Natural Product Syntheses via Carbonylative Cyclizations

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Complete List of Authors:	Ma, Kaiqing; Shanxi University, Martin, Brandon; Purdue University, Department of Chemistry Yin, Xianglin; Purdue University, Department of Chemistry DAI, MINGJI; Purdue University WTHR 465, Department of Chemistry

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Natural Product Syntheses via Carbonylative Cyclizations

Kaiqing Ma,[a,b,c] Brandon S. Martin,[a,c] Xianglin Yin[a,c] and Mingji Dai*[a]

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In this review, we highlight recent examples of natural product total syntheses employing transition metal-mediated/catalyzed carbonylative cyclization strategies to build key ring systems. It mainly covers carbonylative cyclizations for the construction of *O*-heterocycles, *N*-heterocycles and carbocycles including cyclic ketones and phenols. The reaction types include carbonylation of epoxide to β-lactones, carbonylative (macro)lactonization/lactamization, the Semmelhack reaction, tandem hydroformylation-cyclization, the Pauson-Khand reaction, carbonylative C-H activation cyclization, the Stille/Suzuki carbonylation, [n+m+1] carbonylative cycloaddition, the Dötz annulation, and others.

1. Introduction

Transition metal catalyzed reactions such as asymmetric hydrogenations, palladium-catalyzed cross coupling reactions, and olefin metathesis reactions have transformed total synthesis of natural products, discovery and development of lifesaving therapeutics, and many other fields. In this review article, we focus on the application of a series of transition metal-catalyzed/mediated carbonylative cyclization reactions in facilitating total synthesis of complex bioactive natural products. The highlighted carbonylation processes use carbon monoxide as a one-carbon linchpin to rapidly build different ring systems including *O*-heterocycles, *N*-heterocycles, cyclic ketones, and aromatic ring systems. Carbon monoxide is an abundant, cheap and readily available one-carbon chemical stock. Due to its carbene nature, it can coordinate with various transition metals to form carbonyl complexes. It can also undergo migratory insertion into metal-carbon or metal-heteroatom bond to produce acyl-metallo species, which are usually highly reactive and can be intercepted by different nucleophiles to form carbon-carbon or carbon-heteroatom bonds and provide carbonyl-containing products such as ketones, esters, amide, aldehydes, and their derivatives.[1-8] In most of the cases, carbon monoxide gas is used directly in these carbonylation reactions. A variety of user-friendly carbon monoxide surrogates have been developed to avoid the direct use of carbon monoxide gas.[9-11]

[a] *Department of Chemistry, Center for Cancer Research, and Institute for Drug Discovery, Purdue University, West Lafayette, Indiana, 47907, USA. Email: mjdai@purdue.edu. Fax: 001-765-496-2592; Tel: 001-765-496-7898.*
[b] *Modern Research Center for Traditional Chinese Medicine of Shanxi University, No. 92, Wucheng Road, Taiyuan 03006, Shanxi, China.*
[c] *These authors contributed equally to this review article.*

Transition metal-catalyzed carbonylation reactions offer new avenues or complementary ways to access carbonyl containing products. The carbonylative cyclization processes covered here include carbonylation of epoxide to β-lactones, carbonylative (macro)lactonization/lactamization, the Semmelhack reaction, tandem hydroformylation-cyclization, the Pauson-Khand reaction, carbonylative C-H activation cyclization, the Stille/Suzuki carbonylation, [n+m+1] carbonylative cycloaddition, the Dötz annulation, and others. In general, these transformations feature high efficiency in building complex structures, good atom economy, and excellent chemo-, regio- and stereo-selectivity. The carbonyl group derived from carbon monoxide either locates in the ring (*endo*-cyclic carbonylation) or outside of the ring (*exo*-cyclic carbonylation, Fig. 1).

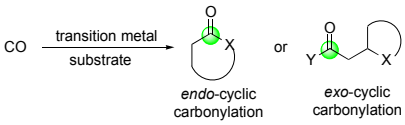

Fig. 1 *Endo*/*exo* carbonylative cyclization

2. Carbonylative *O*-Heterocycle Synthesis

2.1. Epoxide carbonylation to β-lactones and related products

β-Lactones are important structural motifs that prevalently exist in many bioactive natural products. Conventionally, β-lactone syntheses mainly rely on the lactonization of β-hydroxy acid promoted by various activating reagents. Later ketene-aldehyde/ketone [2+2] cycloaddition emerged as a popular method to prepare β-lactones[12] and the related enantioselective [2+2] cycloaddition versions have been developed as well to access β-lactones in optically active form.[13] Due to the intrinsic ring strain, epoxides have demonstrated high reactivity and can undergo various transformations. Many epoxidation methods especially enantioselective ones such as the Sharpless epoxidation, Jacobsen-Katsuki epoxidation, Shi epoxidation, and the recent organocatalytic epoxidation have been developed to synthesize epoxides.[14] Structurally, epoxides are one carbonyl group away from β-lactones. Direct carbon monoxide insertion to epoxide has become an important strategy to access β-lactones.

A pioneering example of epoxide carbonylation in β-lactone total synthesis was reported by Ley and co-workers in 1991 (Fig. 2).[15] Towards their synthesis of valilactone (**4**), they developed a method to convert epoxide **1** derived from directed epoxidation of a homoallylic alcohol to β-lactone **3** with diiron nonacarbonyl complex ($Fe_2(CO)_9$) followed by oxidation lactonization. The initial carbonylation products were isolated as a mixture of *exo* and *endo* complexes in 4:1 ratio. Oxidation of the major *exo* complex **2** with ceric ammonium nitrate (CAN) gave the desired β-lactone in 26% yield. The oxidation yield is higher when the secondary alcohol was protected as an acetate (50% yield). β-Lactone **3** was then advanced to valilactone in two steps.

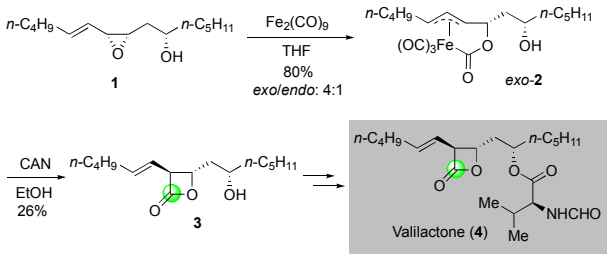

Fig. 2 The Ley synthesis of valilactone (1991)

There are a few drawbacks associated with the diiron nonacarbonyl-promoted epoxide carbonylation. It requires stoichiometric amount of the diiron nonacarbonyl complex and an additional low yielding oxidation step. Coates and co-workers came up with a remarkable solution to these problems by using bimetallic [Lewis acid]$^+$[$Co(CO)_4$]$^-$ catalysts (Fig. 3, **5**→**6**).[16,17] The Lewis-acidic cation of the ion pair would coordinate and activate the epoxide to facilitate a backside attack of the activated epoxide by [$Co(CO)_4$]$^-$. The regioselectivity of the epoxide ring opening can be controlled by the steric and electronic properties of the epoxide. The resulting alkylcobalt intermediate (**8**) would undergo carbon monoxide insertion to generate acyl-species **9**. Lactonization of **9** would complete the catalytic cycle to provide β-Lactone **6** and regenerate the catalyst for the next catalytic cycle. This catalytic epoxide carbonylation reaction provides a direct route to β-lactones from epoxides and has been broadly used in polymer synthesis and natural product total synthesis.

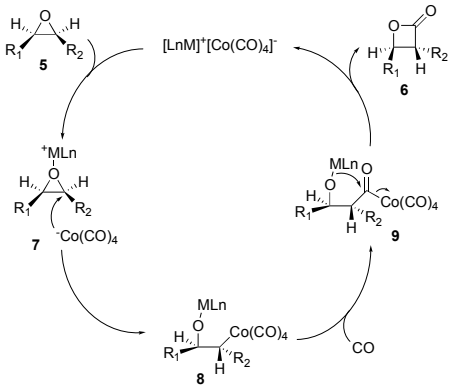

Fig. 3 Bimetallic [Lewis acid]$^+$[$Co(CO)_4$]$^-$-catalyzed carbonylative β-lactone synthesis from epoxide

Oxetanocin (OXT-A, **15**, Fig. 4) is a natural product with an unusual nucleoside-substituted oxetanosyl sugar and has shown potent anti HSV-1, HSV-2, HCMV, and HIV-1 activity. In searching for analogues with improved function, Howell and co-workers reported the first synthesis of *psico*-oxetanocin analog 1′-fluoromethyl-OXT-A, **14**.[18] Their synthesis features the cobalt-catalyzed carbonylation of symmetrical epoxide **10** to β-lactone **11** in 63% yield by using 1 mol% of the aluminium-cobalt ion pair [ClTPPAl][$Co(CO)_4$]. The β-lactone product was then converted to methyleneoxetane **12** via a Petasis olefination. Selectfluor-promoted nucleobase installation

gave a mixture of regio- and stereoisomers with a total yield of 76% and 26% yield of **13**, which was then converted to **14**.

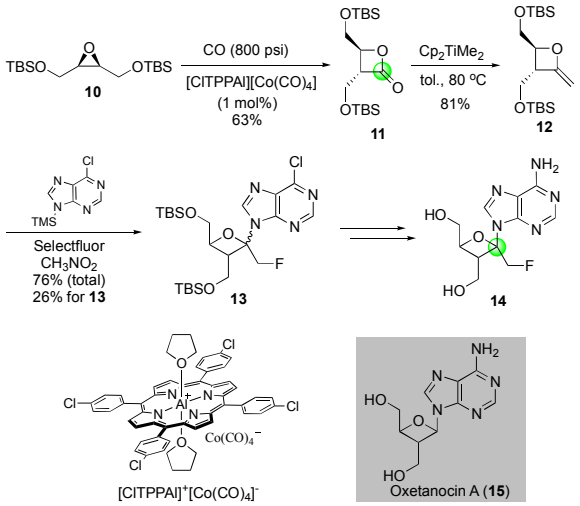

Fig. 4 The Howell synthesis of *psico*-nucleosides (2011)

The same cobalt-catalyzed carbonylation of epoxide was applied by O'Doherty and co-workers to synthesize fridamycin E[19] and tetrahydrolipstatin[20] (Fig. 5). For the synthesis of fridamycin E, epoxide **16** derived from a sequence of Sharpless dihydroxylation and epoxide formation was treated with $[ClTPPAl]^+[Co(CO)_4]^-$ catalyst developed in the Coates group under 900 psi of carbon monoxide in THF at 40 °C to afford β-lactone **17** in 70% yield (Fig. 5A). Interestingly, when the reaction temperature reached to 60 °C, a significant amount of alkene byproduct was observed via a deoxygenation process. After cleavage of the β-lactone ring and removal of the benzyl protecting group, fridamycin E (**18**) was formed. For the tetrahydrolipstatin synthesis (Fig. 5B), O'Doherty and co-workers evaluated both an early-stage and a late-stage (last step, **19**→**20**) installation of the required β-lactone. Both cases worked smoothly and demonstrated the functional group compatibility and reliability of the carbonylative β-lactone synthesis in complex settings. In the end, tetrahydrolipstatin was prepared in an impressive ten steps and 31% overall yield.

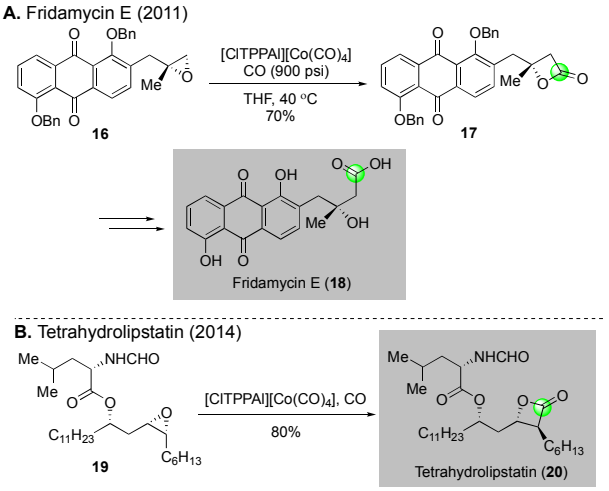

Fig. 5 The O'Doherty synthesis of fridamycin E (2011) and tetrahydrolipstatin (2014)

In a related study, Fürstner and co-workers used a $Co_2(CO)_8$-catalyzed carbonylative epoxide ring opening developed by the Jacobsen group[21] to synthesize amide **22** (Fig. 6), which was one of key building blocks for diyne intermediate **23** for an alkyne ring closing metathesis to close the macrocycle (**23**→**24**). The carbon from carbon monoxide eventually served as C21 of the putative structure of anticancer mandelalide A (**25**).[22] Notably, this synthesis also led to the structural revision of mandelalide A.

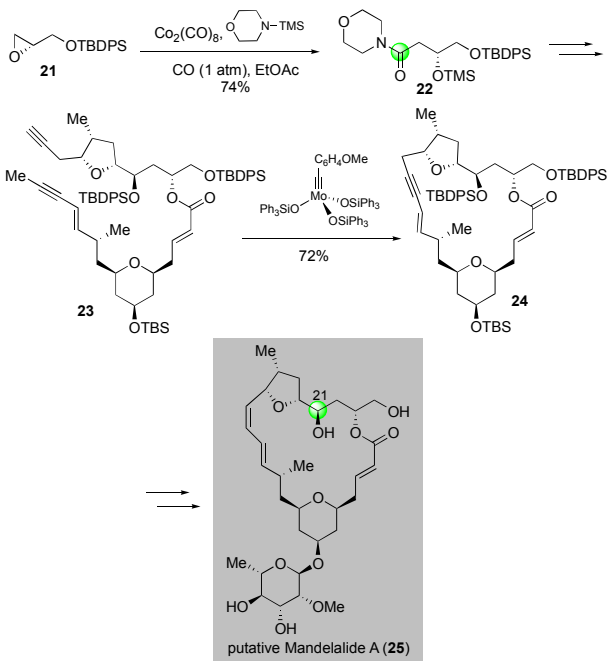

Fig. 6 The Fürstner synthesis of the putative structure of mandelalide A (2015)

2.2. 5 or 6-Membered lactone formation

2.2.1. Palladium-catalyzed carbonylative lactonization

The original palladium-catalyzed Heck carbonylation[23-25] uses an alcohol, amine, or hydride nucleophile to trap the in situ generated acylpalladium species intermolecularly to form an ester, amide, or aldehyde product, respectively.[26-32] When the alcohol or amine nucleophile is tethered in the same molecule, an intramolecular Heck carbonylation reaction can lead to the formation of a lactone or lactam product. Unlike many other lactone synthesis methods, this strategy does not involve the pre-installation of the carboxylate group and offers an efficient way to make lactones. An early classic example is shown in Fig. 7.[33] In this case, Marshall and co-workers used a palladium-catalyzed carbonylation of vinyliodide **30** to install the 5-membered lactone of aristolactone **31**. The vinyliodide **30** was derived from strained cyclic alkyne **29** via a Red-Al reduction followed by iodination. To access cyclic alkyne **29**, Marshall and co-workers developed an impressive chiral amine base (**27**)-promoted transannular [2,3]-sigmatropic rearrangement to build the two adjacent stereocenters and produce **28** in 78% yield and 73% ee. The undesired stereochemistry of the newl formed secondary alcohol was inverted via a Mitsunobu process to afford **29**.

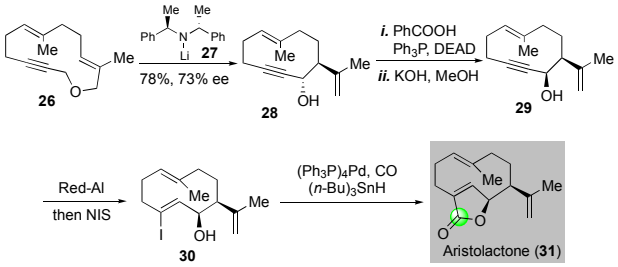

Fig. 7 The Marshall synthesis of aristolactone (1987)

The pumiliotoxin alkaloids were isolated from the skin extracts of the Panamanian poison frogs and have attracted plenty of synthetic attention.[34] In their efforts toward the pumiliotoxin A (**37**, Fig. 8) and related analogues, Kibayashi and co-workers employed a similar palladium-catalyzed carbonylative lactonization to convert vinyliodide **35** to lactone **36**, which was later rearranged to pumiliotoxin A with a 5,6-fused ring system.[35] Vinyliodide **35** was prepared in three steps from proline derivative **32**. The first step involves a $HfCl_4$-catalyzed propargylation of **32** with allenylsilane **33** followed by Boc-protection. A combination of radical stannation with Ph_3SnH and Et_3B and iodination with NIS was able to convert alkyne **34** to vinyliodide **35**.

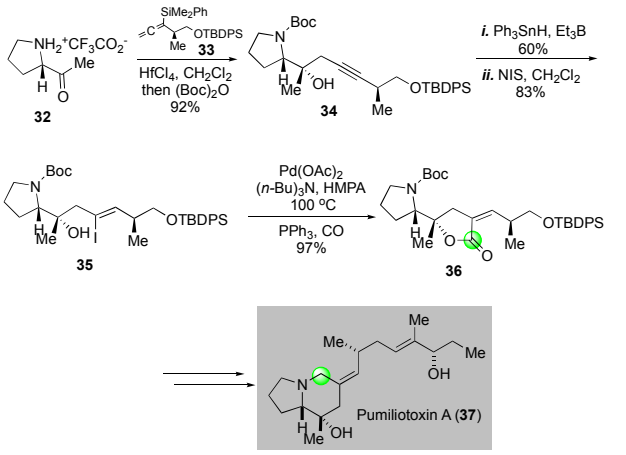

Fig. 8 The Kibayashi synthesis of pumiliotoxin A (2002)

Since their isolation, the phomoidride molecules, due to their promising cholesterol-lowering and anticancer activity and unique structural scaffold, have attracted a significant amount of synthetic attention and inspired numerous synthetic methods and strategies toward their syntheses.[36,37] In their synthetic efforts toward the phomoidride B (CP-263,114, Fig. 9, **41**), Leighton and co-workers orchestrated an impressive tandem sequence of ketal formation, palladium-catalyzed carbonylative lactone formation, and [3,3]-sigmatropic rearrangement to convert vinyltriflate **38** to **40** containing the core structure of phomoidride B via spirolactone intermediate **39**.[38]

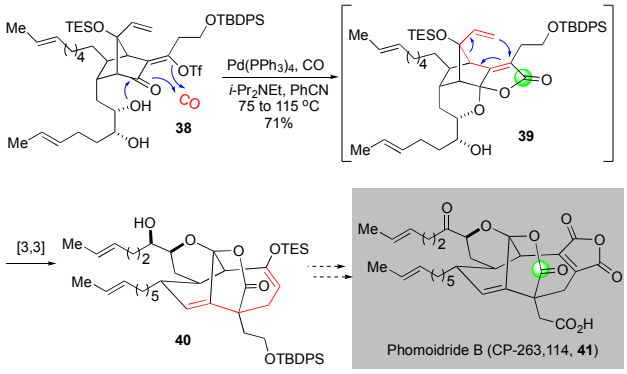

Fig. 9 The Leighton synthesis toward phomoidride B (2003)

In Larock's plicadin synthesis (Fig. 10),[39] an iodine-promoted benzofuran synthesis was used to produce 3-iodobenzofuran **43** from **42** for a palladium-catalyzed carbonylation, which afforded plicadin (**44**) in 57% yield after removal of the tosyl group with TBAF. This strategy also led to the total synthesis of coumestan and coumestrol, and their analogues.

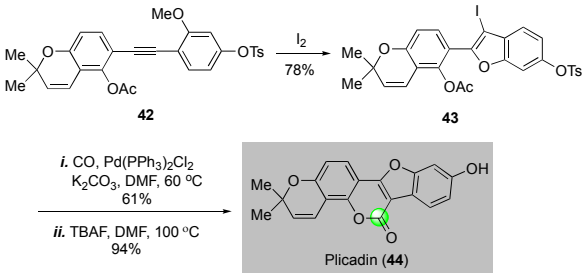

Fig. 10 The Larock synthesis of plicadin (2005)

Hypoestoxide (**49**, Fig. 11), isolated from the tropical shrub *hypoestes rosea*, has demonstrated a broad range of biological profiles including anticancer activity by inhibiting angiogenesis, antimalarial, and anti-inflammatory activity. Structurally, it contains a challenging rigid "inside-outside" bicyclo[9.3.1] ring system. In their efforts toward the total synthesis of hypoestoxide, Njardarson and co-workers used a palladium-catalyzed carbonylative lactonization to convert vinyltriflate **45** to bicyclic lactone **46**.[40] After DIBAL-H reduction of lactone **46** to a diol, they used a titanium-templated relay ring closing metathesis to building the "inside-outside" bicyclo[9.3.1]pentadecane ring system and eventually reached a diene intermediate (**48**) which is one step away from the atropisomer (**49a**) of hypoestoxide. However selectively oxidative cleavage of the extra methylene group of **48** was unsuccessful. In this case, the carbon atom from carbon monoxide could potentially serve as the required *exo*-methylene carbon of **49** or **49a**.

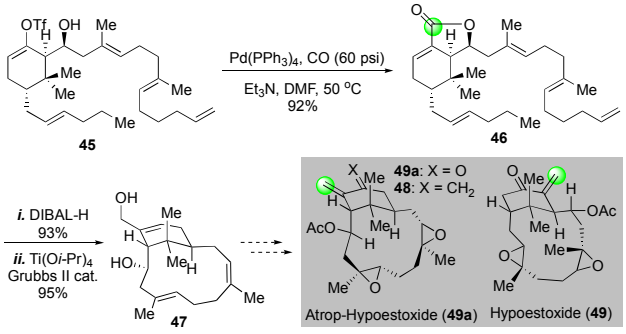

Fig. 11 The Njardarson synthesis toward hypoestoxide (2008)

In 2009, Willis and co-workers reported a palladium-catalyzed intramolecular carbonylation reaction of aryl halides and enolate nucleophiles to build isocoumarins (Fig. 12).[41] Unlike the previous cases which used alcohol or phenol nucleophiles to trap the acyl palladium species, their work employed an in situ generated enolate. A 2-step synthesis of thunberginol A (**51**) was achieved from ketone **50**, which was prepared by a palladium-catalyzed α-arylation.

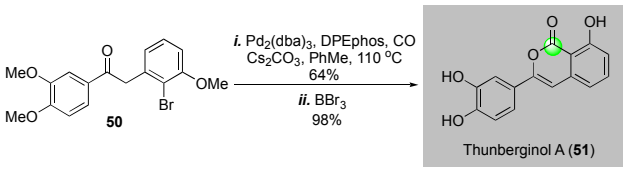

Fig. 12 The Willis synthesis of thunberginol A (2009)

Architecturally unique and complex natural product salvileucalin B (**57**) was isolated by Takeya and co-workers.[42] This molecule features an unusually stable norcaradiene embedded in a polycyclic cage-like skeleton and two five-membered lactone rings. Salvileucalin B also demonstrated promising anti cancer cell proliferation activity. Synthetically, Reisman and co-workers used a palladium-catalyzed carbonylative lactonization to convert vinyltriflate **55** to lactone **56** (Fig. 13).[43] The *iso*-dihydrofuran ring of **56** was then oxidized to the second required lactone by chromium trioxide-3,5-dimethylpyrazole complex to complete the first total synthesis of salvileucalin B. A significant amount of byproduct **58** was also obtained under the oxidation conditions. Vinyltriflate **55** was efficiently synthesized from triyne intermediate **52** via steps including a ruthenium-catalyzed [2+2+2] cycloisomerization to build the aromatic ring and a copper-catalyzed intramolecular [2+1] cycloaddition of α-diazo-β-ketonitrile **53** to provide the norcaradiene moiety. Additionally, in their synthetic efforts toward salvileucalin B, Taber and co-worker used a similar carbonylative lactonization to build the corresponding lactone.[44]

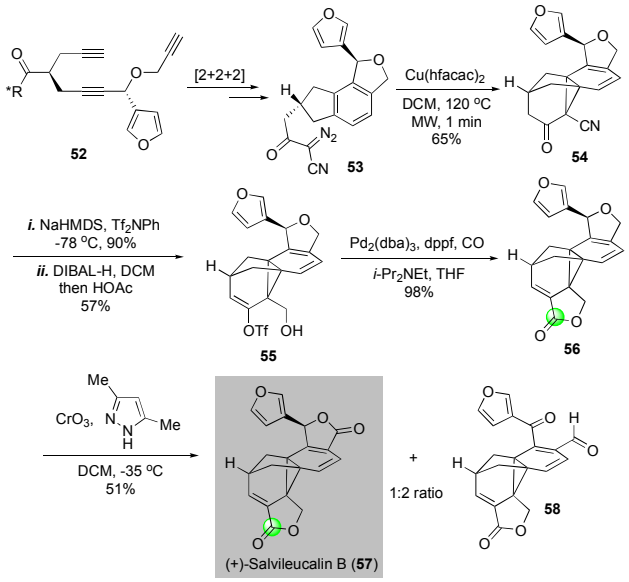

Fig. 13 The Reisman synthesis of salvileucalin B (2010)

In their total synthesis of two diterpenoids amphilectolide (**62**) and sandresolide B (**63**) and two norditerpenoids caribenols A and B (**64**, **65**, Fig. 14),[45,46] Trauner and co-workers used a palladium-catalyzed carbonylative lactonization to convert vinyltriflate **59** to bicyclic lactone **60**. Notably, in this case, the combination of H_2SO_4 and

HCO_2H can be used as effective carbon monoxide gas surrogate. They then transformed the lactone moiety of **60** into furan of **61** via a partial reduction of the lactone to lactol and dehydration. By taking advantage of the reactions of the electron-rich furan such as Friedel-Crafts alkylation/acylation and chiral amine-catalyzed radical cation cyclization, Trauner and co-workers were able to complete the total synthesis of the aforementioned natural molecules.

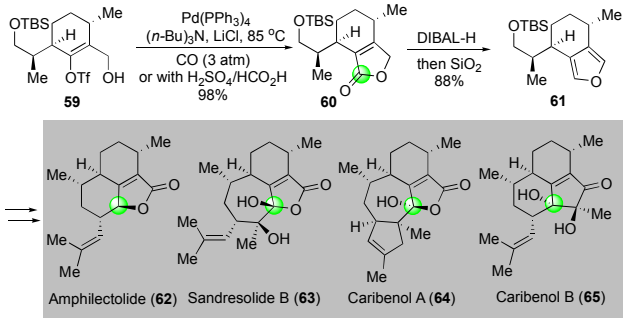

Fig. 14 The Trauner syntheses of amphilectolide, sandresolide B, caribenol A and B (2014&2017)

Leucosceptroids and norleucosceptroids are complex natural products featuring a 5-6-5 tricyclic skeleton (Fig. 15). Magauer and Hugelshofer developed an elegant approach towards these natural products[47,48] by employing a palladium-catalyzed carbonylative lactonization followed by a Hauser-Kraus annulation to rapidly build intermediate **69** with the 5-6-5 tricyclic core from vinyltriflate **66**. Key intermediate **69** was then advanced to a few (nor)leucosceptroid natural products. Again, in this case, the combination of H_2SO_4 and HCO_2H was used as effective carbon monoxide gas surrogate.

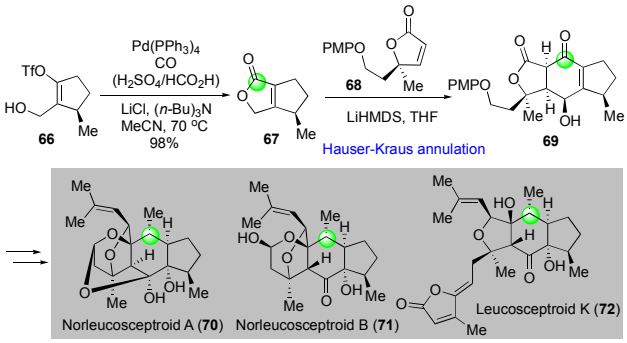

Fig. 15 The Magauer synthesis of (nor)leucosceptroids (2014)

In addition to the above highlighted cases, there are a significant amount of other natural product total syntheses involving the use of palladium-catalyzed carbonylative lactonization of the corresponding aryl/vinyl triflates or halides to build the key ring systems. Some of these natural products are listed in Fig. 16.[49-53]

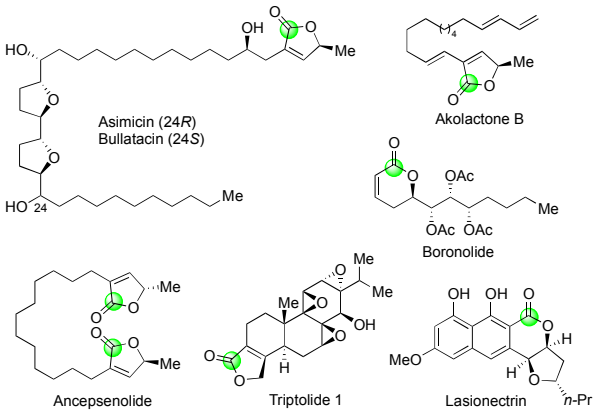

Fig. 16 Selected natural products synthesized via palladium-catalyzed carbonylative lactonizations

While the palladium-catalyzed carbonylative lactonizations of aryl/vinyl triflates or halides with intramolecularly tethered alcohols are common ways to build 5- or 6-membered lactones, several other palladium-catalyzed carbonylations can be used as well. For example, Davies and co-workers used an interesting palladium-catalyzed decarboxylation/carbonylation of 1,3-dioxan-2-one **73** to synthesize γ-butyrolactone **74**, which was then advanced to pilocarpine (**75**) and isopilocarpine (**76**) after PtO_2-catalyzed hydrogenation (Fig. 17).[54] Podlech and co-workers coupled a palladium-catalyzed carbonylation of propargylic mesylate **77** with a following iodolactonization of the resulting acid **78** to synthesize iodolactone **79**, a key intermediate for their altenuic acid III synthesis (Fig. 18).[55]

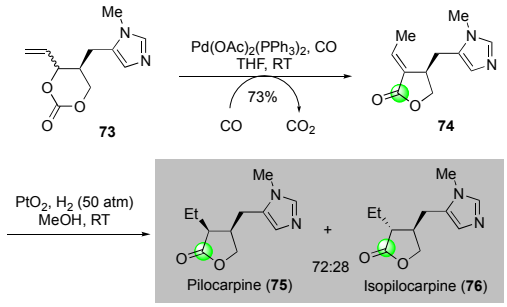

Fig. 17 The Davies synthesis of pilocarpine (2009)

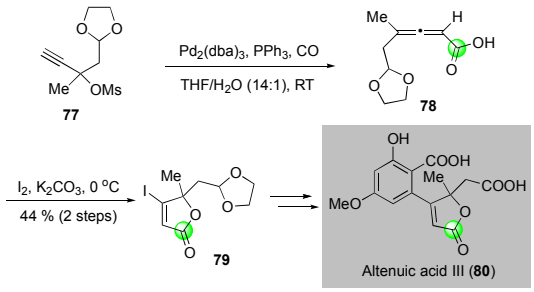

Fig. 18 The Podlech synthesis of altenuic Acid III (2013)

Recently carbonylative C-H functionalizations have emerged as powerful methods for synthesizing carbonyl products.[56-61] Direct C-H functionalization eliminates synthetic steps involved in pre-installation of the corresponding triflates, halides, or their equivalents. Carbonylative C-H functionalizations offer efficient ways to synthesize γ-butyrolactones and δ-valerolactones, but have not been frequently employed in natural product total synthesis. Hong and co-workers demonstrated the efficiency of such strategy in their total synthesis of frutinone A (Fig. 19), a potent inhibitor of the CYP1A2 enzyme. In their synthesis, an intermolecular oxidative C-H activation/Suzuki cross coupling was used to synthesize **83** from **81** and **82**. After removal of the methyl group with BBr_3, a phenol-directed C-H activation followed by carbonylative lactonization gave frutinone A (**84**) in only three steps.[62]

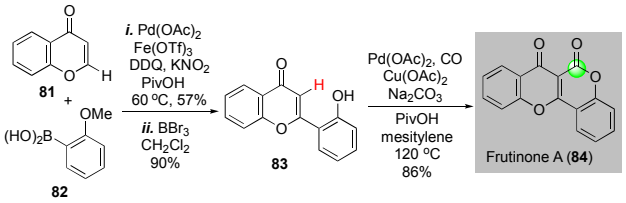

Fig. 19 The Hong synthesis of frutinone A (2015)

In addition to monocyclic lactones, palladium-catalyzed carbonylative lactonization can be used to synthesize spirocyclic ring systems. Dai, Waymouth and co-workers recently developed a tandem oxidative catalytic carbonylation reaction to convert hydroxycyclopropanols (cf. **86**, Fig. 20),[63] which are readily available from the corresponding lactones via the Kulinkovich protocol, to oxaspirolactones (cf. **89**, **90**) in one step. The monocationic dimeric $[Pd(neoc)(OAc)]_2(OTf)_2$ complex developed in the Waymouth group was approved to be an optimal catalyst for this transformation. The catalytic cycle was proposed to go through a palladium(II)-catalyzed β-carbon elimination to cleave the less substituted Walsh bond of cyclopropanol **86** and form palladium-homoenolate **87**. Spiroketal formation followed by carbonylative lactonization gave oxaspirolactones **89** and **90** as a mixture of diastereomers and a palladium(0) catalyst. Oxidation of the latter with benzoqinone regenerated the palladium(II) catalyst and completed the catalytic cycle. The effectiveness of this method was demonstrated in their short total syntheses of α-levantanolide (**89**) and α-levantenolide (**91**).

