Further developments of $\beta, \gamma$-unsaturated $\alpha$-ketoesters as versatile synthons in asymmetric catalysis

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SUMMARY

$\beta, \gamma$-Unsaturated $\alpha$-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 stereoenic 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 $\beta, \gamma$-unsaturated $\alpha$-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 $\beta, \gamma$-unsaturated $\alpha$-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, $\beta, \gamma$-unsaturated $\alpha$-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 stereoenic centers. Consequently, $\beta, \gamma$-unsaturated $\alpha$-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 $\beta, \gamma$-unsaturated $\alpha$-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, $\beta, \gamma$-unsaturated $\alpha$-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, $\beta, \gamma$-unsaturated $\alpha$-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), $\beta, \gamma$-unsaturated $\alpha$-ketoesters function as dual electrophilic reagents (E-E) in [3 + n] annulation reactions. When it comes to the entire C=C-C=O moiety, $\beta, \gamma$-unsaturated $\alpha$-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 $\beta, \gamma$-unsaturated $\alpha$-ketoesters.
The past decades have witnessed significant advancements in this field. In 2013, Desimoni and coworkers reviewed the earlier examples on catalytic asymmetric reactions of \( \beta,\gamma \)-unsaturated \( \alpha \)-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 \( \beta,\gamma \)-unsaturated \( \alpha \)-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 \( \beta,\gamma \)-unsaturated \( \alpha \)-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 \( \beta,\gamma \)-unsaturated \( \alpha \)-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, \( \beta,\gamma \)-unsaturated \( \alpha \)-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 \( \beta,\gamma \)-unsaturated \( \alpha \)-ketoesters (Scheme 1A) (Juste-Navarro...
The authors highlighted the use of aliphatic substrates, which are usually overlooked in comparison with the commonly reported aromatic \( \beta,\gamma \)-unsaturated \( \alpha \)-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 \( \beta,\gamma \)-unsaturated \( \alpha \)-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 \( \alpha \)-amino esters, \( \alpha \)-hydroxy esters and \( \alpha \)-keto amides.

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

\( \text{et al., 2015} \)
In light of the significance of asymmetric Friedel-Crafts reaction of indoles with $\beta,\gamma$-unsaturated $\alpha$-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 $\beta,\gamma$-unsaturated $\alpha$-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$_3$CBr. The standard conditions were applicable to various aromatic $\beta,\gamma$-unsaturated $\alpha$-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($\text{II}$) 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 $\beta,\gamma$-unsaturated $\alpha$-ketoesters $1d$, wherein the chiral Ni($\text{II}$)-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 $\beta,\gamma$-unsaturated $\alpha$-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 $\beta,\gamma$-unsaturated $\alpha$-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 $\beta,\gamma$-unsaturated $\alpha$-ketoesters. For instance, nitro-compounds are useful and appealing nucleophilic reagents, because the nitro group could readily stabilize carbonium 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 $\beta,\gamma$-unsaturated $\alpha$-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 $\beta,\gamma$-unsaturated $\alpha$-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 $\beta,\gamma$-unsaturated $\alpha$-ketoesters has been regarded as one straightforward and powerful protocol. In 2016, the Zhou group reported an asymmetric Michael addition of 1-acetylindolin-3-ones $15$ to $\beta,\gamma$-unsaturated $\alpha$-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 stereoccontrol. 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 $\beta,\gamma$-unsaturated $\alpha$-ketoesters $1f$ (Scheme 2D) (Jaiswal et al., 2020). In addition, $\alpha$-azido indanes $19$ 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 $\alpha$-chiral tertiary azides were afforded with high efficiency and readily converted to enantioenriched spiro $N$-heterocycles.
Scheme 2. Organo-catalyzed asymmetric Michael-addition

A Yan et al. 2015

\[
\begin{align*}
\text{R}^2 \text{\(\text{=C}=\text{O}\)} & \text{Et} \\
11 \quad \text{1) \(\text{C3} \text{ (5 mol\%)}\)} & \text{tollen, r.t.} \\
2) \text{silica gel} & \text{p-xylene, reflux} \\
11 \text{ examples} & 49-88\%, 86-96\% \text{ ee}
\end{align*}
\]

B Bonne and Bugaut et al. 2020

\[
\begin{align*}
\text{R}^1 \text{\(\text{=C}=\text{O}\)} & \text{Et} \\
13 \quad \text{1) \(\text{C4} \text{ (10 mol\%)}\)} & \text{CH}_2\text{Cl}_2, 0^\circ \text{C} \\
7 \text{ examples} & 54-80\%, 53-90\% \text{ ee up to 11:1 dr}
\end{align*}
\]

