienophiles. Indeed, some catalyst are capable of doing both simultaneously.[137] The first study involved the transformation of chalcone **84** to thiochalcone **85** with phosphorous pentasulfide. The product is very unstable in the monomeric form and dimerizes through an HDA cycloaddition by acting as both diene and dienophile. In 1978, Karakasi and Motoki[138] described the preparation of thiochalcone dimers **86**, which they managed to decompose through thermolysis to trap the monomer. Acrylonitrile or acrylamide were added as the dienophile to furnish DA product **88** (Scheme 23). The dimer was formed between equally electron-rich molecules, while the addition of the electron-deficient dienophile led to a normal-electron-demand HDA reaction.

Whereas thiochalcones are very unstable as monomers, selenochalcones **89** are better suited for DA reactions as they dimerize at a slower rate to give the cyclic diselenide **93**. Generally, the carbon-selenium π-bond is an exceptional dienophile component. Ming Li *et al.* synthesized selenochalcones by the reaction of chalcone **1** with *bis*(dimethylaluminum) selenide and employed it as a diene in HDA reactions. They found that its behavior as a diene or dienophile depends on the trapping agent. In case the agent is cyclopentadiene **32**, the reaction takes place within the C–Se bond to deliver **90**. If it is norbornadiene **91**, contrarily, the



Scheme 23. Hetero-Diels-Alder reaction of thiochalcone monomers.

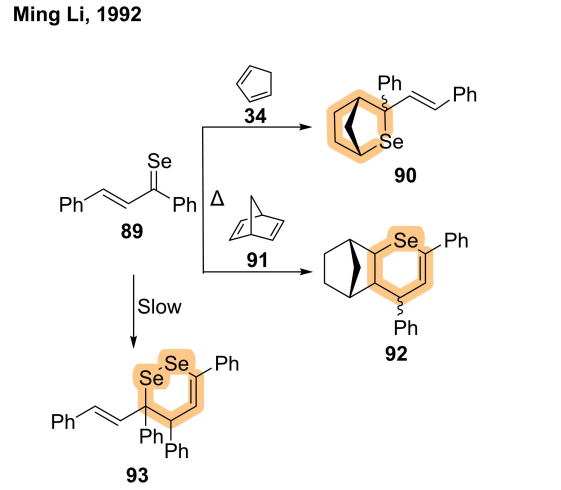
selenochalcone behaves as a diene and compound **92** is afforded with *endo* selectivity (Scheme 24).[139]

In addition to modifying the chalcone with sulfur or selenium to make it a diene or a dienophile, it is also possible to change its nature from a dienophile to a heterodiene. Ortiz *et al.* showed this by performing a series of [4+2] cycloadditions with a chiral cyclic ketene acetal, which is an electron-rich dienophile. The purpose was to demonstrate facial selectivity in the construction of spirocyclic diastereoisomers. Chalcone **1** reacted with the electron-rich dienophile **94** to give HDA adducts **95** (Scheme 25). The diastereomeric ratios were **a**/**b**:43/37 and **c**/**d**:14/6, evidencing a predominant approach from the "bottom" face of the dienophile in a 4:1 ratio. The computational studies concluded that the selectivity was consistent with the most stable calculated transition state.[140]

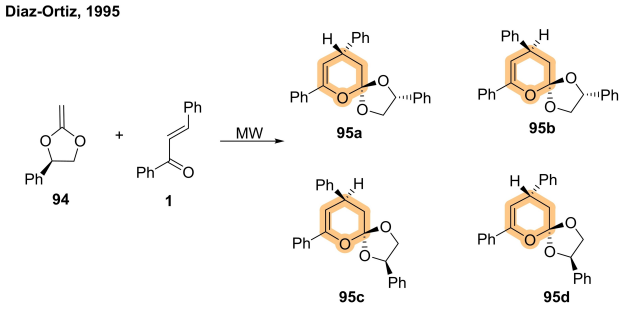
Substitution with electron withdrawing groups at the α- or β-carbon is another effective way to prepare a chalcone for HDA reactions with electron-rich dienophiles. Bogdanowicz and Palaz reported the efficient synthesis of polyfunctionalized 3,4-dihydro-2*H*-pyrans. The condensation between ketones **96** and benzaldehyde derivatives **97** leads to the formation of α-substituted chalcones **98**. The introduction of cyano, ethoxycarbonyl, or sulfur-based groups at the α-position induces intramolecular cycloaddition to deliver pyrans **99** (Scheme 26),[141,142] which provides a mixture of annulated *cis*/*trans* adducts. The *cis* isomer is predominant in all cases. Although there is no significant difference in reactivity between the electron withdrawing groups, the stereoselectivity of the sulfur electron withdrawing groups decreases with an increase in n. On the other hand, the dienophile reactivity diminishes when R=H.

Along the same line, Xing *et al.* reported the synthesis of dihydropyran derivatives **104** through the HDA reaction of *(E)*-α-perfluoroalkanesulfonyl chalcones **102** with enol ethers **103**. A stereospecific synthesis of the α-substituted chalcone was achieved by the Knoevenagel condensation reaction between β-keto perfluoroalkane sulfones **100** and aromatic aldehydes **101** with ammonium acetate as the base. Subsequently, the HDA reaction with **103** resulted in quantitative yields and a mixture of *endo*/*exo* diastereomers, with a predominance of *exo* compounds (*dr*~55:45) (Scheme 27).[143]

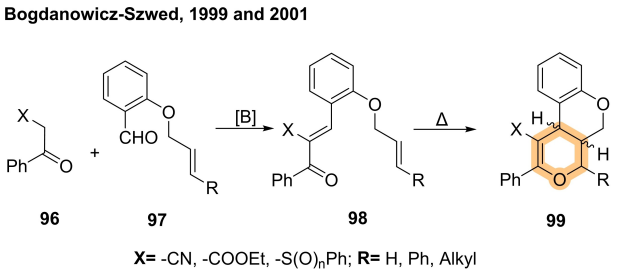
As aforementioned, chalcones can function as dienes or dienophiles. Under certain conditions, it is possible to dimerize them through an HDA cycloaddition, similar to the thio- and seleno-derivatives but involving a slower process. In 2007, Zhao *et al.* described the synthesis of mGluR5-positive allosteric modulators, including a library of analogs of compound **105**. When the biological effect was evaluated in duplicate, compound **105** unexpectedly displayed significantly lower activity on the second test. Interestingly, a certain amount of compound **105** dimerized into **106** when leaving the former stored



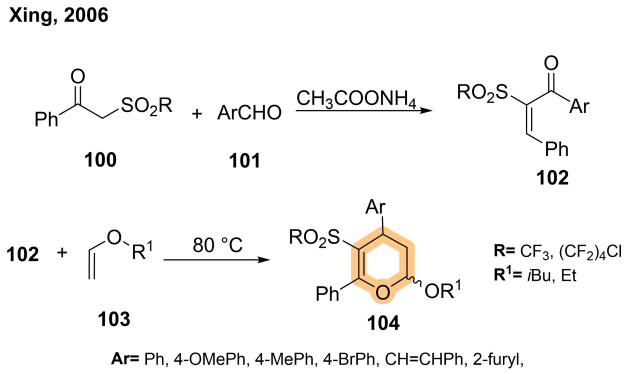
Scheme 24. Hetero-Diels-Alder reaction of selenochalcones with different dienophiles.