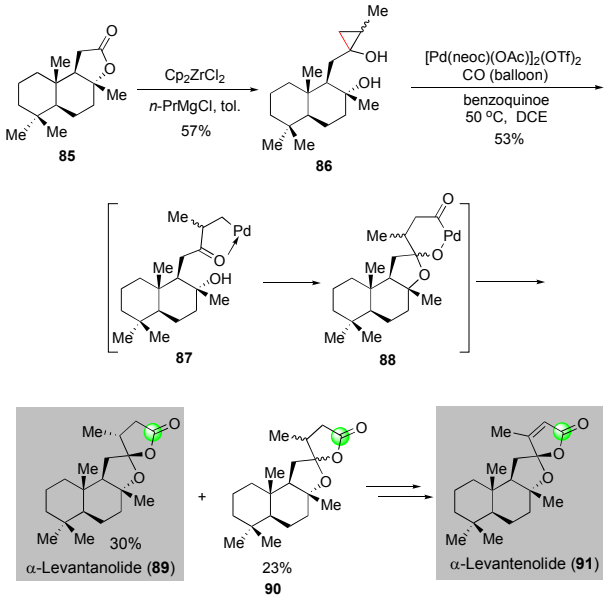

Fig. 20 The Dai/Waymouth synthesis of levanta(e)nolide-2016

2.2.2. Intramolecular Reppe carbonylation of allenes

Reppe carbonylation, originally discovered in 1953 is a three-component process to covert unsaturated hydrocarbons such as alkenes and alkynes into acids, esters, or anhydrides via a hydrocarbonylation process catalyzed by various transition metal complexes particularly the corresponding carbonyl complexes (Fig. 21A).[64] The commonly used nucleophiles to intercept the in situ generated acylmetallo species are water, alcohol and acid. In 2000, Takahashi and co-workers reported a modified Reppe carbonylation by using allenyl alcohols (cf. **92**, Fig. 21B) as substrates.[65] Under 10 atm of carbon monoxide, they were able to covert a variety of allenyl alcohols into γ-butenolides in high yields with $Ru_3(CO)_{12}$ as catalyst. The reaction was proposed to go through a process involving ruthenium-hydride (**92→93**) formation, sequential allene and carbon monoxide migratory insertion (**93→94**), and final lactonization to regenerate the catalyst and produce γ-butenolide **95**.

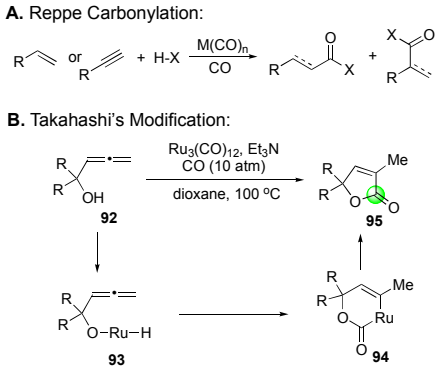

Fig. 21 Reppe carbonylation and Takahashi's modification

The Takahashi's modified Reppe carbonylation provides a rapid approach to prepare γ-butenolides from allenyl alcohols and has been used in a few total syntheses of bioactive natural products (Fig. 22). For example, Bates et al. utilized it to synthesize bicyclic butenolide natural product mintlactone (**98**, Fig. 22A).[66] In their case, the Feringa asymmetric conjugate addition was used to introduce the chiral center bearing the methyl group. This stereocenter then oriented the formation of the secondary alcohol center via a tin(II) chloride-mediated intramolecular 1,2-addition to provide a *cis*-cyclohexyl allene product **97**, which was further advanced to mintlactone with the Takahashi's modified Reppe carbonylation. Hong and co-workers used the Takahashi's modified Reppe carbonylation to build the γ-butyrolactone of stemoamide (**103**, Fig. 22B).[67] Their synthesis features an iron chloride-promoted Speckamp-type cyclization to provide a 3:1 mixture of allenes (**101a** and **101b**) in 86% yield from starting material **99** via acyliminium ion intermediate **100**. The Speckamp-type cyclization favors product **101a** with undesired stereochemistry at the carbon bearing the TBS ether. Interestingly, after releasing the secondary alcohol with tetrabutylammonium fluoride (TBAF), the Takahashi's modified Reppe carbonylation converted both stereoisomers to the same tricyclic γ-butenolide **102** in 81% yield. Apparently, a dynamic kinetic carbonylative lactonization process occurred under the reaction conditions. The undesired secondary alcohol derived from **101a** was epimerized to the desired one via a ketone intermediate and Ru-H complex. Notably, the presence of carbon monoxide was critical for this epimerization as no epimerization was observed when carbon monoxide was excluded from the reaction system. With the γ-butenolide installed, a stereoselective nickel-hydride reduction completed the total synthesis of stemoamide **103**. The third example is from the Jia group, who used the Takahashi's modified Reppe carbonylation to build the γ-butenolide moiety of rugulovasine A by converting allenyl alcohol **104** to **105** (Fig. 22C). A sequential removal of the two Boc-protecting groups completed their total synthesis of rugulovasine A.[68]

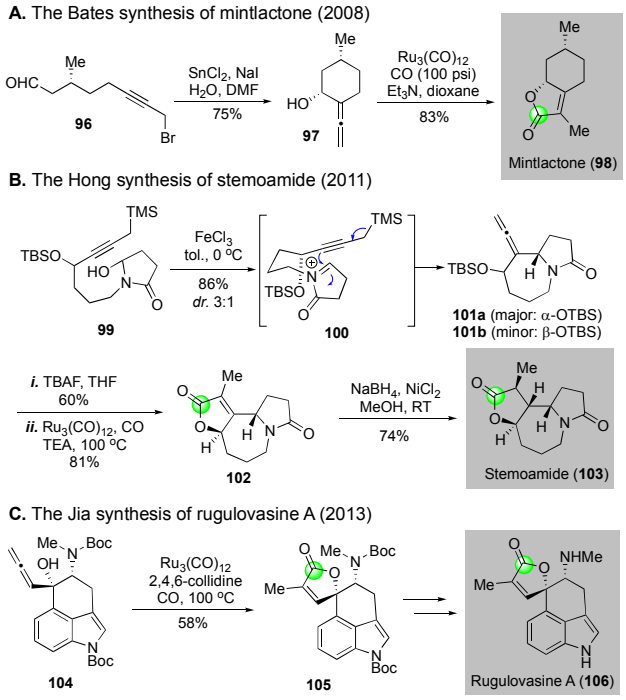

Fig. 22 The Takahashi modified Reppe carbonylation in total synthesis

2.2.3. Hetero-Pauson-Khand reaction

The Pauson-Khand reaction is commonly used to build cyclopentenones (see Section **4.2**). When one of the unsaturated carbon-carbon bonds is replaced with a carbonyl group, the corresponding hetero-Pauson-Khand reaction can result in γ-butyrolactone or γ-butenolide (Fig. 23, **107**→**108**). The pioneering discovery of this type of hetero-Pauson-Khand came from the Buchwald group[69] and the Crowe group[70] independently. Both groups discovered that $Cp_2Ti(PMe_3)_2$ was able to mediate a tandem reductive cyclization-carbonylation reaction of δ,ε-unsaturated carbonyl compounds to yield γ-butyrolactones. Later in 1998, Murai and co-workers generalized a $Ru_3(CO)_{12}$-catalyzed cyclocarbonylation of yne-aldehydes to synthesize γ-butenolides,[71] which was further expanded to internal alkyne substrates by Adrio and Carretero using $Mo(CO)_3(DMF)_3$ as catalyst at room temperature.[72] Meanwhile, in 2002, Kang and co-workers developed an efficient $Ru_3(CO)_{12}$-catalyzed synthesis of α-methylene-γ-butyrolactones from allenyl aldehydes or ketones.[73]

These hetero-Pauson-Khand reactions are highly effective in building γ-butyrolactones or γ-butenolides and have been applied in total synthesis. For example, Zhai and co-workers utilized the conditions developed by Adrio and Carretero to convert yne-aldehyde **109** derived from (-)-citronellol to mintlactone (ent-**98**) in just one step (Fig. 23A).[74] A couple of years later, the same group utilized this hetero-Pauson-Khand strategy to complete a total synthesis of merrilactone A (Fig. 23B).[75] In this case, they were able

to convert yne-aldehyde **110** to tricyclic γ-butenolide in 69% by using the same $Mo(CO)_3(DMF)_3$ catalyst. A following vinylogous Mukaiyama-Michael addition to methylvinylketone gave rise to ketone **112**, which then underwent SmI_2-mediated reductive carbonyl-alkene cyclization to provide tetracyclic intermediate **113**. From **113**, merrilactone A total synthesis was achieved in five steps featuring a homo-Payne rearrangement to build the oxetane ring. In 2017, the hetero-Pauson-Khand strategy was utilized again by Zhai and co-workers for their total synthesis of aplykurodinone-1 (Fig. 23C).[76] A $Mo(CO)_6$-catalyzed hetero-Pauson-Khand reaction enabled a rapid construction of tricyclic γ-butenolide **116** from yne-aldehyde **115**. The former served as a key intermediate in their aplykurodinone-1 total synthesis.

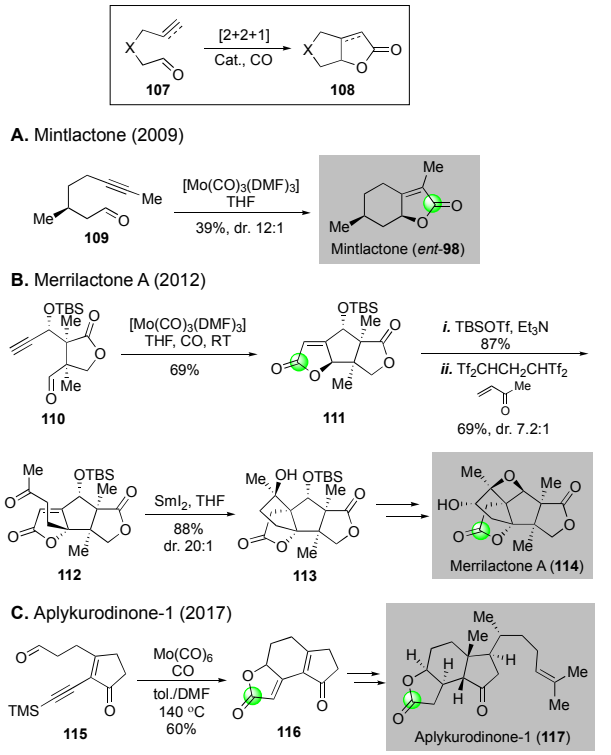

Fig. 23 The Zhai syntheses of mintlactone, merrilactone A, and aplykurodinone-1

In 2015, Shenvi and co-workers reported a remarkable eight-step gram-scale synthesis of jiadifenolide (Fig. 24).[77] Their synthesis features a hetero-Pauson-Khand reaction to convert yne-aldehyde **118** to bicyclic γ-butenolide **119** in the presence of $Mo(CO)_6$ and tetra-*n*-butylammonium bromide. Aldehyde **118** was derived from (+)-citronellal in two steps. They then used a highly convergent and efficient tandem intermolecular Michael addition and intramolecular Michael addition to unite **119** and **120** and form ketolactone **121**, which contains the entire carbon skeleton of jiadifenolide, in a single step in 70% yield with 20:1 diastereoselectivity. After an oxidative α-hydroxylation with *m*-CPBA and stereoselective ketone reduction, advanced intermediate **122** was obtained, which was then converted to jiadifenolide via a sequence of α-bromolactone formation with LDA/CBr_4 and α-hydroxylation with the Davis' oxaziridine. Later in 2017, Shenvi and co-workers successfully converted ketolactone **121** to 11-*O*-debenzoyltashironin (**126**, Fig. 24).[78] This synthesis involves a sequence of α-methylation of ketolactone, hydrolysis of the lactone, and acid-promoted decarboxylation to remove the extra carboxylate and convert **121** to **124**. The latter was then advanced to **125** with a cyclopentene ring. Mukaiyama hydration via a hydrogen atom transfer process afforded an intermediate containing a *trans*-hydrindane ring system with an angular hydroxyl group, which was then rearranged to 11-*O*-debenzoyltashironin with the addition of *p*-toluenesulfonic acid.

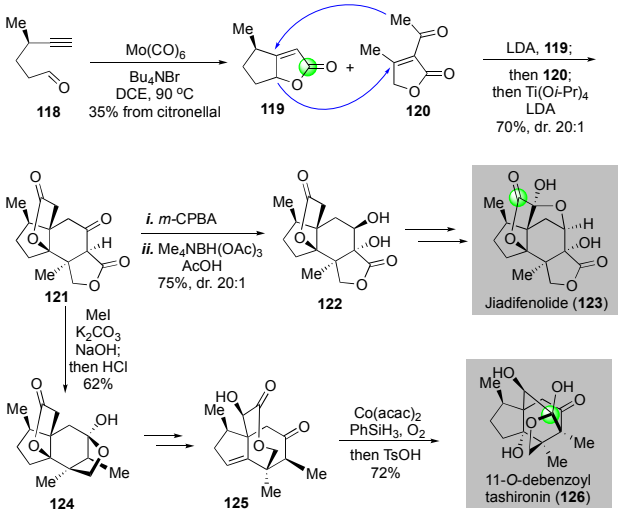

Fig. 24 The Shenvi syntheses of Jiadifenolide (2015) and 11-*O*-debenzoyltashironin (2017)

2.3. THP and THF ring formation

2.3.1. The Semmelhack reaction

In 1984, Semmelhack and Bodurow reported a palladium-catalyzed intramolecular alkoxypalladation-carbonylation of alkenes (**127**) to synthesize tetrahydropyran (THP) or tetrahydrofuran (THF) containing carbonyl products (**130**, **131**).[79,80] The reaction initiates with a Pd(II)-catalyzed oxypalladation of **127** to generate alkyl-palladium **128**, which then undergoes a carbon monoxide migratory insertion to form acyl-palladium **129**. When an external alcohol nucleophile is used to trap the in situ generated acyl-palladium **129**, the ester product **130** can be formed. If the alcohol is tethered in the same molecule, a lactonization process then leads to the bicyclic lactone product **131**. The catalytic cycle ends with a Pd(0) catalyst, which can be oxidized to Pd(II) by an external oxidant such as the commonly used $CuCl_2$ and benzoquinone. Due to its high efficiency, mild reaction conditions, and broad functional group tolerance, the Semmelhack reaction has been widely used in complex natural product total synthesis.[81,82] Some recent examples are highlighted below.

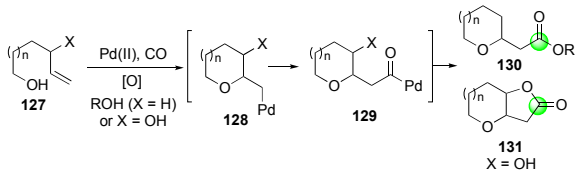

Fig. 25 The Semmelhack reaction

In 2000, Leighton and co-workers developed an elegant total synthesis of leucascandrolide A,[83] a potent anticancer and antifungal natural product isolated from the sponge *Leucascandra caveolata* by Pietra et al. Their synthesis features three carbonylation reactions including one Semmelhack reaction to build the THP ring. As highlighted in Fig. 26, the Leighton synthesis commenced with known alcohol **132**, which underwent $Yb(OTf)_3$-catalyzed oxymercuration with HgClOAc to provide organomercury chloride **133**. Then a rhodium-catalyzed formylation was utilized to convert **133** to aldehyde **134**, which was further advanced to olefin **135** by a Brown asymmetric crotylation. Hydroformylation catalyzed by $Rh(acac)(CO)_2$ followed by hemiacetal formation, the second carbonylation reaction, elaborated **135** to **136** in 89% as a 1:1 mixture of diastereomers. The latter was advanced to **137** in five steps including two allylation reactions to set up the stage for the Semmelhack reaction, which successfully converted **137** to THP ester **138**, a key intermediate for the Leighton total synthesis of leucascandrolide A. Notably, a similar rhodium-catalyzed hydroformylation/hemiacetal formation strategy was employed by Floreancig and co-workers to build the same THP ring in their leucascandrolide A macrolactone synthesis.[84]

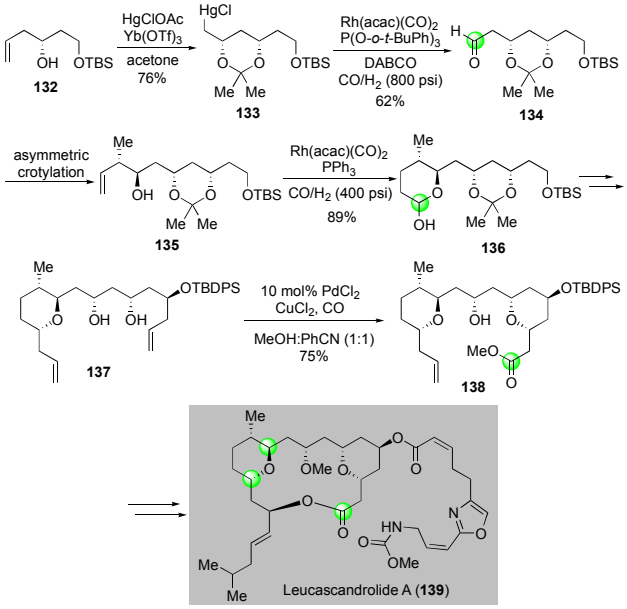

Fig. 26 The Leighton synthesis of leucascandrolide A (2000)

In their synthetic studies toward phorboxazole A, White and co-workers utilized two Semmelhack reactions to install the two of the four THP rings of phorboxazole A (Fig. 27).[85] The first Semmelhack reaction converted **140** to **141** in 86% yield as a single stereoisomer. THP ester **141** was then advanced to **142** for the second Semmelhack reaction to obtain **143**, the C9-C32 segment of phorboxazole A (**144**).

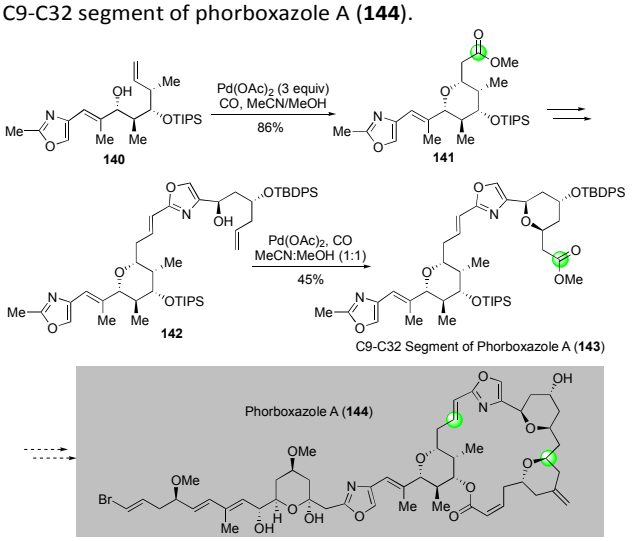

Fig. 27 The White synthetic study toward phorboxazole A (2001)

In 2008, MacMillan and co-workers reported a total synthesis callipeltoside C, which also led to its structural revision (Fig. 28).[86] Similar to leucascandrolide A and phorboxazole A, callipeltoside C and related analogs feature a THP-bridged macrolactone ring system. However, unlike the other two, callipeltoside C contains a hemiactal moiety in the THP ring. The MacMillan synthesis initiated with a proline-catalyzed double diastereo-differentiating aldol reaction between aldehydes **145** and **146** to provide aldehyde **147** in high stereoselectivity (12:1 *anti*/*syn* and >19:1 Felkin/*anti*-Felkin). Subsequent propargyl zinc addition via a Felkin-selective chelation model converted **147** to **148**. They then used the Marshall modified Semmelhack protocol with a terminal alkyne[87] to form THP ester **150** equipped with an acetal in one step in 75% yield. The use of an alkyne substrate offers a direct solution for the required acetal moiety and the process was proposed to go through intermediate **149**. After **150** was advanced to **151**, a chelation-controlled vinyl Grignard addition using **152** gave **153** in 96% yield with 16:1 diastereoselectivity. To close the macrolactone ring, MacMillan and co-workers utilized the Yamaguchi macrolactonization. The aglycone product was then converted to callipeltoside C using the glycosylation procedure developed by Tietze and co-workers.[88]

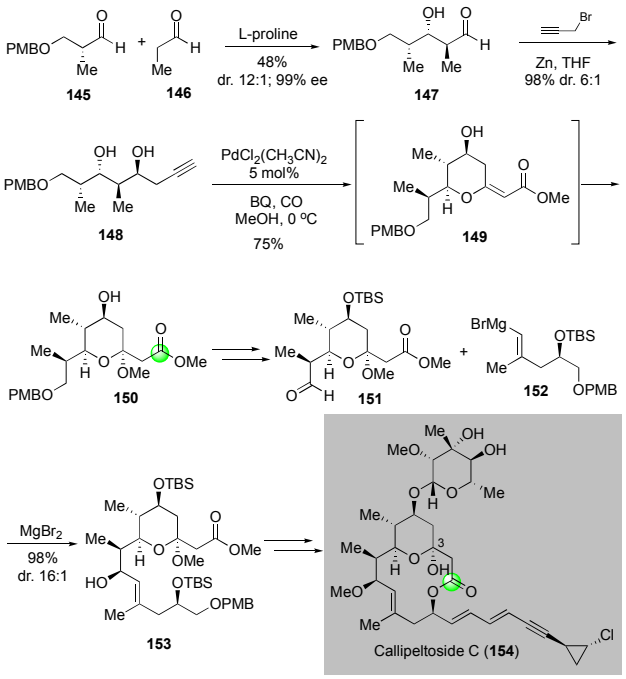

Fig. 28 The MacMillan synthesis of callipeltoside C (2008)

Another application of the Semmelhack reaction in making THP-containing bridged macrolactone came from She and co-workers (Fig. 29).[89] In their total synthesis of potent anticancer natural product neopeltolide, the Semmelhack reaction was used to convert C_2-symmetric diol **156** to THP ester **157** in 83% yield. Diol **156** was synthesized from 1,3-propanediol using the Krische's iridium-catalyzed asymmetric carbonyl allylation method.[90,91] After **157** was converted to diene **158**, ring closing metathesis with the Hoveyda-Grubbs 2nd generation catalyst was employed to form the macrocycle followed by a macrocyclic stereocontrolled hydrogenation to introduce the C9 stereocenter and removal of the benzyl group. The resulting alcohol **159** was then converted to neopeltolide (**160**) by using a Mitsunobu reaction to install the side chain.

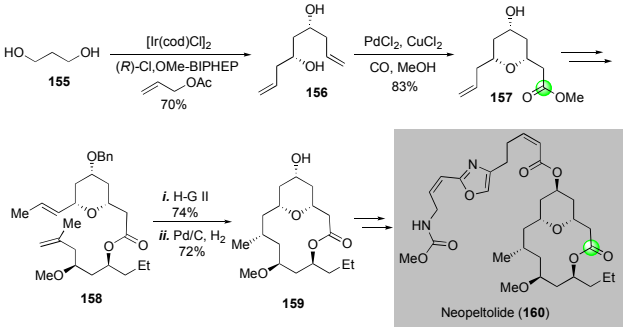

Fig. 29 The She synthesis of neopeltolide (2011)

In addition to alcohols, phenols can be used as nucleophiles for the alkoxypalladation/carbonylation process to synthesize chromane structures. Tietze and co-workers utilized such a strategy toward the total synthesis of 4-dehydroxydiversonol (**163**, Fig. 30).[92] In this case, they have developed an enantioselective version of the Semmelhack reaction by using a combination of $Pd(tfa)_2$ and chiral (*S*,*S*)-Bn-BOXAX ligand **164** to convert phenol **161** to chromane **162** in 80% yield and 96% ee. Compound **162** was then advanced to 4-dehydroxydiversonol in eight steps.

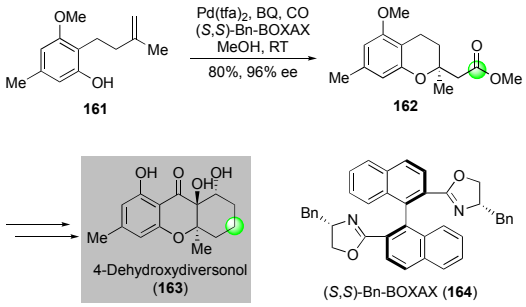

Fig. 30 The Tietze synthesis of 4-dehydroxydiversonol (2008)

The Semmelhack annulation (Fig. 25, **127**→**131**) is an efficient process to build fused bicyclic lactones, which are frequently found in many bioactive natural products. Synthetic chemists have been harnessing its power in making these natural products. For example, Kitching and co-workers have utilized the Semmelhack annulation to install the 5,5-*cis*-fused bicyclic lactone moiety of plakortone D (Fig. 31).[93] In their case, a 63:37 ratio of **167** and **166** were obtained from a 60:40 mixture of diastereomers of **165** by using the standard $PdCl_2/CuCl_2$ catalyst system under carbon monoxide atmosphere in AcOH with NaOAc as base to neutralize the in situ generated HCl.

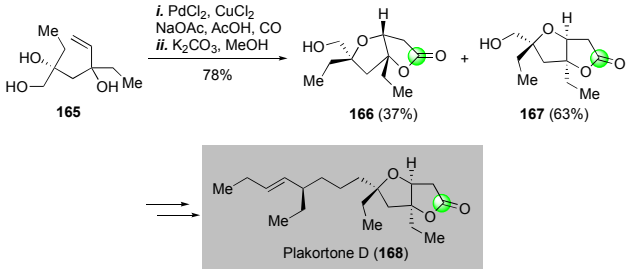

Fig. 31 The Kitching synthesis of plakortone D (2002)

In 2008, Yang and co-workers modified the Semmelhack annulation conditions by introducing tetramethylthiourea (TMTU) as ligand, which was proposed to facilitate carbon monoxide migratory insertion.[94] In addition, propylene oxide was used to quench the in situ generated HCl. Under this modified reaction conditions, they were able to convert diol **169** to bicyclic lactone **170** in 88% yield (Fig. 32).[95] The latter was then advanced to crisamicin A (**171**) via a palladium-thiourea pincer complex-catalyzed homodimerization of the corresponding aryl boronic ester.

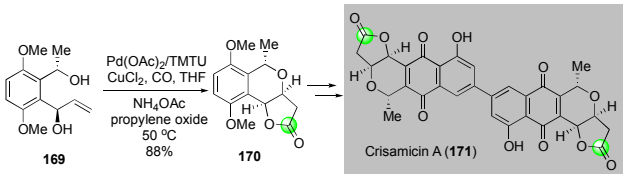

Fig. 32 The Yang synthesis of crisamicin A (2008)

Later in 2011, Tang and co-workers used the Semmelhack annulation as a key step to synthesize kumausallene (**175**), a nonisoprenoid sesquiterpene containing a chiral bromoallene moiety and dioxabicyclo[3.3.0]octane core (Fig. 33).[96] In their case, C_2-symmetric diol **172**, available from acetylacetone in three steps, was successfully converted to bicyclic lactone **173** using the standard Semmelhack carbonylative annulation conditions. After advancing **173** to enyne **174**, they used a biomimetic 1,4-*syn*-bromoetherification promoted by a combination of *N*-bromosuccinimide (NBS) and DMF to form the bromoallene and complete the total synthesis of kumausallene. The use of DMF is critical for the success of the bromoetherification. Notably, McErlean et al. also used a Semmelhack annulation strategy to complete a formal synthesis of kumausallene.[97]

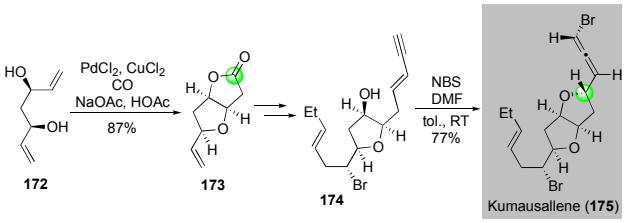

Fig. 33 The Tang synthesis of kumausallene (2011)

In another case from the Yang group, the Semmelhack carbonylative annulation was used at a late stage on a complex polycyclic intermediate to enable the first total synthesis of nortriterpenoid schindilactone A isolated by Sun and co-workers (Fig. 34).[98] Their synthesis features a ring closing metathesis of diene **176** with the Grubbs 2nd generation catalyst to form the 8-membered carbocycle of **177** and a $Co_2(CO)_8$/TMTU-promoted intramolecular Pauson-Khand reaction to convert **178** to cyclopentenone **179**. The use of $MgBr_2$ is important for the ring closing metathesis because it enabled an in situ epimerization of the hemiketal carbon and led to the formation of **177** as a single diastereomer from a mixture of **176**. The Pauson-Khand product **179** was then transformed to **180**, the precursor for the Semmelhack annulation. In this case, Yang et al. developed a unique C_2-symmetric thiourea ligand **182** to facilitate the key carbonylative annulation process[99] and desired product **181** was obtained in 78% yield. In this case, the bulky C_2-symmetric thiourea ligand was proved to be more effective than TMTU for promoting the carbonylation process. The complexity of the substrate and the product highlights the mildness and functional group tolerability of their modified reaction conditions. Compound **181** was then advanced to schindilactone A in six steps.

