

Review

Further developments of β,γ -unsaturated α -ketoesters as versatile synthons in asymmetric catalysisRuixian Deng,^{1,*} Tian-Jiao Han,¹ Xiang Gao,¹ Yuan-Fu Yang,¹ and Guang-Jian Mei^{1,*}

SUMMARY

β,γ -Unsaturated α -ketoesters prove to be versatile organic synthons participating in diverse catalytic asymmetric transformations with the breathtaking development of organo-catalysis, new catalytic systems including ingenious chiral ligands as well as Lewis acid cations. The highly efficient creation of stereogenic centers with excellent enantioselectivity is not a surprise, but owes to the bidentate coordination of its unique 1,2-dicarbonyl motif to artful chiral messenger, establishing a rigid system for the precise chiral-identification of the attack. In the past five years, various reaction modes of β,γ -unsaturated α -ketoesters have been developed, involving their multiple reaction sites, such as the carbon-carbon double bond (C=C), the carbonyl group (C=O), the entire C=C-C=O fragment, and the ester group. In this review, we summarize the state-of-the-art catalytic asymmetric reactions of β,γ -unsaturated α -ketoesters, to provide an updated overview to chemists working in this and related fields, facilitating their discoveries in asymmetric catalysis, natural products synthesis, and drug development.

INTRODUCTION

Rapid preparation of complex structures from readily accessible starting materials with multiple reaction modes in a catalytic asymmetric manner is one of the central themes in synthetic chemistry. The resulting chiral molecules with structural complexity and diversity are not only important synthons in organic synthesis, but also of great significance and value for hit-to-lead optimization efforts in medicinal chemistry (Kim and Li, 2020; Mei et al., 2021; Xiao et al., 2020). In this context, β,γ -unsaturated α -ketoesters are a class of privileged unsaturated carbonyl derivatives, because of their unique 1,2-dicarbonyl system. This large conjugated system has a specific advantage of multiple reactive sites, which could diversify the reaction modes and broaden their applications in organic synthesis. Besides, the bidentate coordination of 1,2-dicarbonyl motifs with chiral catalysts could increase the reactivity of substrates and the enantio-control of reactions. This intrinsic property makes them popular precursors in asymmetric catalysis for efficient creation of stereogenic centers. Consequently, β,γ -unsaturated α -ketoesters have emerged as attractive and versatile synthons in modern organic synthesis.

Structurally, the presence of the adjacent ester group greatly contributes to the electrophilicity of the ketonic carbonyl group and its neighboring carbon-carbon double bond. The combination of this intrinsic electronic feature and their particular conjugated system results in a rich chemistry of β,γ -unsaturated α -ketoesters involving the carbon-carbon double bond (C=C), the carbonyl group (C=O), the entire C=C-C=O fragment, or the ester group (Figure 1). Typically, β,γ -unsaturated α -ketoesters are employed as good acceptors in 1,4-addition reactions of the C=C bond and 1,2-addition reactions of the C=O group. And the resulting chiral ketoester compounds and tertiary alcohols are versatile chiral building blocks in organic synthesis. In addition, β,γ -unsaturated α -ketoesters are useful and appealing precursors for chiral cyclic compounds. For instance, they can serve as two-atom (2A) synthons in various [2 + n] annulation reactions by making use of the C=C bond or the C=O group. Besides, by reacting with dinucleophiles (Nu-Nu), β,γ -unsaturated α -ketoesters function as dual electrophilic reagents (E-E) in [3 + n] annulation reactions. When it comes to the entire C=C-C=O moiety, β,γ -unsaturated α -ketoesters act as ambident reagents (4A) to afford multiple [4 + n] annulation reactions. Finally, their ester group involved transformations further enrich the reaction modes of β,γ -unsaturated α -ketoesters.

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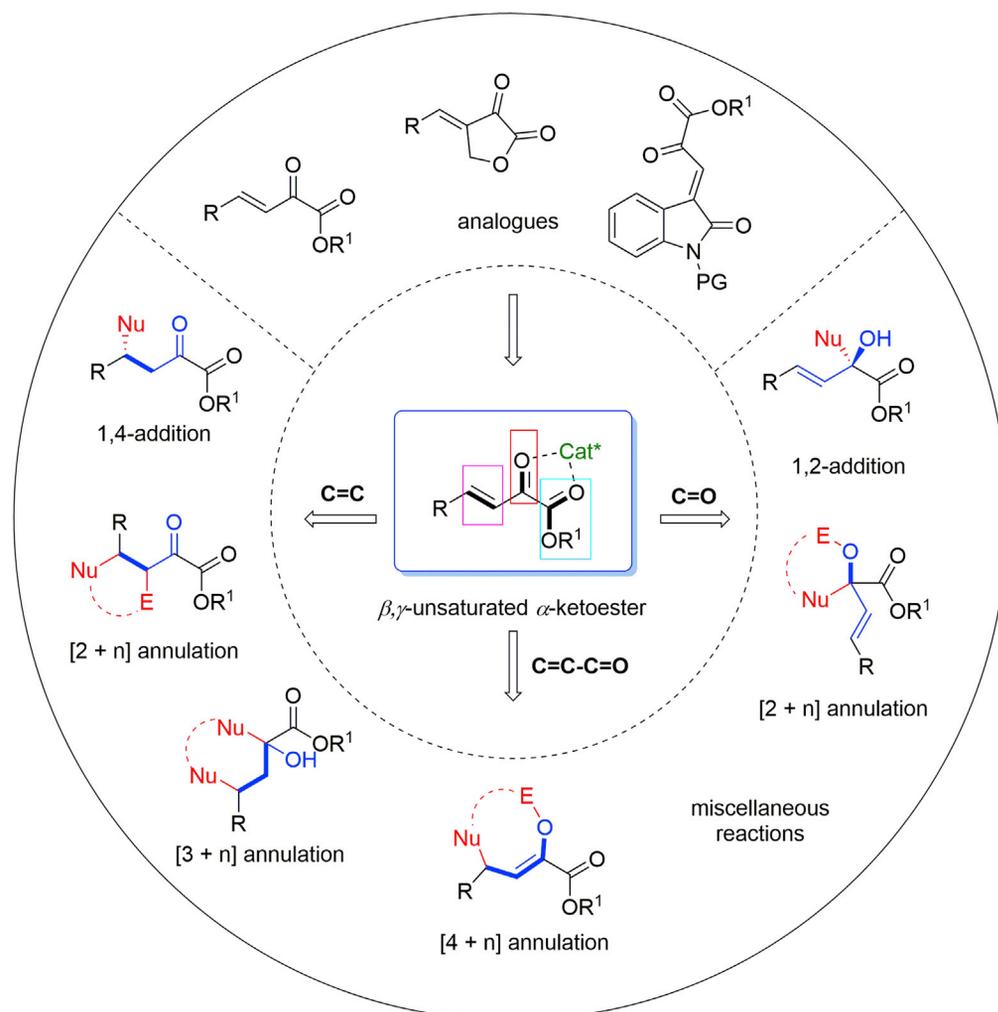


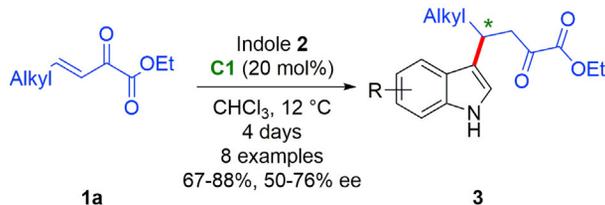
Figure 1. The reaction modes of β,γ -unsaturated α -ketoesters in asymmetric catalysis

The past decades have witnessed significant advancements in this field. In 2013, Desimoni and coworkers reviewed the earlier examples on catalytic asymmetric reactions of β,γ -unsaturated α -ketoesters (Desimoni et al., 2013). Then, Eftekhari-Sis and coworkers demonstrated their power in the synthesis of heterocycles in 2015 (Eftekhari-Sis and Zirak, 2015). With the breathtaking development of chiral ligands and catalysis, the β,γ -Unsaturated α -ketoesters have become versatile organic synthons over the years, especially in asymmetric synthesis. In this timely review, we would like to summarize the latest developments of catalytic asymmetric reactions of β,γ -unsaturated α -ketoesters from 2015, to provide an updated overview to chemists working in this and related fields, facilitating their discoveries in asymmetric catalysis, natural products synthesis, and drug development. We are paying close attention to the diversified reaction modes of β,γ -unsaturated α -ketoesters. This review is categorized accordingly, including 1,4-addition, 1,2-addition, [2 + n] annulation, [3 + n] annulation, [4 + n] annulation, and others.

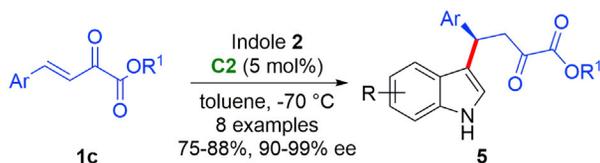
CATALYTIC ASYMMETRIC 1,4-ADDITION REACTIONS

Indole derivatives are fascinating and important heterocyclic compounds, owing to their wide occurrence in a large number of natural products and pharmacologically active agents. The catalytic asymmetric Friedel-Crafts reaction of indoles proves to be one of the most direct approaches to enantiomerically enriched indole compounds. In this context, β,γ -unsaturated α -ketoesters have emerged as particularly interesting activated electrophiles, in terms of their good electrophilicity and easy further manipulation at late stage. In 2015, Marqués-López, Herrera and coworkers developed a thiourea-catalyzed Friedel-Crafts reaction of indoles with aliphatic β,γ -unsaturated α -ketoesters (Scheme 1A) (Juste-Navarro

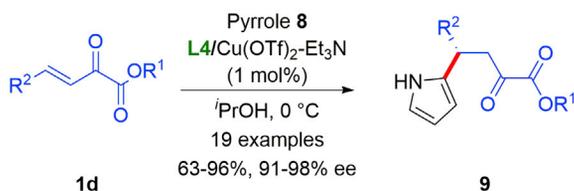
A Marqués-López and Herrera *et al.* 2015



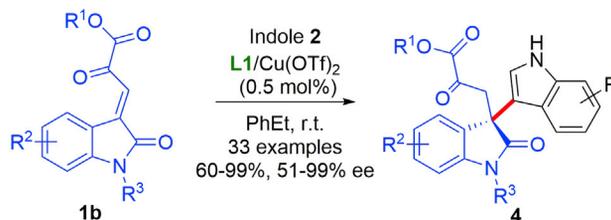
C Luo *et al.* 2015



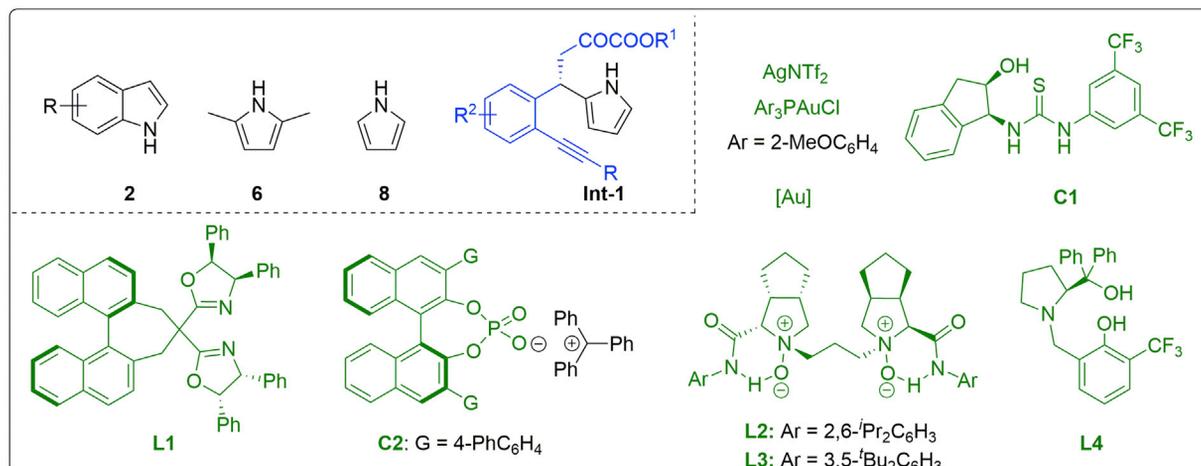
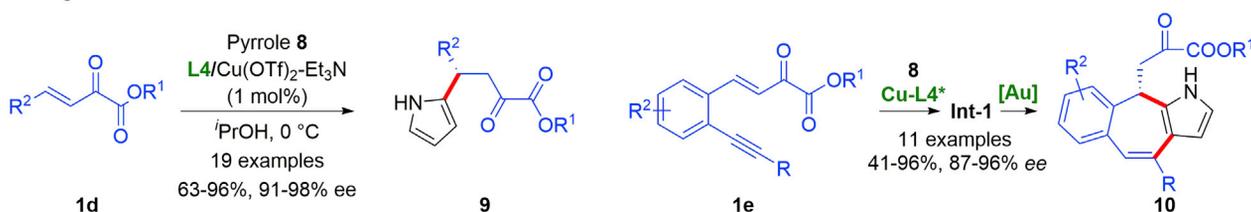
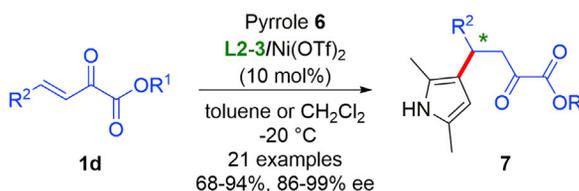
E Wang *et al.* 2015



B Wang *et al.* 2016



D Feng *et al.* 2015



Scheme 1. Catalytic asymmetric Friedel-Crafts reaction with electron-rich heterocycles

et al., 2015). The authors highlighted the use of aliphatic substrates, which are usually overlooked in comparison with the commonly reported aromatic β,γ -unsaturated α -ketoesters. Under mild reaction conditions, the Friedel-Crafts adducts were obtained in good yields (67–88%) and moderate enantiomeric excess (50–76% ee). In 2016, the Wang group demonstrated that the Friedel-Crafts reaction of indoles with isatin-derived β,γ -unsaturated α -ketoesters 1b could be employed as a practical method for chiral bis-indole products 4 bearing a quaternary stereocenter, a kind of naturally occurring motifs (Scheme 1B) (Li *et al.*, 2016b). Chiral BINOL-derived bisoxazoline (BOX)/copper (II) complex was evaluated as the best catalyst with a low loading of 0.5 mol%. The desired products were obtained in excellent yields (60–99%) and enantioselectivities (51–99% ee), which could be transformed to α -amino esters, α -hydroxy esters and α -keto amides.

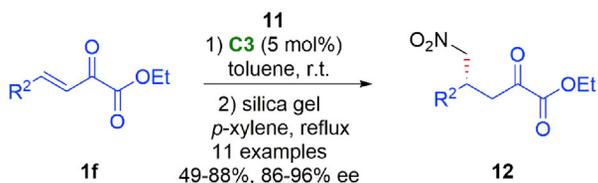
In light of the significance of asymmetric Friedel-Crafts reaction of indoles with β,γ -unsaturated α -ketoesters in organic synthesis, diversified catalytic systems were developed to guarantee the reaction efficiency and enantioselectivity. For instance, Luo et al. found that the asymmetric carbocation catalysis with chiral trityl phosphate could be utilized as an effective strategy for the Friedel-Crafts reaction between unprotected indoles **2** and β,γ -unsaturated α -ketoesters **1c** (Scheme 1C) (Lv et al., 2015). It was reported that the catalytically active chiral ion pair for substrate activation and chiral induction was generated *in situ* via mixing chiral trityl phosphate with Ph_3CBr . The standard conditions were applicable to various aromatic β,γ -unsaturated α -ketoesters **1c**, giving the desired 1,4-addition products **5** in good yields (75–88%) with high enantioselectivities (90–99% ee). Besides, heterogeneous catalysts such as metal-organic frameworks (MOF) (Chen et al., 2017) and polystyrene-supported BOX-Cu(II) complex (Desyatkin et al., 2017), also showed high-performance in this kind of asymmetric Friedel-Crafts reactions.

On the other hand, pyrroles are another class of important aromatic feed stocks; however, they are relatively less explored in catalytic asymmetric Friedel-Crafts reaction, likely due to the regioselectivity and reactivity issues. In 2015, Feng et al. disclosed an asymmetric Friedel-Crafts C3-alkylation of 2,5-dimethyl pyrrole **6** to β,γ -unsaturated α -ketoesters **1d**, wherein the chiral Ni(II)-complexes of *N,N'*-dioxides exhibited high catalytic performance (Scheme 1D) (Zhang et al., 2015). Notably, a dramatic reversal of enantioselectivity was achieved by slightly tuning the amide units of the same type of chiral *N,N'*-dioxides. By using this approach, the two sets of enantiomers **7** were obtained in high yields (68–94%) and enantioselectivities (86–99% ee). Moreover, the substrate scope could be extended to indoles. In the same year, a highly enantioselective, efficient Friedel-Crafts C2-alkylation of pyrrole **8** with β,γ -unsaturated α -ketoesters **1d** was accomplished by the Wang group (Scheme 1E) (Hu et al., 2015). Under the catalysis of the chiral Cu-prolinol derivative complex, good to excellent yields (63–96%) and excellent enantioselectivities (91–98% ee) were achieved. Furthermore, a one-pot construction of the seven-membered ring fused with pyrroles **10** from delicately designed β,γ -unsaturated α -ketoesters **1e** was developed by virtue of the dual metal system of copper and gold catalysis.

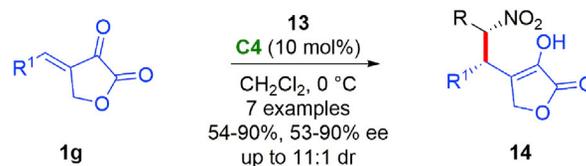
In addition to Friedel-Crafts reactions with aromatic compounds, non-aromatic nucleophiles have been well employed as Michael donors for 1,4-addition reactions of β,γ -unsaturated α -ketoesters. For instance, nitro-compounds are useful and appealing nucleophilic reagents, because the nitro group could readily stabilize carbanions via the conjugate effect and possess good potential for further functional group transformations. In 2015, the Yan group further developed the organo-catalyzed asymmetric 1,4-addition reaction between β,γ -unsaturated α -ketoesters **1f** and nitroacetate **11** (Scheme 2A) (Liu et al., 2015). The following decarboxylation of the primary adducts was achieved via refluxing over silica gel. The nitro-products **12** were yielded in excellent enantioselectivities (86–96% ee) and could be transformed into optically active proline derivatives. Recently, Bonne and Bugaut et al. disclosed that cyclic β,γ -unsaturated α -ketoesters **1g** could serve as suitable acceptors for the asymmetric 1,4-addition reaction with nitroalkanes **13** (Scheme 2B) (Fofana et al., 2020).

Furthermore, chiral indoline derivatives are important structural motifs and building blocks. Extensive attention from both synthetic and medicinal chemists has been attracted. Among them, the asymmetric Michael addition of indole-containing substrates to β,γ -unsaturated α -ketoesters has been regarded as one straightforward and powerful protocol. In 2016, the Zhou group reported an asymmetric Michael addition of 1-acetylintolin-3-ones **15** to β,γ -unsaturated α -ketoesters **1d**, delivering chiral indolin-3-ones **16** with two adjacent tertiary stereogenic centers in high yields (56–99%) with excellent diastereo- and enantioselectivities (91–99% ee, >19:1 dr) mild reaction conditions (Scheme 2C) (Chen et al., 2016). Asymmetric vinylogous Michael addition poses a daunting challenge in organic synthesis, because of the distal stereocontrol. Recently, Singh et al. disclosed that a broad range of enantio-enriched oxindoles **18** could be well synthesized via a highly selective asymmetric vinylogous Michael addition of 3-alkylidene-2-oxindoles **17** to β,γ -unsaturated α -ketoesters **1f** (Scheme 2D) (Jaiswal et al., 2020). In addition, α -azido indanones **19** are valuable structural scaffolds, in view of their easy and useful handle for synthesizing nitrogen-containing molecules and heterocycles. In 2020, the diastereodivergent catalytic enantioselective Michael addition of **19** to **1d** was described by Yu and Zhou et al. (Scheme 2E) (Ding et al., 2020). Interestingly, additive hexafluoroisopropanol (HFIP) played a crucial role to achieve the diastereoselectivity reversal. Although the merger of **C7** and HFIP afforded *syn*-adducts **20**, *anti*-adducts **20** were dominant without the aid of HFIP. Valuable α -chiral tertiary azides were afforded with high efficiency and readily converted to enantio-enriched spiro *N*-heterocycles.

