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A concise update on the synthetic transformation of aurones *via* asymmetric cycloaddition, annulation, and Michael/Mannich reactions

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This review provides a comprehensive overview of the significance of aurone cores in organic chemistry, highlighting their crucial role as synthetic intermediates. With their innate electrophilic reactivity and convenient accessibility, aurone cores play a vital role in catalysing the development of novel methodologies and facilitating the creation of intricate compounds. The objective of this review is to present a current and insightful compilation that summarizes the progress in aurone synthetic transformations, focusing on diverse cycloaddition ([3 + 2], [4 + 2], [4 + 3], [10 + 2]) and annulation reactions.

Introduction

Aurones **1** (Fig. 1) belong to a subgroup of secondary metabolites categorized within the extensive realm of flavonoids. They are particularly abundant in fruits and flowers, playing a crucial role in botanical pigmentation.[1–4] Structurally, aurones feature a benzofuranone heterocyclic pattern and are characterized by incorporating a phenyl unit through a carbon–carbon exocyclic double bond. Notably, the aurone framework holds a special position in medicinal chemistry due to its architectural significance, often linked with various pharmacologically active compounds.[5–8]

A significant breakthrough occurred in 1943 when Geissman and Heaton isolated the first aurone derivative from the flowers of *Coreopsis grandiflora*.[5] Subsequent investigations have unveiled an array of remarkable biological activities demonstrated by aurone derivatives. These activities include anticancer,[9–11] antioxidant,[12,13] metal ion-chelating,[14,15] antitumor,[16] anti-tyrosinase,[17] antiparasitic,[18,19] antibacterial,[20,21] antifungal,[22] antiviral,[23] anti-hormonal,[24] anti-inflammatory,[25,26] anti-diabetic,[27] and anti-obesity.[28] These diverse attributes have spurred significant interest in the scientific community, leading to the integration of aurone-based structures into various medicinal products (Fig. 2).[24,29]

In modern synthetic organic research, there is a strong focus on developing new strategies and chemical reactions. Among the numerous types of reactions discovered in the last 90 years, cyclization and cycloaddition reactions have emerged as highly valuable and extensively studied transformations. These reactions have seen remarkable advancements, leading to the creation of complex and diversely functionalized carbocycles and heterocycles. These compounds are particularly important

in natural products and pharmaceuticals. For instance, methods involving [2 + 1], [2 + 2], [3 + 2], [4 + 2], [4 + 3], [5 + 2], *etc.* cycloaddition reactions have been established for constructing small- to medium-sized rings.[30] Within this context, the cycloaddition and annulation reactions of aurones have garnered significant interest among synthetic chemists. Their significant electrophilic reactivity and easy availability make them incredibly valuable for developing new methodologies
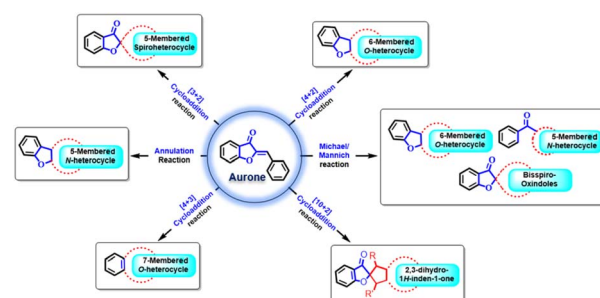

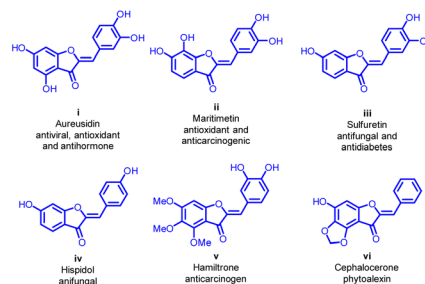Fig. 1 Overview of synthetic transformation of aurones.

Fig. 2 Some aurone molecules being considered as potential drug candidates exhibit significant physiological activity.

Department of Chemistry, Vellore Institute of Technology, Vellore, India. E-mail: johndeepa265@gmail.com; kvngeorge03@gmail.com; ethukr@gmail.com

and synthesizing complex natural products. They're particularly useful for creating spiro benzofuranone-carbocyclic or -heterocyclic structures through various cycloaddition and annulation reactions, often assisted by different organo and transition metal catalysts.[31–39]

Past literature has extensively explored aurones from different angles. In 2003, Boumendjel conducted a meticulous study on aurone synthesis and their biological properties.[1] Notably, Boumendjel and Kirsch independently echoed these efforts in 2012.[24,40] Subsequently, in 2021, Wenming Zhou and co-workers presented a comprehensive review encompassing aurone synthesis and their biological implications.[41] To the best of our knowledge, there has not been any review explaining the synthetic transformation of aurones. Hence, this review aims to offer a timely and insightful compilation that encapsulates the latest advancements in aurone synthetic transformations from 2012 to 2023.

[3 + 2] Cycloaddition reactions (32CA)

The discovery of 32CA reactions dates back to the late 19th century, but it was in 1961 that Huisgen recognized their broad applicability, significance, and underlying mechanism. Huisgen and his team dedicated considerable effort and research to these reactions, leading to their rapid development. Consequently, Huisgen earned the title "father" of "1,3-dipolar cycloadditions". These reactions involve the interaction between a zwitterionic molecule known as a "1,3-dipole" and a multiple-bond system called a "dipolarophile". By adding the multiple bond system to a three-atom component (TAC), which is a neutral species consisting of three closely connected heavy nuclei with a minimum electron density of 8 electrons, these reactions have proven highly valuable in synthesizing five-membered heterocyclic compounds.[42–45]

In 2013, Moncef Msadek and co-workers developed a successful strategy for creating a unique category of extensively substituted pyrazole structures **5**. They achieved this through a 1,3-cycloaddition reaction involving aurone **1** and aryl diazomethane **3** (Scheme 1). Notably, these reactions exhibited exceptional specificity in terms of the regiochemical outcomes.[46]

Chang Guo *et al.*, in 2014 reported a remarkably selective N-heterocyclic carbene (NHC) **8** catalyzed formal [3 + 2] annulation involving α,β-unsaturated aldehydes **7** and aurones **1**, resulting in the formation of spiro-heterocycles (Scheme 2). The spiro heterocycles produced *via* this method adopt a novel NHC protocol and feature a quaternary stereogenic centre with notably high optical purity. The enantioselectivity observed in the formation of spiroheterocycles **12** is attributed to the NHC
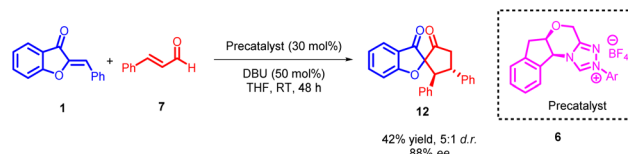

Scheme 2 NHC catalyzed [3 + 2] annulations reaction of enals to form spiroheterocycles.

precatalyst. Likewise, the reverse configuration of spiroheterocycles can be achieved with equivalent yield and enantioselectivity by employing the enantiomer of the NHC precatalyst.

The catalytic cycle, as depicted in Scheme 3, commences with the generation of NHC organocatalyst **8** through the deprotonation of precatalyst salt **6**. Introduction of NHC organocatalyst **8** to enal **7** yields NHC-homoenolate **9**, prompting a Michael addition from the rear face and subsequent coordination through a hydrogen-bonding interaction, as seen in intermediate **10**. Importantly, the stereochemistry observed aligns best with the proposed reaction model illustrated by intermediate **10**. Following the creation of a carbon–carbon bond, a tautomerization process leads to the formation of acyl azolium **11**. This species is believed to undergo *C*-acylation, resulting in the generation of the final product **12** while simultaneously regenerating NHC organocatalyst **8**.[47]

In 2013, Wei-Qiang Hu *et al.*, introduced a 1,3-dipolar cycloaddition approach involving aurone **1** and azomethine ylides **14**. This innovative reaction was effectively facilitated by basic imidazolium salts **13**, resulting in the efficient construction of spirocycles containing highly substituted pyrrolidines. The products were obtained with outstanding yields (Scheme 4).

A plausible bifunctional catalytic mechanism has been proposed for this process. In this mechanism, a nucleophilic butyric anion **13** acts as a base, capturing a proton from the azomethine ylides **14**. Simultaneously, an electrophilic imidazolium cation functions as an electron acceptor, completing the reaction cycle. This mechanistic insight is illustrated in Scheme 5. Activation of azomethine ylides is attributed to the
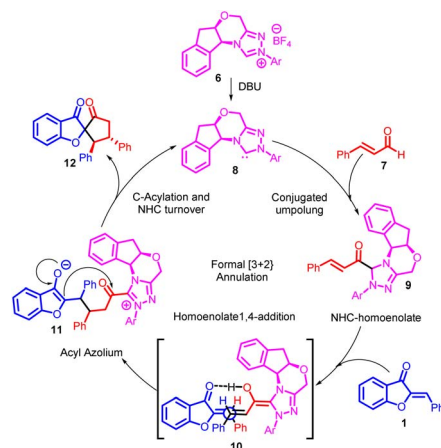
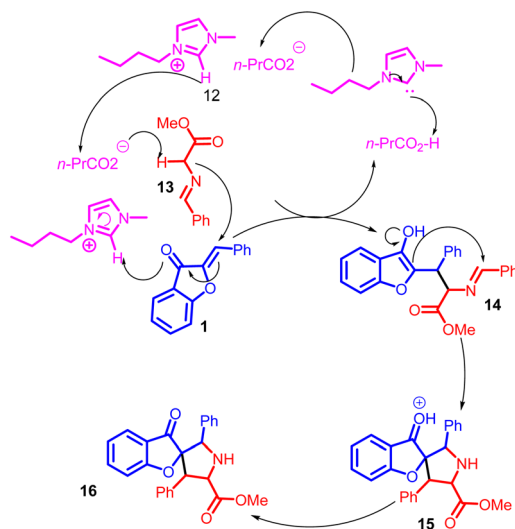Scheme 3 Proposed mechanism for the NHC catalyzed annulation of enals.
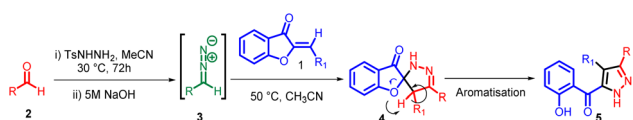
Scheme 1 One-pot synthesis of substituted pyrazole derivatives.

Scheme 4 1,3-Dipolar cycloaddition of aurone and azomethine ylides to form pyrrolidine and 1-indanone derivatives.

Scheme 5 Proposed mechanism for the synthesis of pyrrolidine and 1-indanone derivatives.

involvement of the butyric anion, while the imidazolium cation is believed to activate the aurone **1**.[48]

In 2016, Tao Ding and co-workers achieved a significant breakthrough by establishing a remarkably efficient catalytic system capable of constructing both spiro[pyrrolidine benzofuran-3-one] **20** and spiro[pyrrolidine-benzofuran-2-one] **22** compounds. They pioneered the development of the initial 1,3-dipolar cycloaddition reaction involving aurone **1** and azomethine ylides **19**, employing simple functional ionic liquids as catalysts (Scheme 6). This innovative approach led to the synthesis of a diverse range of spiro[pyrrolidine-benzofuran-3-one] **20** compounds, characterized by highly substituted
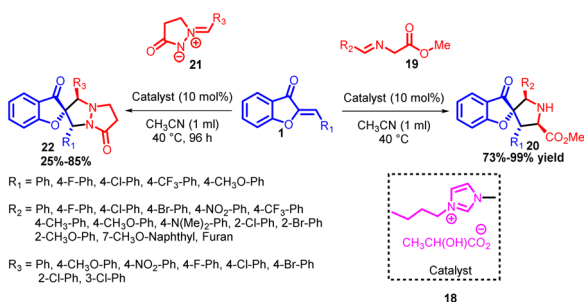
pyrrolidine structures featuring a spiro quaternary stereogenic centre. Remarkably high yields (ranging from 73% to 99%) were achieved using this method. Moreover, the same catalytic system demonstrated its versatility by facilitating the 1,3-dipolar cycloaddition between aurone **1** and pyrazolidinone-based dipoles **21**, yielding spiro[pyrrolidine-benzofuran-2-one] derivatives **22** with yields ranging from 25% to 85%.