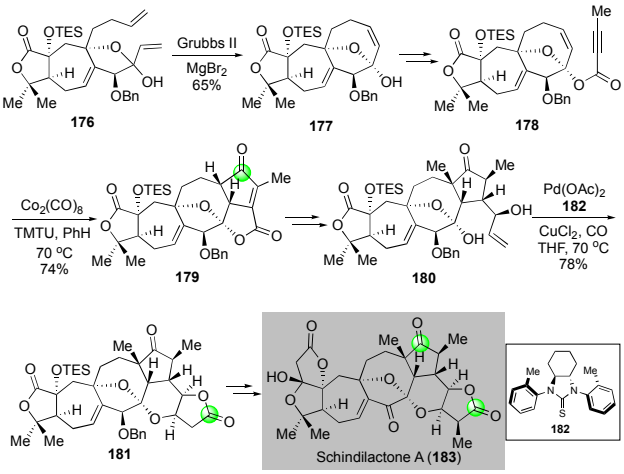

Fig. 34 The Yang synthesis of schindilactone (2011)

Yang's modified alkoxycarbonylative annulation reaction conditions were also utilized in the total syntheses of diterpenoid pallambins by both the Wong group (Fig. 35)[100] and the Carreira group (Fig. 36).[101] The Wong's synthesis of pallambins C and D started with the chiral pool molecule Wieland-Miescher ketone **184**. After converting **184** to **185**, they developed an impressive tandem Grob fragmentation-intramolecular aldol cyclization to obtain bicyclo[3.2.1] enone **187** in 61% yield via intermediate **186**. Enone **187** was then elaborated to **188** for the Semmelhack carbonylative annulation. With the Yang's modified conditions, **188** was transformed to **189** in 78% yield. The total syntheses of pallambins C and D were completed in three more steps: olefination, removal of TBS group, and oxidation of the resulting allylic alcohol.

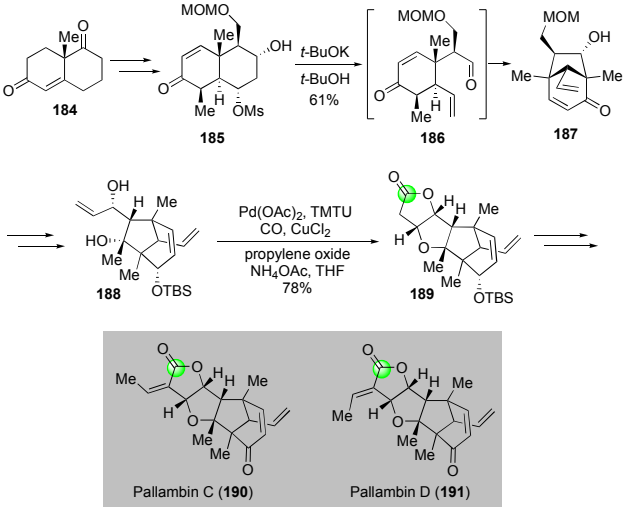

Fig. 35 The Wong synthesis of pallambins C and D (2012)

Structurally, in addition to the same 5-5-5-fused tricyclic ring system

of pallambins C and D, pallambins A and B contain a highly congested tetracyclo[4.4.0^{3,5}.0^{2,8}]decane core (Fig. 36). The Carreira synthesis of pallambins A and B utilized a Diels-Alder reaction between methylacrylate and pentafulvene **193** (generated in situ from **192**) to form **194** and a Simmons-Smith cyclopropanation to install the challenging cyclopropane motif. Product **195** was obtained in 85% yield with greater than 20:1 diastereoselectivity. After **195** was elaborated to methylketone **196**, a sequence of α-diazoketone formation and rhodium-catalyzed intramolecular C-H activation provided **197** in 76% yield, which was then transformed to **198** via vinyltriflate formation followed by Negishi cross coupling with $Zn(Me)_2$ to introduce the methyl group. The resulting trisubstituted olefin then underwent [3+2] cycloaddition with bromonitrile oxide 1,3-dipole derived from the treatment of dibromoformaldoxime with $KHCO_3$ to afford isoxazoline **199** in 91% yield. After converting isoxazoline **199** to aldehyde **200** then to allylic alcohol **201**, Carreira and co-workers used the Yang's modified alkoxycarbonylative annulation procedure to form lactone **202**, which was then converted to pallambins A and B via a sequential aldol reaction and elimination.

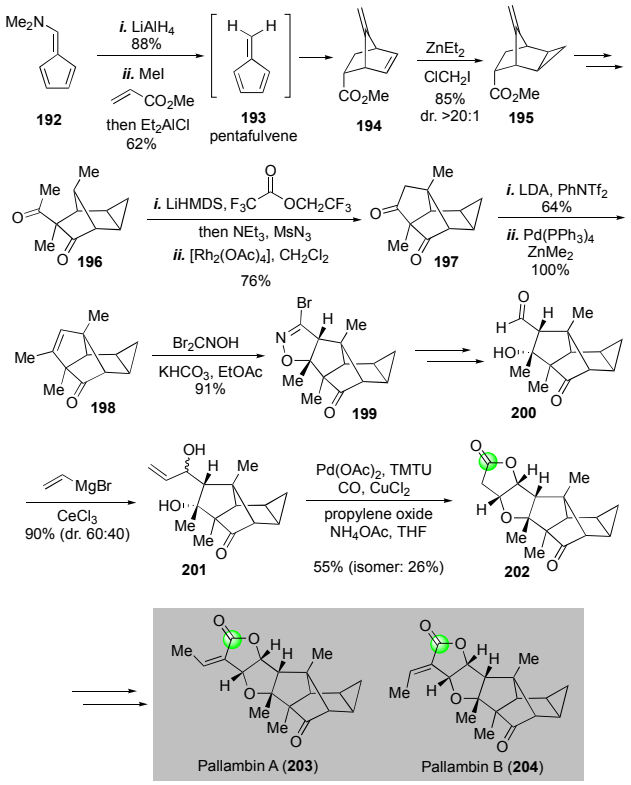

Fig. 36 The Carreira synthesis of pallambins A and B (2015)

2.3.2. Intramolecular carbonylative Heck cyclization

The intramolecular Heck cyclization-carbonylation has also been used to build *O*-heterocycle-containing carbonyl products. The details of the intramolecular Heck cyclization-carbonylation have been studied by the groups of Negishi[102] and Aggarwal.[103] Later, Widenhoefer[104] and Yang[105] expanded this type of transformations to alkenyl indole and aryl alkene substrates, respectively, by employing $CuCl_2$ as oxidant. In 2004, Aggarwal and co-workers utilized the reaction in an asymmetric synthesis of avenaciolide.[106] As known in Fig. 37, bromodiene **205** was converted to **206** in 61% yield via a palladium-catalyzed Heck cyclization-carbonylation. The resulting product was then advanced to avenaciolide via steps involving oxidative cleavage of the *exo*-methylene, reduction of the resulting ketone, lactonization, $RuCl_3$-catalyzed oxidation of the THF ring to a lactone, and α-methylenation.

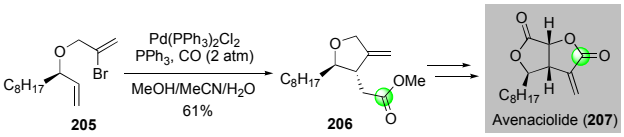

Fig. 37 The Aggarwal synthesis of avenaciolide (2004)

2.3.3. Hydroformylation and hemiacetal formation

Rhodium-catalyzed hydroformylation of olefins has been widely used in organic synthesis in both the academic and industrial settings.[107] As aforementioned both the Leighton group and the Floreancig group have utilized a tandem sequence of hydroformylation and hemiacetal formation to build one key THP ring of leucascandrolide A. Herein, another example from the Krische group is highlighted (Fig. 38).[108] In their total synthesis of zincophorin methyl ester, Krische and co-workers employed a rhodium-catalyzed hydroformylation followed by ketal deprotection and acetal formation to convert olefin **208** to **209** with the key THP ring of zincophorin methyl ester.

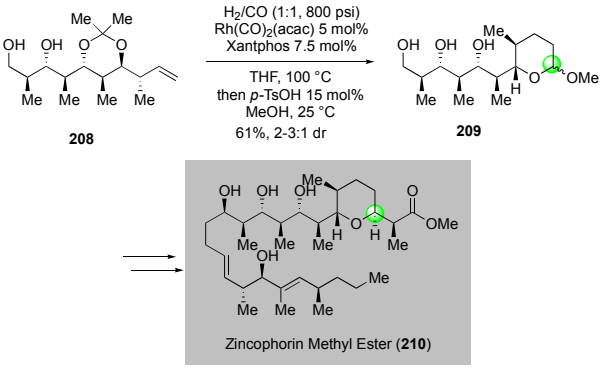

Fig. 38 The Krische synthesis of zincophorin methyl ester (2015)

2.4. Macrolactonization

Over the years, most of the macrolide syntheses have relied on various macrolactonizations of the corresponding seco acids promoted by more than stoichiometric amounts of activating reagents. Catalytic macrolactonization methods have been significantly underexplored.[109] Recently, palladium-catalyzed carbonylative macrolactonization reactions have emerged as an

efficient strategy for building macrolactones. This strategy offers the advantage of not preinstalling the carboxylate group. A highly reactive acylpalladium species is generated in situ; therefore, the use of activating reagents can be avoided. A few examples are highlighted below to showcase the synthetic efficiency of palladium-catalyzed carbonylative macrolactonization in total synthesis of complex natural products.

In 2003, Takahashi and co-workers reported a combinatorial synthesis of a macrosphelide library.[110] Their strategy features two palladium-catalyzed carbonylations on solid polymer support to build the two α,β-unsaturated carboxylates embedded in the 16-membered macrocycle (Fig. 39). They first used a three-component intermolecular carbonylative Heck reaction to synthesize ester **213** from vinyliodide **211**, carbon monoxide, and alcohol **212** bearing a vinylbromide moiety. They then used an intramolecular carbonylative macrolactonization reaction to convert vinylbromide **214** with a remotely tethered secondary alcohol to macrosphelide after acid-cleavage of the polymer support. This strategy enabled the production of a 122-member macrosphelide library for focused anti-cancer study.

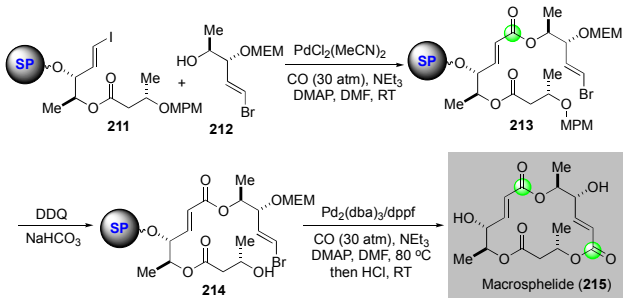

Fig. 39 The Takahashi synthesis of Macrosphelide (2003)

In 2015, Menche and Schmalzbauer reported a concise synthesis of the tricyclic core of salimabromide (Fig. 40).[111] Salimabromide has shown antibiotic activity, but its natural scarcity has hampered further biological study. Menche and Schmalzbauer proposed to synthesize salimabromide from tricyclic intermediate **217**, presumably via a sequence of transannular conjugate addition followed by an elimination. While this transformation hasn't been realized so far, Menche and Schmalzbauer have developed an efficient strategy to synthesize **217** and their synthesis features a palladium-catalyzed chemoselective carbonylative lactonization of **216** to build the desired 8-membered lactone of **217** in 31% yield.

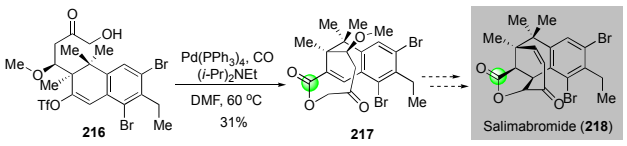

Fig. 40 The Menche synthesis of the salimabromide triyclic core (2015)

Inspired by the original Semmelhack reaction, Dai and co-workers developed a palladium-catalyzed tandem alkoxycarbonylative macrolactonization to build THP/THF-containing bridged macrolactones in one step from relatively simple alkene diols. In their case, the in situ generated acylpalladium species was trapped by a remotely tethered alcohol to form a macrolactone. They further demonstrated the application of this efficient method in their synthesis of 9-demethylneopeltolide.[112] As shown in Fig. 41, alkene diol **219** smoothly underwent the palladium-catalyzed tandem alkoxycarbonylative macrolactonization under the mild reaction conditions to form bridged macrolactone **222** in 58% yield as a single isomer. Notably, the ketal group is critical for the observed high diastereoselectivity. Compound **222** was then advanced to 9-demethylneopeltolide **223** in three steps, namely, removal of the ketal protecting group, reduction of the resulting ketone, and Mitsunobu reaction to introduce the side chain.

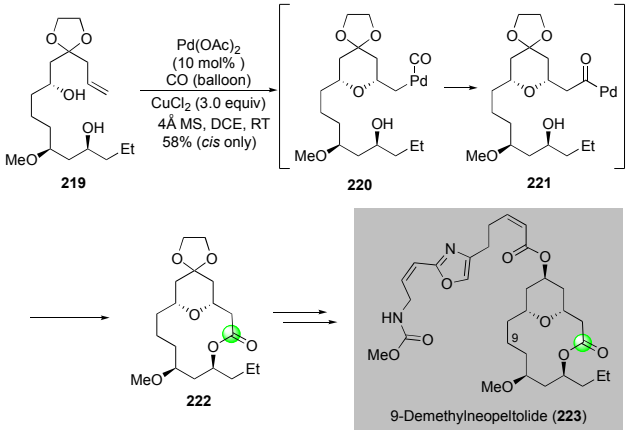

Fig. 41 The Dai synthesis of 9-demethylneopeltolide (2014)

In 2018, Harran and co-workers employed Dai's cascade variant of the Semmelhack reaction to build the key macrolactone of anticancer natural product callyspongiolide.[113] As shown in Fig. 42, readily available building blocks **224** and **225** were joined together by an iridium-catalyzed disastereoselective fragment coupling developed by Krische's group[114,115] to provide homoallylic alcohol **227** as a single diastereomer. Compound **227** was then advanced to ketal **228** in five steps. Harran et al. then used an oxidative fragmentation developed by Schreiber and co-workers[116] to convert **228** to **230**. This process initiated with perhemiketal **229** derived from treating **228** with acid and hydrogen peroxide (H_2O_2). Perhemiketal **229** then underwent a smooth fragmentation in MeOH upon the treatment with $Cu(OAc)_2$ and $FeSO_4$ to afford **230** for the palladium-catalyzed tandem alkoxycarbonylative macrolactonization, which occurred successfully at gram scale to deliver bridged macrolactone **231** as a mixture of diastereomers. The newly formed stereocenter was inconsequential because it was eliminated in the next step to form macrolactone **232**, which was then converted to callyspongiolide uneventfully via key steps involving a photochemical double bond isomerization, Wittig reaction and Sonogashira coupling to append the ene-yne-ene

moiety.

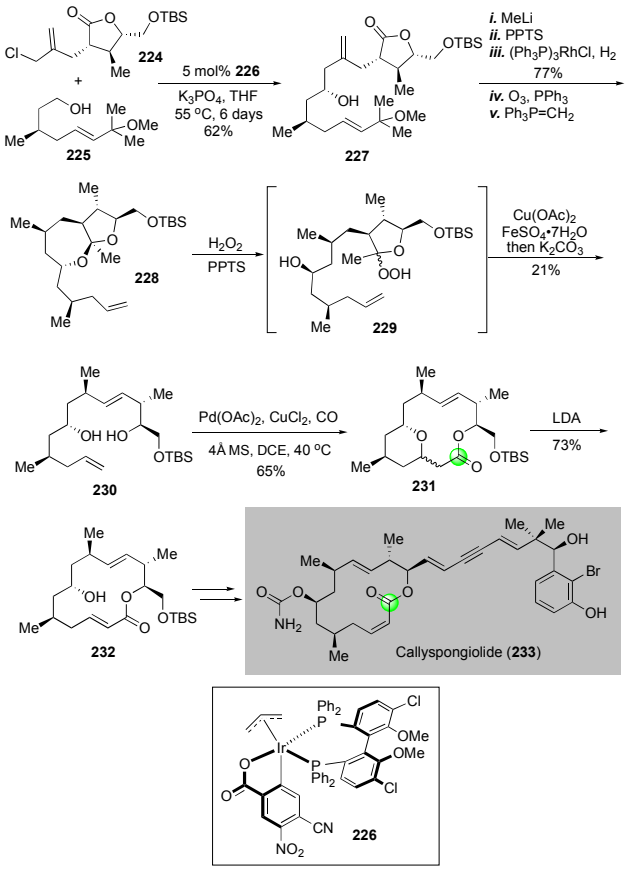

Fig. 42 The Harran synthesis of callyspongiolide (2018)

In their continued interest in developing tandem carbonylation reactions for building spirocycles and macrocycles by using carbon monoxide as a one-carbon linchpin, Dai and co-workers completed a total synthesis of spinosyn A with a palladium-catalyzed carbonylative Heck macrolactonization to form the 5,12-fused ring system embedded in its tetracyclic core.[117] As highlighted in Fig. 43, their spinosyn A total synthesis features a gold-catalyzed propargylic acetate rearrangement to convert **234**, derived from a Corey-Fuchs 1,2-addition of the corresponding readily available dibromoalkene and *trans*-5,6-fused aldehyde, to α-iodoenone **235** in 58% yield in high stereoselectivity. Additionally, NIS-mediated selenide oxidative elimination and TBS-deprotection took place under the same reaction conditions to release the required terminal olefin and secondary alcohol for the carbonylative Heck macrolactonization, which occurred smoothly with the combination of $Pd(OAc)_2$ and $P(2\text{-furyl})_3$ under 3 atm of carbon monoxide in toluene. Desired tetracyclic product **238** was obtained in 43% yield presumably via alkylpalladium intermediate **236** and acylpalladium intermediate **237**. The α-tri-*O*-methyl-L-rhamnose moiety was then installed using the Schmidt glycosylation and the challenging β-D-forosamine moiety was installed using the Yu glycosylation protocol.[118] For the latter, the diastereoselectivity was about 1:1 and needed to be improved probably by developing new glycosylation chemistries.

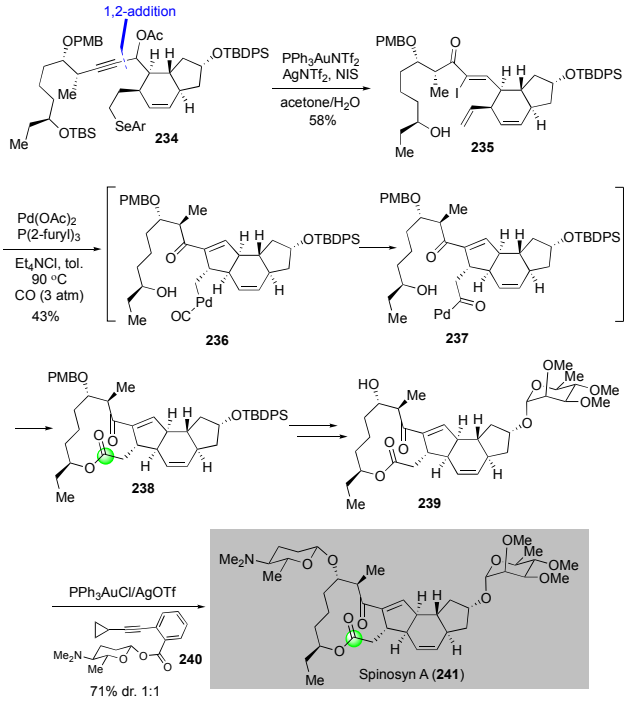

Fig. 43 The Dai synthesis of Spinosyn A (2016)

In 2012, Burke and co-workers coupled an asymmetric hydroformylation and intramolecular Wittig olefination to synthesize the macrolactone ring of patulolide C (Fig. 44).[119] Their synthesis initiated with (2*R*)-8-nonyn-2-ol **242** which underwent a hydroacetoxylation with $[RhCl(COD)]_2$ as catalyst and **243** as ligand to yield *Z*-enol acetate **244** in 82% via a remarkable *anti*-Markovnikov process. Under the conditions of $Rh(acac)(CO)_2$ and (*SSS*)-BDP ligand at 50 °C under 150 psi of CO/H_2, enol acetate **244** was transformed to aldehyde **245** with 100% conversion and high diastereoselectivity and regiocontrol. Aldehyde **245**, without further purification, was treated with the Bestmann ylide **246** in refluxing toluene. A remarkable tandem ester formation and intramolecular Wittig olefination took place to afford 12-membered lactone **247** in 62%. After a 99% yield of enzymatic acetate hydrolysis with *Pseudomonas florescens* lipase *PFL* under neutral buffer conditions, patulolide C was produced in 99% yield and 96.6:3.4 diastereoselectivity.

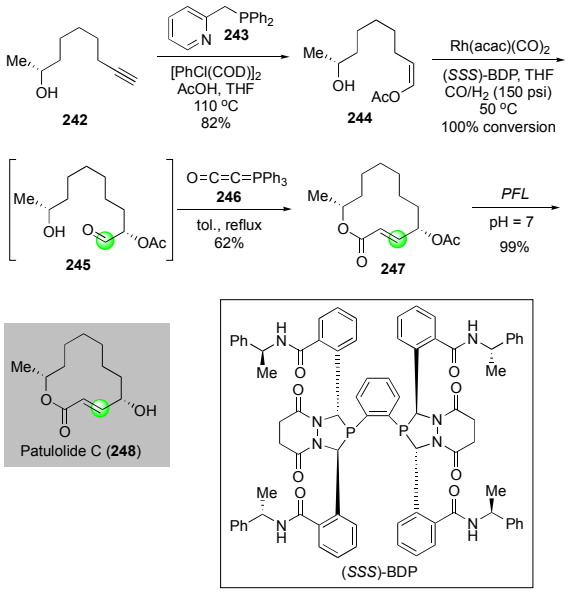

Fig. 44 The Burke synthesis of patulolide C (2012)

3 Carbonylative *N*-Heterocycle Synthesis

Many carbonylative *N*-heterocycle synthesis strategies resemble the ones of the carbonylative *O*-heterocycle syntheses, but amine nucleophiles are used to trap the acyl-metallo species instead of the corresponding alcohols. The following examples highlight different *N*-heterocyclic natural product synthesis via various carbonylation reactions.

3.1. Lactam formation

3.1.1. Carbonylative Heck lactam formation

The original Heck carbonylation of aryl/vinyl halides can be used for a one-carbon homologation amide synthesis when an amine nucleophile is used to trap the acylpalladium species generated in situ. When the amine is tethered in the same molecule with the electrophile, a lactam can be formed (Fig. 45A). Mori and Ban utilized it to construct the (1,4)-benzodiazepine ring system of tomamycin (Fig. 45B).[120] Orito and co-workers combined it with a lactam reduction step to build the tetracyclic ring system of protoberberines, which are known to have antileukemic and antitumor activity.[121] They later applied it to an efficient construction of dehydrolennoxamine by forming the 5-membered lactam ring.[122]

Additionally, in an effort to circumvent the entropic and enthalpic hurdles associated with medium-sized ring formation, Trost and Ameriks employed a Pd-catalyzed carbonylation strategy in the formation of the benzazocine core of FR900482 (**252**, Fig. 45C).[123] Specifically, using a carbonylation strategy benefits from the absence of transannular interactions due to the increased unsaturation in the forming ring. After optimization, they found that conducting the carbonylative lactamization at 80 °C in *N,N*-dimethylacetamide gave **250** in 64% yield from tethered vinyl iodide-hydroxylamine intermediate **249**. Reduction of the lactam gave **251** in 55% yield.

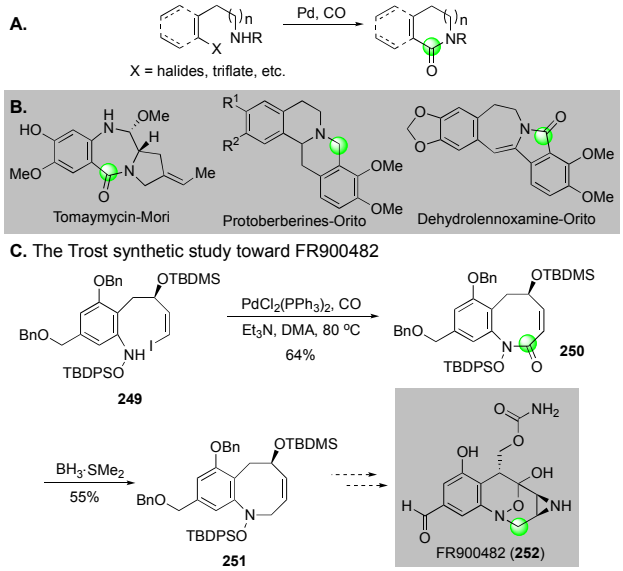

Fig. 45 Carbonylative lactam formation in total synthesis

α-Cyclopiazonic acid (α-CPA, **259**) is a prenylated indole alkaloid with Ca^{2+}-dependent ATPase inhibiting activity. Inspired by the biosynthetic pathway of α-CPA, Aggarwal and co-workers developed an efficient and convergent approach to synthesize α-CPA and its analog *iso*-α-CPA (**260**) in an enantioselective manner (Fig. 46).[124] The Aggarwal synthesis features an aziridination of imine **253** with chiral ylide **254** to afford aziridine **255** in 61% yield with 9:1 *trans*/*cis* selectivity and 98:2 enantioselectivity for the *trans* isomer. The crude aziridination product was then treated with TfOH to trigger an intramolecular [3+2] cycloaddition and pyrrolidine **256** was produced after removal of the nosyl protecting group. A palladium-catalyzed carbonylative lactam formation was used to convert pyrrolidine **256** to lactam **257**. Due to the severe angle strain of the newly formed 5,5-fused bicyclic ring system, an in situ N-O bond reductive cleavage occurred under the carbonylation reaction conditions to open the isoxazole ring and release product **258** in 80% yield. Compound **258** was then converted to α-CPA and *iso*-α-CPA with basic conditions in MeOH-THF-H_2O to remove the tosyl group.

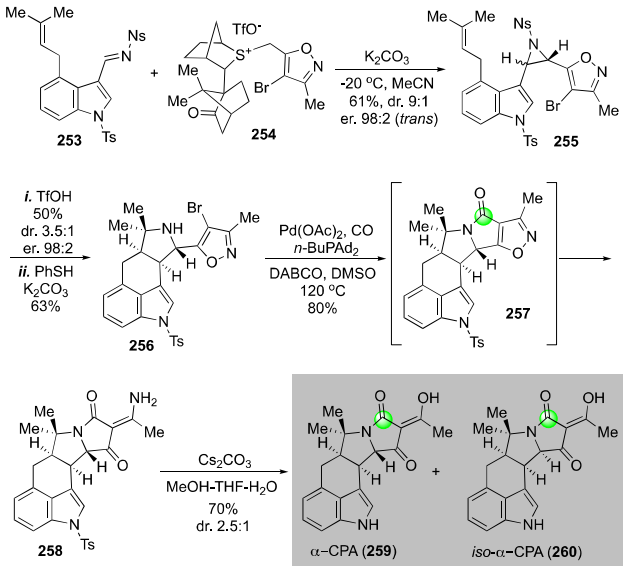

Fig. 46 The Aggarwal synthesis of cyclopiazonic acid (CPA, 2018)

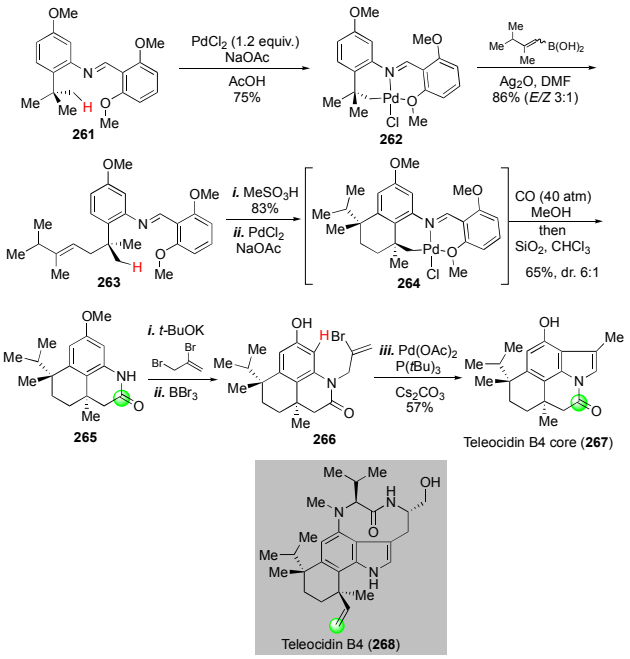

Fig. 47 The Sames synthesis of Teleocidin B4 core (2002)

3.1.2. Carbonylative C-H activation and lactam formation

The palladium-catalyzed Heck-type carbonylative lactam synthesis requires the preinstallation of a halide or its equivalent in the substrate. While significantly more challenging, a direct carbonylative C-H activation-lactam formation is much more appealing and would dramatically improve synthetic efficiency.[125-130] Such a direct carbonylative C-H activation-lactam formation strategy has been employed by Sames and co-workers in their synthesis of the teleocidin B4 core.[131] As shown in Fig. 47, palladacycle **262** was formed by treating Schiff base **261** with stoichiometric $PdCl_2$ via a direct activation of a methyl C-H bond. In the presence of Ag_2O, palladacycle **262** then underwent a transmetallation with a vinyl boronic acid followed by reductive elimination to form **263**. A methanesulfonic acid-mediated Friedel-Crafts cyclization gave rise to the opportunity for a second directed methyl C-H activation/palladacycle formation (**263**→**264**), which was intercepted with carbon monoxide (40 atm) and MeOH to form a methyl ester. The methyl ester was not isolated and transformed to lactam **265** spontaneously during the acidic hydrolysis of the Schiff base. Allylation of the lactam followed by the third direct C-H functionalization catalyzed by $Pd(OAc)_2$ furnished **267** with the core skeleton of teleocidin B4 (**268**). Overall, they successfully orchestrated a series of direct C-H activation reactions to build three key C-C bonds and one lactam ring of teleocidin B4.

In 2015, Takemoto and co-workers reported their synthesis of pyrrolophenanthridine alkaloids based on two C-H functionalization reactions (Fig. 48).[132] They first used a Catellani reaction[133] followed by oxidation to produce **270** in 66% yield. Once carbamoyl chloride **271** was synthesized from **270**, a $Pd(OAc)_2$-catalyzed benzylic C-H functionalization between the carbamoyl chloride and the methyl group of **281** occurred to provide lactam **282** in 30% yield with 60% yield of **270**. The formation of **270** indicated a decarbonylation process after oxidative addition. Therefore, carbon monoxide was utilized to help suppress this byproduct formation process, which renders this transformation a partial carbonylative cyclization. Lactam **272** was then reduced to assoanine (**273**), one of the pyrrolophenanthridine alkaloids.

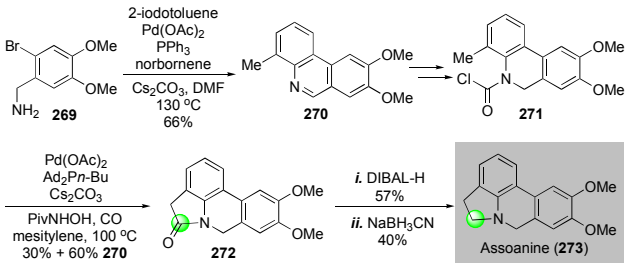

Fig. 48 The Takemoto synthesis of assoanine (2015)

Palladium-catalyzed directed $C(sp^3)$-H carbonylative cyclization is an attractive strategy to access lactams. Recently, Wang and co-workers used a picolinamide directed $C(sp^3)$-H carbonylative lactam formation to convert **274** to **275** (Fig. 49).[134] The latter was hydrolyzed to pregabalin by removing the directing group and opening the lactam ring. Pregabalin is

a clinically used drug to treat epilepsy and other neurological diseases.