Scheme 25. Hetero-Diels-Alder reaction of a chiral dienophile with a chalcone.



Scheme 26. Intramolecular hetero-Diels-Alder reaction of chalcones induced by electron withdrawing groups.

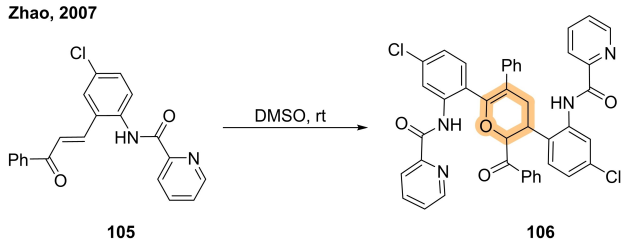


Scheme 27. Hetero-Diels-Alder reaction of α-perfluoroalkanesulfonyl chalcones with enol ethers.

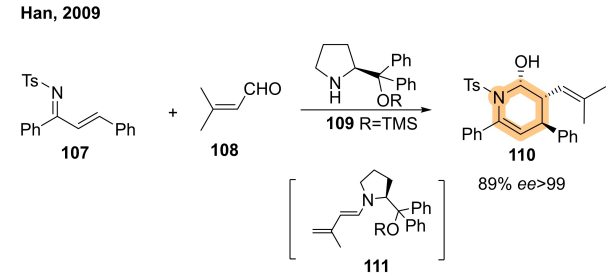
in DMSO stock solution (Scheme 28).[144] None of the other compounds showed dimerization as fast as **105**.

It is also possible to prepare iminochalcones to carry out [4+3] cycloaddition with electron-rich dienophiles. Han *et al.* studied the reaction of different N-sulfonyl-1-aza-1,3-butadienes with dienamines, which were generated *in situ* from aliphatic aldehydes and chiral pyrrolidines to produce optically pure piperidine derivatives. In one of their assays, they performed an HDA reaction between N-Tosyl iminochalcone **107** and aldehyde **108** to synthesize piperidine **110** with catalyst **109** (Scheme 29). The reaction proceeded with regioselectivity, 89% yield, *ee* >99, and *dr* >*99:1*. Because the olefin in intermediary **111** was richer in electrons, this compound was preferred for the HDA reaction with the aza-diene, indicating chemoselectivity.[145]

Azalactones are Michael donors extensively used in the synthesis of α,α-disubstituted α-amino acids. Thus, the Michael addition of chalcones **1** and azalactones **112** is well known.



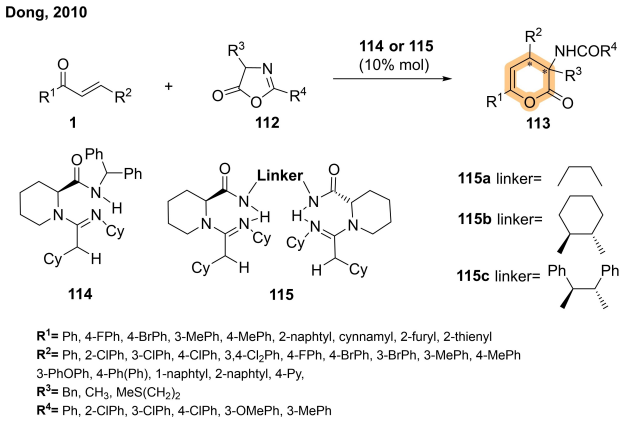
Scheme 28. Hetero-Diels-Alder dimerization of chalcone **105**.



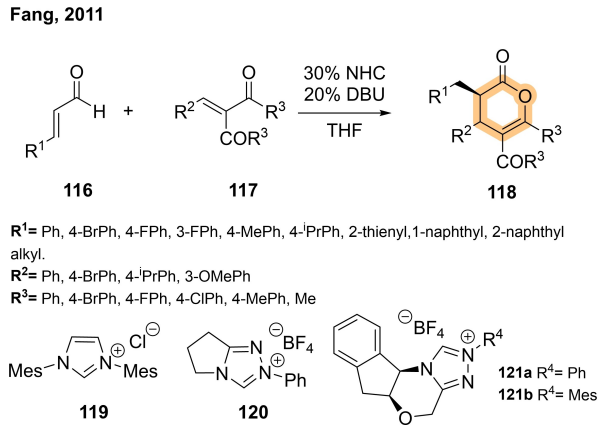
Scheme 29. Enantioselective hetero-Diels-Alder reaction of N-Tosyl iminochalcone through chiral amine catalysis.

However, Dong *et al.* discovered that HDA cycloaddition occurred in the presence of chiral guanidine **114** or bisguanidines **115**, providing chiral γ,δ-unsaturated δ-lactones **113** with a quaternary stereocenter (Scheme 30). In their detailed investigation of the reaction, they tested various chiral bisguanidines (with chiral or achiral linkers) as catalysts, finding a considerable increase in yield and enantioselectivity, especially with the bisguanidine derived from diphenylethylenediamine **115c** (*ee* >*95%*). Different chalcones with electron donating or withdrawing groups on the aryl substituents were also assessed. In each case they displayed only one diastereomer for lactone **113**, afforded in good yields (40–88%) and excellent *ee* (90–99%). The scope of the reaction was surveyed with other azalactones, which rendered high yields and outstanding enantioselectivity regardless of the electronic nature and steric hindrance of substituents in the aromatic ring. Finally, the catalyst was recovered and reused without losing catalytic activity or enantioselectivity.[146] This experiment shows how well-known reactivity can be changed with the aid of a catalyst to mediate the transition state of the reaction and result in a selective inverse-electron-demand DA reaction.

