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Recent development on the [5+2] cycloadditions and their application in natural product synthesis

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The [5+2] cycloaddition is one kind of fascinating and powerful reaction to access seven-membered ring systems existing in complex natural products and pharmaceuticals. In this review, recent developments on the [5+2] cycloadditions and their application in the synthesis of complex natural products are discussed. A focus is given to the way in which the [5+2] cycloadditions have influenced the logical process of the synthesis. This article is organized by reaction types, aiming to provide a clear clue to the latest research trends.

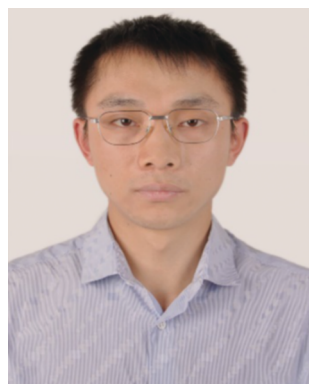
1. Introduction

The development of efficient methodologies and the design of novel strategies for the rapid construction of molecular complexity in a stereoselective manner are of great significance in organic synthesis. With no doubt, cycloaddition reactions are among the most powerful chemical transformations that allow multiple carbon–carbon or carbon–heteroatom bonds to form in one single step, often with satisfactory regio- and stereoselectivities. In the past few decades, various types of these reactions, such as [2+2], [3+2] and [4+2] cycloadditions, have been well developed for the effective assembly of the

corresponding four to six-membered carbocycles.^{1a,b} In comparison, the synthesis of seven-membered rings through a cycloaddition pathway has been less explored. This process is largely driven by the entropic factors derived from the changing of the internal rotations/translations of chemical bonds in the course of cyclization (especially for the intramolecular reactions in larger rings), and also influenced by the non-bonding interactions in the transition state.^{1c,d} Thus, direct cyclization is generally difficult without activation of the substrates.^{1e} Recently, the continuing identification of biologically active natural products that contain a seven-membered skeleton in the core structure has stimulated considerable advancements toward their syntheses. Among them, the [5+2] cycloadditions turned out to be versatile methods, which played important roles in the total syntheses of related complex natural products.²

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hypervalent iodine-mediated reactions and their application in natural products synthesis.



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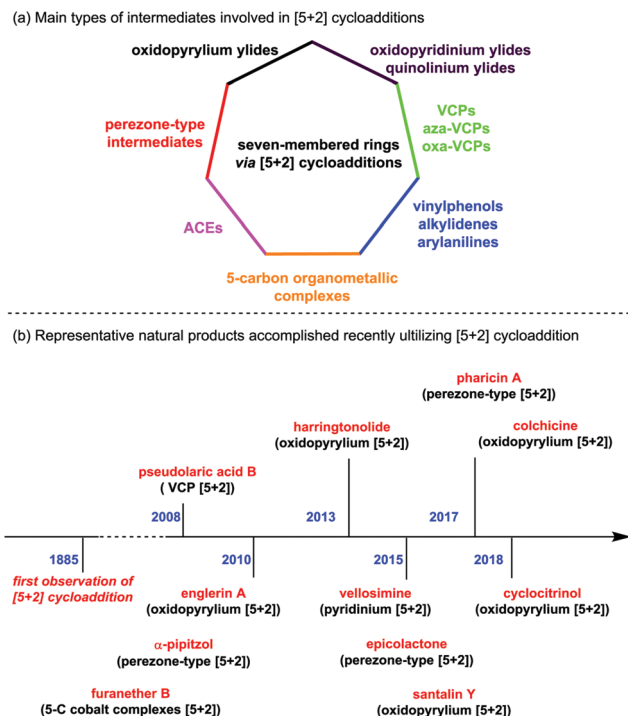


Fig. 1 (a) Main types of intermediates involved in [5+2] cycloadditions. (b) Representative natural products accomplished recently utilizing [5+2] cycloaddition as a key step.

Since the first example described in 1885 by by Anschütz and Leather,³ [5+2] cycloadditions have been paid considerable attention. Apart from miscellaneous works on formal [5+2] cycloaddition⁴ and [5+2] photocycloaddition,⁵ to the best of our knowledge, there are mainly seven types of [5+2] cycloaddition reactions divided according to the structures of the corresponding precursors (Fig. 1a): (1) oxidopyrylium-mediated [5+2] cycloadditions; (2) oxidopyridinium- and quinolinium-mediated [5+2] cycloadditions; (3) perezone-type [5+2] cycloadditions; (4) [5+2] cycloadditions of vinyl substituted three-membered rings,

including vinylcyclopropanes (VCPs), vinylaziridines (aza-VCPs) and vinyloxiranes (oxa-VCPs); (5) [5+2] cycloadditions of five-carbon organometallic complexes; (6) [5+2] cycloadditions of 3-acyloxy-1,4-enynes (ACEs); and (7) formal [5+2] cycloadditions of vinylphenols, alkyldienes and arylanilines. During the past decade, significant progress on this reaction has been made, especially in the field of natural product synthesis (see Fig. 1b for the representative examples as shown by the time axis).

A comprehensive review on the [5+2] cycloadditions was reported by Ylijoki and Stryker in 2012.⁶ On the other hand, Pellissier summarized the progress of [5+2] cycloadditions in two different time span,⁷ and the Li group delivered a review by highlighting the application of [5+2] cycloadditions in natural product synthesis.⁸ Very recently, Murelli *et al.* also disclosed their review devoted solely to oxidopyrylium cycloaddition chemistry.⁹ In view of the incessant springing up of new results in this hot research area, we feel it is very urgent to summarize and update the progress of [5+2] cycloaddition reactions and their corresponding application in natural product synthesis by carefully selected examples over the past decade. Due to the lack of application in natural product synthesis, the last two types of [5+2] cycloadditions mentioned above will not be discussed.^{10,11} We hope this feature article could serve as a meaningful and clear clue to those who are interested in [5+2] cycloaddition chemistry on the latest research trends.

2. Oxidopyrylium-mediated [5+2] cycloaddition

2.1 [5+2] cycloaddition of oxidopyrylium ylides from acetoxy-pyranones and 3-hydroxy-4-pyranones

Although the construction of the bridged seven-membered ring systems has been extensively investigated,¹² no general reactions were disclosed for the direct and efficient assembly of such motifs. Due to the importance of these bicyclic skeletons which are widely found in a number of biologically active



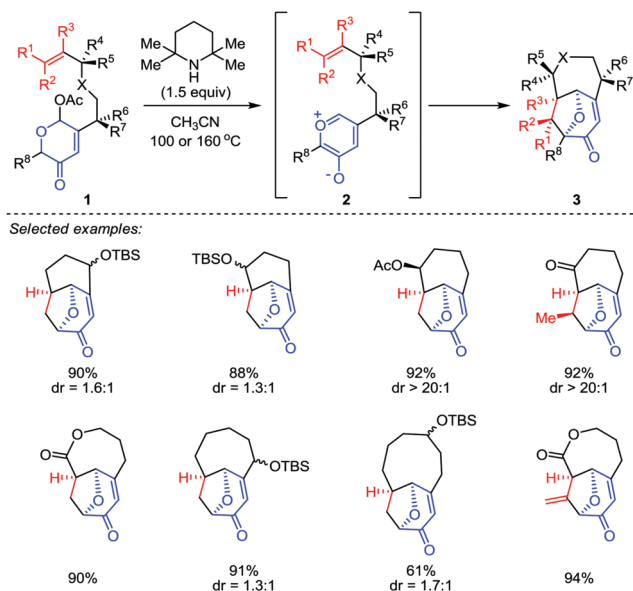
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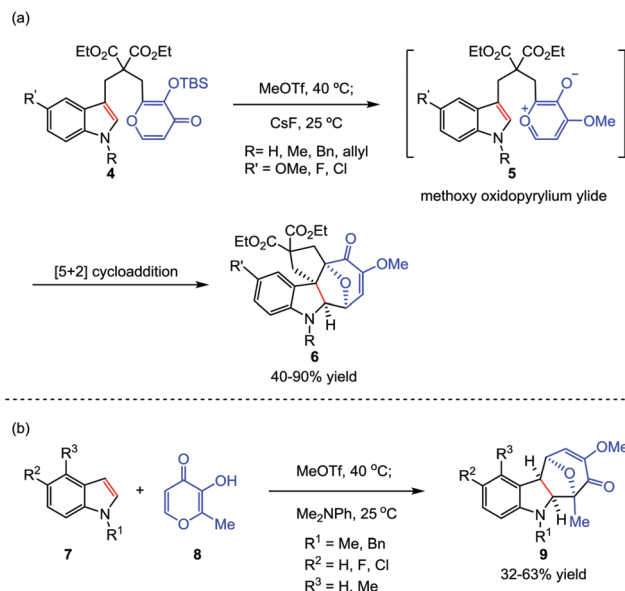
Scheme 1 Type II intramolecular [5+2] cycloaddition by Li and co-workers.

natural products (such as ingenol and cyclocitrinol),^{13,14} their construction continues to capture the attention of synthetic chemists. It was not until 2015, a breakthrough was made by Li and co-workers.¹⁵ In their work, a type II intramolecular [5+2] cycloaddition was carried out by using a well-designed acetoxy-pyranones **1** with a dienophile tether at the C3 position as precursors (Scheme 1). Promoted by 2,2,6,6-tetramethylpiperidine (TMP) in a sealed tube at elevated temperature (100 or 160 °C), a series of functionalized bridged bicyclic products **3**, including bicyclo[4.3.1]decenes, bicyclo[4.4.1]undecenes, bicyclo[5.4.1]dodecenes and bicyclo[6.4.1]tridecenes, could be afforded in excellent yields.

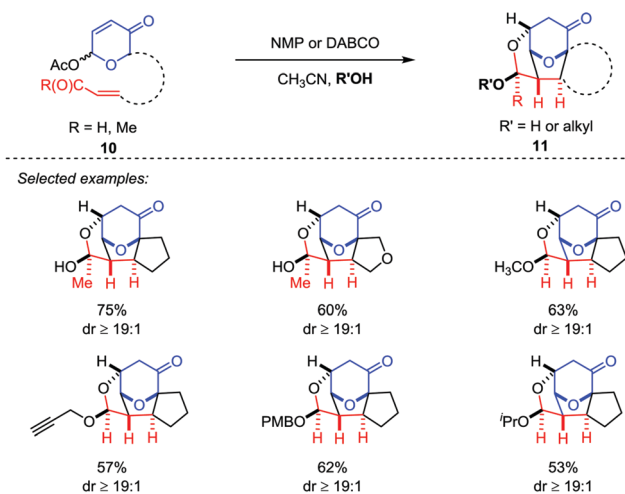
Considering that the high temperature which was required to generate the oxidopyrylium ylide would limit the overall scope and utility of this reaction, the Li group then sought inspiration from the group-transfer strategy developed by Wender and Mascareñas.¹⁶ To this end, MeOTf was chosen as a methylating reagent. Its reaction with kojic acids **4** at 40 °C successfully delivered the corresponding methoxy pyrylium salts. By treatment with CsF at room temperature, compound **4** was conveniently transformed to the oxidopyrylium ylides **5**. This protocol enables both intra- and intermolecular oxidopyrylium ylide-indole [5+2] cycloadditions proceed smoothly, providing highly functionalized and stereochemically challenging oxa-cyclohepta[*b*]indoles **6** and **9** in moderate to high yields, respectively (Scheme 2).¹⁷

Recently, Tantillo and Mitchell described an oxidopyrylium-alkene [5+2] cycloaddition/oxa-Michael addition cascade sequences by the employment of acetoxy-pyranone-enals (or enones) **10** as oxidopyrylium ylide precursors with a variety of potential nucleophiles, which provided a platform to access the caged ethers **11** bearing up to four new bonds and six contiguous stereocenters with good yields and excellent diastereoselectivities (Scheme 3).¹⁸

Despite the widespread use of oxidopyrylium-mediated [5+2] cycloaddition in organic synthesis, asymmetric examples,

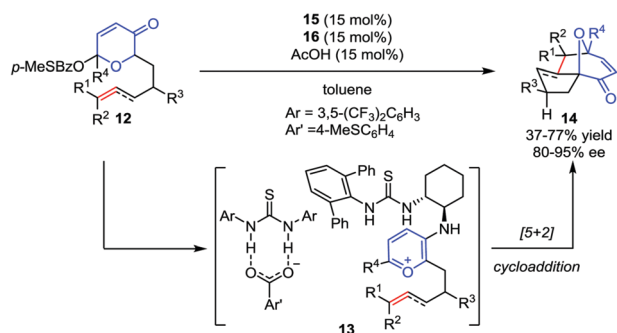


Scheme 2 Oxidopyrylium ylide-indole [5+2] cycloadditions by Li and co-workers.