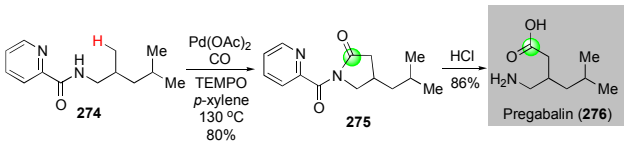

Fig. 49 The Wang synthesis of pregabalin (2015)

In 2016, Gaunt *et al.* disclosed an impressive synthesis of K-252c (staurosporinone) by employing a sequential C-H functionalization of arenes including three copper-catalyzed C(sp^2)-H functionalizations to construct two C-C bonds and one C-N bond, one palladium-catalyzed carbonylative C-H activation to form the desired 5-membered lactam, and a Cadogan nitrene cyclization to build another key C-N bond.[135] As shown in Fig. 50, they first used a copper-catalyzed C-H functionalization to unite diphenyliodium triflate and dibenzyl *p*-toluidine **277** to form biaryl product **278**, which was further transformed to **279** for the second copper-catalyzed C-H arylation with diphenyliodium triflate to afford **280**. After a nitration to convert **280** to **281**, a copper-catalyzed C-H amination developed by Chang and co-workers was used to form a C-N bond and afford carbazole **282** in 88% yield with [bis(trifluoroacetoxy)iodo]benzene ($PhI(TFA)_2$) as oxidant. Carbazole **282** was subjected to a radical bisbromination at the benzylic position followed by DMF and K_2CO_3 treatment to produce the corresponding aldehyde, which underwent reductive amination to furnish 2,6-dimethylbenzylamine **283**. The use of 2,6-dimethylbenzylamine is critical for the next palladium-catalyzed carbonylative C-H lactam formation because the two methyl groups can block the potential competitive C-H activation pathways and desired lactam was produced in 96% yield with $Pd(OAc)_2$ as catalyst and $Cu(OAc)_2$ and air as oxidants. Finally, a Cadogan nitrene cyclization upon the treatment of nitro compound **284** with $P(OEt)_3$ followed by removal of the 2,6-dimethylbenzyl group with BCl_3 and TBAI under heating conditions completed the total synthesis of K-252c.

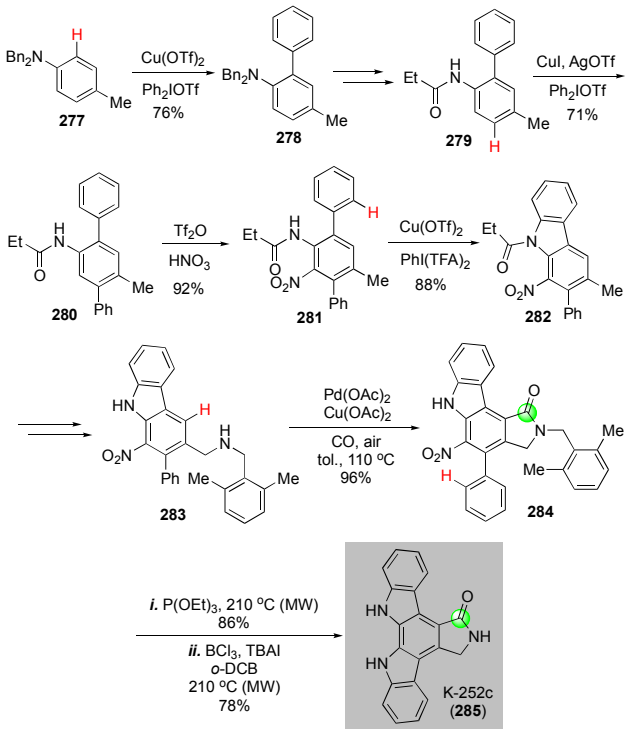

Fig. 50 The Gaunt synthesis of K-252c (2016)

3.1.3. Hydrocarbonylative lactamization

Another thought-provoking natural product total synthesis via palladium-catalyzed carbonylative lactamization is the total synthesis of rhazinilam reported by Sames and co-workers in 2002 (Fig. 51).[136] Their synthesis commenced with alkylation of imine **286** with *o*-nitrocinnamyl bromide to form iminium salt **287**, which underwent a smooth silver carbonate-promoted cyclization and aromatization to provide pyrrole **288**. Once **288** was converted to platinum complex **289**, addition of triflic acid resulted in the loss of a methane molecule and generation of a cationic platinum complex, which under thermolysis in CF_3CH_2OH was transformed to alkene-platinum-hydride complex **290** in high yield via a process involving a direct C(sp^3)-H activation, loss of another methane molecule and β-hydride elimination. Decomplexation of **290** with KCN followed by releasing the aniline group with NH_2OH gave **291** in 60% yield. They then developed a remarkable hydrocarbonylative macrolactam formation catalyzed by 5 mol% of Pd/C with 1,4-bis(diphenylphosphino)butane (dppb) as ligand under 10 atm of carbon monoxide followed by removal of the methyl ester to complete their total synthesis of rhazinilam.

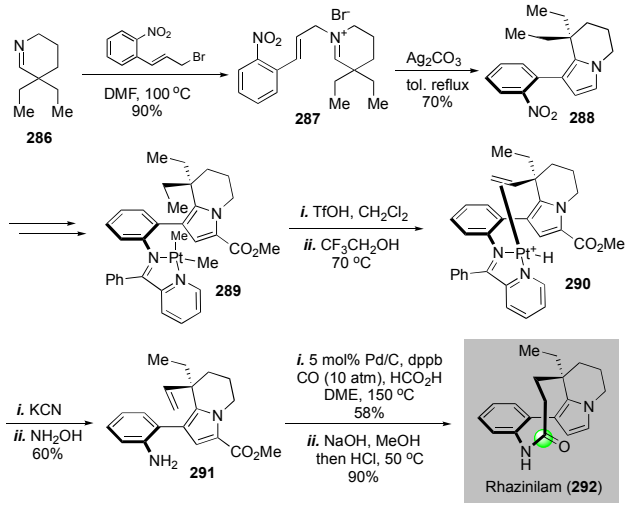

Fig. 51 The Sames synthesis of rhazinilam (2002)

3.1.4. Other carbonylative lactamization

In addition to palladium, other transition metals can be used to promote carbonylative lactam formation as well. For example, a $Co_2(CO)_8$/tetramethylthiourea (TMTU) catalyzed aza-Pauson-Khand reaction of alkyne-containing carbodiimide **294** was disclosed by Mukai and co-workers for the synthesis of physostigmine (Fig. 52).[137] Specifically, treatment of 1-alkynyl aniline **293** with triphosgene and Et_3N followed by methylamine gave a methyl urea, and dehydration of the urea with CBr_4 and PPh_3 provided carbodiimide **294**. A combination of $Co_2(CO)_8$ and TMTU successfully effected the aza-Pauson-Khand reaction to afford **295** in 55% yield. A sequential one-pot reduction, hydroxymethylation, and *N*-methylation advanced **295** to **296**. The latter can be converted to a known intermediate for the total synthesis of physostigmine.

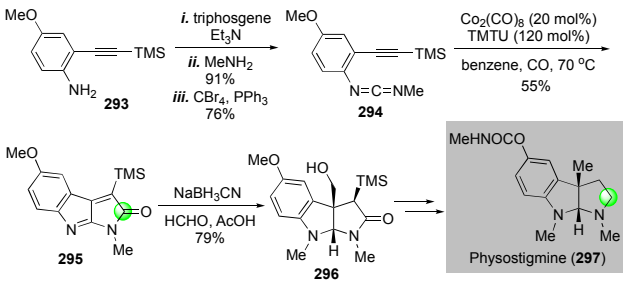

Fig. 52 The Mukai synthesis of physostigmine (2006)

The substituted maleinimide natural products, of which himanimide A and B are members, and their synthetic derivatives are known to possess various biological activities including antimicrobial activities, cytotoxicity, and kinase inhibiting properties. Beller and co-workers reported an efficient approach to these maleinimide natural products in 2010 (Fig. 53).[138] In their case, internal alkyne substrate **298**, prepared by Sonogashira coupling of the corresponding terminal alkyne and aryl bromide, was subjected to $Fe_3(CO)_{12}$-catalyzed carbonylation under 20 atm of carbon monoxide and excess NH_3 in THF via a formal [2+1+1+1] annulation to construct the maleinimide ring of **299** in 78% yield. Oxidative dehydrogenation then gave himanimide A (**300**) in 48% overall yield. Conversion of himanimide A to himanimide B in 90% yield and 60% ee was realized by Sharpless asymmetric dihydroxylation.

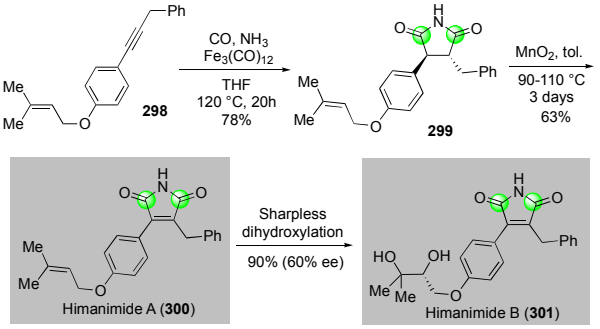

Fig. 53 The Beller synthesis of himanimide A and B (2010)

In 2017, Sarlah and co-workers reported an elegant total synthesis of pancratistatin and 7-deoxypancratistatin from benzene (Fig. 54).[139] The pancratistatins belong to the Amaryllidaceae alkaloid family with substantial in vitro and in vivo anticancer activity. The Sarlah approach presents a rapid synthetically simplified entry into the pancratistatin core, which could be potentially used for supplying material for further biomedical development and future structural editing to identify analogues with improved funtions. Their synthesis started with a visible-light-promoted *para*-cycloaddition of N-N arenophile MTAD to benzene to form a benzene-MTAD [4+2] cycloadduct, which without purification was then subjected to an enantioselective nickel-catalyzed aryl Grignard addition to form the *trans*-1,4-carboamination product **303** in 65% yield and 98:2 er at over 10g scale with (R,R_p)-*i*-Pr-Phosferrox as ligand. Chemo- and diastereoselective epoxidation and hydrolysis followed by Upjohn dihydroxylation installed the four contiguous hydroxy substituents of **305**. After releasing of the free amine and bromination, they utilized a photochemical carbonylation with $NaCo(CO)_4$ under UV light and carbon monoxide atmosphere to give (+)-7-deoxypacratistatin in 72% yield in one pot. A final C-H hydroxylation via cupration with $(TMP)_2Cu(CN)Li_2$ followed by *in situ* oxidation completed the total synthesis of pacratistatin in seven steps and 12% overall yield.

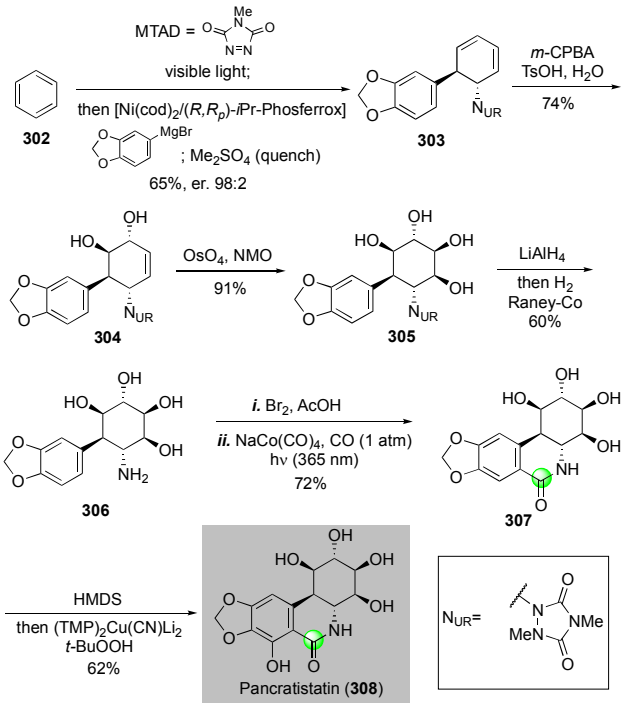

Fig. 54 The Sarlah synthsis of pancratistatins (2017)

3.2. Other *N*-heterocycle formation

Rhodium-catalyzed hydroformylation-aminal cyclization has been useful in building *N*-heterocycles such as piperidine (Fig. 55) or pyrrolidine (Fig. 56), which are commonly found in bioactive natural products and lifesaving drug molecules. For the piperidine case, Ojima and workers used a $Rh(acac)(CO)_2$-catalyzed tandem hydroformylation-intramolecular enamine formation sequence to convert **311** to **312**, then to homomainoid **313** for the identification of kainic acid analogues as kainite receptor agonists for excitatory transmission in the central nervous system.[140] Intermediate **311** can be readily accessed from (*R*)-serine (**309**). Wulff and Ren used a similar hydroformylation-intramolecular enamine formation strategy to convert homoallylic amine **310** to **311**[141] with a catalyst system developed by Morimoto and co-workers ($[RhCl(cod)]_2$ as catalyst and BIPHEP and NiXantphos as ligands).[142] In this case, paraformaldehyde was used as both the hydrogen and carbonyl sources. The generation of a cooperative dual catalyst system is the key for the success of this transformation because two catalytic processes are involved. One is the decarbonylation of formaldehyde and the other one is the hydroformylation of the terminal olefin of **318**. To synthesize homoallylic amine **318**, Wulff and Ren used a boroxinate (**316**)-catalyzed asymmetric aza-Cope rearrangement and hydrolysis sequence developed in the Wulff lab to realize the union of **314** and **315** and provide **317** in 61% yield, which was subsequently converted to **318** with a simple TBS protection. In 2013, Bates and co-worker used a double hydroformylation process to convert **321** to **322** after one of the two newly formed aldehydes cyclized with the sulfonamide to form an enamine (Fig. 55).[143]

Enamine **322** was then advanced to azimic acid in a few steps.

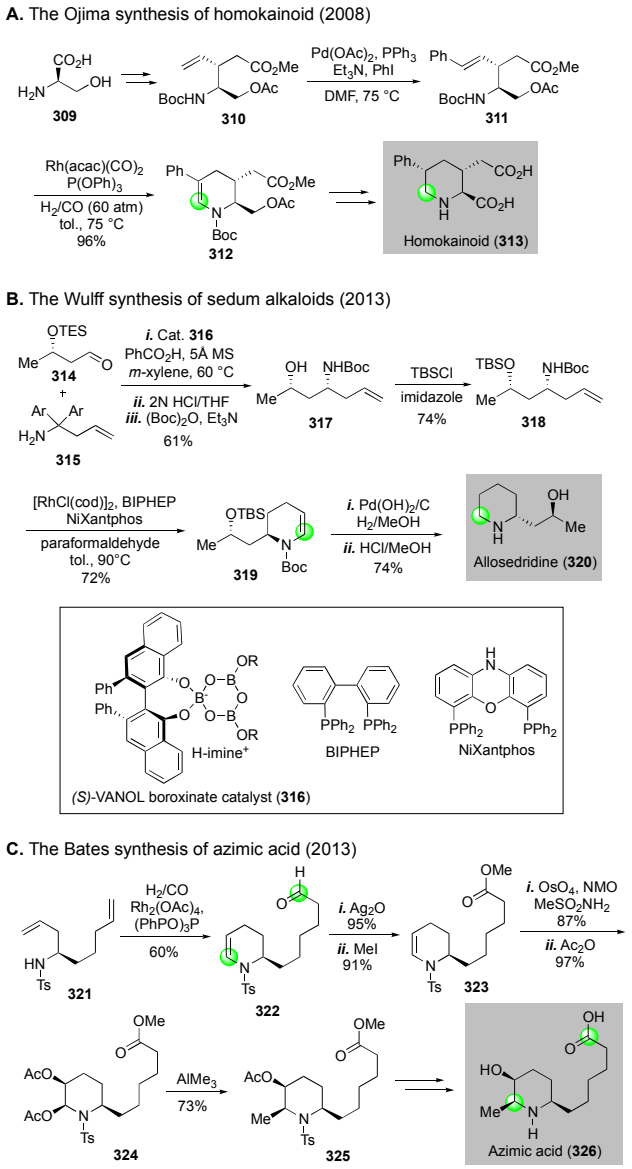

Fig. 55 Hydroformylation-aminal cyclization toward piperidine-containing natural products

When allylic amines are used in the rhodium-catalyzed hydroformylation-aminal cyclization process, pyrrolidine derivatives can be obtained. Helmchen and co-workers achieved a rapid synthesis of (*S*)-nicotine with this strategy (Fig. 56A).[144] In their case, the allylic amine substrate **329** was obtained by an iridium-catalyzed asymmetric allylic amination of allylic carbonate **327** with chiral ligand **328**. Then, a $Rh(acac)(CO)_2$/Biphephos-catalyzed tandem hydroformylation-intramolecular aminal formation followed by further hydrogenation gave (*S*)-nicotine **330** in 61% yield and 99% ee. In 2013, Chiou and co-workers developed an interesting synthesis of alkaloid physostigmine by employing a rhodium-catalyzed hydroformylation-double cyclization as the key

step to afford pyrrolidinoindoline **332** in one step from **331** (Fig. 56B).[145] Radical benzylic bromination of **332** with the treatment of 1,3-dibromo-5,5-dimethylhydantoin and AIBN afforded **333**, which then underwent methylation with $ZnMe_2$ smoothly in refluxing toluene to yield **334** for their formal synthesis of physostigmine. Additionally, the same strategy was used for their formal synthesis of physovenine.

In general, for these rhodium-catalyzed hydroformylation-aminal cyclization processes (Fig. 55 and 56), the substituents on the nitrogen and the product ring sizes affect the identity of the final cyclized products. For the case of converting **329** to **330**, the use of alkyl groups such as benzyl and methyl groups are critical for the successful one-pot reduction to form pyrrolidine product directly. When tosyl or Boc groups were used, the reactions stopped at hemiaminal stage for pyrrolidines but enamine stage for piperidines.

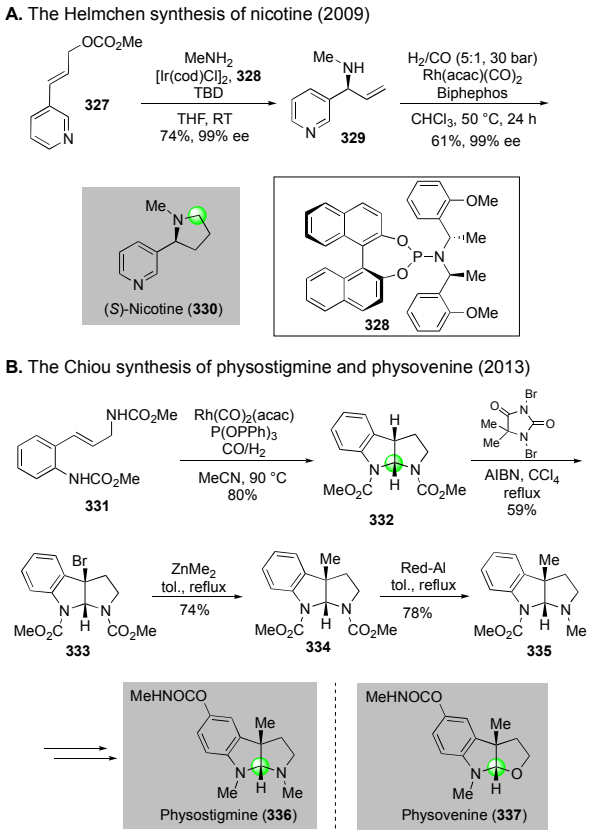

Fig. 56 Hydroformylation-aminal cyclization toward pyrrolidine-containing natural products

In addition to the above *endo*-carbonylative cyclization pathways (carbon monoxide ends in the ring), *exo*-carbonylative cyclizations (carbon monoxide ends outside of the ring) are useful for preparing *N*-heterocycles. In 2003, Weinreb and co-workers reported an intramolecular carbonylative cyclization to yield oxindole product **339** from **338** (Fig. 57).[146] The reaction initiated with a 5-*exo*-*trig* cyclization via a Heck-type olefin migratory insertion to form an all-carbon quaternary center and an alkylpalladium species. Since β-hydride elimination was blocked in this case, a carbon monoxide migratory insertion took place to generate an acylpalladium species, which was trapped by methanol to form ester **339**. The carbonylation product **339** was then advanced to **340** with the two adjacent all-carbon quaternary centers which are required for synthesizing perophoramidine (**341**).

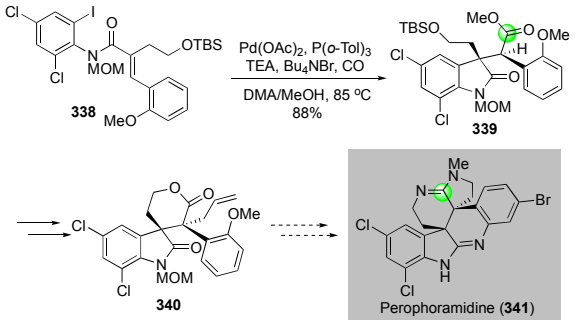

Fig. 57 The Weinreb synthesis of perophoramidine core (2003)

In 2009, Denmark and co-workers disclosed their total synthesis of isodomoic acids G and H via an innovative carbonylative silylcarbocyclization to build the key 3-carboxymethylproline moiety (Fig. 58).[147] Isodomoic acids G and H differ at the configuration of the tetrasubstituted double bond and both belong to the family of kainoid amino acids. Fig. 58 highlights their total synthesis of isodomoic acid H. Treatment of enyne **342** and $HSiMe_2Ph$ with $Rh(acac)(CO)_2$ catalyst under 500 psi of carbon monoxide at 120 °C delivered an inseparable mixture of diastereomers in an 8:1 ratio favouring the *trans* isomer **344**. After oxidizing the newly formed aldehyde to ester **345**, an ICl-promoted iododesilylation proceeded smoothly to give *Z*-alkenyl iodide **347** in 86% yield. A complete inversion of the tetrasubstituted double bond configuration occurred in the iododesilylation process, which was rationalized by the neighboring group participation of the ester carbonyl via intermediate **346**. A Hiyama cross coupling between **347** and **348** was effective with a combination of $Pd_2(dba)_3$ and TBAF. The resulting diene **349** was elaborated to isodomoic acid H after hydrolyzing all three methyl esters with LiOH and removing the tosyl group using sodium amalgam. By using a similar approach, but a configuration retentive iododesilylation, they also completed the total synthesis of isodomoic acid G.

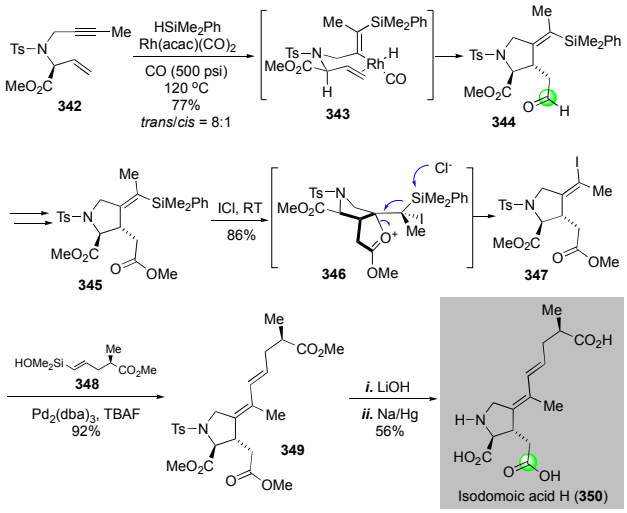

Fig. 58 The Denmark synthesis of isodomoic acid H (2009)

4. Carbonylative Ketone Synthesis

In addition to *O*- and *N*-heterocycles, carbonylative cyclization strategy is very effective in building carbocycles particularly cyclic ketones and aromatic products. In this review, we mainly focus on the recent use of the Stille carbonylation-Nazarov cyclization, the Pauson-Khand Reaction, Rh-catalyzed [n+m+1 (CO)] cycloaddition, and the Dötz annulation in natural product total synthesis. Notably, in the 1990s Oppolzer and co-workers developed a series of cascade palladium-catalyzed ene cyclization-carbonylation to synthesize polycyclic ketone products[148] including 3-isorauniticine[149] and hirsutene,[150] which have been reviewed previously[1] and are not discussed in detail here.

4.1. Palladium-catalyzed carbonylative ketone synthesis

4.1.1 The Stille/Suzuki carbonylation-Nazarov cyclization

The Stille/Suzuki carbonylation reactions are convergent and modular three-component processes to synthesize carbonyl products such as dienones, diarylketones, arylenones and others (Fig. 59A). Since the regio- and stereo-chemistry of the Stille/Suzuki carbonylations are predetermined by the position of the pre-installed functional groups in the coupling partners, these two processes often proceed with high regio- and stereo-chemical control and have been frequently used in total synthesis.[151-153] Furthermore, when the Stille/Suzuki carbonylation reactions are coupled with a Nazarov cyclization, synthetically useful cyclopentenones can be assembled rapidly. In addition to Stille's seminal $\Delta^{9(12)}$-capnellene synthesis, a few recent applications are highlighted in Fig. 59.

In 1984, Stille and co-workers achieved an elegant total synthesis of $\Delta^{9(12)}$-capnellene by orchestrating two consecutive Stille carbonylation-Nazarov cyclizations (Fig. 59B).[154] The first one commenced with vinyltriflate **351** and (trimethylsilyl)vinylstannane, which were linked together with a molecule of carbon monoxide to dienone **352**. A silicon-directed Lewis acid-promoted Nazarov cyclization occurred next to yield **353**, which was advanced to **354**, then to $\Delta^{9(12)}$-capnellene **355** via another Stille carbonylation-Nazarov cyclization cascade to build the last cyclopentane ring.

In 2000, Ishikura and co-workers employed a combination of Suzuki carbonylation-Nazarov cyclization to their total synthesis of bis-indole alkaloid natural product yuehchukene (Fig. 59C).[155] In this case, a lithiated "ate" complex **356** underwent Suzuki carbonylation smoothly with triflate **357**. The newly generated indole-vinyl ketone was converted to **358** via a TFA-promoted Nazarov cyclization. After ketone reduction and indole alkylation, a total synthesis of yuehchukene was reached.

Nakiterpiosin (**363**, Fig. 59D) is a scarce anticancer C-nor-D-homosteroid isolated from marine sponge *Terpios hoshinota*. To solve the material supply problem and understand its mode of actions, Chen and co-workers developed a highly convergent total synthesis of nakiterpiosin.[156] Their synthesis features an effective Stille carbonylation to couple two acid- and base-sensitive building blocks **360** and **361** together. After a photochemical Nazarov cyclization and epimerization at C9, complex cyclopentanone product **362** was obtained in 37% overall yield. They completed the total synthesis of nakiterpoisin from **362** in four more steps.

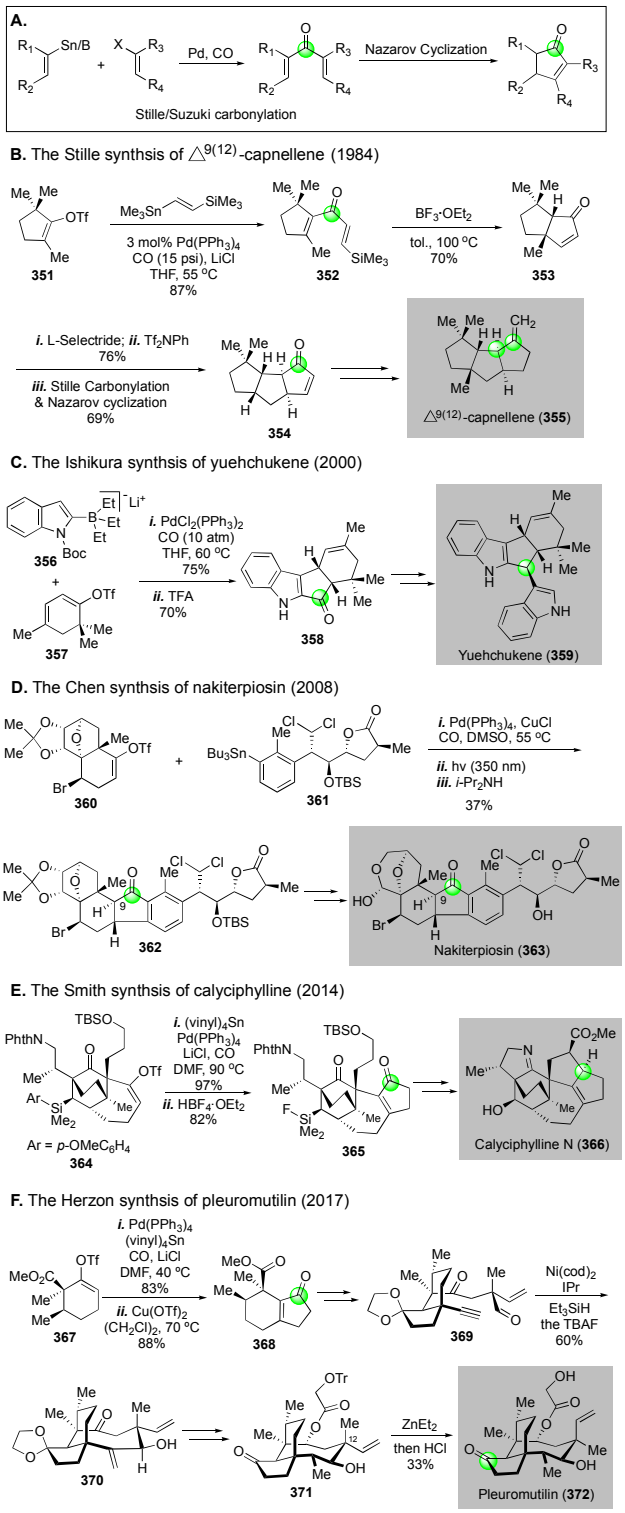

Fig. 59 The Stille/Suzuki carbonylation-Nazarov cyclization in total synthesis

In 2014, Smith and Shvartsbart completed a total synthesis of architecturally complex *Daphniphyllum* alkaloid calyciphylline N,[157,158] isolated by Kobayashi and co-workers in 2008.[159] The Smith synthesis utilized the Stille carbonylation-Nazarov cyclization sequence to convert vinyltriflate **364** to cyclpentenone **365**, which was then advanced to calyciphylline N (Fig. 59E).

Very recently, the Stille carbonylation-Nazarov cyclization sequence was utilized by Herzon and co-workers in their modular and enantioselective synthesis of the pleuromutilin antibiotics (Fig. 59F).[160] Pleuromutilin is a diterpene fungal metabolite with growth inhibiting activity against Gram-negative pathogens by binding to the highly conserved peptidyl transferase center of the bacterial ribosome. The Herzon synthesis used the Stille carbonylation-Nazarov cyclization sequence to provide bicyclic enone **368** from vinyltriflate **367**, derived from cyclohexenone in three steps including one copper-catalyzed asymmetric conjugate addition-C-acylation to introduce the first chiral center of their synthesis. After **368** was furnished to alkynyl aldehyde **369**, a nickel-catalyzed reductive cyclization built the strained macrocycle and afforded **370** in 60% yield. Compound **370** was further transformed to **371** via a few functional group manipulations, but **371** contains opposite stereochemistry at the C12 all-carbon quaternary center in comparison to pleuromutilin. The final epimerization was achieved by treating **371** with Et_2Zn via a retroallylation-allylation process. A following in situ removal of the trityl group afforded pleuromutilin in 33% yield along with 12-*epi*-pleuromutilin in 56% yield.