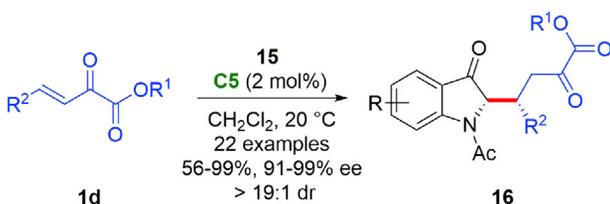
A Yan *et al.* 2015



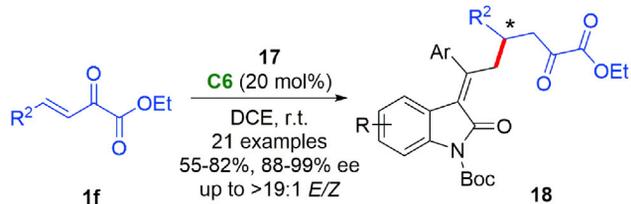
B Bonne and Bugaut *et al.* 2020



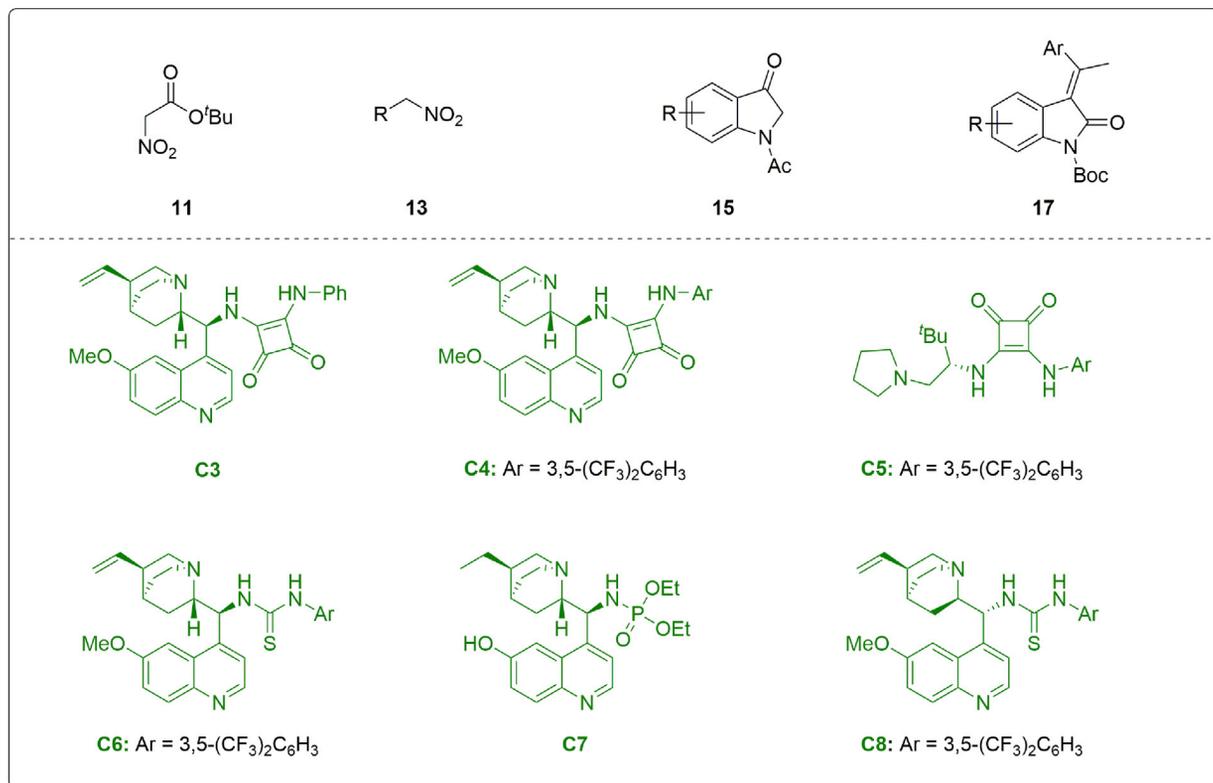
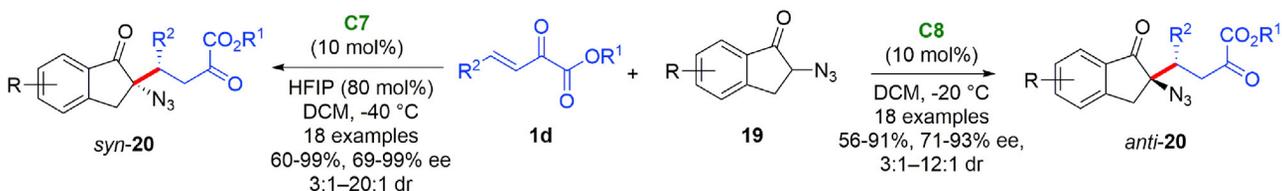
C Zhou *et al.* 2016



D Singh *et al.* 2020

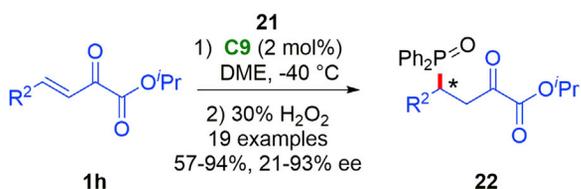


E Yu and Zhou *et al.* 2020

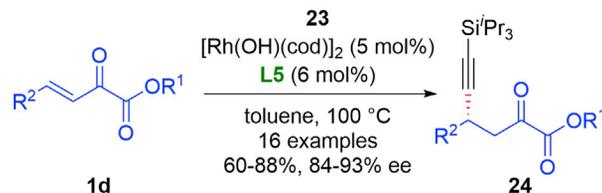


Scheme 2. Organo-catalyzed asymmetric Michael-addition

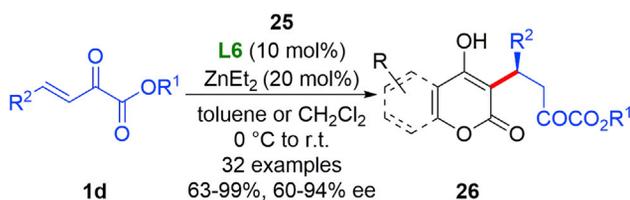
A Liu, Imamoto and Zhang *et al.* 2015



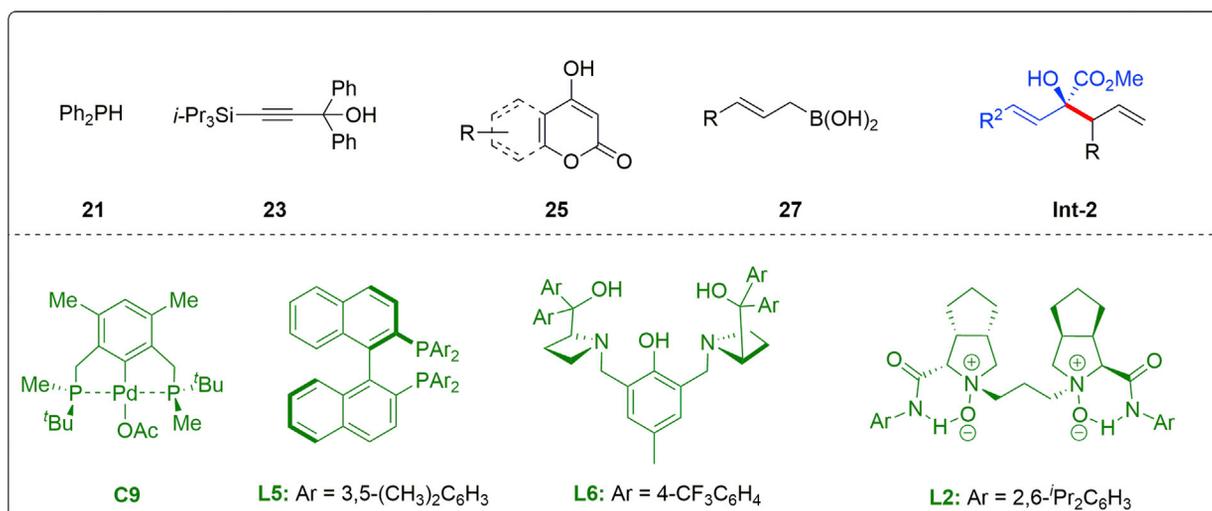
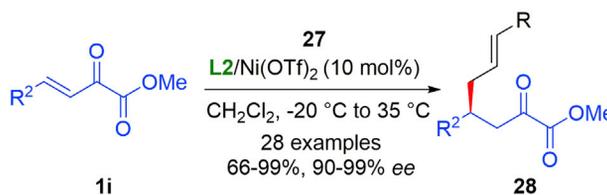
B Lu, Dou *et al.* 2017



C Wang *et al.* 2019



D Dong and Feng *et al.* 2019



Scheme 3. Metal-catalyzed asymmetric conjugate additions with other nucleophilic reagents

Despite the many progresses made in organo-catalyzed versions, metal-catalyzed conjugate 1,4-additions of β,γ -unsaturated α -ketoesters with various nucleophiles satisfy more diversified demand for α -keto carbonyl compounds bearing a γ -chiral center. In 2015, the Zhang group reported an asymmetric Michael addition of diphenylphosphine **21** to β,γ -unsaturated α -ketoesters **1h**, using their developed P-stereogenic pincer-Pd complex as the catalyst (Scheme 3A) (Xu *et al.*, 2015). The corresponding products **22**, phosphonate-containing compounds, were generated in good yields (57–94%) with moderate to good enantioselectivities (21–93% ee). Asymmetric conjugate addition of sp -carbon nucleophile to β,γ -unsaturated α -ketoesters remains elusive and challenging. In 2017, the first example of catalytic asymmetric conjugate alkylation of β,γ -unsaturated α -ketoesters was accomplished by the Dou group (Scheme 3B) (Zhi *et al.*, 2017). By using a chiral rhodium catalytic system, diphenyl [(triisopropylsilyl)ethynyl]methanol **23** acted as the alkynylating reagent generated *in situ*. The alkylation products **24** bearing a propargylic chiral center at γ -position were created in good yields (60–88%) with high enantioselectivities (84–93% ee). Latter, the heterogeneous chiral rhodium nanoparticle system with a chiral diene ligand was proven to be effective for the asymmetric conjugate 1,4-addition of arylboronic acids (Miyamura *et al.*, 2019). Featured by Lewis acidic and Brønsted basic sites, dinuclear Zinc-Pro-Phenol complex has emerged as a powerful catalyst to simultaneously activate both nucleophile and electrophile in the same chiral environment, facilitating a broad range of asymmetric C-C bond formations (Trost *et al.*, 2020). In 2019, azetidine-derived dinuclear Zinc-catalyzed asymmetric conjugate addition of 4-hydroxyl pyrones or 4-hydroxycoumarins **25** to β,γ -unsaturated α -ketoesters was developed by the Wang group (Scheme 3C) (Liu *et al.*, 2019). The protocol was applicable to

a wide range of substrates under mild conditions, leading to biologically important coumarins and pyranones in good to excellent ee values (60–94% ee).

In addition, metal-catalyzed conjugate additions of β,γ -unsaturated α -ketoesters can be achieved via an unusual process. In spite of the well-developed racemic 1,4-allylations, such catalytic asymmetric versions are less investigated. In 2019, the Feng group reported a highly enantioselective formal conjugate allyl addition of allylboronic acids **27** to β,γ -unsaturated α -ketoesters **1i**, providing a facile route to γ -allyl- α -ketoesters with good yields (66–99%) and excellent ee values (90–99%) (Scheme 3D) (Tang et al., 2019). In the presence of chiral Ni^{II}/N,N'-dioxide complex, this transformation readily occurred via an allylboration/oxy-Cope rearrangement sequence, which was confirmed by the isolation of 1,2-allylboration products Int-2. Recently, a series of enantioenriched γ -allyl (aryl)- α -ketoesters was well synthesized by Chai and Chang et al. via (R)-3,3'-Br₂-BINOL-catalyzed enantioselective Michael addition of organic boronic acids to β,γ -unsaturated α -ketoesters (not shown) (Zhao et al., 2021).

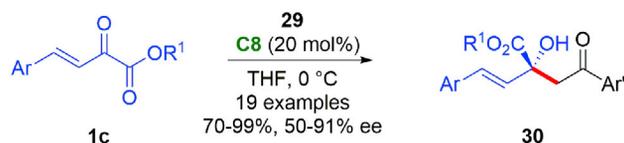
CATALYTIC ASYMMETRIC 1,2-ADDITION REACTIONS

In conjugated systems, 1,2-addition reactions are challenging and commonly regarded as competing reactions to 1,4-addition reactions. However, these concerns could be addressed by selection of suitable catalytic systems and matching reactants. Ketones proved to be a class of versatile nucleophiles for construction of C-C and C-X (X = N, O, S, Cl, Br etc.) bonds, thanks to the facile deprotonation at the α -position. Among these transformations, the asymmetric catalytic aldol condensation gathered much attention, revealing a dependable access to chiral β -hydroxy carbonyl compounds. Recently, great progress has been made in asymmetric aldol reactions of ketones with β,γ -unsaturated α -ketoesters. In 2015, Zhao and co-workers developed an enantioselective aldol addition of acetophenones **29** to β,γ -unsaturated α -ketoesters **1c** (Scheme 4A) (Konda et al., 2015). The desired aldol products **30** were obtained in high yields (70–99%) with moderate to excellent ee values (50–91% ee), under the catalysis of a quinidine-derived thiourea. Notably, the substrate concentration showed a marked impact on the reactivity. Only a small amount of THF was necessary, because lower yield and ee value was received in dilute or neat reaction condition. In addition, this presented protocol could be extended to the aldol reaction of phenylglyoxal hydrates and cyclic ketones (not shown).

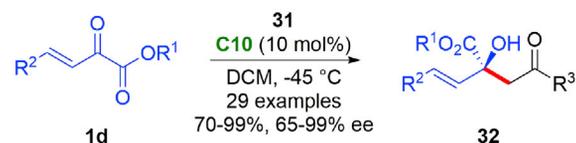
In the same year, a chiral Ni (II) complex **C10** catalyzed enantioselective decarboxylative aldol reaction of β,γ -unsaturated α -ketoesters **1d** with β -ketoacids **31** was described by Ma et al. to synthesize highly functionalized chiral tertiary alcohols **32** (Scheme 4B) (Wei et al., 2015). The transformation proceeded smoothly for a broad range of β -ketoacids and β,γ -unsaturated α -ketoesters with high chemo-, regio-, and enantioselectivities (65–99% ee). The ¹³C NMR spectroscopic indicated one of the diamine ligands could be released from the Ni-complex **C10** to give way to β -ketoacids **31** instead of β,γ -unsaturated α -ketoesters **1d**, and the liberated diamine could then deprotonate the metalbound β -ketoacid. In 2006, enzyme catalysis was applied to the asymmetry aldol reaction between β,γ -unsaturated α -ketoesters and aliphatic ketones by He and Guan et al. (Li et al., 2016c). Although enantioselectivities were not ideal, as an environment-friendly and sustainable biocatalyst, the enzyme catalysis showcased a wide application future in this field.

Addition to the versatile reactivity, coumaran-3-ones exhibit the importance in synthesis, for their unique motif widely displayed in diverse natural products and intermediates with pharmaceutical and biological activities. Lately, an efficient copper-catalyzed asymmetric aldol reaction between β,γ -unsaturated α -ketoesters **1c** and coumaran-3-ones **33** was developed by Zhang and Wang et al. (Scheme 4C) (Li et al., 2021). The desired chiral tertiary alcohol derivatives **34** containing the coumaran-3-one structure were obtained in excellent yields (87–96%) and stereoselectivities (84–95% ee) with a wide range of functional group tolerance, offering a great latitude for further structural elaborations for biologically important chiral coumaran-3-one derivatives. In the same year, Hu and Jiang et al. described a decarboxylative aldol reaction of β,γ -unsaturated α -ketoesters **1c** with 2-oxotetrahydrofuran-3-carboxylic acid **35**/2-oxochroman-3-carboxylic acid derivatives **37** (Scheme 4D) (He et al., 2021b). The desired product α -substituted β -hydroxy butyrolactones **36** and dihydrocoumarins **38** were well generated in the presence of a bidentate oxazoline-Ni(II) catalysis. High levels of functional-group compatibility, reaction yields (59–83%), diastereo- and enantioselectivities (74–99% ee, 2:1 to 12:1 dr) were received. The high resolution mass spectroscopy (HRMS) analysis of the reaction indicated that the bidentate coordination existed between the Ni(II) and 2-oxotetrahydrofuran-3-carboxylic acid **35** and decarboxylation might occur after the aldol addition.

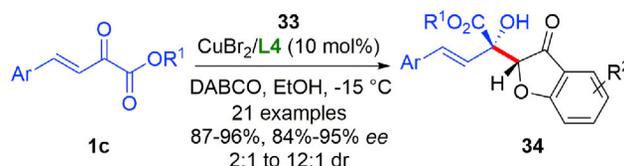
A Zhao et al. 2015



B Ma et al. 2015



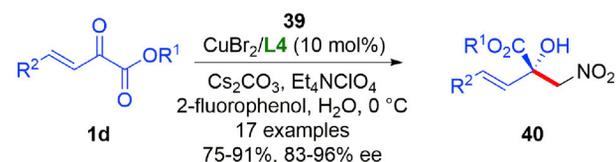
C Zhang and Wang et al. 2021



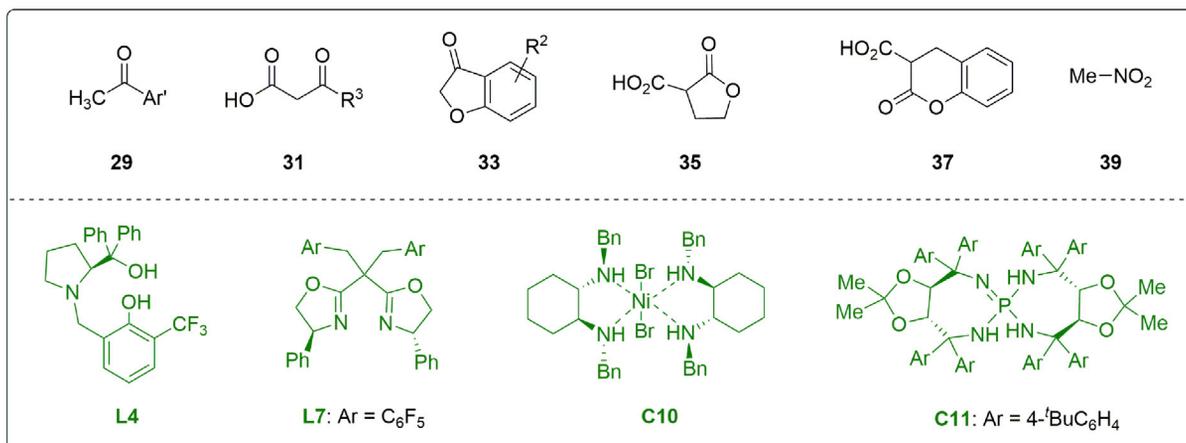
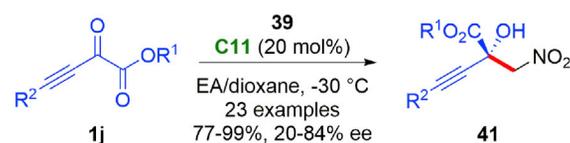
D Hu and Jiang et al. 2021



E Wang et al. 2017



F Wu and Han et al. 2019

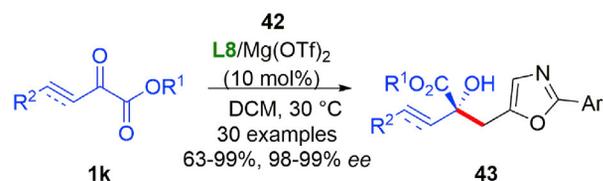


Scheme 4. Catalytic asymmetric 1,2-addition reactions

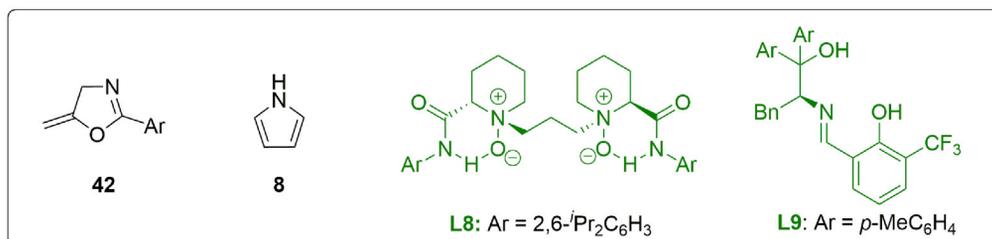
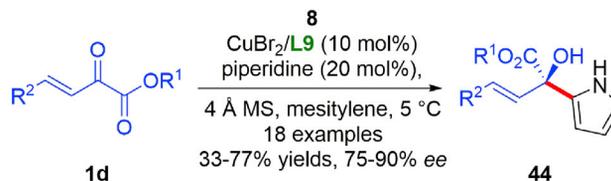
β -Nitroalcohol derivatives are intermediates of value, which could take part in diverse transformations to produce useful nitrogen-containing compounds conveniently, such as aminoalcohols, unnatural sugars, and nitroolefins. In this regard, the asymmetric Henry reaction has attracted much attention and been widely applied in the construction of β -nitroalcohol motifs. In 2017, the Wang groups reported a chiral copper complex catalyzed highly enantioselective Henry reaction of β,γ -unsaturated α -ketoesters **1d** with nitromethane in water (Scheme 4E) (Li et al., 2017b). A series of unsaturated β -nitro- α -hydroxy esters **40** bearing tetrasubstituted carbon stereocenters were gathered in high yields (75–91%) with excellent ee values (83–96% ee). In 2019, Wu and Han et al. described an enantioselective Henry reaction of β,γ -alkynyl ketoesters **1j** with nitromethane catalyzed by tartaric acid derived chiral iminophosphoranes **C11** (Scheme 4F) (Zhang et al., 2019b). The desired products β -nitroalcohols **41** were generated in moderate to excellent yields (77–99%).