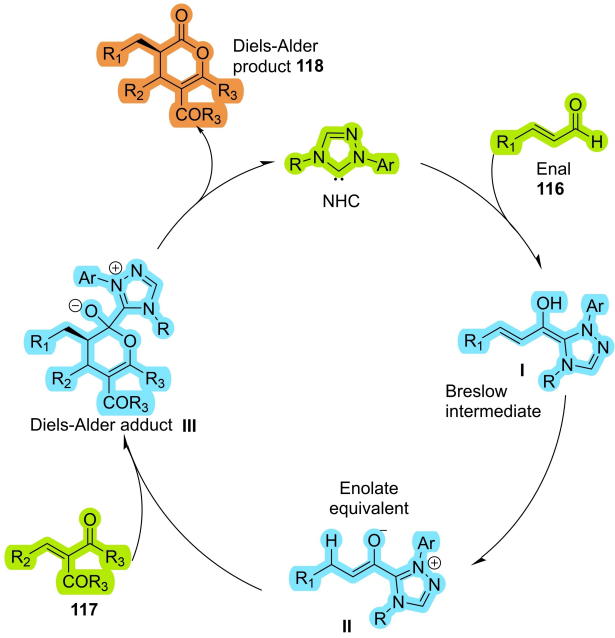
The following year (2011), Fang *et al.* achieved simultaneous activation of the dienophile and modification of the chalcone substituents to steer the reactivity of chalcones toward HDA cycloadditions. Chalcones bearing an electron withdrawing group at the α-position of the 2,3-propen-1-one moiety were employed to obtain HDA adducts by cycloaddition with activated N-heterocyclic carbene (NHC)-enals. On the other hand, different NHCs were combined with a strong base to give high yields, but the electronic properties and steric hindrance within the NHC structure influenced the results. Those effects could lead the reaction through the typical homoenolate path to produce either the desired HDA adduct or the undesired Stetter adduct.[147] By assaying various NHCs, the authors found that mediation of the HDA reaction with triazolium-based compound **121b** provided greater yields and excellent diastereo- and enantioselectivity (dr >12:1, *ee* >99%), allowing for the synthesis of optically pure lactones (Scheme 31). Firstly, the Breslow intermediate **I** is formed by the reaction between enal **116** and the catalyst, followed by protonation of the β-carbon



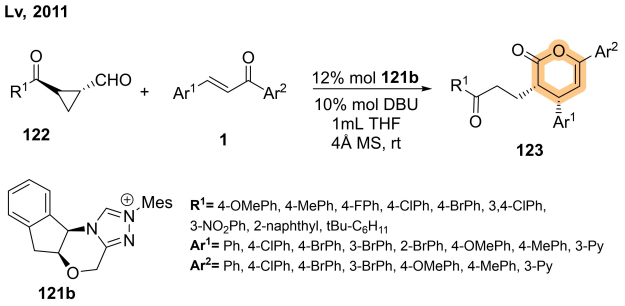
Scheme 30. Guanidine-based catalysts utilized for the hetero-Diels-Alder reaction of chalcones and azalactones.



Scheme 31. Hetero-Diels-Alder reaction of chalcones with enals through N-heterocyclic carbene catalysis.



Scheme 32. Reaction pathway for the hetero-Diels-Alder reaction catalyzed by N-heterocyclic carbenes.



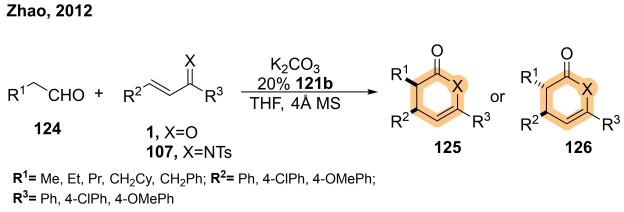
Scheme 33. N-heterocyclic carbene catalysis of the hetero-Diels-Alder reaction between chalcones and formyl cyclopropanes.

to furnish enolate equivalent **II**. Finally, the HDA reaction between enolate equivalent **II** and the α-substituted chalcone **117** affords lactone **118** and releases the catalyst (Scheme 32).[148]

Continuing with the line of research of dienophile activation with an NHC, Lv *et al.* managed to use formyl cyclopropanes **122** as enolate precursors with NHC **121 b** as the catalyst. These enolates have greater reactivity and are able to enter into HDA cycloaddition with simple chalcones **1** in the absence of an α-electron withdrawing group (Scheme 33). Excellent reaction enantioselectivity (*ee* >99%) and diastereoselectivity (dr >20:1) was found for lactones **123**. An evaluation was made of chalcones with different electron donating and withdrawing groups in the phenyl rings. Higher yields and lower reaction times were observed for those containing electron withdrawing groups.[149] The proposed reaction pathway was comparable to that described by Fang *et al.*, except that it was suggested to be a stepwise HDA cycloaddition rather than a concerted mechanism.

The only drawback in the studies by Fang *et al.* and Lv *et al.* was the limited scope of the reaction caused by generating enolates with NHCs and pre-functionalized substrates. It was more desirable to utilize a stable and readily available precursor for this reaction. In 2012, Zhao *et al.* reported that simple aliphatic aldehydes can serve as the substrates for the highly enantioselective synthesis of lactones and lactams through NHC activation of the aldehyde. Aldehyde **124** combines with catalyst **121 b** to give the desired enolates, which undergoes HDA cycloaddition with simple chalcones **1** and N-tosyl iminochalcones **107**. Interestingly, the major isomer is the *cis*-lactone **125** when chalcones are the substrate, and the *trans*-lactam **126** with iminochalcones as the substrate (Scheme 34).[150] The difference in the outcome was not explained by the authors. However, the stepwise mechanism proposed by Lv *et al.* might be the key because the bulkier tosylimino group could change the transition state when the ring closes.

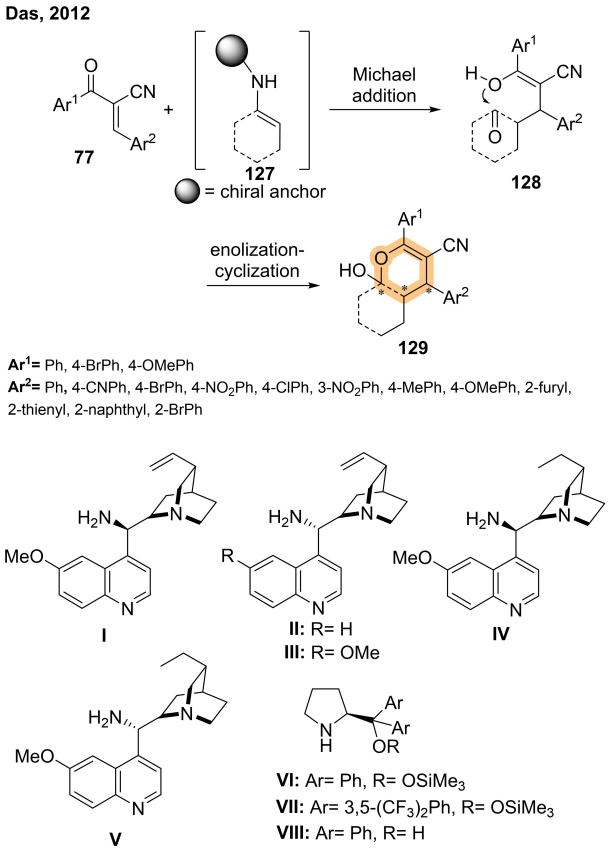
As aforementioned, chiral amines are extraordinary catalysts for the activation of dienophiles and the induction of inverse-electron-demand cycloadditions. *Trans*-trisubstituted electron-poor alkenes, such as the α-cyano chalcones **77**, were at one time considered restricted substrates in the field of organocatalysis due to the scarce examples of their reactivity. Then Das *et al.* reported the activation of cyclohexanone and aliphatic aldehydes with catalytic quantities of amines containing chiral anchors (**I**–**VIII**), utilizing organic acids as co-catalysts.



