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Review

Recent advances towards catalytic asymmetric Conia-ene-type reactions

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ABSTRACT

Conia-ene reactions, as a type of ene reactions, have not become a remarkable focus until the beginning of 21st century, when Lewis acids served as powerful catalysts and found an increasingly broad utilization in this field. Consequently, the catalytic Conia-ene reactions have gained great significance in synthetic chemistry due to their high efficiency and atom economy on the construction of valuable cyclic molecules. During the past two decades, the rapid development of transition-metal catalysis and organocatalysis has imposed a profound impact on the exploration of asymmetric Conia-ene reactions. As a result, several strategies have been developed and applied successfully. Organized on the basis of the catalytic system, this review comprehensively presents a summary of recent progress achieved in this emerging domain, aimed at highlighting the reactions' features, practicalities, and the mechanistic rationale is presented where possible.

1. Introduction

Ene reactions [1], generally considered as the intra- or intermolecular organic reactions between an olefin bearing an allylic hydrogen atom and an enophile (alkene or alkyne; in a broader scope, enophile can also be carbonyl, thiocarbonyl and imine compounds) *via* a concerted [1,5]-hydrogen shift, have been an intriguing kind of reactions for the formation of new carbon-carbon bonds in the regard of high atom economy. As a representative example of this class, Conia-ene reaction was first presented by Conia and Le Perchec in 1975 [2], referring to the thermal cyclization of unsaturated carbonyl compounds bearing an alkenyl or alkynyl moiety *via* an enolization process (Scheme 1).

This thermal cyclization usually leads to the construction of five- or six-membered cyclic compounds, which are valuable structural motifs and precursors for diverse applications in organic synthesis. Despite the promising prospects described, the transformation has been strongly limited to harsh reaction conditions, especially high temperature (over 200 °C). To overcome the major drawback of the original procedure, considerable efforts were devoted to the optimization of the reaction system. It was not until the early 21st century that Lewis acids evolved as a powerful tool for promoting Conia-ene reaction under mild conditions, leading to rapid and significant progress in this active field.

During the past two decades, a diverse range of catalytic methods were widely applied to the development of Conia-ene reaction and several activation modes were well established [3]. However, these achievements were mostly restricted to racemic reactions and asymmetric versions were rarely exploited, though important and desirable. In this review, we summarize three main strategies that have been employed in the enantioselective Conia-ene-type reactions, including transition-metal catalysis, cooperative catalysis of transition-metal and organic catalysts, and organocatalysis.

2. Asymmetric Conia-ene-type reactions *via* transition-metal catalysis

2.1. Transition-metal catalyzed reactions involving two different metals

In 2004, Toste and co-workers disclosed a pioneering example of gold-catalyzed intramolecular addition of β-ketoesters to

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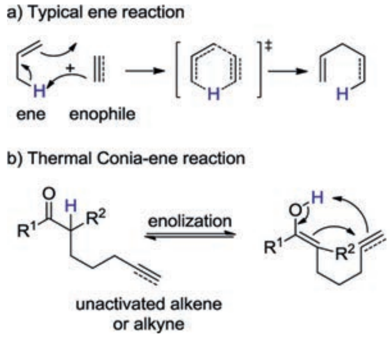
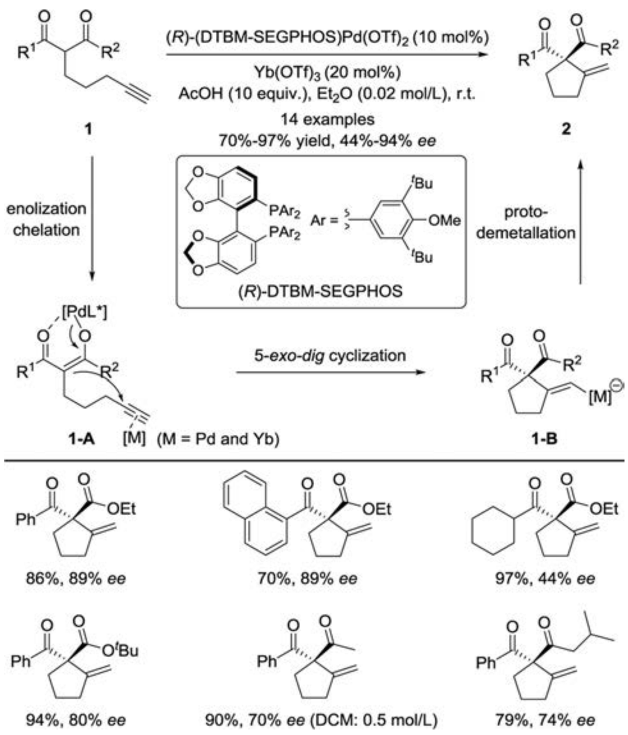


Scheme 1. Typical ene reaction and Conia-ene reaction.

alkynes for the preparation of structurally interesting cyclopentane derivatives with a broad substrate scope [4], providing the foundation of further research on the transition-metal catalyzed asymmetric Conia-ene-type reaction. In the next year, the same group realized the first enantioselective carbocyclization of acetylenic *β*-dicarbonyl compounds through the introduction of chiral metal complex [5]. While examining chiral Au, Cu, Ni and Pt complexes with poor enantioselectivity, they found that the treatment of substrate **1** with a catalytic amount of (DTBM-SEGPHOS)Pd$(OTf)_2$ afforded the desired product **2** with good enantiomeric excess. Subsequent investigation on the reaction conditions revealed that the addition of 20 mol% $Yb(OTf)_3$ as a cocatalyst and 10 equiv. of AcOH dramatically promoted the yield with a slight improvement of enantiomeric excess (Scheme 2). Under the optimized operations, a wide variety of *β*-dicarbonyls **1** could undergo this chiral Pd/Yb-cocatalyzed asymmetric Conia-ene-type process. The transformation was compatible with various substituted *β*-ketoesters and diketones, delivering the corresponding cyclopentanes **2** bearing an all-carbon quaternary stereocenter in moderate to excellent yields with high enantioselectivities. Importantly, this impressive work opens the field of enantioselective Conia-ene-type reaction and paves the way for further development.



