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Review

Evolution of Pauson-Khand Reaction: Strategic Applications in Total Syntheses of Architecturally Complex Natural Products (2016–2020)

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Received: 23 September 2020; Accepted: 14 October 2020; Published: 16 October 2020

Abstract: Metal-mediated cyclizations are important transformations in a natural product total synthesis. The Pauson-Khand reaction, particularly powerful for establishing cyclopentenone-containing structures, is distinguished as one of the most attractive annulation processes routinely employed in synthesis campaigns. This review covers Co, Rh, and Pd catalyzed Pauson-Khand reaction and summarizes its strategic applications in total syntheses of structurally complex natural products in the last five years. Additionally, the hetero-Pauson-Khand reaction in the synthesis of heterocycles will also be discussed. Focusing on the panorama of organic synthesis, this review highlights the strategically developed Pauson-Khand reaction in fulfilling total synthetic tasks and its synthetic attractiveness is aimed to be illustrated.

Keywords: metal-mediated reactions; Pauson-Khand reaction; cyclopentenones; natural products total syntheses

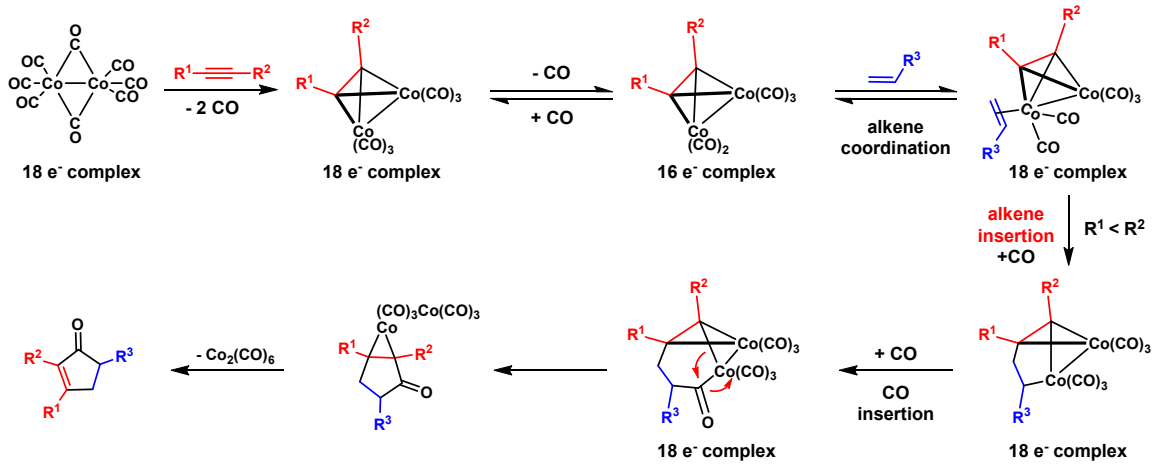
1. Introduction

The metal-mediated reaction plays an important role in constructing complex organic molecules [1–3]. The Pauson-Khand reaction (PKR), an effective set of annulation protocol defined in 1973 [4] for the construction of cyclopentenone-containing moieties, stands as a promising method to permit efficient cyclic frameworks. Its efficient and atom-economic elaboration to substituted cyclopentenones renders this process highly prized in the construction of architecturally complex natural products. Since reported more than 40 years ago [5–12], it has been developed with different metal catalytic systems, including Co [13–17], Rh [18–25], Ru [26–30], Ti [31–34], Ir [35–37], Ni [38], Mo [39,40], Fe [41]; and other metals could promote the PKR to build the heterocycle frameworks [42–44]. By identifying reactivity patterns for diverse PKR precursors in the prominent synthetic application, we aim to elevate this powerful reaction to a method of choice in the synthetic designation of complex biologically active entities.

1.1. Classic PK Reaction Catalyzed by Co

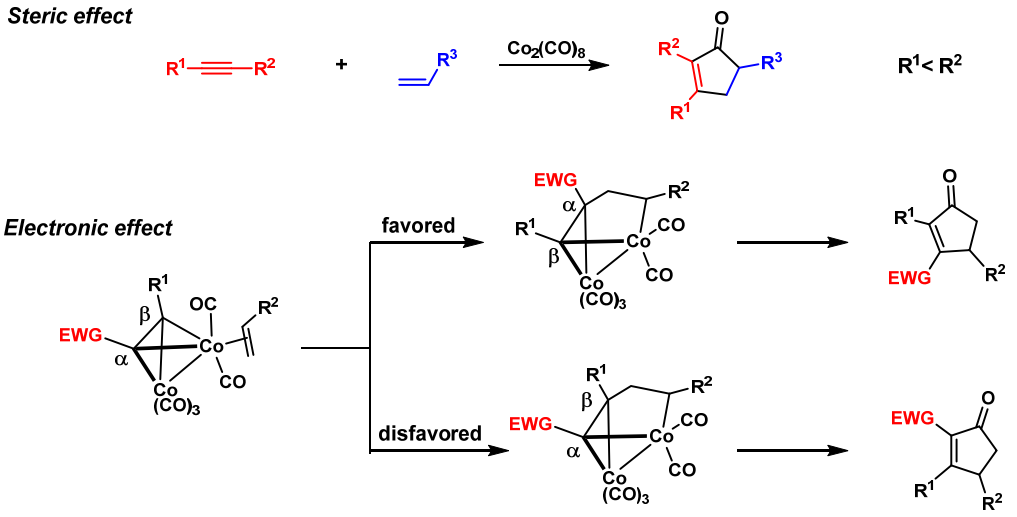
In 1973, I.U. Khand and P.L. Pauson found that the generation of enyne/$Co_2(CO)_6$ complex with olefin as substrates could lead to the formation of cyclopentenone. Moving forward, P.L. Pauson

explored the substrate scope and limitations of this reaction [45]. Although the specific mechanism of PKR involving $Co_2(CO)_8$ is still uncertain, the mechanism proposed by Magnus [46–48] and Schore [49] is widely recognized based on the reaction results of regioselectivity and stereoselectivity (Scheme 1). The rate-determining step is alkene coordination with the cobalt and then insertion into cobalt–carbon bond to form the cobaltacycle, accounting for the regiochemical and stereochemical outcomes.



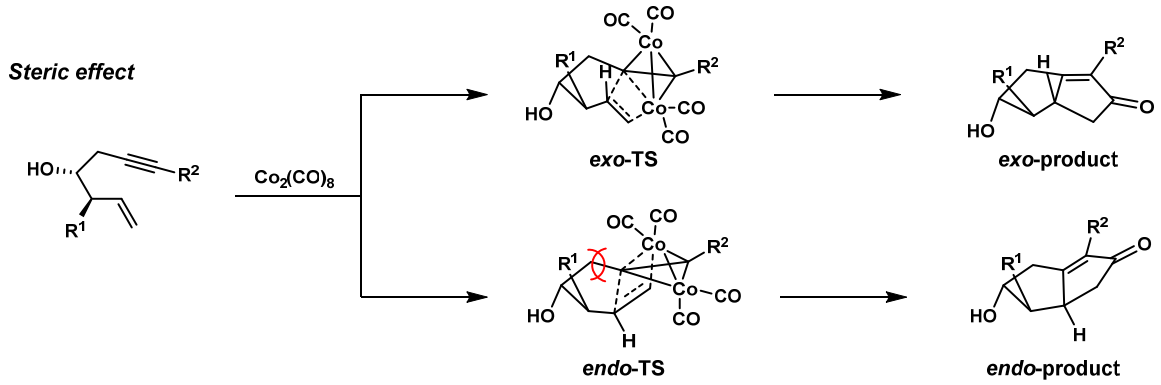
Scheme 1. Generally accepted mechanism of Pauson-Khand reaction with $Co_2(CO)_8$.