This catalytic system's efficiency was evident in its wide applicability to diverse substrate ranges; all achieved under mild reaction conditions. Importantly, these studies not only offer a vital approach for producing two distinct classes of highly substituted pyrrolidines featuring spiro[pyrrolidine-benzofuranone] motifs but also present an avenue for their *in situ* generation from benzofuranone derivatives.[49]

Łukasz Albrecht and co-workers in 2016 introduced a novel and highly selective strategy for synthesizing pyrrolidine derivatives featuring a benzofuran-3(2*H*)-one framework. This pioneering method relies on a [3 + 2] cycloaddition process that involves aurone **1** and imines **24**, derived from salicylaldehyde and diethyl aminomalonates (Scheme 7). Initial experimentation with complex catalysts yielded unsatisfactory results. However, a significant improvement in the reaction outcomes was achieved by substituting these advanced catalysts with a simpler cinchona alkaloid, known as quinine.

Further exploration, which involved examining different cinchona alkaloids and their derivatives under basic conditions, highlighted the critical role of the C-9 hydroxyl group in recognizing substrates and, consequently, creating a well-defined stereochemical environment for the cycloaddition reaction. This method demonstrates impressive versatility with a wide range of applicable substrates, emphasizing efficiency in both chemical synthesis and stereochemical precision while maintaining a straightforward operational process. Furthermore, it is evident that lowering the reaction temperature had an adverse impact on the stereoselectivity of both diastereoselection and enantioselection. A similar effect was observed when altering the concentration of the reaction, with both increasing and diluting the reaction solution leading to a decrease in the stereoselectivity of the cycloaddition process. These findings provide valuable insights into the optimization of conditions to achieve desired stereochemical outcomes in cycloaddition reactions. These compounds are synthesized with excellent yields and meticulous attention to stereochemical accuracy. The resulting compounds feature two biologically significant heterocyclic components and three neighbouring stereogenic centers, one of which is quaternary.[50]

**Scheme 6** 1,3-Dipolar cycloaddition of aurones derivatives and azomethine ylides.
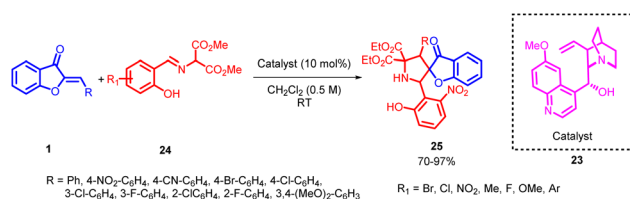
Scheme 7 Asymmetric organocatalyzed synthesis of pyrrolidine derivatives bearing a benzofuran-3(2*H*)-one.

Azaoxyallyl cation intermediates, derived from α-halo hydroxamates in the presence of organic or inorganic bases, have emerged as versatile substitutes for "1,3-dipole" entities. These intermediates have been effectively utilized in diverse cycloaddition reactions, including [3 + 1], [3 + 2], [3 + 3], and [4 + 3] processes, involving sulphur ylides, aldehydes, indoles, 2-alkenylindoles, nitrones, and electron-rich dienes. Building upon prior research in this synthetic methodology of azaoxyallyl cations, Pan Lin Shao and co-workers in 2017 introduced the pioneering [3 + 2] cycloaddition reaction between *in situ* generated azaoxyallyl cations **27** and aurone **1** under mild reaction conditions (Scheme 8). The proposed mechanism for this reaction is provided in Scheme 9.[51]
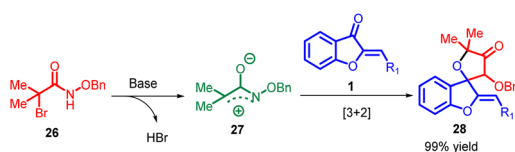
This approach led to the successful synthesis of a range of spiro-4-oxazolidinones **28** with exceptional yields, some reaching up to 99%. The impressive efficiency of this method, combined with its straightforward implementation, positions it as an appealing strategy for spiro-4-oxazolidinone **28** synthesis.

In 2018, Zhi-Peng Wang and co-workers introduced a transition metal-free cyclization strategy employing NaOH for the reaction between methyl isocyanates **29** and aurone analogs **1** (Scheme 10). This method led to the efficient synthesis of diverse 2,3 and 4-polysubstituted pyrroles **30** with high efficacy.
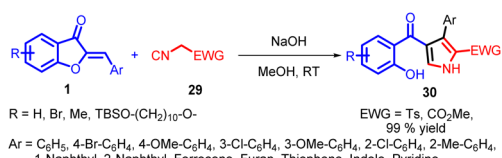
In an endeavour to enhance comprehension of the reaction profile, deuterium labelling studies were carried out. d^1-**1a** (88% deuterium) and d^2-**29a** (99% deuterium) were prepared for the cyclization. As shown in Scheme 11, under the optimized reaction conditions, **30** was obtained in 99% yield, replacement of
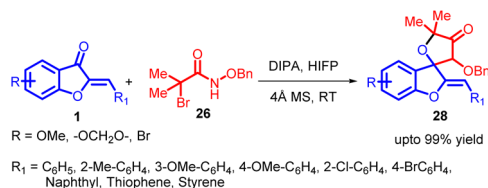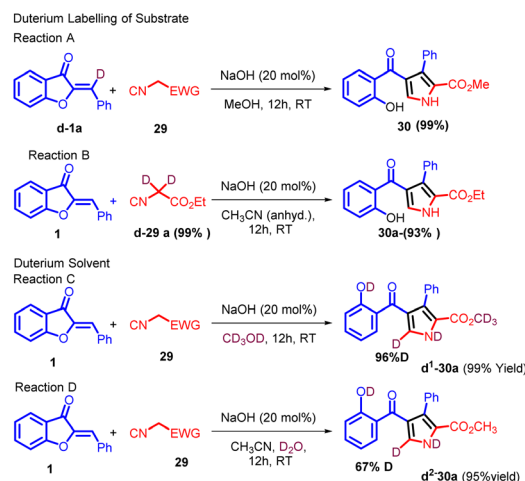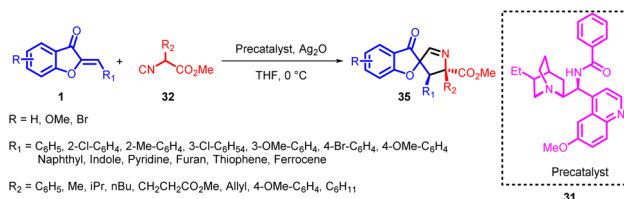

Scheme 11 Deuterium labelling studies.

the solvent with anhydrous MeCN, **30a** could also be formed in high yield, no deuterium labelling was observed on both of the products (Reaction A and B, Scheme 11). However, the use of CD$_3$OD as reaction media resulted in significant deuterium labelling (96% deuterium) at the 5-position on the pyrrole ring, and further investigation revealed that the proton at 5-position can also be labelled by deuterium (67% deuterium) when 3.0 equivalents of D$_2$O was added with anhydrous MeCN as solvent (Reaction C and D, Scheme 11). This intriguing finding implies that an active proton facilitates proton transfer, aligning with the pronounced solvent effect observed.

This transformation employs readily available, versatile starting materials, an economical catalyst, and proceeds under mild conditions, all without reliance on transition metals. The method holds practical promise for synthesizing pharmaceutically relevant polysubstituted pyrroles **30**, particularly regarding substitution patterns and compatibility with functional groups.[52]

In 2018, Zhi-Peng Wang *et al.*, devised an enantioselective formal [3 + 2] cycloaddition process involving isocyanoacetates **32** and aurone analogs **1** (Scheme 12). This reaction employed a chiral Ag-complex catalyst. Despite the potential for the 1,3-dipole enolate derived from isocyanoacetate **32** to engage in a [4 + 3] reaction sequence, the study exclusively unveiled the [3 + 2] cyclization pathway, resulting in the formation of spiropyrroline **35**. Intriguingly, no evidence of a [4 + 3] annulation product **36** emerged.

Scheme 8 Cycloaddition of azaoxyallyl cations with aurones to form spiro-4-oxazolidinones.

Scheme 9 Proposed mechanism for the synthesis of spiro-4-oxazolidinones.

Scheme 10 Transition metal-free synthesis of polysubstituted pyrrole *via* cyclization of methyl isocyanoacetate with aurone.


Scheme 12 Catalytic asymmetric [3 + 2] cycloaddition reaction between aurones and isocyanoacetates to form spiropyrrolines.

While the precise mechanism of the reactions described in this study is still not fully understood, a plausible transition-state model, **34**, has been proposed. This model is based on experimental findings and the absolute configuration of the major isomer **35**. In this proposed model, the α-proton of iso-cyanoacetate **32** is readily deprotonated by the tertiary amine on the precatalyst, facilitated by the activation of Ag(I), which is chelating to the terminal carbon of the isocyano group. Additionally, the central metal Ag(I) could form chelation bonds with the amide nitrogen and the Lewis base phosphorus on the precatalyst. Due to steric hindrance, the ester motif is positioned beneath the bulky phenyl groups. Consequently, the isocyanoacetate would approach the aurone olefin from the *Re*-face. Simultaneously, the oxygen atom of the aurone is involved in hydrogen bonding with the precatalyst and coordinated to Ag(I) to stabilize the transition state **34**. As a result of these interactions, a 5-*endo*-dig cyclization occurs, leading to the formation of the spiropyrroline product, complete with three newly formed stereocenters (Scheme 13).

When employing precatalysts **31** along with Ag$_2$O, excellent yield and stereoselectivity were achieved. Furthermore, reducing the reaction temperature to 0 °C improved both yield and the levels of diastereoselectivity and enantioselectivity. However, changing the solvent did not have a positive impact on enantioselectivity. The protocol demonstrated remarkable tolerance for a diverse array of isocyanoacetates **32** and aurones **1**, encompassing varying electronic and steric attributes. This led to the formation of optically active spiropyrrolines featuring three adjacent stereogenic centres, with exceptional outcomes in terms of yields and diastereo- and enantioselectivities (achieving yields up to 99%, *dr* exceeding 20 : 1, and *ee* surpassing 99%).[53]

In 2018, Ting Du *et al.*, developed an asymmetric [3 + 2] cycloaddition process involving aurones **1** and imino esters **38** (Scheme 14). Various quaternary ammonium salts, including amide, urea, and thiourea derivatives, were tested as potential catalysts, each serving as an H-donor. Interestingly, the use of a L-isoleucine-derived quaternary ammonium salt as the catalyst resulted in a 92% yield of product **39**, accompanied by a 73% enantiomeric excess (*ee*) and a 6 : 1 diastereomeric ratio (*dr*). In contrast, other quaternary ammonium salts employing urea as the double H-donor did not significantly improve enantioselectivity, although they did enhance diastereoselectivity to 14 : 1. It is well-established that thiourea exhibits both higher H-bond strength and acidity compared to urea. Utilizing catalyst **37**, derived from L-isoleucine, led to a remarkable improvement in
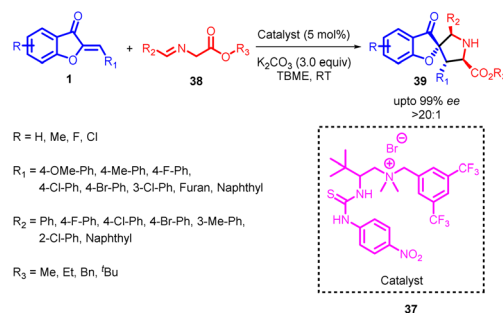

Scheme 14 Enantioselective 1,3-dipolar cycloaddition of imino esters with benzofuranone derivatives catalyzed by thiourea quaternary ammonium salt.

enantioselectivity, resulting in a 98% *ee* and an 11 : 1 *dr*. These findings underscore the influence of catalyst structure and composition on the stereochemical outcomes of the reaction. The reactions exhibited high efficiency, enabling the straightforward synthesis of diverse chiral pyrrolidine derivatives **39** that featured a benzofuran-3(2*H*)-one framework. Notably, these reactions occurred with exceptional enantioselectivity and satisfactory diastereoselectivity, all conducted under mild reaction conditions.[54]