Besides, chiral alcohols with heteroaromatics are a class of important pharmaceutical intermediates, and widely distributed in natural products, microbial and bioactive molecules. Metal-catalyzed asymmetric 1,2-additions of β,γ -unsaturated α -ketoesters with heterocycles represent as a practicable synthetic method. The synthesis of chiral tertiary alcohols bearing oxazole fragments **43** was developed by the Feng group in 2015 via a catalytic asymmetric carbonyl-ene reaction of β,γ -unsaturated α -ketoesters **1k** with 5-methyleneoxazolines **42** (Scheme 5A)

A Feng et al. 2015



B Wang et al. 2017



Scheme 5. Metal-catalyzed Asymmetric 1,2-addition reactions involving heterocycles

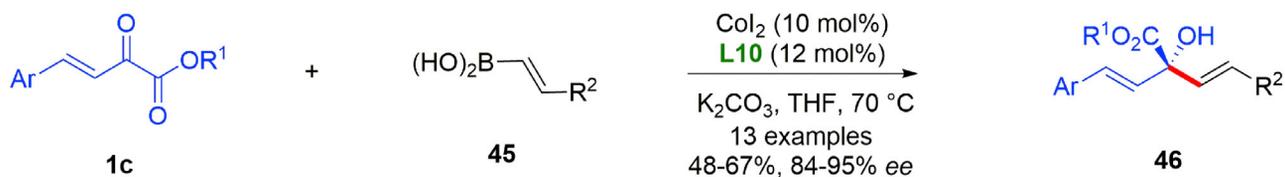
(Luo et al., 2015). The transformation was facilitated by the utilization of a chiral *N,N'*-dioxide/ Mg^{II} catalyst, giving the desired products in good to excellent yields (63–99%) with excellent enantioselectivities (98–99% ee) under mild reaction conditions. The afforded results demonstrated a high level of functional-group compatibility for both β,γ -alkenyl α -ketoesters and β,γ -alkynyl α -ketoesters. It was proposed that β,γ -unsaturated α -ketoesters could be coordinated to the Mg^{II} in a bidentate fashion with its dicarbonyl motif, and the steric hindrance on the phenyl ring of the ligand played a key role in promoting both the enantioselectivity and reactivity. Pyrroles could readily react with various electrophilic reagents bearing prochiral centers to give enantiomerically enriched pyrrole derivatives, taking advantage of the electron-rich aromatic rings. In 2017, the Wang group reported a copper catalyzed asymmetry 1,2-addition reaction of β,γ -unsaturated α -ketoesters 1d with pyrrole, as opposite to the previous 1,4-addition (Scheme 5B) (Sun et al., 2017). The desired products 44 were obtained in moderate to good yields (33–77%) with excellent enantioselectivities (75–90% ee), under the catalysis of copper-complex.

In spite of above-mentioned achievements, 1,2-addition reactions with allylic nucleophiles remain underdeveloped. The products allylic alcohols are among the most abundant and significant structural motifs in organic synthesis, which could be facilely converted to a range of stereodefined compounds of value in chemistry and medicine in a stereoselective fashion. In 2016, The Zhao group developed an unprecedented vinylation of β,γ -unsaturated α -ketoesters 1c using vinyl boronic acid reagents 45 (Scheme 6A) (Huang et al., 2016b). The reactions were carried out in the presence of commercially available cobalt halides and chiral bisphosphine ligands. Transmetalation of vinyl boronic acid with cobalt halide was facilitated by K_2CO_3 , and followed by an enantioselective nucleophilic addition to the carbonyl group of β,γ -unsaturated α -ketoesters, affording the desired highly optically enriched (84–95% ee) allylic alcohols 46. It is noteworthy that this catalytic system could be further expanded to the asymmetry vinylation of α -ketoesters, isatins, and imines. Recently, the Li group revealed that $\text{Bi}(\text{OAc})_3$ /chiral phosphoric acid catalyst system also showed high catalytic and stereocontrolling abilities in this kind of asymmetric 1,2-allylation reaction of allylboronic acid pinacol esters to β,γ -unsaturated α -ketoesters (Liu et al., 2021). In addition, the Johnson group completed a three-component reductive coupling reaction between β,γ -unsaturated α -ketoesters, dimethyl phosphite and aldehydes (scheme 6B) (Horwitz et al., 2016). The transformation was conducted by a chiral triarylaminophosphorane C12, offering the desired products hydroxy phosphates 49 in high yields (43–87%) with excellent diastereoselectivities and enantioselectivities (64–97% ee, 4:1 to 20:1 dr). It was proposed that the transformation proceeded a Pudovik addition of a dimethyl phosphite to β,γ -unsaturated α -ketoesters, triggering the phospho-Brook rearrangement and subsequent catalyst controlled trapping of the resultant enolate Int-4 with an aldehyde 48.

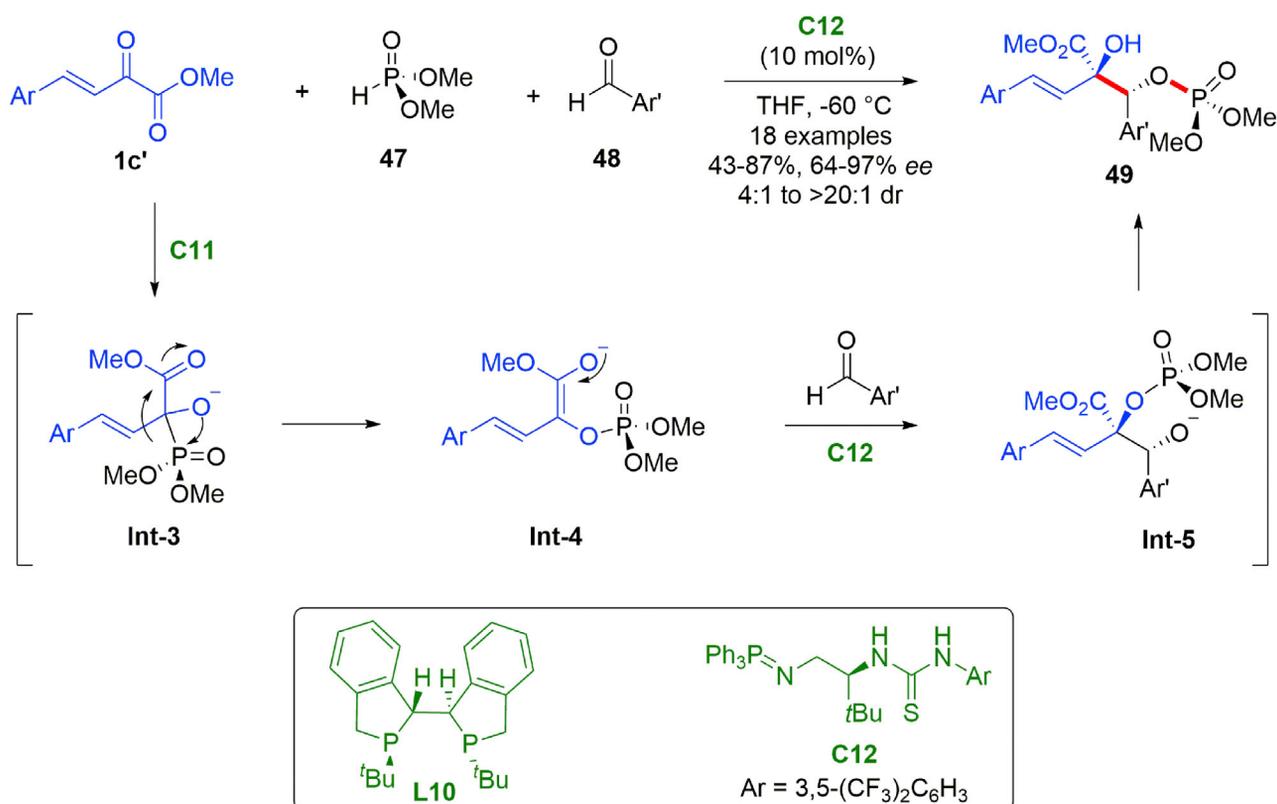
CATALYTIC ASYMMETRIC [2 + N] ANNULATION REACTIONS

Although 1,4- and 1,2-additions with diversified nucleophiles lead to straightforward and powerful protocols for enantio-enriched ketoesters and tertiary alcohols, multiform cyclization reactions including [2 +

A Zhao et al. 2016



B Johnson et al. 2016



Scheme 6. Catalytic asymmetric 1,2-additions with other nucleophilic reagents

n), $[3 + n]$ and $[4 + n]$ annulation afford efficient and convenient approaches to various ring skeletons, as such structural motifs are widely present in medicinal chemistry and natural products.

Catalytic asymmetric [2 + 1] annulation reactions

Enantio-enriched cyclopropanes are common structural moieties in natural products and pharmacologically active agents. Despite the tremendous achievement that has been made, the synthesis of these molecules still meets challenges, possibly because of the ring strain. In this context, β,γ -unsaturated α -ketoesters proved to be versatile precursors for chiral cyclopropanes. In 2017, the Luo group completed an enantioselective cyclopropanation of β,γ -unsaturated α -ketoesters with diazoesters catalyzed by the complex of InBr_3 and chiral calcium phosphate (scheme 7A) (Zhong et al., 2017). β,γ -Unsaturated α -ketoesters were activated by bidentate coordination with the cationic indium complex, setting a rigid system for the chiral-identification. Weak π -interaction between chiral phosphoric acid and diazo ylide was supposed to contribute to a facial attack and the following back attack cyclization with loss of nitrogen. Highly functionalized chiral cyclopropanes 51 were prepared in moderate to good yields (54–77%) with excellent ee values (99% ee) as a single diastereoisomer. A demonstrable fluoro substitution effect was observed in this binary

Lewis acid catalysis while increasing the number of fluoro substituent on the ligand dramatically benefited the enantioselective control. The reactions were regarded to proceed via a 1,4-addition-cyclopropanation sequence. Notably, Chen and Xiao highlighted the cooperative effect of the hydrogen-bond on stereoinduction origination in the chiral ureas catalyzed asymmetric cyclopropanation of β,γ -unsaturated α -ketoesters with stabilized sulfur ylides in 2011 (not shown) (Cheng et al., 2011). In 2018, Liu and Feng et al. described a diastereodivergent asymmetric Michael-alkylation between 3-Cl oxindoles and β,γ -unsaturated- α -ketoesters (scheme 7B) (Kuang et al., 2018). By tuning metal catalysts and adjusting the ligands and temperature, *rel*-(1*R*,2*S*,3*R*) and *rel*-(1*S*,2*S*,3*R*) spiro cyclopropane oxindoles were obtained separately in high yields (50–99%) with excellent enantioselectivities (72–99% ee). It is proposed that the *rel*-(1*S*,2*S*,3*R*) diastereoisomers 53 were obtained via a intramolecular trapping of the chiral *aza-ortho*-xylylene intermediate Int-6 after Michael addition, whereas the other diastereoisomers (*iso*)-53 were generated from Int-7 via a direct S_N2 substitution pathway, which was because of the different characteristics of the metal catalysts.

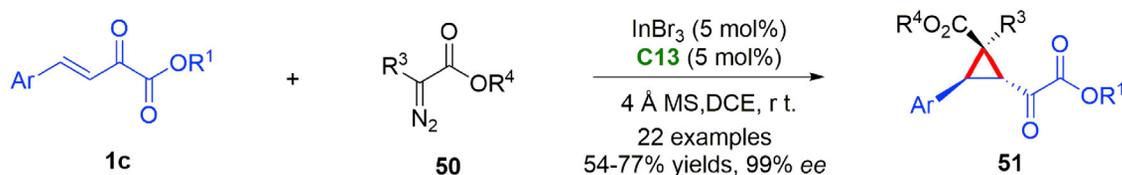
Catalytic asymmetric [2 + 3] annulation reactions

Over the past decades, the asymmetry 1,3-dipolar cycloaddition of nitrones has become one of the most powerful synthetic methods for enantio-enriched five-membered heterocycles. In this regard, β,γ -unsaturated α -ketoesters involving the electron-deficient carbon-carbon double bond proved to be useful acceptors for 1,3-dipolar cycloaddition. A highly stereoselective 1,3-dipolar cycloaddition of β,γ -unsaturated α -ketoesters with nitrones was presented by the Fu group in 2017 (scheme 8A) (Xie et al., 2017). The reaction was conducted by a chiral bis(indano-oxazoline)-based Ni complex to provide isoxazolidines 55 possessing three contiguous stereocenters in high yields (70–95%) with excellent diastereoselectivities and enantioselectivities (88–99% ee, >20:1 dr). This method showcased a reliable approach toward the synthesis of isoxazolidines, γ -amino alcohols and other related bioactive derivatives. Later, enantioselective [2 + 3] cycloaddition of β,γ -alkynyl ketoesters and nitrones has been developed by the Mikami group, using a cationic chiral Pd(II) Lewis acid catalyst (Scheme 8B) (Honda and Mikami, 2018).

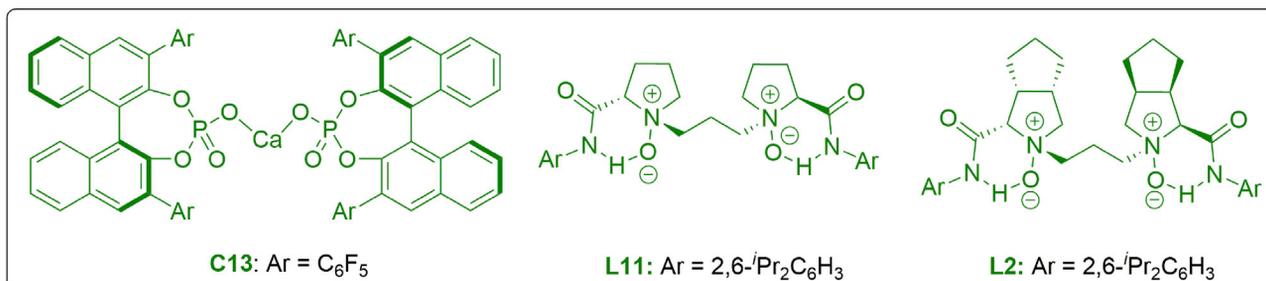
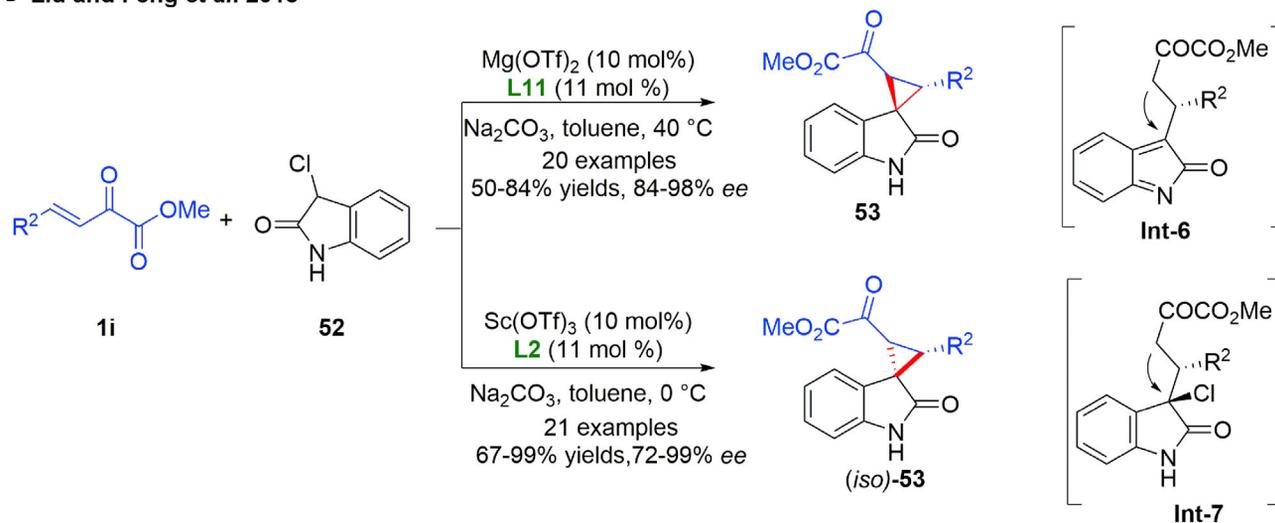
Meanwhile, the development of new synthetic methods of 3,3'-disubstituted oxindoles is of considerable interest in view of their widespread occurrence in natural products, drugs, and pharmaceutically active compounds. In 2019, Cui and Chen et al. accomplished a chiral tertiary amine catalyzed enantioselective [2 + 3] annulation reaction of β,γ -unsaturated α -ketoesters and 1,3-dipole Int-8 generated *in situ* from isatin-derived MBH carbonates 57 via addition-eliminations (scheme 8C) (Chen et al., 2019). The transformation proceeded a nucleophilic α -attack of the Int-8 to β,γ -unsaturated α -ketoesters via the hydrogen bonding activation, followed by an intramolecular conjugate addition cyclization. An allylic deprotonation was facilitated by base to give the catalysis regeneration. A various of spirocyclic compounds 58 with three contiguous stereocenters were obtained in moderate to high yields (55–94%) with excellent diastereo- and enantioselectivities (89–99% ee, >99:1 dr). In the same year, Chen and Yuan et al. completed an asymmetric domino Mannich-cyclization of β,γ -unsaturated α -ketoesters 1d with 3-isothiocyanato oxindoles 59 (scheme 8D) (Bai et al., 2019). The desired products spirocyclic oxindoles 60 incorporating 3,3'-disubstituted oxindole frameworks were gathered in high yields (89–99%) with good to excellent diastereo- and enantioselectivities (81–99% ee, 73:27 to >99:1 dr) under the catalysis of a thiourea-secondary amine. This transformation revealed a valuable method for the synthesis of a wide range of densely functionalized spirocyclooxindole derivatives bearing two contiguous stereogenic centers and enol motifs. Recently, the enantioselective [2 + 3] annulation reactions of β,γ -unsaturated α -ketoesters with keto amides generated *in situ* from *N*-benzylisatine 62 and benzylamine had been developed by the Šebesta groups (scheme 8E) (Peňásková et al., 2021). The transformations proceeded smoothly under mild conditions with a chiral quinine-based squaramide catalyst to afford spirocyclic oxindole pyrrolidines 63 in moderate to high yields and ee values (43–87% yields, 28–60% ee). It is noteworthy that the reaction was carried out to mix the *N*-benzylisatine 62 with benzylamine firstly to prevent the undesired competitive reaction between benzylamine and β,γ -unsaturated α -ketoesters.

Beside the β,γ -C=C bond, a novel [2 + 3] annulation reaction involving α,β -position also attracts much attention. In 2015, the Singh group completed an enantioselective interrupted Feist-Bénary reaction of β,γ -alkynyl α -ketoesters (scheme 9A) (Sinha et al., 2015). Under the catalysis of the chiral phosphine-silver(I) complex, the transformation started with 1,2-addition of 1,3-diketones to β,γ -alkynyl ketoesters, which was followed by a tandem 5-*exo-dig* cyclization. Dihydrofuran derivatives 65 were obtained in moderate to excellent yields (40–95%) with high values of enantioselectivity (71–98% ee). In addition, in 2019, the

A Lv and Luo *et al.* 2017



B Liu and Feng *et al.* 2018



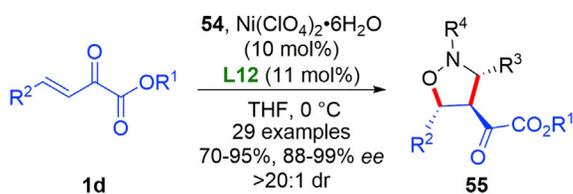
Scheme 7. Catalytic asymmetric [2 + 1] annulation reactions of β,γ -unsaturated α -ketoesters

Kesavan group described an asymmetric [3 + 2] formal cycloaddition reaction between oxindole α -keto esters 1b and enals 66 (scheme 9B) (Muthusamy and Kesavan, 2019). The reaction progress possibly involved the generation of 1,3-dien-1-amine intermediate Int-13 from enals 66, followed by 1,4-addition to the oxindole α -keto esters 1b, intramolecular cyclization and the final isomerization. By treatment with DAMP and Boc₂O in one pot, the final products multi-functionalized carbocyclic oxindoles 67 were separated in moderate yields (62–80%) with good enantioselectivities (65–91% ee).