The regioselectivity of PKR is influenced by both steric and electronic effects (Scheme 2). For electrically neutral substrates, the insertion of olefins to enyne/$Co_2(CO)_6$ complex correlates with steric hindrance. The regioselectivity also has been demonstrated to be related to the electronegativity of alkynyl groups [50–52]. Under most circumstances, the electron-withdrawing group will be installed at the β position of cyclopentenone. It is noteworthy that the frontier molecular orbital (FMO) theory could be used to analyze the influence of olefins in PKR [53,54]. Moreover, subordinate interaction and the guiding group can affect the regioselectivity [55–57]. For allene-involved intramolecular PKR, a 5,7-bicyclic product is more inclined to be formed [58,59].



Scheme 2. Regioselectivity study of Pauson-Khand reaction.

As for the diastereoselectivity of intramolecular PKR, both substrate conformation (especially the allyl chiral center) and electronic effect are relevant parameters (Scheme 3). Krafft reported their reaction with electron-deficient alkynes, and the PKR product could be obtained with a high *dr* value when norbornene was involved as an olefin substrate [51,60].



Scheme 3. Diastereoselectivity study of intramolecular Pauson-Khand reaction.

Most of the Co-catalyzed PKR conditions require a relatively high temperature and long reaction time. To accelerate the reaction rate, Smit and Caple's group found that PKR could be promoted in a stepwise manner [61]. *N*-methylmorpholine oxide (NMO), acting as an additive, was reported to improve the reaction rate through oxidizing CO into CO_2 on the enyne/$Co_2(CO)_6$ complex [62], forcing the cobalt to release a vacant orbital which can be coordinated with olefins [63]. Recently, the Dionicio Martinez-Solorio group demonstrated the value of 4-FBnSMe as a new, efficient, and recoverable/reusable thioether promoter in PKR by modulating the Lewis basicity of thioether to influence the rate of alkene insertion [64].

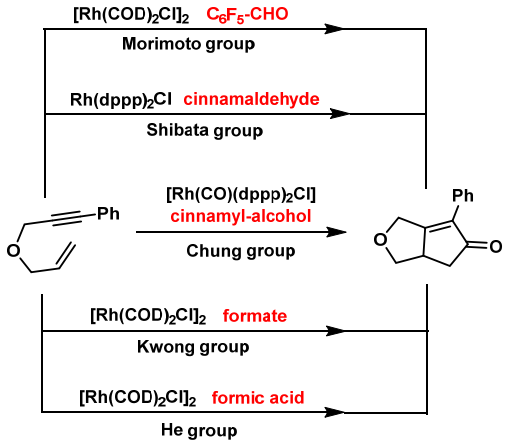
To circumvent the use of stoichiometric catalysts, some Lewis bases were discovered to achieve the catalytic version of PKR, such as phosphine ligand [65], tetramethyl thiourea [66], phosphane sulfide [14], and primary amines [67]. In 2005, the Milet and Gimbert groups converted to the density functional theory (DFT) and calculated the energy change of the PKR process with Lewis base [68]. The results indicate that the enyne/$Co_2(CO)_6$-alkene insertion is a reversible process, but the Lewis base coordination could reduce the energy and therefore make the olefin insertion process irreversible.

1.2. PK Reaction Catalyzed by Rh and Pd

The first example of $[RhCl(CO)_2]_2$ catalyzed PKR was reported by Narasaka et al. in 1998 [18]. In their studies, the use of toluene as a reaction media reduced the loading of Rh catalysts and a good reaction reactivity was achieved with electron-deficient alkynes [69]. Moreover, under a low partial pressure of CO, it can effectively speed up the reaction and decrease the reaction temperature. Jeong et al. reported the first case of rhodium-catalyzed asymmetric PKR in the presence of 2,2′-*bis*(di-*p*-tolylphosphino)-1,1′-binaphthyl(BINAP) and AgOTf [21]. Consiglio's group used the molecular sieve to adsorb CO, greatly reducing the reaction temperature and accelerating the rate [70]. They accomplished the asymmetric PKR at 0 °C with a 99% *ee* value. In the course of Wender and his co-workers' studies on the rhodium(I)-catalyzed intra- and intermolecular dienyl [2 + 2 + 1] PKR, they observed that when a diene was used in place of an alkene the reaction rate was significantly accelerated [71,72].

As the Rh-catalyzed PKR has several advantages, it has attracted the attention of many research groups to report their work in this area. Typical PKR requires the utilization of highly toxic CO gas. An important breakthrough was made by the Morimoto and Shibata groups, respectively by introducing metal carbonyl compounds as a masked CO source through transition metal decarbonylation to in situ generate CO in PKR [73]. Moreover, Chung's group developed the use of a highly beneficial cinnamyl-alcohol as a CO source in the presence of the Rh catalyst to obtain corresponding hetero-Pauson-Khand (hPK) products in an inexpensive, safe, and environmentally friendly manner [74]. The catalytic dehydrogenation of cinnamyl alcohol could produce cinnamaldehyde, followed by Wilkinson decarbonylation and carbonylation constructed the desired cyclic product. Benzyl formate [75] has also been exploited as a non-gas CO surrogate. In 2019, they further

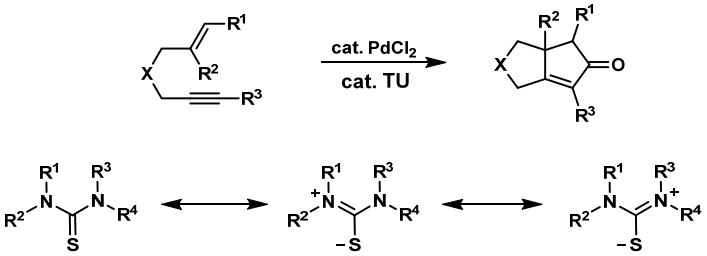
demonstrated the utilization of the formic acid as a CO source in the formation of various bicyclic cyclopentenones. In their protocol, formic acid was employed as a bridging molecule for the conversion of CO_2 to CO, which represented an indirect approach for the chemical valorization of CO_2 in the construction of valuable heterocycles [76] (Scheme 4).



Scheme 4. Non-gas CO surrogates in the Pauson-Khand reaction for heterocycle's formation.

The theoretical analysis of Rh-catalyzed PKR diastereoselectivity was demonstrated by Baik's group [25]. They revealed that two possible mechanistic scenarios and the optimum selectivity could be attributed to a five-coordinate organorhodium complex. The larger energy gap between the diastereomers and the Rh meta-cyclization trend to occur at the *cis*-position site dominated the diastereoselectivity. Based on the high efficiency, reliability and excellent diastereoselectivity of Rh-catalyzed PKR, its extraordinary impact on the synthetic campaign as a key step has been recognized [77].