4.1.2. Palladium-Catalyzed Cascade Carbonylative Cyclization

Palladium-catalyzed cascade carbonylative cyclization is an effective strategy to build cyclic ketones. In 2010, Fukuyama, Esumi, and co-workers employed two palladium-catalyzed carbonylation reactions in their enantioselective formal synthesis of neovibsanin B, a neurotrophic diterpenoid (Fig. 60).[161] They first used a carbonylative reaction between vinyliodide **373** and oxazolidinone derivative **374** synthesize amide **375** in 68% yield. Asymmetric conjugate addition with a vinylcuprate nucleophile provided **376**, which was further advanced to vinyliodide **377** in nine steps. They then used a palladium-catalyzed double carbonylation to convert 377 to 378 in 69% yield (dr. 2.6:1). The latter was transformed into a known intermediate for the total synthesis of neovibsanin B.

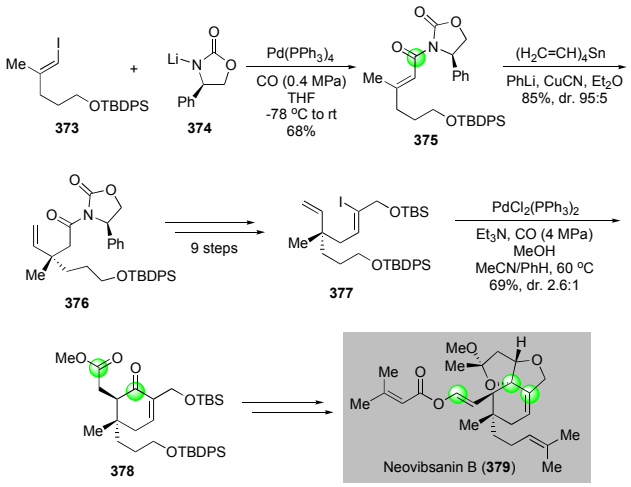

Fig. 60 The Fukuyama-Esumi formal synthesis of neovibsanin B (2010)

Very recently, Zhao and co-workers utilized a palladium-catalyzed cascade carbonylative cyclization to rapidly build the 6-5-6 tricyclic ring system of cephanolides, which culminated in the first total synthesis of cephanolides B and C (Fig. 61).[162] Their synthesis commenced with 5-bromo-2-methylanisole, which was advanced to lactone **380** in seven steps. Zhao and co-workers then developed a palladium-catalyzed carbonylative C-H annulation to convert **380** to polycyclic ketone products **381** and **382**. While the palladium-catalyzed carbonylative C-H annulation was effective to build the desired cyclopentanone imbedded in the 6-5-6 tricyclic ring system, product **367** with undesired stereochemistry at the *cis* 5,6-fused ring junction was produced as the major stereoisomer because the lactone moiety is less sterically hindered than the methyl substituted ethylene moiety of the bicyclic [2.2.2] ring system. To circumvent this undesired stereochemical outcome, lactone **380** was then converted to acetal **383** with the thought that the acetal would be more sterically hindered than the lactone. Indeed, with this subtle change, carbonylative annulation product **384** was produced in high yield with desired the stereochemistry at the *cis*-fused ring junction. After oxidizing the acetal back to the corresponding lactone with *m*-CPBA, a formal deoxygenation with the treatment of TfOH/Et_3SiH afforded 370 in 70% yield. A subsequent removal of the methyl group completed the total synthesis of cephanolide B. To convert **385** to cephanolide C, two benzylic C-H oxidation steps were employed. The first DDQ oxidation introduced the tertiary hydroxyl group and the second PCC oxidation installed the ketone functionality and delivered 372, which was then advanced to cephanolide C in three steps to remove the extra methoxy group.

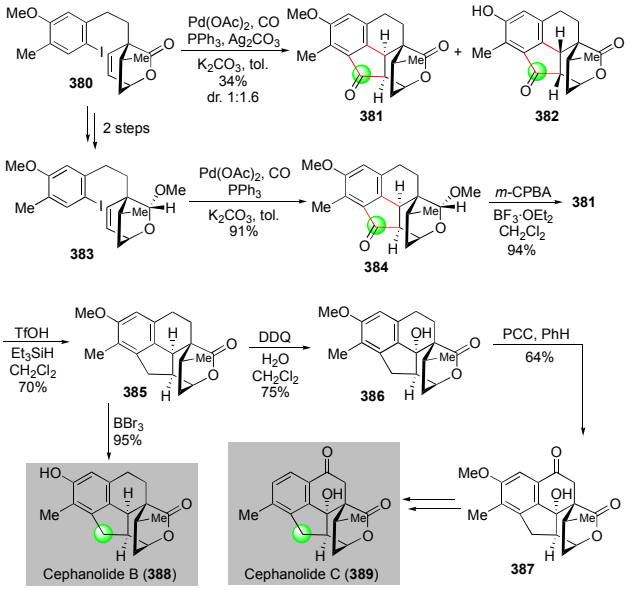

Fig. 61 The Zhao synthesis of cephanolides B and C (2018)

4.2. The Pauson-Khand Reaction

The Pauson-Khand reaction, first developed in 1973, is arguably the most efficient process to construct cyclopentenones. It formally goes through a [2+2+1] cycloaddition involving an alkyne, an alkene and a carbon monoxide with a transition metal complex. Both intermolecular and intramolecular versions of the Pauson-Khand reactions have been developed. When the alkene and alkyne are tethered in the same molecule, a bicyclic ring system can be formed in one step. Since its discovery, the Pauson-Khand reaction has been widely used in natural product total synthesis. This topic has been frequently reviewed as well.[163-167] In this part, we highlight some recent applications of the Pauson-Khand reaction in making complex natural products.

4.2.1. Alkyne-Alkene Pauson Khand reaction

One classic application of the alkyne-alkene Pauson-Khand reaction in natural product total synthesis is the Schreiber synthesis of epoxydictymene (Fig. 62).[168] Their synthesis features an Et_2AlCl-promoted Nicholas reaction to convert enyne **390** to cobalt complex **391** and build the key eight-membered carbocycle. Conversion of primary alcohol **391** to olefin **392** requires a mild reaction condition because the dicobalthexacarbonyl moiety is oxidatively labile. This transformation was realized by using the Grieco method with the Davis phenyloxaziridine as oxidant for the corresponding selenoether oxidative elimination. *N*-methylmorpholine *N*-oxide-promoted intramolecular Pauson-Khand reaction delivered tetracyclic intermediate **393** from **392** in 70% with 11:1 diastereoselectivity, but favoring the undesired stereochemistry at C12. The remaining installation of the required strained *trans*-5,5-fused ring system was nontrivial and took them a

detour to achieve this goal and complete the total synthesis of epoxydictymene.

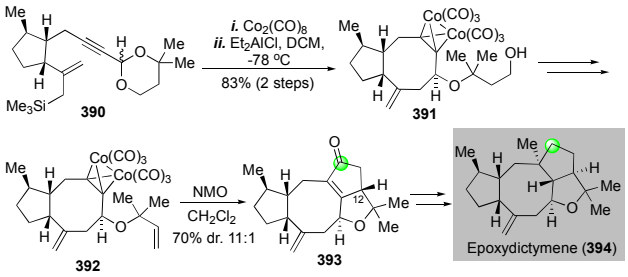

Fig. 62 The Schreiber synthesis of epoxydictymene (1997)

Serratine is a member of the *lycopodium* alkaloids with a 5-6-5-6 fused tetracyclic skeleton. Zard and co-workers reported a total synthesis of 13-deoxyserratine in 2002 (Fig. 63).[169] Their synthesis utilized a Pauson-Khand reaction to convert acyclic enyne **395** to bicyclic product **396** in 89% yield with 93:7 diastereoselectivity. Compound **396** was then elaborated to *O*-benzoyl-*N*-(2-chloroallyl)hydroxamine **397** for a tandem radical cyclization to install the other two ring systems. Under the conditions of slow addition of Bu_3SnH and 1,1'-azobis(cyclohexanecarbonitrile) (ACCN) to a refluxing solution of **397** in trifluorotoluene, a sequential 5-*exo-trig* and 6-*endo-trig* radical cyclization took place to give tetracyclic intermediate **399** in 52% yield. Notably, the use of *N*-(2-chloroallyl)hydroxamine is critical for the desired 6-*endo-trig* cyclization process. Without the chloride, a 5-*exo-trig* cyclization would occur to give a pyrrolidine ring instead of the required piperidine ring. Compound **399** was then transformed to 13-deoxyserratine uneventfully. In this case, the Pauson-Khand reaction and the tandem radical cyclization enabled a rapid construction of the tetracyclic structure of 13-deoxyserratine.

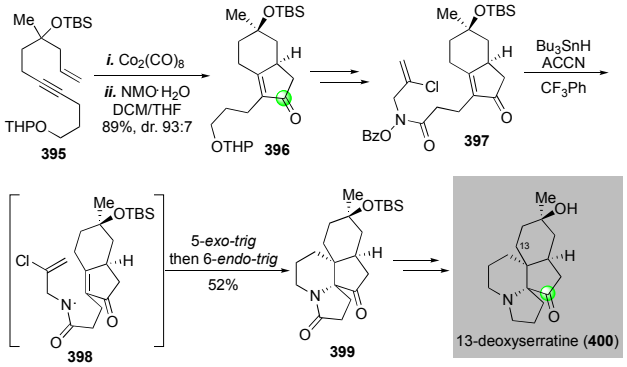

Fig. 63 The Zard synthesis of 13-deoxyserratine (2002)

Magellanine and related natural products are also family members of the *lycopodium* alkaloids, but they share a common 6-5-5-6 tetracyclic framework with multiple stereogenic centers. Both Mukai's group[170] and Ishizaki's group[171] have employed the Pauson-Khand reaction as the key strategy to build these molecules, but their corresponding bond disconnections are quite different (Fig. 64). Ishizaki and co-workers used the Pauson-Khand reaction to build the B,C-ring system by converting **401** to **402**, then to magellanine (**403**). Mukai and co-workers first used the Pauson-Khand reaction to form the A,B-ring system (**404**→**405**). They then employed a Stork radical cyclization strategy[172] to elaborate **405** to **407**. The latter was converted to enyne **408** for the second Pauson-Khand reaction, which built the C,D-ring system and afforded tetracyclic intermediate **409**. After oxidative fragmentation of the newly formed cyclopentenone ring followed by constructing the piperidine ring, they were able to finish several magellanine family members including magellanine itself and magellaninone. Notably, in 2013, Mukai and co-workers employed a similar Pauson-Khand/Stork radical cyclization strategy to accomplish the total synthesis of several other *lycopodium* alkaloids including fawcettimine, fawcettidine, lycoflexine, and lycoposerramine Q.[173]

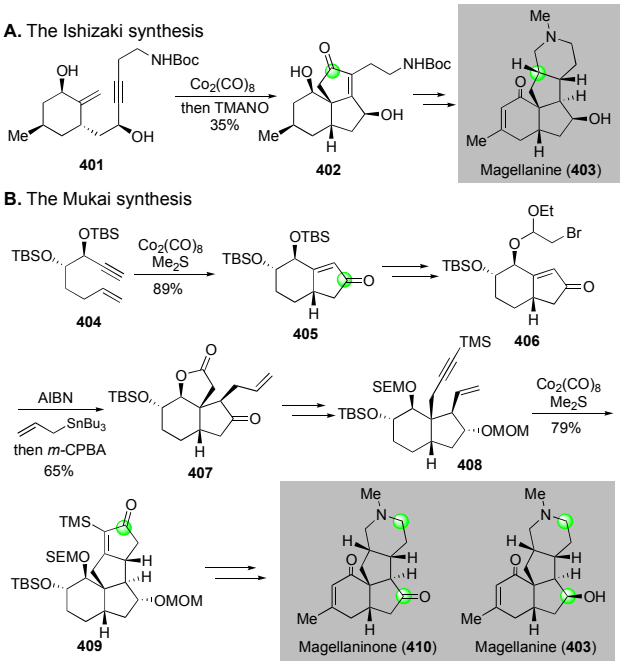

Fig. 64 The Mukai (2007) and Ishizaki (2003) synthesis of magellanine

In 2007, Fox and co-worker reported a Pauson-Khand strategy to an enantioselective total synthesis of pentalenene, an angular triquinane natural product.[174] In particular, the Pauson-Khand reaction involving chiral cyclopropene **413** provided tricyclic product **414** in 80% yield and 4:1 diastereoselectivity. It also built the angular all-carbon quaternary center. Notably, the TMS group of substrate **413** is essential for the success of the Pauson-Khand reaction. Substrate **412** failed to undergo the desired Pauson-Khand reaction under various reaction conditions. The chiral cyclopropene substrate was prepared in 80% yield and 91% ee via an enantioselective and chemoselective cyclopropenation of diyne **411** using Corey's $Rh_2(OAc)(R,R\text{-DPTI})_3$ catalyst. After removal of the silyl groups of the Pauson-Khand reaction product with TBAF, Fox et al.

used a Pd/C-catalyzed hydrogenation to reduce the double and cleave the cyclopropane ring. Bicyclic product **415** was obtained and further advanced to pentalenene.

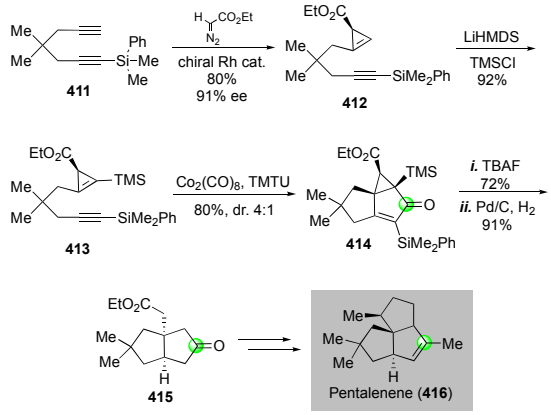

Fig. 65 The Fox synthesis of pentalenene (2007)

Alstonerine features an azabicyclo[3.3.1] substructure that is fused with an indole ring. It has shown cytotoxic activity against a few human cancer cell lines. In 2007, Martin and Miller disclosed a concise total synthesis of alstonerine involving a remarkable Pauson-Khand reaction to convert enyne **417** to **418** and build the azabicyclo[3.3.1] substructure in 94% yield (Fig. 66).[175] An oxidative cyclopentenone cleavage strategy was next developed to provide lactone **421** in high yield via a sequence of enone reduction with Karstedt's catalyst **419**, Lemieux-Johnson silyl enol ether oxidative cleavage, aldehyde reduction and acid-promoted lactonization. Lactone **421** was then advance to alstonerine in six steps.

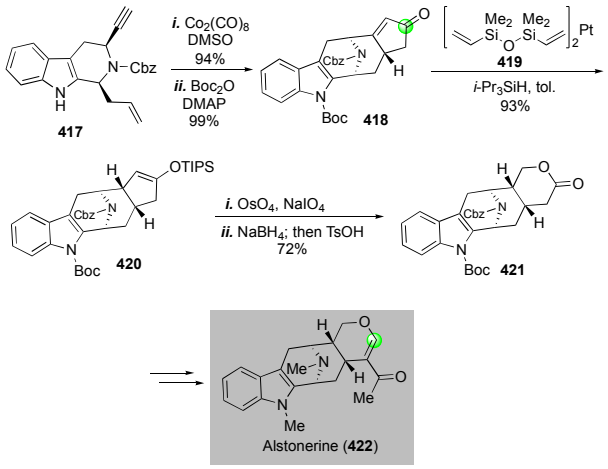

Fig. 66 The Martin synthesis of alstonerine (2007)

In the same year, Danishefsky and Min reported the first total synthesis of paecilomycine A with potent neurotrophic activity in fostering neurite outgrowth of PC_{12} cells (Fig. 67).[176] Their synthesis commenced with a Diels-Alder reaction between diene **423** and alkyne-activated dienophile **424**, which occurred smoothly even at 0 °C to form cyclohexene product **425** in 58% yield and high *endo*-selectivity. Cycloadduct **425** was then converted to the Pauson-Khand reaction precursor **426** in four steps. Under the conditions of $Co_2(CO)_8$ in toluene at 100 °C, tricyclic product **427** was produced in 37% yield. After Luche reduction of the ketone, a directed cyclopropanation followed by reductive ring opening strategy was used to install the required methyl group and build the all-carbon quaternary center. The Furukawa reagent was effective for the cyclopropanation. After the Ley oxidation and dissolving metal reduction, ketone **429** was obtained, then advanced to paecilomycine A. Notably, in 2012, Mehta and co-workers used a similar strategy to synthesize paecilomycine A.[177]

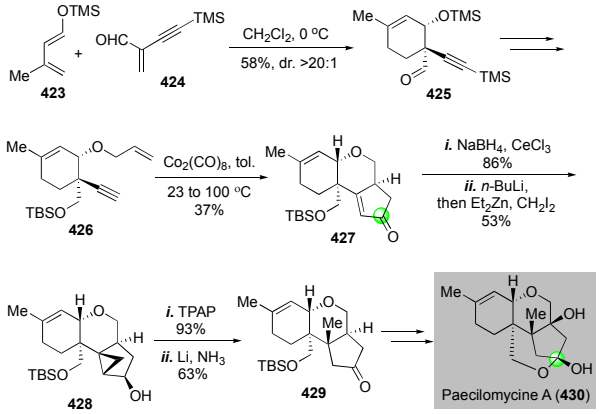

Fig. 67 The Danishefsky synthesis of paecilomycine A (2007)

Since its isolation by Kobayashi and co-workers, the complex marine anticancer alkaloid nakadomarin A has attracted a significant amount of synthetic attention. Among these, the Mukai group[178] and the Clark group[179] have used a Pauson-Khand strategy to build the key 5,6-fused bicycle (Fig. 68). Mukai and co-workers used a $Co_2(CO)_8$-mediated Pauson-Khand reaction to convert **431** to **432**, then to a formal synthesis of nakadomarin A. Clark and Xu used an efficient cobalt-catalyzed asymmetric Pauson-Khand reaction developed by Hiroi and co-workers[180] to set the first chiral center of their entire total synthesis and produce **434** in 72% yield and 97% ee from simple enyne **433**. Notably, a similar Pauson-Khand strategy was also employed by Magnus and co-workers in their synthetic efforts toward nakadomarin A and the manzamines.[181]

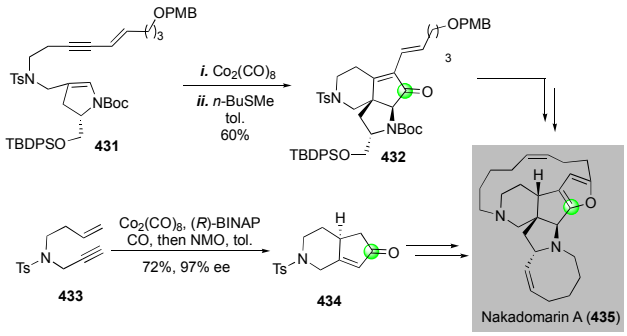

Fig. 68 The Mukai (2010) and Clark (2016) synthesis of nakadomarin A

Axinellamines A and B (**447**, **448**, Fig. 69) represent the most complex members of the bioactive pyrrole-imidazole marine alkaloid family. They present a daunting challenging to synthetic chemists. In 2011, Baran and co-workers revealed a remarkable synthetic approach which can be used to prepare gram-scale of both axinellamines A and B.[182,183] In their synthesis, a Pauson-Khand reaction between symmetric alkene **436** and terminal alkyne **437** under the conditions of $Co_2(CO)_8$, NMO and ethylene glycol in CH_2Cl_2 delivered cyclopentenone **438** in 46-58% yield and formed the cyclopentane core of the axinellamines. Notably, the combination of ethylene glycol and NMO is critical for the success of the Pauson-Khand reaction. It was hypothesized that they both were involved in the formation of a more reactive cobalt complex. The Pauson-Khand product was then transformed to trichloride **439** via Luche reduction and trichlorination with NCS/PPh_3. An unprecedented Zn/In-mediated Barbier reaction was developed for the union of trichloride **439** and aldehyde **440**, producing homoallylic alcohol **441** in 61% overall yield from **438**. After intermediate **441** was advanced to aminoimidazole **442** in five steps, DMDO oxidation with a subsequent TFA-promoted cyclization afforded **443** as a mixture of isomers. Baran and co-workers then employed a C-H oxidation mediated by silver(II) picolinate **444** to install the required hydroxyl group. A one-pot azide reduction with PtO_2/H_2 and acylation with 2,3-dibromo-5-trichloroacetylpyrrole led to the total syntheses of axinellamines A and B.

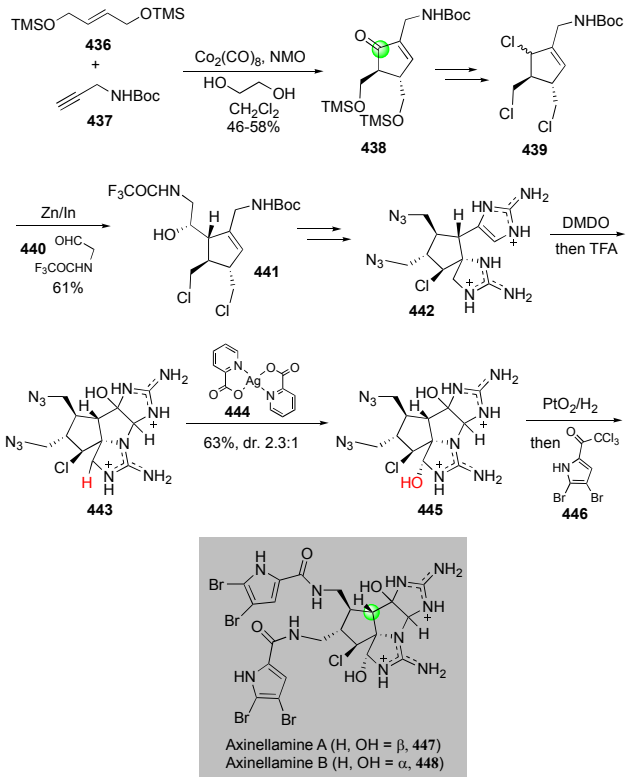

Fig. 69 The Baran synthesis of axinellamines-Baran (2011)

Jiadifenin, isolated by Fukuyama and co-workers from the pericarps of *Illicium jiadifengpi*, exhibited impressive neurotrophic activity in promoting neurite outgrowth of fetal rat cortical neuronal cells and has been a popular target for total synthesis. In 2012, Zhai and workers reported their total synthesis of jiadifenin, which features key steps such as the Ireland-Claisen rearrangement, the Pauson-Khand reaction, [2+2]-cycloaddition, and cyclobutanone fragmentation (Fig. 70).[184] In details, an Ireland-Claisen rearrangement was used to convert **449** to **450** in 54% yield with 7:1 diastereoselectivity. After protecting group manipulations, a $Co_2(CO)_8/Bu_3PS$-mediated Pauson-Khand reaction led to the conversion of enyne **451** to tricyclic intermediate **452**, which then underwent photochemical [2+2] cycloaddition with an allene to afford **453** in 87% yield (dr. 4.8:1). A fragmentation process involving ozonolysis of the newly formed *exo*-methylene and NaOMe-promoted C-C bond cleavage gave **454** in 89% yield, which was eventually advanced to jiadifenin in five steps.

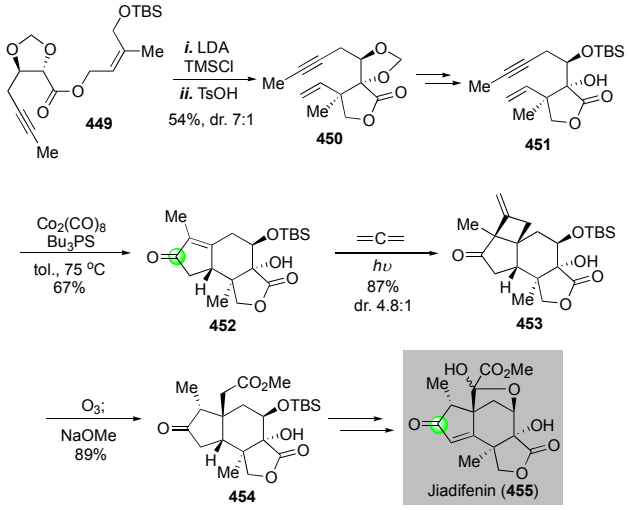

Fig. 70 The Zhai synthesis of jiadifenin (2012)

Since 2011, Yang and co-workers disclosed a series of impressive applications of the Pauson-Khand reaction in total synthesis of polycyclic bioactive natural products (Fig. 34 and Fig. 71).[185] In addition to their schindilactone A synthesis discussed in Fig. 34, their efforts toward pentalenolactone A methyl ester,[186] fusarisetin A,[187] propindilactone G,[188] retigeranic acids,[189] presilphiperfolanes,[190] and lancifodilactone G[191] are chronologically summarized in Fig. 71.

Pentalenolactones (**460**, Fig. 71A) are complex angular tricyclic natural products produced by prokaryotic organisms and have demonstrated a broad range of antimicrobial activities. Yang and co-workers utilized an intramolecular Pauson-Khand reaction of **456** upon the treatment of $Co_2(CO)_8$ under carbon monoxide atmosphere to furnish bicyclic enone **457** in 79% yield, which was subsequently converted to phosphonate **458**. An impressive

tandem conjugate addition and Horner-Wadsworth-Emmons *exo*-methylenation converted **458** to angular tricyclic lactone **459** in 60% yield, which was then advanced to pentalenolactone A methyl ester via a few functional group manipulations.

Fusarisetin A (**465**, Figure 71B) was reported to inhibit cancer cell migration and invasion without showing any significant cytotoxicity. Its intriguing effect on cancer metastasis coupled with its novel pentacyclic structure have rendered it an appealing target for total synthesis. Yang and co-workers used a $Co_2(CO)_8$-mediated Pauson-Khand reaction to convert enyne **461** to cyclopentenone **462** containing the fused 6-6-5 tricyclic carbon core. After **462** was transformed to vinytriflate **463**, a Heck carbonylation introduced the required carboxylate and resulted in **464** in 65% yield, from which fusarisetin A can be reached in seven steps.

Propindilactone G (**470**, Fig. 71C) belongs to a novel group of nortriterpenoid isolated by Sun and co-workers. In their continuing interest in synthesizing nortriterpenoids, Yang and co-workers accomplished an asymmetric synthesis of propindilactone G in 2015. Their synthesis features a Pauson-Khand reaction to build the fused 5-7-6-5 tetracyclic carbon skeleton by converting **466** to **467**. After the latter was advanced to **468**, an oxidative enolether heterodimerization initiated by ceric(IV) ammonium nitrate (CAN) oxidation was developed to append the side chain and produce **469** in high yield but as a mixture of four diastereomers. A sequence of Horner-Wadsworth-Emmons olefination, OsO_4-catalyzed dihydroxylation and concurrent lactonization was able to deliver propindilactone G in good yield.

In their synthetic studies toward the retigeranic acids (cf. **476**, Fig. 71D), Yang and co-workers used a $Co_2(CO)_8$/TMTU-mediated Pauson-Khand reaction to deliver **475** equipped with the desired tetracyclic core skeleton. Notably, they developed a novel rhodium-catalyzed [3+2] cycloaddition to convert **471** to **473** in 91% yield. This highly effective transformation was proposed to go through intermediate **472**, derived from a rhodium-catalyzed C-C bond cleavage. A formal [3+2] cycloaddition occurred next to form **473** with two challenging adjacent all-carbon quaternary centers.

In 2017, Yang and co-workers developed a tandem sequence of the Pauson-Khand reaction and 6π-electrocyclization to rapidly build the strained tricyclic core of presilphiperfolanols. As shown in Fig. 71E, a Sonogashira coupling between vinyltriflate **477** and enyne **478** led to the formation of **479** in 92% yield, which underwent a $Co_2(CO)_8$/TMTU-mediated Pauson-Khand reaction smoothly to produce triene **480**. Under the same reaction conditions, a 6π-electrocyclization took place to yield **481** in 94% yield from linear precursor **479**. Two presilphiperfolane analogs **482** and **483** were prepared from **481**.

In the same year, they also reported an elegant total synthesis of lancifodilactone G acetate (**486**, Fig. 71F). Similar to their schindilactone A synthesis, a $Co_2(CO)_8$/TMTU-mediated Pauson-Khand reaction was used to build the 5,5-fused ring system and convert **484** to **485**, then to lancifodilactone G acetate **486**.

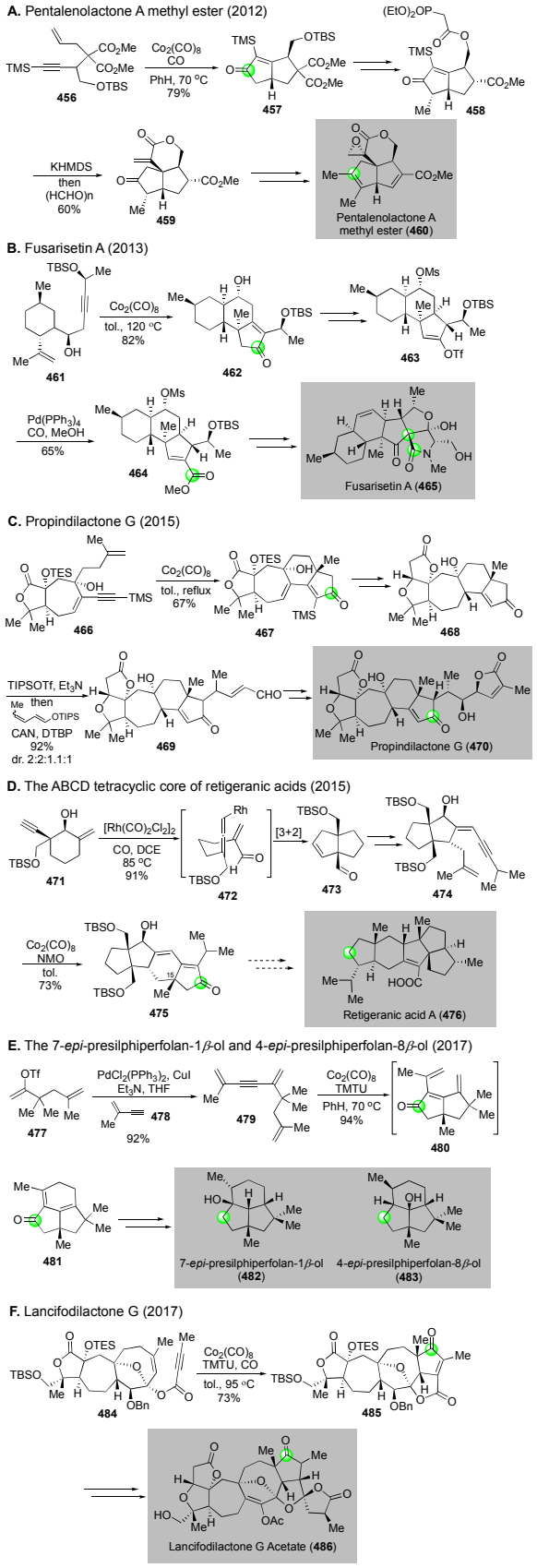

Fig. 71 Total synthesis via Pauson-Khand reaction from Yang and co-workers.