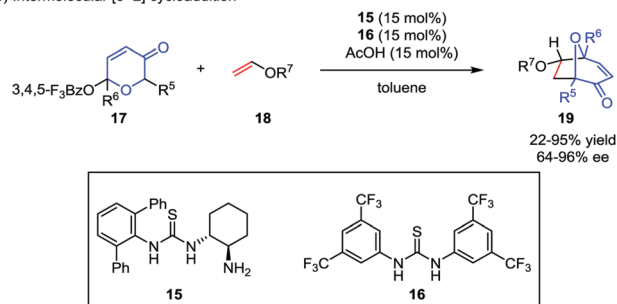
Scheme 3 Oxidopyrylium-alkene [5+2] cycloaddition/oxa-Michael addition cascade by Tantillo *et al.*

especially for enantioselective catalytic methods are rather limited. As one of their research interests in small-molecule chiral hydrogen-bond-donor catalysis, Jacobsen and co-workers envisioned the potential application of anion-binding catalysis in the oxidopyrylium formation and the following cycloaddition. Later, they developed a dual thiourea catalyst system consisting of a chiral primary aminothiurea **15** and another achiral thiourea **16** for intramolecular oxidopyrylium [5+2] cycloaddition of racemic acetoxy-pyranone **12**, which became the first enantioselective approach to valuable tricyclic products **14** with up to 77% yield and 95% ee (Scheme 4a).^{19a} It was found that the generation of thiourea-complexed aminopyrylium salts **13** was necessary to undergo cycloaddition with high enantioselectivities. Shortly after this work, they also successfully

(a) Intramolecular [5+2] cycloaddition



(b) Intermolecular [5+2] cycloaddition

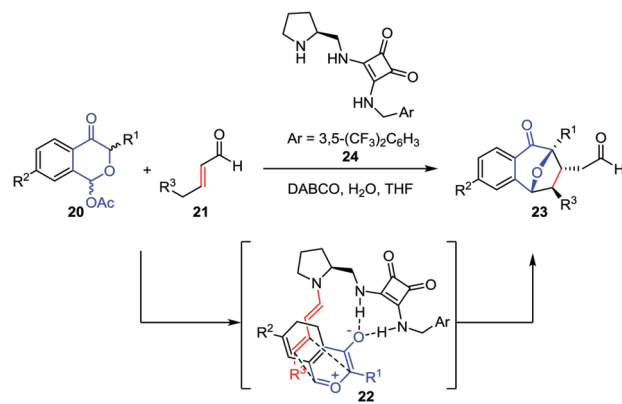


Scheme 4 The enantioselective oxidopyrylium-alkene [5+2] cycloaddition by Jacobsen and co-workers.

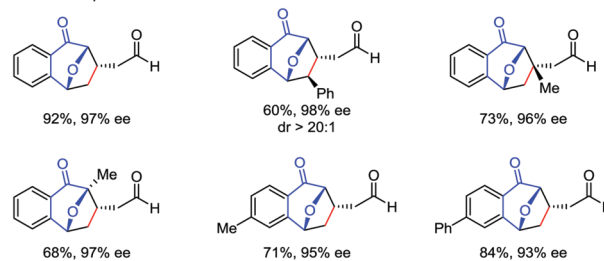
achieved an intermolecular [5+2] cycloaddition reaction by using the electron-deficient pyranones **17** in the presence of the same dual thiourea catalyst system,^{19b} providing the cycloadducts **19** in low to good yields and with moderate to excellent enantioselectivities (Scheme 4b).

Based on the pioneering work of Jacobsen, Reyes and Vicario proposed another asymmetric catalytic model featured by dienamine activation.²⁰ They reported a catalytic *enantioselective* [5+2] cycloaddition between benzopyrylium ylides generated *in situ* from 1-acetoxyisochroman-4-ones **20** and α,β -unsaturated aldehydes **21** in the presence of a bifunctional secondary amine/squaramide catalyst **24** (Scheme 5). This method provides the direct access to 8-oxabicyclo[3.2.1]octane frameworks **23** with excellent dr and ee values. Mechanistically, the secondary amine catalyst **24** reacted with the enal **21** to form an activated dienamine intermediate **22**, which played as an electron-rich alkene in this [5+2] cycloaddition. As a comparison, the chiral aminocatalyst **15** condensed with benzoyloxypyranone derivatives **12** to generate the reactive pyrylium ylide **13** in Jacobsen's process (Scheme 4).¹⁹

In most cases, the facile tautomerization or rearrangement of α -hydroxy- γ -pyrones to generate the oxidopyrylium ylides that are capable of undergoing [5+2] cycloaddition is only effective in an intramolecular fashion, presumably due to the short lifespan of the reactive ylide.²¹ To overcome this limitation, the Wender group firstly employed a methyl triflate-derived pre-ylide salt in a modified version of this reaction in 1991.¹⁶ Recently, Murelli and Brenner-Moyer prepared an oxidopyrylium ylide dimer **26** derived from methyl triflate salt **25**, which was then subjected to the three-component [5+2] cycloaddition cascade reaction



Selected examples:



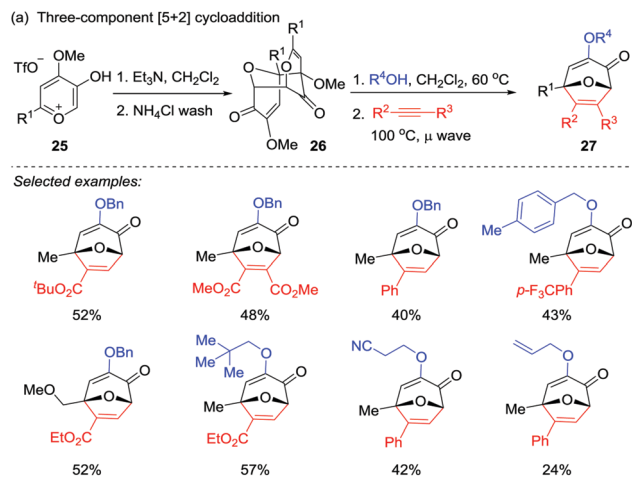
Scheme 5 The enantioselective oxidopyrylium-alkene [5+2] cycloaddition by Vicario and co-workers.

with an alcohol and an alkyne (Scheme 6a).^{22a} By slightly heating a mixture of the purified oxidopyrylium dimer **26** in the presence of the alcohol prior to the addition of alkyne, a broad range of oxabicyclic compounds **27** were obtained in moderate yields. Interestingly, oxidopyrylium dimer **26a** could also be employed as ylide source in an asymmetric version (Scheme 6b),^{22b} enabling the first catalytic enantioselective [5+2] cycloaddition of a 3-hydroxy-4-pyrone-derived oxidopyrylium ylide in the presence of catalyst **29** through chiral iminium activation of β -substituted enal **28**. Of note, the products **31** possess four stereocenters were formed with up to 99:1 dr and 99% ee.

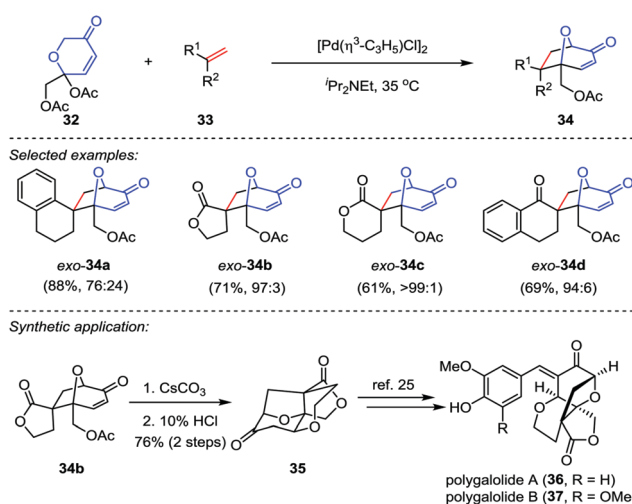
Recently, Suga and co-workers described an efficient methodology to generate oxidopyrylium ylides from 2H-pyran-3(6H)-ones **32** through [Pd(η^3 -C₃H₅)Cl]₂ catalysis,²³ which subsequently underwent the [5+2] cycloaddition with a variety of dipolarophiles **33** to afford the cycloadducts **34** in good to excellent yields (Scheme 7). To demonstrate the synthetic utility of this reaction, the cycloadduct **34b** was converted to tetracycle **35** through a saponification/intramolecular oxa-Michael addition/lactonization sequence.²⁴ Following the reported procedures from Nakamura and Hashimoto,²⁵ polygalolides A (**36**) and B (**37**) could be uneventfully accessed.

2.2 Natural product synthesis

Isolated from the stem bark of *Phyllanthus engleri*, englerins A and B belong to the guaiane sesquiterpene family and exhibit potent and selective growth inhibitory activities against renal cancer cell lines.²⁶ In 2011, Nicolaou, Chen and co-workers reported the racemic total synthesis of these two molecules.²⁷ As shown in Scheme 8, lactol **39** was prepared from readily

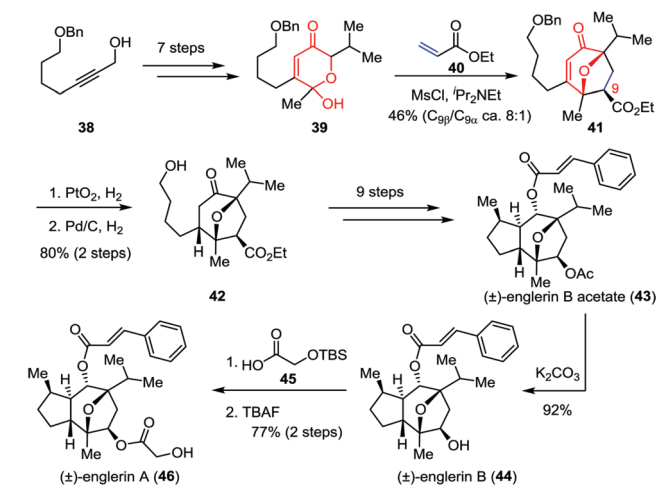


Scheme 6 [5+2] Cycloaddition of oxidopyrylium dimer **26** by Murelli and Brenner-Moyer.



Scheme 7 The $[Pd(\eta^3-C_3H_5)Cl]_2$ -catalyzed [5+2] cycloaddition by Suga and co-workers.

available starting material **38** within seven steps. The crucial [5+2] cycloaddition between **39** and ethyl acrylate **40** successfully delivered oxabicyclic enone **41** and its C9-epimer in 46% combined yield (8:1 dr). Subsequently, the sequential hydrogenative reduction of the olefin moiety and removal of the benzyl group afforded **42** in 80% yield, which was then

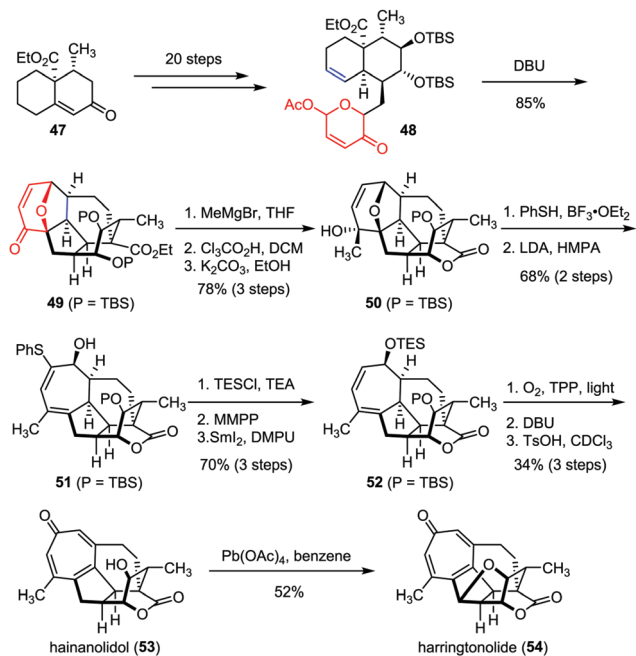


Scheme 8 Total synthesis of englerins A and B by Nicolaou, Chen and co-workers.

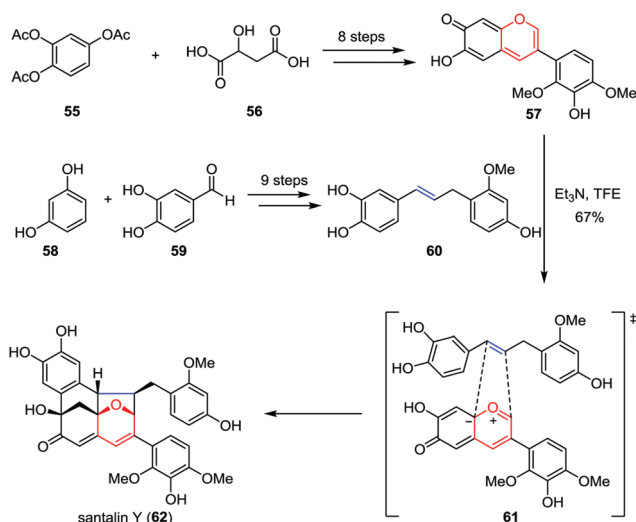
transformed to englerin B acetate (**43**) through several conventional operations. Further elaboration of **43** led to englerins A (**46**) and B (**44**) with high efficiency.