In 2020, Yulai Hu and co-workers reported an effective and regioselective [3 + 2] dipolar cycloaddition reaction involving benzoaurone **1b** and *in situ* generated nitrile imine 40 (Scheme 15). This protocol provides facile access to various interesting spiro naphthofuranone-pyrazoline **41** compounds in good to excellent yields. The proposed mechanism (Scheme 16) involves the reaction of hydrazonoyl chloride **40a** with K$_2$CO$_3$, leading to the formation of nitrile imines with distinct resonance structures **A–D**. These nitrile imines then react with benzoaurone **1b**. Notably, the resonance allenic **C** of the nitrile imine plays a significant role in the [3 + 2] cycloaddition, participating *via* an asynchronous transition state (**42**). This transition state involves a two-centre interaction between the carbenoid carbon of **C** and the electrophilic centre of benzoaurone **1b**. Consequently, the reaction yields the spiro naphthofuranone-pyrazoline compound **41a**, exhibiting high regioselectivity.[55]

In 2021, Prakash K. Warghude and co-workers developed a remarkably selective [3 + 2] annulation method involving Morita–Baylis–Hillman (MBH) carbonates of isatin **43** with aurone **1** (Scheme 17). This approach was successful in producing diverse spiro-heterocycles, including spiro-oxindole
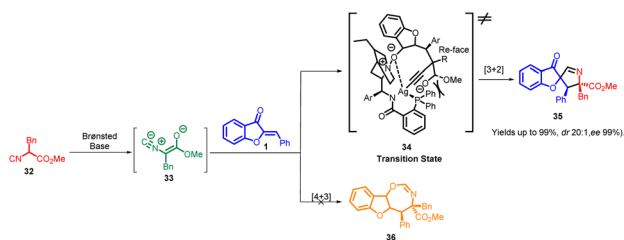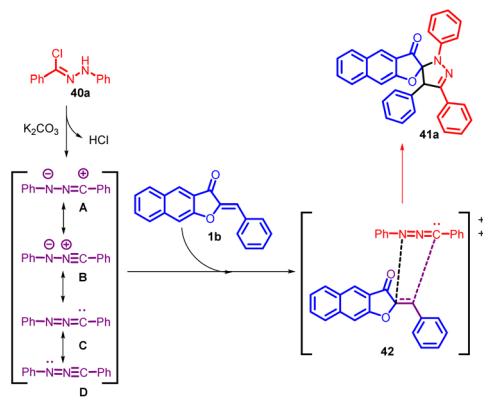

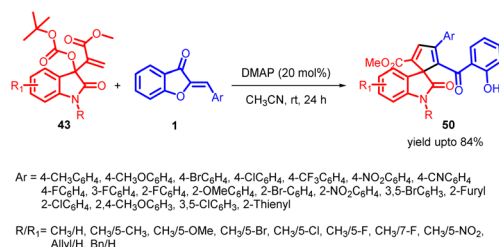**Scheme 13** Proposed mechanism for the synthesis of spiropyrrolines.
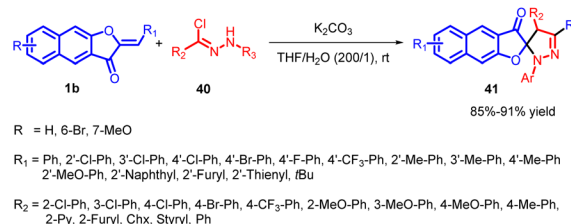
Scheme 15 Synthesis of the spiro-pyrazolines with nitrile imines *via* [3 + 2] cycloaddition.

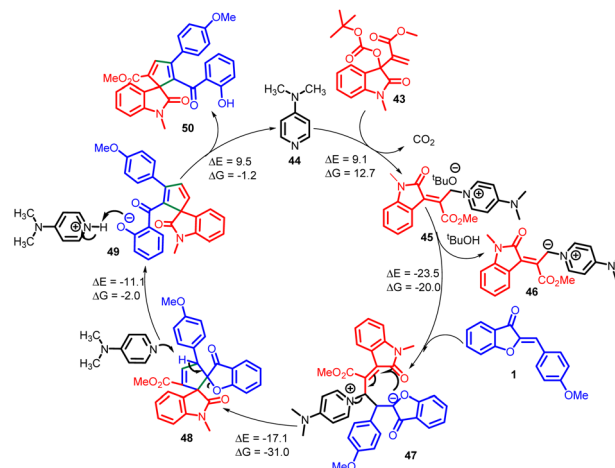**Scheme 16** Proposed mechanism for the [3 + 2] cycloaddition.

Scheme 17 Synthesis of multifunctional cyclopentadiene- and cyclopentene-spirooxindoles *via* [3 + 2] annulation.

Scheme 18 Proposed reaction mechanism for the formation of spirooxindole cyclopentadiene.

Scheme 19 Dinuclear zinc-catalyzed enantioselective formal [3 + 2] cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines with low reactivity aurone derivatives.
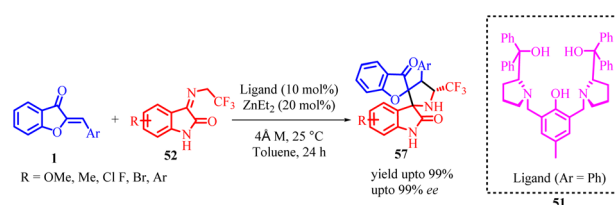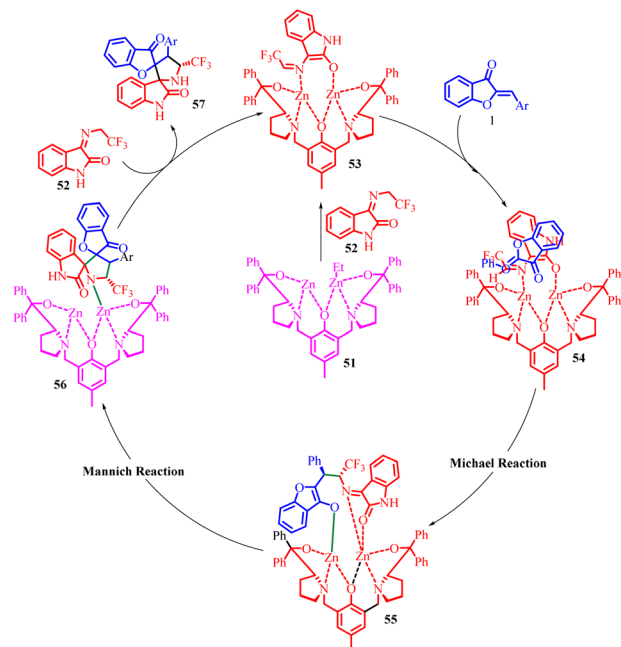
cyclopentadiene **50** derivatives. The reactivity of Lewis bases, particularly DMAP, played a crucial role in driving this synthetic transformation.

According to their observations, the process begins with nucleophilic DMAP **44** attacking MBH carbonate **43**, forming quaternary ammonium salt **45** while liberating carbon dioxide and *tert*-butoxide. However, this initial step is found to be thermodynamically unstable ($\Delta G = 12.7$ kcal mol^{-1}). The *tert*-butoxide generated *in situ* subsequently removes a proton from quaternary ammonium salt **45**, leading to the formation of an allylic nitrogen-ylide **46**. The resulting ylide **46** then reacts with aurone **1**, generating intermediate **47** (reaction free energy $\Delta G = -20.0$ kcal mol^{-1}). This intermediate readily undergoes an intramolecular Michael addition, facilitated by its highly favourable energy profile ($\Delta G = -31.0$ kcal mol^{-1}), leading to the formation of intermediate **48** and the elimination of DMAP. Continuing the reaction, DMAP abstracts a proton from the intermediate **48**, causing ring opening and the formation of a phenoxide intermediate **49**. Finally, this intermediate undergoes protonation, leading to the desired compound **50**, while also regenerating DMAP to complete the catalytic cycle (Scheme 18).[56]

In 2021, Rui-Li Wang *et al.*, developed a highly enantioselective method for synthesizing chiral spiro[benzofuran-pyrrolidine] **57** derivatives (Scheme 19). They achieved this by utilizing chiral dinuclear zinc catalysts and starting from aurones **1** and *N*-2,2,2-trifluoroethylisatin ketimines **52**. The reaction involved a [3 + 2] cycloaddition mechanism,

progressing through a domino Michael/Mannich reaction. The researchers obtained the desired products with excellent diastereoselectivities and enantioselectivities, all achieved under mild reaction conditions.

In the proposed reaction mechanism (Scheme 20), the synthesis begins with the formation of a dinuclear zinc complex **51** *in situ* through the reaction of the ligand with two equivalents of Et$_2$Zn. The *N*-2,2,2-trifluoroethylisatin ketamine **52** is then deprotonated by the dinuclear zinc complex, resulting in the formation of the activated azomethine ylide **53** and the release of ethane. Subsequently, the aurone coordinates to both zinc atoms, generating intermediate **54**. This coordination enables a Michael addition reaction to occur, leading to the formation of complex **55**. Following that, an intramolecular Mannich reaction takes place within the same catalytic system, facilitating the cycloaddition process. The catalytic cycle restarts as intermediate **56** undergoes a proton exchange with another imine. This step is succeeded by the release of the activated azomethine ylide **52** and the desired spiro[benzofuran-pyrrolidine] product **57**.

The catalytic asymmetric control of this chemical transformation was assessed using a variety of chiral ligands with different substituents and backbones. These included various ProPhenol ligands, AzePhenol ligands, and non-C2 symmetric ligands. The outcomes of these experiments revealed that the choice of chiral ligands significantly influenced the
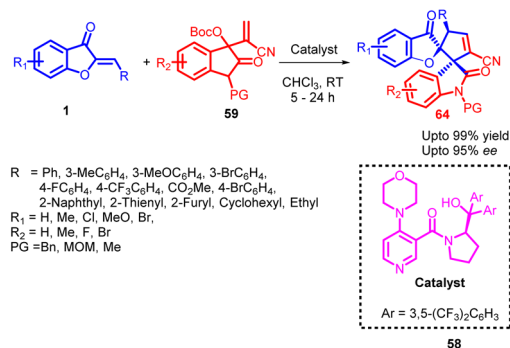
Scheme 20 Proposed mechanism for the synthesis of spiro[benzo-furan-pyrrolidine].

Scheme 21 Asymmetric [3 + 2] annulations of aurone derivatives for the construction of spiroheterocycles.

enantioselectivity. Notably, the alternative ligands examined did not lead to an improvement in enantioselectivity. To enhance both the yield and enantioselectivity of compound **57**, several additives were introduced, such as 4 Å molecular sieves (MS), Ph_3PO, Ph_3PS, and NEt_3. The inclusion of 40 mg of 4 Å MS as an additive resulted in the completion of the 1,3-dipolar cycloaddition reaction within 12 hours, yielding the product in an impressive 85% yield with a 94% enantiomeric excess (*ee*). Further optimization involved a solvent screening, revealing that toluene was the most suitable solvent, leading to a slight improvement in the *ee* value. Subsequent experimentation at an elevated temperature (25 °C) yielded the desired product in a 90% yield with a 95% *ee*, ultimately establishing the optimal reaction conditions.

These reactions not only present a new methodology for building the chiral spiro[benzofuran-pyrrolidine] structure **57** but also enhance the application of the chiral dinuclear zinc cooperative strategy in synthesizing complex compounds. This research widens the scope of constructing intricate molecules with specific chirality, offering valuable insights for the development of novel catalytic systems.[57]

In 2021, Ying-Chun Chen and co-workers[58] introduced a novel method for the asymmetric α-regioselective [3 + 2] annulation reactions of aurone derivatives **1** with isatin-derived Morita–Baylis–Hillman (MBH) carbonates **59** (Scheme 21). This reaction was carried out under the catalysis of a chiral DMAP-type catalyst **58**, resulting in the efficient synthesis of a diverse range of spiro-benzofuran **64** frameworks with remarkable levels of diastereo- and enantioselectivity. Upon comparing various chiral DMAP-type catalysts, it was evident that those bearing 3,5-bis(trifluoromethyl)phenyl groups in catalyst **58** exhibited higher enantioselectivity and superior stereocontrol.