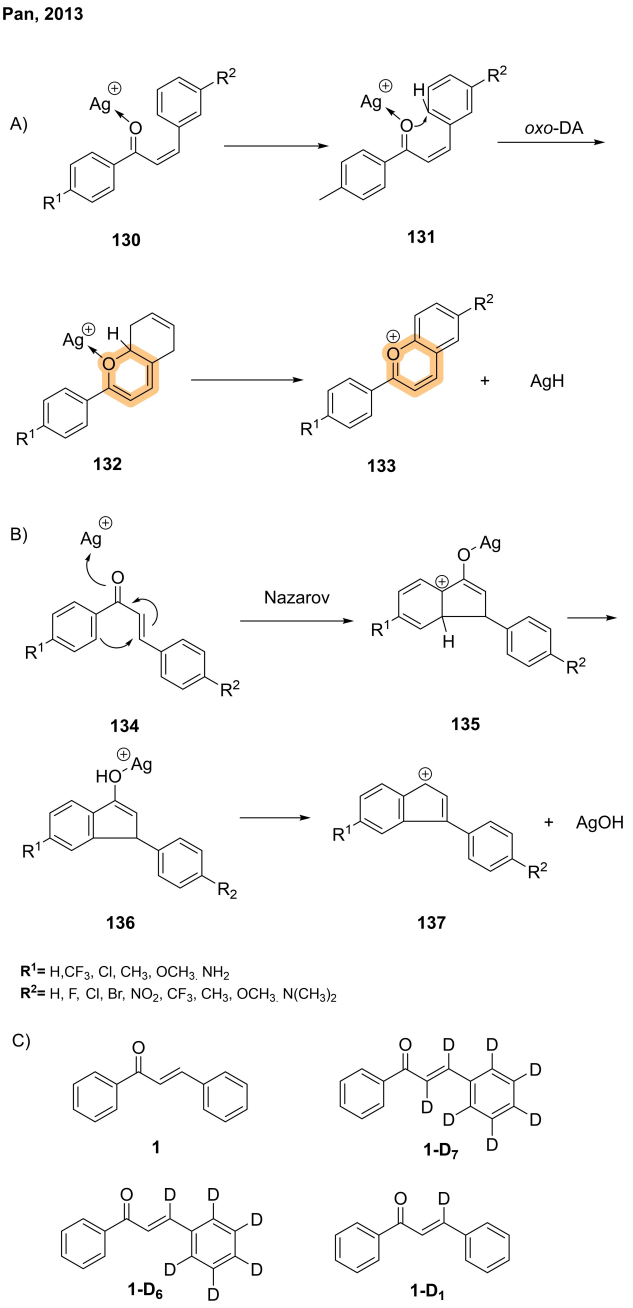
Scheme 34. Hetero-Diels-Alder reaction of chalcones and iminochalcones with aliphatic aldehydes.

The enamine **127** formed by this activation undergoes Michael addition to α-cyano chalcone **77** to produce intermediate **128**. The latter suffers ring closure through an enolization-cyclization process (Scheme 35) to give pyran ring **129** in good yields and selectivity (*dr* > 3:1, *ee* = 96-60%). Among the screened amines, secondary amines were obtained in lower yields by cycloaddition, while the use of 2-fluorobenzoic acid as a co-catalyst resulted in higher enantioselectivity (*ee* > 95%). The reaction was described as a cascade Michael addition-cyclization, which can also be considered a formal HDA reaction.[151] The synthetic advantage of the reaction is the functionalization of electron-poor alkenes, achieved with readily available chalcones.

In 2013, Pan *et al.* observed that the phenyl rings in chalcones **1** contribute separately to the silver-induced cyclization upon collisional activation. The phenyl ring of the benzoyl moiety participates in Nazarov cyclization (NC), while the other one partakes in an oxo-Diels-Alder (ODA) reaction. By performing CID-mass spectrometry, the mechanism for the preparation of the ODA adduct **133** and the NC adduct **137** was investigated in the gas-phase of silver(I)/chalcone complexes. The formation of **133** was assessed by measuring the elimination of AgH, and that of **137** by determining the elimination of AgOH. When employing deuterated chalcones (depicted in Scheme 36C), the predominant elimination of AgD was detected. Considering the position of deuterium in the molecule, a reaction mechanism for the elaboration of **136** was proposed (Scheme 36A). Due to the less abundant elimination of AgOH versus AgOD and the lack of deuterium in the benzoyl ring (Scheme 36B), the presence of adduct **137** was inferred. The addition of distinct substituents at the *para* position of either phenyl ring led to interesting results. Whereas electron donating groups favored the elimination of AgH and AgOH, electron withdrawing groups promoted the formation of Ag^+, indicating that the chalcone complex was easily dissociated. Thus, the chelating strength of Ag^+ for chalcones affected the competition between cyclization and dissociation.



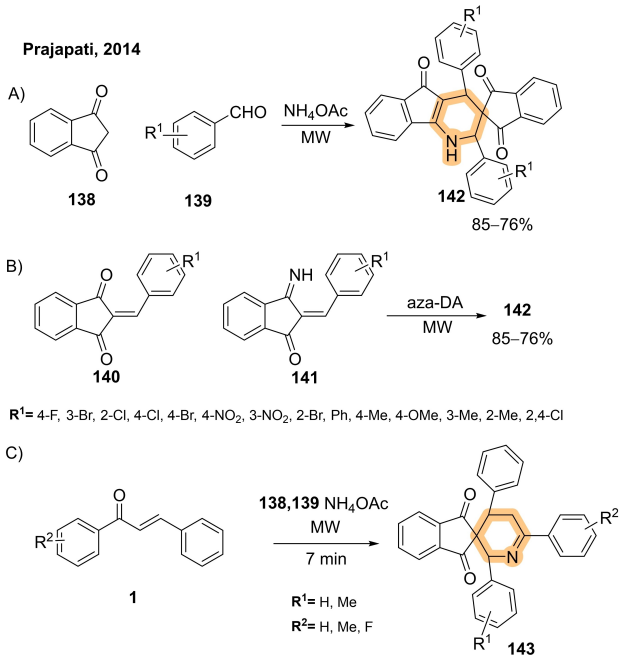
Scheme 35. Formal hetero-Diels-Alder reaction of chalcones with chiral enamines synthesized by using amines **I**–**V**.