C Zhou et al. 2016

\[
\begin{align*}
\text{R}^2 \text{\(\text{=C}=\text{O}\)} & \text{R}^1 \\
15 \quad \text{1) \(\text{C5} \text{ (2 mol\%)}\)} & \text{CH}_2\text{Cl}_2, 20^\circ \text{C} \\
22 \text{ examples} & 56-99\%, 91-99\% \text{ ee > 19:1 dr}
\end{align*}
\]

D Singh et al. 2020

\[
\begin{align*}
\text{R}^1 \text{\(\text{=C}=\text{O}\)} & \text{Et} \\
17 \quad \text{1) \(\text{C6} \text{ (20 mol\%)}\)} & \text{DCE, r.t.} \\
21 \text{ examples} & 55-82\%, 88-99\% \text{ ee up to >19:1 E/Z}
\end{align*}
\]

E Yu and Zhou et al. 2020

\[
\begin{align*}
\text{R} \text{\(\text{=C}=\text{O}\)} & \text{R}^2 \text{CO}_{2}\text{R}^1 \\
18 \quad \text{1) \(\text{C7} \text{ (10 mol\%)}\)} & \text{HFIP (80 mol\%), DCM, -40^\circ \text{C} \\
18 \text{ examples} & 60-99\%, 69-99\% \text{ ee 3:1–20:1 dr}
\end{align*}
\]

Scheme 2. Organo-catalyzed asymmetric Michael-addition
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 diphenylphospine 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 alkynylation 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 alkynylation 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 allylboronation/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 synthetized by Chai and Chang et al. via (R)-3,3′-Br$_2$-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 $^{13}$C NMR spectroscopic indicated one of the amin 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., 2016c). Although enantioselectivities were not ideal, as an environmental-friendly and sustainable biocatalyst, the enzyme catalysis showcased a wide application future in this field.
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).

Scheme 4. Catalytic asymmetric 1,2-addition reactions
The transformation was facilitated by the utilization of a chiral \(\text{N},\text{N}^-\)-dioxide/Mg\(\text{II}\) 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 \(\beta,\gamma\)-alkenyl \(\alpha\)-ketoesters and \(\beta,\gamma\)-alkynyl \(\alpha\)-ketoesters. It was proposed that \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters could be coordinated to the Mg\(\text{II}\) 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 \(\beta,\gamma\)-unsaturated \(\alpha\)-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 \(\beta,\gamma\)-unsaturated \(\alpha\)-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\(_2\)CO\(_3\), and followed by an enantioselective nucleophilic addition to the carbonyl group of \(\beta,\gamma\)-unsaturated \(\alpha\)-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 \(\alpha\)-ketoesters, isatins, and imines. Recently, the Li group revealed that Bi(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 \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters (Liu et al., 2021). In addition, the Johnson group completed a three-component reductive coupling reaction between \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters, dimethyl phosphate and aldehydes (scheme 6B) (Horwitz et al., 2016). The transformation was conducted by a chiral triaryliminophosphorane 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 phosphate to \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters, triggering the phospha-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 enatio-enriched ketoesters and tertiary alcohols, multiform cyclization reactions including [2 +
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 InBr3 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 proceeded to provide 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-C1 oxindoles and β,γ-unsaturated-α-ketoesters (scheme 7B) (Kuang et al., 2018). By tuning metal catalysts and adjusting the ligands and temperature, rel-(1R,2S,3R) and rel-(1S,2S,3R) spiro cyclopropane oxindoles were obtained separately in high yields (50–99%) with excellent enantioselectivities (72–99% ee). It is proposed that the rel-(1S,2S,3R) diastereoisomers 53 were obtained via an intramolecular trapping of the chiral aza-ortho-xyylene intermediate Int-6 after Michael addition, whereas the other diastereoisomers (iso)-53 were generated from Int-7 via a direct S8,2 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 a-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, >99:1 dr) under the catalysis of the chiral ureas secondary amine. 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
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...
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 ZnII 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.
On the other hand, great progress also has been made in organo-catalyzed asymmetric [2 + 4] annulation reactions of \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters. The catalytic asymmetric aza-Michael-Michael cascade derived from \(\beta,\gamma\)-unsaturated \(\alpha\)-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 \(\beta,\gamma\)-unsaturated \(\alpha\)-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 \textit{in situ} via mixing the Fe(III)-based bisphosphate anion with Ph\textsubscript{3}CCl. The desired
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 \( b,g \)-unsaturated a-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 10. Catalytic asymmetric [2 + 4] annulation reactions of C=C bond