The complex diterpene natural product ryanodol has been a long-standing synthetic challenge. Biologically, ryanodol and related analogs modulate intracellular calcium-ion release at the ryanodine receptors. In 2016, Reisman, Chuang, and Xu disclosed a remarkable 15-step total synthesis of ryanodol (Fig. 72).[192] Starting from chiral pool molecule (*S*)-pulegone (**487**), Reisman et al. quickly accessed intermediate **488**, which was subjected to Grignard addition with ethoxyethynylmagnesium bromide followed by a silver(I)-catalyzed cyclization and elimination cascade to afford α,β-unsaturated lactone **489** in good yield. A subsequent conjugate addition with vinylcuprate derived from vinylMgBr and CuI led to the formation of an all-carbon quaternary center and produced enyne **490** for the following Pauson-Khand reaction. While cobalt or molybdenum carbonyl complexes are effective for the Pauson-Khand reaction, $[RhCl(CO)_2]_2$ was optimal for catalyzing the desired [2+2+1] cycloaddition under 1 atm of carbon monoxide at 110 °C. Enone **491** was produced in 5.7 g at a single pass. They then discovered an amazingly effective triple oxygenation to convert **491** to **492** by simply heating **491** in presence of SeO_2. With **492** in hand, the 2-propenyl group was introduced via a sequential vinyl triflate formation using the Comins' reagent and Stille cross coupling with 2-propenylstannane. Product **493** was produced in good yield then advanced to epoxide **494** in three steps. Subjection of **494** to Li/NH_3 triggered a reductive cyclization to afford ryanodol in 38% yield.

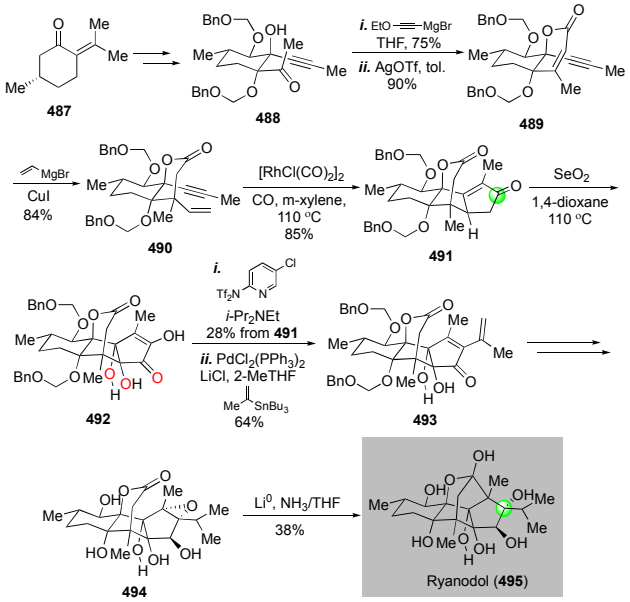

Fig. 72 The Reisman synthesis of ryanodol (2016)

In 2016 and 2017, Trauner and co-workers reported their total synthesis of lycopalhine A[193] and sinoracutine[194] respectively. Both syntheses used the Pauson-Khand strategy to construct the key cyclopentenone intermediates. In particular, $Co_2(CO)_8$-mediated [2+2+1] cycloaddition converted enyne **496** to cyclopentenone **497**.

A subsequent conjugate addition led to the formation of **498**, which was then elaborated to lycopalhine A (**499**) with steps involving Mannich cyclization and intramolecular aldol reaction to build the additional ring systems (Fig. 73A). In their sinoracutine synthesis, Pauson-Khand reaction of **500** under oxidative reaction conditions resulted in the formation of tricyclic intermediate **501**, which was then reduced to the corresponding allylic alcohol. After the failures of using Eschenmoser or Johnson-Claisen strategy to convert **501** to **502** with an all-carbon quaternary benzylic stereocenter, Trauner and co-workers used the Mandai two-step protocol to realize this transformation. Particularly, oxa-Michael addition to vinyl sulfoxide followed by elimination of sulfenic acid and subsequent [3,3] sigmatropic rearrangement delivered aldehyde **502** in 57% yield. A combination of reductive amination, iodoamination and Kornblum oxidation was able to convert **502** to **503**. Sinoracutine was reached from **503** via a sequence of Mukaiyama oxidation, elimination of the silyl alcohol and debenzylation.

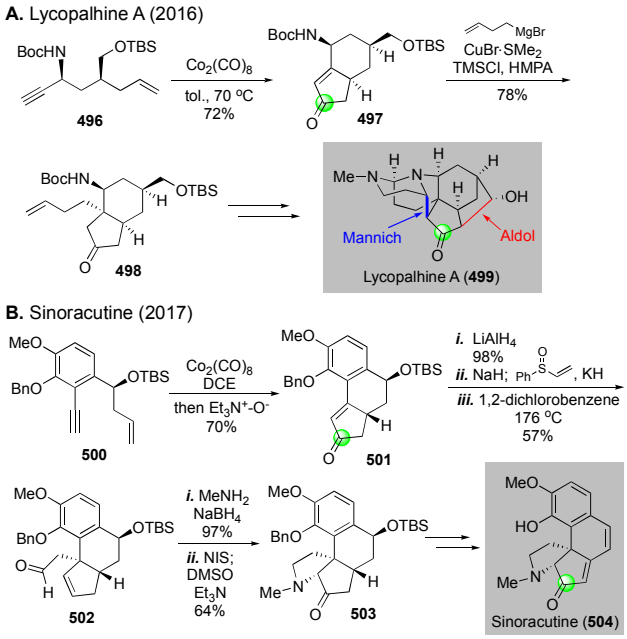

Fig. 73 The Trauner synthesis of lycopalhine A and sinoracutine

Astellatol contains a unique bicyclo[4.1.1]octane moiety and a strained *trans*-hydrindane, both of which are tempting and challenging for synthetic chemists. In 2018, Xu and co-workers offered a solution to these problems and completed the first total synthesis of astellatol (Fig. 74).[195] Their synthesis used an intramolecular Pauson-Khand reaction to convert enyne **505** to polycyclic compound **506**, which was further advanced to **507** via a sequential base-promoted elimination, ethyl ester formation, DIBAL-H reduction, and the Ley-Griffith TPAP oxidation. Compound **507** was next treated with SmI_2 to trigger a reductive 1,6-radical addition to build the bicyclo[4.1.1]octane moiety and a mixture of **508** and **509** was obtained in 64% total yield. Both **508** and **509** were then converted to **510** via hydrogenation to reduce the corresponding dienes and TPAP oxidation of the secondary alcohol. Compound **510** was eventually transformed to astellatol in seven steps including one hydroxy group-directed hydrogenation using Crabtree's catalyst to build the *trans*-hydrindane ring system.

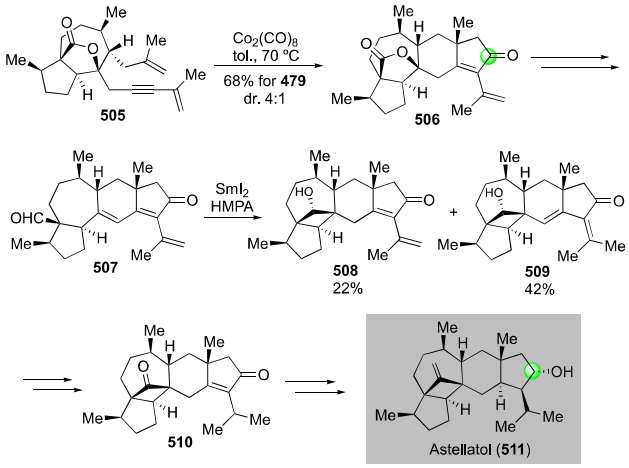

Fig. 74 The Xu synthesis of astellatol (2018)

The *Daphniphyllum* alkaloids are a large group of natural products containing fascinating polycyclic architectures that have attracted many synthetic efforts. In 2012, Dixon and co-workers reported an expedient synthesis of the 7-5-5 tricyclic core of the *Daphniphyllum* alkaloids daphnilongeranin B and related analogs using a key intramolecular Pauson-Khand reaction to construct the 5,5-fused ring system.[196] The Pauson-Khand strategy was also employed by Li and co-workers to build the same 5,5-fused ring system, but at a much late strategy, which eventually led to the total synthesis of daphnilongeranin B, hybridaphniphylline B, and two other natural analogs (Fig. 75).[197] In particular, compound **512** underwent the desired [2+2+1] cycloaddition with $Co_2(CO)_8$ to afford **513** as a mixture of two diastereomers, both of which were then converged to **514** via a K_2CO_3-promoted isomerization process and **514** was obtained in 63% yield from **512**. Reduction of the thiolactam with Raney Ni led to the formation of daphnilongeranin B (**515**) at gram scale. On the other hand, Luche reduction of **514** yielded alcohol **516** in 99% yield. When a mixture of **516** and **517** (derived from natural product genipin) was heated at 160 °C in presence of $MgSO_4$, a tandem dehydration and intermolecular Diels-Alder reaction took place to afford a mixture of four isomers in total 61% yield. The major isomer was isolated as **518** in 24% yield, which was advanced to hybridaphniphylline B via Raney Ni reduction of the thiolactam and removal of all the acetyl groups.

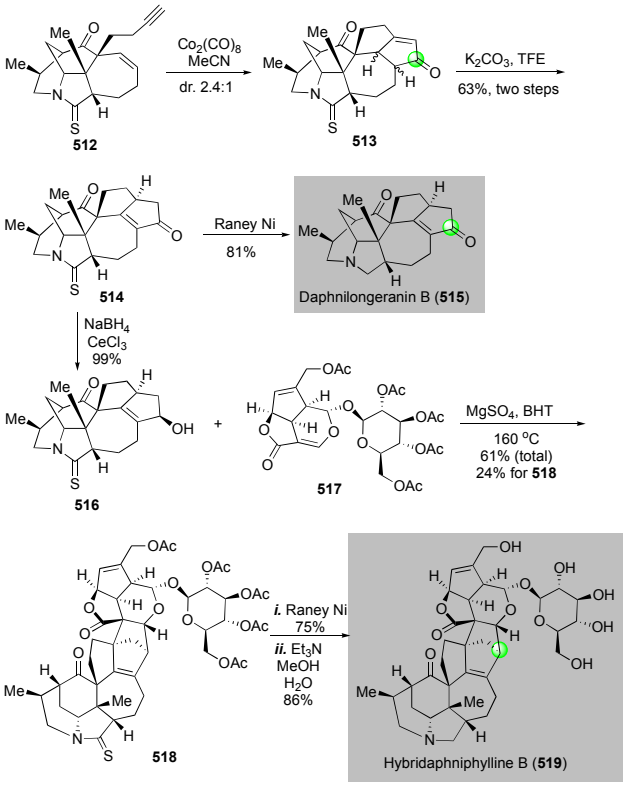

Fig. 75 The Li synthesis of daphnilongeranin B and hybridaphniphylline B (2018)

In addition to the above discussed cases, alkyne-alkene Pauson-Khand reaction has been widely used in many other natural product total syntheses as well as synthetic studies.[198-204] A collection of natural products completed via an alkyne-alkene Pauson-Khand reaction as a key step is listed in Fig. 76.[205-223]

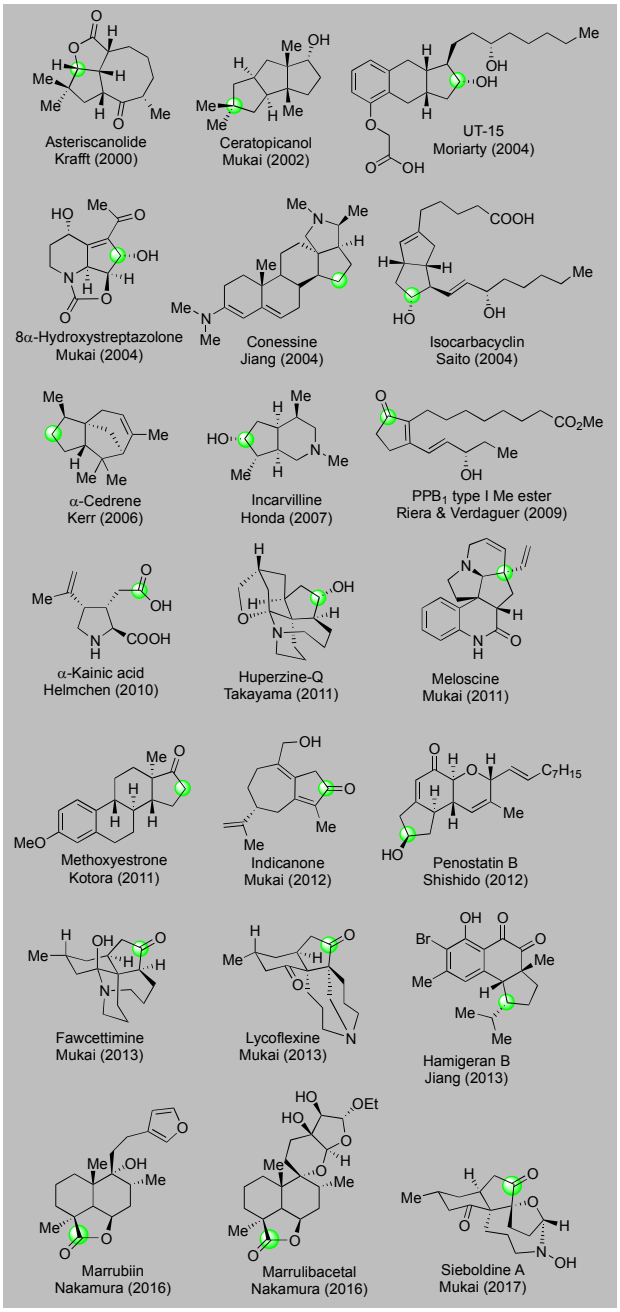

Fig. 76 Selected natural products synthesized after 2000 via a Pauson-Khand reaction.

4.2.2. The allenic Pauson-Khand reaction

After the seminal discovery of the alkyne-alkene Pauson-Khand reaction, another major breakthrough was discovered by Brummond and co-workers, who first reported that allenic substrates were effective for the Pauson-Khand [2+2+1] cycloaddition.[224-226] In general, under the catalytic system of $[Rh(CO)_2Cl]_2$ or $Mo(CO)_4$ in the presence of carbon monoxide, allene-alkyne substrate **520** can be converted to cycloaddition

product **521** or **522** in high yield and selectivity by tuning the reaction conditions and the substrate structure (Fig. 77A).[227] Brummond and co-workers have utilized these novel cycloaddition strategies to create both natural products and unnatural small-molecule libraries. For example, in 1999, they completed an elegant total synthesis of hydroxymethylacylfulvene **525** by using their allenic Pauson-Khand reaction to covert **523** to **524** with a stoichiometric amount of $Mo(CO)_6$ (Fig. 77B).[228] They also utilized a silicon-tethered allenic Pauson-Khand strategy to construct the highly unsaturated cyclopentenone ring system of a prostaglandin molecule **528** by converting **526** to **527** (Fig. 77C).[229] The synthetic efficiency in building polycyclic ring systems through the allenic [2+2+1] strategy has been further showcased by their rapid construction of the tricyclic core skeletons of the guancastepenes (Fig. 77D)[230] as well as the 6,12-guaianolides (Fig. 77E).[231] In particular, with 10 mol% of $[Rh(CO)_2Cl]_2$ under carbon monoxide atmosphere, substrates **529** and **532** were converted to **530** and **533** respectively in good yields.

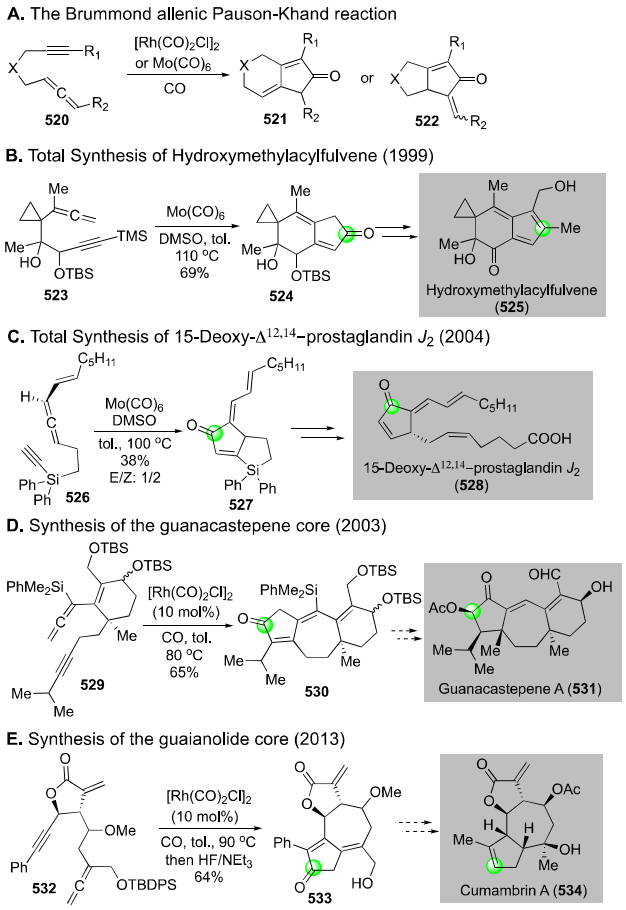

Fig. 77 The Brummond allenic Pauson-Khand reaction

In 2013, Baran and co-workers reported a remarkable 14-step synthesis of ingenol by starting from (+)-3-carene (Fig. 78).[232,233] One of their key steps involves a Brummond allenic [2+2+1] cycloaddition catalyzed by $[Rh(CO)_2Cl]_2$ to convert **535** to **536** with a fused 5-7-6-3 tetracyclic carbon skeleton. The latter was then advanced to **537** for a vinylogous pinacol rearrangement to deliver the in,out-[4.4.1] carbon skeleton of ingenol. The rearrangement was ultimately realized by treating **537** with BF_3 etherate in CH_2Cl_2 at low reaction temperatures followed by quenching with NEt_3 and MeOH and **538** was obtained in 80% yield. With **538** in hand, two SeO_2-mediated allylic oxidations, one Martin's sulfurane dehydration, and removal of the carbonate delivered the final product ingenol **539** in a total fourteen steps.

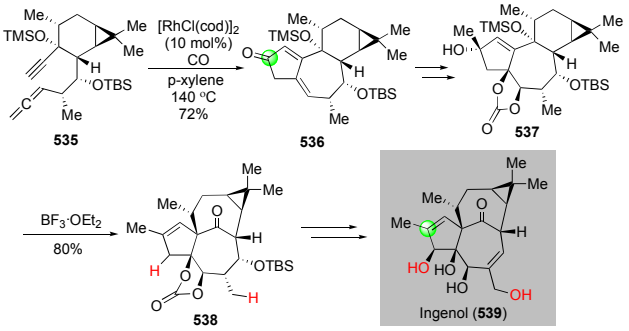

Fig. 78 The Baran synthesis of ingenol (2013)

Ileabethoxazole was isolated by Rodriguez and co-workers from the Caribbean octocoral *Pseudopterogorgia elisabethae* in 2006. This unique but scarce natural product has exhibited potent inhibition activity against *Mycobacterium tuberculosis* ($H_{37}R_v$). In 2014, Williams and Shah reported an enantioselective total synthesis of ileabethoxazole (Fig. 79).[234] They uncovered an iron carbonyl complex-mediated allenic [2+2+1] cycloaddition to convert **540** to cyclopentenone **542** under ambient reaction temperatures. Other carbonyl complexes such as $Mo(CO)_6$ and $Co_2(CO)_8$ were ineffective mainly because these complexes require elevated reaction temperatures, but substrate **540** was heat sensitive. The iron-mediated allenic [2+2+1] cycloaddition was proposed to go through three-membered iron metallacycle **541**. After converting **542** to **543**, an intramolecular aldol condensation was employed to form the central aromatic ring and product **544** was obtained in 93% with KO*t*-Bu as base. Compound **544** was eventually transformed to ileabethoxazole after introduction of the three chiral centers in the cyclopentane ring and installation of the side chain.

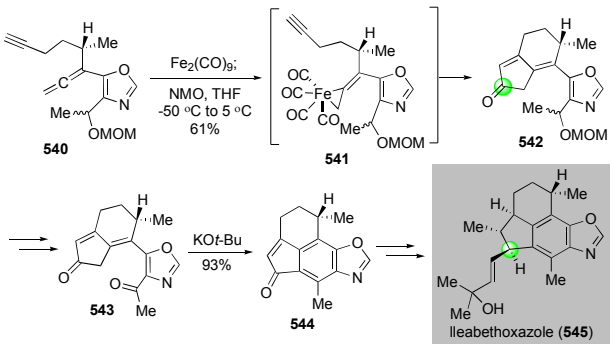

Fig. 79 The Williams synthesis of ileabethoxazole (2014)

In 2015, Cramer and Heinz revealed an elegant total synthesis of fijiolide A, a secondary marine metabolite with inhibition activity against transcription factor NFκB (Fig. 80).[235] Structurally, fijiolide A is believed to be derived from a putative enediyne precursor pre-fijiolide via a biradical Bergman cyclization followed by chlorination to form the aromatic ring embedded in the 5-5-6 fused tricyclic system. Their synthesis commenced with a boronate-templated [2+2+2] cyclotrimerization of **546**, **547**, and **548** catalyzed by Cp*Ru(cod)Cl to yield arylboronate **549** in 59% yield. A subsequent Cu-catalyzed chlorination delivered **550** in 70% yield. After removal of the three silyl groups and isomerization of the propargyl group to an allene with TBAF (cf. **551**) and protecting the 1,2-diol as TBS-ethers, a $Mo(CO)_6$-mediated allenic Pauson-Khand reaction gave indenylcyclopentenone **552**, which was ultimately advanced to fijiolide A (**553**).

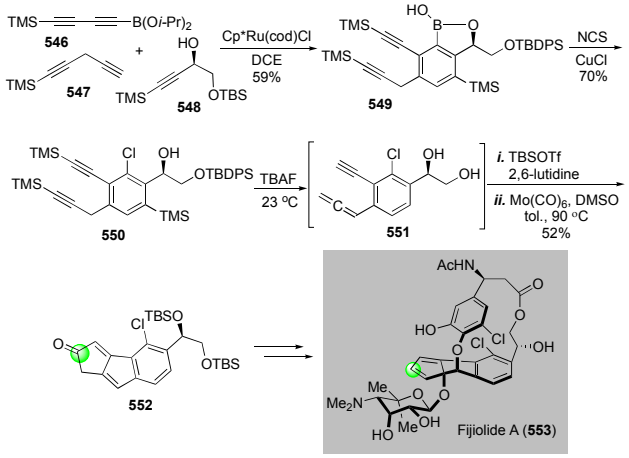

Fig. 80 The Cramer synthesis of fijiolide A (2015)

In addition to the aforementioned allene-alkyne [2+2+1] cycloadditions, allene-alkene [2+2+1] cycloaddition has been used in natural product synthesis. In 2008, Mukai and co-workers completed the total syntheses of two sesquiterpene natural products with a palladium-catalyzed carbonylative allenoate synthesis and allene-alkene Pauson-Khand reaction as key transformations (Fig. 81).[236] Using the procedure developed by Tsuji et al.,[237] propargyl carbonate **554** was elaborated to allenoate **555** with $Pd(OAc)_2/PPh_3$ as catalyst in MeOH under 10 atm of carbon monoxide. A subsequent $[RhCl(cod)]_2$-catalyzed intramolecular [2+2+1] cycloaddition led to the formation of **556**, which was then converted to sesquiterpenoid 1 (**557**) and its analog.

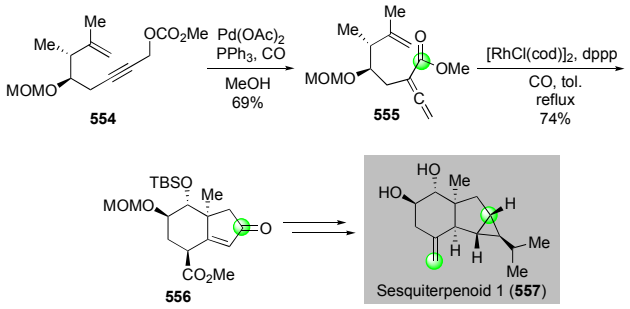

Fig. 81 The Mukai synthesis of sesquiterpenoid 1 (2008)

Perforanoid A was isolated from Meliaceae and Simaroubaceae species. Its gross structure was determined by NMR analysis, but the C10 configuration remained unclear. Hao, Yang and co-workers had recourse to total synthesis to solve this structural issue after failing in obtaining a crystal structure of the natural product. Their synthesis features a $[Rh(CO)_2Cl]_2$-catalyzed intramolecular [2+2+1] cycloaddition to build the 5-6-5 fused tricyclic product **559** from **558** in 85% yield (Fig. 82).[238] Rapid access to **559** enabled them to prepare both perforanoid A and its C10 epimer and finally elucidate the correct configuration at C10.

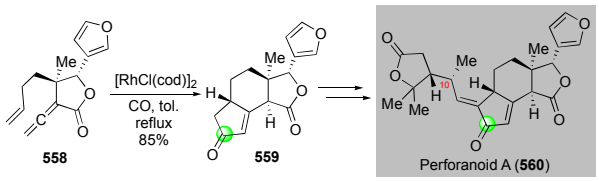

Fig. 82 The Hao and Yang synthesis of Perforanoid A (2016)

4.3. Rh-catalyzed [n+m+1] carbonylative cycloaddition

Pioneered by Wender,[239-244] Yu,[245] Tang,[246] Evans,[247] Bower[248-250] and others, the rhodium-catalyzed [n+m+1] carbonylative cycloaddition reactions have been effective methods in building cyclic ketones with different ring sizes. In this section, the application of rhodium-catalyzed [3+2+1], [5+1], and [5+2+1] cycloadditions in natural product synthesis are highlighted.

4.3.1. [3+2+1] cycloaddition

By replacing one of the unsaturated double or triple bond of the Pauson-Khand reaction substrate with a vinylcyclopropane, Yu and co-workers developed a novel rhodium-catalyzed [3+2+1] carbonylative cycloaddition process to convert 1-yne/ene-vinylcyclopropanes **561** to cyclohexe(a)nones **562** (Fig. 83),[251,252] which are prevalent in many bioactive natural products. The use of vinylcyclopropane is critical for the high yield of this transformation, as Narasaka et al. demonstrated it required harsh reaction conditions for simple cyclopropane-alkyne substrates and the corresponding yields were generally low.[253] The vinyl group serves as an activating group for a rhodium-catalyzed cyclopropane ring cleavage (**561**→**563**). A subsequent alkyne or alkene insertion

would give intermediate **564**. Carbon monoxide migratory insertion to the Rh-C bond would afford rhodacyclohepte(a)none **565**, which could be converted to product **562** via a reductive elimination process.

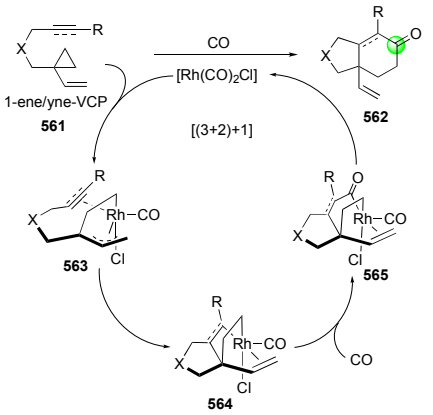

Fig. 83 Rhodium-catalyzed [3+2+1] carbonylative cycloaddition

Since its discovery, the rhodium-catalyzed 1-yne/ene-vinylcyclopropanes [3+2+1] carbonylative cycloaddition process has been utilized by Yu and co-workers to synthesize a series of natural products including α-agarofuran, lycoramine,[254] galanthamine, gracilamine,[255] and cloven-2,9-dione (Fig. 84).[256] In general, the yields for the key [3+2+1] cycloadditions are good to excellent with modest to high diastereoselectivity. For the cases of **566**, **573**, and **576** containing a 1-yne-vinylcyclopropane moiety, the corresponding cyclohexenones were produced. Substrate **569** contains a 1-ene-vinylcyclopropane, leading to the formation of the cyclohexanone product.

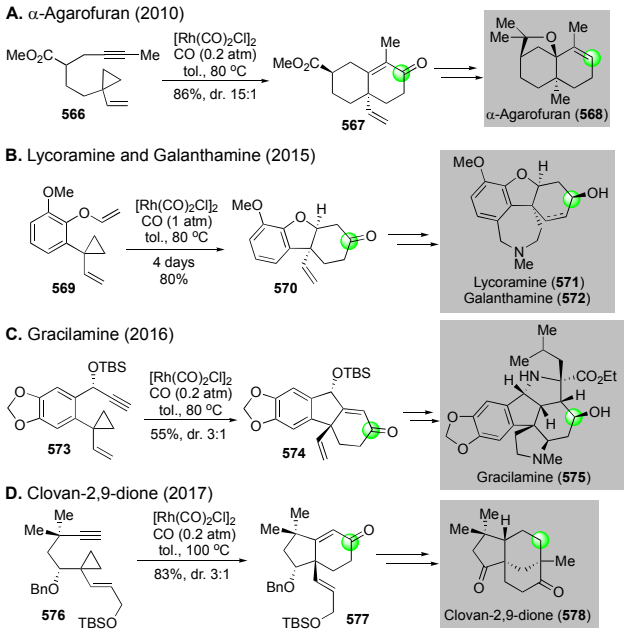

Fig. 84 Rhodium-catalyzed [3+2+1] cycloaddition in total synthesis

4.3.2. [5+1] cycloaddition

When there is no alkene/alkyne tethered in the same molecule with a vinylcyclopropane, a [5+1] carbonylative cycloaddition could take place to build a cyclohexenone motif (Fig. 85A). The reaction is generally mediated by a transition metal carbonyl complex such as $Fe(CO)_5$ or catalyzed by a rhodium catalyst under carbon monoxide atmosphere. Sarel et al. reported an early example in 1969.[257] When $Fe(CO)_5$ was used, both thermal and photoirradiation conditions were effective in promoting the [5+1] cycloaddition. The latter was extensively studied by Taber and co-workers[258-260] and applied in several of their natural product syntheses (Fig. 85B and 85C).[261-263] For example, a $Fe(CO)_5$-mediated photochemical vinylcyclopropane [5+1] cycloaddition in combination with a DBU-promoted isomerization were used to convert **586** to delobanone **587** in 64% yield. Vinylcyclopropane **586** was derived from nitrile **585**, which was prepared via a double alkylation of CH_3CN with epoxide **584** in high yield. They also utilized a similar protocol to convert vinylcyclopropane **588** to cyclohexenone **589** to complete a total synthesis of coronafacic acid **590**.

In addition to using stoichiometric iron carbonyl complexes, de Meijere et al. revealed that the vinylcyclopropane [5+1] cycloaddition can be catalyzed by $Co_2(CO)_8$ and $[Rh(CO)_2Cl]_2$ under carbon monoxide atmosphere.[264] This catalytic process was later generalized by Yu and co-workers by using cationic rhodium catalysts.[265] They further demonstrated the catalytic vinylcyclopropane [5+1] cycloaddition process in an asymmetric total synthesis of mesembrine (Fig. 85D).[266] As shown, with a 15 mol% of [Rh(dppp)]OTf, under 1 atm of carbon monoxide in DCE at 90 °C, vinylcyclopropane **591** was converted to **592** in 73% yield. A subsequent $Pd(OAc)_2$/(*S*)-Antphos-catalyzed enantioselective intermolecular Heck reaction using arylbromide **593** afforded **594** with an all-carbon quaternary center. After removal of the Boc protecting group and an intramolecular aza-conjugate addition, mesembrine **595** was obtained in 73% and 86% ee.