Scheme 36. A) Mechanism for the oxo-Diels-Alder reaction of chalcones that led to the formation of AgH. B) Mechanism for the Nazarov cyclization reaction of chalcones that resulted in the formation of AgOH; C) Deuterated chalcones used to track the formation of AgD or AgOD.

The traditional DA reaction is a temperature-dependent cycloaddition. Heating with microwave or infrared irradiation is very common, being within the green approach. In some cases, these techniques are able to change the reactivity of the substrate, allowing for the construction of new synthetic blocks.

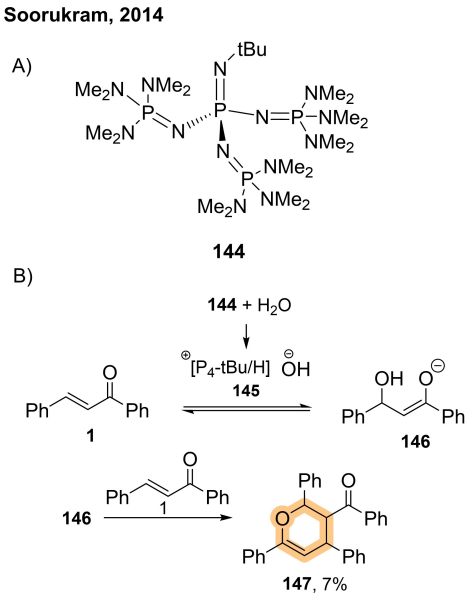
In 2014, Prajapadi *et al.* reported a novel way to synthesize spiroindenotetrahydropyridine derivatives via a solvent-free reaction assisted by microwave heating. Hence, the preparation of the spiro compounds **142** and **143** was carried out by generating both the diene and dienophile *in situ*. The condensation of 1,3-indandione **138** with benzaldehyde derivative **139** and ammonium acetate proceeds through a Knoevenagel reaction to afford the dienophile **140**, as illustrated in Scheme 37. The addition of ammonium acetate furnishes chalcone-like imine **141**, which acts as the diene. Subsequently, both reactants undergo the aza-HDA reaction, which proceeds in an orderly fashion to deliver the *spiro*-compound **142** in high yields. The reaction mechanism was confirmed by performing the reaction steps separately and isolating the diene and dienophile separately (Scheme 37B). When chalcones **1** were employed to prepare spirocyclic pyridine **143** under the same conditions, the reaction was not of the HDA type (Scheme 37C). According to the proposal of the authors, compound **138** may react with chalcone **1** through a Michael addition, leading to cyclization with ammonium acetate and the aldehyde to give pyridine **143**. Nevertheless, this idea was not investigated.[152] Prajapadi *et al.* explored different solvents, but found none to be the best condition for the transformation. Indeed, most of the solvents showed no reaction.



Scheme 37. A) One-pot synthesis of spiro compound **142**. B) Step-wise synthesis of spiro compound **142** through the aza-Diels-Alder reaction between chalcone-like indanediones **140** and **141**. C) One-pot synthesis of spiro compound **143** by the aza-Diels-Alder reaction of chalcones **1** with the *in-situ* formed compound **140**.

For simple chalcones, as previously mentioned, the process of HDA dimerization is slow. As part of the research efforts to increase the reaction rate, one possibility has been the inclusion of a Schwesinger base (P_4-^{t}Bu, **144**, Scheme 38A), an organo-superbase commonly used for the direct formation of the CF_3^- anion from CHF_3. This approach was evaluated by Soorukram *et al.* to directly obtain stable $PhSCF_2^-$ from $PhSCF_2H$, a typical fluoroalkylation reactant. The latter served as a nucleophile with a direct attack on carbonyl compounds. Upon attempting to explain the mechanism leading to the observed byproducts and the 7% yield, the authors proposed a [4 + 2] dimerization of chalcone **1**. Considering that pyran **147** was generated in the absence of $PhSCF_2H$, the Schwesinger base interacts with trace amounts of water to afford the hydroxide-like ionic species **145**, which in turn reacts with the chalcone to reversibly provide intermediate **146**. When this intermediate reacts with a second molecule of chalcone **1**, the HDA adduct **147** is furnished (Scheme 38B).[153] Even though the dimerized adduct was a side product with low yield, the achievement should offer new insights into how to steer future reactions towards pyran synthesis with simple chalcones.

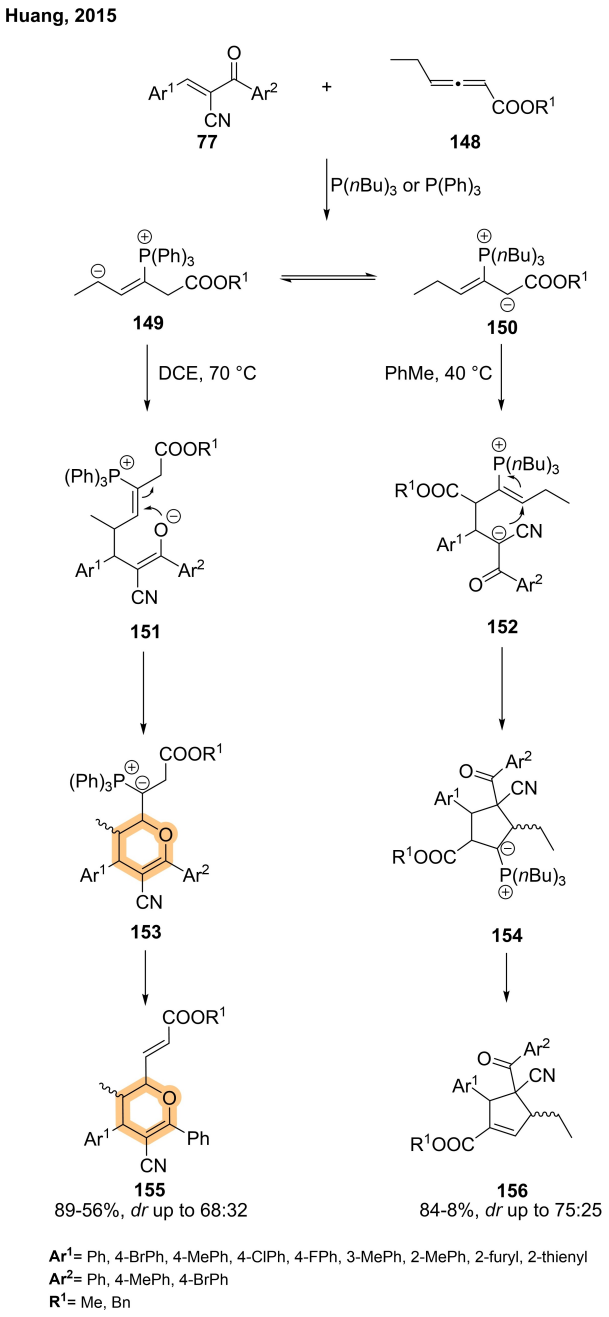
Activation of the dienophile by catalysts can result in the desired cycloaddition under the right conditions. With small modifications in the catalyst, for example, it is possible to steer reactions to the synthesis of specific molecules. Indeed, this is the ultimate goal of organocatalysis. Huang *et al.* found a domino annulation reaction catalyzed with phosphines. The application of distinct phosphine substituents leads to different types of behavior. The reaction of allenoate **148** with α-cyano chalcones **77** under phosphine catalysis provides dihydropyran **155** and cyclopentene **156** in different ratios in accordance with the solvent, temperature, and phosphine applied. The synthesis is initiated when allenoate **148** reacts with the selected