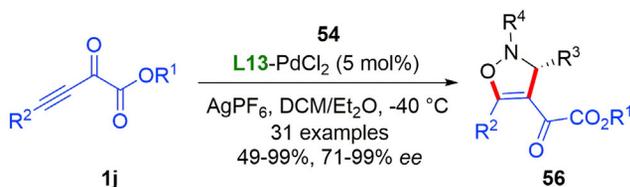
Catalytic asymmetric [2 + 4] annulation reactions

There is no doubt that the [2 + 4] annulation including carbo- and hetero Diels-Alder reaction is one of most available methods in organic synthesis. Both the electron-deficient carbon-carbon double bond and activated carbonyl group of β,γ -unsaturated α -ketoesters serve as useful acceptors for [2 + 4] annulation reaction. In 2016, Lin and Feng *et al.* described a highly efficient catalytic asymmetric [2 + 4] cycloaddition of β,γ -unsaturated α -ketoesters with silyloxyvinylindoles (Scheme 10A) (Zhao *et al.*, 2016). The transformation proceeded smoothly under mild conditions, affording the desired products carbazole derivatives 69 bearing three contiguous stereocenters in high yields (47–98%) with excellent diastereo- and enantioselectivities (86–99% ee, >19:1 dr). It is noteworthy that the steric hindrance of amide substituents on the ligand L15 was crucial for enantiocontrol. Subsequently, a catalytic asymmetric Diels-Alder reaction of

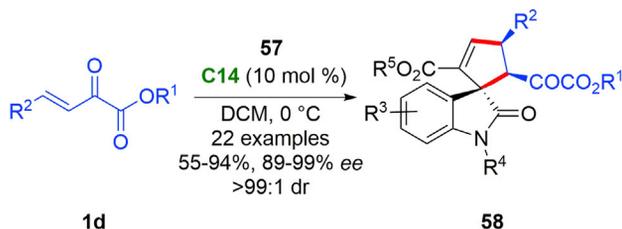
A Fu et al. 2017



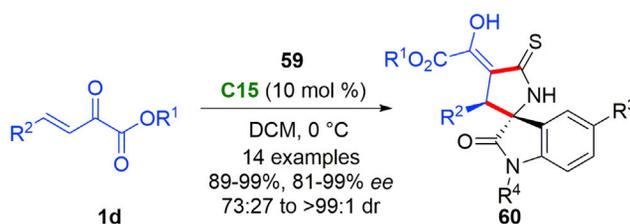
B Mikami et al. 2018



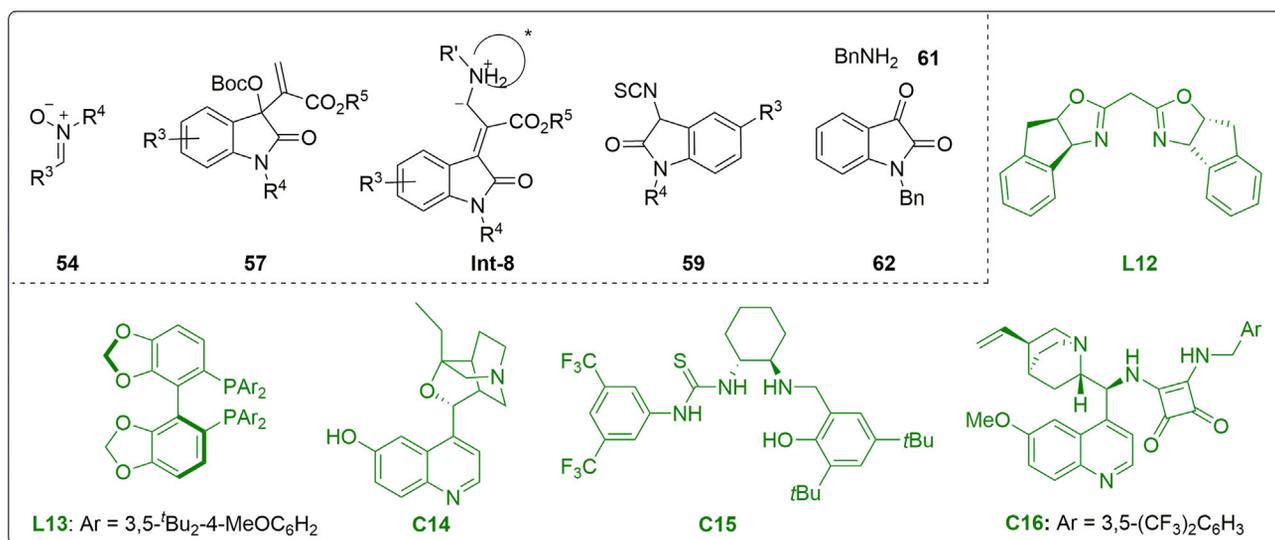
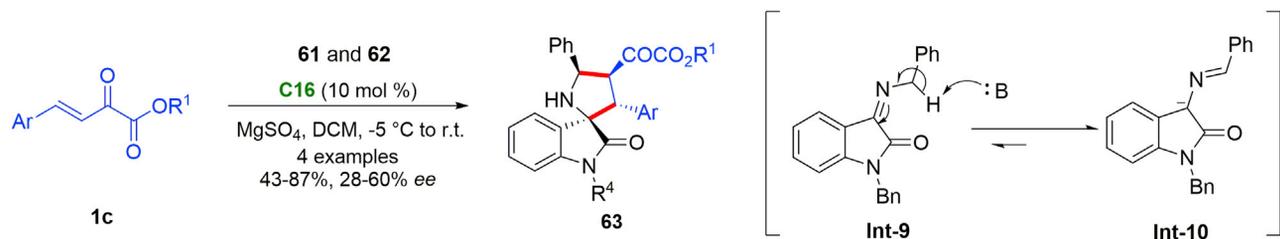
C Cui and Chen et al. 2019



D Chen and Yuan et al. 2019



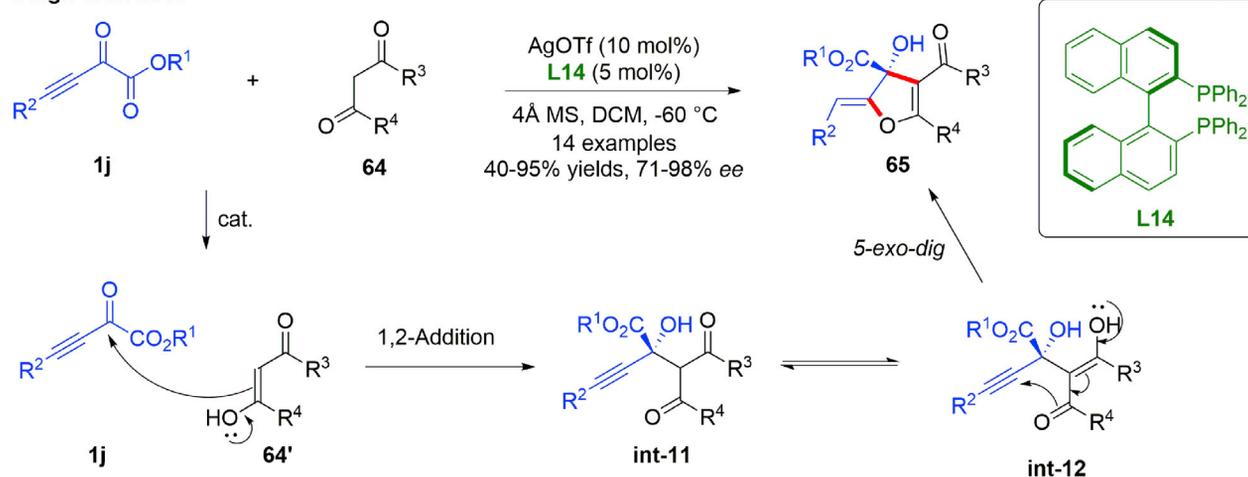
E Šebesta et al. 2021



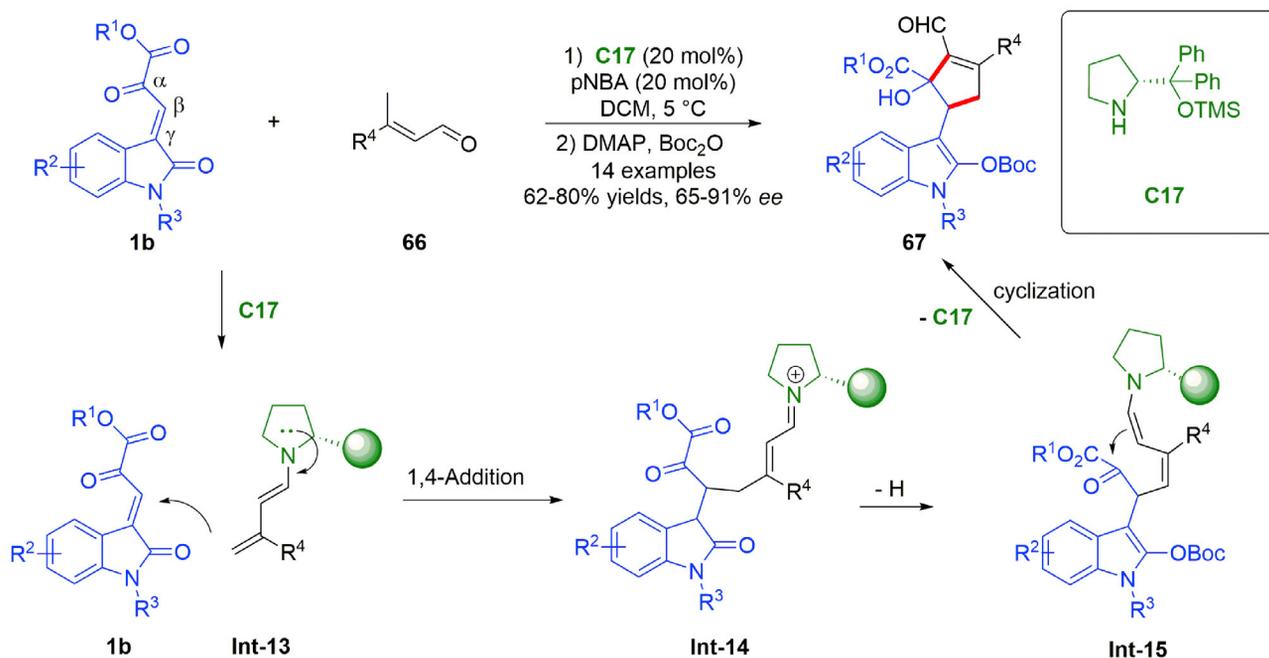
Scheme 8. Catalytic asymmetric [2 + 3] annulation reaction involved β,γ -C=C bond

β,γ -unsaturated α -ketoesters with (*E*)-1-phenyl dienes 70 was accomplished by the same group in 2018, using a chiral *N,N'*-dioxide/zinc(II) complex as catalyst (Scheme 10B) (Xiong et al., 2018). Excellent diastereo- and enantioselectivities (88–99% ee, >19:1 dr) were observed. HRMS analysis and operando IR experiments implied that the Zn^{II} center was coordinated to four oxygens of the *N,N'*-dioxide and two oxygens of β,γ -unsaturated α -ketoester (Int-16) to decrease the LUMO energy of β,γ -unsaturated α -ketoester for the Diels-Alder reaction. The steric hindrance of amide substituents on the ligand occupied a key role to compel the (*E*)-1-phenyl dienes to attack from the *Re*-face of the β,γ -unsaturated α -ketoester.

A Singh et al. 2015



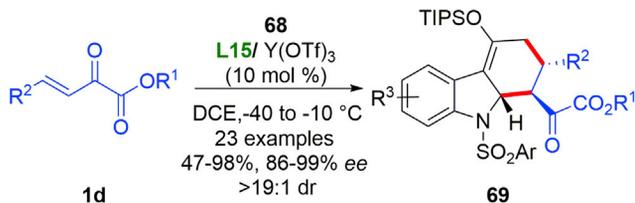
B Kesavan et al. 2019



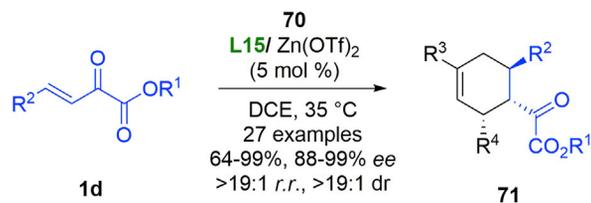
Scheme 9. Catalytic asymmetric [2 + 3] annulation reaction involved α,β -position

On the other hand, great progress also has been made in organo-catalyzed asymmetric [2 + 4] annulation reactions of β,γ -unsaturated α -ketoesters. The catalytic asymmetric aza-Michael-Michael cascade derived from β,γ -unsaturated α -ketoesters and 2-aminochalcones 72 was developed by the Li group to prepare enantiomerically enriched tetrahydroquinoline derivatives 73 in 2018 (Scheme 10C) (Duan et al., 2018). Three contiguous stereogenic centers were created with high enantio- and diastereoselectivities in the presence of a bifunctional squaramide catalyst. The combination of the trityl cation and chiral weakly coordinating metal-based bisphosphate anions was utilized in numbers of novel transformation as a highly active carbocation Lewis acid catalyst by the Luo group in recent years. In 2019, Lv and Luo et al. demonstrated that asymmetric carbocation catalysis with chiral weakly coordinating Fe(III)-based bisphosphate anion was an effective catalytic system for the enantioselective Diels-Alder reactions of β,γ -unsaturated α -ketoesters with unsubstituted anthracene (Scheme 10D) (Zhang et al., 2019a). It was regarded that the catalytically active chiral ion pair for substrate activation and chiral induction was generated *in situ* via mixing the Fe(III)-based bisphosphate anion with Ph₃CCl. The desired

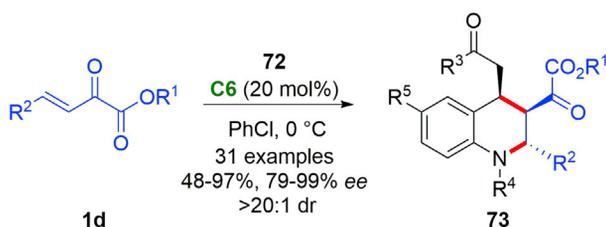
A Lin and Feng *et al.* 2016



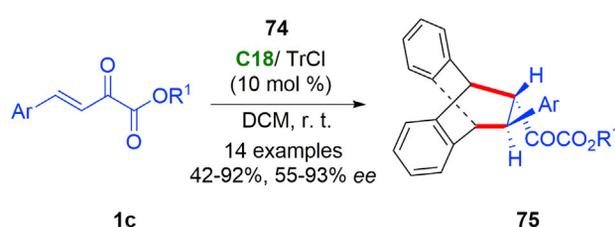
B Lin and Feng *et al.* 2018



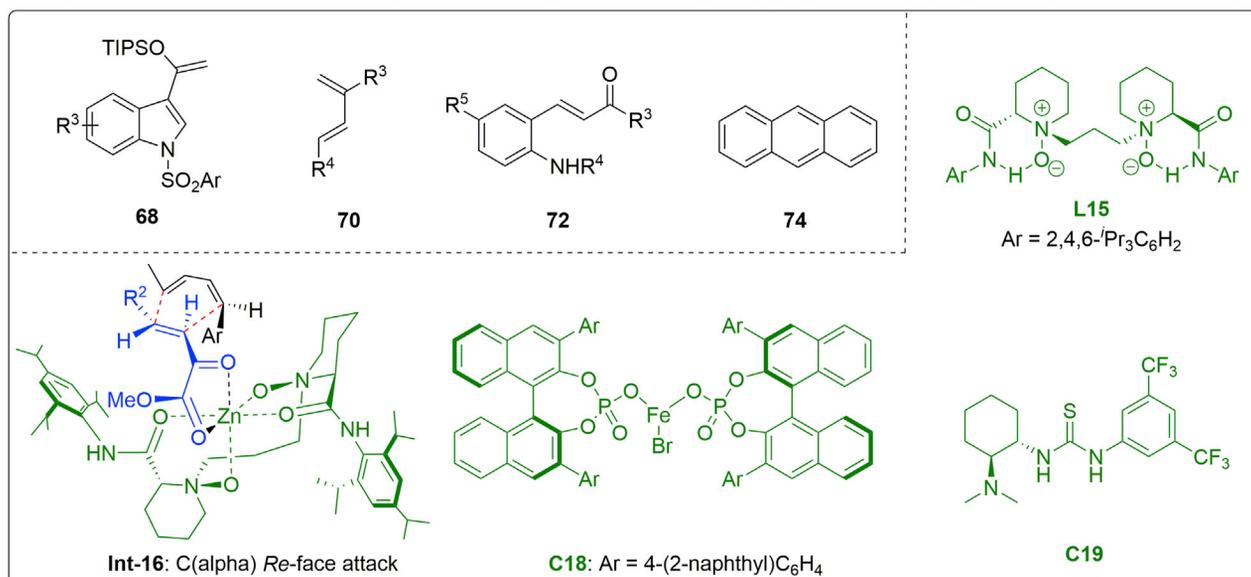
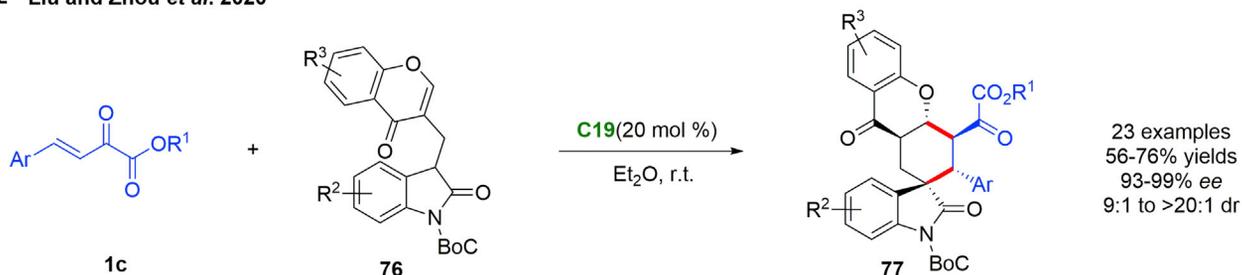
C Li *et al.* 2018



D Lv and Luo *et al.* 2019

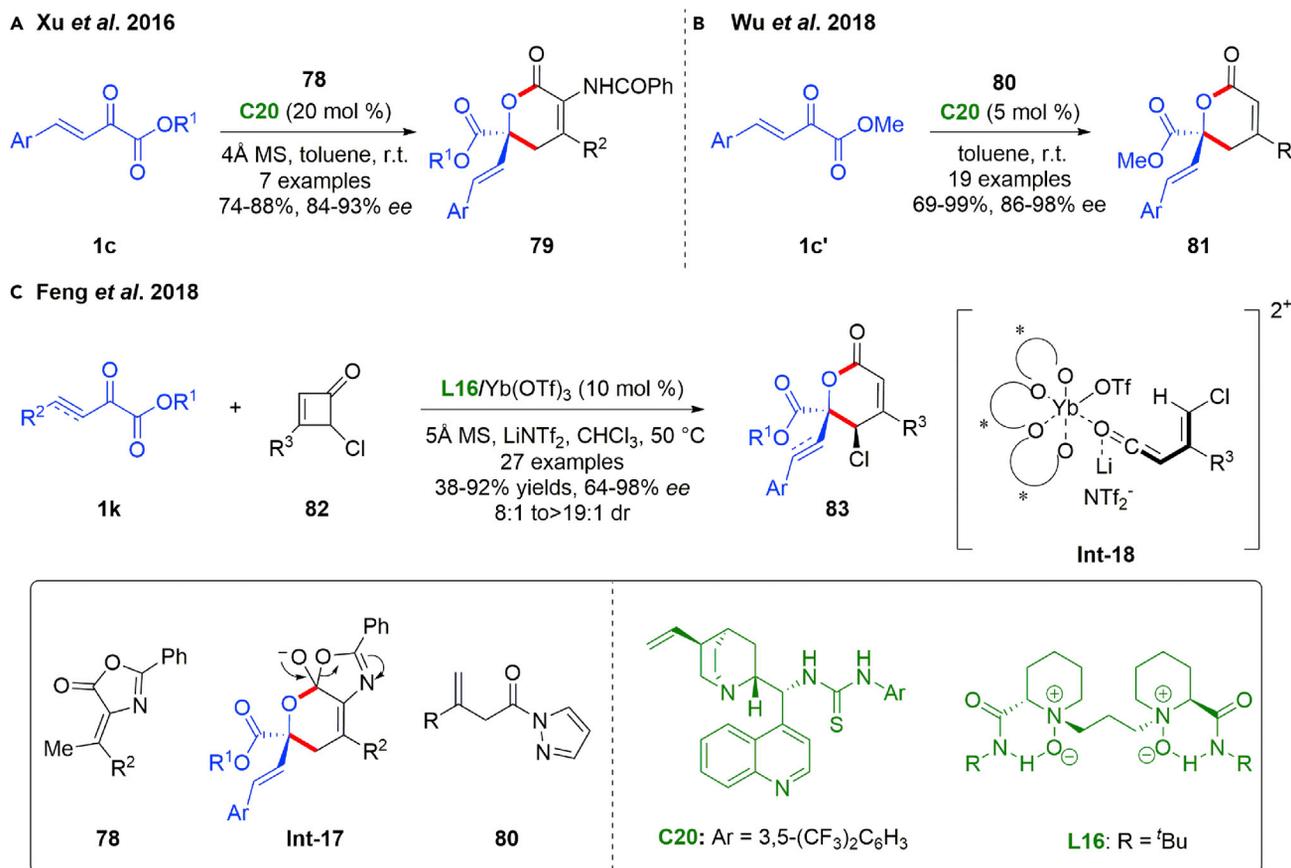


E Liu and Zhou *et al.* 2020



Scheme 10. Catalytic asymmetric [2 + 4] annulation reactions of C=C bond

annulation products **75** were yielded with moderate to excellent ee values (55–93% ee). In 2020, Liu and Zhou *et al.* conducted a domino Michael/annulation reaction between β,γ -unsaturated α -ketoesters and bifunctional oxindole-chromones **76** (Scheme 10E) (Zhou *et al.*, 2020). The process was catalyzed by a chiral thiourea under a mild condition to deliver structurally diverse polysubstituted hexahydroxanthones **77** with five contiguous stereogenic centers including one spiro quaternary center in good yields (56–76%) with excellent ee values (93–99% ee).