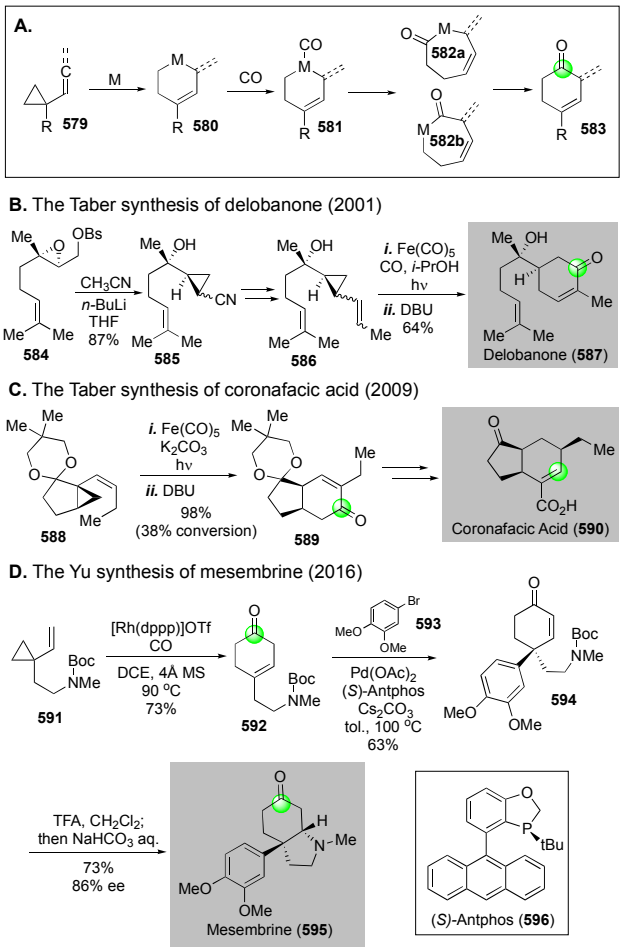

Fig. 85 Vinylcyclopropane [5+1] cycloaddition

When an allenylcyclopropane is used as substrate in the [5+1] carbonylative cycloaddition, a cyclohexenone product with an additional *exo*-olefin can be prepared. A few transiton metal complexes such as $Co_2(CO)_8$,[267,268] $IrCl(CO)(PPh_3)_2$,[269] and $[Rh(CO)_2Cl]_2$[270] have been shown to be able to promote or catalyze this [5+1] cycloaddition mode. In 2012, Tang and Zhang utilized the rhodium-catalyzed allenylcyclopropane [5+1] cycloaddition strategy to build the key cyclohexenone core of welwitindolinones.[271] As shown in Fig. 86A, chlorination of α-diazoester **597** delivered unstable chloro-α-diazoester **598**, which upon subjection to the Du Bois' $Rh_2(esp)_2$-catalyzed intramolecular cyclopropanation was converted to **599** in 50-60% yield. Compound **599** was then advanced to the key allenylcyclopropane intermediate **600** in six steps. A $[Rh(CO)_2Cl]_2$-catalyzed [5+1] cycloaddition converted **600** to **601** containing the desired indole and cyclohexenone ring for their future synthesis of welwitindolinones. In 2016, Yu et al. reported their second formal synthesis of galanthamine (Fig. 86B).[272] Their new approach features an early stage $[Rh(CO)_2Cl]_2$-catalyzed [5+1] cycloaddition to convert allenylcyclopropane **603** to cyclohexenone **604**. Subsequent CBS-reduction of the resulting ketone gave allylic alcohol **605** in 79% yield and 97% ee. After transforming **605** to **606** in three steps, they used an intramolecular radical cyclization initiated by AIBN/Bu_3SnH to provide **607**, which was eventually advanced to galanthamine.

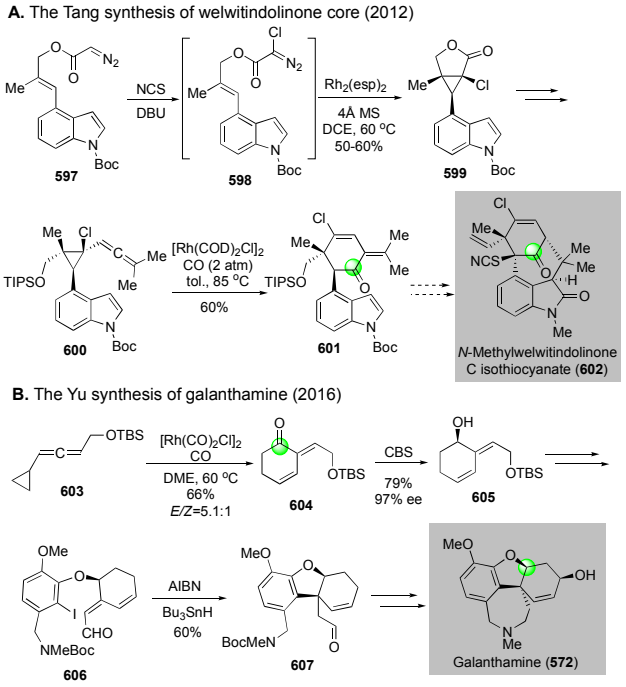

Fig. 86 Allenylcyclopropane [5+1] cycloaddition

In 2013, Tang and co-workers revealed a different type of rhodium-catalyzed [5+1] cycloaddition involving 3-hydroxy-1,4-enyne as the 5-carbon component instead of using the aforementioned vinyl/allenylcyclopropanes as substrates (Fig. 87).[273] As a result, polysubstituted phenols could be produced. They have employed this novel transformation to complete a total synthesis of mahanimbine (**610**) and a few other carbazole-containing natural products.[274] For example, upon the treatment of a catalytic amount of $[Rh(CO)_2Cl]_2$ under carbon monoxide atmosphere in DCE at 60 °C, 3-hydroxy-1,4-enyne **608** was converted to carbazole **609** in a single step. The catalytic cycle was proposed to initiate with coordination of enyne substrate on the rhodium metal center to trigger a tandem cyclization process to convert complex **611** to rhodacycle **612**. The latter would then undergo a 6π-electrocyclic ring opening reaction to give rhodium carbenoid **613**. Carbon monoxide insertion would convert **613** to ketene **614**. A subsequent 6π-electrocyclic ring closure process would deliver enone **615**, which could tautomerize to carbazole **609**. After removal of the Boc-protecting group, a simple heating of the resulting carbazole with citral completed the total synthesis of mahanimbine.

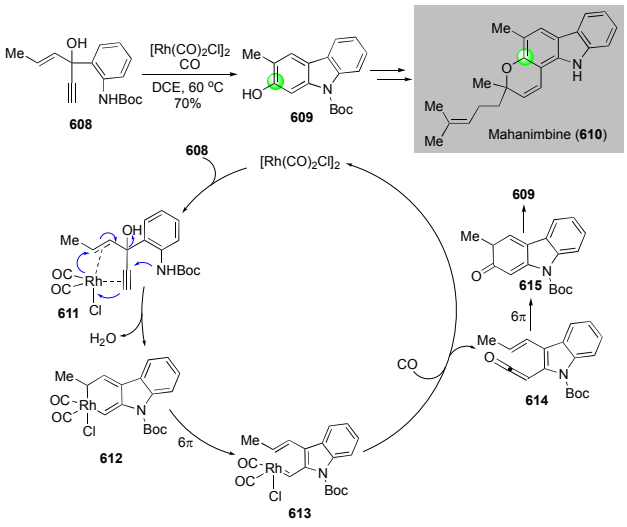

Fig. 87 The Tang synthesis of mahanimbine (2016)

In 2016, Tang and co-workers disclosed a modified rhodium-catalyzed [5+1] carbonylative cycloaddition to synthesize highly substituted benzofurans (Fig. 88, **616**→**617**).[275] In this case, 1-furylpropargylic esters are used as substrates. As shown in Fig. 88, a rhodium-catalyzed 1,2-pivalate migration via **618** would convert **616** to **619**, which would then undergo a sequence of carbon monoxide migratory insertion, ketene formation, 6π-electrocyclic ring closure and tautomerization to give rise to benzofuran **617**. Compound **617** was then converted to a few benzofuran natural products including viniferifuran (**622**) via two palladium-catalyzed cross coupling reactions to append the styrene and aryl moieties.

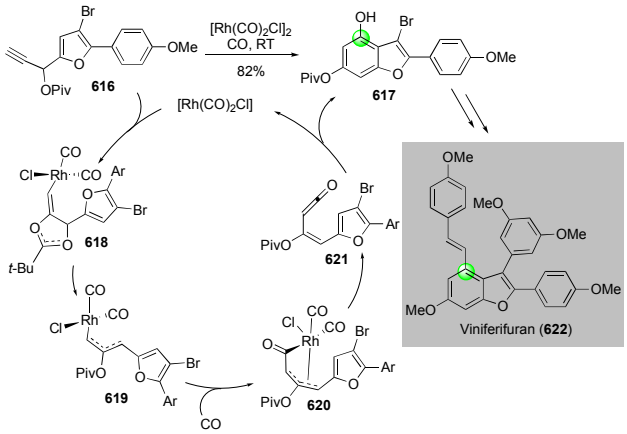

Fig. 88 The Tang synthesis of viniferifuran (2017)

4.3.3. [5+2+1] cycloaddition

While eight-membered carbocycles are frequently found in many bioactive natural products, efficient construction of strained eight-membered carbocycles still presents a synthetic challenge. In continuation of their studies in [n+m+o] cycloaddition reactions, the Wender group reported the first transition metal-catalyzed three-component [5+2+1] carbonylative cycloadditions to provide a rapid access of cyclooctenone products (Fig. 89A).[276,277] In this case, a vinylcyclopropane (**623**) and an active alkyne (**624**) were used to undergo cycloaddition with a molecule of carbon monoxide in the presence of $[Rh(CO)_2Cl]_2$ catalyst. They also demonstrated that an acid-promoted transannular aldol reaction could convert the cyclooctenone product **625** to a 5,5-fused bicyclic product **626**. Later in 2007, with the guidance of computational calculations, Yu and co-workers developed a rhodium-catalyzed two-component [5+2+1] cycloaddition of ene-vinylcyclopropane **627** with carbon monoxide to access cyclooctenone **630** via metallocycles **628** and **629** (Fig. 89B).[278] This new [5+2+1] cycloaddition strategy has been applied by Yu and co-workers to synthesize several natural products.

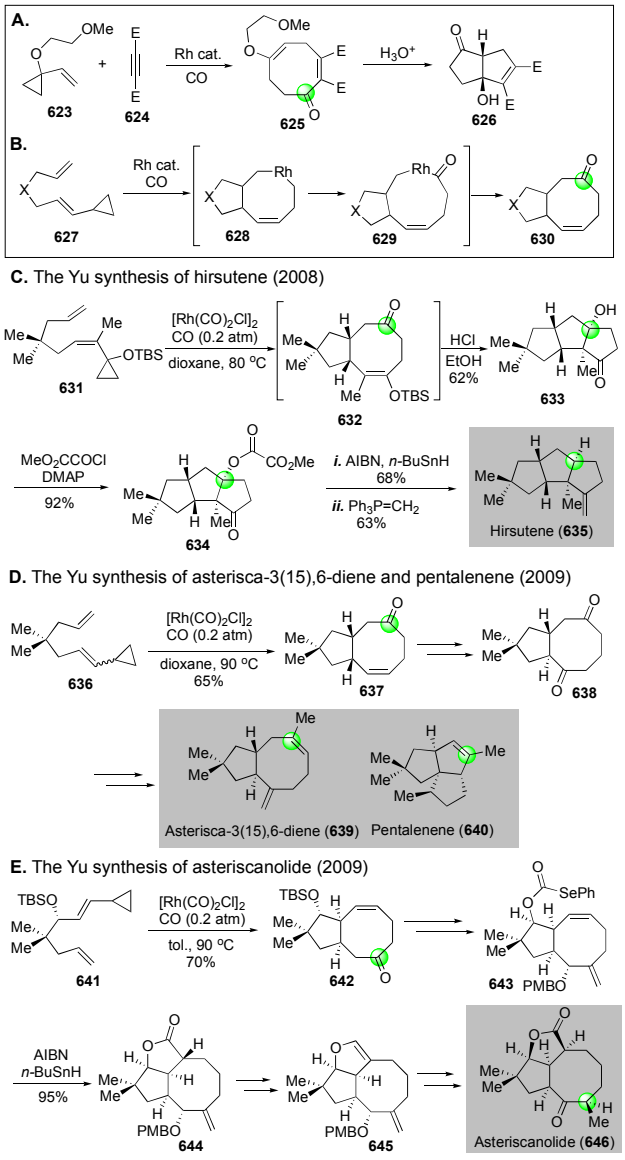

Fig. 89 [5+2+1] cycloaddition in total synthesis

They first utilized it for a total synthesis of hirsutene and related analogs in 2008 (Fig. 89C).[279] Upon the treatment of siloxy-ene-vinylcyclopropane **631** derived from a Simmons-Smith reaction with 5 mol% of $[Rh(CO)_2Cl]_2$ catalyst under 0.2 atm of carbon monoxide in dioxane at 80 °C, desired product **632** was obtained, which underwent a subsequent acid-promoted transannular aldol reaction to deliver **633** in 62% yield. After a radical deoxygenation process via oxalate **634** and a Wittig methylenation, a concise total synthesis of hirsutene was completed. In 2009, Yu and co-workers employed a similar strategy to complete formal syntheses of asterisca-3(15),6-diene (**639**) and pentalenene (**640**).[280] The rhodium-catalyzed [5+2+1] cycloaddition converted **636** to **637** in 65% yield (Fig. 89D). The latter served as a key intermediate for their asterisca-3(15),6-diene and pentalenene syntheses. The same strategy was also used to build the cyclooctanone moiety of asteriscanolide (**646**, Fig. 89E).[281] After forming cyclooctenone **642** from ene-vinylcyclopropane **641**, an intramolecular acyl radical cyclization was employed to build the 5-membered lactone and afford 95% yield of **644**, which was later converted to asteriscanolide.

4.4. Macroketonization

Catalytic carbonylation is also capable of forming macrocyclic ketones. One classic example is from the Stille-Hegedus collaborative synthesis of jatrophone (Fig. 90A), where they used the Stille carbonylation reaction to build the macrocyclic dienone system of jatrophone (**647**→**648**).[282] Later in 2001, Rawal and co-workers used stannyl triflate **649** to create the macrocyclic ketone of phomactins C and D (Fig. 90B).[283] Under the Stille carbonylative cross coupling conditions, product **650** was produced in modest yield. This carbonylative macrocyclization offers an efficient approach to access the bridged bicyclic core of the phomactins. In general, despite the power of assembling macrocyclic ketones, the carbonylative macroketonization is underused.

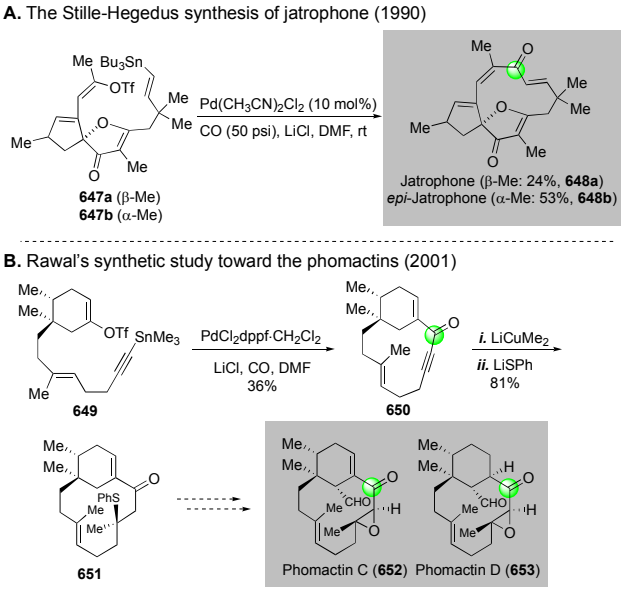

Fig. 90 The Stille carbonylative macroketonization

5. Miscellaneous Catalytic Carbonylative Cyclizations

The carbonylative benzannulation mediated by Fisher carbenes, the Dötz annulation, is highly effective in synthesizing densely oxygenated arenes (Fig. 91A). The three-component reaction involves an α,β-unsaturated chromium carbene, an alkyne, and a molecule of carbon monoxide and goes through a sequential alkyne insertion and carbon monoxide insertion to form vinylketene **657** for a 6π-electrocyclic ring closure to form phenol product **658**. Since its discovery, the Dötz annulation has been frequently used in natural product synthesis.[284] Two recent examples are highlighted in this section.

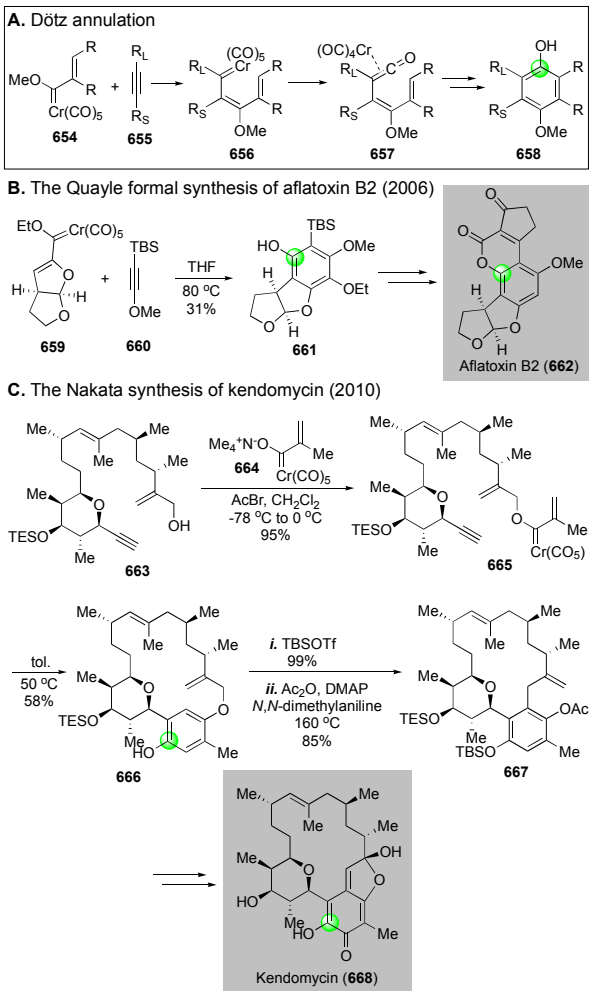

Fig. 91 The Dötz annulation

In 2006, Quayle and co-workers utilized the Dötz annulation to convert Fisher carbene **659** and alkyne **660** to tricyclic phenol **661** in 31% yield (Fig. 91B). The bulky TBS group was used to impart high regioselectivity and was removed at a later stage. A formal synthesis of aflatoxin B2 was achieved by using the Dötz annulation strategy.[285]

The second example is from Nakata, Saikawa and co-workers (Fig. 91C),[286] who employed an impressive macrocyclic Dötz annulation developed by Wulff[287] and co-workers to construct the cyclophane motif of kendomycin, a potent antibacterial and anticancer natural product isolated from *Streptomyces*. The macrocyclization precursor **665** was prepared by reacting alcohol **663** with an acetoxychromium carbene complex generated in situ from chromate **664** via AcBr treatment. The subsequent macrocyclic Dötz annulation occurred in toluene at 50 °C to provide cyclophane **666** in 58% yield. After protecting the resulting phenol as TBS-ether, a sequence of macrocyclic Claisen rearrangement and acetate formation delivered **667** in 85% yield. The in situ trapping of the newly formed phenol with Ac_2O/DMAP was critical for preventing the formation of a dihydrobenzofuran byproduct via a 5-*exo*-*trig* cyclization of the phenol on the *exo*-methylene moiety. Compound **667** was eventually transformed to kendomycin in ten steps.

In 1998, Mitsudo and co-workers developed a hydroquinone synthesis via a $Ru_3(CO)_{12}$-catalyzed [2+2+1+1] cycloaddition of an alkyne, 2-norbornene and two molecules of carbon monoxide.[288] This four-component process can lead to unsymmetrically substituted hydroquinones in high yields and has been utilized by Sarpong and co-workers in their formal synthesis of *cis*-trikentrin A and herbindole B.[289] As shown in Fig. 92, the $Ru_3(CO)_{12}$-catalyzed [2+2+1+1] cycloaddition united alkyne **669**, strained bicyclic alkene **670** and two carbon monoxide molecules to provide symmetric hydroquinone **671** in 39% yield. The two hydroxyl groups were then differentially converted to a triflate and a tosylate for a sequential palladium-catalyzed Stille cross coupling to install the methyl group and Buchwald-Hartwig amination to introduce the free amine group. After obtaining aniline triflamide **674** from **673**, Sarpong and co-workers developed a tandem palladium-catalyzed intramolecular C-H amination and oxidation of the resulting indoline to provide indole **675** in 66% yield. Indole **675** was then converted to a Kerr's intermediate for their herbindole B synthesis.[290] Additionally, the triflate group of **674** was reduced via Pd/C-catalyzed hydrogenation. Following a similar process for the herbindole synthesis, the reduced product **676** was then advanced to another Kerr's intermediate to complete a formal synthesis of *cis*-trikentrin A.

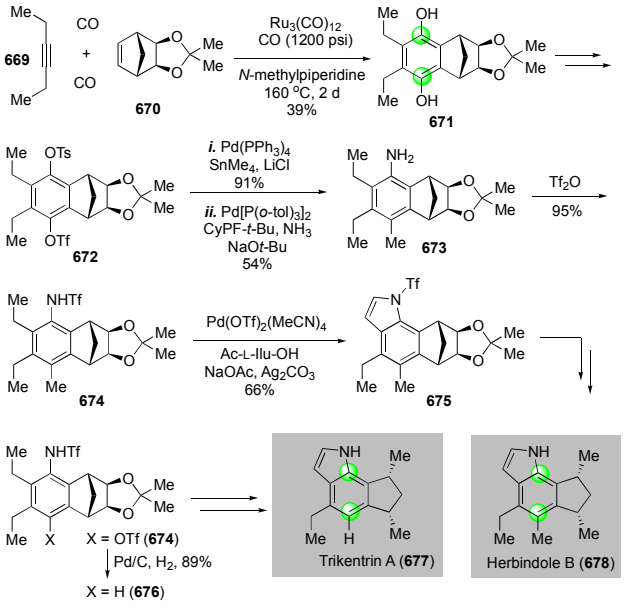

Fig. 92 The Sarpong formal synthesis of trikentrin A and herbindole B (2016)

6. Conclusions

In summary, we have summarized recent applications of carbonylative cyclizations in total synthesis of natural

products. The highlighted carbonylative cyclization reactions include carbonylation of epoxide, carbonylative (macro)lactonization/lactamization, the Semmelhack reaction, tandem hydroformylation-cyclization, the Pauson-Khand reaction, carbonylative C-H activation cyclization, the Stille/Suzuki carbonylation, the [n+m+1] carbonylative cycloaddition, the Dötz annulation, and others. In these transformations, carbon monoxide serves as an important one-carbon linchpin to quickly increase structural complexity under either stoichiometric or catalytic conditions. In general, these carbonylative cyclizations are effective in forming 4 to 7-membered ring systems. There are some examples of forming macrocycles, but this area needs further expansion in terms of both reaction type and efficiency. Carbonylative cyclization of alkyl electrophiles and/or nucleophiles,[291] enantioselective carbonylative cyclization, carbonylative C-H activation cyclization particularly the non-directed variety are in need of future development as well.

7. Acknowledgements

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8. Notes and references

1 Y. Bai, D. C. Davis and M. Dai, *J. Org. Chem.*, 2017, **82**, 2319.
2 X.-F. Wu, H. Neumann and M. Beller, *Chem. Rev*., 2013, **113**, 1.
3 S. Quintero-Duque, K. M. Dyballa, and I. Fleischer, *Tetrahedron Lett.*, 2015, **56**, 2634.
4 P. H. Gehrtz, V. Hirschbeck, B. Ciszek and I. Fleischer, *Synthesis*, 2016, **48**, 1573.
5 W. Fang, H. Zhu, Q. Deng, S. Liu, X. Liu, Y. Shen and T. Tu, *Synthesis*, 2014, **46**, 1689.
6 G. Kiss, *Chem. Rev.*, 2001, **101**, 3435.
7 C. F. J. Barnard, *Organometallics*, 2008, **27**, 5402.
8 X.-F. Wu and H. Neumann, *ChemCatChem*, 2012, **4**, 447.
9 T. Morimoto and K. Kakiuchi, *Angew. Chem. Int. Ed.*, 2004, **43**, 5580.
10 L. Wu, Q. Liu, R. Jackstell and M. Beller, *Angew. Chem. Int. Ed.*, 2014, **53**, 6310.
11 H. Konishi and K. Manabe, *Synlett*, 2014, **25**, 1971.
12 H. W. Yang and D. Romo, *Tetrahedron*, 1999, **55**, 6403.
13 J. E. Wilson and G. C. Fu, *Angew. Chem. Int. Ed.*, 2004, **43**, 6358.
14 Y. Zhu, Q. Wang, R. G. Cornwall and Y. Shi., Chem. Rev., 2014, **114**, 8199.
15 R. W. Bates, R. Fernandez-Moro and S. V. Ley, *Tetrahedron*, 1991, **47**, 9929.
16 Y. D. Y. L. Getzler, V. Mahadevan, E. B. Lobkovsky and G. W. Coates, *J. Am. Chem. Soc.*, 2002, **124**, 1174.
17 M. Mulzer, B. T. Whiting and G. W. Coates, *J. Am. Chem. Soc.*, 2013, **135**, 10930.
18 Y. Liang, N. Hnatiuk, J. M. Rowley, B. T. Whiting, G. W. Coates, P. R. Rablen, M. Morton and A. R. Howell, *J. Org. Chem.*, 2011, **76**, 9962.
19 Q. Chen, M. Mulzer, P. Shi, P. J. Beuning, G. W. Coates and G. A. O'Doherty, *Org. Lett*, 2011, **13**, 6592.
20 M. Mulzer, B. J. Tiegs, Y. Wang, G. W. Coates and G. A. O'Doherty, *J. Am. Chem. Soc.*, 2014, **136**, 10814.
21 S. N. Goodman and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2002, **41**, 4703.
22 J. Willwacher, B. Heggen, C. Wirtz, W. Thiel and A. Fürstner, *Chem. Eur. J.*, 2015, **21**, 10416.
23 A. Schoenberg, I. Bartoletti and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3318.
24 A. Schoenberg and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3327.
25 A. Schoenberg and R. F. Heck, *J. Am. Chem. Soc.*, 1974, **96**, 7761.
26 A. Brennführer, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2009, **48**, 4114.
27 H. Li, Q. Chen, Z. Lu and A. Li, *J. Am. Chem. Soc.*, 2016, **138**, 15555.
28 A. M. Camelio, T. C. Johnson, and D. Siegel, *J. Am. Chem. Soc.*, 2015, **137**, 11864.
29 S.-i. Kusaka, S. Dohi, T. Doi and T. Takahashi, *Tetrahedron Lett.*, 2003, **44**, 8857.
30 H. Herzner, E. R. Palmacci and P. H. Seeberger, *Org. Lett.*, 2002, **4**, 2965.
31 A. W. Schuppe, and T. R. Newhouse, *J. Am. Chem. Soc.*, 2017, **139**, 631.
32 J. E. Rixson, B. W. Skelton, G. A. Koutsantonis, K. M. Gericke and S. G. Stewart, *Org. Lett.*, 2013, **15**, 4834.
33 J. A. Marshall and J. Lebreton, *Tetrahedron Lett.*, 1987, **28**, 3323.
34 A. S. Franklin and L. E. Overman, *Chem. Rev.*, 1996, **96**, 505.
35 S. Aoyagi, S. Hirashima, K. Saito and C. Kibayashi, *J. Org. Chem.*, 2002, **67**, 5517.
36 For a review, D. A. Spiegel, J. T. Njardarson, I. M. McDonald and J. L. Wood, *Chem. Rev.,* 2003, **103**, 2691.
37 For a recent total synthesis: J. C. Leung, A. A. Bedermann, J. T. Njardarson, D. A. Spiegel, G. K. Murphy, N. Hama, B. M. Twenter, P. Dong, T. Shirahata, I. M. McDonald, M. Inoue, N. Taniguchi, T. C. McMahon, C. M. Schneider, N. Tao, B. M. Stoltz and J. L. Wood, *Angew. Chem. Int. Ed.*, 2018, **57**, 1991 (references 3 and 4 therein).
38 M. M. Bio and J. L. Leighton, *J. Org. Chem.*, 2003, **68**, 1693.
39 T. Yao, D. Yue and R. C. Larock, *J. Org. Chem.*, 2005, **70**, 9985.
40 N. A. McGrath, C. A. Lee, H. Araki, M. Brichacek and J. T. Njardarson, *Angew. Chem. Int. Ed.*, 2008, **47**, 9450.
41 A. C. Tadd, M. R. Fielding and M. C. Willis *Chem. Commun.*, 2009, 6744.
42 A. C. Tadd, M. R. Fielding and M. C. Willis *Chem. Commun.*, 2009, 6744.
43 S. Levin, R. R. Nani and S. E. Reisman, *J. Am. Chem. Soc.*, 2011, **133**, 774.
44 D. F. Taber and C. M. Paquette, *J. Org. Chem.*, 2014, **79**, 3410.
45 H.-D. Hao and D. Trauner, *J. Am. Chem. Soc.,* 2017, **139**, 4117.
46 I. T. Chen, I. Baitinger, L. Schreyer and D. Trauner, *Org. Lett.,* 2014, **16**, 166.
47 C. L. Hugelshofer and T. Magauer, *J. Am. Chem. Soc.,* 2015, **137**, 3807.
48 C. L. Hugelshofer and T. Magauer, *Angew. Chem. Int. Ed.,* 2014, **53**, 11351.
49 T. R. Hoye and L. Tan, *Tetrahedron Lett.*, 1995, **36**, 1981.
50 H. Xu, H. Tang, H. Feng and Y. Li, *J. Org. Chem.*, 2014, **79**, 10110.
51 G. Hikosaka, Y. Hattori and H. Makabe, *Tetrahedron: Asymmetry*, 2014, **25**, 1367.
52 Y. Kurogome, Y. Hattori and H. Makabe, *Tetrahedron Lett.*, 2014, **55**, 2822.
53 V. L. Poral, D. P. Furkert and M. A. Brimble, *Org. Lett.*, 2015, **17**, 6214.
54 S. G. Davies, P. M. Roberts, P. T. Stephenson, H. R. Storr and J. E. Thomson, *Tetrahedron*, 2009, **65**, 8283.