As two typical members of *Cephalotaxus norditerpenes*, harringtonolide and hainanolidol were isolated from *C. harringtonia*²⁸ and *C. hainanensis*,²⁹ respectively. Preliminary bioactivity investigations revealed that harringtonolide possesses antiviral and antineoplastic properties, while hainanolidol without the tetrahydrofuran ring was found inactive.³⁰ In 2013, Tang and co-workers achieved the efficient construction of the core structure of harringtonolide and hainanolidol *via* an intramolecular oxidopyrylium-mediated [5+2] cycloaddition.³¹ As shown in Scheme 9, the anticipated cycloaddition of **48**, which was prepared from enone **47** in twenty steps, proceeded smoothly in the presence of DBU, providing the adduct **49** as a single diastereomer in 85% yield. Stereoselective Grignard 1,2-addition of **49** followed by desilylation-induced lactonization afforded hexacycle **50**. Subsequently, a two-step sequence was employed to cleave the ether bridge of **50** and gave diene **51** in 68% yield. Finally, hainanolidol (**53**) and harringtonolide (**54**) were obtained through a series of late-stage functionalizations involving a sequential [4+2] cycloaddition, a Kornblum-DeLaMare rearrangement and double elimination.

Santalin Y, a novel yellow pigment, was isolated from *Pterocarpus santalinus* by Nohara and co-workers in 1995.³² It possesses a unique [6,6,6,5]-oxafenestrane skeleton, which features a catechol moiety and partially methylated pyrogallol and resorcinol substituents. Recently, Trauner and Tantillo disclosed a biomimetic total synthesis of santalin Y (Scheme 10).³³ Their synthesis commenced by aiming at the construction of anhydrobase **57**, which was prepared from 1,2,4-triacetoxybenzene **55** and malic acid **56** in eight steps.³⁴ On the other hand, the requisite benzylstyrene **60** could be obtained from readily available resorcinol **58** and protocatechualdehyde **59** by using olefin cross-metathesis as a key step. Upon treatment of a solution of **57** and **60** in trifluoroethanol ($c = 0.06$ M) at the solubility limits of these two intermediates with triethylamine



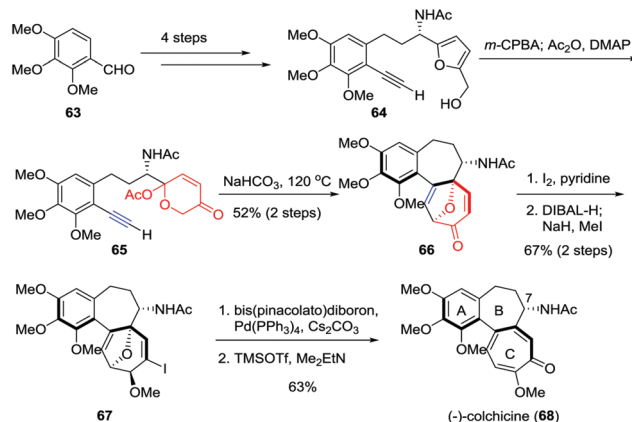
Scheme 9 Total synthesis of hainanolidol and harringtonolide by Tang and co-workers.



Scheme 10 Biomimetic total synthesis of santalin Y by Trauner and co-workers.

at $-20\text{ }^{\circ}\text{C}$ to initiate the oxidopyrylium-mediated [5+2] cycloaddition, racemic santalin Y (**62**) was formed in 67% isolated yield.

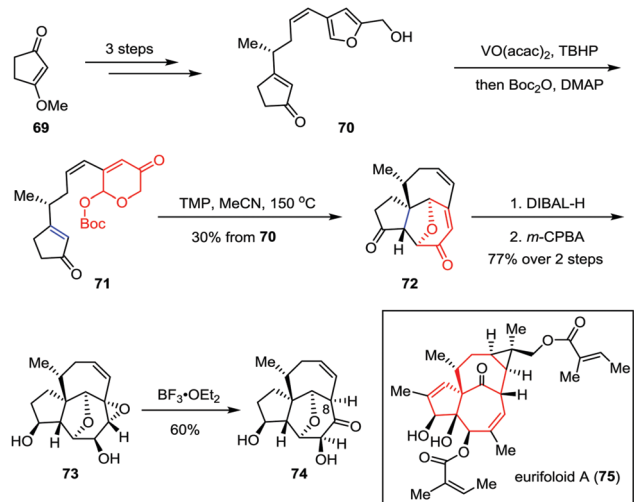
As the first tubulin-destabilizing agent reported in the literature, colchicine exhibits remarkable antimitotic activity that has been identified by a variety of indications. Due to its curative ability, this alkaloid is widely employed for the treatment of acute gout, familial Mediterranean fever and chronic myelocytic leukemia.³⁵ Moreover, it has also been used as a neurotoxin in animal models in the research of Alzheimer's disease and epilepsy.³⁶ Structurally, colchicine contains an unusual [6,7,7] tricyclic system. Furthermore, the single stereocenter at



Scheme 11 Enantioselective synthesis of (-)-colchicine by Li and co-workers.

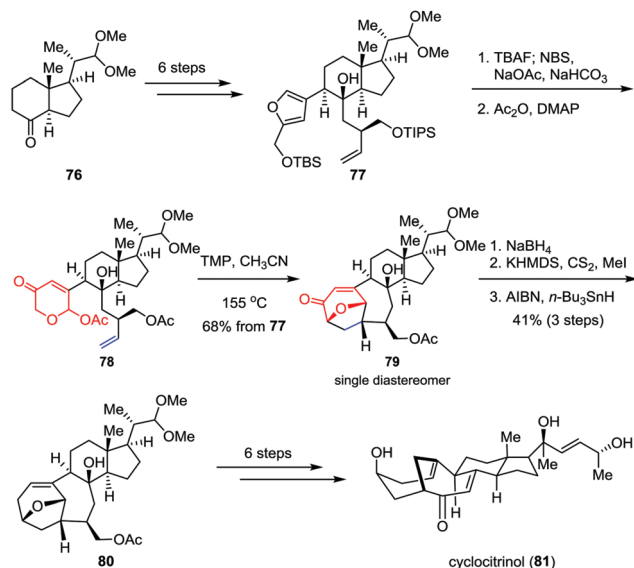
C7 as well as the α R-configured stereogenic axis defined by the pivot bond joining the A and C rings represents a formidable synthetic challenge. In 2017, Li and co-workers reported an enantioselective and scalable synthesis of (-)-colchicine (9.2% overall yield, $>99\%$ ee).³⁷ As shown in Scheme 11, their total synthesis began with the preparation of furan-alkyne **64**, which was realized in gram scale from aldehyde **63** over four steps. Subsequently, a two-step sequence involving Achmatowicz rearrangement and the oxidopyrylium-mediated [5+2] cycloaddition was utilized to build up the [6,7,7] tricyclic core structure of colchicinoids, providing **66** in 52% yield. The α -iodonization of **66** followed by ketone reduction/methylation resulted in the formation of **67** in 67% yield. Finally, the total synthesis of (-)-colchicine (**68**) was accomplished through a Suzuki–Miyaura cross coupling and double elimination of the oxa-bridge.

Eurifoloid A is a highly oxygenated tetracyclic diterpenoid, which was isolated from *Euphorbia nerifolia* in 2014.³⁸ Structurally, eurifoloid A features a congested stereogenic *cis*-triol segment as well as an unusual and highly strained bicyclo[4.4.1]-undecane ring system with *trans*-bridgehead (also known as in/out stereochemistry), which posed considerable synthetic challenges. In 2017, Li and co-workers described the synthetic studies toward eurifoloid A (Scheme 12).³⁹ Their synthesis commenced with the preparation of furan **70**, which was derived from 3-methoxycyclopent-2-en-1-one **69** in three steps. The Achmatowicz rearrangement of **70** using VO(acac)₂ and TBHP followed by a one-pot Boc-protection of the resultant anomeric hydroxy group gave **71**. The latter compound then underwent an intramolecular type II [5+2] cycloaddition to afford [5,7,7] tricycle **72** in 30% yield over two steps. Diastereoselective reduction of diketone followed by regio- and facial selective epoxidation delivered epoxide **73** as a single isomer in 77% yield over two steps. Finally, treatment of **73** with BF₃·OEt₂ afforded **74** in 60% yield. Although the Meinwald rearrangement of **73** gave the core structure of eurifoloid A (**75**) with undesired stereochemistry at C8, the above outcomes provided useful information for the design of new synthetic approach to this natural product.



Scheme 12 Synthetic studies toward eurifoloid A by Li and co-workers.

As an unusual C25 steroid, cyclocitrinol contains an unprecedented bicyclo[4.4.1]undecane ring system and a strained *anti*-Bredt bridgehead double bond. In preliminary studies, cyclocitrinol showed some interesting biological activities. For example, it can induce the generation of cAMP in GPR12-transfected CHO cells at 10 μ M.⁴⁰ However, the relative scarcity of this molecule from natural sources has impeded its further biological evaluation progress. Recently, Li and co-workers achieved the first and asymmetric total synthesis of cyclocitrinol (Scheme 13).⁴¹ Their synthesis began with the preparation of chiral furan 77, which could be derived from the commercially available starting material 76 in six steps. Desilylation of 77 followed by Achmatowicz rearrangement and acetylation generated the key precursor 78 smoothly. The intramolecular type II [5+2] cycloaddition was achieved by using TMP (2,2,6,6-tetramethylpiperidine) as a base in sealed tube and



Scheme 13 Asymmetric total synthesis of cyclocitrinol by Li and co-workers.

provided pentacycle 79 as a single diastereomer in 68% overall yield over three steps. The remaining ketone was then removed through 1,2-reduction followed by Barton deoxygenation, affording 80 in 41% yield over three steps. Finally, cyclocitrinol (81) was accessed through several conventional manipulations.

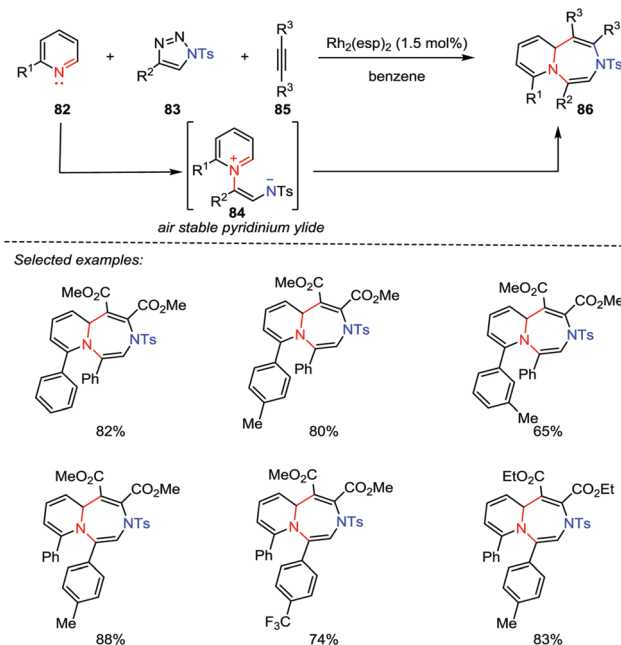
3. [5+2] cycloaddition of pyridinium and quinolinium ylides

3.1 Rh-catalyzed [5+2] cycloaddition of pyridinium ylides

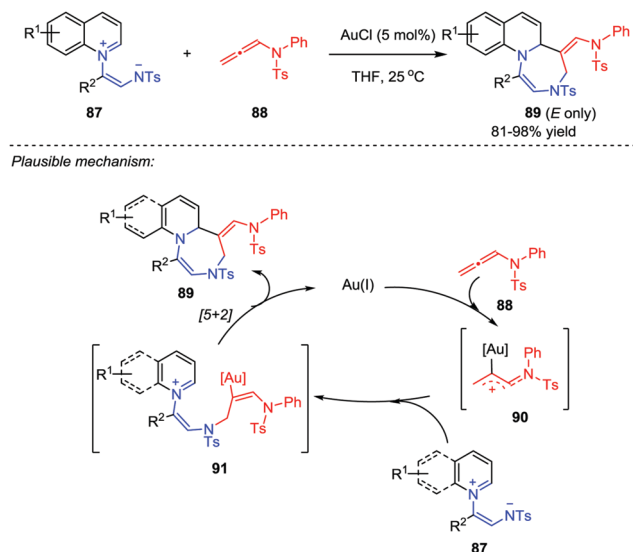
Although great progress has been made for the preparation of five- and six-membered heterocycles through catalytic [3+2] and [4+2] cycloadditions, the synthesis of seven-membered rings by using [5+2] cycloaddition reactions has not been investigated thus far ever since the seminal work of Wender *et al.* in 2002.⁴² Recently, Yoo and co-workers reported the first example of Rh-catalyzed multicomponent aza-[5+2] cycloaddition between the pyridines 82, 1-sulfonyl-1,2,3-triazoles 83 and alkynes 85. A variety of 1,4-diazepines 86 were obtained in good to excellent yields (Scheme 14).⁴³ Mechanistically, with the use of a catalytic rhodium catalyst, a stable pyridinium ylide 84 was generated, which acted as a 1,5-dipole to react with the activated alkynes 85.