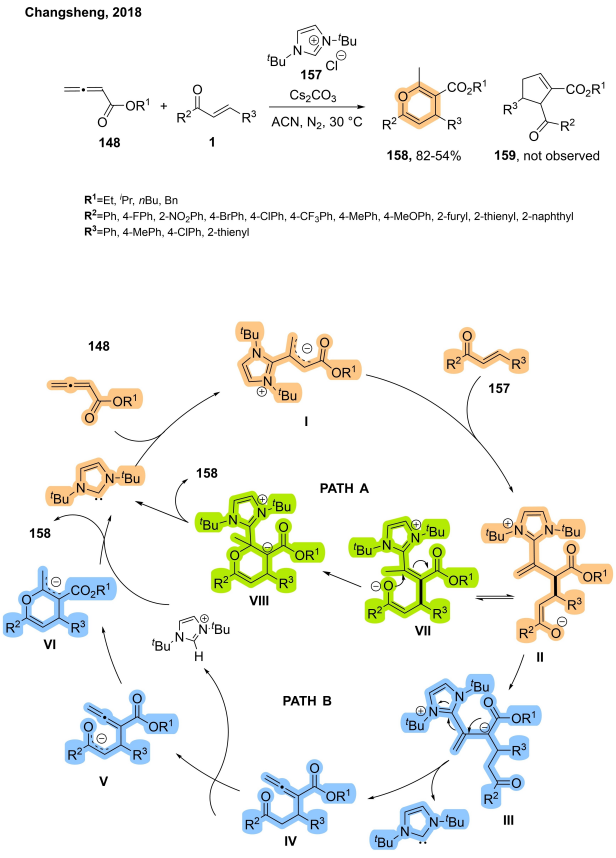
Scheme 38. A) Schwesinger base structure. B) Hetero-Diels-Alder reaction of chalcone **1** with species **146**, the latter formed by the reaction of a chalcone and the Schwesinger base/hydroxide-like species **145**.

phosphine, and zwitterionic species **149** and **150** are formed in equilibrium. The balance of the equilibrium tips toward **149** with $P(Ph)_3$ and toward **150** with $P(n\text{-}Bu)_3$. Regarding species **149**, the reaction proceeds through a Michael addition on chalcone **77** to furnish adduct **151**, which undergoes ring closure to deliver dihydropyran **153**. Finally, product **155** is obtained with the proton-transfer process. Overall, this mechanism can be considered a formal HDA. Alternatively, $P(nBu)_3$ leads equilibrium toward species **150**, which goes through double nucleophilic addition to afford **156** (Scheme 39). Reaction conditions were an important factor. For instance, utilizing DCE as a solvent and heating at 70° resulted in greater ratios of **155** (68:8), while the application of toluene at 40 °C was preferred in order to yield the cyclopentene adduct **156** (79:7). The downside was low diastereoselectivity and the replacement of the γ-substituent at the allenoate with methyl, isopropyl, or n-butyl, thus generating unidentified products and reducing the scope of the reaction.[154]

Chalcones and allenoates have also been employed with an NHC catalyst to synthesize pyranyl carboxylates. In contrast to the previous reports, Changsheng *et al.* explored the reaction of chalcone **1** with allenoate **148**, but the expected [3+2] annulation to furnish **159** was not found. Rather, the pyranyl carboxylate **158** resulted from an HDA reaction (Scheme 40). To understand the formation of the unexpected product, two paths were proposed. The first one poses that the 1,4-addition of **I** to the chalcone provides enolate **II**, and then the alkene isomerization followed by ring closure through conjugate addition delivers target product **VIII** with the release of the NHC catalyst (Scheme 40, path A). According to the second proposal (Scheme 40, path B), proton transfer promotes the elimination of NHC in intermediate **III** and gives allenoate intermediate **IV**. The released NHC acts as a base to deprotonate **IV** and obtain **V**, which undergoes 6-*exo*-dig cyclization to afford the final product. The substituents in the chalcone had a strong influence on the isolated yield, which increased with electron



Scheme 39. Reaction of cyanochalcones with allenes by using different phosphine catalysts, leading to a formal hetero-Diels-Alder reaction (PPh_3) or a [3+2] annulation (P^nBu_3).



Scheme 40. Hetero-Diels-Alder reaction between chalcones and allenoates with N-heterocyclic carbene catalysis. The proposed reaction pathways are indicated.

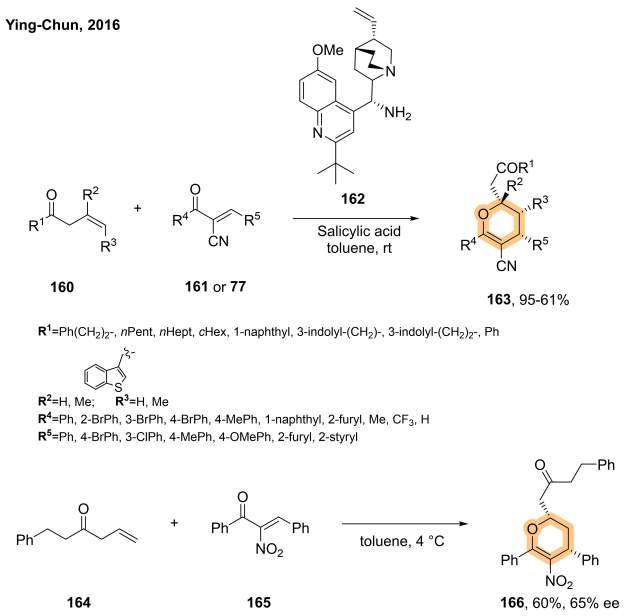
withdrawing groups and decreased with methyl and methoxy electron donating groups. Varying the catalysts in the reaction of allenoates and chalcones offers great versatility in steering the process towards the particular requirements.[155]

In the prior studies on HDA reactions, reactivity was examined with different substrates and catalysts. However, most of the adducts generated had low stereoselectivity. Ying-Chun *et al.* reported that with catalyst **162**, pyran **163** was the major product, and the reaction allowed for controlled formation of up to three chiral centers derived from HDA annulation. The authors decided to use α-cyano-α,β-unsaturated ketones **161** and chalcones **77** (due to their availability) in an HDA reaction with deconjugated ketones **160**. A series of pyran **163** analogs were synthesized with good yields and up to 99% *ee*. A lower *ee* was observed when the carbonyl substituent in ketones **161** was CF_3 or H. Aryl substituents, which are typical of chalcone analogs, had better stereoselectivity. Under similar conditions, α-nitro chalcones **165** furnished the desired product **166**, expanding the current application of α-substituted chalcones in highly stereoselective synthesis. *Dear Author, please mention* Scheme 41.