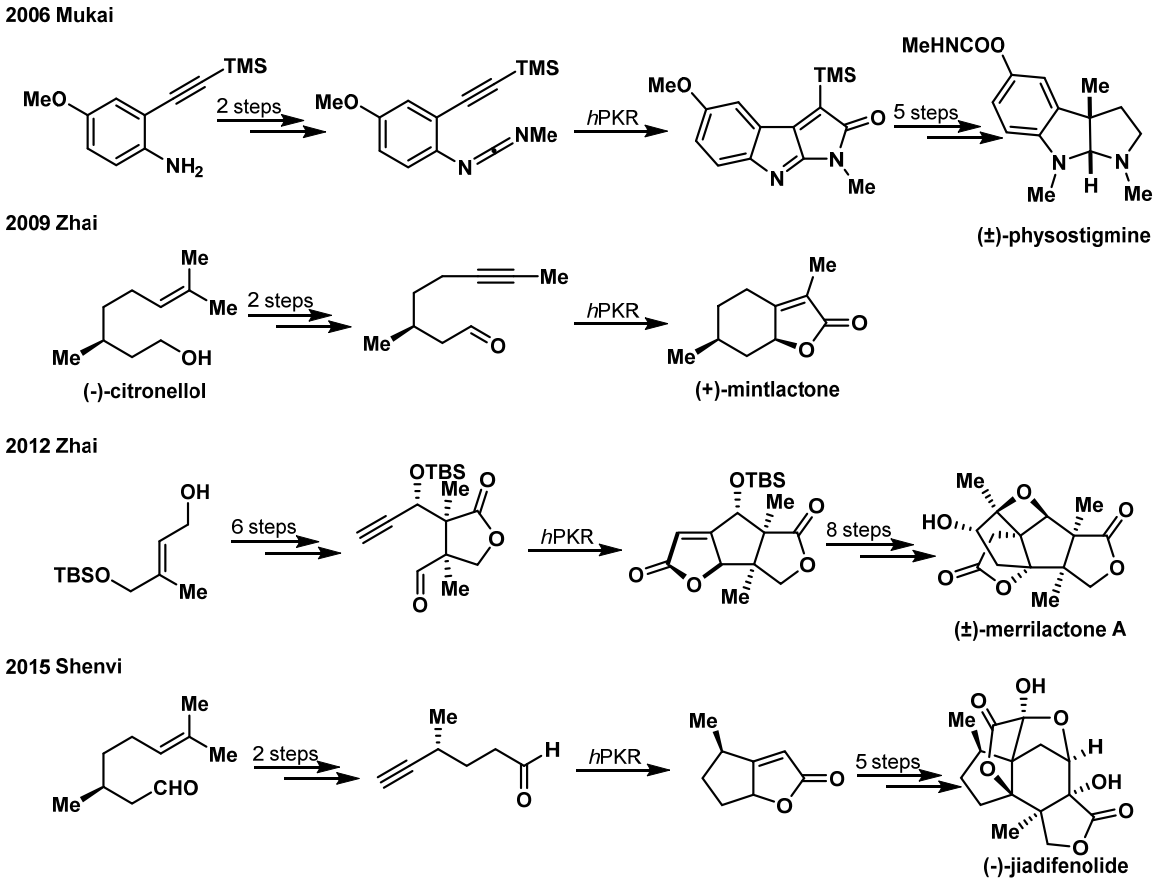
Few metals could be applied in the catalytic PKR (Co, Ti, Rh, Ir, Ru) as most of them are air and moisture sensitive, and as such, it accounted for some limitations in synthetic applications. A series of thiourea and Pd-catalyzed reactions were developed by Yang's group [78–81] (Scheme 5). $PdCl_2$ coordinated to a thiourea ligand could catalyze an intramolecular PKR under mild conditions [81,82], and some interesting features were observed in this novel step. It could be catalyzed by $PdCl_2$ alone with a low yield, whereas using thiourea, especially tetramethyl thiourea (TMTU), as a reaction additive could greatly increase the yield; the Lewis acids addition such as LiCl can increase both the reaction rate and yield. Based on this observed phenomenon, further DFT calculation and mechanism investigation were carried out [83]. According to the coordination mode of the transition state, the TMTU ligand and substrate are lying both on the same side of the Pd catalyst thus the trans-diastereomer in substituted cases outperformed its diastereoisomer. It is speculated that changes in thiourea ligands may affect the diastereoselectivity of PKR through steric effect and π-π interaction, etc.



Scheme 5. Tetramethyl thiourea (TMTU) and Pd-catalyzed Pauson-Khand reaction.

1.3. Hetero-Pauson-Khand Reaction

The hetero-Pauson-Khand reaction has been harnessed as an effective tactic in the concise construction of functionalized polycyclic butenolides and α, β-unsaturated lactams (Scheme 6). In 1996, Crowe et al. reported the direct synthesis of bicyclic γ-butyrolactones via tandem reductive cyclization-carbonylation of tethered enals and enones [84,85]. In the same year, Buchwald et al. presented the heteroatom variant of the intramolecular PKR catalyzed by $Cp_2Ti(PMe_3)_2$, in which the alkene could be replaced with a carbonyl for the diastereoselective synthesis of γ-butyrolactones or a fused butenolide, respectively [86,87]. Later on, chemists devoted themselves in the development of hetero-Pauson-Khand reaction, including Murai [28,88], Carretero [89], Saito [90], and Snapper [91]. However, the application of hPK in a natural product total synthetic work is relatively rare and therefore is underexplored in the synthetic version [92–96].



Scheme 6. Hetero-Pauson-Khand reaction in natural products total syntheses.

1.4. Summary

Cobalt, rhodium, and palladium were involved in PK reactions represented in different advantageous patterns, among which the outstanding superiorities are as follows: a. Cobalt-catalyzed PKRs can overcome the high tension and construct an all-carbon quaternary chiral center [7,97–99]; b. rhodium-catalyzed PKRs normally exhibit excellent diastereoselectivity and are attractive in building a variety of ring structures; c. palladium-catalyzed PKRs could lead to the opposite stereoselectivity compared with others and are more operable due to the stability of Palladium species. Co/Rh-catalyzed PKRs are already widely applied in natural products total syntheses, in contrast, restriction existed in Pd-catalyzed PKRs and most of the work is still under methodological study.

The stereoselective formation of quaternary chiral centers is challenging in the construction of the cyclic system. PKR is an effective method for generating 5,5-bicyclic ring systems and has already

been studied comprehensively. In 1984, Schore's group reported the first case of PKR to construct a 5,5,5-tricyclic skeleton containing an all-carbon quaternary chiral center [100]. Numerous research groups reported their studies and applications in natural products total syntheses. Joseph M. Fox et al. applied a thiourea-facilitated PKR in establishing the quaternary center and built a 5,5,3-tricyclic framework, and then completed the enantioselective total synthesis of (−)-pentalenene [101]. In the past few years, many chemists have made their efforts to broaden the application of the intramolecular PKR in natural products total syntheses, with some reviews already published [5–12]. In this mini-review, a perspective on the development of strategic Pauson-Khand reaction within natural products total syntheses portfolio over the past five years is presented by the categories of the constructed bicyclic ring systems (5,5/5,6/5,7- and macrocycles), with the aim to provide an updated overview of its tremendous power and versatility.

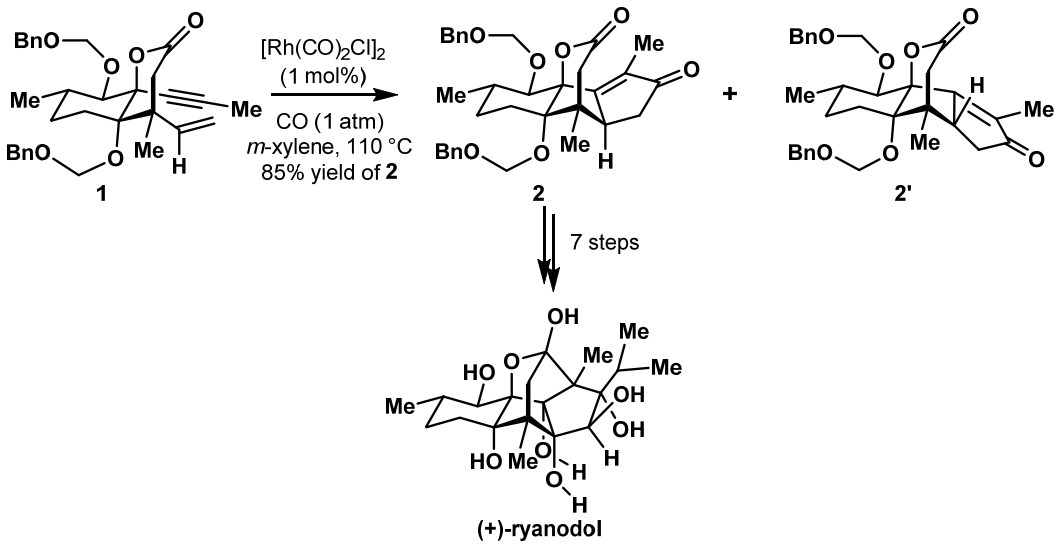
2. Recent Pauson-Khand Reaction Applications in Natural Products Total Syntheses

PKR proved to be a powerful strategy in natural products syntheses, particularly in those containing fused five-membered rings. The tethered length plays an important role in the efficiency and viability of all intramoleculars.

Pauson-Khand-like reactions [102], and the substrates with tethers that result in the formation of a five-membered ring are most effective in a great variety of intramolecular reactions [103]. Collections of 5,5/5,6/5,7-bicyclic ring systems or even macrocycles could be accessed depending on substrate identity as shown in this review.