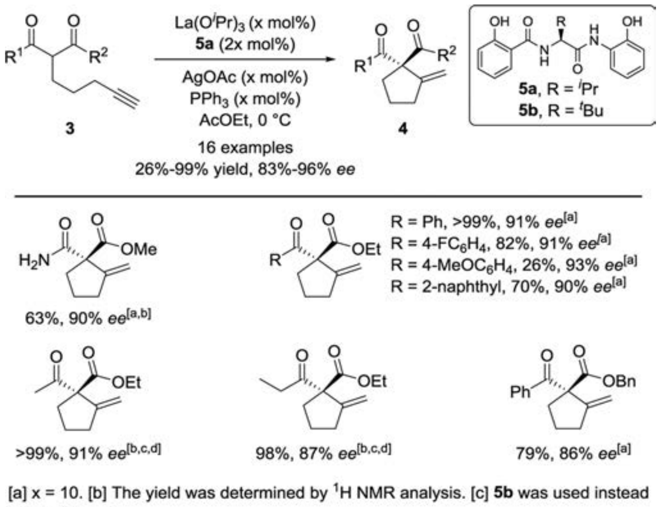
Scheme 2. Pd/Yb-cocatalyzed asymmetric Conia-ene-type reaction of acetylenic *β*-dicarbonyls **1**.

Although the concrete mechanism for Pd/Yb dual catalytic system was not elucidated in the article, the author envisioned that the reaction featured a palladium enolate species **1-A** as the key intermediate to provide chiral induction (Scheme 2). On the basis of previous studies [6] and Toste's research (there is one case in the article that the reaction could proceed smoothly in the absence of $Yb(OTf)_3$), the activation of alkyne by a single metal (Yb or Pd) is excluded. In other words, there is a possibility that both Yb and Pd play a crucial role on the alkyne activation. Subsequently, intramolecular 5-*exo-dig* cyclization of **1-A** generates vinyl metal intermediates **1-B**, followed by protodemetallation to produce the final products **2**.

Encouraged by the cooperative strategy, in 2011 Shibasaki and co-workers employed the synergistic heterobimetallic catalytic system comprised of lanthanum and silver for the asymmetric Conia-ene-type reaction [7]. In the combined system, the chiral La complex functioned as hard Lewis acid to activate the dicarbonyl group (hard Lewis base) and induce the enantioselectivity, while the Ag catalyst served as soft Lewis acid to coordinate to the triple bond (soft Lewis base) after extensive screening of transition-metal salts. The reaction tolerated malonamic acid ester and also occurred smoothly with different functionalized *β*-ketoesters **3** bearing aromatic and aliphatic substituents, affording the chiral cyclopentanes **4** in generally good to excellent yields with high enantioselectivities (Scheme 3).

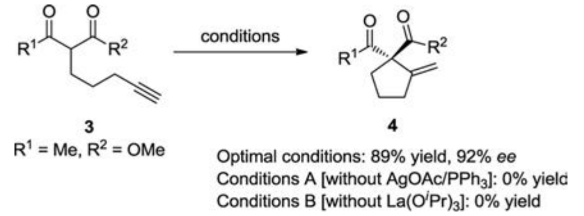
The cooperative function of La/Ag catalytic system was confirmed by the control experiments depicted in Scheme 4. When the reaction was performed in the absence of AgOAc/PPh_3 or $La(O^iPr)_3$ under standard conditions, none of the cyclization product was formed, indicating the simultaneous activation by La and Ag cooperative catalysis.

Besides terminal alkynes, the asymmetric Conia-ene-type reaction of internal alkynes was also achieved by Shibata and co-workers in 2012 [8]. They disclosed an unprecedented protocol for the enantioselective 5-*endo-dig* carbocyclization of *β*-ketoesters **6** with internal alkynyl moieties. After the test of multiple Lewis acids and chiral bisoxazoline ligands, a combined catalytic system, $Zn(OAc)_2$/BOX-Ph/$Yb(OTf)_3$/HFIP, enabled the cyclization successfully to provide chiral cyclopentenes **7** in high yields with acceptable to excellent enantioselectivities under mild conditions (Scheme 5). The exploration of substrate scope demonstrated that

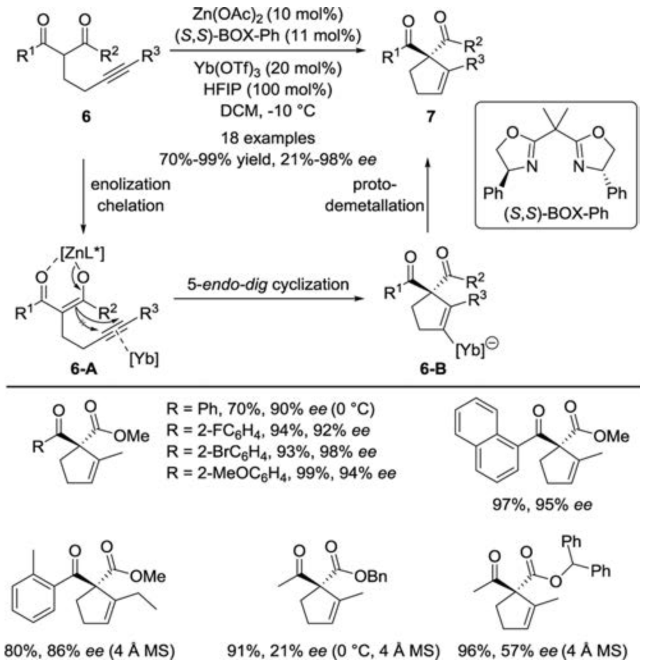


[a] x = 10. [b] The yield was determined by ^1H NMR analysis. [c] **5b** was used instead of **5a**. [d] x = 5.

Scheme 3. La/Ag-cocatalyzed asymmetric Conia-ene-type reaction for the synthesis of chiral cyclopentanes **4**.



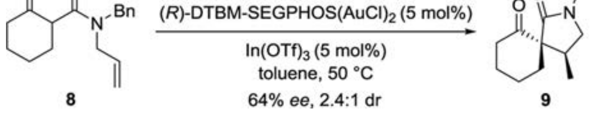
Scheme 4. Control experiments of La/Ag-cocatalyzed asymmetric Conia-ene-type reaction.