Scheme 11. Catalytic asymmetric [2 + 4] annulation reactions of C=O bond

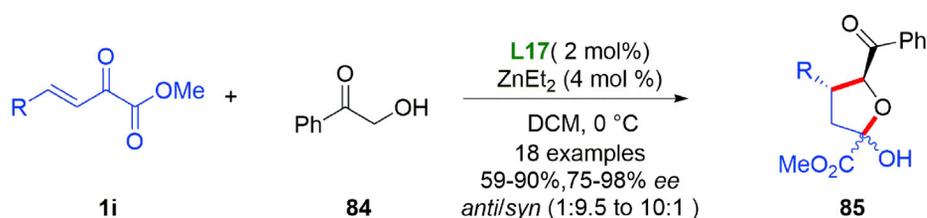
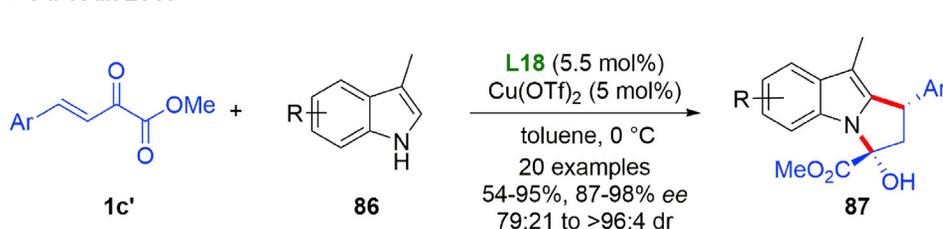
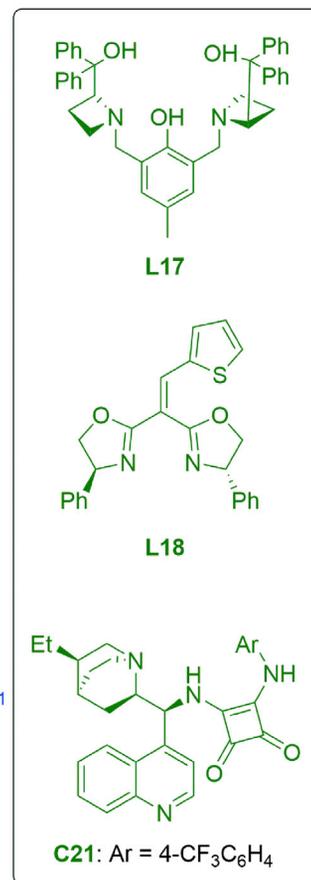
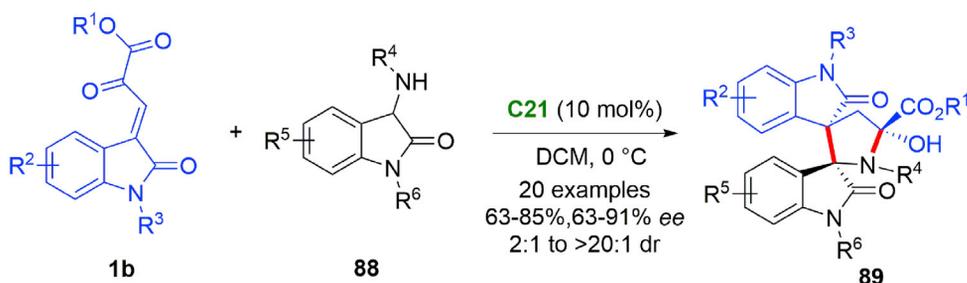
Catalytic asymmetric [2 + 4] annulation reactions of C=O bond

In addition, utilizing the carbonyl group of β,γ -unsaturated α -ketoesters as C2 synthon for asymmetry [2 + 4] annulation reactions proved to be a reliable access to chiral 5,6-dihydropyran-2-ones, which were presented in a series of biologically active compounds. In 2016, the Xu group accomplished an enantioselective organo-catalytic [2 + 4] annulation of β,γ -unsaturated α -ketoesters with dienes generated *in situ* from olefinic azlactones **78** (Scheme 11A) (Gao et al., 2016). Under the catalysis of tertiary amine-thiourea **C20**, hetero-Diels–Alder reaction occurred to form Int-17 and followed by an isomerization, affording chiral dihydropyranones **79** in good yields (74–88%) with excellent ee values (84–93% ee). It is noteworthy that this catalytic system was also adapted to the reaction of arylglyoxalates with olefinic azlactones. Similarly, the Wu group achieved the [4 + 2] annulation of β,γ -unsaturated α -ketoesters with β,γ -unsaturated amide (Scheme 11B) (Zhang et al., 2018). In 2018, the Feng group reported an N,N' -dioxide/Yb(III) complex catalyzed asymmetric [2 + 4] cycloaddition of β,γ -unsaturated α -ketoesters with cyclobutenones (Scheme 11C) (Yao et al., 2018). A broad range of 4,5,6-trisubstituted dihydropyran-2-ones **83** bearing contiguous stereogenic centers were obtained in good yields (38–92%) with excellent enantioselectivities and diastereoselectivities (64–98% ee, 8:1 to >19:1 dr). The Yb³⁺ was coordinated with the oxygens of amine-oxide and amide of **L16** in a tetradentate manner, establishing a chiral pocket. The proposed reaction mechanism involved the generation of the activated *cis*-vinylketene intermediate Int-18, coordination of 1,2-dicarbonyl motif with Yb(III) complex and the final [2 + 4] annulation occurring between the *Re*-face of β,γ -unsaturated α -ketoesters and the *Si*-face of the vinylketene.

CATALYTIC ASYMMETRIC [3 + N] ANNULATION REACTIONS

Catalytic asymmetric [3 + 2] annulation reactions

By treatment with dinucleophiles (Nu–Nu), β,γ -unsaturated α -ketoesters could be employed as C3 synthons in [3 + n] annulation reactions, on account of the 1,3-dual electrophilic sites. In 2015, Wang and

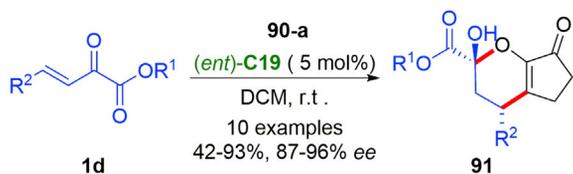
A Wang and Chang *et al.* 2015B Fu *et al.* 2015C Du *et al.* 2018Scheme 12. Catalytic asymmetric [3 + 2] annulation reactions of β,γ -unsaturated α -ketoesters

Chang *et al.* described a dinuclear zinc-AzePhenol complex catalyzed enantioselective domino Michael/hemiketalization reaction of β,γ -unsaturated α -ketoesters with α -hydroxyacetophenone, showcasing an available access to 2,2,4,5-tetrasubstituted chiral tetrahydrofurans **85** in high yields (59–90%) with good to excellent enantioselectivities (75–98% ee) (Scheme 12A) (Hua *et al.*, 2015). Simple treatment with sulfuric acid converted **85** to corresponding dihydrofurans. In the same year, a catalytic enantioselective Friedele–Crafts alkylation/*N*-hemiacetalization cascade reaction of β,γ -unsaturated α -ketoesters and 3-methylindoles **86** was described by the Fu group for the preparation of chiral pyrroloindole derivatives **87** (Scheme 12B) (Ma *et al.*, 2015). The reaction was performed with addition of a heteroarylidene-tethered bisoxazoline ligands-copper (II) complex as catalysis to yield the nitrogen-heterocycles with high to excellent enantioselectivities and diastereoselectivities (87–98% ee, 79:21 to >96:4 dr). It is important to note that the reaction of [3 + 2] annulation reactions of substituted indoles and β,γ -unsaturated α -ketoesters was also previously described by Chen and Xiao *et al.*, in 2013 (not shown) (Cheng *et al.*, 2013; Zhu *et al.*, 2012). In 2017, the Wang group disclosed a similar synthetic strategy with catalysis of Pd-complex to construct optically active spiro-polycyclic indoles (Li *et al.*, 2017a). In 2018, the Du group reported an enantioselective Michael/*N*-hemiketalization cascade reaction of isatin-derived β,γ -unsaturated α -ketoesters and 3-aminoindoles **88** (Scheme 12C) (Lin *et al.*, 2018). This cinchona-derived bifunctional squaramide catalyzed event afforded various chiral 3,3'-pyrrolidinyl-bispirooxindoles **89** in moderate to good yields (63–85%) with high diastereo- and enantioselectivities (63–91% ee, 2:1 to >19:1 dr) under mild conditions.

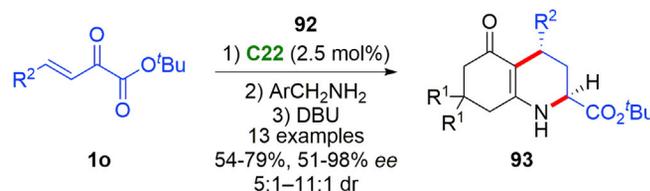
Catalytic asymmetric [3 + 3] annulation reactions

In the meantime, the catalytic asymmetric [3 + 3] annulation reaction of β,γ -unsaturated α -ketoesters has received great attention in recent years, and a number of methodologies have been developed for synthesis of various of six-member carbo- or heterocyclic compounds. In 2015, the Lopp group exhibited the

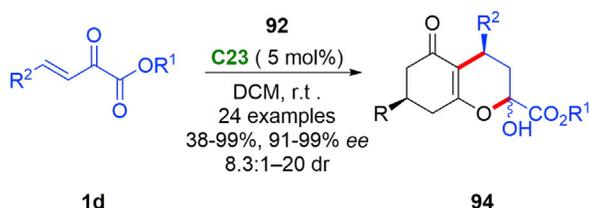
A Lopp *et al.* 2015



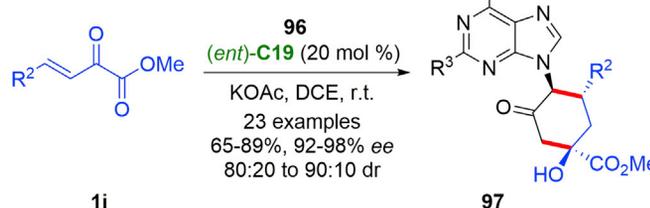
B Shi *et al.* 2016



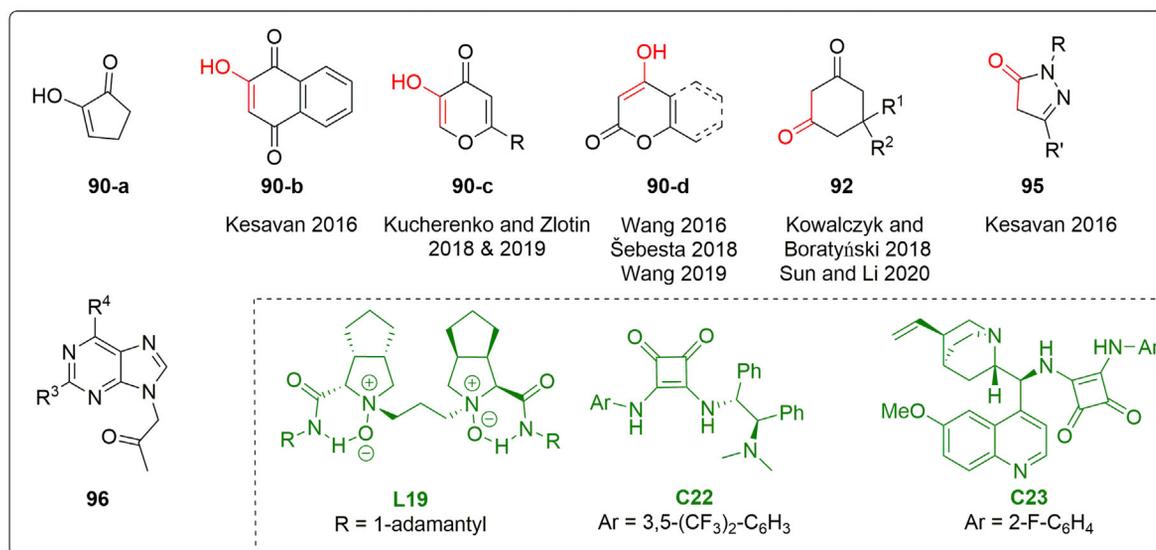
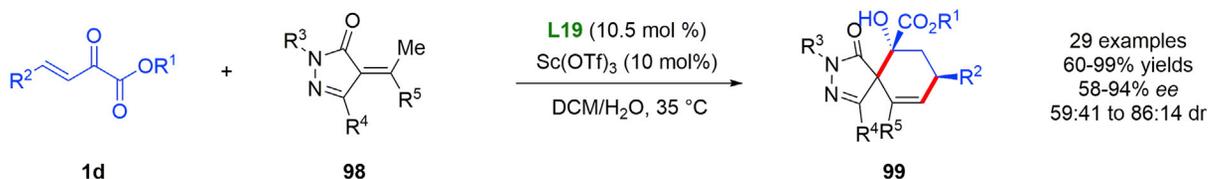
C Kowalczyk *et al.* 2020



D Niu and Guo *et al.* 2018



E Feng *et al.* 2019



Scheme 13. Catalytic asymmetric [3 + 3] annulation reactions with dinucleophile analogues

feasibility of organo-catalyzed cascade Michael addition–cyclization reaction of β,γ -unsaturated α -ketoesters with enols 90-a (scheme 13A) (Lopp *et al.*, 2015). The adducts 91 bearing a chiral hemiketal unit were created as a single diastereoisomer in excellent yields (42–93%) and enantioselectivities (87–96% ee). In 2016, one-pot synthesis of optically active hydroquinoline-2-carboxylates 93 was described by Shi *et al.* (Scheme 13B) (Rong *et al.*, 2016). This chiral base catalyzed [3 + 3] process was enabled by a sequential asymmetric Michael/transamination/cyclization process. The desired products were obtained from 1,3-cyclohexanediones, β,γ -unsaturated α -ketoesters, and benzylamine with good diastereoselectivity and high enantioselectivity (51–98% ee, 5:1 to 11:1 dr). Recently, Kowalczyk *et al.* applied this [3 + 3] strategy to the catalytic asymmetric desymmetrization of prochiral cyclic 1,3-diketones 92 (Scheme 13C) (Dajek *et al.*,

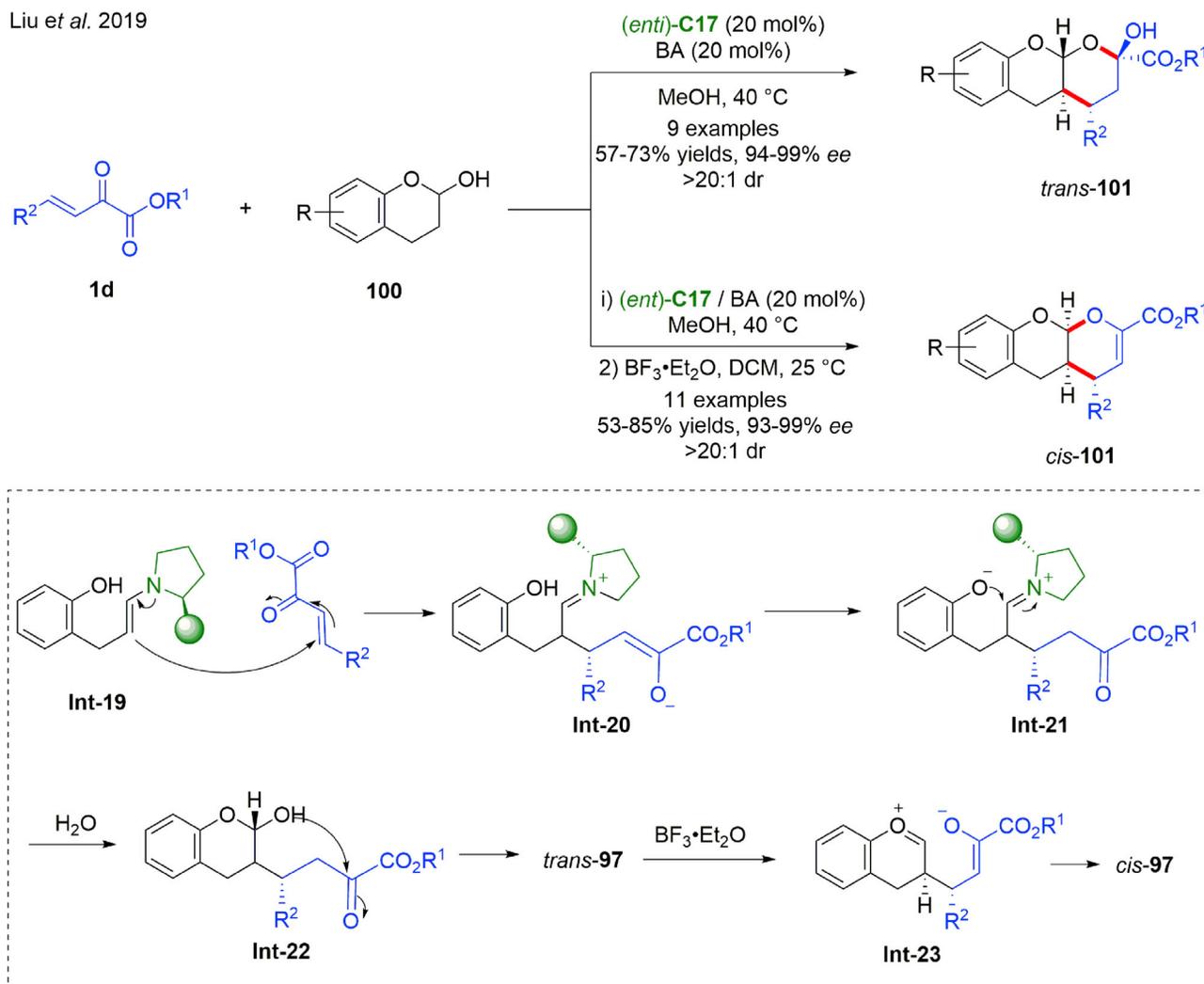
2020). The unprecedented desymmetrization of the parent C- and O-centered dinucleophiles led to hemiacetals 94 with high stereoselectivities (91–99% ee), which were readily transformed to 1,4-dihydropyridines without erosion of optical purity. Moreover, other dinucleophile analogues, such as enols 90b-d (Kostenko et al., 2018; Liu et al., 2019; Modrocka et al., 2018; Pratap Reddy Gajulapalli et al., 2016; Tikhvatshin et al., 2019; Yin et al., 2016), as well as pyrazolones 95 (Kumarswamyreddy and Kesavan, 2016) and 1,3-cyclohexanediones 92 (Dajek et al., 2018; Yang et al., 2020), which could easily be tautomerized to its enol form, served as suitable C3 synthons in catalytic asymmetric [3 + 3] annulation reactions with β,γ -unsaturated α -ketoesters.