2.1. Construction of 5,5-Bicyclic Ring Systems

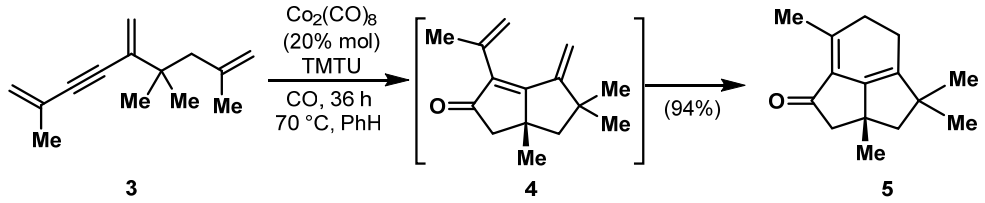
Ryanodol is a bioactive and complex poly-alcohol containing natural product which is a potent modulator of the calcium release channel [104,105]. In 2016, Reisman's group reported a highly efficient way to rapidly build the carbon framework of ryanodol through intramolecular PKR which was promoted by the rigidity of the bicyclic conformation [106]. Starting from *S*-pulegone, the PK precursor **1** could be achieved after seven steps of transformation. In their promising reaction protocol, submitting **1** with 1 mol% $[RhCl(CO)_2]_2$ under an atmosphere of CO afforded enone **2** in an 85% yield as a single diastereomer. More impressively, the efficient protocol could be performed on the multi-gram scale and provided a 5.7 g of PK product (Scheme 7).



Scheme 7. Reisman's total synthesis of (+)-ryanodol.

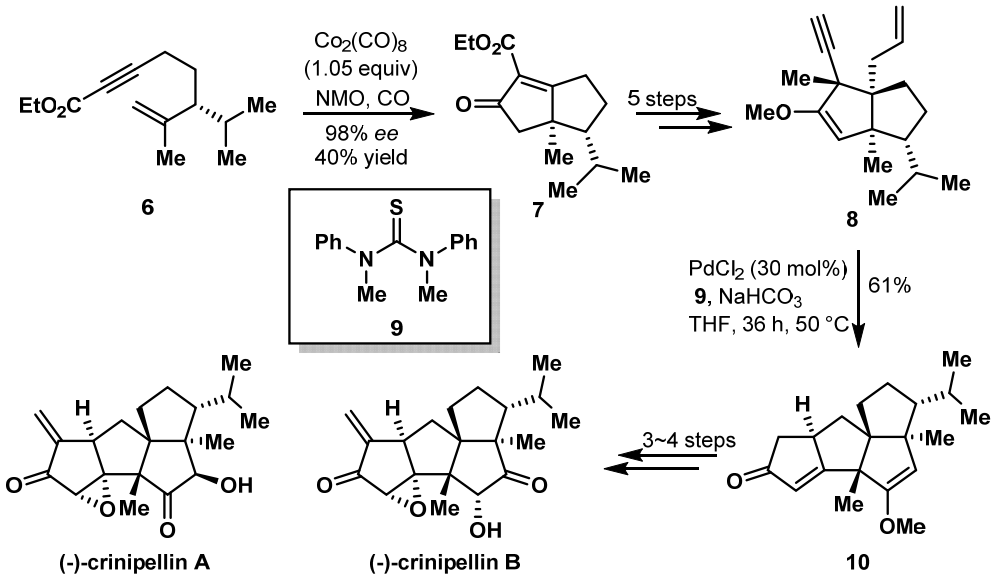
Tetramethyl thiourea (TMTU) has proven to be an efficient additive in the PKR based on Yang's previous investigations [66]. In 2017, they developed a Co–TMTU catalyzed PKR and 6π

electrocyclization tandem reactions to construct the highly strained core skeleton of presilphiperfolanols and related natural products [107,108]. Treatment of **3** with a catalytic amount of $[Co_2(CO)_8]$ (0.2 equiv.) and TMTU (1.2 equiv.) in benzene resulted in the rapid construction of the tricyclic scaffold **5** with great regio- and stereochemical control in a 94% yield through one single operation. Most recently, they applied this PKR model to the synthesis of 4-desmethyl-rippertenol and 7-epi-rippertenol [109] (Scheme 8).



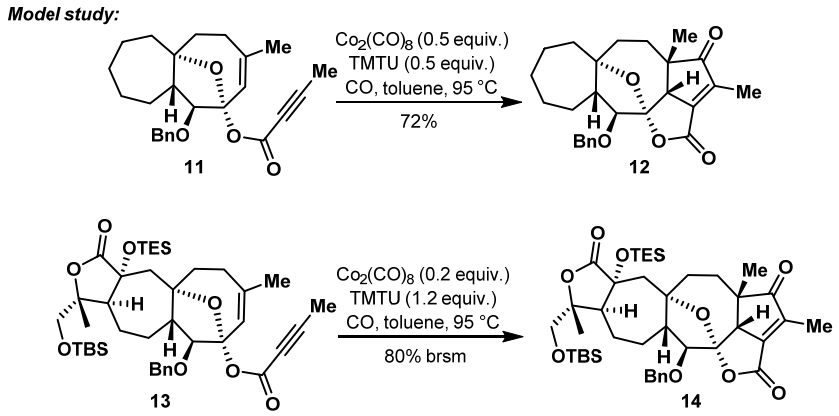
Scheme 8. Yang's concise synthesis of presilphiperfolane core.

In the total synthesis of the potent antibiotic compounds (−)-crinipellin A and (−)-crinipellin B reported by Yang et al. [97], the fully functionalized tetraquinane core was achieved by a novel thiourea/palladium-catalyzed PKR. They implemented two PKRs in their synthetic strategy with the first being a conversion of **6** into **7** with a 40% yield and 98% *ee* after crystallization. As generally proved, the electron-deficient alkyne is not a perfect ligand for $Co_2(CO)_8$, gradual warming is essential for constructing the desired enyne/$Co_2(CO)_6$ complex. The other PKR allows the concise formation of the tetraquinane **10**. Treatment of **8** in the presence of $NaHCO_3$ as the base provided the desired tetraquinane core **10** in a 61% yield, with the undesired isomer suppressed to a 16% yield (Scheme 9).



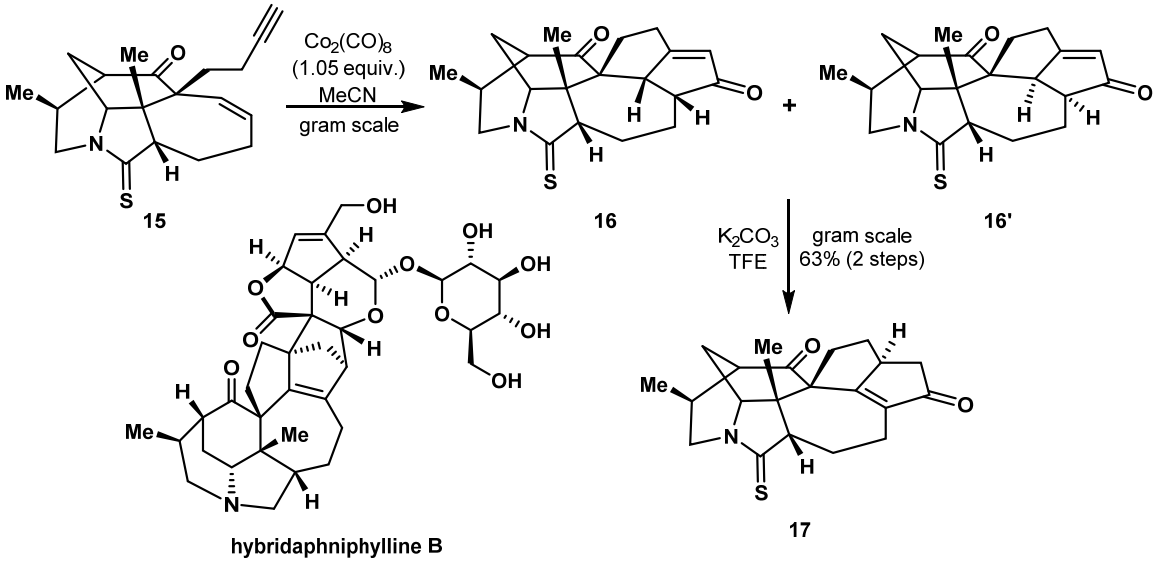
Scheme 9. Yang's total synthesis of crinipellins.