Scheme 5. Zn/Yb-cocatalyzed asymmetric Conia-ene-type reaction of β-ketoesters **6**.

the approach exhibited a wide functional group tolerance and thereby confirmed the applicability of this method. Based on previous works, the reaction involving a four-component catalyst system was proposed to proceed initially with the generation of zinc enolates **6-A**. Due to the ring strain, intermediates **6-A** undergo 5-*endo-dig* cyclization predominantly rather than 4-*exo-dig* cyclization to form the vinyl ytterbium intermediates **6-B**, which are eventually transformed into the desired products **7** (Scheme 5).

All previous studies described are treated with the cyclization of carbonyl-tethered alkynes, and alkene-related examples are quite rare. Initial attempts on the achievement of such a reaction were presented by Gandon and co-workers in 2014, in which an Au/Lewis acid bimetallic system was investigated (Scheme 6) [9]. Although the spirocycle **9** was obtained with only moderate stereoselectivity, it was an impressive case to expand the field of asymmetric Conia-ene-type reaction.



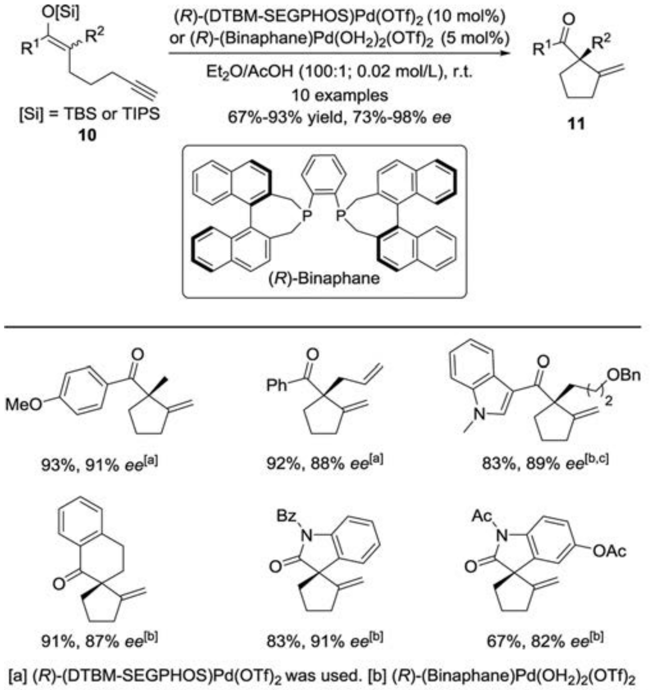
Scheme 6. Au/In-cocatalyzed asymmetric Conia-ene-type reaction for the synthesis of spirocycle **9**.

2.2. Transition-metal catalyzed reactions involving one single metal

Although the cooperative bimetallic catalysis has proven to be an effective tool for the enantioselective Conia-ene-type reaction, the development of novel methodologies is still highly attractive. Compared with dual activation by two different metals, the pure activation by one single metal can simplify the screening of catalysts, but it requires more judicious design of substrate or chiral metal complex.

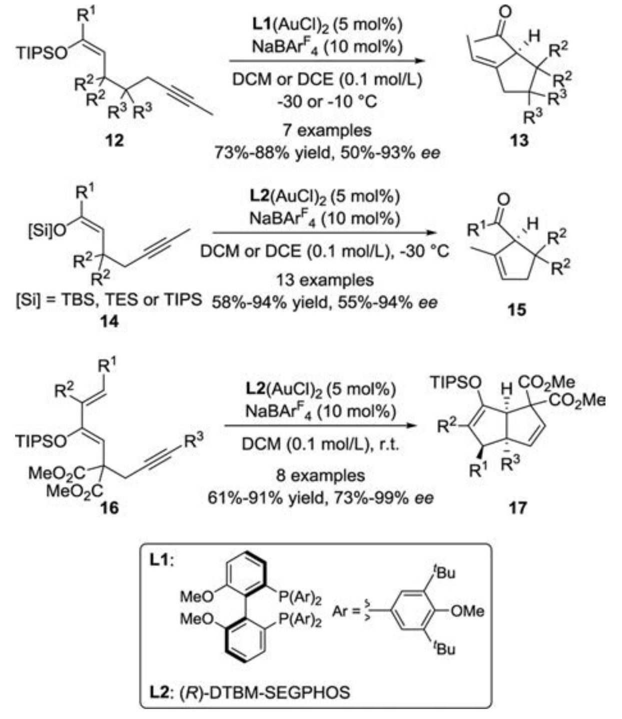
In 2007, the Toste group disclosed an elegant procedure for palladium-catalyzed asymmetric cycloisomerization of silyloxy-1,6-enynes [10]. The introduction of silyl enol ethers derived from ketones made the substrates highly reactive and avoided an additional use of metal catalyst to activate the ketone group. As outlined in Scheme 7, the palladium-catalyzed asymmetric cyclization of alkynyl silyl enol ethers **10** provided an efficient access to various substituted cyclopentane adducts **11** with good to excellent enantioselectivities. Aromatic silyl enol ethers were suitable substrates to undergo smooth carbocyclization, allowing the facile preparation of corresponding products in high yields. In addition, the application of cyclic siloxy-1,6-enynes led to the formation of spiro-carbocycles and spiro-oxindoles with good enantiocontrol. The synthetic utility of this Pd-catalyzed enantioselective enyne cyclization was further exemplified in the total synthesis of (-)-laurebiphenyl [11].

Apart from palladium catalysis, the same group in 2012 developed a novel method for the enantioselective cyclization of siloxyenynes catalyzed by chiral cationic gold complexes [12]. In the presence of chiral bisphosphinegold complex and $NaBAr^F_4$, 5-*exo-dig* cyclization of siloxy-1,6-enynes **12** and 5-*endo-dig* cyclization of siloxy-1,5-enynes **14** resulted in the rapid construction of cyclopentanes **13** and cyclopentenes **15** with high enantioselectivities, respectively. Furthermore, the treatment of silyloxy-1,3-dien-7-ynes **16** with this catalytic system produced the chiral bicyclo[3.3.0] octane derivatives **17** with excellent diastereoselectivities and enantioselectivities (Scheme 8).



[a] (R)-(DTBM-SEGPHOS)Pd(OTf)₂ was used. [b] (R)-(Binaphane)Pd(OH₂)₂(OTf)₂ was used instead. [c] The reaction was performed in DCM/AcOH (100:1; 0.02 mol/L).

Scheme 7. Pd-catalyzed asymmetric carbocyclization of alkynyl silyl enol ethers **10**.