Conversely, alternative catalysts displayed moderate catalytic activity and enantioselectivity. To elucidate the catalytic process further, a proposed mechanism was developed based on the product's absolute configuration.

The absolute configuration of the product played a crucial role in proposing a plausible catalytic mechanism for this asymmetric annulation reaction (Scheme 22). According to their proposed mechanism, catalyst **58** acts as an activator for the MBH carbonate **59**, leading to the formation of a zwitterionic allylic ylide **60**. Subsequently, this intermediate **60** attacks the aurone substrate **1** from the *Si*-face, with a possible hydrogen-bonding interaction between the hydroxy group of **58** and the carbonyl group of **1** facilitating the process. This step affords an intermediate **62**. Finally, through cyclization and the
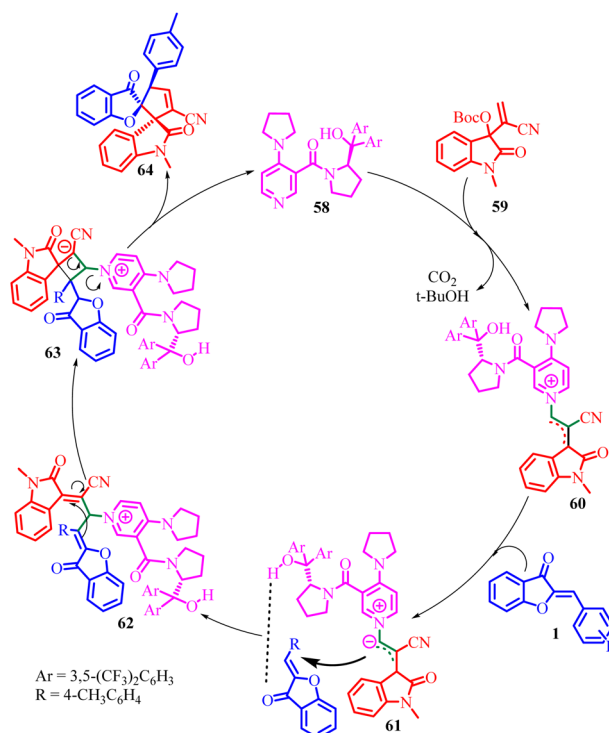
Scheme 22 Proposed mechanism for the asymmetric [3 + 2] annulations of aurone.

subsequent release of catalyst **58**; the desired product **64** was generated.

The synthetic strategy developed in this study enables the rapid construction of intricate spiroheterocyclic compounds with excellent enantioselectivity, utilizing readily available starting materials. This approach holds great potential for further applications in the fields of synthetic chemistry and medicinal chemistry.[58]

In 2022, Jie Huang *et al.*, developed an efficient method for synthesizing poly-substituted pyrazoles **68** using tosyldiazomethane (TsDAM) **65** and (*Z*)-aurones **1** as starting materials (Scheme 23). This protocol involved the use of Cs_2CO_3 as a catalyst in water/protic solvents. The reaction proceeded through a series of steps, as depicted in Scheme 24 of their study. Initially, 2-diazo-1-aryl-2-tosylethanone **65** reacted with water in the presence of a base, leading to the formation of an intermediate **66**. This intermediate underwent 1,3-dipolar cycloaddition with (*Z*)-aurones **1**, resulting in the formation of intermediate **67**. Subsequently, intermediate **67** underwent aromatization, causing the aurone ring to open and yielding fully aromatized poly-substituted pyrazole derivatives **68**.

This method was successful in synthesizing novel and interesting pyrazoles **68**. The domino reaction between (*Z*)-aurones **1** and *in situ* generated TsDAM proceeded smoothly, providing the desired tosyl-substituted pyrazoles **68** in good to excellent yields. The reaction yield varied depending on the substitution pattern of the (*Z*)-aurones **1**. Generally, *para*-substituted (*Z*)-aurones yielded higher yields compared to *ortho*- and *meta*-substituted ones, primarily due to steric effects. It is noteworthy that electron-donating groups yielded slightly better results than electron-withdrawing groups. However, when nitro (a strong electron-withdrawing group) substrates were used, the yields were low. Among the three nitro substrates, the *para*-substituted nitro substrate showed the lowest yield.
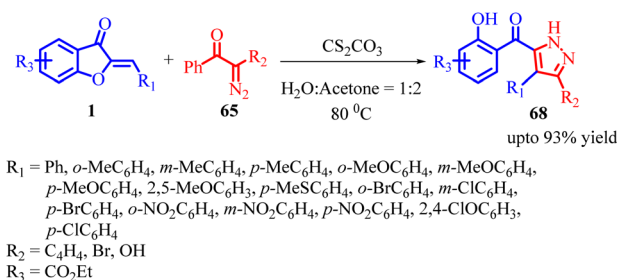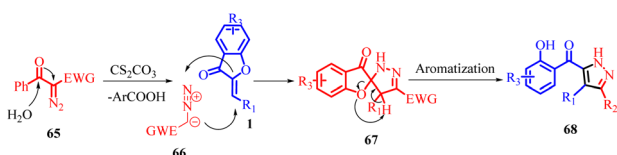
Additionally, various diazo compounds are used as reactants alongside 2-diazo-1-phenyl-2-tosylethan-1-one as dipole component. It was found that 2-diazo-1-phenyl-2-tosylethan-1-one performed better than 2-diazo-3-oxobenzoate in terms of reaction yield.[59]

In 2022, Wang *et al.*, introduced an innovative method involving DBU catalysis for a [3 + 2] cycloaddition of aurones **1** and 3-homoacyl coumarins **69**. This strategy enabled the creation of spiro-fused pentacyclic spiro-benzofuranones **72** that possess a combination of spiro[benzofuranone-cyclopentane] and coumarin components. This technique proved effective in producing a variety of functionalized spiro-benzofuranone derivatives **72** with high yields and impressive diastereoselectivity, demonstrating its versatility for synthesis (Scheme 25).[60]

Indanone-fused polycyclic frameworks are commonly found in bioactive natural compounds and are significant in medicinal chemistry due to their unique structural properties. Ji-Ya Fu and co-workers in 2023 have successfully developed a regioselective reaction, known as [3 + 2] cycloaddition, between 2-benzylidene-1-indenones **73** and aurone **1** (Scheme 26). By employing 1,4-diazabicyclo [2.2.2]octane (DABCO) as a base under mild conditions, they have been able to create a novel class of indanone-fused cyclopentane backbones. This reaction method utilizes the electrophilic C3-position of 2-benzylidene-1-indenones **73** and the nucleophilic C4-position of aurone **1** to construct cyclopentane rings with five consecutive chiral centres. The functional olefins act as both nucleophiles and electrophiles, participating in the [3 + 2] cycloaddition reaction. This metal-free approach enables the efficient synthesis of indanone-fused cyclopentane frameworks with five continuous chiral centres, allowing for the production of diverse indanone-fused cyclopentane polycycles with multiple substituents in high yields.

The proposed mechanism involves the conversion of 2-benzylidene-1-indenone **73** into an intermediate compound in the presence of the base, followed by a [3 + 2] cycloaddition reaction between the intermediate and aurone **1** to yield the

Scheme 23 Base–catalysed cascade [3 + 2] spiroannulation/aromatization of tosyldiazomethane (TsDAM) with (*Z*)–aurones.

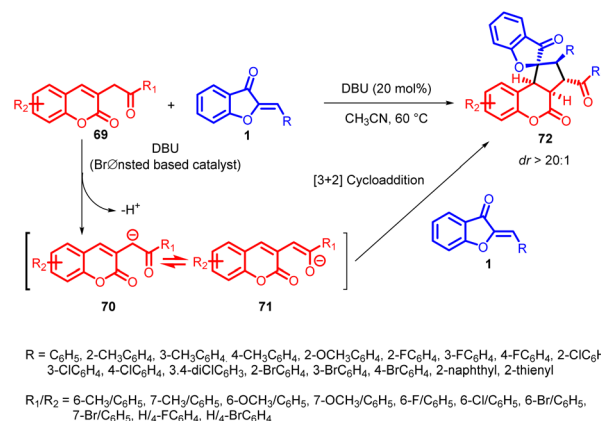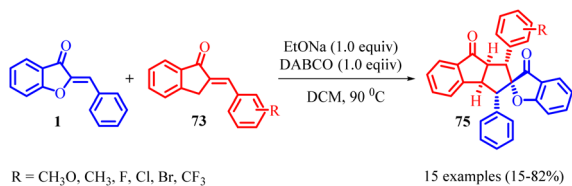R_1 = Ph, *o*-MeC$_6$H$_4$, *m*-MeC$_6$H$_4$, *p*-MeC$_6$H$_4$, *o*-MeOC$_6$H$_4$, *m*-MeOC$_6$H$_4$, *p*-MeOC$_6$H$_4$, 2,5-MeOC$_6$H$_3$, *p*-MeSC$_6$H$_4$, *o*-BrC$_6$H$_4$, *m*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *o*-NO$_2$C$_6$H$_4$, *m*-NO$_2$C$_6$H$_4$, *p*-NO$_2$C$_6$H$_4$, 2,4-ClOC$_6$H$_3$, *p*-ClC$_6$H$_4$
R_2 = C$_4$H$_4$, Br, OH
R_3 = CO$_2$Et

Scheme 24 Proposed mechanism for base catalyzed [3 + 2] spiroannulation/aromatization.

Scheme 25 Synthesis of spiro[benzofuranone–cyclopentane] derivatives *via* annulations of aurones derivatives with various 3–homoacyl coumarins derivatives.

R = C$_6$H$_5$, 2-CH$_3$C$_6$H$_4$, 3-CH$_3$C$_6$H$_4$ 4-CH$_3$C$_6$H$_4$, 2-OCH$_3$C$_6$H$_4$, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 3,4-diClC$_6$H$_3$, 2-BrC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-naphthyl, 2-thienyl
R$_1$/R$_2$ = 6-CH$_3$/C$_6$H$_5$, 7-CH$_3$/C$_6$H$_5$, 6-OCH$_3$/C$_6$H$_5$, 7-OCH$_3$/C$_6$H$_5$, 6-F/C$_6$H$_5$, 6-Cl/C$_6$H$_5$, 6-Br/C$_6$H$_5$, 7-Br/C$_6$H$_5$, H/4-FC$_6$H$_4$, H/4-BrC$_6$H$_4$

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Scheme 26 [3 + 2] Cycloaddition reaction of 2-benzylideneinden-1-ones with 3-benzylidenebenzofuran-2(3H)-one.
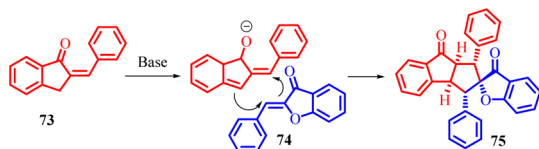
**Scheme 27** Proposed mechanism for [3 + 2] cycloaddition of aurones with 2-benzylideneinden-1-ones.

desired product (Scheme 27). The successful synthesis of the desired fused tricyclic and spirocyclic scaffolds was achieved by subjecting less reactive aurone **1** to standard reaction conditions in the presence of 2-benzylideneinden-1-one. Interestingly, the reaction predominantly yielded a crossover product. Expanding the scope of this transformation, a range of 2-benzylidene-1-indenones **73** containing *para-*, *meta-*, and *ortho-* substituted aryl rings were employed. This systematic exploration resulted in the synthesis of a diverse collection of fused tricyclic and spirocyclic compounds, demonstrating the versatility and applicability of this reaction methodology.[61]

[4 + 2] Cycloaddition reaction

The inception of the [4 + 2] cycloaddition reaction dates back to 1928, when Otto Diels and his student, Kurt Alder, documented their findings on the cycloaddition of cyclopentadiene with quinone. Subsequently, there has been a continuous growth in the body of literature focusing on various facets of the [4 + 2] cycloaddition. This reaction, known as the Diels–Alder reaction in honor of its pioneers, has evolved into the most versatile means of producing six-membered carbon and heterocyclic structures. In the contemporary landscape, this method remains unsurpassed for the synthesis of such structures. Presently, the application of this reaction extends beyond the use of conjugated 1,3-dienes; conjugated nitroalkenes have emerged as frequent candidates as hetero-analogues of dienes. Hetero-analogs of ethene play a pivotal role in this cycloaddition process, encompassing molecular units that incorporate nitrogen, oxygen, sulphur, selenium, and other elements.[62–64]