55 G. Nemecek, R. Thomas, H. Goesmann, C. Feldmann and J. Podlech, *Eur. J. Org. Chem.*, 2013, 6420.
56 R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 14082.
57 R. Giri, J. K. Lam and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 686.
58 H. Zhang, R. Shi, P. Gan, C. Liu, A. Ding, Q. Wang and A. Lei *Angew. Chem. Int. Ed.*, 2012, **51**, 5204.
59 Z. Lian, S. D. Friis and T. Skrydstrup, *Chem. Commun*., 2015, **51**, 1870.
60 X.-F. Wu, P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2010, **49**, 7316.
61 J. Tjutrins and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2015, **137**, 12050.
62 Y. Shin, C. Yoo, Y. Moon, Y. Lee and S. Hong, *Chem. Asian J.,* 2015, **10**, 878.
63 D. C. Davis, K. L. Walker, C. Hu, R. N. Zare, R. M. Waymouth and M. Dai, *J. Am. Chem. Soc.*, 2016, **138**, 10693.
64 G. Kiss, *Chem. Rev.*, 2001, **101**, 3435.
65 E. Yoneda, T. Kaneko, S.-W. Zhang, K. Onitsuka and S. Takahashi, *Org. Lett.*, 2000, **2**, 441.
66 R. W. Bates and S. Sridhar, *J. Org. Chem.*, 2008, **73**, 8104.
67 Y. Wang, L. Zhu, Y. Zhang and R. Hong, *Angew. Chem. Int. Ed.*, 2011, **50**, 2787.
68 Y.-A. Zhang, Q. liu, C. Wang and Y. Jia, *Org. Lett.*, 2013, **15**, 3662.
69 N. M. Kablaoui, F. A. Hicks and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 4424.
70 W. E. Crowe and A. T. Vu, *J. Am. Chem. Soc.*, 1996, **118**, 1557.
71 N. Chatani, T. Morimoto, Y. Fukumoto and S. Murai, *J. Am. Chem. Soc.*, 1998, **120**, 5335.
72 J. Adrio and J. C. Carretero, *J. Am. Chem. Soc.*, 2007, **129**, 778.
73 S. K. Kang, K. J. Kim and Y. T. Hong, *Angew. Chem. Int. Ed.*, 2002, **41**, 1584.
74 P. Gao, P.-F. Xu and H. Zhai, *J. Org. Chem.*, 2009, **74**, 2592.
75 J. Chen, P. Gao, F. Yu, Y. Yang, S. Zhu and H. Zhai, *Angew. Chem. Int. Ed.*, 2012, **51**, 5897.
76 C. Tao, J. Zhang, X. Chen, H. Wang, Y. Li, B. Cheng and H. Zhai, *Org. Lett.*, 2017, **19**, 1056.
77 H.-H. Lu, M. D. Martinez and R. A. Shenvi, *Nat. Chem.*, 2015, **7**, 604.
78 M. Ohtawa, M. J. Krambis, R. Cerne, J. M. Schkeryantz, J. M. Witkin and R. A. Shenvi, *J. Am. Chem. Soc.*, 2017, **139**, 9637.
79 M. F. Semmelhack and C. Bodurow, *J. Am. Chem. Soc.*, 1984, **106**, 1496.
80 M. F. Semmelhack, C. Kim, N. Zhang, C. Bodurow, M. Sanner, W. Dobler and M. Meier, *Pure Appl. Chem*. 1990, **62**, 2035.
81 K. J. Light-Wahl, B. E. Winger and R. D. Smith, *J. Am. Chem. Soc.*, 1993, **115**, 5869.
82 G. A. Kraus and J. Li, *J. Am. Chem. Soc.*, 1993, **115**, 5859.
83 K. R. Hornberger, C. L. Hamblett and J. L. Leighton, *J. Am. Chem. Soc.*, 2000, **122**, 12894.
84 H. H. Jung, J. R. Seiders and P. E. Floreancig, *Angew. Chem. Int. Ed.*, 2007, **46**, 8464.
85 J. D. White, C. L. Kranemann and P. Kuntiyong, *Org. Lett.*, 2001, **3**, 4003.
86 J. Carpenter, A. B. Northrup, d. Chung, J. J. M. Wiener, S. G. Kim and D. W. C. MacMillan, *Angew. Chem. Int. Ed.*, 2008, **47**, 3568.
87 J. A. Marshall and M. M. Yanik, *Tetrahedron Lett.*, 2000, **41**, 4717.
88 L. F. Tietze, R. Fischer, H. J. Guder, A. Goerlach, M. Meumann and T. Krach, *Carbohydr. Res*., 1987, **164**, 177.
89 Z. Yang, B. Zhang, G. Zhao, J. Yang, X. Xie and X. She, *Org. Lett.*, 2011, **13**, 5916.
90 Y. Lu, I. S. Kim, A. Hassan, D. J. Del Valle, M. J. Krische, *Angew. Chem., Int. Ed.* 2009, **48**, 5018.
91 S. B. Han, A. Hassan, I. S. Kim and M. J. Krische, *J. Am. Chem. Soc.*, 2010, **132**, 15559.
92 L. F. Tietze, D. A. Spiegl, F. Stecker, J. Major, C. Raith and C. Große, *Chem. Eur. J.*, 2008, **14**, 8956.
93 P. Y. Hayes and W. Kitching, *J. Am. Chem. Soc.*, 2002, **124**, 9718.
94 Z. Li, Y. Gao, Z. Jiao, N. Wu, D. Z. Wang and Z. Yang, *Org. Lett.*, 2008, **10**, 5163.
95 Z. Li, Y. Gao, Y. Tang, M. Dai, G. Wang, Z. Wang and Z. Yang, *Org. Lett.*, 2008, **10**, 3017.
96 J. B. Werness and W. Tang, *Org. Lett.*, 2011, **13**, 3664.
97 C. L. Nesbitt and C. S. P. McErlean, *Tetrahedron Lett.* 2009, **50**, 6318.
98 Q. Xiao, W. W. Ren, Z. X. Chen, T. W. Sun, Y. Li, Q. D. Ye, J. X. Gong, F. K. Meng, L. You, Y. F. Liu, M. Z. Zhao, L. M. Xu, Z. H. Shan, Y. Shi, Y. F. Tang, J. H. Chen and Z. Yang, *Angew. Chem. Int. Ed.*, 2011, **50**, 7373.
99 M. Dai, B. Liang, C. Wang, J. Chen and Z. Yang, *Org. Lett.*, 2004, **6**, 221.
100 X.-S. Xu, Z.-W. Li, Y.-J. Zhang, X.-S. Peng and H. N. C. Wong, *Chem. Commun.*, 2012, **48**, 8517.
101 C. Ebner and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2015, **54**, 11227.
102 E.-i. Negishi, C. Copéret, S. Ma, T. Mita, T. Sugihara and J. M. Tour, *J. Am. Chem. Soc.*, 1996, **118**, 5904.
103 V. K. Aggarwal, P. W. Davies and W. O. Moss, *Chem. Commun.*, 2002, 972.
104 C. Liu and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2004, **126**, 10250.
105 S. Li, F. Li, J. Gong and Z. Yang, *Org. Lett.*, 2015, **17**, 1240.
106 V. K. Aggarwal, P. W. Davies and A. T. Schmidt, *Chem. Commun.*, 2004, 1232.
107 For a review: R. Franke, D. Selent and A. Börner, *Chem. Rev.*, 2012, **112**, 5675.
108 Z. A. Kasun, X. Gao, R. M. Lipinski and M. J. Krische, *J. Am. Chem. Soc.*, 2015, **137**, 8900.
109 For a review: Y. Li, X. Yin and M. Dai, *Nat. Prod. Rep.*, 2017, **34**, 1185.
110 T. Takahashi, S. Kusaka, T. Doi, T. Sunazuka and S. Ōmura, *Angew. Chem. Int. Ed.*, 2003, **42**, 5230.
111 B. Schmalzbauer and D. Menche, *Org. Lett.*, 2015, **17**, 2956.
112 Y. Bai, D. C. Davis and M. Dai, *Angew. Chem. Int. Ed.*, 2014, **53**, 6519.
113 F. Manoni, C. Rumo, L. Li and P. G. Harran, *J. Am. Chem. Soc.*, 2018, **140**, 1280.
114 A. Hassan, I. A. Townsend and M. J. Krische, *Chem. Commun.*, 2011, **47**, 10028.
115 I. Shin, S. Hong and M. J. Krische, *J. Am. Chem. Soc.*, 2016, **138**, 14246.
116 S. L. Schreiber, *J. Am. Chem. Soc.*, 1980, **102**, 6163.
117 Y. Bai, X. Shen, Y. Li and M. Dai, *J. Am. Chem. Soc.*, 2016, **138**, 10838.
118 B. Yu, *Acc. Chem. Res.*, 2018, **51**, 507.
119 R. M. Risi and S. D. Burke, *Org. Lett.*, 2012, **14**, 1180.
120 M. Mori, Y. Uozumi, M. Kimura and Y. Ban, *Tetrahedron*, 1986, **42**, 3793.
121 K. Orito, M. Miyazawa, R. Kanbayashi, M. Tokuda and H. Suginome, *J. Org. Chem.*, 1999, **64**, 6583.
122 Y. Onozaki, N. Kurono, H. Senboku, M. Tokuda and K. Orito, *J. Org. Chem.*, 2009, **74**, 5486.
123 B. M. Trost and M. K. Ameriks, *Org. Lett.*, 2004, **6**, 1745.
124 O. Zhurakovskyi, Y. E. Türkmen, L. E. Löffler, V. A. Moorthie, C. C. Chen, M. A. Shaw, M. R. Crimmin, M. Ferrara, M. Ahmad, M. Ostovar, J. V. Matlock and V. K. Aggarwal, *Angew. Chem., Int. Ed.* 2018, **57**, 1346.
125 E. J. Yoo, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 17378.

126 K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita and M. Tokuda, *J. Am. Chem. Soc.*, 2004, **126**, 14342.
127 A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, *Nature*, 2014, **510**, 129.
128 D. Willcox, B. G. N. Chappell, K. F. Hogg, J. Calleja, A. P. Smalley, and M. J. Gaunt, *Science*, 2016, **354**, 851.
129 W. Li, Z. Duan, Z. Zhang, H. Zhang, M. Wang, R. Jiang, H. Zeng, C. Liu and A. Lei, *Angew. Chem. Int. Ed.*, 2015, **54**, 1893.
130 Z.-H. Guan, M. Chen and Z.-H. Ren, *J. Am. Chem. Soc*., 2012, **134**, 17490.
131 B. D. Dangel, K. Godula, S. W. Youn, B. Sezen and D. Sames, *J. Am. Chem. Soc.*, 2002, **124**, 11856.
132 C. Tsukano, N. Muto, I. Enkhtaivan and Y. Takemoto, *Chem. Asian J.*, 2014, **9**, 2628.
133 M. Catellani, E. Motti and N. Della Ca', *Acc. Chem. Res.* 2008, **41**, 1512.
134 P.-L. Wang, Y. Li, Y. Wu, C. Li, Q. Lan and X.-S. Wang, *Org. Lett.*, 2015, **17**, 3698.
135 J. C. Fox, R. E. Gilligan, A. K. Pitts, H. R. Bennett and M. J. Gaunt, *Chem. Sci.*, 2016, **7**, 2706.
136 J. A. Johnson, N. Li and D. Sames, *J. Am. Chem. Soc.*, 2002, **124**, 6900.
137 C. Mukai, T. Yoshida, M. Sorimachi and A. Odani, *Org. Lett.*, 2006, **8**, 83.
138 S. Prateeptongkum, K. M. Driller, R. Jackstell and M. Beller, *Chem. Asian J.*, 2010, **5**, 2173.
139 L. W. Hernandez, J. Pospech, U. Klöckner, T. W. Bingham and D. Sarlah, *J. Am. Chem. Soc.*, 2017, **139**, 15656.
140 W. Chiou, A. Schoenfelder, A. Mann and I. Ojima, *Pure Appl. Chem.*, 2008, **80**, 1019.
141 H. Ren and W. D. Wulff, *Org. Lett.*, 2013, **15**, 242.
142 G. Makado, T. Morimoto, Y. Sugimoto, K. Tsutsumi, N. Kagawa and K. Kakiuchi, *Adv. Synth. Catal.*, 2010, **352**, 299.
143 R. W. Bates and S. Kasinathan, *Tetrahedron*, 2013, **69**, 3088.
144 P Dübon, A Farwick, G Helmchen, *Synlett*, 2009, 1413.
145 W.-H. Chiou, C.-L. Kao, J.-C. Tsai and Y.-M. Chang, *Chem. Commun.*, 2013, **49**, 8232.
146 G. D. Artman and S. M. Weinreb, *Org. Lett.*, 2003, **5**, 1523.
147 S. E. Denmark, J. H.-C. Liu and J. M. Muhuhi, *J. Am. Chem. Soc.*, 2009, **131**, 14188.
148 W. Oppolzer, J. Z. Xu and C. Stone, *Helv. Chim. Acta*, 1991, **74**, 465.
149 W. Oppolzer, H. Bienayme and A. Genevois-Borella, *J. Am. Chem. Soc.*, 1991, **113**, 9660.
150 W. Oppolzer and C. Robyr, *Tetrahedron*, 1994, **50**, 415.
151 For a review: K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem. Int. Ed.*, 2005, **44**, 4442.
152 S. R. Angle, J. M. Fevig, S. D. Knight, R. W. Marquis and L. E. Overman, *J. Am. Chem. Soc.*, 1993, **115**, 3966.
153 S. D. Knight, L. E. Overman and G. Pairaudeau, *J. Am. Chem. Soc.*, 1995, **117**, 5776.
154 G. T. Crisp, W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, 1984, **106**, 7500.
155 M. Ishikura, K. Imaizumi and N. Katagiri, *Heterocycles 2000, **53***, 553.
156 S. Gao, Q. Wang, L. J. S. Huang, L. Lum and C. Chen, *J. Am. Chem. Soc.*, 2010, **132**, 371.
157 A. Shvartsbart and A. B. Smith, III, *J. Am. Chem. Soc.*, 2015, **137**, 3510.
158 A. Shvartsbart and A. B. Smith, *J. Am. Chem. Soc.,* 2014, **136**, 870.
159 H. Yahata, T. Kubota and J. Kobayashi, *J. Nat. Prod.* 2008, **72**, 148.
160 S. K. Murphy, M Zeng and S.B. Herzon, *Science*, 2017, **356**, 956.
161 T. Esumi, T. Mori, M. Zhao, M. Toyota and Y. Fukuyama, *Org. Lett.*, 2010, **12**, 888.
162 L. Xu, C. Wang, Z. Gao and Y.-M. Zhao, *J. Am. Chem. Soc.,* 2018, **140**, 5653.
163 K. M. Brummond and J. L. Kent, *Tetrahedron*, 2000, **56**, 3263.
164 H. Lee and F. Kwong, *Eur. J. Org. Chem.,* 2010, 789.
165 B. M. Trost, M. U. Frederiksen and M. T. Rudd, *Angew. Chem. Int. Ed.*, 2005, **44**, 6630.
166 J. E. Zweig, D. E. Kim and T. R. Newhouse, *Chem. Rev.,* 2017, **117**, 11680.
167 S. P. Simeonov, J. P. M. Nunes, K. Guerra, V. B. Kurteva and C. A. M. Afonso, *Chem. Rev.,* 2016, **116**, 5744.
168 T. F. Jamison, S. Shambayati, W. E. Crowe and S. L. Schreiber, *J. Am. Chem. Soc.,* 1997, **119**, 4353.
169 J. Cassayre, F. Gagosz and S. Z. Zard, *Angew. Chem. Int. Ed.,* 2002, **41**, 1783.
170 T. Kozaka, N. Miyakoshi and C. Mukai, *J. Org. Chem.*, **72**, 10147.
171 M. Ishizaki, Y. Niimi, O. Hoshino, H. Hara and T. Takahashi, *Tetrahedron*, 2005, **61**, 4053.
172 G. Stork, R. Mook, S. A. Biller and S. D. Rychnovsky, *J. Am. Chem. Soc.,* 1983, **105**, 3741.
173 N. Itoh, T. Iwata, H. Sugihara, F. Inagaki and C. Mukai, *Chem. Eur. J.* 2013, **19**, 8665.
174 M. K. Pallerla and J. M. Fox, *Org. Lett.* 2007, **9**, 5625.
175 K. A. Miller and S. F. Martin, *Org. Lett.,* 2007, **9**, 1113.
176 S. J. Min and S. J. Danishefsky, *Angew. Chem. Int. Ed.,* 2007, **46**, 2199.
177 G. Mehta, R. Samineni and P. Srihari, *Tetrahedron Lett.,* 2012, **53**, 829.
178 F. Inagaki, M. Kinebuchi, N. Miyakoshi and C. Mukai, *Org. Lett.,* 2010, **12**, 1800.
179 J. S. Clark and C. Xu, *Angew. Chem. Int. Ed.,* 2016, **55**, 4332.
180 K. Hiroi, T. Watanabe, R. Kawagishi and I. Abe, *Tetrahedron: Asymmetry*, 2000, **11**, 797.
181 P. Magnus, M. R. Fielding, C. Wells and V. Lynch, *Tetrahedron Lett.,* 2002, **43**, 947.
182 R. A. Rodriguez, D. Barrios Steed, Y. Kawamata, S. Su, P. A. Smith, T. C. Steed, F. E. Romesberg and P. S. Baran, *J. Am. Chem. Soc.,* 2014, **136**, 15403.
183 S. Su, R. A. Rodriguez and P. S. Baran, *J. Am. Chem. Soc.,* 2011, **133**, 13922.
184 Y. Yang, X. Fu, J. Chen and H. Zhai, *Angew. Chem. Int. Ed.,* 2012, **51**, 9825.
185 L. Shi and Z. Yang, *Eur. J. Org. Chem.,* 2016, 2356.
186 Q. Liu, G. Yue, N. Wu, G. Lin, Y. Li, J. Quan, C. C. Li, G. Wang and Z. Yang, *Angew. Chem. Int. Ed.,* 2012, **51**, 12072.
187 J. Huang, L. Fang, R. Long, L. L. Shi, H. J. Shen, C. C. Li and Z. Yang, *Org. Lett.,* 2013, **15**, 4018.
188 L. You, X. Liang, L. Xu, Y. Wang, J. Zhang, Q. Su, Y. Li, B. Zhang, S. Yang, J. Chen and Z. Yang, *J. Am. Chem. Soc.,* 2015, **137**, 10120.
189 J. Zhang, X. Wang, S. Li, D. Li, S. Liu, Y. Lan, J. Gong and Z. Yang, *Chem. Eur. J.* 2015, **21**, 12596.
190 Z. Zhang, Y. Li, D. Zhao, Y. He, J. Gong and Z. Yang, *Chem. Eur. J.* 2017, **23**, 1258.
191 D. D. Liu, T. W. Sun, K. Y. Wang, Y. Lu, S. L. Zhang, Y. H. Li, Y. L. Jiang, J. H. Chen and Z. Yang, *J. Am. Chem. Soc.,* 2017, **139**, 5732.
192 K. V. Chuang, C Xu, and S. E. Reisman, *Science* 2016, **353**, 912.
193 M. W. Benjamin and D. Trauner, *Angew. Chem. Int. Ed.*, 2016, **55**, 2191.

194 G. Volpin, N. A. Vepřek, A. B. Bellan and D. Trauner, *Angew. Chem. Int. Ed.,* 2017, **56**, 897.
195 N. Zhao, S. Yin, S. Xie, H. Yan, P. Ren, G. Chen, F. Chen and J. Xu, *Angew. Chem. Int. Ed.,* 2018, **57**, 3386.
196 B. Darses, I. N. Michaelides, F. Sladojevich, J. W. Ward, P. R. Rzepa and D. J. Dixon, *Org. Lett.,* 2012, **14**, 1684.
197 W. Zhang, M. Ding, J. Li, Z. Guo, M. Lu, Y. Chen, L. Liu, Y. H. Shen and A. Li, *J. Am. Chem. Soc.,* 2018, **140**, 4227.
198 W. Chen, J.-H. Tay, J. Ying, M. Sabat, X. Q. Yu and L. Pu, *Chem. Commun.,* 2013, **49**, 170.
199 J. Ying and L. Pu, *Chem. Eur. J.* 2014, **20**, 16301.
200 J. D. Winkler, E. C. Y. Lee and L. I. Nevels, *Org. Lett*., 2005, **7**, 1489.
201 J. P. Chen, W. He, Z. Y. Yang and Z. J. Yao, *Org. Lett.,* 2015, **17**, 3379.
202 P. A. Wender and F. E. McDonald, *Tetrahedron Lett.,* 1990, **31**, 3691.
203 L. A. Paquette and S. Borrelly, *J. Org. Chem.*, 1995, **60**, 6912.
204 G. R. Dake, E. E. Fenster and B. O. Patrick, *J. Org. Chem.*, 2008, **73**, 6711.
205 M. E. Krafft, Y. Y. Cheung, and C. A. Juliano-Capucao, *Synthesis,* 2000, **7**, 1020.
206 C. Mukai, M. Kobayashi, I. J. Kim and M. Hanaoka, *Tetrahedron,* 2002, **58**, 5225.
207 T. Ishikawa, H. Ishii, K. Shimizu, H. Nakao, J. Urano, T. Kudo and S. Saito, *J. Org. Chem.*, 2004, **69**, 8133.
208 A. Farwick and G. Helmchen, *Org. Lett.,* 2010, **12**, 1108.
209 I. Nomura and C. Mukai, *J. Org. Chem.*, 2004, **69**, 1803.
210 B. Jiang and M. Xu, *Angew. Chem. Int. Ed.,* 2004, **43**, 2543.
211 R. M. Moriarty, N. Rani, L. A. Enache, M. S. Rao, H. Batra, L. Guo, R. A. Penmasta, J. P. Staszewski, S. M. Tuladhar, O. Prakash, D. Crich, A. Hirtopeanu and R. Gilardi, *J. Org. Chem.*, 2004, **69**, 1890.
212 J. J. Crawford, W. J. Kerr, M. McLaughlin, A. J. Morrison, P. L. Pauson and G. J. Thurston, *Tetrahedron*, 2006, **62**, 11360.
213 T. Honda and K. Kaneda, *J. Org. Chem.*, 2007, **72**, 6541.
214 A. Vázquez-Romero, L. Cárdenas, E. Blasi, X. Verdaguer and A. Riera, *Org. Lett.,* 2009, **11**, 3104.
215 A. Nakayama, N. Kogure, M. Kitajima and H. Takayama, *Angew. Chem. Int. Ed.,* 2011, **50**, 8025.
216 Y. Hayashi, F. Inagaki and C. Mukai, *Org. Lett.,* 2011, **13**, 1778.
217 R. Betík and M. Kotora, *Eur. J. Org. Chem.,* 2011, 3279.
218 Y. Hayashi, K. Ogawa, F. Inagaki and C. Mukai, *Org. Biomol. Chem.*, 2012, **10**, 4747.
219 K. Fujioka, H. Yokoe, M. Yoshida and K. Shishido, *Org. Lett.,* 2012, **14**, 244.
220 N. Itoh, T. Iwata, H. Sugihara, F. Inagaki and C. Mukai, *Chem. Eur. J.,* 2013, **19**, 8665.
221 B. Jiang, M. M. Li, P. Xing and Z. G. Huang, *Org. Lett.,* 2013, **15**, 871.
222 H. Yamakoshi, Y. Sawayama, Y. Akahori, M. Kato and S. Nakamura, *Org. Lett.,* 2016, **18**, 3430.
223 M. K. Abd El-Gaber, S. Yasuda, E. Iida and C. Mukai, *Org. Lett.,* 2017, **19**, 320.
224 J. L. Kent, H. Wan and K. M. Brummond, *Tetrahedron Lett.,* 1995, **36**, 2407.
225 K. M. Brummond and H. Wan, *Tetrahedron Lett.,* 1998, **39**, 931.
226 K. M. Brummond, H. Wan and J. L. Kent, *J. Org. Chem.*, 1998, **63**, 6535.
227 K. M. Brummond and D. Chen, *Org. Lett.,* 2008, **10**, 705.
228 K. M. Brummond, J. Lu and J. Petersen, *J. Am. Chem. Soc.,* 2000, **122**, 4915.
229 K. M. Brummond, P. C. Sill and H. Chen, *Org. Lett.,* 2004, **6**, 149.
230 K. M. Brummond and D. Gao, *Org. Lett.,* 2003, **5**, 3491.
231 B. Wen, J. K. Hexum, J. C. Widen, D. A. Harki and K. M. Brummond, *Org. Lett.,* 2013, **15,** 2644.
232 L. Jørgensen, S. J. McKerrall, C. A. Kuttruff, F. Ungeheuer, J. Felding and P. S. Baran, *Science*, 2013, **341**, 878.
233 S. J. McKerrall, L. Jørgensen, C. A. Kuttruff, F. Ungeheuer and P. S. Baran, *J. Am. Chem. Soc.,* 2014, **136**, 5799.
234 D. R. Williams and A. A. Shah, *J. Am. Chem. Soc.,* 2014, **136**, 8829.
235 C. Heinz and N. Cramer, *J. Am. Chem. Soc.,* 2015, **137**, 11278.
236 Y. Hayashi, N. Miyakoshi, S. Kitagaki and C. Mukai, *Org. Lett.,* 2008, **10**, 2385.
237 J. Tsuji, T. Sugiura and I. Minami, *Tetrahedron Lett.,* 1986, **27**, 731.
238 C. Lv, X. Yan, Q. Tu, Y. Di, C. Yuan, X. Fang, Y. Ben‐David, L. Xia, J. Gong, Y. Shen, Z. Yang and X. Hao, *Angew. Chem. Int. Ed.,* 2016, **55**, 7539.
239 P. A. Wender, M. P. Croatt and N. M. Deschamps, *J. Am. Chem. Soc.,* 2004, **126**, 5948.
240 P. A. Wender, N. M. Deschamps and T. J. Williams, *Angew. Chem. Int. Ed.,* 2004, **43**, 3076.
241 P. A. Wender, M. P. Croatt and N. M. Deschamps, *Angew. Chem., Int. Ed.* 2006, **45**, 2459.
242 W. H. Pitcock Jr, R. L. Lord and M.-H. Baik, *J. Am. Chem. Soc.,* 2008, **130**, 5821.
243 M. P. Croatt and P. A. Wender, *Eur. J. Org. Chem.,* 2010, 19.
244 P. A. Wender, *Tetradron*, 2013, **69**, 7529.
245 Y. Wang and Z.-X. Yu, *Acc. Chem. Res*., 2015, **48**, 2288.
246 D. Shu, X. Li, M. Zhang, P. J. Robichaux, I. A. Guzei and W. Tang, *J. Org. Chem.*, 2012, **77**, 6463.
247 S. Mazumder, D. Shang, D. E. Negru, M.-H. Baik and P. A. Evans, *J. Am. Chem. Soc.,* 2012, **134**, 20569.
248 G.-W. Wang and J. F. Bower, *J. Am. Chem. Soc.,* 2018, **140**, 2743.
249 G.-W. Wang, N. G. McCreanor, M. H. Shaw, W. G. Whittingham and J. F. Bower, *J. Am. Chem. Soc.,* 2016, **138**, 13501.
250 For a review: M. H. Shaw and J. F. Bower, *Chem. Commun.*, 2016, **52**, 10187.
251 L. Jiao, M. Lin, L. G. Zhuo and Z.-X. Yu, *Org. Lett.,* 2010, **12**, 2528.
252 M. Lin, F. Li, L. Jiao and Z.-X. Yu, *J. Am. Chem. Soc.,* 2011, **133**, 1690.
253 K. Yuji and N. Koichi. *Chem. Lett.* 1999, **7**, 705.
254 Y. Feng and Z.-X. Yu, *J. Org. Chem.,* 2015, **80**, 1952.
255 J. Yang, W. Xu, Q. Cui, X. Fan, L. N. Wang and Z.-X. Yu, *Org. Lett.,* 2017, **19**, 6040.
256 J. Yang, W. Xu, Q. Cui, X. Fan, L. N. Wang and Z.-X. Yu, *Org. lett.*, 2017, **19**, 6040.
257 R. Ben-Shoshan and S. Sarel, *J. Chem. Soc., Chem. Commun.,* 1969, 883.
258 D. F. Taber, K. Kanai, Q. Jiang and G. Bui, *J. Am. Chem. Soc.*, 2000, **122**, 6807.
259 D. F. Taber, P. V. Joshi and K. Kanai, *J. Org. Chem.*, 2004, **69**, 2268.
260 D. F. Taber, P. Guo and N. Guo, *J. Am. Chem. Soc.,* 2010, **132**, 11179.
261 D. F. Taber, G. Bui and B. Chen, *J. Org. Chem.*, 2001, **66**, 3423.
262 D. F. Taber and R. B. Sheth, *J. Org. Chem.*, 2008, **73**, 8030.
263 D. F. Taber, R. B. Sheth and W. Tian, *J. Org. Chem.*, 2009, **74**, 2433.
264 T. Kurahashi and A. de Meijere, *Synlett*, 2005, **17**, 2619.
265 G. J. Jian, X. F. Fu, Q. Li and Z.-X. Yu, *Org. Lett.,* 2012, **14**, 692.

266 L. N. Wang, Q. Cui and Z.-X. Yu, *J. Org. Chem.*, 2016, **81**, 10165.
267 N. Iwasawa, Y. Owada and T. Matsuo, *Chem. Lett.* 1995, **24**, 115.
268 Y. Owada, T. Matsuo and N. Iwasawa, *Tetrahedron*, 1997, **53**, 11069.
269 M. Murakami, K. Itami, M. Ubukata, I. Tsuji and Y. Ito, *J. Org. Chem.*, 1998, **63**, 4.
270 D. Shu, X. Li, M. Zhang, P. J. Robichaux and W. Tang, *Angew. Chem. Int. Ed*, 2011, **50**, 1346.
271 M. Zhang and W. Tang, *Org. Lett.,* 2012, **14**, 3756.
272 C. H. Liu and Z.-X. Yu, *Org. Biomol. Chem.,* 2016, **14**, 5945.
273 X. Li, W. Song and W. Tang, *J. Am. Chem. Soc.,* 2013, **135**, 16797.
274 W. Song, X. Li, K. Yang, X. l. Zhao, D. A. Glazier, B.-m. Xi and W. Tang, *J. Org. Chem.*, 2016, **81**, 2930.
275 J. T. Liu, C. J. Simmons, H. Xie, F. Yang, X. l. Zhao, Y. Tang and W. Tang, *Adv. Synth. Catal.,* 2017, **359**, 693.
276 P. A. Wender, G. G. Gamber, R. D. Hubbard and L. Zhang, *J. Am. Chem. Soc.,* 2002, **124**, 2876.
277 P. A. Wender, G. G. Gamber, R. D. Hubbard, S. M. Pham and L. Zhang, *J. Am. Chem. Soc.,* 2005, **127**, 2836.
278 Y. Wang, J. Wang, J. Su, F. Huang, L. Jiao, Y. Liang, D. Yang, S. Zhang, P. A. Wender and Z.-X. Yu, *J. Am. Chem. Soc.,* 2007, **129**, 10060.
279 L. Jiao, C. Yuan and Z.-X. Yu, *J. Am. Chem. Soc.,* 2008, **130**, 4421.
280 X. Fan, L. G. Zhuo, Y. Q. Tu and Z.-X. Yu, *Tetrahedron*, 2009, **65**, 4709.
281 Y. Liang, X. Jiang, X. F. Fu, S. Ye, T. Wang, J. Yuan, Y. Wang and Z.-X. Yu, *Chem. Asian J.,* 2012, **7**, 593.
282 A. C. Gyorkos, J. K. Stille and L. S. Hegedus, *J. Am. Chem. Soc.,* 1990, **112**, 8465.
283 T. J. Houghton, S. Choi and V. H. Rawal, *Org. Lett.,* 2001, **3**, 3615.
284 For a review: W. Song, S. A. Blaszczyk, J. Liu, S. Wang and W. Tang, *Org. Biomol. Chem.* 2017, **15**, 7490 and references therein.
285 S. A. Eastham, S. P. Ingham, M. R. Hallett, J. Herbert, P. Quayle and J. Raftery, *Tetrahedron Lett.,* 2006, **47**, 2299.
286 K. Tanaka, M. Watanabe, K. Ishibashi, H. Matsuyama, Y. Saikawa and M. Nakata, *Org. Lett.,* 2010, **12**, 1700.
287 H. Wang and W. D. Wulff, *J. Am. Chem. Soc.,* 1998, **120**, 10573.
288 N. Suzuki, T. Kondo and T. Mitsudo, *Organometallics*, 1998, **17**, 766.
289 R. A. Leal, C. Bischof, Y. V. Lee, S. Sawano, C. C. McAtee, L. N. Latimer, Z. N. Russ, J. E. Dueber, J. Q. Yu and R. Sarpong, *Angew. Chem. Int. Ed*, 2016, **55**, 11824.
290 S. K. Jackson and M. A. Kerr, *J. Org. Chem.,* 2007, **72**, 1405.
291 K. S. Bloome and E. J. Alexanian, *J. Am. Chem. Soc.,* 2010, **132**, 12823.