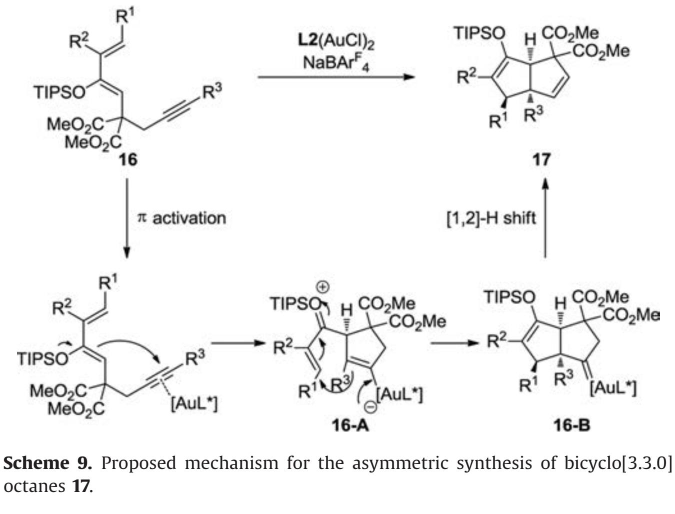


Scheme 8. Au-catalyzed asymmetric carbocyclization/tandem reaction of alkynyl silyl enol ethers.

A plausible mechanism for the asymmetric synthesis of bicyclo[3.3.0]octanes **17** was depicted in Scheme 9. The reaction is initiated by 5-*endo-dig* cyclization of **16** to generate the vinyl gold intermediates **16-A**. Subsequent 1,4-conjugate addition on the unsaturated carbonyl provides gold carbenes **16-B**, followed by 1,2-hydrogen shift, affording the bicyclic products **17**.

Very recently, an interesting enantioselective carbocyclization of the silyl enol ether tethered ynamide *via* chiral copper complex-catalyzed kinetic resolution was disclosed by Ye and co-workers, albeit with moderate enantioselectivity [13].

When the atom economy is strictly considered, the utilization of silyl enol ether group may not be the best option for the asymmetric Conia-ene reaction. An alternative method is to search for chiral metals which can activate both the enol and the triple bond, but certainly it is a highly challenging task. Gratifyingly, White and co-workers averted their attention to new iron catalyst and implemented it in such a cyclization in 2014 [14]. Preliminary endeavor on the modification of chiral ligands and investigation of metal complexes indicated that iron-salen **20** bearing a *cis*-2,5-diaminobicyclo[2.2.2]octane skeleton was the most suitable to forge *exo*-methylenecyclopentanes **19** in satisfactory results (Scheme 10). Besides β-ketoesters, this process was compatible with α-functionalized (sulfonyl, nitro, cyano) ketones as well, granting access to the corresponding products with excellent enantiomeric excess. Interestingly, the strategy was nicely expanded to the synthesis of cyclohexane and cycloheptane derivatives, and even strained cyclobutane was obtained albeit in moderate yield. A reaction mechanism involving the Fe(III) core of **20** activating both the alkyne and enolate moieties in an enantioselective manner was also proposed by the authors.

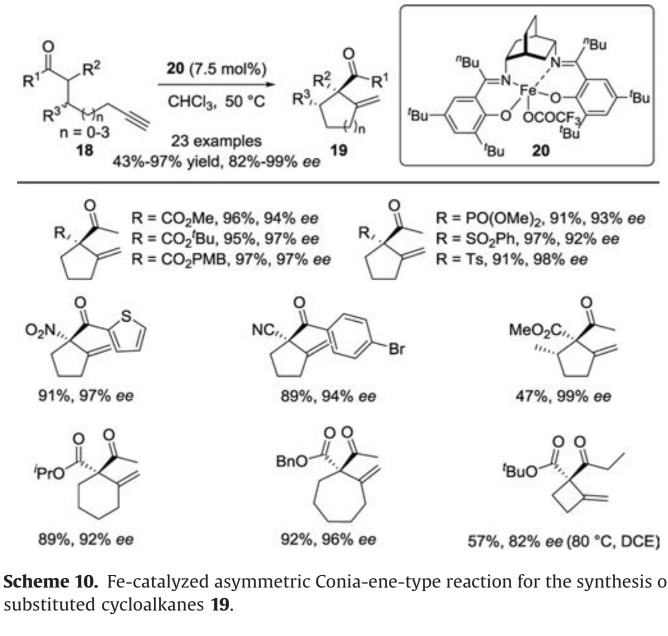


Scheme 9. Proposed mechanism for the asymmetric synthesis of bicyclo[3.3.0]octanes **17**.

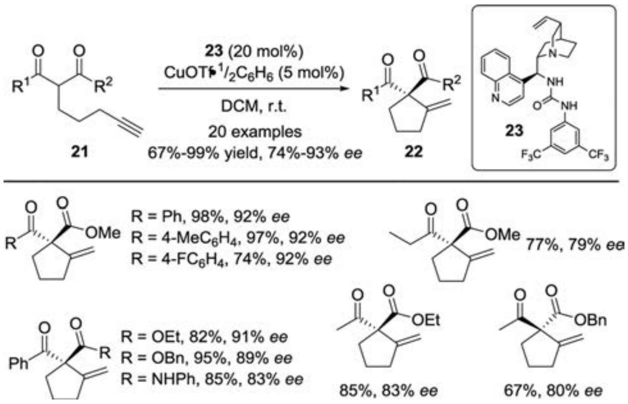
3. Asymmetric Conia-ene-type reactions *via* cooperative catalysis of transition-metal and organic catalysts

The combination of metal catalysis and organocatalysis is of enormous importance in organic and medicinal synthesis [15], permitting chemical transformations inaccessible by single function. When the concept was put forward, a special effort was contributed to the practical application of this strategy on diverse kinds of reactions including Conia-ene reaction [16]. The first asymmetric entry was traced back to 2009, when Dixon and co-workers reported an enantioselective Conia-ene-type reaction *via* the cooperation of Lewis acid and Brønsted base [17]. Among the combined systems screened, it was confirmed that the collaboration of CuOTf and urea **23** as precatalyst was the system of choice for the intramolecular asymmetric cyclization of β-ketoesters **21**, rendering chiral cyclopentanes **22** in good to excellent yields with remarkable enantioselectivites (Scheme 11).