3.2 Gold-catalyzed [5+2] cycloaddition of quinolinium ylide

Based on their previous work on the [5+2] cycloaddition using a unique isolable pyridinium ylide as a 1,5-dipole, the Yoo group further developed a ligand-free gold-catalyzed [5+2] cycloaddition between quinolinium ylides 87 and allenamides 88 (Scheme 15).⁴⁴ With the use of AuCl as catalyst, a series of stereospecific (*E*)-1,4-diazepines 89 were obtained in good to excellent yields. A plausible mechanism was proposed. Firstly, a



Scheme 14 The multicomponent aza-[5+2] cycloaddition by Yoo and co-workers.



Scheme 15 The ligand free gold-catalyzed [5+2] cycloaddition by Yoo and co-workers.

gold-bound allylic cation **90** was generated by the activation of allenamide with gold catalyst, which was then attacked by the negative nitrogen of the quinolinium ylide **87** to yield the tethered intermediate **91**. Subsequently, the intramolecular cyclization of **91** afforded the desired product and regenerated the catalyst. In addition, the described protocol could tolerate a broad scope of the substrates, whose potential and versatility has also been proved by a gram-scale feasibility test.

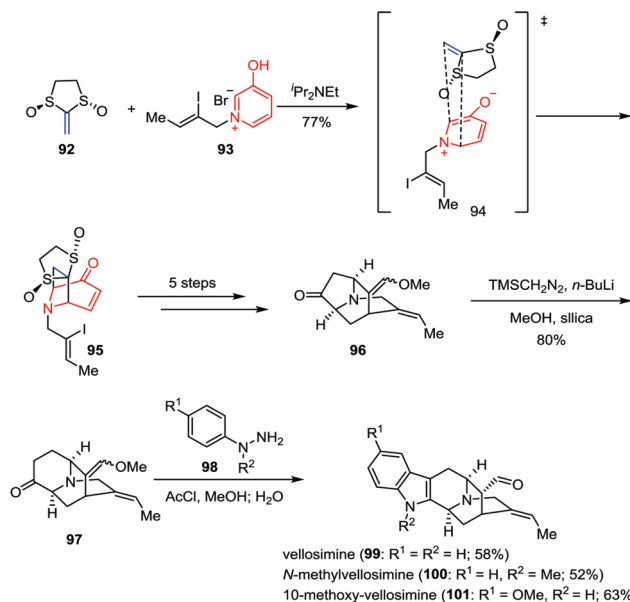
3.3 Natural product synthesis

To date, more than ninety congeners of the sarpagine family have been isolated from the plant *Apocynaceae*.⁴⁵ Due to the scarcity of these alkaloids and the lack of the synthetic analogues, the biological potential of these intricate architectures has rarely been investigated. In 2015, Gaich and co-workers demonstrated a general synthetic route to sarpagine alkaloids and completed the enantioselective total synthesis of vellosimine (**99**), *N*-methylvellosimine (**100**) and 10-methoxyvellosimine (**101**) in a concise manner (Scheme 16).⁴⁶ Their synthesis commenced with a [5+2] cycloaddition between oxidopyridinium ion **93** and Aggarwal's chiral ketene equivalent **92** (93% ee),⁴⁷ which provided the desired cycloadduct **95** and its regioisomer as a 2:1 mixture in 77% combined yield. After being converted to ketone **96** in five steps, the following ring enlargement proceeded smoothly and regioselectively, leading to the formation of **97** in 80% yield. Finally, vellosimine (**99**), *N*-methylvellosimine (**100**) and 10-methoxyvellosimine (**101**) were synthesized with high yields through Fischer indole synthesis by treatment of **97** with phenylhydrazines **98** bearing different substitution patterns.

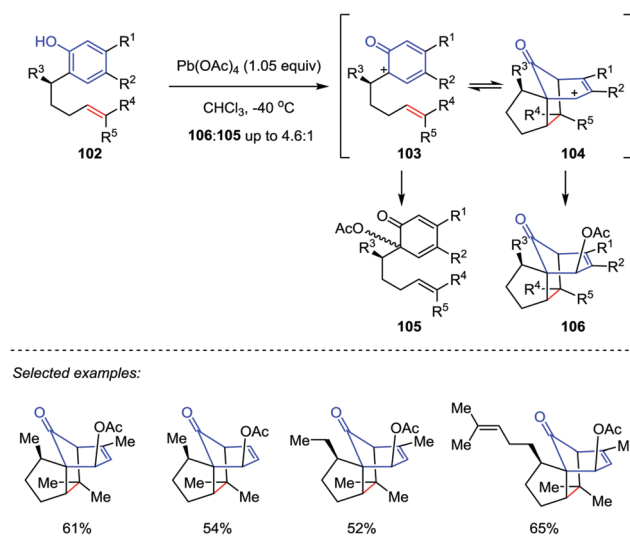
4. Perezzone-type [5+2] cycloaddition

4.1 Oxidative dearomatization-induced [5+2] cascade reaction

Inspired by the proposed biosynthesis of cedrol, Pettus and co-workers reported an efficient method for the construction of



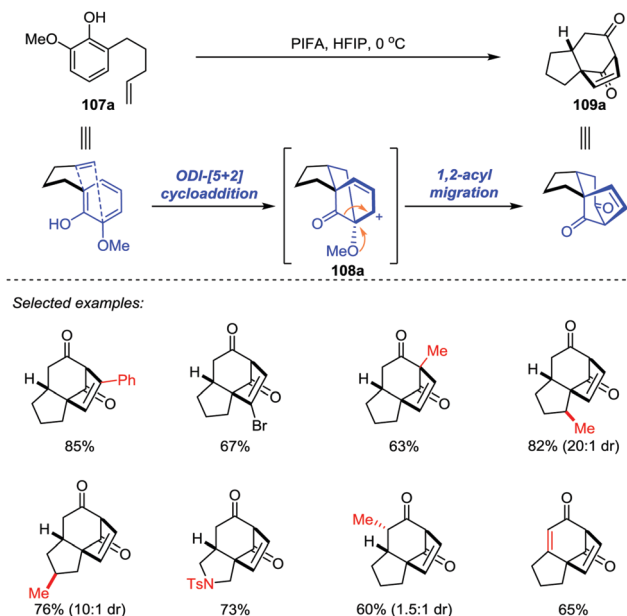
Scheme 16 Total synthesis of sarpagine alkaloids by Gaich and co-workers.



Scheme 17 ODI-[5+2] cycloaddition by Pettus and co-workers.

the tricyclo[5.3.1.0^{1,5}]undecane skeletons from curcuphenol derivatives (Scheme 17).⁴⁸ The cascade reaction began with the oxidative dearomatization of *ortho*-(pent-4-enyl)-phenols **102** followed by an intramolecular [5+2] cycloaddition of the corresponding phenoxonium intermediate **103** with tethered olefin by using Pb(OAc)₄ as an oxidant. The benzylic substituents and trisubstituted olefin subunits were found critical to the success of the oxidative dearomatization-induced (ODI) [5+2] cascade reaction, which afforded the cedrene-type skeletons **106** in good to moderate yields with high diastereoselectivities. Otherwise, the reaction gave the *ortho*-acetoxy compounds **105** as the major product.

In 2017, Ding and co-workers developed an ODI-[5+2] cycloaddition/pinacol-type 1,2-acyl migration cascade reaction



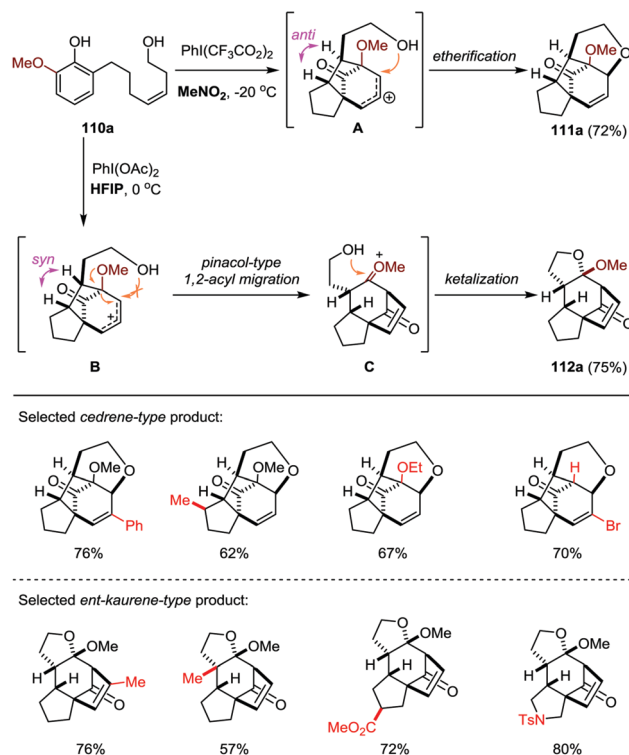
Scheme 18 ODI-[5+2] cycloaddition/pinacol-type 1,2-acyl migration cascade by Ding and co-workers.

to assemble the highly oxygenated bicyclo[3.2.1]octane system (Scheme 18).⁴⁹ With the use of $\text{PhI}(\text{CF}_3\text{CO}_2)_2$ (PIFA) as the oxidant and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as the solvent, various vinylphenols **107** with different substituents on the aromatic ring or functionalities on the side chain such as monosubstituted and disubstituted alkenes, and even alkynes were transformed into the respective products **109** with up to 85% yield. Mechanistically, the cationic cedrene-type skeleton intermediate was generated through an ODI-[5+2] cycloaddition and the preinstalled methoxy group at the *ortho* position of the phenol promoted the pinacol-type 1,2-acyl migration to forge the desired *ent*-kaurene-type skeleton.

Based on this work, the Ding group further developed a solvent-dependent ODI-[5+2] cascade reaction in the presence of hypervalent iodine oxidants (such as $\text{PhI}(\text{OAc})_2$ and $\text{PhI}(\text{CF}_3\text{CO}_2)_2$), which led to the facile and divergent construction of functionalized cedrene and *ent*-kaurene-type skeletons with good yields and excellent diastereoselectivities (Scheme 19).⁵⁰ By employment of MeNO_2 as the solvent, the cedrene-type product **111a** was obtained through an ODI-[5+2] cycloaddition followed by interception of the *in situ* generated allylic carbocation with the appendant hydroxyl group through an intramolecular etherification. On the other hand, with the use of HFIP as the solvent, the *ent*-kaurene-type product **112a** was achieved through an ODI-[5+2] cycloaddition followed by pinacol-type 1,2-acyl migration and intramolecular ketalization.

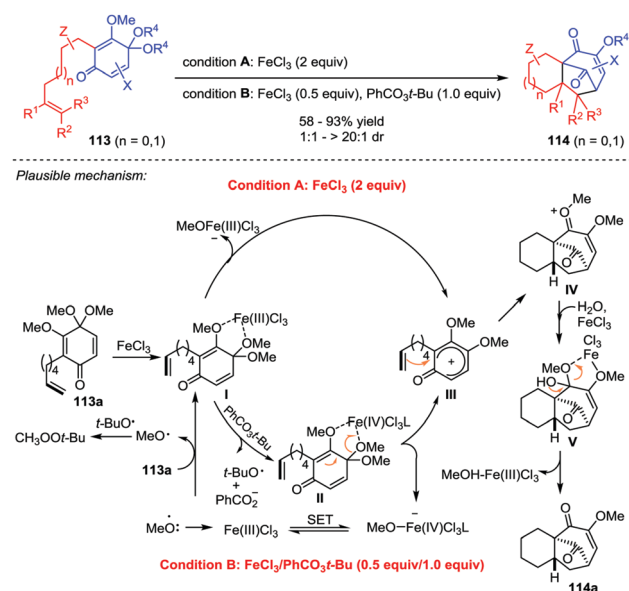
4.2 Iron-catalyzed [5+2] cycloaddition

Natural products and pharmaceutical intermediates containing diverse tricyclo[6.3.1.0^{1,6}]dodecane core structures often exhibit remarkable biological activities.⁵¹ Recently, Liu and co-workers presented an iron-catalyzed perezzone-type [5+2] cycloaddition reaction of substrate **113** to afford tricyclo[6.3.1.0^{1,6}]dodecane



Scheme 19 ODI-[5+2] cascade approach for the divergent synthesis of cedrene and *ent*-kaurene-type product by Ding and co-workers.