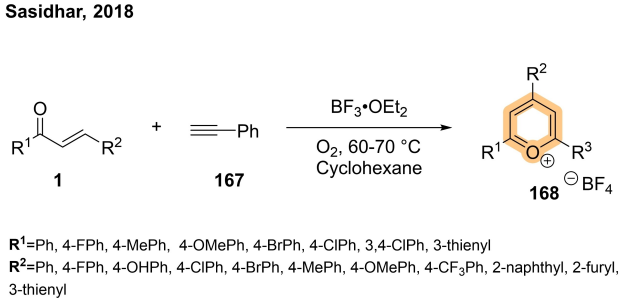
Efforts have been made to meet the challenges implied in elaborating pyrylium salts **168** owing to their great utility in the industrial sector. Given that traditional methods[156,157] afford only symmetrical molecules, a new synthetic method was developed by Sadidhar *et al.* to fine tune the properties of these molecules. They utilized HDA cycloaddition between chalcones **1** and arylacetylenes **167**, thus widening the scope of pyrylium salt synthesis (Scheme 42). Electron donating groups performed better than electron withdrawing groups. Since this is an inverse-electron-demand DA reaction, BF_3 plays a crucial role as a catalyst by coordinating with the carbonyl in the chalcone and lowering the energy of the LUMO.[158] Activation of the chalcone triggers HDA cycloaddition, which otherwise would not happen.

As previously stated, oxo-Diels-Alder reactions represent an extraordinary tool for constructing complex molecules from chalcones. In this sense, 6,8-dioxabicyclo[3.2.1]octane (DOBCO) is a privileged structure found in different natural products, although its synthesis involves difficult challenges. Qing-Zhu *et al.* explored an intramolecular HDA annulation involving the condensation of vinylethylene carbonates with *o*-aminoaryl chalcones.[159] DOBCO **172** was prepared in good yields and with a *dr.* up to 19:1 when using vinylethylene carbonates **169** and aminoaryl chalcones **170** with catalytic amounts of palladium (Scheme 43). The halogen-bonding donor **171** employed as a co-catalyst enhanced the yield and diastereoselectivity, possibly by cooperating with palladium and triggering the cascade reaction. However, diastereoselectivity decreased in the event that the carbonate contained naphthyl or heteroarenes. Hence, TsOH was added as a co-catalyst in a new experiment, leading to improved results.[159]

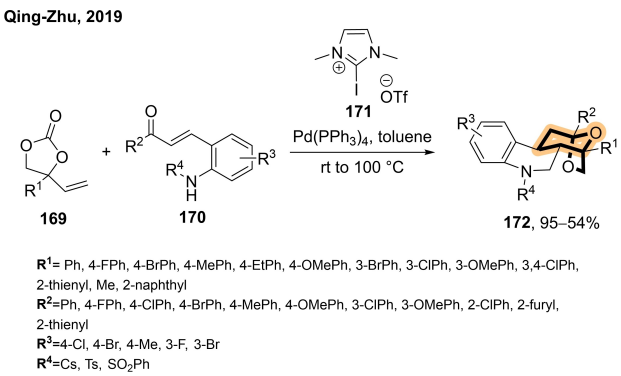
Albrecht and Mloston *et al.* have extensively researched the reactivity of the thiochalcone moiety in cycloadditions and asymmetric cycloadditions. Compared to the products typically furnished by heterodienes containing oxygen or nitrogen, those bearing sulfur, a less electron-negative atom, provide a unique opportunity to generate adducts with different regioselectivity. The inclusion of a chiral auxiliary led to unprecedented reactivity. Albrecht found such behavior in the synthesis of 3,4-



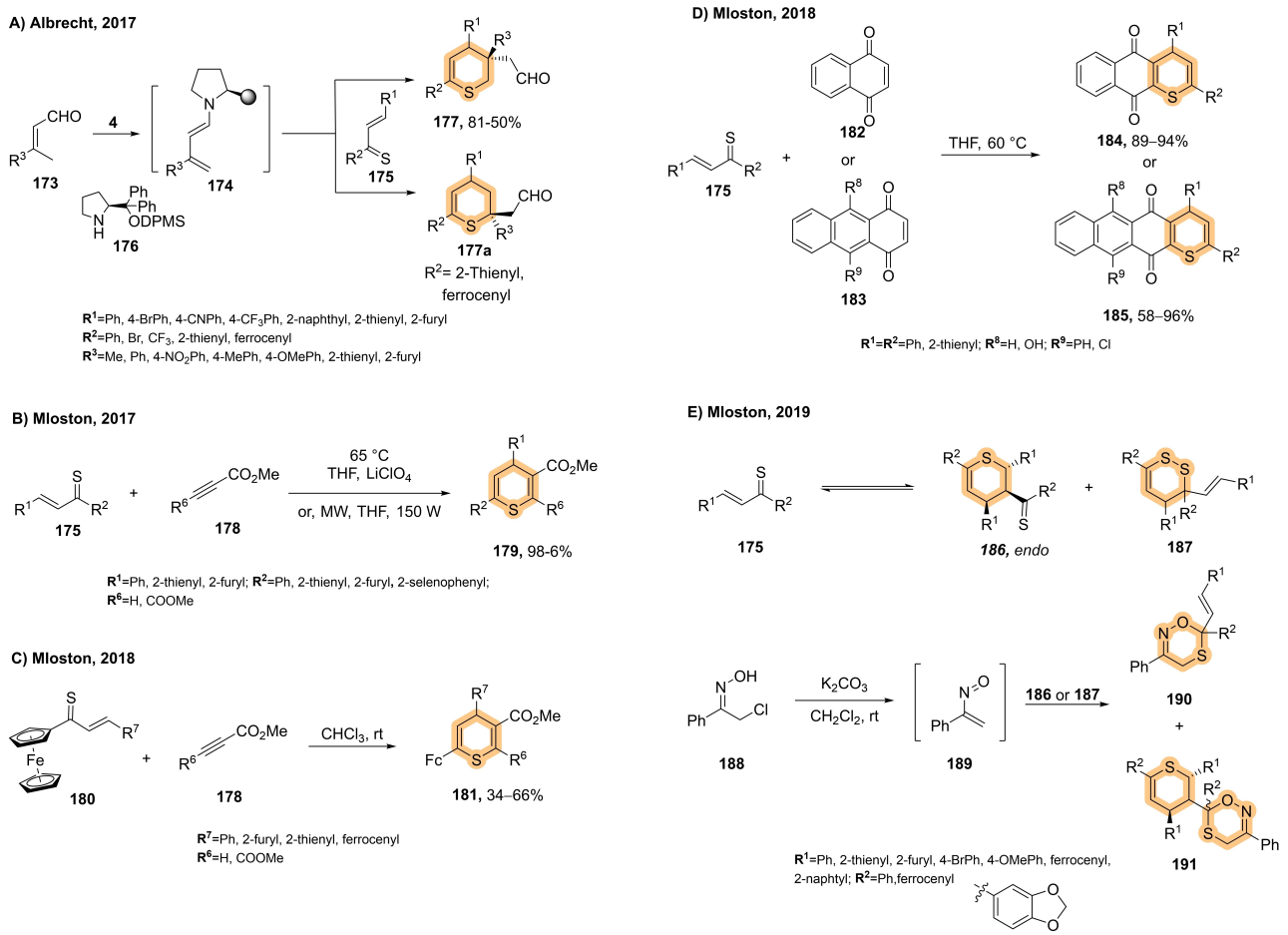
Scheme 41. Asymmetric hetero-Diels-Alder reaction of α-substituted chalcones with different dienophiles catalyzed by a chiral amine.