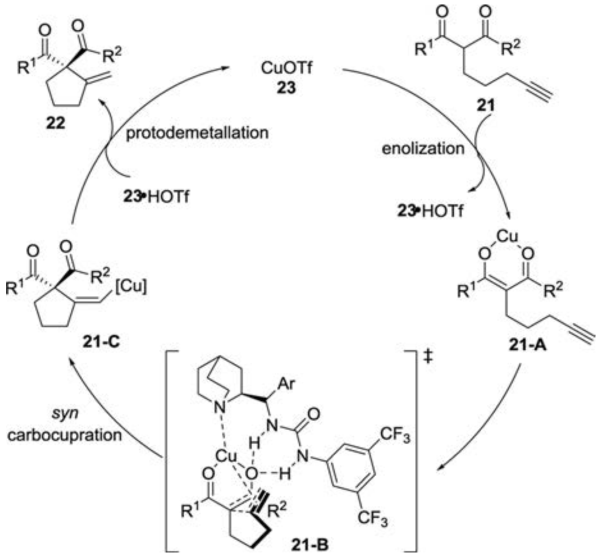
When the controlled and deuterium labeling experiments were completed towards the elucidation of the mechanism, a plausible pathway for this cyclization was postulated, as shown in Scheme 12. Initially, the basic property of urea **23** accelerates the deprotonation process of β-ketoesters **21** to generate the copper enolates **21-A**. In the transition structures **21-B**, the urea catalyst also serves as a chiral ligand where the nitrogen of quinuclidine framework is coordinated to the copper center and the urea N—H bonds are interacted with the oxygen of ketone group, thereby promoting the enolates to undergo a stereoselective *syn* carbocupration. Finally, the newly formed vinyl copper species



Scheme 10. Fe-catalyzed asymmetric Conia-ene-type reaction for the synthesis of substituted cycloalkanes **19**.



Scheme 11. Cu/urea-catalyzed asymmetric Conia-ene-type reaction of β-ketoesters **21**.

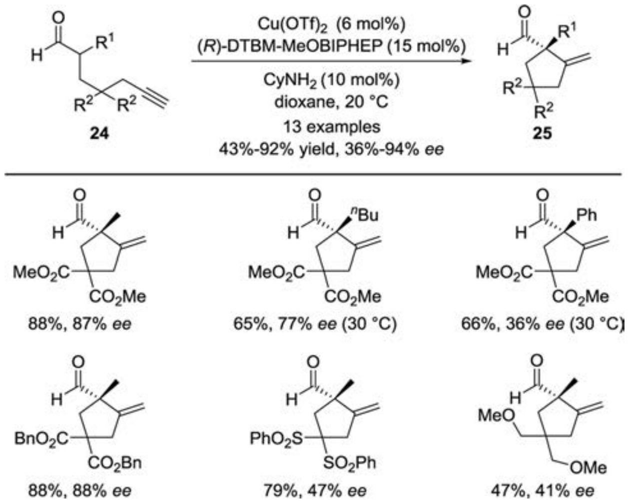


Scheme 12. Plausible mechanism for Cu/urea-catalyzed asymmetric Conia-ene-type reaction.

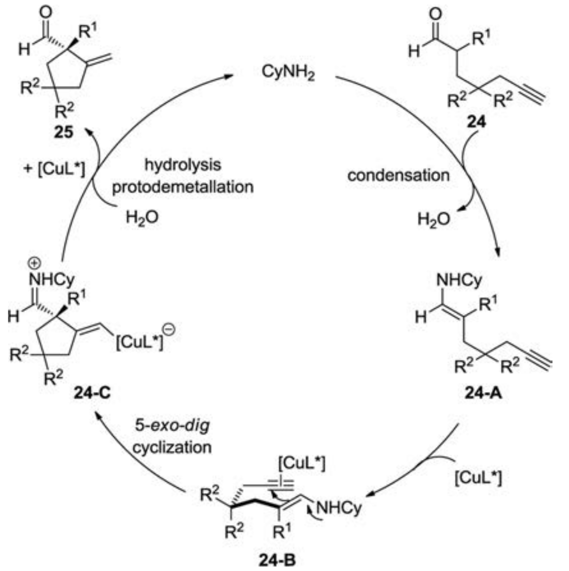
21-C can be converted to the desired cyclopentanes **22** through protodemetallation along with the regeneration of CuOTf and urea **23**.

In 2012, Michelet and Ratovelomanana-Vidal also reported a novel synthetic route to enantioenriched cyclopentanes by merging a chiral copper complex and an aminocatalyst [18]. The enantioselective metallo-organocatalyzed cyclization of formyl-alkynes **24** in the presence of 6 mol% of Cu(OTf)$_2$, 15 mol% of (*R*)-DTBM-MeOBIPHEP and 10 mol% of CyNH$_2$ produced a broad variety of cyclopentanes **25** with an all-carbon quaternary stereocenter in 43%–92% yields with 36%–94% *ee* (Scheme 13).

Supported by the experimental results and absolute configuration of cyclopentanes **25**, the author proposed a tentative mechanism in Scheme 14. The reaction commences with the condensation of the substrate and amine to furnish (*E*)-enamine intermediates **24-A**, where the alkyne moiety is subsequently activated by the copper complex. In the model **24-B** for enantioselectivity, chair conformation is presumably crucial in which R^2 group imposed the steric effect with the bulky ligand, leading to the formation of imines **24-C** with good enantiocontrol. The following hydrolysis and protodemetalation afford the desired products **25**.

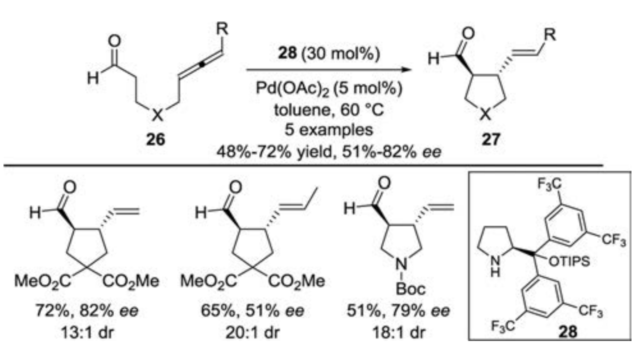


Scheme 13. Cu/CyNH$_2$-cocatalyzed asymmetric Conia-ene-type reaction of formyl-alkynes **24**.