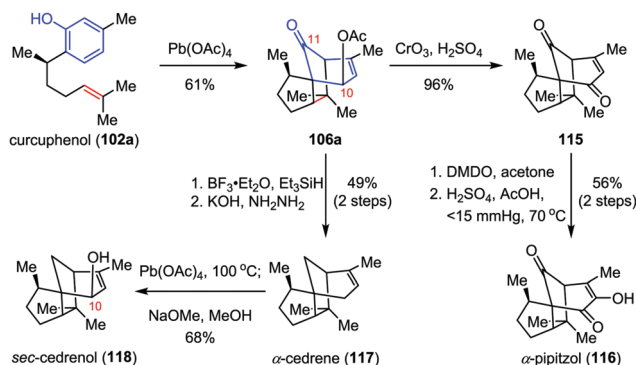
scaffolds **114**, which created two new C–C bonds and four stereogenic centers in one single operation with good yields and excellent dr values (Scheme 20).⁵² The products were accessible with two different reaction conditions, stoichiometric FeCl_3 (2 equiv.) and catalytic $\text{FeCl}_3/\text{PhCO}_2t\text{-Bu}$ (0.5/1 equiv.). Mechanistically, the reaction of **113a** for both conditions might share the same pathway involving the iron-mediated generation of a



Scheme 20 [5+2] Cycloaddition toward tricyclo[6.3.1.0^{1,6}] skeleton by Liu and co-workers.

4.3 Natural product synthesis

ent-Kaurene diterpenoids display a wide range of bio-activities such as antimalarial, antitumor and antiviral properties.⁵⁹ Among them, pharicin A (**129**) was found to induce tumor cell apoptosis and suppress tumor growth.⁶⁰ The construction of the bicyclo[3.2.1]octane carbon framework embedding in these molecules usually requires multiple reaction sequences, thus inevitably increased the functional group transformation and resulted in lengthier linear routes. Recently, Ding and co-workers reported the concise total synthesis of pharicin A and its congeners in a straightforward manner by using the

[illegible]

ODI-[5+2] cycloaddition cascade as a key step (Scheme 22).⁴⁹ Their synthesis commenced with the preparation of acetylene aldehyde **120**, which was derived from the readily available bicyclic ketone **119** in four steps. Partial hydrogenation of the acetylene moiety with Lindlar catalyst followed by 1,2-addition with the organolithium reagent generated from bromophenol **121** and *n*-BuLi afforded a 2:1 mixture of vinylphenol **122a** and **122b** in 80% combined yield. The latter isomer could be recycled *via* an efficient oxidation/reduction sequence, affording a 3:1 mixture of diastereomers favoring **122a**. Treatment of **122a** with $\text{PhI}(\text{CF}_3\text{CO}_2)_2$ and K_2CO_3 in HFIP delivered the desired tetracyclic diketone **123** as a single diastereomer in 70% yield even on gram scale. Subsequently, epimerization at C7 through Dess–Martin oxidation followed by global reduction provided triol **124** in 83% yield as a mixture of diastereomers (2.5:1 dr at C12). Unfortunately, the exclusive generation of the undesired α -OH at C14 was also observed. To address this problem, a two-step sequence involving monoacetylation at C7 and regioselective oxidation at C12 was firstly carried out, which delivered alcohol **125** in 85% yield. After an extensive investigation, it was found that the inversion of the

stereochemistry at C14 proceeded smoothly in the presence of catalytic *p*-TsOH, delivering **127** in 78% yield through a retroaldo/aldol process. Finally, pharicin A (**129**) was achieved through a stereoselective ketone reduction and Schenck ene reaction. Further one or two-step elaboration of **129** led to the completion of the total synthesis of pharicin B (**130**), 7-*O*-acetylpsurata C (**131**) and psurata C (**132**) in high yields.

Epicolactone, a highly compact natural product, was isolated from endophytic fungi of the species *Epicoccum*.⁶¹ It exhibits both antimicrobial and antifungal activities. Trauner and co-workers described a biomimetic synthesis of epicolactone (**139**) in only eight steps from readily available vanillyl alcohol **133** (Scheme 23a).⁶² Their synthesis commenced with the preparation of bromobenzaldehyde **134**, which was derived from vanillyl alcohol **133** in four steps through a reported procedure.⁶³ Installation of another phenol hydroxyl group at 5-position of **134** via copper-catalyzed hydroxylation followed by reduction of the aldehyde furnished catechol **135** in 59% yields over two steps. It should be noted that the existing of a phenolic methyl ether at 3-position of substrate **135** is crucial to the success of this approach, which reduced the possibility of

dimerization and provided a stable intermediate in the next key step. The other partner, epicoccine **136**, could be prepared in five steps from eudesmic acid on a multigram scale.⁶³ Subjection of **135** to a buffer solution of $K_3[Fe(CN)_6]$ followed by slow addition of **136** afforded epicolactone methyl ether **137** in 42% yield, along with the regioisomeric heterodimer **138** in 16% yield. Further demethylation of both isomers led to epicolactone (**139**) and isoepicolactone (**140**) in 75% and 96% yields, respectively.

The features of the divergent [5+2] cycloaddition lie in two aspects: (1) the reaction proceeded under biomimetic conditions and finished in seconds; and (2) the complex caged product comprising five condensed rings bearing three contiguous quaternary carbons and a tertiary alcohol could be formed in a single operation from two relatively simple phenols. The initial [5+2] cycloaddition closely matches the proposed biosynthetic route while utilizing the methoxy *o*-quinone (**143**) instead of the unmasked hydroxy *o*-quinone (Scheme 23b).⁶⁴ The cycloaddition led to the formation of carbonyl-bridged intermediate **144**, and hence the following steps were all intramolecular, avoiding enormous steric hindrances. Similarly, the [5+2] cycloaddition of **143** with **142**, a tautomer of **141**, afforded an intermediate (**145**) en route to the minor regioisomer **138**.

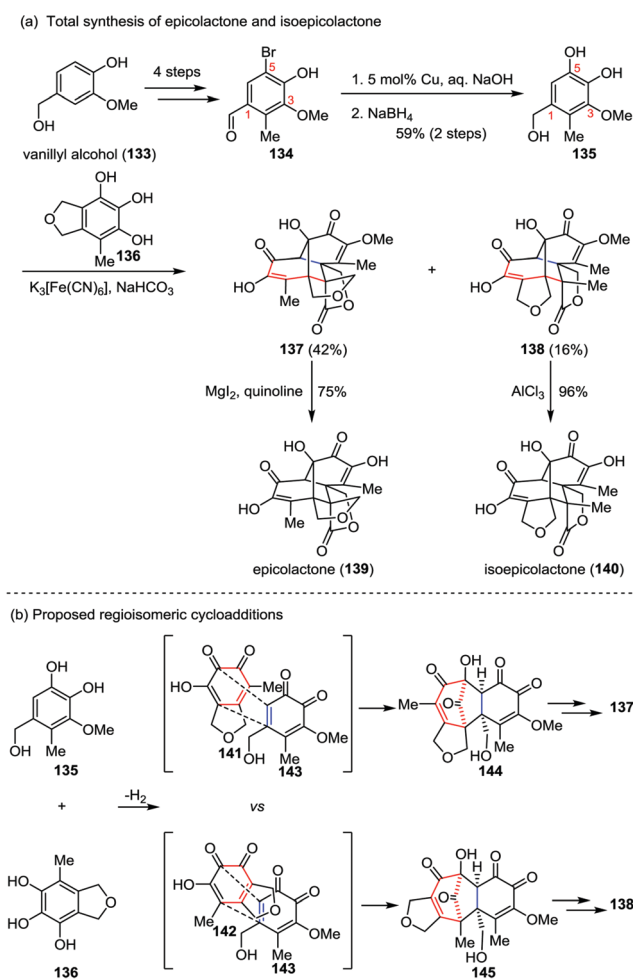
5. [5+2] Cycloaddition of vinyl/allenyl substituted three-membered rings

5.1 [5+2] cycloaddition of vinyl/allenyl cyclopropanes

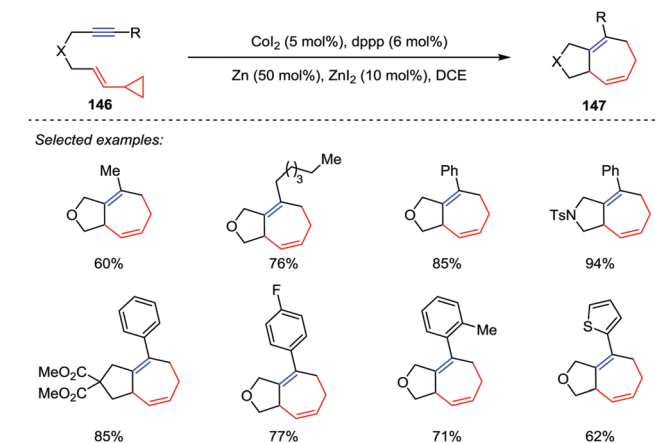
Highly strained cyclopropane derivatives have served as useful and powerful C3 building blocks for the construction of various ring systems.⁶⁵ In this area, the metal-catalyzed cleavage of the activated carbon-carbon σ bond of the cyclopropane ring is one of the most attractive methods from a synthetic point of view.⁶⁶ Among them, the transition metal-catalyzed [5+2] cycloaddition of vinyl cyclopropanes (VCPs) is a straightforward way to access seven-membered carbocycles. In 1995, Wender and co-workers reported the first example of transition metal-catalyzed [5+2] cycloaddition between VCPs and alkynes, providing a conceptually new method for the synthesis of seven-membered rings.⁶⁷ Since then, a variety of reactions concerning metal-catalyzed [5+2] cycloaddition of VCPs with different π -systems were successively reported.

Among them, other transition-metals have also been successfully developed as catalysts in a number of intramolecular [5+2] cycloadditions recently, including ruthenium,⁶⁸ nickel,^{69a} iron,^{69b} iridium.^{69c} Recently, Yoshikai and co-workers addressed a cobalt-catalyzed intramolecular [5+2] cycloaddition reaction of VCPs and alkynes (Scheme 24).⁷⁰ A wide range of tethered VCP/alkyne substrates **146** were tolerated by using the optimized catalytic conditions comprising CoI_2 (5 mol%), dppp (6 mol%) and Zn dust as a reductant, thus providing the corresponding cycloheptadienes **147** in good to excellent yields.

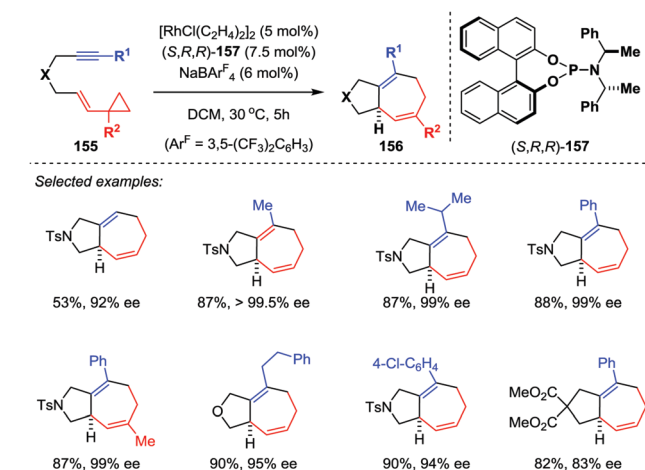
Recently, the Wender group made much progress in the area of intermolecular [5+2] cycloaddition of VCPs. In 2010,



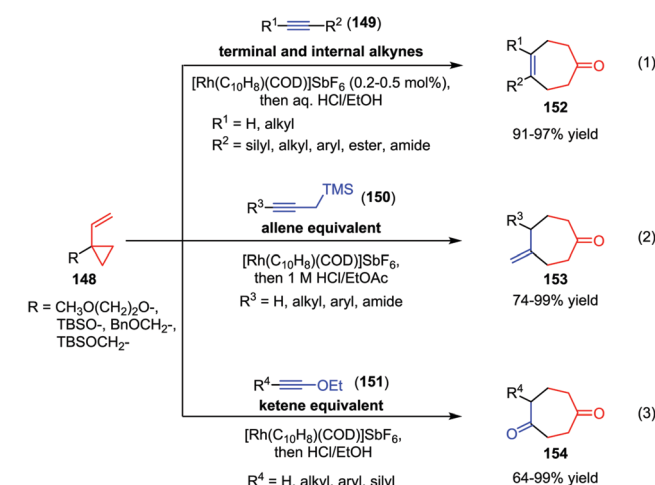
Scheme 23 (a) Total synthesis of epicolactone and isoepicolactone by Trauner and co-workers. (b) Proposed mechanism for the divergent [5+2] cycloaddition.



Scheme 24 Cobalt-catalyzed intramolecular [5+2] cycloadditions by Yoshikai and co-workers.