Moreover, in consideration of the facile deprotonation at both α -positions, aliphatic ketones could be employed as alternative dinucleophiles for C3 synthons for [3 + 3] annulation reactions. In this context, a catalytic asymmetric Michael addition-proton transfer-aldol reaction cascade reaction of α -purine-substituted acetones 96 with β,γ -unsaturated α -ketoesters was accomplished by Niu and Guo et al., in 2018 (scheme 13D) (Huang et al., 2018). By using bifunctional thiourea catalysis, chiral six-membered carbocyclic purine nucleoside analogues 97 bearing three chiral stereocenters including a chiral tetrasubstituted carbon center were readily created in high yields (65–89%) with excellent diastereo- and enantioselectivities (92–98% ee, 80:20 to 90:10 dr). Interestingly, a weak base as an additive was necessary to enhance the yields. Later, the asymmetric [3 + 3] annulation reactions of β,γ -unsaturated α -ketoesters and cyclohexanones for the synthesis of bridged compounds were reported by the Juaristi group (Cruz-Hernández et al., 2018; Obregón-Zúñiga et al., 2017). Because pyrazolones were frequently found as an important structural unit in a variety of valuable nitrogen heterocycles, α,β -unsaturated pyrazolones possessing a γ -hydrogen have been employed as nucleophiles in organic synthesis. In 2019, Feng et al. achieved an asymmetry [3 + 3] annulation reaction between β,γ -unsaturated α -ketoesters and α -arylidene pyrazolinones 98 via a Michael–aldol domino process (scheme 13E) (Xu et al., 2019b). Chiral N,N' -dioxide-Sc(III) complex displayed excellent catalytic capability under aqueous media, affording a series of spirocyclohexene pyrazolones 99 with three stereocenters including vicinal tetrasubstituted stereocenters in good to high yields (60–99%) with excellent ee values (58–94% ee). It is noteworthy that spirocyclic quaternary carbon centers could be epimerized because of the retro-aldol process even in the absence of bases. Besides, organo-catalysts such as quinidine (Krishna et al., 2020) and 9-Amino-(9-deoxy)epi-quinine-based thiourea (Sun et al., 2020) were also applicable to this kind of asymmetric process.

Besides, as another type of important reactive intermediate, enamine has a very extensive application in organocatalysis. In 2019, the Liu group developed a [3 + 3] annulation reactions of β,γ -unsaturated α -ketoesters with chroman-2-ols 100 via an enamine-catalyzed sequential process (scheme 14) (Lv et al., 2019). Fused polycyclic hemiketal derivatives *trans*-101 bearing three stereocenters were obtained in high yields (57–73%) with excellent diastereo- and enantioselectivities (94–99% ee, >20:1 dr). By simply treatment with boron trifluoride etherate, the enantiomers *cis*-101 were prepared in a highly stereoselective fashion via dehydration-condensation. It is noteworthy that the catalytic system retained high catalytic and stereocontrolling abilities after multiple recycle.

Notably, electron-rich aromatics could be utilized as right partners in catalytic asymmetric [3 + 3] annulation reactions of β,γ -unsaturated α -ketoesters. Out of them, 2-naphthols have attracted much attention as versatile electron donor in various addition and oxidation reactions at 1-position. A organo-catalyzed asymmetric [3 + 3] annulation of β,γ -unsaturated α -ketoesters 1b with 2-naphthols 102 was established by the Kesavan group in 2016 (scheme 15A) (Muthusamy et al., 2016). The protocol showcased a highly enantioselective synthetic strategy to construct spirooxindole-naphthopyran scaffold via a Friedel-Crafts type/hemiketalization sequential process followed by a dehydration by treating with sulfuric acid. Subsequently, Liu and Feng et al. expanded the [3 + 3] annulation of β,γ -unsaturated α -ketoesters to electron-rich phenols, using their developed N,N' -dioxide scandium (III) catalytic system (scheme 15B) (Hao et al., 2017). Excellent yields (71–97%) and high enantioselectivities with high diastereoselectivities (80–95% ee, 6:1 to 14:1 dr) were achieved under mild conditions. Interestingly, probably owing to the high reactivity and steric resistance, substrates containing N,N' -dimethylamino failed to produce the corresponding chiral product even with a high yield. In addition, pyrrole and indole derivatives served as suitable 1,3-dinucleophiles, in light of their biological significance. In 2018, the Wang group described a metal and organo co-catalyzed sequential Friedel-Crafts/aldol tandem reaction of isatin-derived β,γ -unsaturated α -ketoesters 1b and 3-pyrrolyloxindoles 106 (scheme 15C) (Li et al., 2018a).⁸¹ Bispirooxindoles 107 and diastereomeric (*iso*)-107 (not shown) were separately prepared in high yields (62–92%) with excellent diastereo- and enantioselectivities (81–97% ee, 90:1 to >20:1 dr).

Liu *et al.* 2019



Scheme 14. Catalytic asymmetric [3 + 3] annulation reactions involving enamine intermediate

For tackling the influences of the coordinative groups in asymmetric catalysis, the Tang group is devoted to developing a side arm strategy for chiral ligand design. In 2018, Wang and Tang *et al.* described a Ni(II)/L22 catalyzed asymmetric cascade annulation of β,γ -unsaturated α -ketoesters with electron-rich phenols (scheme 15D) (Ren *et al.*, 2018). A broad range of substrates containing amino or methoxy groups were obtained in high yields (87–98%) and excellent enantioselectivities (89–99% ee). Noteworthy, the highly efficient synthesis of potential anticancer agents highlighted the synthetic utility of this method in preparation of chroman-based medicines.

Later, in 2020, one pot synthesis of tetrahydroindolizines 111 in three steps from β,γ -unsaturated α -ketoesters and 2-(pyrrol-1-yl)acetic acids 110 was reported by the Smith group (scheme 15E) (Zhang *et al.*, 2020). The proposed reaction progress involved an enantioselective Michael lactonization of 2-(pyrrol-1-yl)acetic acids with β,γ -unsaturated α -ketoesters, ring-opening of the cyclized intermediate int-25 and a following spontaneous cyclization of the pyrrole ring with the pendant ketone group. Recently, Antilla *et al.* demonstrated a catalytic asymmetric C7 Friedel-Crafts alkylation/N-hemiacetalization cascade reaction derived from β,γ -unsaturated α -ketoesters and 4-aminoindoles 112 (scheme 15F) (He *et al.*, 2021a). The C4-alkylamine substituent as a para-directing group was necessary for the regioselective C7 Friedel-Crafts alkylation. The reactions occurred smoothly in the presence of a chiral magnesium phosphate catalyst, resulting in the polycyclic 4*H*-pyrrolo [3,2,1-*ij*]quinoline derivatives 113 in high yields (80–96%) with good to excellent ee values (76–99% ee).

CATALYTIC ASYMMETRIC [4 + N] ANNULATION REACTIONS

Catalytic asymmetric [4 + 2] annulation reactions

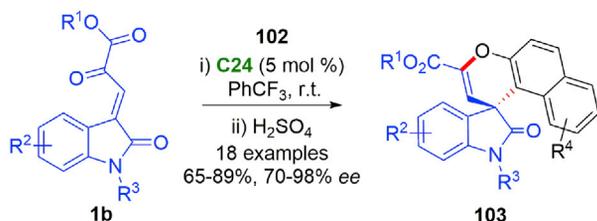
Six-membered rings are one of the most common motifs in natural products, pharmaceuticals as well as functional materials. Catalytic asymmetric [4 + 2] annulation reactions represent the most direct and convenient strategy to such six-membered rings including carbo- and hetero-cycles. For example, chiral 1,4-dihydropyridines are a class of important heterocycles found in numerous natural and non-natural products, such as alkaloids, calcium channel blockers and drugs. The development of the synthetic methodology for chiral 1,4-dihydropyridines is of considerable interest. In this regard, asymmetric [4 + 2] annulations involving β,γ -unsaturated α -iminoester proved to be an efficient approach. In 2015, Zheng and Zhang et al. reported an asymmetric Michael addition-cyclocondensation reaction derived from β,γ -unsaturated α -ketoesters, arylamines and 1,3-dicarbonyl compounds (scheme 16A) (An et al., 2015). In the optimization of the conditions, a H_8 -BINOL type chiral imidodiphosphoric acid showed high catalytic and stereocontrolling abilities to offer a series of 1,4-dihydropyridines 116 in moderate yields (34–61%) with excellent ee values (75–97% ee). The proposed reaction progress involved a dehydration condensation of β,γ -unsaturated α -ketoesters and arylamines to produce β,γ -unsaturated α -iminoesters, the following Michael addition with 1,3-dicarbonyl compounds, and the final intramolecular dehydration condensation. Independently, a similar enantioselective three-component aza-Diels–Alder reaction of β,γ -unsaturated α -ketoesters, cyclic ketones and arylamines was developed by the Wang group using a chiral bimetallic catalysis (Deng et al., 2015).

In addition, without the assistance of amines, [4 + 2] annulations between β,γ -unsaturated α -ketoesters and aldehydes were viable. In 2016, a proline-derived thiourea catalyzed asymmetry [4 + 2] cycloaddition of β,γ -unsaturated α -ketoesters and cyclic β -oxoaldehydes was reported by the Kesavan group (scheme 16B) (Vishwanath et al., 2016). The transformation was supposed to start with a 1,4-Michael addition of β,γ -unsaturated α -ketoesters, followed by a hemiacetalization cyclization. Dihydropyran-oxindole architectures containing three contiguous chiral centers were created in an efficient and highly stereoselective fashion. Subsequently, the Headley group reported a diarylprolinol silyl ethers catalyzed enantioselective [4 + 2] annulation of β,γ -unsaturated α -ketoesters and aldehydes (scheme 16C) (Katakam et al., 2017). The proposed reaction mechanism involved generation of enamines from aldehydes and secondary amine catalysis, 1,4-addition to the β,γ -unsaturated α -ketoesters, cyclocondensation and the final hydrolysis. *trans*-2-Oxo-3,4-dihydro-2H-pyran derivatives 120 were obtained by simple oxidation of PCC in high yields (51–94%) with excellent diastereo- and enantioselectivities (93–98% ee). Differently, Kano and Maruoka et al. reported that *cis*-dihydropyrans derivatives 121 were prepared as dominant product (scheme 16D) (Kano et al., 2018). The hydrogen bonding between the amino diol catalyst and substrate could stabilize the less favored transition state and lead to *cis*-isomers.

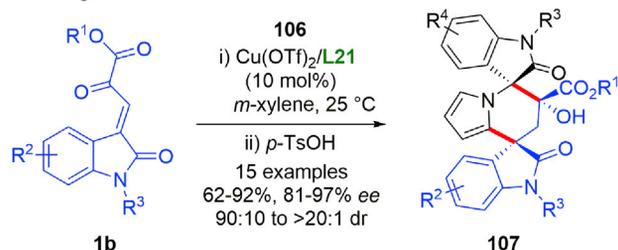
Besides, the Zhao group completed an asymmetric tandem inverse-electron-demand hetero-Diels–Alder/oxa-Michael reaction catalyzed by the modularly designed organocatalysts (MDOs) which were self-assembled from amino acids and cinchona alkaloid derivatives in the reaction medium (Scheme 16E) (Huang et al., 2016a). The reactions were derived from β,γ -unsaturated α -ketoesters 1d and the aldehydes 122. The catalytic cycle started with formation of enamine intermediate from aldehydes and secondary amine catalysis. Hydrogen bonding between dicarbonyl of β,γ -unsaturated α -ketoesters and thiourea contributed to decreasing the LUMO energy of β,γ -unsaturated α -ketoester and promoting the inverse-electron-demand Diels–Alder reaction. Hydrolysis occurred to give the catalysis regeneration and hemiacetals int-30, and was followed by final Michael cycloaddition. Under the catalysis of different combination of amino acids and cinchona alkaloid derivatives, enantiomers of *cis*- and *trans*-fused 123 were separately obtained in high yields (70–95%) with excellent diastereo- and enantioselectivities (94–99% ee, 88:12 to 99:1 dr).

The Michael addition-lactonization process has also been employed as a practical strategy for [4 + 2] annulation reactions of β,γ -unsaturated α -ketoesters. For instance, Xu and Yuan et al. accomplished a chiral bifunctional thiourea-tertiary amine catalyzed enantioselective Michael addition-lactonization of β,γ -unsaturated α -ketoesters with arylacetyl phosphonates in 2016 (Scheme 17A) (Zhang et al., 2016). This method set up a new approach toward highly enantioenriched *syn*-3,4-dihydropyranone derivatives 125. Good yields (54–78%), excellent stereoselectivities (92–99% ee) and high functional group tolerance were achieved.

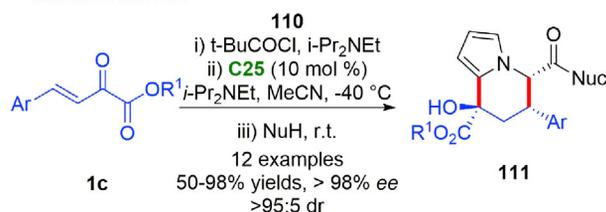
A Kesavan et al. 2016



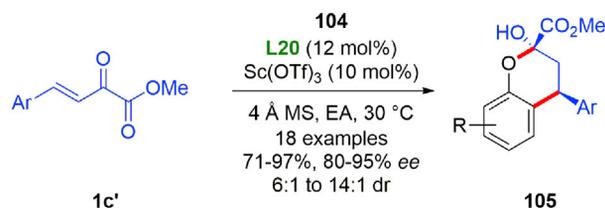
C Wang et al. 2018



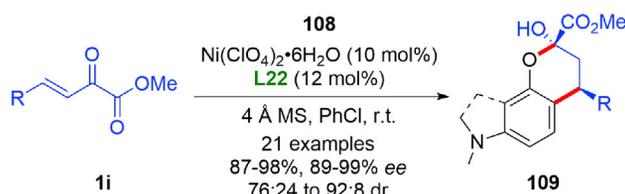
E Smith et al. 2020



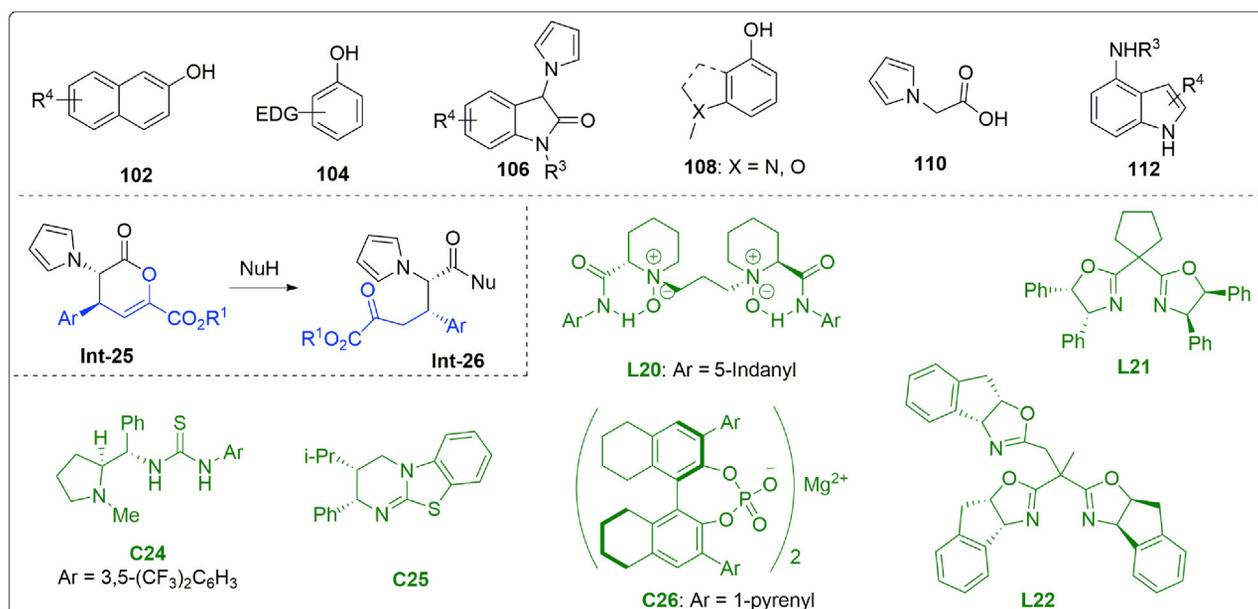
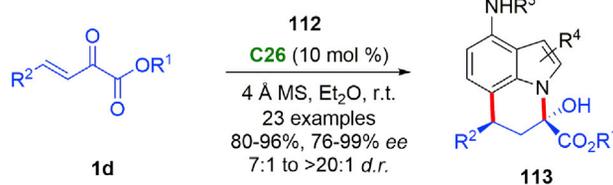
B Lin and Feng et al. 2017



D Wang and Tang et al. 2018



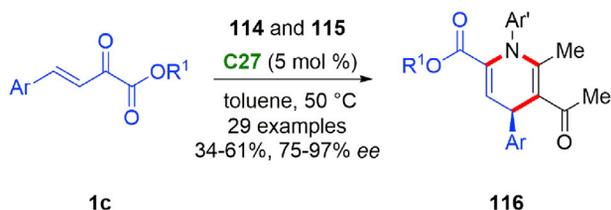
F Antilla et al. 2021



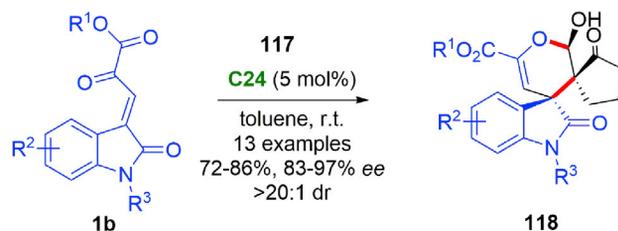
Scheme 15. Catalytic asymmetric [3 + 3] annulation reactions with electron-rich aromatics

Especially, α -aroyloxyaldehydes are a class of important azolium enolate precursors, which could be employed as versatile nucleophilic reagents as well as good nucleophilic acceptors. In 2017, the Smith group developed an NHC-catalyzed enantioselective hetero-Diels–Alder reactions of β,γ -unsaturated α -ketoesters 1c and α -aroyloxyaldehydes 126 (scheme 17B) (Taylor et al., 2017). The catalytic cycle was initiated by the generation of azolium enolate int-31 via addition-eliminations. The following 1,4-addition to β,γ -