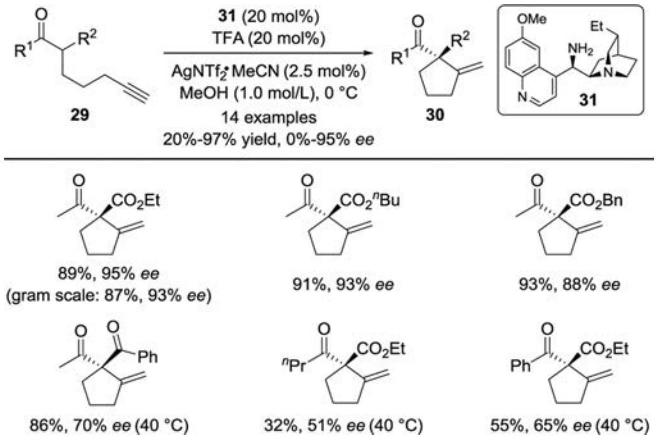


Scheme 14. Plausible mechanism for Cu/CyNH$_2$-cocatalyzed asymmetric Conia-ene-type reaction.

In addition to alkynes, allenes can also be treated as electrophiles in Conia-ene reactions. As illustrated in Scheme 15, the Dixon group in 2012 demonstrated an creative strategy that a joint catalytic system consisting of Pd(OAc)$_2$ and prolinol-derived



Scheme 15. Pd/amine-cocatalyzed asymmetric Conia-ene-type reaction of allene-tethered aldehydes **26**.

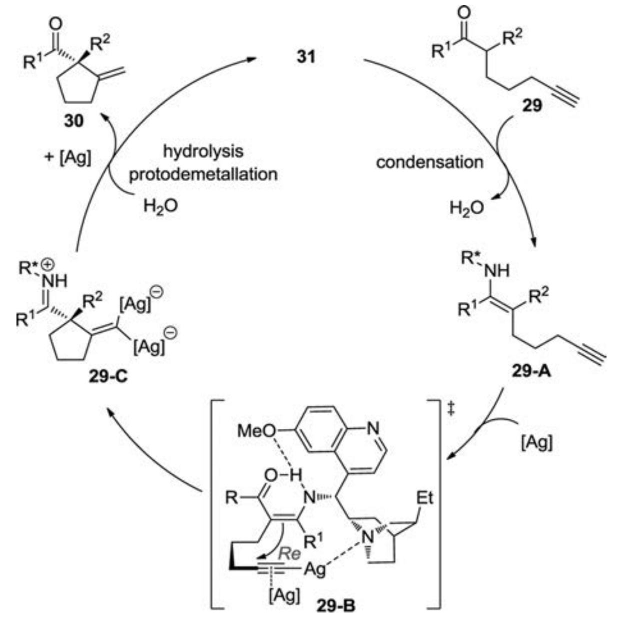


Scheme 16. Ag/amine-cocatalyzed asymmetric Conia-ene-type reaction of dicarbonyl compounds **29**.

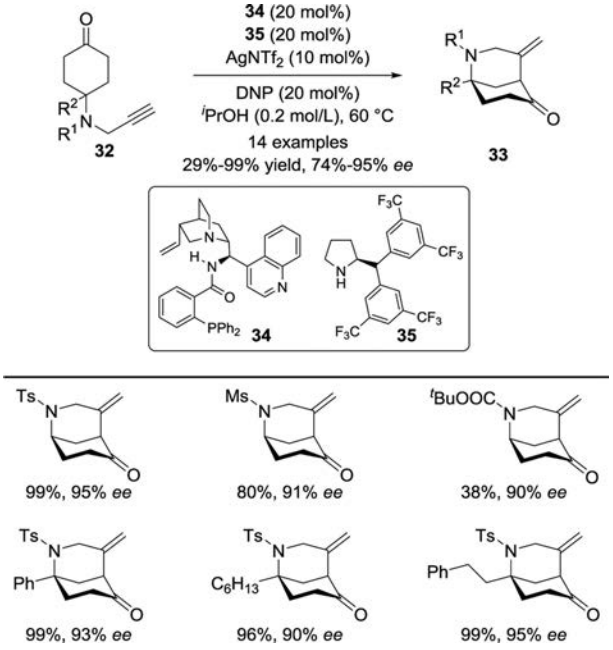
organocatalyst **28** promoted the asymmetric cyclization of allene-tethered aldehydes **26**, resulting in the synthesis of chiral cyclopentane and pyrrolidine scaffolds **27** with up to 82% *ee* and high diastereoselectivities [19].

Later in 2017, another ingenious approach for the efficient Conia-ene reaction was provided by Enders and co-workers [20]. They envisaged that the presence of chiral primary amine in combination with metal catalyst would enable this transformation, where the metal center could be coordinated to an additional functional moiety of amine to introduce the enantioselectivity. With the catalytic system established, a series of dicarbonyl compounds **29** were exposed to amine/silver-cocatalyzed carbocyclization to synthesize the cyclopentanes **30** in satisfying results (Scheme 16). The feasibility of the route was further verified by a gram-scale preparation of model product with good maintenance of yield and chirality.

To gain deep insight into the mechanism, the author carried out deuterium labeling experiments, suggesting that a silver acetylide species was involved in the catalytic cycle (Scheme 17). Upon the catalysis of a second silver salt, the enamines favor *re* attack onto the alkyne in the proposed transition states **29-B**, which accounts for the stereocontrol of this reaction. Subsequently, the cyclic products **30** are obtained after protodeargentation and hydrolysis of intermediates **29-C**.

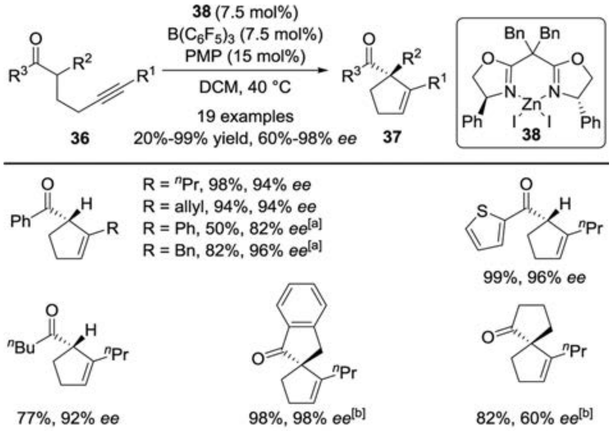


Scheme 17. Proposed mechanism for Ag/amine-cocatalyzed asymmetric Conia-ene-type reaction.