Scheme 26 Rh-catalyzed asymmetric [5+2] cycloadditions of alkyne-VCPs by Shintani and Hayashi.



Scheme 25 [5+2] Cycloadditions of alkynes and VCPs by Wender and co-workers.

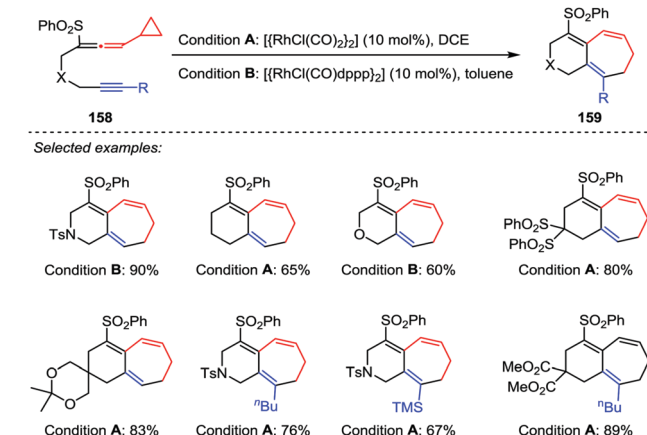
they described a cationic rhodium(I) complex-catalyzed intermolecular [5+2] cycloaddition of 1-alkoxy- or 1-alkyl-VCPs **148** with a wide range of terminal and internal alkynes **149** (Scheme 25).^{71a} High efficiencies (91–97% yields) were observed under low catalyst loadings (0.2–0.5 mol%) and practical reaction concentrations (0.5–0.1 M) (eqn (1)). As conventional allenes are ineffective 2-carbon components in many intermolecular cycloadditions including metal-catalyzed [5+2] cycloadditions, the Wender group employed propargyl-trimethylsilanes (**150**) as allene surrogates and developed a stepwise intermolecular [5+2] cycloaddition/protodesilylation reactions, affording the corresponding cycloheptanone **153** in good to high yields (eqn (2)).^{71b} In this work, **150** functioned as the safe, easily handled synthetic equivalents of gaseous allenes or monosubstituted allenes that are difficult to access. Furthermore, they also used ynol ethers **151** as ketene equivalents in the Rh-catalyzed intermolecular [5+2] cycloadditions with VCPs **148** (eqn (3)).^{71c} These cycloaddition reactions proceeded smoothly at ambient temperature and afforded the substituted cyclohepta-1,4-diones **154** with up

to 99% yield. In addition, a wide range of functionalities, such as chloro, methoxyl, and ester groups were tolerated in this reaction.

For asymmetric transition-metal-catalyzed [5+2] cycloadditions of VCPs, the catalyst-controlled method is envisioned more efficient and powerful than the substrate-controlled pathway. Wender and co-workers firstly used a rhodium-BINAP chiral catalyst in the asymmetric [5+2] cycloaddition reaction of VCPs and alkenes.⁷² In their results, asymmetric cycloaddition with alkenes could afford enantiomeric excesses as high as 99%. However, similar reactions with alkyne substrates were not as successful, giving only moderate enantioselectivities. To address this limitation, Shintani and Hayashi developed a highly efficient asymmetric intramolecular [5+2] cycloaddition of alkyne-VCPs **155** through rhodium catalysis (Scheme 26).⁷³ After an extensive investigation, they found the combination of $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ with chiral phosphoramidite ligand **157** in the presence of NaBARF_4 is the optimal condition, providing cycloadducts **156** with excellent enantioselectivities (up to 99.5% ee).

In 2010, Mukai *et al.* developed a Rh(I)-catalyzed intramolecular [5+2] cycloaddition reaction between phenylsulfonylallenes **158** containing a cyclopropyl group at the allene terminus and alkynes under mild conditions (Scheme 27).⁷⁴ This reaction provided the desired products **159** in moderate to good yields with the reactants possessing an internal or terminal alkyne in the presence of $[\{\text{RhCl}(\text{CO})_2\}_2]$ or $[\{\text{RhCl}(\text{CO})\text{dppp}\}_2]$. The results are in sharp contrast with those results obtained from the $[\{\text{RhCl}(\text{CO})_2\}_2]$ -catalyzed [5+2] cycloaddition of alkyne-VCPs,⁷⁵ in which an internal alkyne consistently and efficiently afforded the corresponding ring-closed product, whereas no [5+2] cycloaddition product was observed when a terminal alkyne was involved.

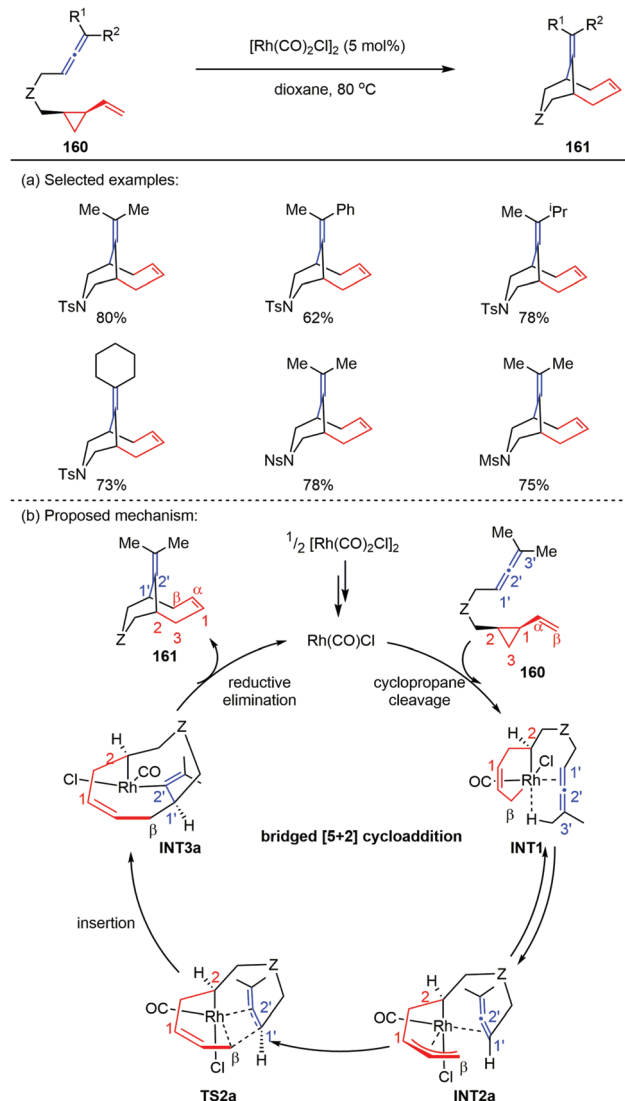
The previous report by Yu and co-workers showed that *cis*-ene-VCPs underwent a Rh-catalyzed [5+2] cycloaddition to provide 5,7-fused bicyclic products,⁷⁶ where VCPs acted as five-carbon synthons. However, when they replaced the 2π component of *cis*-ene-VCPs with allene subunits, the corresponding



Scheme 27 [5+2] Cycloadditions of alkynes and allenyl cyclopropanes by Mukai and co-workers.

cis-allene-VCPs **160** occurred an unprecedented bridged [5+2] cycloaddition to give the bicyclo[4.3.1]decane skeletons **161** (Scheme 28a).⁷⁷ Preliminary DFT calculations revealed that the bridged [5+2] cycloaddition can reduce the repulsion effects by placing the allene moiety away from the VCP moiety in the allene insertion transition state (TS2a), thus affording the inversed allene insertion intermediate (INT3a). Finally, the reductive elimination led to the bridged cycloadducts **161** in good yields (Scheme 28b).

With the great progress of metal-catalyzed [5+2] cycloadditions between VCPs and alkenes/alkynes/allenes, mechanism studies on these reactions were successively reported by the group of Houk, Wender and Yu.⁷⁸ Generally, these reactions occur through a series of elementary reactions including oxidative addition, alkene/alkyne/allene insertion, and reductive elimination. It is worth to note that recently the Yu group also contributed an important mechanism research work on the metal-free [5+2] reactions of *N*-methoxycarbonyl-2,3-homopyrrole **162** and homofuran **167** with dienophiles reported by Fowler (eqn (1) and (2)) and Ugi (eqn (3)) in 1971 and 1985, respectively (Scheme 29a).⁷⁹ The [5+2] cycloaddition between *N*-methoxycarbonyl-2,3-homopyrrole **162** and *N*-phenylmaleimide **163** has been studied through the model reaction of *N*-methoxycarbonyl-2,3-homopyrrole and *N*-hydrogen-maleimide. DFT calculations of all four pathways a–d demonstrated that the reaction favors stepwise pathway a, giving diradical intermediate **INT1**, while in the concerted pathway b the cycloaddition between the existing-in-transition-state 1,5-dipole and dienophiles is disfavored. Moreover, although the *a-exo* is very similar to the *a-endo* pathway, it is disfavored by 1.6 kcal mol^{−1} in gas phase (1.7 kcal mol^{−1} in solution). These results indicate that the *endo*-cycloadduct is the favored one. In contrast, DFT calculations showed the [5+2] cycloaddition between homofuran **167** and maleic anhydride **168** prefers to occur concertedly *via* pathway b to give both the *endo* and *exo* [5+2] cycloadducts, while the competing diradical pathway a is marginally disfavored by 1 kcal mol^{−1}. In addition, pathways c and d are not favored for both of the [5+2] cycloadditions studied, presumably due to the less resonance stabilization of



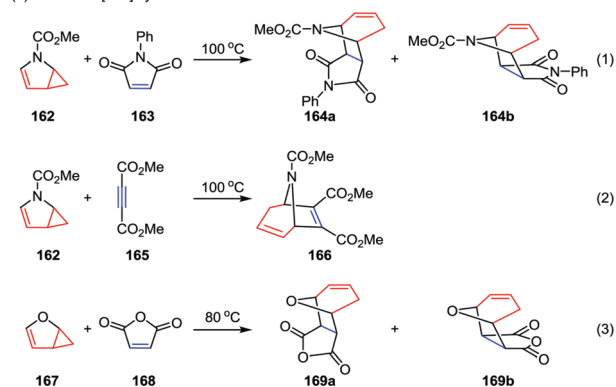
Scheme 28 [5+2] Cycloadditions of *cis*-allene-VCPs by Yu and co-workers.

the corresponding intermediates **INT2** and **INT3** compared with those in pathways a and b.^{79c}

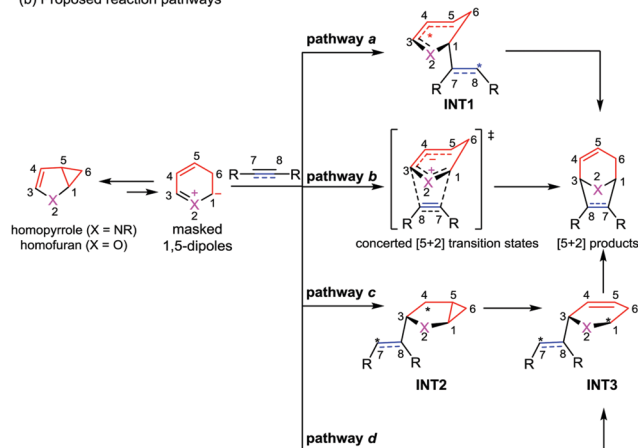
5.2 Hetero-[5+2] cycloaddition of vinyl aziridines and vinyl oxiranes

2-Vinyl aziridine is a strained and reactive cyclic amine, and a variety of reactions of vinyl aziridines involving the cleavage of the C–N bond have been reported.⁸⁰ Among them, the intermolecular [5+2] cycloadditions of vinyl aziridines with unsaturated compounds represents one of the most efficient approaches for the synthesis of azepane frameworks. In 2012, Saito and co-workers demonstrated that the [5+2] cycloaddition reactions of 2-vinyl aziridines **170** with sulfonyl isocyanates **171** could take place without the aid of any catalysts, and the seven-membered cyclic ureas **172** were obtained in good to high yields (Scheme 30).⁸¹ Notably, the use of reactive sulfonyl isocyanates and the choice of dichloromethane as the solvent are two crucial factors for the proceeding of this reaction.