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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 ropyran-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 [2 + 4] annulation reactions of C=O bond**

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**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 synths in [3 + n] annulation reactions, on account of the 1,3-dual electrophilic sites. In 2015, Wang and

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

__A Xu et al. 2016__

![Image 1](https://example.com/image1)

__B Wu et al. 2018__

![Image 2](https://example.com/image2)

__C Feng et al. 2018__

![Image 3](https://example.com/image3)
Chang et al. described a dinuclear zinc-AzePhenol complex catalyzed enantioselective domino Michael/hemiketalization reaction of \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters with \(\alpha\)-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 Friedel-Crafts alkylation/N-hemiacetalization cascade reaction of \(\beta,\gamma\)-unsaturated \(\alpha\)-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 \(\beta,\gamma\)-unsaturated \(\alpha\)-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 \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters and 3-aminoxindoles 88 (Scheme 12C) (Lin et al., 2018). This cinchona-derived bifunctional squaramide catalyzed event afforded various chiral 3,3\(^0\)-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 \(\beta,\gamma\)-unsaturated \(\alpha\)-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

\[ R\text{=4-CF}_3C_6H_4 \]
feasibility of organo-catalyzed cascade Michael addition-cyclization reaction of $\beta,\gamma$-unsaturated $\alpha$-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, $\beta,\gamma$-unsaturated $\alpha$-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., 2019).
The unprecedented desymmetrization of the parent C- and O-centered dinucleophiles led to hemi-acetals 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; Tukhvatshin et al., 2019; Yin et al., 2016), as well as pyrazolones 95 (Kumarsamyreddy and Kesavan, 2016) and 1,3-cyclohexanediones 92 (Dajek et al., 2018; Yang et al., 2020), which could easily be tautomized to its enol form, served as suitable C3 synths 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 synths 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 carboxylic 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; Obrégón-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 pyrazolines 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, organocatalysts 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] annihilation 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] annihilation 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-possition. A organo-catalyzed asymmetric [3 + 3] annihilation 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] annihilation 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 diastereoselectivity products (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-pyrylloxindoles 106 (scheme 15C) (Li et al., 2018a). 81 Bispyrroloindoles 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).
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 \( \beta,\gamma \)-unsaturated \( \alpha \)-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). Noteworthily, 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 \( \beta,\gamma \)-unsaturated \( \alpha \)-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 \( \beta,\gamma \)-unsaturated \( \alpha \)-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 \( \beta,\gamma \)-unsaturated \( \alpha \)-ketoesters and 4-aminoindoles 112 (scheme 15F) (He et al., 2021a). The C4-alkyamine 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 4H-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$_2$-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 bimetallocatalysis (Deng et al., 2015).

In addition, without the assistance of amines, [4 + 2] annihilations 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 catalysis reported 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 cyclodaddition. 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.

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Especially, α-aryloxyaldehydes 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-aryloxyaldehydes 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-
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 of NHC.
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

Scheme 17. Catalytic symmetric [4 + 2] annulation reactions via Michael addition–lactonization
3',4'-dihydropyranoines 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 annihilations, 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] annihilation 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-dihydropyranoines 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] cycladdition 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] annihilation of β,γ-unsaturated α-ketoesters and non-activated allenes readily occurred to prepare the corresponding C3-selective dihydropyranoines 135 in good yields (35–90%) with high enantioselectivities (66–99% ee) (Scheme 18B) (Wang et al., 2017). Later, they found the electron-rich alkyloallenes were also tolerated (Li et al., 2018b).

Then, in 2019, the Zhang group reported an imidodiophosphoric 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-2H-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,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 2016, Liu and Feng et al. demonstrated an asymmetric [4 + 2] annihilation reactions of β,γ-unsaturated α-ketoesters with alkynyl alcohols and amides (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. But, ketalization was achieved in oxidation of 2-unsubstituted 3,4-dihydropyranoines 133 by the Shi 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

Alkynyl alcohols and amides could undergo intramolecular cyclization to form enol ethers, which are versatile activated C2-synthons, participating in diverse transformations especially annihilation reactions. In 2016, Liu and Feng et al. demonstrated an asymmetric [4 + 2] annihilation 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(II)/chiral N,N'-dioxide nickel (II) complex. The corresponding spiroketal 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(II)/chiral Rh(III) Lewis acid was utilized as an effective catalytic system in [4 + 2] annihilation 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
Scheme 18. Catalytic asymmetric inverse-electron-demand hetero-Diels–Alder reactions

A. Lu et al. 2015

1d + C34 (10 mol %) in Et2O, r.t. leads to 132.