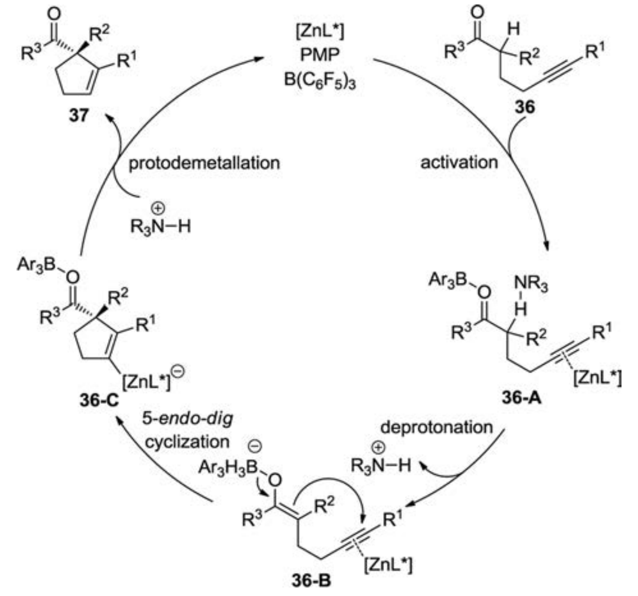
Scheme 18. Ag/amine-cocatalyzed enantioselective desymmetrizing carbocyclization of 4-propargylamino cyclohexanones **32**.

The morphan skeleton (2-azabicyclo[3.3.1]nonane) [21], existing in a large number of natural products and bioactive molecules, is a type of valuable structural motifs. However, the efficient construction of enantioenriched 6,6-bicyclic morphan framework was hardly explored [22]. Continuing towards the discovery and application of Conia-ene reaction, the Dixon group performed a prominent protocol for the enantioselective desymmetrizing cycloisomerization of 4-propargylamino cyclohexanones **32** in 2017 (Scheme 18) [23]. The synergistic catalysis of chiral silver complex and secondary amine facilitated the highly practical and economical synthesis of morphan derivatives **33** with wide substrate scope, and excellent diastereoselectivities and enantioselectivities.



[a] The reaction was carried out at 60 °C in the presence of 10 mol% **38**, 10 mol% $B(C_6F_5)_3$, 20 mol% PMP. [b] 1-Methylpiperidine was used instead of PMP. PMP = 1,2,2,6,6-pentamethylpiperidine

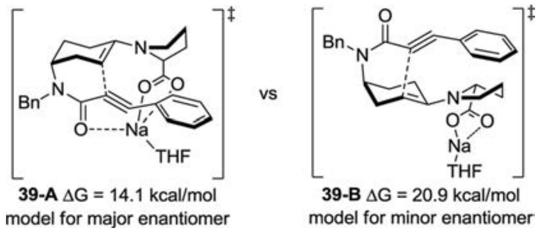
Scheme 19. $Zn/B(C_6F_5)_3$/amine–cocatalyzed asymmetric Conia-ene-type reaction of alkynyl ketones **36**.



Scheme 20. Plausible mechanism for Zn/B(C_6F_5)$_3$/amine–cocatalyzed asymmetric Conia-ene-type reaction.

The development of frustrated Lewis pairs (FLPs) has attracted extensive interest for their wide utilization in the activation of small molecules, and simultaneously offers an alternative to prevent mutual quenching in the combined acid/base catalysis [24]. Very recently, a highly enantioselective Conia-ene-type cyclization was presented by Wasa and co-workers where a three-component catalyst system, comprised of B(C_6F_5)$_3$, *N*-alkylamine and ZnI_2/BOX, exhibited an enabling ability (Scheme 19) [25]. Under the optimal conditions, the transformation of a range of diversely substituted alkynyl ketones **36** proceeded smoothly, and generally, moderate to excellent yields and enantioselectivities were obtained in all cases. This direct approach was compatible with alkyl and aryl substituents on the internal alkyne (R^1) as well as ketone (R^3). It was noteworthy that the method could provide further route to the synthesis of several spiro-carbocycles bearing a quaternary stereogenic center.

Although not fully validated, a mechanistic pathway is described in Scheme 20. Initially, a pair of Lewis acid B(C_6F_5)$_3$ and Brønsted base PMP concurrently promote deprotonation of the ketones **36** to furnish the enolates **36-B** and ammonium ions. Subsequent enantiodetermining nucleophilic attack of the enolate group onto the activated alkyne affords the cyclized intermediates **36-C**. Finally, the cyclopentanes **37** are delivered after protodemetallation, which concomitantly regenerates these catalysts.



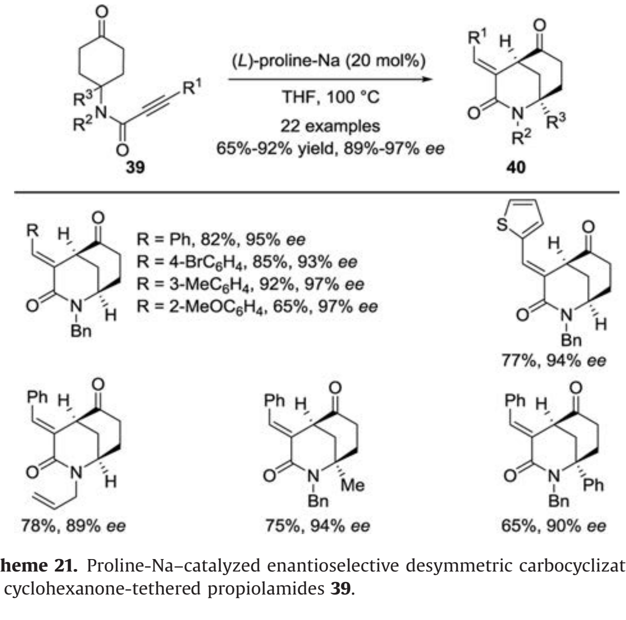
Scheme 22. Models for enantioselectivity.