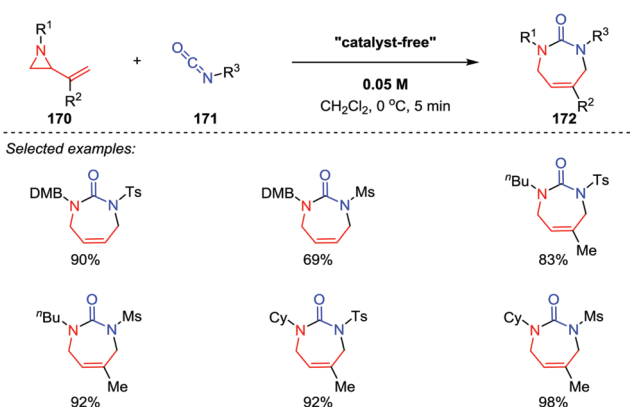
(a) Metal-free [5+2] cycloadditions



(b) Proposed reaction pathways

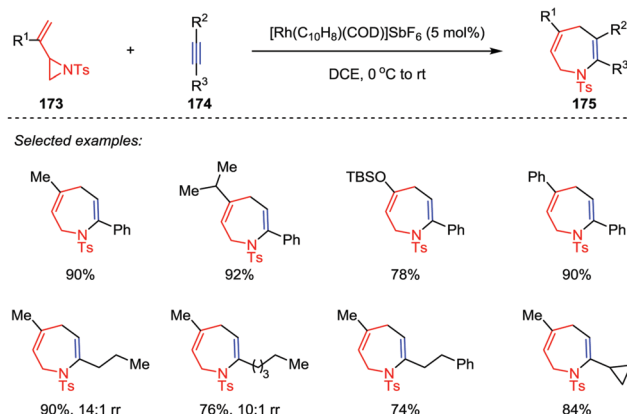


Scheme 29 (a) Metal-free [5+2] cycloadditions by Fowler and Ugi; (b) proposed concerted and stepwise pathways of the [5+2] cycloaddition by Yu and co-workers.



Scheme 30 [5+2] Cycloadditions of vinyl aziridines and sulfonyl isocyanates by Saito and co-workers.

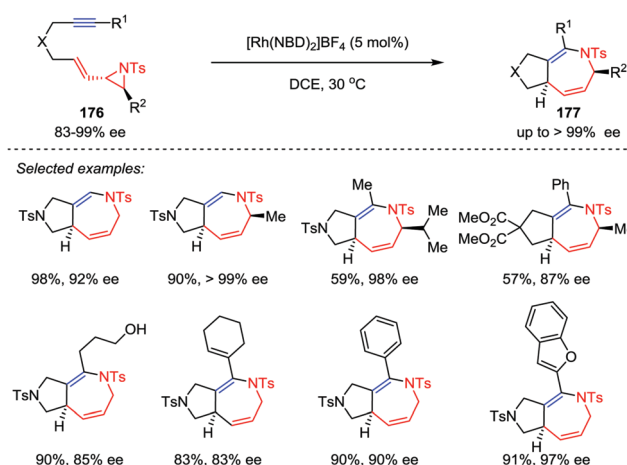
Although the intermolecular [3+2] cycloadditions of vinyl aziridines and activated alkenes have been explored and represent a powerful tool to obtain multi-substituted pyrrolidines, the more challenging intermolecular [5+2] cycloadditions of vinyl aziridines as five-atom components with general alkynes have rarely been explored. It was not until 2016, Zhang and co-workers disclosed the rhodium-catalyzed intermolecular



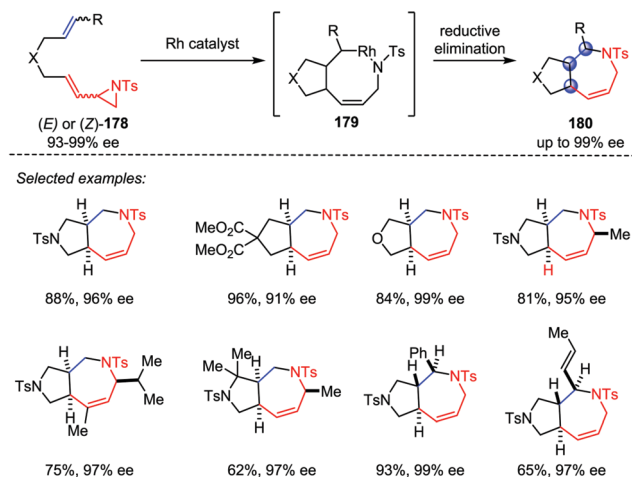
Scheme 31 Intermolecular [5+2] cycloadditions of vinyl aziridines and alkynes by Zhang and co-workers.

[5+2] cycloaddition of vinyl aziridines **173** and alkynes **174** (Scheme 31).⁸² With the use of [Rh(C₁₀H₈)(COD)]SbF₆ as catalyst, various aromatic and aliphatic terminal alkynes were converted to the corresponding cycloadducts **175** with high to excellent yields. In most cases, only one regioisomer was detected, except for some aliphatic alkynes (such as propyl and amyl substituted alkynes) affording the corresponding azepines **175** and their isomers in moderate to high ratios. Unfortunately, the internal alkynes were not applicable to this [5+2] cycloaddition.

The development of new cycloaddition reactions to access polysubstituted and ring-fused azepines, especially the enantiomerically pure ones, from readily available acyclic precursors remains highly desirable in both organic and medicinal chemistry.⁸³ Zhang and co-workers recently disclosed the stereo-selective synthesis of fused 2,5-dihydroazepine derivatives *via* hetero-[5+2] cycloadditions of optically pure vinyl aziridine-alkyne substrates **176** in the presence of 5 mol% [Rh(NBD)₂]BF₄ catalyst (Scheme 32).⁸⁴ Substrates with both internal and terminal alkyne moieties were compatible to afford the corresponding cycloaddition adducts **177** with high enantioselectivities.



Scheme 32 Hetero-[5+2] cycloadditions of vinyl aziridines and alkynes by Zhang and co-workers.

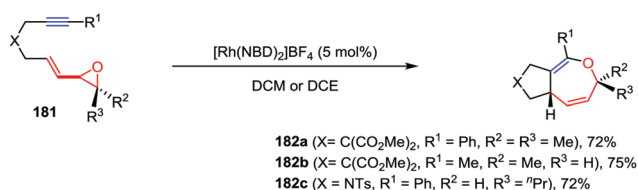


Scheme 33 Hetero-[5+2] cycloadditions of vinyl aziridines and alkenes by Zhang and co-workers.

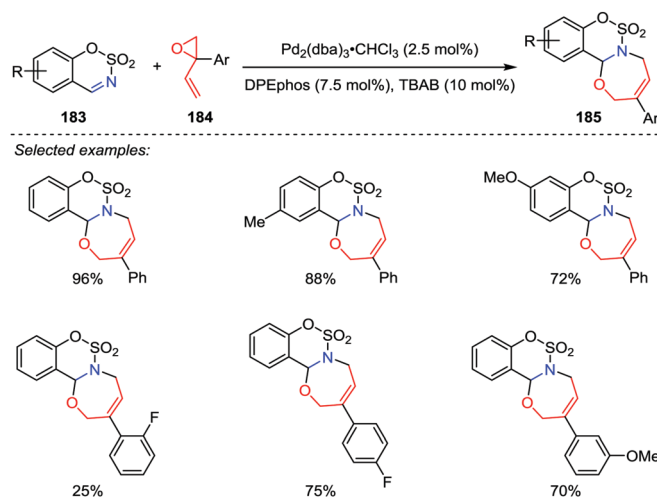
Moreover, this stereospecific cycloaddition reaction could be carried out on gram-scale with a reduced catalyst loading (2 mol% Rh).

Based on the above work, Zhang and co-workers also developed a Rh-catalyzed intramolecular hetero-[5+2] cycloaddition of vinyl aziridines and alkenes (Scheme 33).⁸⁵ Both internal and terminal alkenes were tolerated in this transformation. Various chiral-fused bicyclic azepines **180** with multiple contiguous stereogenic centers were obtained from the corresponding chiral starting materials **178** with good yields and high stereoselectivities under mild conditions.

Oxepine derivatives represent a ubiquitous class of oxygen-containing seven-membered heterocycles with wide occurrence in many bioactive natural products and pharmaceuticals. Compared with the reactions that have been well established for five- and six-membered oxygen-containing heterocycles, the construction of oxepine skeletons is much more difficult due to the unfavorable entropic factors and transannular interactions.⁸⁶ Owing to the inherent reactivity of their constrained ring systems, cyclopropane and oxirane derivatives constitute valuable building blocks for organic synthesis. In contrast to VCPs, vinyloxiranes and their derivatives have served as attractive ring-expansion motifs in metal-catalyzed [3+2] cycloaddition, epoxide carbonylation and substitution reactions.⁸⁷ Recently, Zhang and co-workers described an intramolecular hetero-[5+2] cycloaddition of vinyloxirane-alkynes **181** in the presence of 5 mol% of $[\text{Rh}(\text{NBD})_2]\text{BF}_4$, affording the corresponding bicyclic 2,5-dihydrooxepine derivatives **182** in high yields (Scheme 34).⁸⁸



Scheme 34 Intramolecular [5+2] cycloadditions of vinyl oxiranes and internal alkynes by Zhang and co-workers.

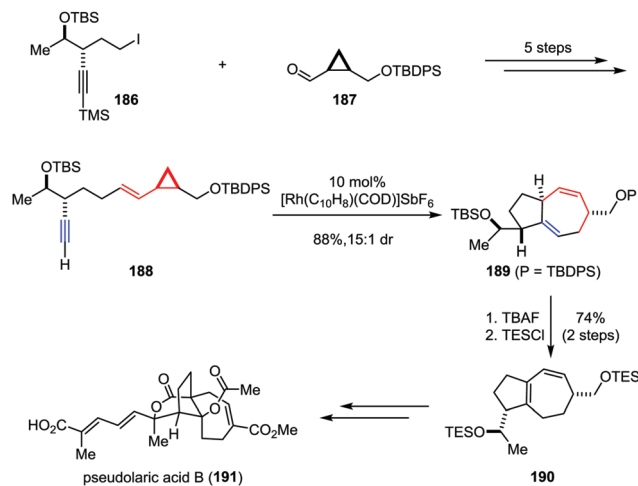


Scheme 35 [5+2] Cycloadditions of vinyl oxiranes and cyclic imines by Guo and co-workers.

1,3-Oxazepines are seven-membered heterocyclic compounds bearing both nitrogen and oxygen atoms in the ring, which have been extensively studied due to their potent biological activities. Although a considerable number of ways for the synthesis of 1,3-oxazepine ring have been reported,⁸⁹ most of these methods suffered from the drawbacks such as substrate preparation, multiple-step reactions and low yields. Therefore, novel and efficient protocols for the oxazepine ring construction are highly desirable. In 2017, Guo and co-workers reported a palladium-catalyzed [5+2] cycloaddition of sulfamate-derived cyclic imines **183** with 2-aryl-2-vinyloxiranes **184**, affording biologically interesting sulfamate-fused 1,3-oxazepine derivatives **185** in good to excellent yields with satisfactory regioselectivities (Scheme 35).⁹⁰ However, the unsubstituted vinyloxiranes and alkyl-substituted vinyloxiranes were found unable to undergo this reaction.

5.3 Natural product synthesis

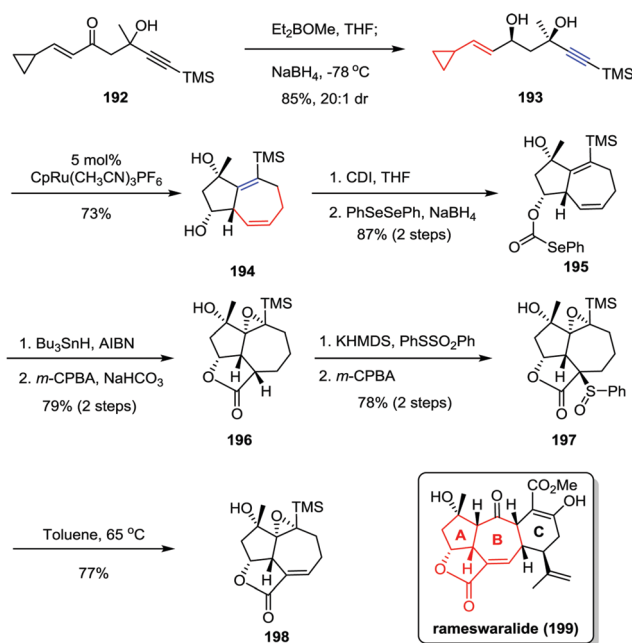
Pseudolaric acid B, a diterpene acid, was isolated from the bark of *Pseudolarix kaempferi* Gordon (pinaceae).⁹¹ It has been identified as a potent antifungal, antifertility, and cytotoxic agent.⁹² Furthermore, pseudolaric acid B inhibits angiogenesis by diminishing the secretion of vascular endothelial growth factor (VEGF) in tumor cells and has been shown to induce apoptosis through several pathways in human melanoma cells.⁹³ The remarkable biological properties and the low toxicity of pseudolaric acid B have rendered it an attractive target for synthetic studies. However, the unusual *trans*-fused [5,7] bicyclic ring system (polyhydroazulene) makes the stereoselective approach toward this molecule a daunting task. In 2007, Trost and co-workers described the total synthesis of pseudolaric acid B (Scheme 36).⁹⁴ Their synthesis began with the preparation of linear precursor **188**, which could be derived from iodide **186** and aldehyde **187** in five steps. The planned Rh-catalyzed intramolecular [5+2] cycloaddition of **188** proceeded smoothly to construct the polyhydroazulene core, providing the desired product **189** in 88% yield with 15:1 dr. Subsequently, the TBAF-induced isomerization of 1,4-diene to 1,3-diene followed



Scheme 36 Total synthesis of (–)-pseudolaric acid B by Trost and co-workers.

by resilylation afforded **190** in 74% yield over two steps. Further elaboration of **190** led to pseudolaric acid B (**191**).