Jin-Pei Cheng and co-workers developed a highly enantioselective [4 + 2] cycloaddition method employing allenoates **77** and aurone **1** as substrates (Scheme 28). This transformation was facilitated by the application of the (DHQD)$_2$AQN catalyst **76**, the structure of which is provided. This innovative approach enabled the controlled synthesis of optically active dihydropyran-fused benzofurans, showcasing significant
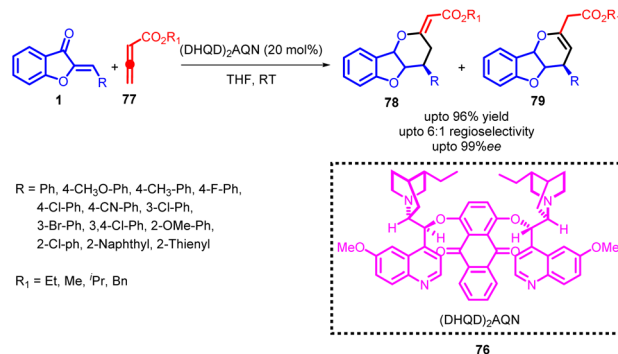
Scheme 28 Enantioselective [4 + 2] cycloaddition of allenoates and 2-olefinic benzofuran-3-ones.

enantioselectivity. The research delved into the investigation of cycloaddition using various catalysts. Through a comprehensive comparative analysis, it was established that (DHQD)$_2$AQN **76** proved to be the optimal catalyst in terms of both catalytic reactivity and enantioselectivity. Subsequently, the reaction was subjected to optimization by examining factors such as solvent, concentration, and additives, all in the presence of (DHQD)$_2$-AQN **76**. Screening various solvents revealed that THF delivered the most favourable results among the solvents tested. A slight increase in reaction concentration led to a reduction in reaction time. The introduction of 4 Å molecular sieves to the reaction mixture significantly improved regioselectivity but had a notable adverse effect on enantioselectivity.

The absolute configuration of the products was assigned based on the crystallographic analysis. Considering the molecular structure of the resulting product, a plausible transition state **80** was conceptualized (Fig. 3). The (DHQD)$_2$AQN catalyst **76**, adopting an open conformation, interacted with the aurone **1**. This substrate was stabilized by π–π stacking interactions between the phenyl ring of benzofuranone and the quinoline moiety. The attack occurred at the *Re*-face of the substrate, with the zwitterion intermediate formed by the combination of the allenoate and the quinuclidine nitrogen atom. A notable feature of this methodology was its successful cyclization strategy, which enabled the creation of an all-carbon tertiary chiral centre within the dihydropyran-fused benzofuran framework. Consequently, a series of chiral dihydropyran-fused benzofuran derivatives were obtained with satisfactory regioselectivity.[65]

In 2015, Rasmas Mose and co-workers showcased an organocatalytic approach for cross-dienamine activation, leading to
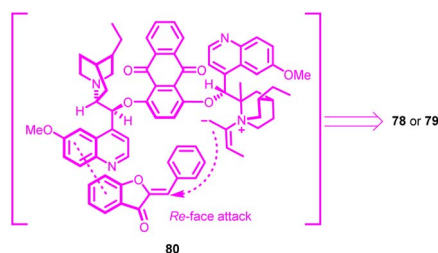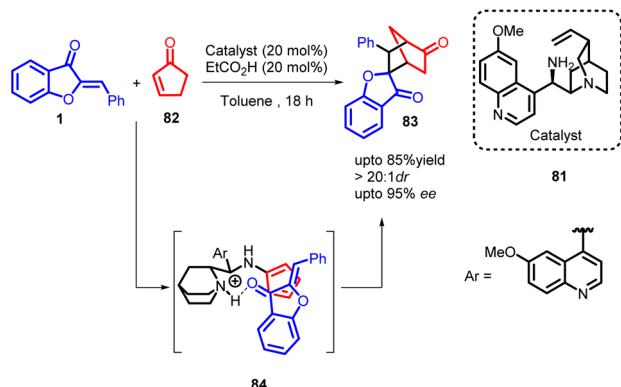
Fig. 3 The transition state.

Scheme 29 Synthesis of multifunctionalized norcamphor scaffolds by asymmetric organocatalytic Diels−Alder reactions.

Scheme 30 Palladium−titanium relay catalysis enables synthesis of spiro-heterocycle.

the synthesis of chiral multifunctionalized norcamphor compounds **83** with a wide range of substitution patterns (Scheme 29). The mechanistic insights into the organocatalytic intramolecular aldol reaction catalysed by primary amines derived from cinchona alkaloids suggest a closely related transition state **84** for this intermolecular aminocatalyzed Diels–Alder reaction. Initially, the cinchona alkaloid aminocatalyst undergoes condensation with cyclopentenone to form a cross-dienamine intermediate. The dienophile is then activated and guided to the appropriate position *via* hydrogen bonding upon protonation of the quinuclidine part of the catalyst. Following the cycloaddition step, the resulting enamine is hydrolyzed to produce the corresponding ketone while releasing the amino-catalyst. Considering the diastereoselectivity achieved, it appears that the reaction likely proceeds through an asynchronous concerted cycloaddition, given the high diastereomeric ratio of more than 20 : 1.

The investigation demonstrated that the catalyst derived from quinine outperformed all other catalysts employed, leading to a favourable yield of compound **83** with high enantioselectivity. This method presents a direct and versatile approach for generating 5,6-substituted norcamphor derivatives **83** through an asymmetric organocatalytic process. Importantly, the reaction conditions exhibited a remarkable level of versatility, enabling the use of common electron-deficient olefins in the cycloaddition reaction without requiring extensive modifications. The resulting norcamphor scaffolds **83** were consistently obtained with good to high yields and displayed a high degree of stereoselectivity. This approach provides an efficient and streamlined route for synthesizing a significant class of essential privileged structures.[66]

In 2018 L. C. Yang *et al.*, reported a different Lewis-acid-assisted palladium catalysed method for the syntheses of [5,5] and [6,5] spiro heterocycles **91** (Scheme 30). There was an extraordinary switch from alkoxide-*p*-allyl to dienolate reactivity which was achieved by using Pd–Ti relay catalysis and also Umpolung reactivity of the vinylethylene carbonates **85** was represented.

The mechanism for the [4 + 2] cycloaddition is shown in Scheme 31, which describe palladium–titanium relay catalysis.
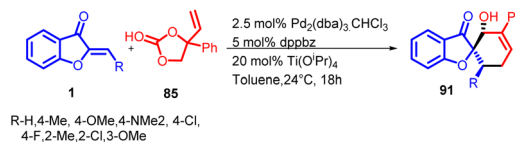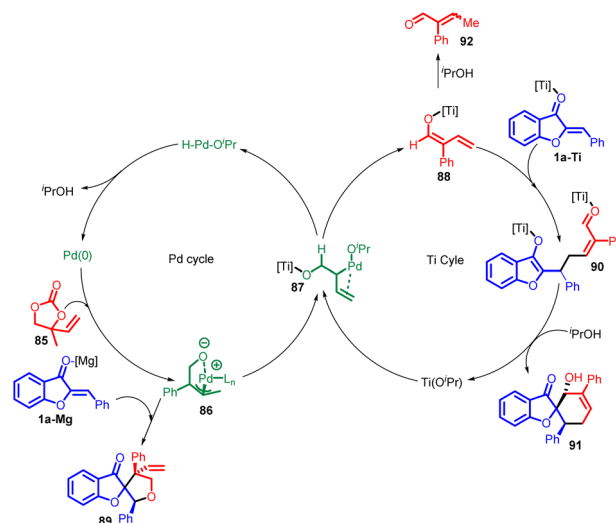
Scheme 31 Proposed mechanism for the synthesis of spiro-heterocycle.

The Pd-π-allyl intermediate **86** is formed from **85** and Pd (0). On one hand, **86** could undergo standard [3 + 2] cycloaddition with the electrophilic aurone **1a** (using Mg as a Lewis acid) to produce **89**. On the other hand, **86** may react with Ti(O^{i}Pr)$_4$ to form an alternative intermediate **87**, in which ligand exchange between Ti and Pd is proposed to free up the alkoxide–Pd coordination and enable β-hydride elimination to produce the titanium-dienolate **88**. The palladium–hydride isopropoxide complex released from this step then undergoes reductive elimination to complete the palladium catalytic cycle. In the titanium catalytic cycle, the formation of **88** converts the electrophilic Pd-π-allyl into a nucleophilic titanium-dienolate. The aurone **1a** is also likely activated by the titanium-based Lewis acid, and undergoes a reaction with **87** in a formal vinylogous Michael addition. The resultant intermediate **90** undergoes intramolecular aldol followed by protonation to yield the desired product **91**. In the presence of a chiral titanium complex, the formation of **90** may proceed in an enantioselective fashion.[67]

[4 + 3] Cycloaddition reaction

The [4 + 3] cycloaddition reaction involves a formal cycloaddition between an allylic cation and a diene, resulting in the creation of a seven-membered ring. Apart from its intrinsic significance as a potentially pericyclic reaction involving a reactive entity, this reaction pattern is notable for forming

a seven-membered ring structure. The notation [4 + 3] indicates the total count of atoms participating in the ring-forming process. Electron-wise, the reaction corresponds to a [4 + 2] cycloaddition since the allylic cation dienophile possesses only two π electrons. As such, this reaction can be seen as a counterpart of the Diels–Alder reaction in terms of electron count and mechanism.[68–70]

Zuo and Trost in 2019 reported a significant advancement in the field of organic synthesis involving a palladium-catalysed enantioenriched asymmetric [4 + 3] cycloaddition to create seven-membered scaffolds. This innovative process led to the production of numerous benzo[b]oxepines **95** using a wide range of donors and acceptors, showcasing exceptional levels of chemo-, regio-, diastereo-, and enantioselectivity (Scheme 32).

The reaction follows a sequence involving the zwitterionic Pd-trimethylenemethane (Pd-TMM) intermediate **96** (Fig. 4). This intermediate is formed *in situ* through the ionization of the donor. Subsequently, base-assisted deprotonation occurs, followed by nucleophilic addition to the acceptors. This series of steps leads to the creation of the zwitterionic Pd-TMM intermediate. The nucleophilic attack onto the Pd-π-allyl intermediate can occur from either end of the allyl anion, resulting in the formation of different cyclic products. The regioselectivity of this process heavily relies on the substantial contrast in nucleophilicity and steric hindrance between these positions. Notably, the nucleophilic attack at the terminal position of the π-allyl intermediate is favoured over the internal nucleophilic attack, leading to the formation of a solitary [4 + 3] cycloadduct. The enantioselective and diastereoselective [4 + 3] product by induction of chiral palladium species.