In 2018, Yang's group described a stereoselective construction of the CDEFGH ring system of lancifodilactone G acetate and a 28-step asymmetric total synthesis [110,111]. They performed an intramolecular PKR for the construction of the sterically congested F ring. In their model study, the authors observed that the butynoic ester was effective for the regio- and stereoselectivity in constructing the cyclopentenone ring system bearing two chiral centers. The developed well-orchestrated PKR facilitated the stereoselective synthesis of **14** from enyne **13** (Scheme 10).



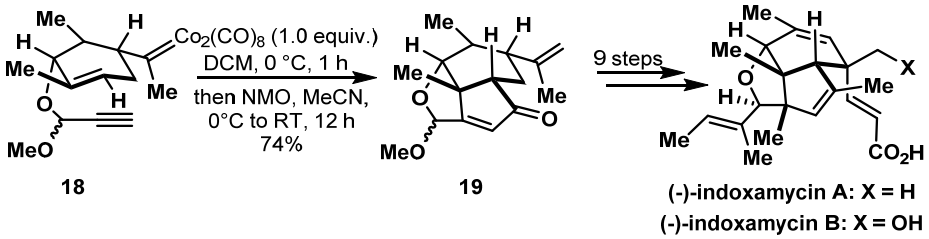
Scheme 10. Yang's asymmetric total synthesis of lancifodilactone G acetate.

Li et al. reported the first total synthetic work of hybridaphniphylline B featuring a late-stage intermolecular Diels–Alder reaction [112]. They implemented a PKR and C=C bond migration strategy to achieve the key intermediate **17**. Through the investigation of Pauson-Khand conditions, it is determined that MeCN is an effective accelerator to transform the alkyne dicobalt complex into the desired product, which was depicted the same as Pauson's work [113]. Under this condition, the two PKR products **16** and **16'** were constructed in a 73% yield with the ratio of ca. 2.4:1. Then, submitting the mixture to K_2CO_3/TFE realized the C=C bond migration and gave the more substituted enone **17** (Scheme 11).



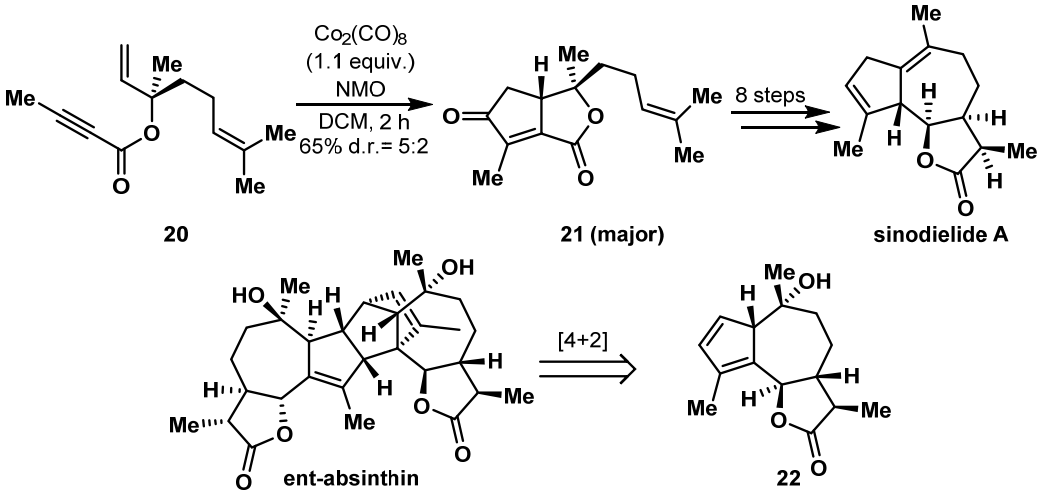
Scheme 11. Li's total synthesis of hybridaphniphylline B.

Liang et al. described a concise total synthesis towards (−)-indoxamycins A and B, a novel class of polyketide natural products, which contain a highly congested cage-like carbon skeleton featuring six contiguous chiral centers [114]. The key step for rapidly constructing the framework bearing a quaternary carbon was an intramolecular PKR. Enyne **18** was converted into the 5,5,6-tricyclic compound **19** smoothly with a 74% yield, which could be further transformed into the target natural products (Scheme 12).



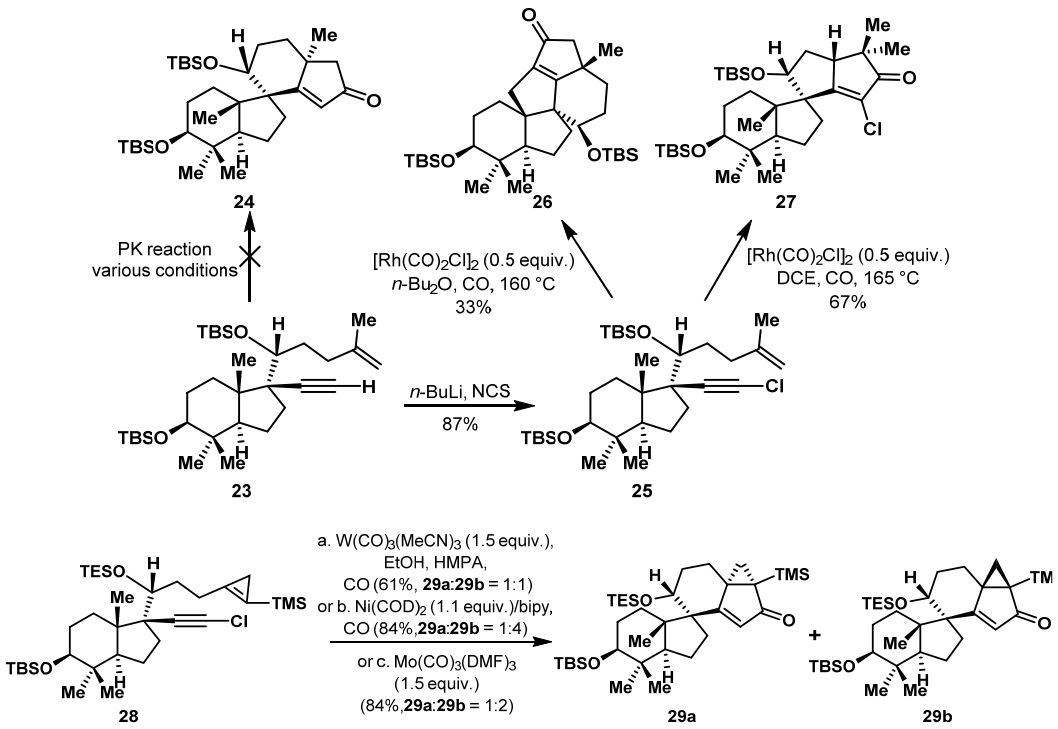
Scheme 12. Liang's total synthesis of (−)-indoxamycins A and B.

Guaianolide sesquiterpenes represent a particularly prolific class of terpene natural products, which have attracted biological and chemical communities for decades given their extensive documented therapeutic properties and fascinating chemical structures. Recently, the cobalt- mediated intramolecular PKR was applied in the total synthesis of sinodielide A and ent-absinthin by Mainone et al. [115]. Ester **20**, converted from (−)-linalool via deprotonation and a subsequent reaction with the mixed anhydride of 2-butynoic acid, underwent a smooth PKR reaction using $Co_2(CO)_8$ and resulted in strained bicyclic lactone **21** (65% yield, 5:2 d.r.), which enabled concise and collective total syntheses of guaianolide sesquiterpenes (Scheme 13).