Scheme 42. Synthesis of pyrylium salts through oxo-[4 + 2] cycloaddition of chalcones.



Scheme 43. Synthesis of DOBCOs through an intramolecular hetero-Diels-Alder reaction of chalcones.



Scheme 44. Recent hetero-Diels-Alder reactions with thiochalcones.

dihydro-2*H*-thiopyrans **177** by utilizing electron-poor thiochalcone **175** and electron-rich dienophile **174** obtained from the reaction of **173** with the proline derived organocatalyst **176**. The regioselectivity and diastereoselectivity of the reaction are controlled in an orderly fashion. For example, regioselectivity changes in case the substituent in the thiocarbonyl group is a thienyl group, resulting in **177 a**. The effect is more evident when ferrocenyl is the substituent in this position (Scheme 44A).[160]

Over the next few years, Mloston extended the investigation of thiochalcones to additional reactions. Access to 4*H*-thiopyranes 5 was achieved by HDA annulation of heteroaryl thiochalcones **175** with acetylene carboxylates **178**, finding low to high yields. Another study broadened the use of ferrocenyl thiochalcones **180** to synthesize analogous thiopyranes **181** in moderate yields. Regioselectivity was maintained in both reactions (Scheme 44B, C).[161,162] A further study applied 1,4-quinones **182** and **183** as dienophiles, promoting the formation of the expected products **185** and **186** and attaining regioselectivity for the former.[163]

Finally, the reactivity of α-nitrosoalkenes was evaluated. As aforementioned, thiochalcones tend to form dimers that participate in the subsequent reaction. Thus, oxime **188** treated with a base gives α-nitrosoalkene **189**, which in the presence of the thiochalcone dimers **186**/**187** furnishes 4*H*-1,5,2-oxathiazines **190**. However, if the thiocarbonyl substituent is electron-rich (thienyl, furyl, or 1,3-benzodioxole), **191** is favored. The electron-rich substituents disfavor equilibrium toward the monomer, although the preparation of **191** passes through an HDA reaction with the *endo*-dimer **186** (*exo*-dimer **187** is not observed due to process kinetics).[164] These reactions establish thiochalcones as exceptional synthetic scaffolds in HDA cycloadditions.

3. Conclusions

There is great interest in the chemistry of chalcones as dienes and dienophiles because of their utility in constructing organic hetero- and carbocycles that are crucial for many synthetic and natural compounds. One of the main advantages of chalcones as substrates is their availability. Although this family of compounds is found in nature, isolation of chalcones from plants yields very small quantities. Fortunately, their preparation is accessible to any research group through the use of aryladehydes and ketones, which form part of the most common reactants for organic synthesis.

Access to different functional groups improves the scope of the reactions with chalcones and reduces costs. The α, β-unsaturated carbonyl core has extraordinary potential for the transformation of the carbonyl moiety, including the conversion to thio-, imino-, and selenochalcones. The latter are simple transformations capable of completely changing the chemical properties of the compound.

The current microreview highlights the dual role of chalcones in [4+2] cycloadditions. As dienophiles, chalcones have been extensively studied for the construction of six-membered carbocycles by one of the most emblematic reactions in organic synthesis, the Diels-Alder reaction. Chalcones have been employed not only as precursors of natural and synthetic molecules, but also in the development of novel protocols and catalysts for asymmetric Diels-Alder annulation, reflecting their versatility. When chalcones are utilized as dienophiles, the many catalysts able to induce stereoselectivity range from chiral organometallic catalysts to novel and greener DNA- and protein-based catalysts. These can achieve cycloaddition reactions with high yields and enantioselectivity, which is always desirable in the event that a reaction leads to the formation of new stereocenters.

It is also possible for chalcones to behave as dienes in Diels-Alder cycloadditions with inverse-electron-demand kinetics as well as formal [4+2] cycloadditions, which are stepwise Diels-Alder annulations. Accordingly, it is easy to generate six-membered heterocycles, including pyrans, thiopyrans, and hydropyridines. Considering that these heterocycles are part of many molecules of biological importance, the ability to obtain them as optically pure compounds has great value for organic synthesis. Since there are few published examples of exploiting the chemistry of chalcones as dienes, an exciting opportunity exists for future research. Hence, due to their dual role in Diels-Alder cycloadditions, chalcones have broad possibilities in organic synthesis. We would like to see the continued development of novel synthetic strategies that exploit the full potential of this family of compounds.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Diels-Alder · Chalcone · Inverse electron demand · Catalysis · Cycloaddition

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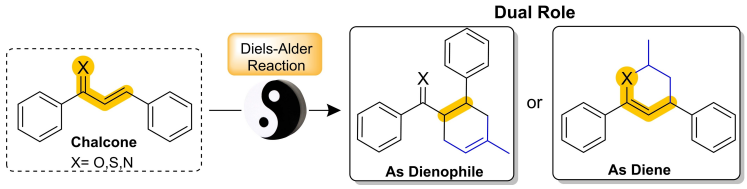
REVIEW



The current review highlights chalcones as a privileged scaffold for the synthesis of carbocycles and heterocycles through Diels-Alder reactions. These natural compounds have a unique reactivity in [4+2] cycloadditions, both as dienophiles and dienes. Due to their ease of synthesis and availability, chalcones are excellent building blocks for the discovery of new molecules and the development of novel catalysts for Diels-Alder reactions.

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1 – 28

Chalcones, a Privileged Scaffold: Highly Versatile Molecules in [4+2] Cycloadditions

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