Unlike the conventional TMM cycloaddition process, this approach exhibits distinctive regioselectivity. The practical advantage of employing two easily accessible reactants
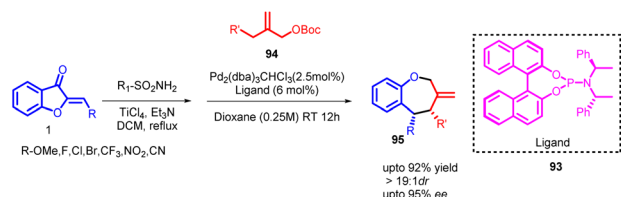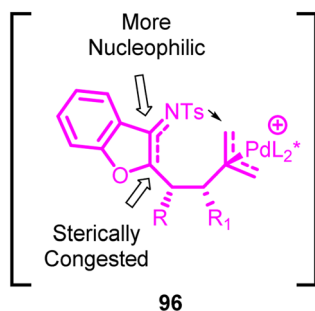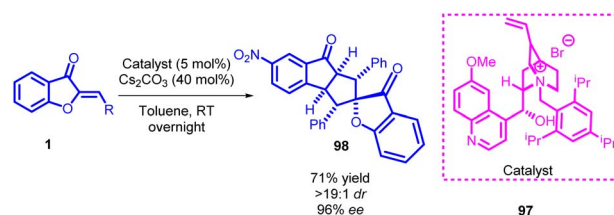
significantly influences the feasibility of this synthetic strategy. Furthermore, the resulting seven-membered products constitute foundational structures in numerous vital bioactive compounds.[71]

[10 + 2] Cycloaddition reaction

Exploring higher-order cycloaddition processes offers an intriguing strategy for constructing intricate polycyclic frameworks through a convenient one-step reaction. Despite the well-established nature of the Diels–Alder and 1,3-dipolar cycloaddition reactions involving 6π-electrons, the advancement of higher-order cycloadditions encompassing more than 6π-electrons has been relatively limited. This restraint is likely attributed to challenges posed by intricate regio- and chemoselectivity, along with potential competing pathways. Through a comprehensive examination of existing literature, it has been identified that cyclic polyene species known as isobenzofulvenes, initially investigated by Hafner and Bauer in 1968, exhibit notable potential as highly reactive 8π- or 10π-synthons in diverse cycloaddition reactions.[62] Classified as a pericyclic reaction, the [10 + 2] cycloaddition follows a cyclic transition state and involves the reconfiguration of pi-electrons. This reaction has gained notable attention for its capacity to efficiently generate intricate and complex structures within a single step. It finds application in the synthesis of a wide array of compounds, particularly in the construction of innovative and distinctive cyclic architectures, holding significant promise across diverse realms of chemistry.[72,73]

In 2020, Yang Yang *et al.*, introduced a groundbreaking advancement in the realm of organic synthesis. They presented a chemoselective and asymmetric cross [10 + 2] cycloaddition reaction. This novel process involved a diverse range of activated electron-deficient alkenes, such as aurones **1**. Even when utilizing catalyst loadings as low as 1 mol%, the reaction displayed impressive results, yielding a variety of fused molecular frameworks that exhibited multifunctional characteristics. These outcomes were achieved with remarkable levels of diastereo- and enantioselectivity (Scheme 33).

The research unveiled that activated aurones **1** can engage in highly selective cross-formal [10 + 2] cycloaddition reactions with various electron-deficient alkene substrates. Under chiral phase transfer catalytic conditions, aurones could be effectively converted into dearomative 1-hydroxyl isobenzofulvene-type species. Notably, despite the spatial separation between the

Scheme 32 Synthesis of tetrahydroazepines and benzo[b]oxepines through palladium–catalyzed [4 + 3] cycloaddition reactions.

Fig. 4 Transition state.

Scheme 33 Asymmetric cross [10 + 2] cycloadditions of aurones and activated alkenes.

reactive site and the chiral ion pair complex, exceptional dia-stereo- and enantioselectivity were consistently achieved. This was accomplished through the utilization of a newly devised cinchona-based ammonium salt **97** featuring a sizable substituent. Impressively, this catalyst design operated at notably low loadings (1 mol%), leading to a diverse array of fused frameworks characterized by substantial structural intricacy and adaptability.[73]

Annulation reaction

The term "annulation" originates from the Latin word "annulatus," meaning "ringed," and it pertains to the creation of rings in organic chemistry. This concept involves the process of introducing a ring structure onto an existing system, regardless of its cyclic or non-cyclic nature. The newly added ring can vary in size, although 5- and 6-membered rings are the most common. This wide-ranging definition encompasses reactions that might not traditionally be seen as annulation reactions, such as Diels–Alder reactions, acid-catalyzed polyolefinic cyclizations, photochemical, radical, and thermal cyclizations. Annulation reactions can be categorized based on how a 3-ketoalkyl chain is attached, which includes Michael reactions, nucleophilic additions (using Grignards, ylides, *etc.*), and alkylations. Additionally, annulation reagents can be further classified into those designed to add single rings sequentially (known as mon-annulation reagents) and those that introduce multiple ring segments simultaneously, referred to as bis- or tris-annulation reagents.[74]

In 2018, Xueji Ma *et al.*, introduced an efficient method for the annulation of α-imino rhodium carbenes with aurones **1** (α,β-unsaturated ketones) (Scheme 34). This innovative approach resulted in the synthesis of versatile 2,3-dihydropyrrole derivatives **103** with multiple substituents. Importantly, this method was also effective with typical linear α,β-unsaturated ketones.

The proposed catalytic cycle for generating the desired products (compounds **103** and **104**) is delineated in Scheme 35. This depiction draws upon both experimental observations and established scientific literature. Initially, a triazole compound **99** triggers the generation of α-imino rhodium carbene species **100**, facilitated by the presence of a Rh(II) catalyst. Subsequently, the oxygen atom of the α,β-unsaturated ketone participates in a nucleophilic attack on the carbene species, leading to the formation of oxonium ylide species **101**. The imino group of
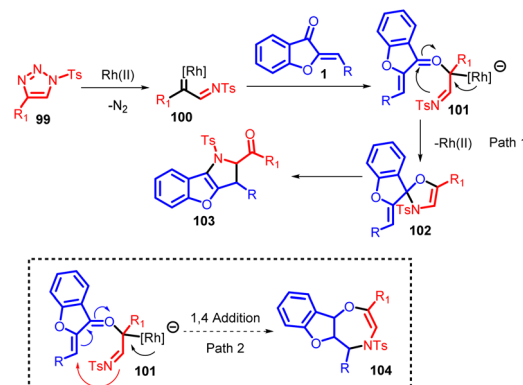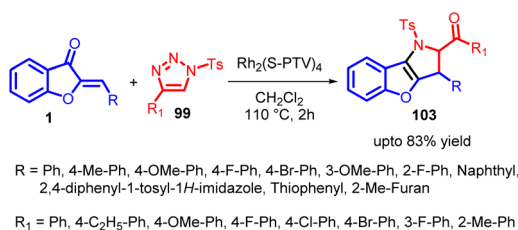

Scheme 35 Proposed mechanism for the synthesis of 2,3-dihydropyrrole.

species **101** then engages in a nucleophilic attack on the carbon atom of the carbonyl group, resulting in a 1,2-addition process that yields oxazole compound **102**. However, due to its inherent instability, compound **102** undergoes cleavage of the C–O bond, leading to rearrangement and ultimately generating the multi-substituted 2,3-dihydropyrrole **103**. Alternatively, species **101** can undergo intramolecular ring closure reactions, forming seven-membered heterocyclic products. Notably, the entire experimental study did not detect any products arising from 1,4-addition reactions. This high degree of selectivity can be attributed to the strong electron-attracting nature of carbonyl groups toward amino groups, promoting the formation of five-membered rings as the preferred outcome over seven-membered rings.

The methodological procedure outlined in this study underscores the evident nucleophilic behaviour of α,β-unsaturated ketones towards α-imino rhodium carbenes. This observation holds significant potential for rapidly generating molecular complexity, a valuable trait for synthesizing diverse bioactive pharmaceutical compounds.[75]

Michael/Mannich reaction of aurones

The Mannich–Michael reaction stands as a potent organic transformation, combining the fundamental Mannich reaction and Michael addition. This sequential process enables the synthesis of intricate molecules bearing diverse functionalities and stereocenters. In the Mannich reaction, a primary or secondary amine reacts with a carbonyl compound (aldehyde or ketone) and a proton-source compound (like enolizable ketones or imines). This leads to the nucleophilic addition of the amine to the carbonyl, followed by the elimination of a leaving group, resulting in β-amino carbonyl compounds.[76] Conversely, Michael addition involves a nucleophile (often enolates or enols) reacting with an α,β-unsaturated carbonyl compound (α,β-unsaturated ketone or ester), forming a new carbon–carbon bond.[77,78] In the Mannich–Michael reaction, an amine reacts with an α,β-unsaturated carbonyl compound in the presence of a proton-source substance. The amine's initial interaction with the carbonyl generates an intermediate through Mannich

Scheme 34 Rhodium-catalyzed annulation of α-imino carbenes with α,β-unsaturated ketones.

R = Ph, 4-Me-Ph, 4-OMe-Ph, 4-F-Ph, 4-Br-Ph, 3-OMe-Ph, 2-F-Ph, Naphthyl, 2,4-diphenyl-1-tosyl-1*H*-imidazole, Thiophenyl, 2-Me-Furan

R_1 = Ph, 4-C_2H_5-Ph, 4-OMe-Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 3-F-Ph, 2-Me-Ph

reaction, followed by Michael addition with another molecule of the carbonyl compound. This yields complex molecules with new carbon–carbon bonds and often multiple stereocenters. The Mannich–Michael reaction's versatility facilitates intricate structure creation and multiple bond and stereocenter formation in one step, finding application in synthesizing natural products, pharmaceuticals, and intricate molecules.[79]

In 2014, Song Ye and co-workers conducted a study wherein they utilized bifunctional N-heterocyclic carbenes (NHCs) **105** possessing a free hydroxy group as highly effective catalysts (Scheme 36). The aim was to facilitate the [3 + 4] annulation reaction between enals and aurones, yielding benzofuran-fused γ-lactones **110** with favourable outcomes in terms of yield, diastereoselectivity, and enantioselectivity. Importantly, this bifunctional NHC catalysis prevented the competitive formation of corresponding [3 + 2] cycloadducts. Their experiments demonstrated that the [3 + 4] cycloadducts were kinetically favoured over the thermodynamically preferred [3 + 2] cycloadducts. This behaviour changed when a non-bifunctional NHC catalyst was introduced, indicating that the [3 + 4] cycloadducts could transform into the [3 + 2] cycloadducts under these conditions.

The suggested mechanism for this catalytic process is illustrated in Scheme 37. Initially, the NHC **105** added to enals, generating the vinyl Breslow intermediate **107**. This

intermediate then underwent a Michael addition reaction with aurones, leading to the formation of adduct **108**. The presence of a possible hydrogen bonding interaction between the hydroxy group of the NHC **105** and aurones **1** was proposed to enhance reactivity and regulate both diastereoselectivity and enantioselectivity. Subsequently, intramolecular acylation of adduct **109** occurred, resulting in the formation of the ultimate cycloadduct **110** and concurrently regenerating the NHC catalyst. Another potential intramolecular hydrogen bonding interaction between the hydroxy and acyl azonium groups was suggested to transform the carbonyl into a stronger Lewis acid. This transformation facilitated the harder Lewis basic O-acylation of the enolate, favouring the production of the kinetically favoured [3 + 4] cycloadduct **110** while discouraging the formation of the [3 + 2] cycloadduct, which would result from a softer Lewis basic C-acylation pathway.