Rameswaralide, a novel diterpene with a tetracyclic ring skeleton, was isolated from the soft coral *Sinularia dissecta* near the Mandapam coast of India in 1998.⁹⁵ Rameswaralide and its derivatives could function as effective anti-inflammatory agents for the treatment of a variety of inflammatory disorders, including arthritis, psoriasis, and inflammatory bowel disease.⁹⁶ In 2011, the Trost group reported an efficient synthetic approach toward the tricyclic structure containing A/B rings of rameswaralide (**199**), which featured the formation of the challenging [5,7] bicyclic skeleton and the exocyclic α,β -unsaturated lactone subunit (Scheme 37).⁹⁷ After the preparation of *syn*-1,3-diol **193** through



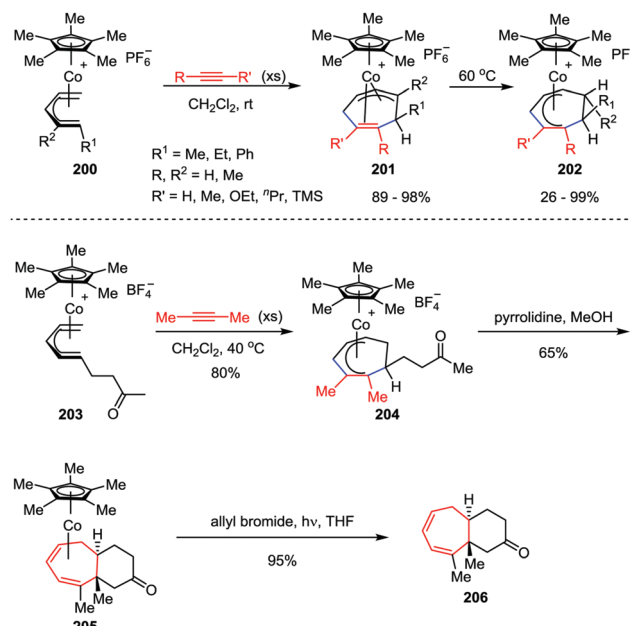
Scheme 37 Synthesis of the tricyclic core of rameswaralide by Trost and co-workers.

a diastereoselective 1,2-reduction of enone **192**, the Ru-catalyzed intramolecular [5+2] cycloaddition resulted in the formation of the [5,7] bicycle **194** as a single isomer in good yield. Subsequent reductive radical cyclization followed by oxidation/regioselective elimination afforded the desired lactone **198** smoothly.

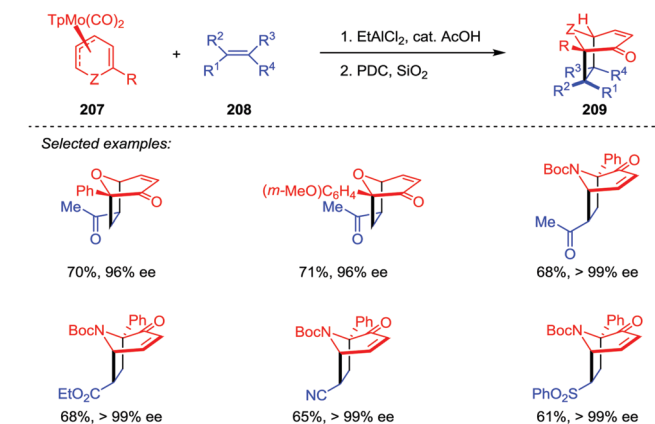
6. [5+2] Cycloadditions of 5-carbon organo-metallic complexes

6.1 [5+2] Cycloadditions of 5-carbon cobalt and molybdenum complexes

Novel transition-metal-mediated reactivity patterns also provided the conceptual basis for the development of new synthetic reactions. Despite considerable advancements having been made, the [5+2] cycloaddition reaction of an alkyne and η^5 -pentadienyl complex still remains an attractive topic for organic chemists. In 2008, Stryker and co-workers discovered an interesting [5+2] cycloaddition of acyclic (open) η^5 -pentadienyl cobalt complexes **200** and alkynes under notably mild conditions (Scheme 38).⁹⁸ The reaction selectively afforded the cycloheptadienyl ring as the η^2,η^3 -coordinated isomer **201**, which was an unusual coordination mode for unbridged cycloheptadienyl systems. Through gentle heating, the isomer could be transformed to the fully conjugated η^5 -cycloheptadienyl product **202**. They further investigated this reaction manifold by extending the reaction to tandem cycloaddition/nucleophilic cyclization to generate fused bicyclic compounds.⁹⁹ The cycloaddition of η^5 -pentadienyl ketone complex **203** with high concentrations of 2-butyne afforded η^5 -cycloheptadienyl ketone complex **204**. Upon exposure of **204** to pyrrolidine, the expected bicyclic complex **205** was obtained as a single diastereoisomer in a reasonable yield. The subsequent photolytic decomplexation



Scheme 38 Cobalt-mediated η^5 -pentadienyl/alkyne [5+2] cycloaddition by Stryker and co-workers.



Scheme 39 [5+2] Cycloaddition of η^3 -pyranyl- and η^3 -pyridinylmolybdenum complexes and alkenes by Liebeskind and co-workers.

proceeded smoothly, delivered bicyclic ketone **206** with 95% isolated yield. Gratifyingly, no loss of stereochemical or compositional integrity was detected (Scheme 38).

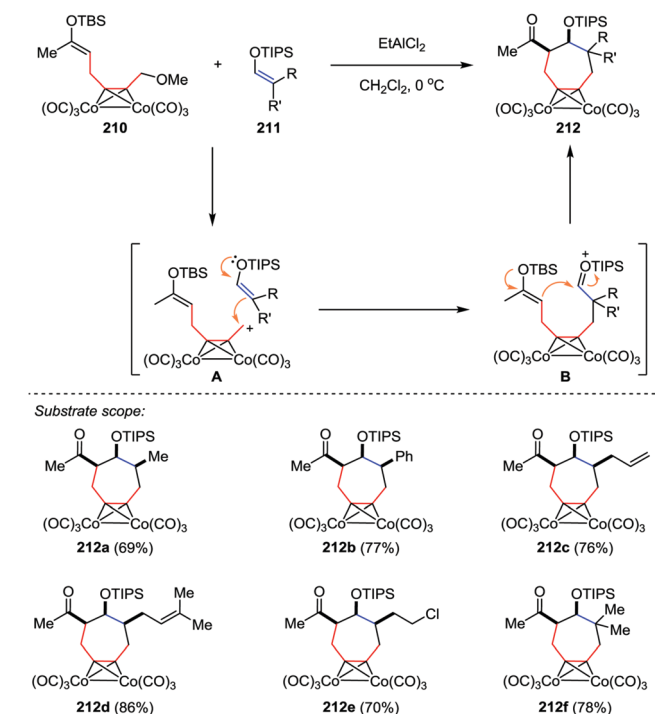
The oxa- and azabicyclo[3.2.1]octene skeletons are key structural subunits existing in a large and diverse array of biologically important natural products. Although their synthesis through [5+2] cycloadditions of 3-oxidopyrylium and 3-oxidopyridinium dipoles has been extensively studied, these approaches often suffered from drawbacks such as the limited methods in asymmetric version and the lack of facial- and regioselective control in cycloaddition. An intriguing progress was reported by Liebeskind and co-workers.¹⁰⁰ As shown in Scheme 39, a series

of 6-substituted η^3 -pyranyl- and η^3 -pyridinylmolybdenum scaffolds **207** have been prepared, which were then applied in a novel Brønsted acid-catalyzed [5+2] cycloaddition and served as chiral substrates reacting with a range of electron-deficient alkenes **208**. After the oxidative demetalation by using PDC/SiO₂, a variety of 2-substituted oxa- and azabicyclo[3.2.1]octene rings **209** were obtained with complete retention of high enantioselectivities. Moreover, this reaction enabled the formation of four stereogenic centers in one step, as well as the control of both regio- and stereoselectivities.

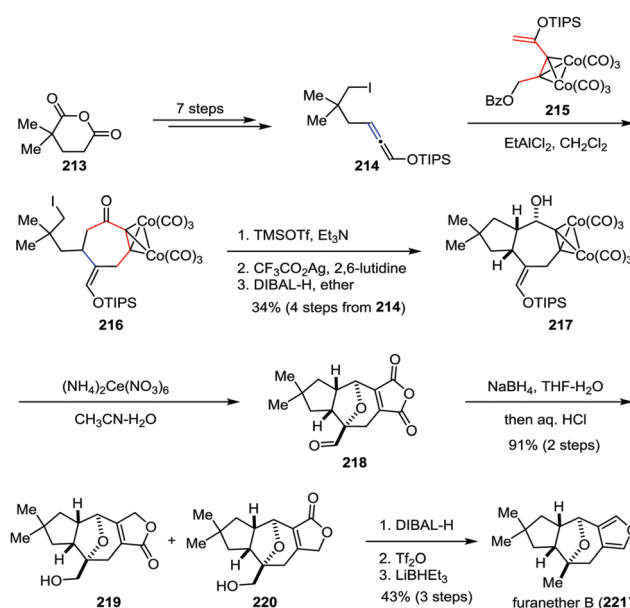
The cycloheptane ring bearing various kinds of substituents is a common skeleton in a number of natural products. Efficient methods have been reported for the construction of these seven-membered carbocycles through [4+3] cycloaddition of dienes or furan derivatives and allylic cationic species.¹⁰¹ However, much less attention was paid to the [5+2] cycloaddition. In 2014, Tanino and co-workers reported a [5+2] cycloaddition of dicobalt acetylene complexes **210** and enol silyl ethers **211** (Scheme 40).¹⁰² This reaction proceeded stepwisely through intermolecular addition of cationic species A with an enol silyl ether followed by the intramolecular cyclization of silyloxonium ion B in the presence of EtAlCl₂, affording the cycloheptanes **212** in good yields with high stereoselectivities. Further structural analysis revealed that three substituents on the cycloheptane ring of **212a–e** are all *cis* to each other.

6.2 Natural product synthesis

Recently, Tanino and co-workers developed a novel [5+2] cycloaddition reaction between a dicobalt hexacarbonyl propargyl cation species and a silyloxyallene for the formation of functionalized cycloheptanones.¹⁰³ This methodology was subsequently applied as a key step in the total synthesis of furanether B (Scheme 41). Their synthesis commenced with the preparation of allene **214**, which was derived from commercially available



Scheme 40 [5+2] Cycloaddition reactions of dicobalt acetylene complexes with enol silyl ethers by Tanino and co-workers.



Scheme 41 Total synthesis of furanether B by Tanino and co-workers.

2,2-dimethylglutaric anhydride **213** in seven steps. An intermolecular [5+2] cycloaddition reaction between allene **214** and cobalt complex **215** afforded the desired cycloheptanone **216**. After the cyclopentane formation and stereoselective 1,2-reduction of the ketone subunit, bicyclic alcohol **217** was formed in 34% yield over four steps. Upon treatment of **217** with an excess amount of cerium(IV) ammonium nitrate led to the formation of aldehyde **218**. The results indicate that the secondary hydroxy group of the substrate underwent transannular oxidative coupling with the enol silyl ether moiety, which allowed the total synthesis to finish more quickly. NaBH₄ reduction of aldehyde **218** followed by acidic workup gave rise to hydroxy lactone **219** as a mixture with its regioisomer **220** in high yield. Finally, furanether B (**221**) was furnished through further reduction.

7. Conclusions and outlook

This review summarized the recent advances in [5+2] cycloadditions, especially on instructive and fascinating applications in natural product synthesis. The rapid generation of molecular complexity in a relatively concise manner has rendered the [5+2] cycloaddition protocol a highly useful tool, which were highlighted with the latest progress in various reaction intermediates involved, such as oxidopyrylium ylides, oxidopyridinium ylides, perezzone-type intermediates, vinylsubstituted three-membered rings and 5-carbon organometallic complexes. As demonstrated in these examples, the steric effects of the tethered side chains or chiral auxiliaries are vital for the retention of the geometry of the active ions. On the other hand, biomimetic syntheses have proven to be promising protocols for the construction of highly complex fused seven-membered ring skeletons, and the efficiencies on the ODI-[5+2] cycloaddition cascade approach to forge the complex polycyclic core structures have also been demonstrated.

With the continuing attention paid to this area, we believe more effective methods and strategies for the development of new types of [5+2] cycloadditions would certainly emerge and be successfully applied in the total synthesis of more natural products with biological importance.

Conflicts of interest

The authors declare no competing financial interest.

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