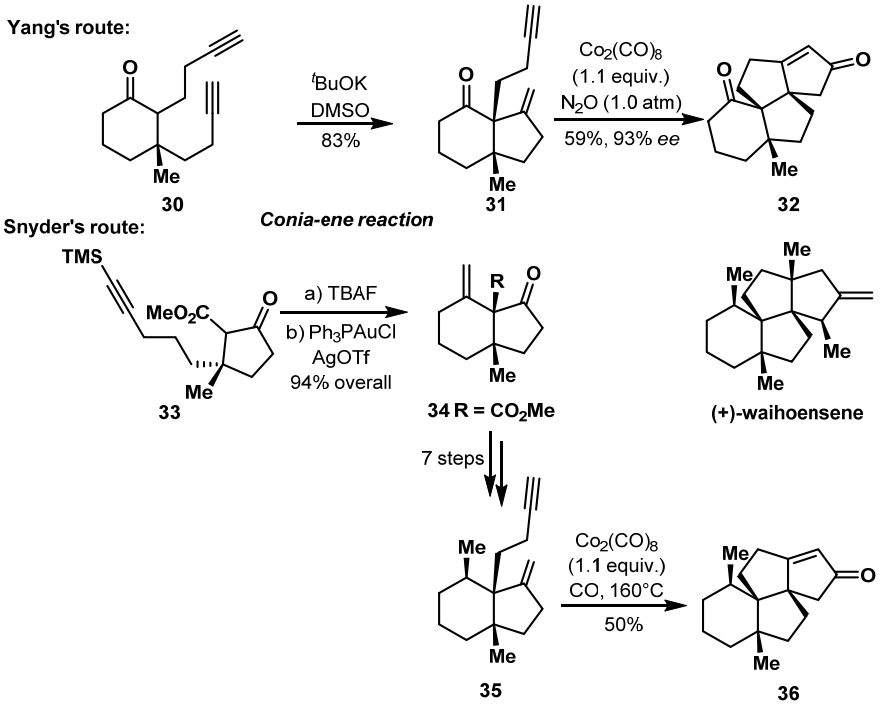
Scheme 13. Maimone's allylative approaches to the synthesis of complex guaianolide sesquiterpenes.

Yang et al. recently described the first asymmetric total synthesis of (−)-spirochensilide A featuring a tungsten-mediated cyclopropene-based PKR to install the quaternary chiral center [116]. Initially, they attempted various conditions to construct the cyclopentenone motif in **24** but all proved in vain presumably due to the low reactivity of enyne **23** and its steric rigidity. Recognizing the inherent of a chloride, they employed it as an σ electron-withdrawing group to promote polarization and reduce the activation barrier, with the idea in hand they prepared chloroenyne **25**. However, reaction conditions screening only resulted in the undesired ring-closing compounds **26** and **27,** respectively, which was generated by an Rh-catalyzed carbonylative C-H insertion and a double bond isomerization followed by a PKR. Then, they considered taking advantage of cyclopropene's inherent strain and altered the pathway to construct enyne **28**. After an investigation of many conditions, the $W(CO)_3(MeCN)_3$, $Ni(COD)_2$/bipy, and $Mo(CO)_3(DMF)_3$-catalyzed PKR could lead to the formation of the desired **29a**, which could be further transformed into (−)-spirochensilide A (Scheme 14).



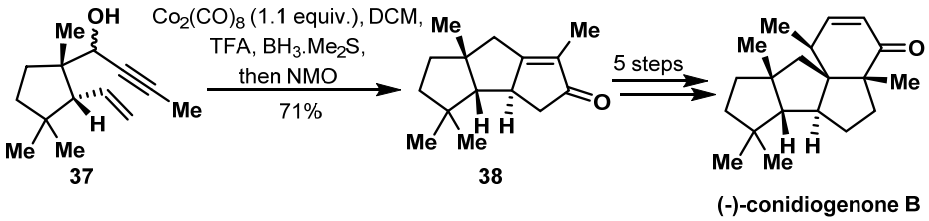
Scheme 14. Yang's asymmetric total synthesis of (−)-spirochensilide A.

Very recently, Yang and Snyder's group both reported their total synthesis towards the challenging target (+)-waihoensene [98,99], which contains four contiguous quaternary carbon centers. In their strategies, they all involved a diastereoselective Conia-ene type reaction and an intramolecular PKR. The polycyclic skeleton of Waihoensene was achieved by the $Co_2(CO)_8$-mediated PKR under CO atmosphere (Scheme 15).



Scheme 15. Yang's and Snyder's total synthesis of (+)-waihoensene.

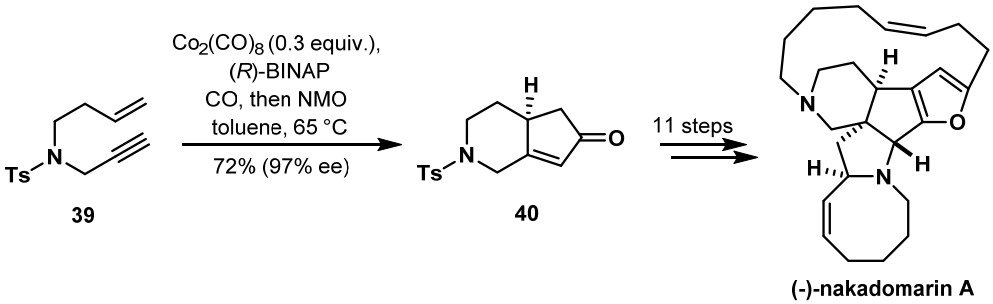
(−)-Conidiogenone B, (−)-conidiogenone, and (−)-conidiogenol feature a highly strained 6/5/5/5 tetracyclic core and 6-8 consecutive stereocenters. The concise total syntheses have been accomplished by Zhai et al. [117]. The key linear triquinane **38** was constructed as a single diastereomer in a 71% yield via a tandem Nicholas and amine-N-oxide-promoted PKR from **37** with the borane-methyl sulfide complex as the hydride source (Scheme 16).



Scheme 16. Zhai's total synthesis of (−)-conidiogenone B.

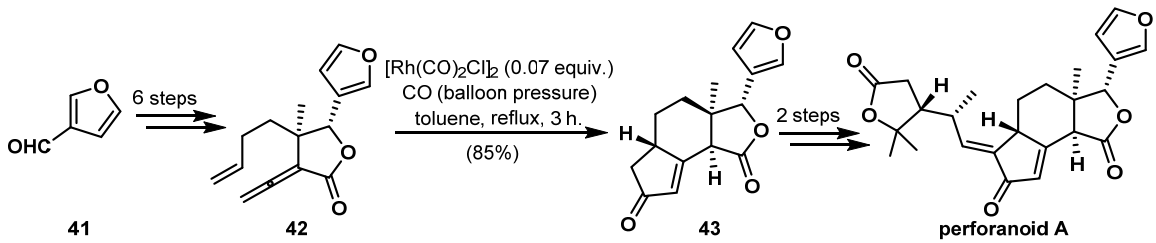
2.2. Construction of 5,6-Bicyclic Ring Systems

Clark et al. elucidated an efficient 12-step synthesis of the marine alkaloid (−)-nakadomarin A [118], which contains a unique hexacyclic structure featuring fused 5-, 6-, 8-, and 15- membered rings and exhibits cytotoxicity against murine lymphoma L1210 cells, antimicrobial and inhibitory activity against cyclin-dependent kinase 4. The fused bicyclic enone **40** was constructed in a good yield and with an excellent *ee* value using the asymmetric cobalt-catalyzed PKR, which was developed by Hiroi et al. earlier before (Scheme 17).



Scheme 17. Clark's total synthesis of (−)-nakadomarin A.

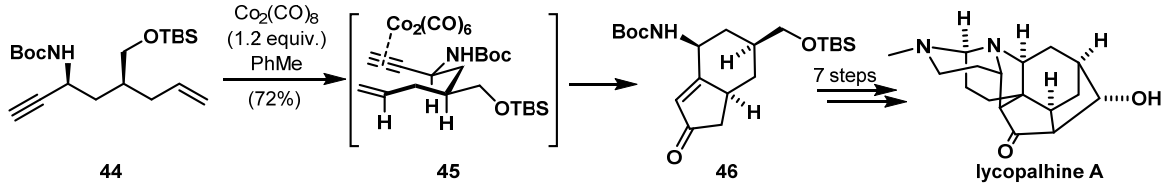
In the Hao et al. studies toward the 10 step-synthesis of a novel limonoid perforanoid A [119], they investigated Rh-catalyzed intramolecular PKR to build the cyclopentenone ring. Under their optimum conditions, treatment of **42** in toluene for 3 h at a reaction concentration of 8 mM with $[Rh(CO)_2Cl]_2$ (7 mol%) as the catalyst gave **43** in 85% as a single isomer (Scheme 18).