The synergistic catalysis merging transition metals and organocatalysts also offers new opportunities for the innovation of asymmetric cascade transformations involving Conia-ene reaction. To date, domino aldol/Conia-ene and Michael addition/Conia-ene carbocyclizations have been achieved for one-pot synthesis of target molecular complexity, which are not discussed in details owing to the similar strategies applied [26].

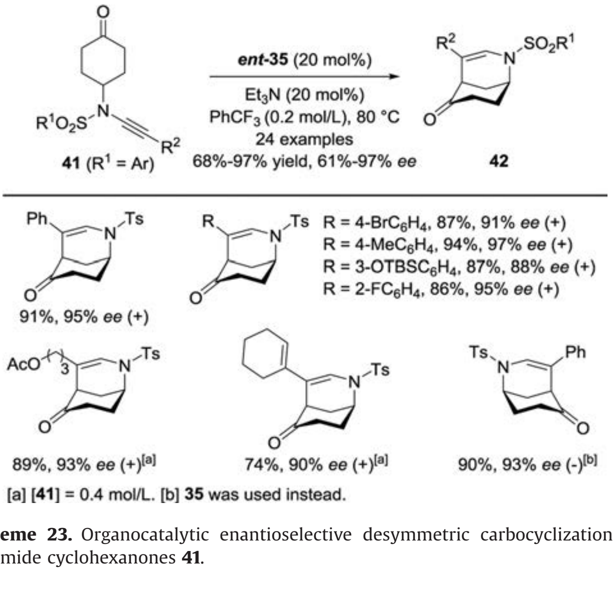
4. Asymmetric Conia-ene-type reactions *via* organocatalysis

From the point of view in theory, the capability of elevating the reactivity of the triple bond and providing chiral induction makes transition-metal complex essential in the asymmetric Conia-ene-type reaction. Due to the restriction, it is extremely anticipated to develop a metal-free protocol. In 2019, Jia and co-workers discovered that the selection of available sodium (*L*)-prolinate could efficiently catalyze the intramolecular desymmetric cyclization of cyclohexanone-tethered propiolamides **39**, leading to the elaboration of versatile morphan scaffolds **40** in good yields with excellent enantioselectivities (Scheme 21) [27]. Remarkably, in contrast to traditional Michael additions, an unusual α-addition to electron-deficient alkynes was observed in this transition-metal free protocol.

To clarify the stereochemical result of the reaction, DFT calculations of enamine intermediates were employed and two main transition states were illustrated in Scheme 22. It turns out that the important characteristic of carboxylate unit is to form a

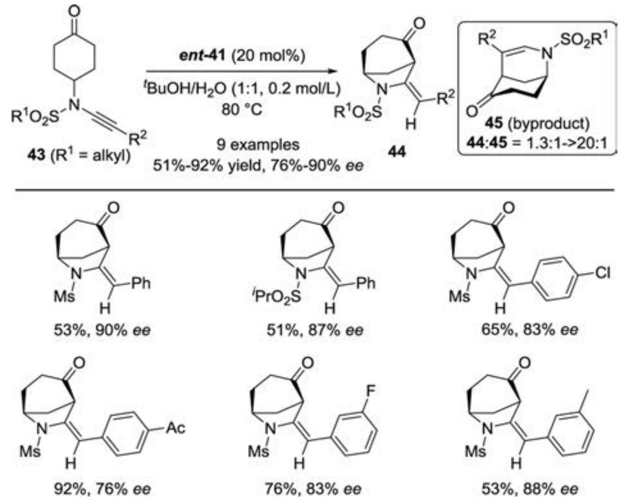


Scheme 21. Proline-Na–catalyzed enantioselective desymmetric carbocyclization of cyclohexanone-tethered propiolamides **39**.



[a] [**41**] = 0.4 mol/L. [b] **35** was used instead.

Scheme 23. Organocatalytic enantioselective desymmetric carbocyclization of ynamide cyclohexanones **41**.



Scheme 24. Organocatalytic enantioselective regiodivergent synthesis of normorphans **44**.

salt bridge between the oxygen of amide and sodium, as shown in model **39-A**, contributing to an obvious decrease in free energy. Consequently, the preference in thermodynamic stability accounts for the control of good enantioselectivity.

Shortly thereafter, an unprecedented approach towards organocatalytic Conia-ene-type carbocyclization was pursued by Ye and Lu, which was completely metal-free compared with previous studies [28]. As depicted in Scheme 23, a broad scope of arylsulfonyl-protected ynamide cyclohexanones **41** underwent this transformation for the straightforward preparation of synthetically valuable morphans **42** with good to excellent enantiocontrol, regardless of electronic and steric effect. Notably, a rare β-addition of ynamides was achieved in all these cases [29].

Intriguingly, when it came to the alkylsulfonyl-protected ynamides **43**, the regiodivergent synthesis of normorphans **44** was accomplished with high enantioselectivity (Scheme 24). Under the established operations, the functionalized normorphans were isolated as the major products, and in particular excellent *E*/*Z* ratios of exocyclic olefins were detected for all the products. Furthermore, DFT computations were performed to rationalize the origins of regioselectivity and enantioselectivity in this reaction.

5. Conclusions and outlook

Since the inception of the first report on Conia-ene reaction, this fruitful filed has drawn considerable attention and therefore substantial progress has been made during the past two decades. The employment of transition metals significantly enhances the practicality of Conia-ene reaction in the organic synthesis. Moreover, the application of metal ligands and organocatalysts substantially broadens the scope of asymmetric catalysis. A range of innovative strategies have been developed, including transition-metal catalysis, cooperative catalysis of transition-metal and organic catalysts, and organocatalysis. In conclusion, the methods aforementioned not only enrich the creation of this area but also provide efficient approaches to the atom-economical construction of chiral cyclic compounds, especially spiro and bridged cycles. Despite these achievements, there are still several problems and challenges waiting to be addressed: (1) More theoretical calculations are needed to clarify the mechanisms for some transition-metal-catalyzed asymmetric examples, particularly the stereochemical outcomes; (2) Different substrates should be designed reasonably aimed at the production of valuable enantioenriched heterocycles and even the total synthesis of natural products; (3) Novel catalytic systems are required to be developed to achieve more types of enantioselective Conia-ene reactions; (4) Some focus should be put on the utilization of alkenes as electrophiles. We sincerely hope that this review can offer helpful information and guidance for chemists committed to exploring the related transformations, and strongly believe that new fascinating chemical reactions will be demonstrated in due time.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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