1d → R1-O-CH-OR1

71-95%, 97-99.8% ee

B. Lv and Luo et al. 2017

1d + InBr3 (5 mol %) + C35 (10 mol %) in CHCl3, 4Å MS, r.t.

134 → R4-CH-OR1

35-90%, 66-99% ee

Z/E (1:1 to 11:1)

C. Zhang et al. 2019

1c + C36 (5 mol %) in CCl4, -20 °C

136 → R2-O-CH-OR1

70-99%, 73-99% ee

>20:1 dr

D. Huang et al. 2019

1d + C37 (5 mol %) in CH3CN, -40 °C

138 → R2-O-CH-OR1

61-99%, 99 -> 99% ee

79:24 to ->95.5 139

E. Xu et al. 2019

1c + L23 (12 mol %) + Cu(SbF6)2 (10 mol %) in DCM, 30 °C

140 → R2-O-CH-OR1

54-94%, 99-99.5% ee

endo/exo (75:25 to 93.7)

141

Scheme 18. Catalytic asymmetric inverse-electron-demand hetero-Diels–Alder reactions
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,N0-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 alkenes int-39, and final Mg(II)-catalyzed inverse-electron-demand hetero-Diels–Alder reactions. 6,6-Spiro-ketals 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,N0-dioxide/Ni(II) catalyzed cascade cyclization/inverse-electron-demand hetero Diels–Alder reaction to prepare a series of fused products.

Scheme 19. Catalytic asymmetric [4 + 2] annulation reactions with enol ethers.
bicyclic N,O-acetals and O,O-acetals 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 AgNTf2, indicating the electron-deficient gold(I) catalysis was favored for the transformation. Besides, [4 + 2] annulation reactions of \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters with preformed enol ether had been established by Wang, Xia and Wang et al., utilizing their newly developed C\(\text{2}\)-symmetric chiral bis-oxalamides/Cu(II) complex as catalyst (scheme 19E) (Chen et al., 2020). The authors highlighted the carbonyl coordination of the chiral ligand to Cu(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 \(\beta,\gamma\)-unsaturated \(\alpha\)-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 \(\beta,\gamma\)-unsaturated \(\alpha\)-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 \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters and Morita–Baylis–Hillman carbonates to prepare a series of 2,3-dihydrofurans 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 \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters and diazoimides (scheme 20B) (Xu et al., 2019a). The reaction’s progress involved a [4 + 3] annulation of \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters and isomünchhones 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 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...
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 1l bearing nucleophilic NH group on the phenyl ring. In 2017, L-proline-derived secondary amine catalyzed asymmetric cascade aza-Michael-IED/HAD reaction of 1l with enals 158 was achieved (scheme 21A) (Dai et al., 2017). A variety of tetrahydropyranoquinoline 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.

Scheme 21. Catalytic asymmetric cascade reaction for synthesis of polycyclic compounds
By using a similar modified $\beta,\gamma$-unsaturated $\alpha$-ketoesters $1m$, Qiao and Wang et al. reported a Takemoto thiourea catalyst and triflimide cooperatively catalyzed Michael/hemiketalization/Pictet–Spengler cyclization with 3-pyrrollyloxindoles 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 Brensted 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 $\beta,\gamma$-unsaturated $\alpha$-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, >99:1 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 $\beta$-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 $\beta,\gamma$-unsaturated $\alpha$-ketoesters and $\alpha$-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 thiocromanes 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 $\beta,\gamma$-unsaturated $\alpha$-ketoesters.

**CONCLUSIONS**

$\beta,\gamma$-Unsaturated $\alpha$-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 $\beta,\gamma$-unsaturated $\alpha$-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 $\beta,\gamma$-Unsaturated $\alpha$-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) $\beta,\gamma$-Unsaturated $\alpha$-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 $[4 + n]$ ($n \geq 3$) annihilations. (3) $\beta,\gamma$-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
endavors 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.

ACKNOWLEDGMENTS

Financial support from the Scientific Research Starting Foundation of Zhengzhou University, application research plan of key scientific research projects in Colleges and universities of Henan Province (22A150056), and China Postdoctoral Science Foundation (2021TQ0290) are gratefully acknowledged.

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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