Scheme 18. Hao's asymmetric total synthesis of perforanoid A.

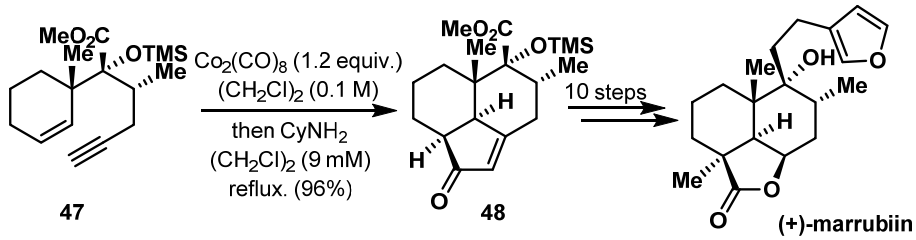
Zard, Takayama, and Mukai groups have explored the diastereoselective study of intramolecular PKR in the context of Lycopodium alkaloids syntheses [120–122]. Based on their previous study, Trauner et al. used a similar strategy to synthesize enone **46** with the desired stereoselectivity,

which was proposed through a chair-like conformation of intermediate **45** ensuing the bicycle [4.3.0] nonenone [123] (Scheme 19).



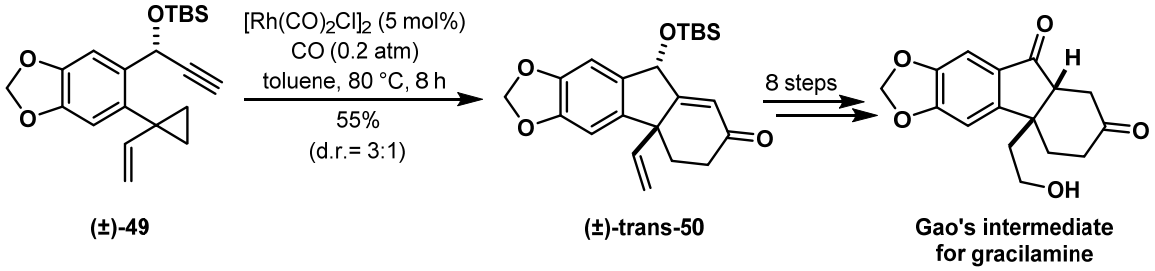
Scheme 19. Trauner's expedient synthesis of (+)-lycopalhine A.

Nakamura et al. have accomplished the stereoselective total synthesis of (+)-marrubiin involving a $CyNH_2$-promoted PKR and subsequent oxidative cleavage of the resultant cyclopentenone ring [124,125]. According to their DFT studies, the irreversible olefin insertion step is critical to the stereochemistry of PKR. The steric interaction could be avoided through a trans-fused chair−boat-like TS and therefore the exclusive isomer **48** was afforded (Scheme 20).



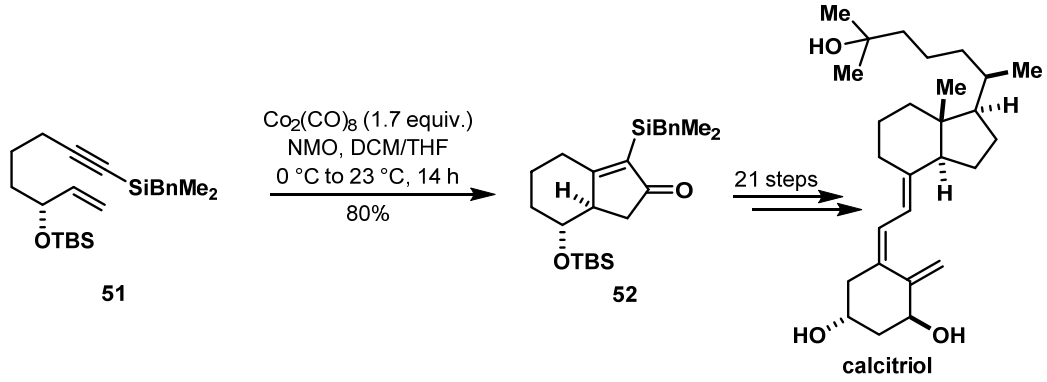
Scheme 20. Nakamura's total synthesis of (+)-marrubiin and (−)-marrulibacetal.

Yu et al. have developed an Rh(I)-catalyzed [3 + 2 + 1] cycloaddition of 1-ene/yne−vinylcyclopropanes (VCPs) and CO, which was used to construct 5,6-bicyclic advanced intermediate **50** from yne-VCP (±)-**49** [126]. The advanced intermediate **50** can be transformed into Gao's intermediate for the formal synthesis of gracilamine [127]. This cycloaddition provided a solution to construct the bridgehead quaternary carbon center. The diastereoselectivity was realized by the repulsion between the OTBS (TBS = *t*-butyldimethylsilyl) group and the vinyl moiety (Scheme 21).



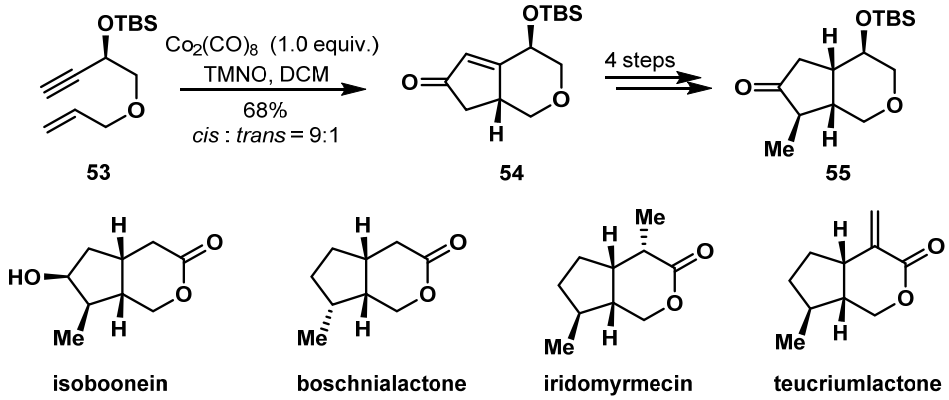
Scheme 21. Yu's formal synthesis of gracilamine.

In the synthesis of calcitriol, the active form of vitamin D_3, Mourino et al. utilized the NMO promoted PKR to form the 5,6-bicyclic core **52** in a diastereoselective way [128]. Intermediate **52** underwent Si-assisted allylic substitution and some other transformations to complete the synthesis of calcitriol (Scheme 22).



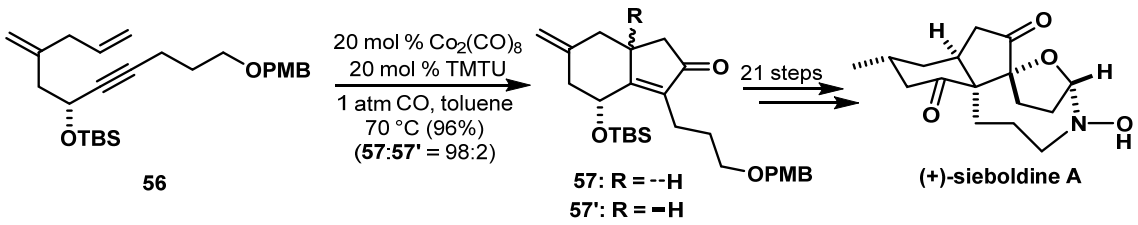
Scheme 22. Mourino's total synthesis of calcitriol.

Khan et al. delineated the collective total synthesis of iridolactones [129]. The newly constructed iridoid framework **54** was accomplished by a diastereoselective intramolecular PKR [130]. With the key intermediate **55** in hand, they demonstrated a general and simple route to access structurally divergent iridolactones (Scheme 23).