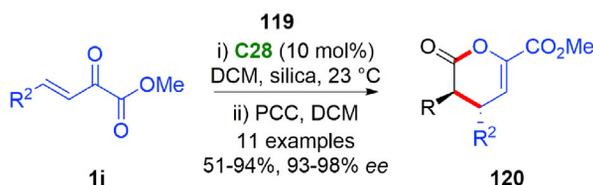
A Zheng and Zhang *et al.* 2015



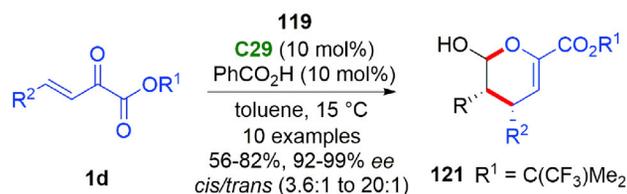
B Kesavan *et al.* 2016



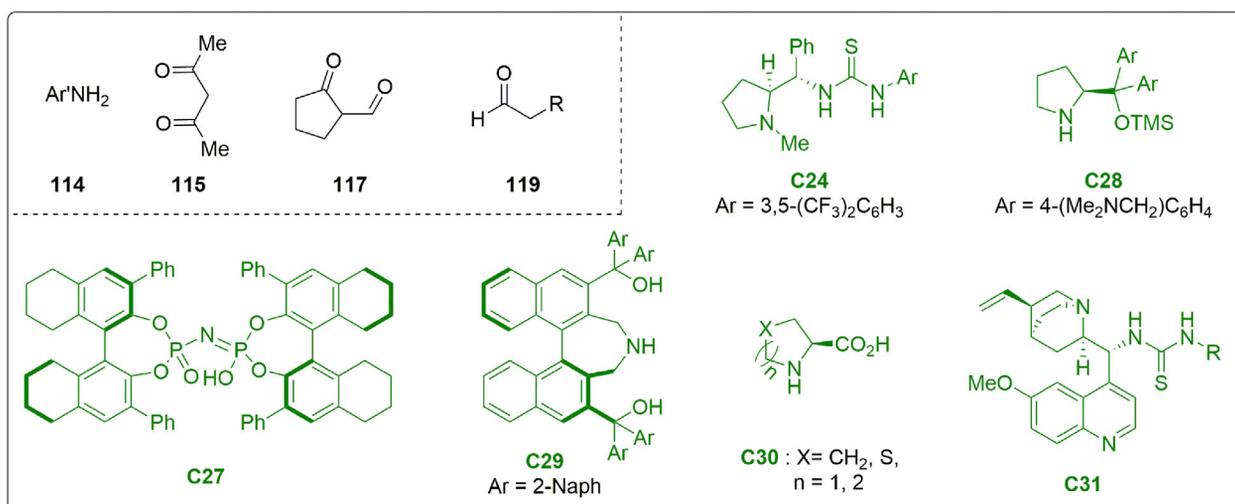
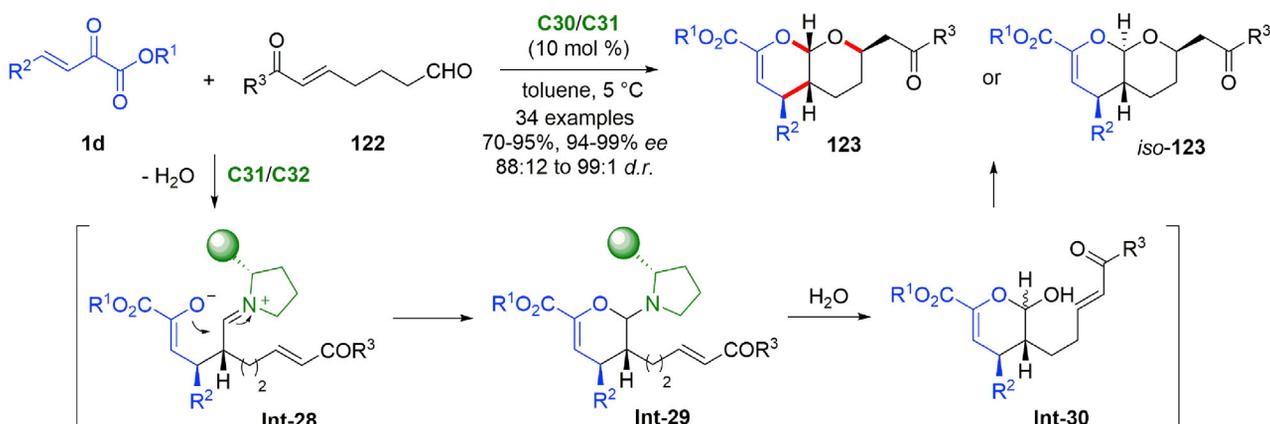
C Headley *et al.* 2017



D Kano and Maruoka *et al.* 2018



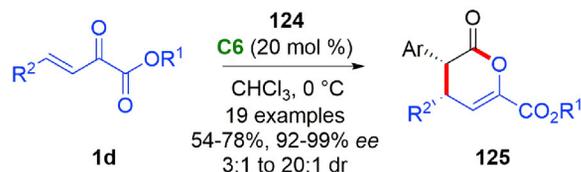
E Zhao *et al.* 2016



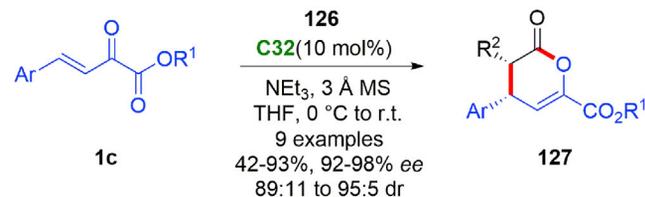
Scheme 16. Catalytic asymmetric [4 + 2] annulation reactions via Michael addition-cyclocondensation

unsaturated α -ketoesters and lactonization led to the adducts and NHC regeneration. Excellent diastereo- and enantioselectivities (92–98% ee, 89:11 to 95:5 dr) were achieved. The *syn*-dihydropyranone products bearing electron-deficient aryl were more susceptible to epimerize at the C(4)-position in the presence

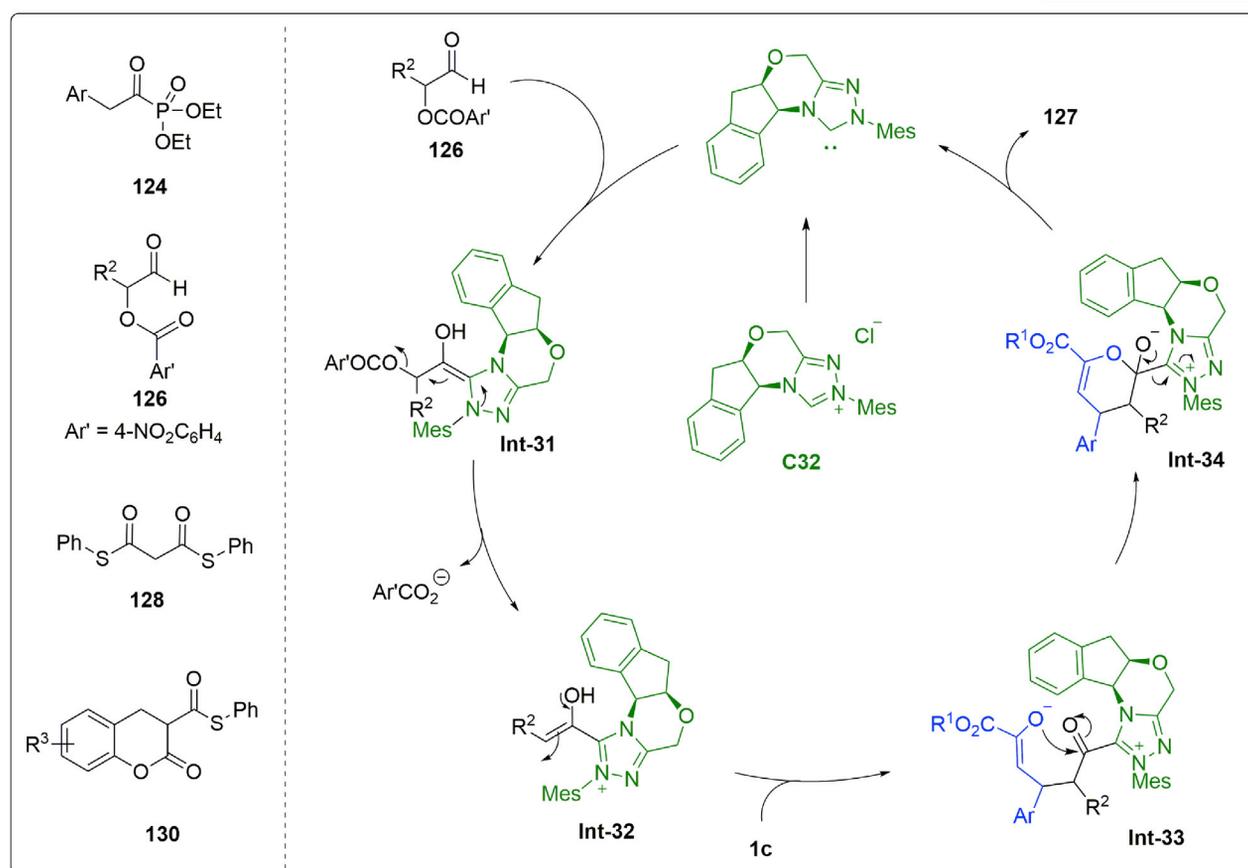
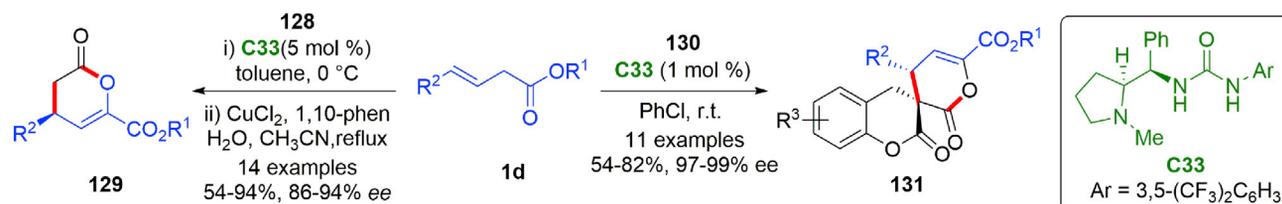
A Xu and Yuan et al. 2016



B Smith et al. 2017



C Ryu et al. 2018



Scheme 17. Catalytic symmetric [4 + 2] annulation reactions via Michael addition–lactonization

of base, and reduced diastereoselectivity were observed. In addition, this catalytic system was also adapted to the α,β -unsaturated γ -ketoester substrates (not shown).

Subsequently, in 2018, the Ryu group reported a proline-derived urea catalyzed enantioselective Michael addition-lactonization reactions of β,γ -unsaturated α -ketoesters and thioesters (scheme 17C) (Jin et al., 2018). Chiral 3,4-dihydropyranones 129 were obtained in high yield (54–94%) with excellent enantioselectivities (86–94% ee) via [4 + 2] annulation reactions with disulfide malonate followed by hydrolysis–decarboxylation with retention of optical purities. In addition, spiro-3,4-dihydrocoumarin-fused

3',4'-dihydropyranones 131 were created in excellent stereoselectivities (97–99% ee) by means of this protocol using *S*-Phenyl-2-oxochroman-3-carbothioates 130.

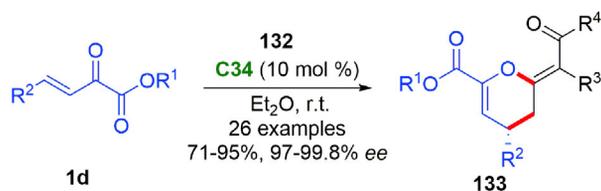
In addition to above Michael-addition type cascade annulations, inverse-electron-demand (IED) hetero-Diels–Alder reaction of β,γ -unsaturated α -ketoesters with electron rich alkenes proved to be a powerful protocol for six-member heterocycle construction. As a special compound containing a cumulative diene functionality, allene has many novel reaction performances especially in cyclization transformations. Among them, asymmetric [4 + 2] annulation reactions of β,γ -unsaturated α -ketoesters and allenes provided a powerful method for chiral six-membered heterocycles. In 2015, the Lu group developed a catalytic asymmetry [4 + 2] annulation between β,γ -unsaturated α -ketoesters and allene ketones (Scheme 18A) (Yao et al., 2015). This transformation proceeded smoothly with catalysis of dipeptide-based bifunctional phosphines, producing enantiomerically enriched 3,4-dihydropyrans 133 in high yields (71–95%) with excellent enantioselectivities (97–99.8% ee). The envisaged progress started with a nucleophilic addition of phosphine catalyst at the β -position of α -substituted allene ketone to produce α -anion Int-35. Isomerization encountered to form the γ -anion followed by an 1,4 addition to the β,γ -unsaturated α -ketoesters. The presence of α -alkyl group of the allene was crucial, which could suppress [3 + 2] cycloaddition by preventing enolate C-attack at the carbonyl α -position. The enolate O-attack at the β -position led to the formation of six-member heterocycle. In spite of the achievements with allene ketones, unactivated allenes involved catalytic enantioselective [4 + 2] annulation remains challenging. The elegant work came from the Luo group, by employing their developed cationic indium (III)/phosphate strategy. The [4 + 2] annulation of β,γ -unsaturated α -ketoesters and non-activated allenes readily occurred to prepare the corresponding C3-selective dihydropyrans 135 in good yields (35–90%) with high enantioselectivities (66–99% ee) (Scheme 18B) (Wang et al., 2017). Later, they found the electron-rich alkoxyallenes were also tolerated (Li et al., 2018b).

Then, in 2019, the Zhang group reported an imidodiphosphoric acid catalyzed inverse-electron-demand hetero-Diels–Alder reaction of β,γ -unsaturated α -ketoesters 1c and 3-vinylindoles 136 (scheme 18C) (Guan et al., 2019). 3,4-Dihydro-2*H*-pyran structural motifs bearing three contiguous stereogenic centers were created highly efficiently with excellent diastereo- and enantioselectivities (73–99% ee, >20:1 dr). Double hydrogen bond between catalyst and two reactants accounted for the enantio-control. In the same year, a dienolate-mediated asymmetric IED hetero-Diels–Alder reaction of β,γ -unsaturated α -ketoesters and β,γ -unsaturated amides was established by the Huang group (scheme 18D) (Qin et al., 2019). High yields (61–99%), excellent diastereo- and enantioselectivities (99–>99% ee, 76:24 to >95:5 dr) were achieved under the catalysis of chiral thiourea. Similarly, a chiral bifunctional squaramide catalyst was utilized in the catalytic asymmetric inverse-electron-demand hetero-Diels–Alder of isatin-derived β,γ -unsaturated α -keto esters with allyl ketones by the Du group in 2020 (Lin et al., 2020). In addition, Zhang and Shi et al. described a Lewis acid-catalyzed [4 + 2] hetero-Diels–Alder reaction of 3-alkyl-2-vinylindoles with β,γ -unsaturated α -ketoesters recently (Sun et al., 2022).

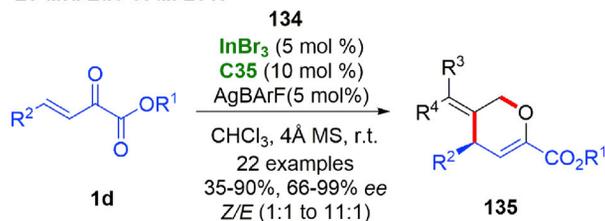
It is worth noting that organic azides have attracted extensive attention over the last few decades, many of which exhibit biological activity and are employed as versatile organic synthons in diverse transformations. In 2019, the Xu groups developed a copper (II)/BOX-catalyzed IED hetero-Diels–Alder reactions of β,γ -unsaturated α -ketoesters with vinyl azides (scheme 18E) (Thirupathi et al., 2019). A broad range of optically active cyclic azides 141 were obtained in high yields (54–94%) with excellent enantioselectivities (90–99.5% ee). In contrast, cyclohexenyl azide 142 served as dienophiles and led to normal Diels–Alder reactions.

Alkynyl alcohols and amides could undergo intramolecular cyclization to form enol ethers, which are versatile activated C2-synthons, participating in diverse transformations especially annulation reactions. In 2016, Liu and Feng et al. demonstrated an asymmetric [4 + 2] annulation reactions of β,γ -unsaturated α -ketoesters with alkynyl alcohols and amides (scheme 19A) (Li et al., 2016a). The transformation proceeded smoothly with catalysis of a bimetallic gold(I)/chiral *N,N'*-dioxide nickel (II) complex. The corresponding spiroketals and spiroaminals 145 rather than fused bicyclo products were obtained in good yields (34–99%) with excellent diastereo- and enantioselectivities (75–99% ee, 2:1 to >19:1 dr). In addition, gold(I)/chiral Rh(III) Lewis acid was utilized as an effective catalytic system in [4 + 2] annulation reactions of β,γ -unsaturated α -ketoesters with alkynyl alcohols by the Kang group in 2018 (scheme 19B) (Gong et al., 2018). Good diastereo- and excellent enantioselectivities (93–98% ee, 8:1 to >20:1 dr) were achieved owing to the superior asymmetric induction of newly designed chiral Rh(III) complex with steric bulk around

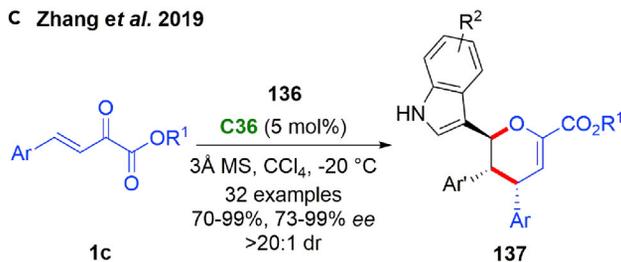
A Lu *et al.* 2015



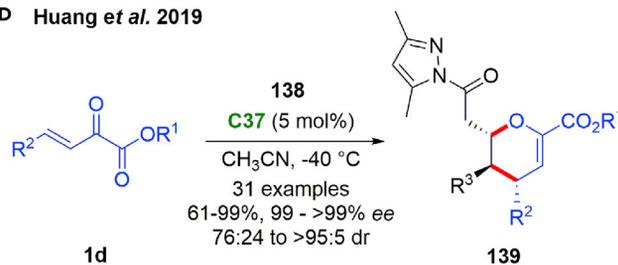
B Lv and Luo *et al.* 2017



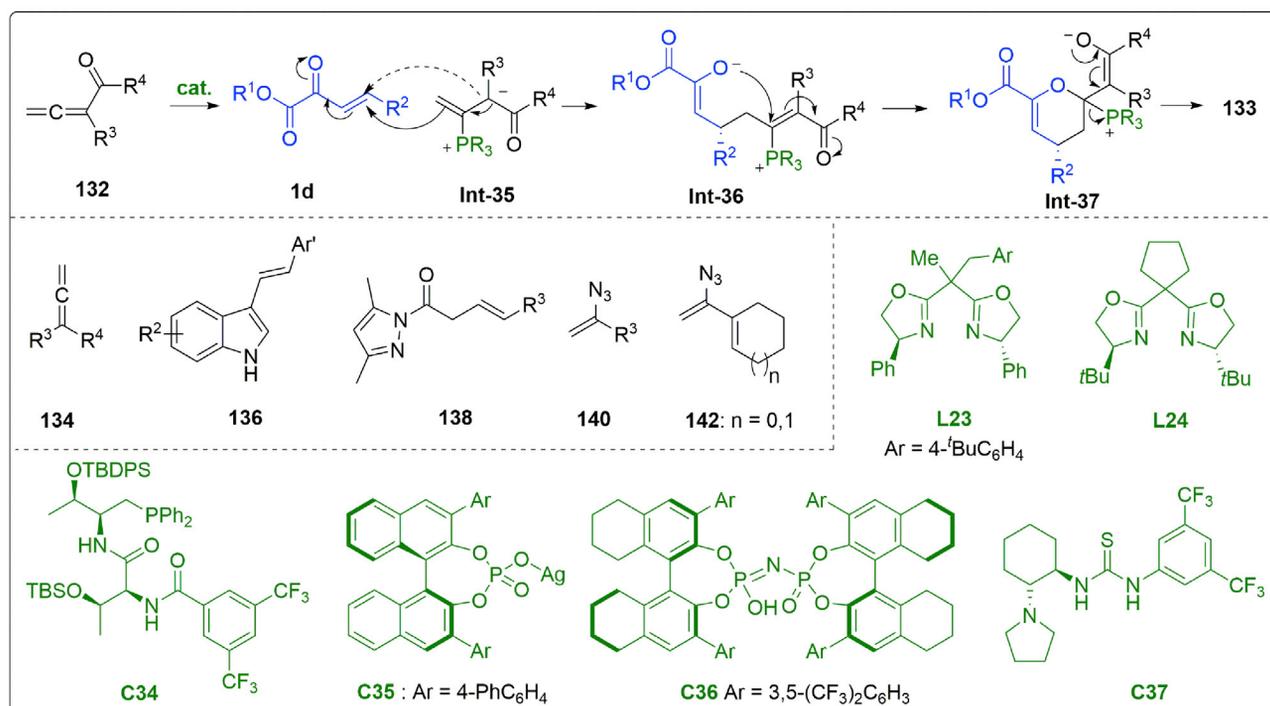
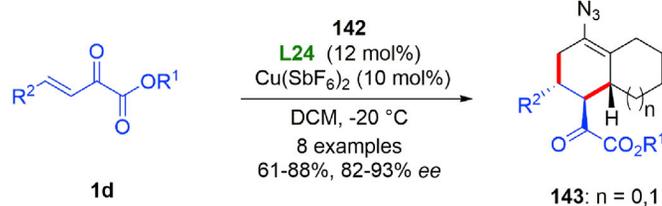
C Zhang *et al.* 2019