Pre-NHCs with hydroxy groups exhibiting higher acidity showed improved yields and similar levels of diastereoselectivity and enantioselectivity. During solvent evaluation, the most favorable results were obtained in 1,4-dioxane, leading to enhanced diastereomeric ratios (*dr*) and enantiomeric excess (*ee*). Additionally, a minor improvement in diastereoselectivity and enantioselectivity was observed when potassium acetate was used as the base, and a slight excess of the base had a positive impact on reaction yield. Ultimately, the reaction could be conducted at 40 °C, resulting in a high yield without compromising diastereoselectivity or enantioselectivity. These findings provide valuable insights for optimizing the reaction conditions for this process.[80]

In 2016, Satavisha Kayal *et al.*, introduced a novel cascade reaction that combines Michael addition and cyclization processes to achieve the synthesis of 3,2′-pyrrolidinyl bispirooxindole **113** derivatives with high enantioselectivity. This innovative approach involves the interaction between 3-isothiocyanato oxindoles **112** and exocyclic α,β-unsaturated ketones (aurone) **1**, all catalyzed by a quinine-derived bifunctional tertiary amino-squaramide catalyst **111** (Scheme 38). The resulting products, which possess three contiguous stereogenic centres, are exclusively obtained as a single diastereomer, typically with excellent yields and remarkable levels of enantioselectivity.[81]

In 2019, Wenjin Yan and co-workers synthesized a series of compounds showcasing inventive bispiro[benzofuranoxindole-pyrrolidine] **116** cores. This achievement was realized through the utilization of a thiourea-catalysed **114** 1,3-dipolar cycloaddition procedure (Scheme 39). A comprehensive assessment of catalysts helped in the identification of a more selective thiourea
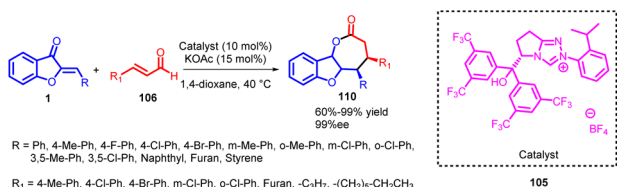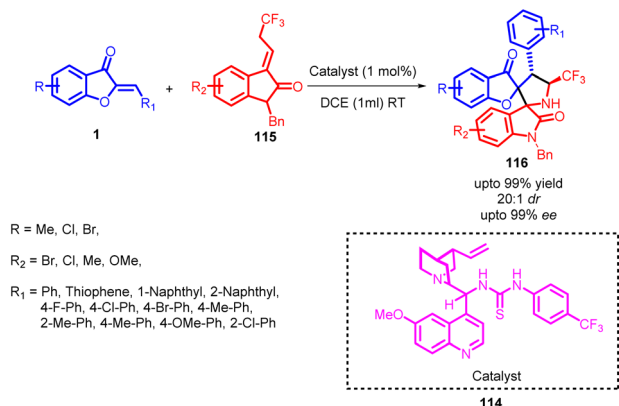

Scheme 36 Bifunctional N-heterocyclic carbene catalyzed [3 + 4] annulation of enals and aurones.
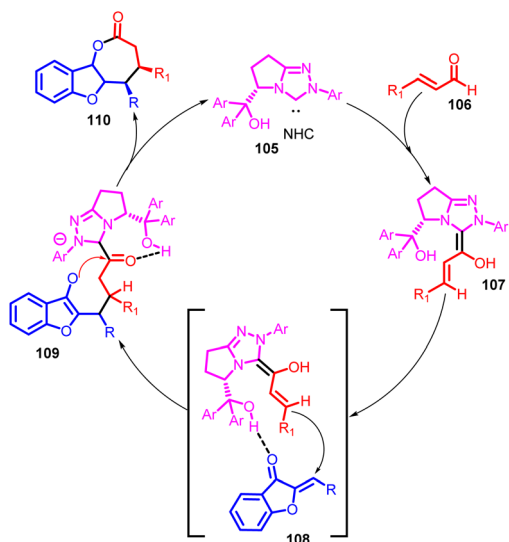
Scheme 37 Proposed catalytic cycle for the NHC catalyzed [3 + 4] annulation of enals and aurone.
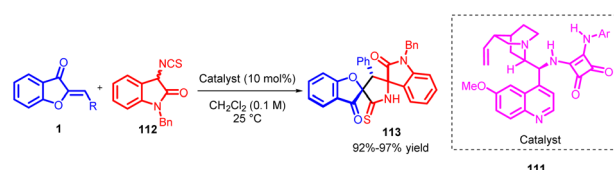
Scheme 38 Synthesis of 3,2′-pyrrolidinyl bispirooxindoles from 3-isothiocyanato oxindoles and α,β-unsaturated ketones.

Scheme 39 Synthesis of bispiro[benzofuran-oxindole-pyrrolidine]s through organocatalytic cycloaddition.

catalyst. This catalyst achieved an exceptional enantiomeric excess of 99%. Subsequent investigation into the impact of solvents revealed that alkyl halides were superior in terms of stereoselective performance compared to other solvents. Notably, 1,2-dichloroethane emerged as the optimal solvent, resulting in a remarkable 99% yield and an enantiomeric excess exceeding 99%. Given the remarkable efficiency of catalyst **114**, the study explored the use of lower catalyst loadings. Surprisingly, even with only 1 mol% of catalyst, the reaction maintained excellent enantioselectivity, diastereoselectivity, and yield, albeit with a slightly extended reaction time. These findings highlight the remarkable potential of this catalyst and its versatility in achieving high-quality results with reduced catalyst quantities. These products were characterized by their impressive yields and selectivity in terms of stereoisomer formation.

The reaction pathway involved the Michael/Mannich transformation of N-2,2,2-trifluoroethylisatin ketimines **115** with aurones **1**, ultimately giving rise to the production of cycloadducts. By analysing the X-ray crystallography of the resulting product's structure, a potential transitional state **117** (Fig. 5) was suggested for the gradual cycloaddition process. Initially, the activated azomethine ylide engages in a Michael addition to the aurone substrate, yielding an intermediate. This intermediate subsequently carries out an intramolecular Mannich reaction, directing its attack towards the Re-face of the imine. This sequence ultimately leads to the formation of the cycloadduct.[82]
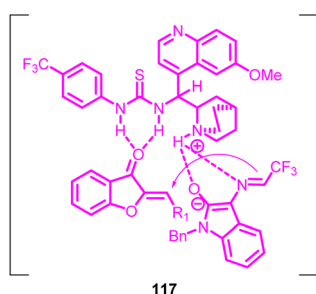
In 2022, Ze Zhang and co-workers introduced a successful iodine-promoted domino reaction involving aurones **1** and amidines **118**. This reaction unfolds in a sequential fashion, involving a series of steps including Michael addition, iodination, intramolecular nucleophilic substitution-driven cyclization, and spiro ring opening to achieve dehydrogenative aromatization. By adopting this innovative approach, a range of 1,2,4-trisubstituted 5-(O-hydroxybenzoyl)imidazoles were effectively synthesized with moderate to good yields, utilizing readily available starting materials (Scheme 40).

A plausible mechanism (Scheme 41) for this iodine-promoted domino reaction to generate fully substituted 5-(o-hydroxybenzoyl)imidazole **124** is postulated. Initially, an aza-Michael addition transpires between the reactants **1** and **118** in the presence of I_2, resulting in the formation of an adduct that exists in an equilibrium between ketone/imine **119** and enol/enamine **120**. Subsequent iodination of this adduct by I_2 leads to the creation of intermediate iodide **121**, which undergoes an intermolecular nucleophilic substitution event to yield the intermediate spiroimidazoline **123**. LC-MS analysis detects intermediates **119/120** and **121** during these stages. Concomitantly, 2 equivalents of HI are generated and captured by DMAP. Further, a base-mediated spiro ring opening of **123** facilitates dehydrogenative oxidation and aromatization, eventually yielding the desired product, imidazole **124**. Additionally, the interaction between I_2 and the oxygen atom within the spiro ring can potentially facilitate cleavage of the C–O bond.

This approach boasts several advantages, including being metal-free, operating under mild reaction conditions, promoting high atom economy, accommodating a broad substrate range, not necessitating the use of specialized or costly starting materials, and not requiring an excess of
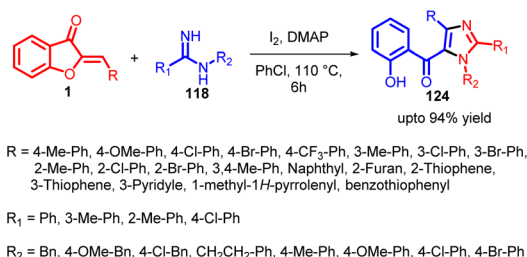
Scheme 40 Synthesis of fully substituted 5-(o-hydroxybenzoyl) imidazoles.


Fig. 5 Intermediate.
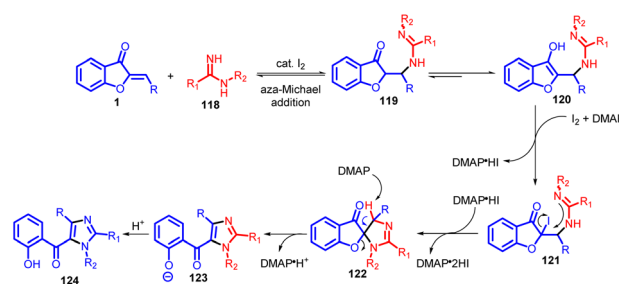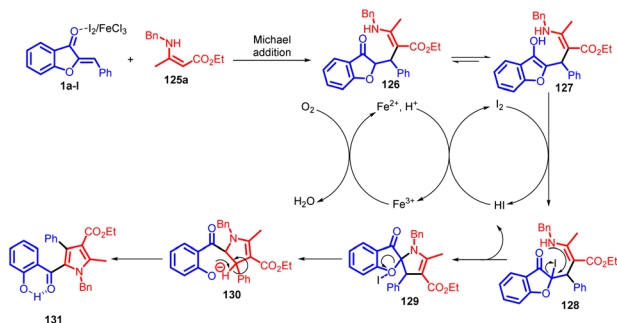

Scheme 41 Proposed mechanism.

oxidants. The strategy of spiro ring opening for the dehydrogenative aromatization of spiro compounds may have the potential for extension to the construction of diverse conjugated heterocycles.[83]

In 2022, Hui Xu *et al.*, introduced an innovative and effective $I_2/FeCl_3$-catalyzed domino reaction, combining aurones with enamino esters through a sequence of Michael addition, iodination, intramolecular nucleophilic substitution, and spiro ring opening processes (Scheme 42). This method initiates with a Michael addition involving **1** and **125** in the presence of either I_2 or $FeCl_3$, forming adduct **126**. This compound tautomerizes into the enol-form adduct **127**. Subsequently, **127** engages with I_2 through an electrophilic substitution to generate intermediate **128**, which then undergoes intramolecular nucleophilic substitution to yield spiro intermediate **129**. In the course of iodination from **127** to **128** and the subsequent cyclization of **128** into **129**, the generated HI is both further oxidized by Fe(III) to regenerate I_2 and simultaneously produce Fe(II). Oxygen then oxidizes Fe(II) back into Fe(III) to complete the catalytic cycle. Following this, aromatization occurs, leading to the final product **131** *via* an E_1-elimination of **130**, formed through spiro ring opening of intermediate **129** with the assistance of Lewis acid I_2 or $FeCl_3$ to facilitate C–O bond cleavage (Scheme 43).

This method facilitates the synthesis of a diverse range of highly functionalized pyrroles (**131**) with moderate to high yields and good functional group compatibility. The presence of a phenolic hydroxy group in the products offers the potential for subsequent functionalization. Notably, this novel reaction
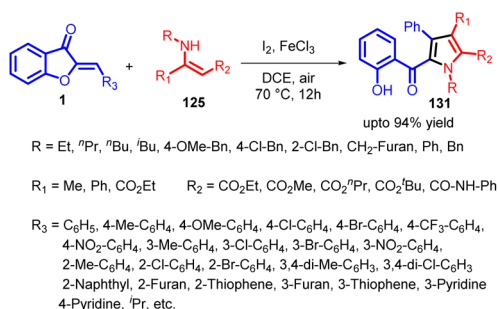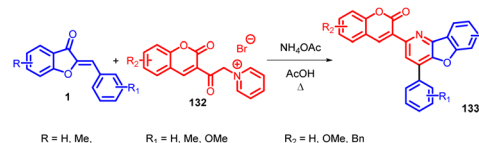
offers the benefits of operating under mild conditions, promoting high atom economy, and being suitable for large-scale synthesis. As a result, it is expected to emerge as a significant route for constructing conjugated nitrogen-containing heterocycles.[84]
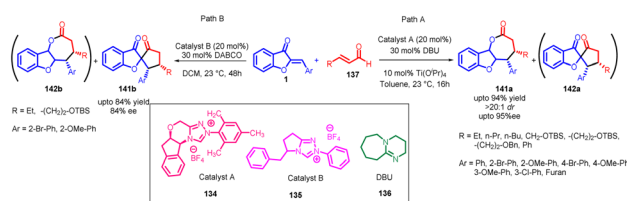
General reactions

Anil K. Patel *et al.*, in 2010 accomplished the synthesis of 3-(4-aryl-benzofuro[3,2-*b*]pyridin-2-yl)coumarins **133** using Kröhnke's reaction (Scheme 44). This transformation was achieved through the utilization of 3-coumarinoyl methyl pyridinium salts **132** and 2-arylidene aurones **1** as reactants. The reaction was facilitated by the presence of ammonium acetate and acetic acid as additives.[85]

In 2014, Min Wang *et al.*,[86] devised a method utilizing NHC catalysis for the divergent annulation of enals **137** with aurones **1**. This innovative approach yields either benzofuran-containing ε-lactones **141a** & **141b** or spiro-heterocycles **142a** & **142b** with remarkable diastereo- and enantioselectivity (Scheme 45). Notably, the selectivity is directed by the chiral catalyst's structural framework.