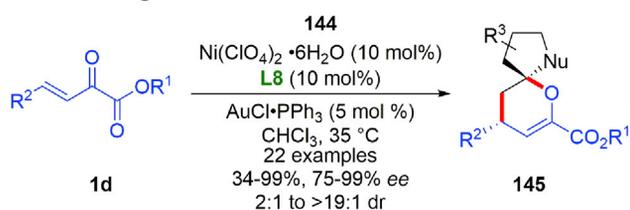
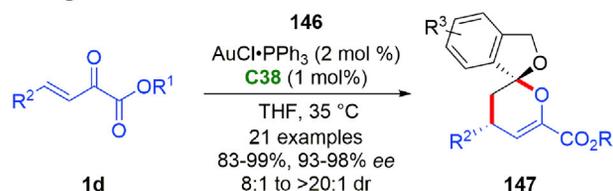
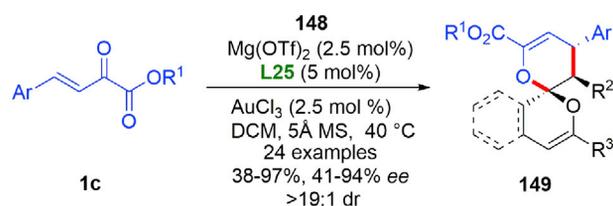
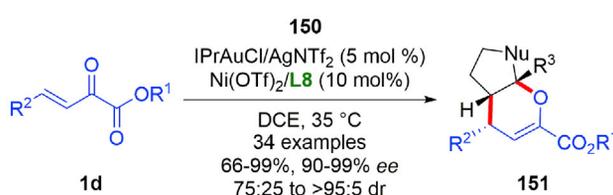
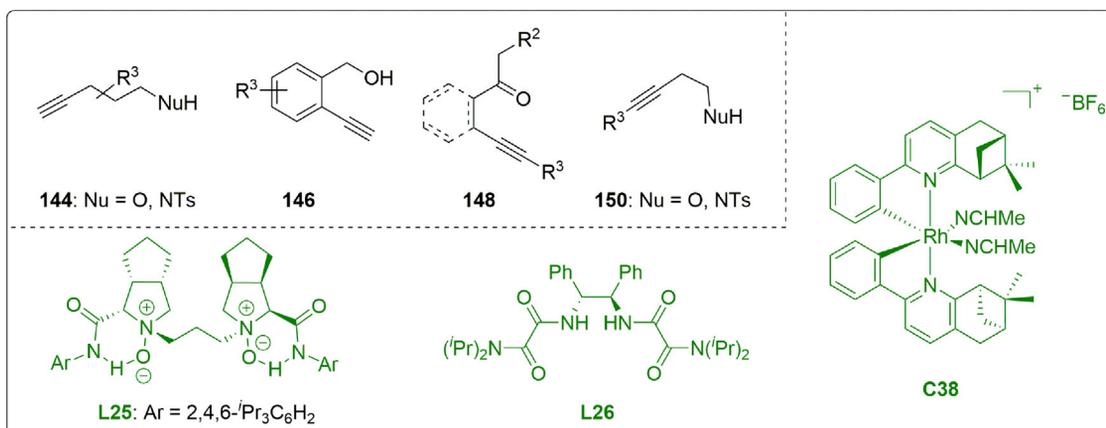
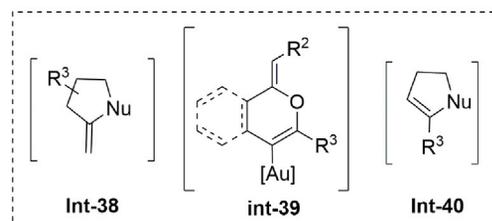
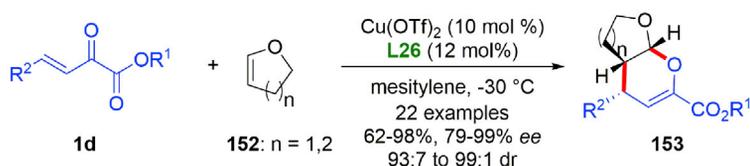
D Huang *et al.* 2019



E Xu *et al.* 2019



Scheme 18. Catalytic asymmetric inverse-electron-demand hetero-Diels-Alder reactions

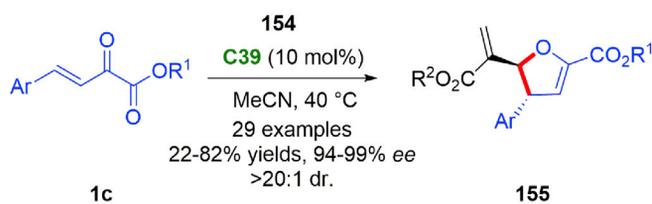
A Liu and Feng *et al.* 2016B Kang *et al.* 2018C Feng *et al.* 2019D Feng *et al.* 2018E Wang, Xia and Wang *et al.* 2020

Scheme 19. Catalytic asymmetric [4 + 2] annulation reactions with enol ethers.

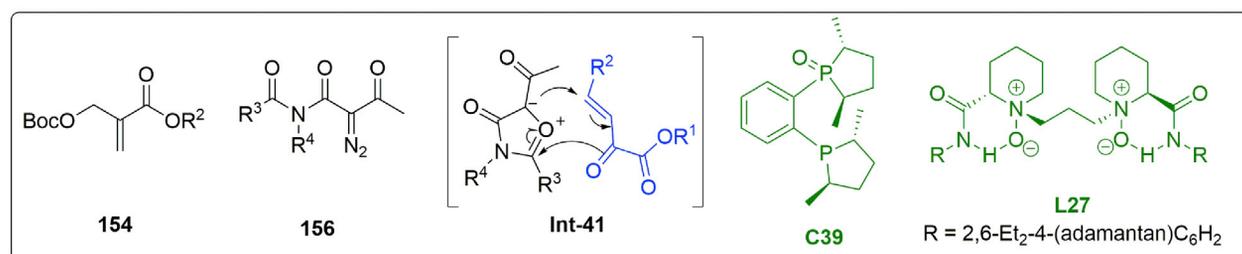
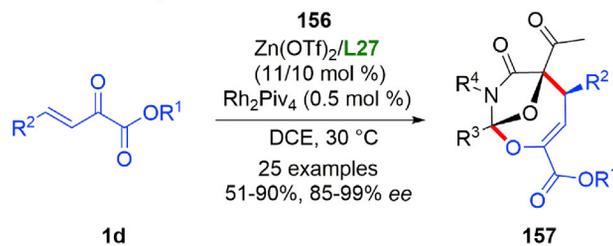
rhodium center. β -Alkynyl ketones have received great attention as fascinating precursors for construction of biologically interesting cyclic units. In 2019, the Feng group reported an asymmetric bimetallic gold (III) and chiral *N,N'*-dioxide/Mg(II) catalyzed cascade cycloisomerization/[4 + 2] annulation of β,γ -unsaturated α -ketoesters with β -alkynyl ketones (scheme 19C) (Ge *et al.*, 2019). The proposed reaction mechanism involved Au(III)-catalyzed 6-*endo-dig* oxo-cyclization of β -alkynyl ketones to generate key gold-bound alkene int-39, and final Mg(II)-catalyzed inverse-electron-demand hetero-Diels–Alder reactions. 6,6-Spiroketals 149 bearing three contiguous stereocenters were prepared in high yields (38–97%) with excellent diastereo- and enantioselectivities (41–94% ee, >19:1 dr).

On the other hand, because the *endo*-enol ether intermediate is more stable than the *exo*-isomer, it is credible for the isomerization of *exo*-enol ether intermediate into the *endo*-isomer, which could undergo [4 + 2] annulation reactions with β,γ -unsaturated α -ketoesters to prepare the corresponding fused bicyclic products. In 2018, Feng *et al.* completed an asymmetric bimetallic gold(I) and chiral *N,N'*-dioxide/Ni(II) catalyzed cascade cyclization/inverse-electron-demand hetero Diels–Alder reaction to prepare a series of fused

A Li et al. 2017



B Liu and Feng et al. 2019



Scheme 20. Catalytic asymmetric [4 + 1] and [4 + 3] annulation reactions

bicyclic N,O -acetals and O,O -acetals **151** containing a chiral tetrasubstituted carbon center in moderate to excellent yields (66–99%) with excellent diastereo- and enantioselectivities (90–99% ee, 75:25 to >95:5 dr) (Scheme 19D) (Hu et al., 2018). It is noteworthy that the yield of the fused bicyclic product could be further increased by addition of AgNTf_2 , indicating the electron-deficient gold(I) catalysis was favored for the transformation. Besides, [4 + 2] annulation reactions of β,γ -unsaturated α -ketoesters with preformed enol ether had been established by Wang, Xia and Wang et al., utilizing their newly developed C_2 -symmetric chiral bis-oxalamides/ $\text{Cu}(\text{II})$ complex as catalyst (scheme 19E) (Chen et al., 2020). The authors highlighted the carbonyl coordination of the chiral ligand to $\text{Cu}(\text{II})$ contributing to superior asymmetric induction.

Catalytic asymmetric [4 + 1] and [4 + 3] annulation reactions

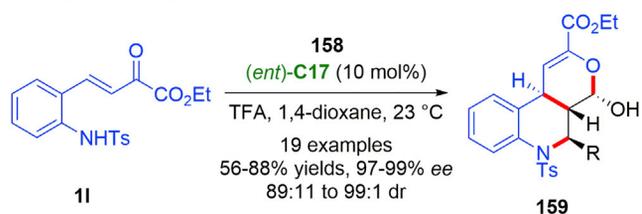
In contrast to the well-developed [4 + 2] annulations, catalytic asymmetric [4 + 1] and [4 + 3] annulation reactions of β,γ -unsaturated α -ketoesters received less attention despite the biological and synthetic importance of the corresponding five- and seven-membered heterocycles. For example, 2,3-dihydrofuran scaffolds are present in numbers of important molecules, many of which have been reported to exhibit interesting biological activities. Asymmetric [4 + 1] annulation reactions involving β,γ -unsaturated α -ketoesters provided an available tool for construction of these five-membered heterocycles. In 2017, the Li group reported a chiral phosphine-catalyzed enantioselective [4 + 1] annulation reactions between β,γ -unsaturated α -ketoesters and Morita–Baylis–Hillman carbonates to prepare a series of 2,3-dihydrofurans **155** in moderate to high yields (22–82%) with excellent asymmetric induction (94–99% ee, >20:1 dr) (Scheme 20A) (Cheng et al., 2017). This presented catalytic system was also adapted to other electron-deficient olefins.

Furthermore, tandem cyclization or cycloaddition reactions provide a powerful method for convenient access to polycyclic compounds. In 2019, Liu and Feng et al. reported a catalytic asymmetric cascade reaction of β,γ -unsaturated α -ketoesters and diazoimides (scheme 20B) (Xu et al., 2019a). The reaction's progress involved a [4 + 3] annulation of β,γ -unsaturated α -ketoesters and isomünchnones **Int-41** generated *in situ* from diazoimides. Bimetallic relay catalysis of rhodium (II) and chiral N,N' -dioxide-zinc(II) complex under mild conditions facilitated the synthesis of structurally sophisticated oxa-bridged oxazocine products **157** in moderate to excellent yields (51–90%) and excellent ee values (85–95% ee).

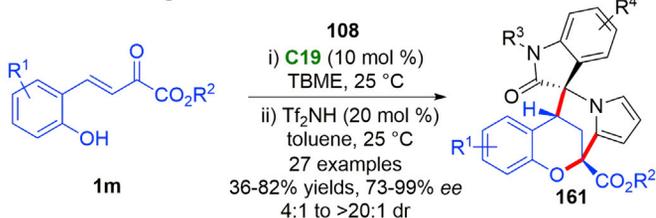
MISCELLANEOUS REACTIONS

Polycyclic compounds bearing fused ring, bridge ring or spiro ring have occupied a central role in the annals of the natural products, fine chemicals, ligands or catalysis as well as other complex molecules, and still pose a great challenge to organic synthesis. It is an appealing strategy to construct polycyclic

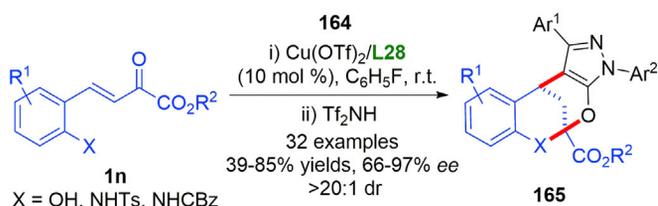
A Zeng and Zhong et al. 2017



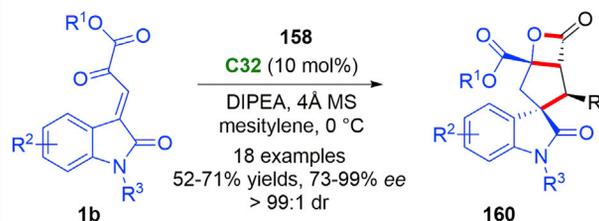
C Qiao and Wang et al. 2017



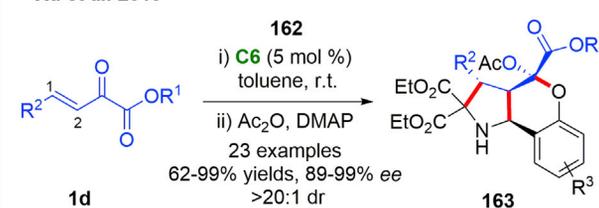
E Wang and Wang et al. 2020



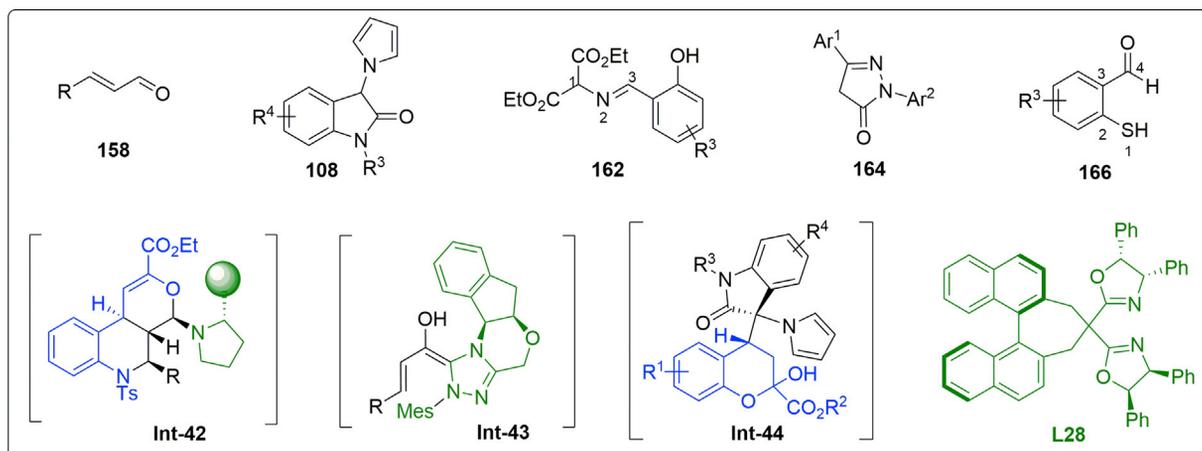
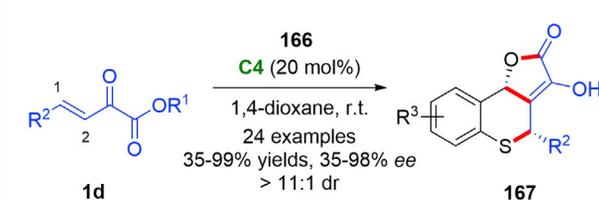
B Wang et al. 2017



D Xu et al. 2019



F Li et al. 2021



Scheme 21. Catalytic asymmetric cascade reaction for synthesis of polycyclic compounds

skeletons straightforwardly by taking advantage of the multiple reactive sites of β,γ -unsaturated α -ketoesters in reaction cascades.

For instance, Zeng and Zhong et al. developed a modified β,γ -unsaturated α -ketoesters **11** bearing nucleophilic NH group on the phenyl ring. In 2017, *L*-proline-derived secondary amine catalyzed asymmetric cascade aza-Michael-IED/HAD reaction of **11** with enals **158** was achieved (scheme 21A) (Dai et al., 2017). A variety of tetrahydropyranquinoline derivatives **159** with four stereogenic centers were prepared conveniently in moderate to good yields (56–88%) with excellent diastereo- and enantioselectivities (97–99% ee, 89:11 to 99:1 dr). The crystallographic analysis, NMR studies *in situ* and isolation of the key intermediate **Int-42** indicated the reaction mechanism involved the aza-Michael addition between sulfonamide and an activated iminium ion derived from enals and secondary amine, the intramolecular [4 + 2] annulation and the final substitution of H₂O to give the desired products and secondary amine catalysis regeneration.

By using a similar modified β,γ -unsaturated α -ketoesters **1m**, Qiao and Wang et al. reported a Takemoto thiourea catalyst and triflimide cooperatively catalyzed Michael/hemiketalization/Pictet–Spengler cyclization with 3-pyrroloxyindoles **108** for the construction of bridge-ring skeletons (scheme 21C) (Fan et al., 2017). The projected reaction was initiated by organo-catalyzed Michael addition, which was the enantio-determining step. The following intramolecular hemiketalization resulted in Int-44. The final Pictet–Spengler cyclization was promoted by a Brønsted acid. One tetrasubstituted spiro stereogenic carbon center and two bridgehead carbon centers were created with excellent diastereoselectivities and enantioselectivities (73–99% ee, 4:1 to >20:1 dr). In a follow-up research, the reaction cascade of β,γ -unsaturated α -ketoesters **1n** with pyrazolones **164** was set up by the same group via a Michael/ketalization process (scheme 21E) (Fan et al., 2020). The transformation was conducted by a chiral binaphthyl box-copper catalysis, and afforded a series of functionalized bicyclononane skeletons **165** in high yields (39–85%) with excellent enantio- and diastereoselectivities (66–97% ee, >20:1 dr).

In 2017, the Wang groups accomplished an NHC catalyzed asymmetric Michael-intramolecular aldol-lactonization cascade for spirocyclic oxindole skeletons construction (scheme 21B) (Zhang et al., 2017). The transformation proceeded the generation of Breslow homoenolate intermediate Int-43 by addition of the chiral aminoindanol-derived triazolium-based NHC to enals. The subsequent [3 + 2] annulation reaction was initiated by Michael addition, and the final intramolecular acylation reaction accounted for the lactone formation and NHC regeneration. The desired β -propiolactone-fused spiro [cyclopentane-oxindoles] **160** bearing four contiguous stereocenters including a spiro all-carbon quaternary stereogenic center were yielded with excellent diastereo- and enantioselectivities (73–99% ee, >99:1 dr).

Besides, in 2019, one pot synthesis of chromenopyrrolidines **163** containing four contiguous stereocenters was established by Xu et al. (scheme 21D) (Cao et al., 2019). The chemical event included enantioselective [2 + 3] annulation/hemiketalization reaction cascade between β,γ -unsaturated α -ketoesters and *o*-hydroxy aromatic aldimines **162** and the following acylation. The desired products were obtained in high yields with excellent stereoselectivities under the catalysis of a chiral bifunctional thiourea-tertiary amine. Similarly, the Li group demonstrated that isotetronic acid-fused thiochromanes **167** could be prepared via the sulfa-Michael/aldol/lactonization cascade in a highly stereoselective fashion (Scheme 21F) (Mo et al., 2021). The authors highlighted the lactonization of a less-explored ester carbonyl group of β,γ -unsaturated α -ketoesters.

CONCLUSIONS

β,γ -Unsaturated α -ketoesters have become versatile organic synthons participating in diverse catalytic asymmetric transformations with the breathtaking development of organo-catalysis, new catalytic system including ingenious chiral ligands as well as Lewis acid cation. This review summarized the recent developments of β,γ -unsaturated α -ketoesters according to the below reaction modes: (1) thanks to different characteristics of the catalytic system, the regioselective 1,4- and 1,2-additions with diversified nucleophiles reveal straightforward and powerful protocols for enantio-enriched ketoesters and tertiary alcohols, (2) multiform cyclization reactions including [2 + 3], [2 + 4], [3 + 2], [3 + 3] and [4 + 2] annulation afford efficient and convenient approaches to five- and six-membered ring skeletons, (3) especially we highlighted the utilization of β,γ -Unsaturated α -ketoesters in construction of polycyclic skeletons. In general, the highly efficient creation of stereogenic centers with excellent enantioselectivities is not a surprise, but owes to the bidentate coordination of its unique 1,2-dicarbonyl motif to artful chiral messenger, establishing a rigid system for the precise chiral-identification of the attack.

In spite of the tremendous achievement achieved, persistent efforts are required for rising to some challenges remaining in this research area, including but not limited to the followings. (1) β,γ -Unsaturated α -ketoesters showed a strong partiality for C-attack according to reported literature, whereas various nucleophiles including organosilicons, sulfides, and phosphides etc. are highly desired. (2) Most research mainly focused on developing new synthetic methodologies for five or six-member carbo- and heterocycles, and there is a great prospect for applications in construction of strained small rings via [2 + 1] or [2 + 2] annulations or macrocycles via [3 + *n*] (*n* \geq 4) or [4 + *n*] (*n* \geq 3) annulations. (3) β,γ -Alkynyl ketoesters are among one of the important analogue but with limited investigations. (4) With manipulatable functional groups, the chiral products are important and useful synthetic intermediates. There is tremendous potential waiting to be excavated for application in natural product synthesis, pharmaceutical chemistry, material science and other fields. The authors believe that these targets will be realized with the continuous

endeavors of chemists in exploiting new reaction modes and catalytic systems. The next decades will witness a flourishing and prosperous panorama in this exciting area of research.

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AUTHOR CONTRIBUTIONS

T.-J.H., X. G., Y.-F.Y., and G.-J. M. collected the references. R.D. and G.-J.M. conceived the project and prepared this manuscript. G.-J.M. overall supervised the project.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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