Building upon the distinctive stereochemical outcomes and drawing insights from earlier research by the Scheidt and Ye groups, a plausible mechanism was postulated. The process involves the generation of a homoenolate intermediate **138** through interaction between the enal and carbene catalyst. This intermediate then attacks the heterocyclic enone, yielding enolate **140**. The configuration of the newly formed stereocenters is orchestrated by the influence of the chiral catalyst, depicted in the transitional state model **139** (Scheme 46). It is worth noting that the enantioselectivity displayed similar levels for both the ε-lactones and spirocycle series, suggesting a shared intermediate. In cases where the enals bear linear aliphatic substituents (R), an impressive diastereomeric ratio of 20 : 1 was achieved. Conversely, when R is replaced with a bulkier aromatic group, steric interactions between –R, –Ar,

Scheme 42 $I_2/FeCl_3$ catalysed domino reactions of aurones with enamino esters.

Scheme 43 Proposed mechanism for the domino reaction to form pyrroles.

Scheme 44 Synthesis of 3-(4-arylbenzofuro[3,2-*b*]pyridine-2-yl) coumarins from aurones.

Scheme 45 Stereoselective synthesis of ε-lactones or spiro-heterocycles through NHC-catalysed annulation.
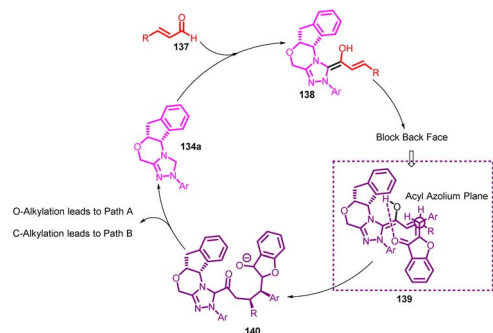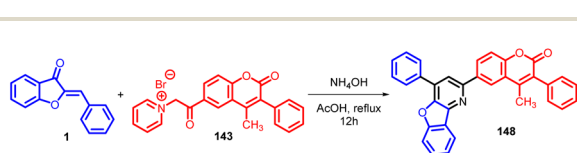
Scheme 46 Proposed mechanism for the stereoselective synthesis of ε-lactones or spiro-heterocycles.

and the heterocyclic backbone might trigger alternative conformations, leading to reduced diastereoselectivity.[86]
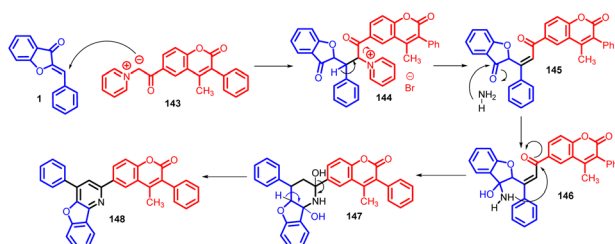
In 2015, Rakesh R. Giri *et al.*, synthesised 4-methyl-3-phenyl-6-(4-phenyl-benzofuro[3,2-*b*] pyridin-2-yl) coumarins **148** *via* Michael addition approach, involving the nucleophilic attack of the active methylene group from 4-methyl-3-phenyl-6-coumarinoyl methyl pyridinium salt **143** onto the α,β-unsaturated carbonyl moiety presents in aurones **1** (Schemes 47 and 48).

Subsequently, the synthesized compounds were subjected to antimicrobial testing against a range of microorganisms including *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Salmonella typhi*, *Candida albicans*, and *Aspergillus niger*. The outcome of these assays revealed noteworthy antimicrobial efficacy of the synthesized compounds against the tested strains.[87]

During investigations into the synthesis and chemical properties of spiroheterocycles, Moncef Msaddek and co-workers in 2014 revealed that when they subjected aurone **1** derivatives to a reaction with 2-diazopropane **149**, it led to the formation of spirocyclopropane **150** compounds. While the anticipated outcome primarily comprised the formation of cycloadducts, there was an unexpected result in certain

instances: the generation of oxadiazole **151** compounds. This unforeseen occurrence added an interesting dimension to their research findings (Scheme 49).[88]

Łukasz Albrecht and coworkers in 2016 reported an enantioselective synthesis of spirocyclic tetrahydrothiophene **154** compounds featuring a benzofuran-3(2*H*)-one structural motif. This innovative approach makes use of aurone **1** and 2-thioacetaldehyde, which is formed *in situ* from 1,4-dithiane-2,5-diol **153**, as the initial building blocks (Scheme 50). The process follows a sequential cascade mechanism involving a thio-Michael-aldol reaction sequence.

The stereochemical outcome of this reaction was finely controlled through the utilization of a bifunctional catalyst derived from cinchona alkaloids, with a squaramide functional group. This strategy allowed for precise manipulation of the desired stereochemistry in the resulting compounds.[89]

Shanshan Ma *et al.*, in 2020 developed a novel phosphine promotion to facilitate a domino reaction between aurone derivatives **1** and MBH carbonate **155** (Scheme 51). This strategy enables the efficient synthesis of [6-5-5-6-6] pentacyclic compounds that incorporate benzothiophene and tetrahydroquinoline frameworks **163** and **164**. These intricate structures are typically challenging to construct using conventional synthetic methods. The researchers successfully prepared a diverse array of [6-5-5-6-6] pentacyclic compounds **163** and **164** in a highly efficient manner.
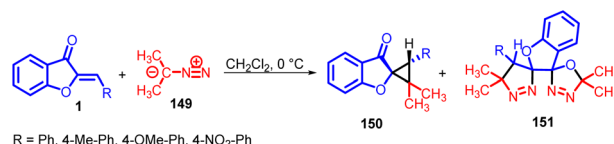
Scheme 49 Synthesis of spirocyclopropane and oxadiazole from aurones.

Scheme 47 Synthesis of modified pyridine-substituted coumarins from aurones.

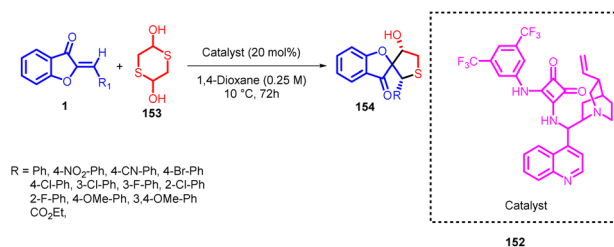**Scheme 50** Enantioselective synthesis of spirocyclic tetrahydrothiophene derivatives bearing a benzofuran-3(2*H*)-one scaffold.

Scheme 48 Proposed mechanism for the synthesis of modified pyridine substituted coumarines.
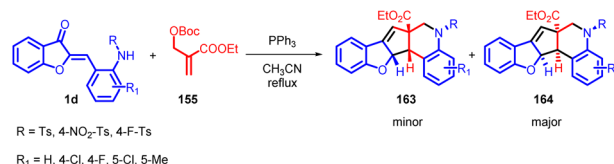
Scheme 51 Synthesis of [6-5-5-6-6] pentacyclic *via* phosphine catalysed domino reaction.

The proposed mechanism involves the interaction between MBH carbonate **155** and PR$_3$ to generate a phosphorus ylide **156**, along with ^{t}BuOH and CO$_2$ (Scheme 52). The ensuing deprotonation of **1d** by phosphorus ylide **157** leads to the formation of intermediate **158**. Subsequent steps encompass the nucleophilic addition of **158** to **157**, accompanied by the removal of PPh$_3$, resulting in intermediate **159**. This intermediate is subject to nucleophilic attack by PPh$_3$ at the terminal alkene carbon, initiating a cycloaddition reaction that yields intermediate **161**. A proton transfer process leads to the formation of intermediate **162**. Ultimately, an intramolecular Wittig reaction involving intermediate **162** brings forth the desired products **163** and **164**, completing the synthetic pathway.[90]

Arjun Kafle *et al.*, attempted to prepare azido-substituted aurones *via* a copper catalysed azidation in 2020 (Scheme 53). But the intended product could not be produced instead an uncommon triazole product **165** was formed. During the further studies it was noted that copper catalyst is not required for this synthesis instead simple thermal treatment with sodium azide in a polar aprotic solvent was enough to achieve this uncommon product.

The mechanism of the reaction is unclear. It uncertain that some form of Michael addition/elimination/cyclization sequence, a cycloaddition/elimination sequence, or elimination to an intermediate ynone followed by cycloaddition is occurring. Elimination/cycloaddition would seem to be the simplest mechanistic explanation for this reaction in view that ynones are reacting with sodium azide to produce triazoles. Although attempts for aynone intermediate was unsuccessful. The product triazoles have two distinct sites for alkylation chemistry and offer several opportunities for modification. It is believed that, given this potential and their accessibility, they may prove to be novel, untested scaffolds for more development.[91]
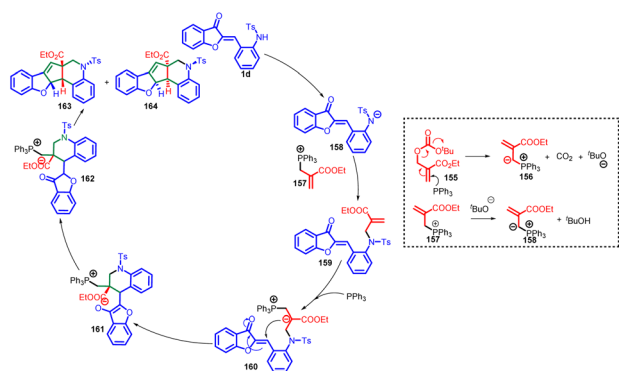
Scheme 52 Proposed mechanism for the synthesis of [6-5-5-6-6] pentacyclic skeleton.

R–Br, Cl, F, Me
Ar-4-NCC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 4-MeC$_6$H$_4$
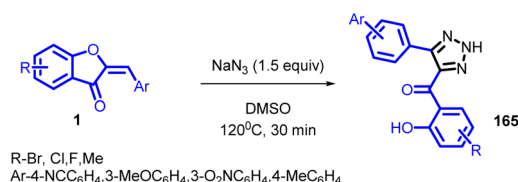
Scheme 53 Triazole synthesis from aurones.

Conclusion

In summary, this concise review offers an insightful update on the versatile synthetic capabilities of aurones, primarily attributed to their distinctive electronic properties. These properties render aurones valuable candidates for a wide array of chemical reactions, including cycloadditions, annulations, and Michael/Mannich reactions. The pivotal role of the α,β-unsaturated ketone within aurones is evident, facilitating favoured nucleophilic addition at the carbonyl carbon and β-carbons, while also promoting electrophilic addition at the carbonyl oxygen. Notably, cycloaddition reactions with aurones have yielded intricate and intriguing molecular structures, encompassing benzofuranone-appended spiro-heterocyclic scaffolds through [3 + 2] cycloadditions, benzofuranone-fused pyrans *via* [4 + 2] cycloadditions, and even oxepane ring formation *via* [4 + 3] cycloadditions. Furthermore, aurones demonstrate exceptional selectivity in cross-formal [10 + 2] cycloaddition reactions with electron-deficient alkene substrates, resulting in the formation of dearomative 1-hydroxyl isobenzofulvene-type species. Additionally, under various conditions, Michael/Mannich reactions of aurones yield diverse products, including benzofuranone-appended spiro-heterocyclic compounds, benzofuran-fused oxepanones, and ring-opened derivatives. An in-depth understanding of these synthetic transformations, including their proposed mechanisms, not only enhances our comprehension of these processes but also encourages the scientific community to explore the myriad possibilities offered by aurone cores, thus propelling advancements in the field of organic synthesis.

Abbreviations

(DHQD)$_2$AQN	Hydroquinidine(anthraquinone-1,4-diyl)diether
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMAP	Dimethylaminopyridine
dr	Diastereoselectivity
ee	Enantiomeric excess
LC-MS	Liquid chromatography-mass spectrometry
MBH	Morita–Baylis–Hillman
NHC	N-Heterocyclic carbene
Pd-TMM	Pd-trimethylenemethane
TAC	Three atom components
TBME	*tert*-Butyl methyl ether
THF	Tetrahydrofuran
TsDAM	Tosyldiazomethane
32CA	[3 + 2] Cycloaddition

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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