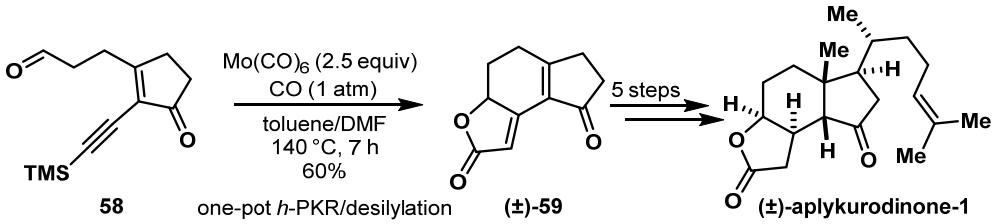
Scheme 23. Khan's total synthesis of several iridolactones.

A fawcettimine-type Lycopodium alkaloid (+)-sieboldine A contains an unprecedented fused tetracyclic skeleton and has been found to inhibit acetylcholinesterase with an IC_{50} value of 2.0 μM [131]. Mukai et al. have applied PKR to afford the bicyclo [4.3.0] nonenone derivative **57** with high stereoselectivity with an *ee* value of 93% in their total synthesis of (+)-sieboldine A [132] (Scheme 24).



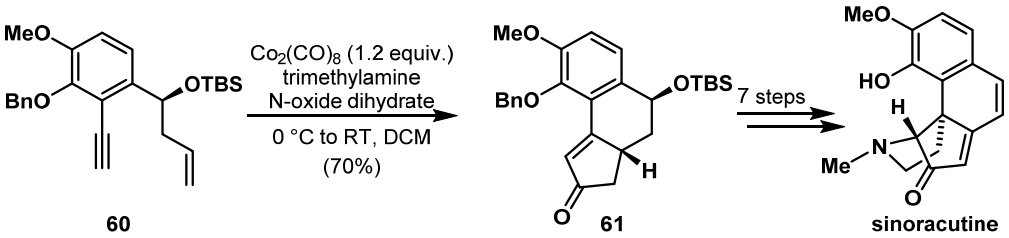
Scheme 24. Mukai's enantioselective total synthesis of (+)-sieboldine A.

Since the hPKR variant is much less reported, Zhai et al. applied an interesting hPKR in the formal synthesis of (±)-aplykurodinone-1 [133]. The tricyclic framework **59** has been constructed with a 60% yield through expeditiously one-pot intramolecular hPKR followed by the desilylation sequence. The hPKR is relatively rare to be found in natural product synthesis, and this application provided worthwhile insights for expanding the scope and boundaries (Scheme 25).



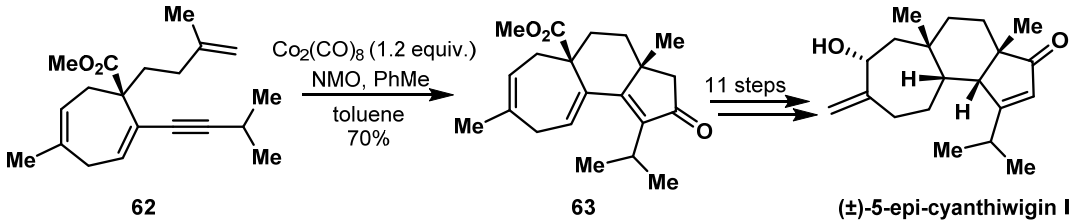
Scheme 25. Zhai's formal synthesis of (±)-aplykurodinone-1.

(−)-Sinoracutine, isolated from *Stephania cepharantha* in 2010 [134], proves to be a promising template for new neuroprotective reagents intervention as it was shown to increase cell viability against hydrogen peroxide-induced damage in PC12 cells [135]. Structurally, it features an unprecedented tetracyclic 6/6/5/5 skeleton that bears an N-methylpyrrolidine ring fused to acyclopentenone. In the first total synthesis of (−)-sinoracutine [136], Trauner et al. utilized intramolecular PKR under the oxidative condition as a key transformation to construct the tricycle product **61** from an enyne precursor **60**. The reaction was carried out in the presence of N-oxide dihydrate together with $Co_2(CO)_8$. The resulting tricyclic product **61** allows the concise total synthesis of (−)-sinoracutine with several steps of transformations, including a Mandai–Claisen reaction to install the quaternary stereocenter (Scheme 26).



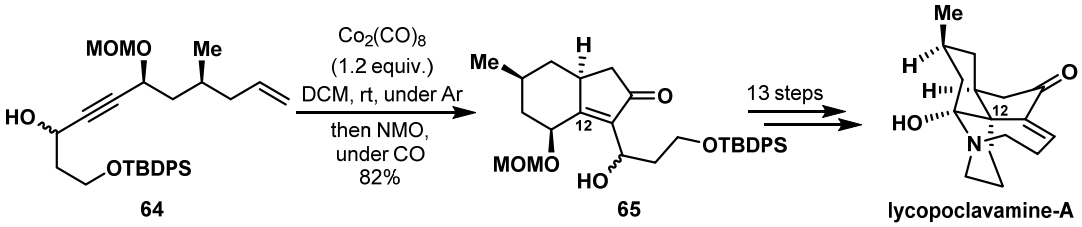
Scheme 26. Trauner's enantioselective synthesis and racemization of (−)-sinoracutine.

Cyanthiwigin type diterpenes are biologically important marine natural products mostly isolated from marine sponges *Epipolasis reiswigi* and *Mermekioderma styx*. Particularly, cyanthiwigin C and F show medium cytotoxicity against A549 cell lines [137]. In 2019, Yang et al. reported the total synthesis of 5-epi-cyanthiwigin I [138]. The key [5–6–7] tricarbocyclic fused core structure was constructed via a well-orchestrated Co-mediated intramolecular PKR, which has two cis-configured all-carbon quaternary chiral centers and an isopropyl group. Enyne **62** could be transformed into the tricyclic product **63** as the sole isomer in a 70% yield in the presence of a stoichiometric amount of $Co_2(CO)_8$ combined with NMO as the additive (Scheme 27).



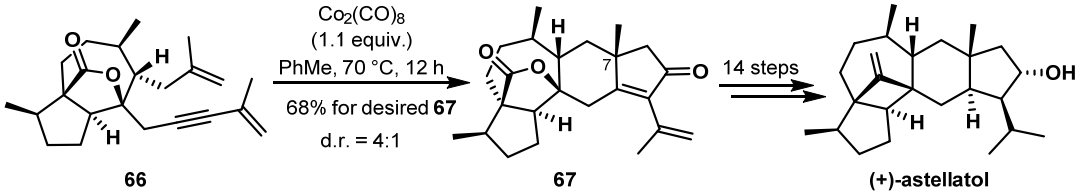
Scheme 27. Yang's stereoselective total synthesis of (±)-5-epi-cyanthiwigin I.

Lycopodium alkaloids are neuropharmacologically valuable scaffolds for central nervous system drug discovery. Takayama et al. reported an asymmetric total synthesis of lycopoclavamine A via a strategy involving a stereoselective PKR and a stereoselective conjugate addition to construct a quaternary carbon center at C12 [139]. The cobalt-mediated intramolecular PKR afforded a desired bicyclic enone **65** in a high yield as well as good diastereoselectivity (Scheme 28).



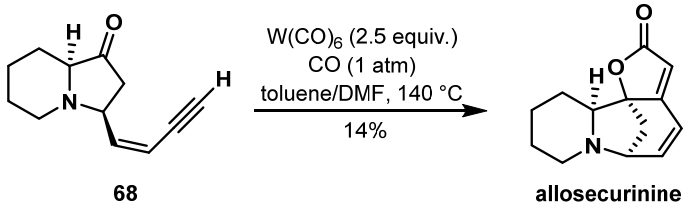
Scheme 28. Takayama's asymmetric total synthesis of lycopoclavamine-A.

Complex sesterterpenoids astellatol and astellatene were isolated from *Aspergillus stellatus* in 1989 [140], which feature highly congested and unusual pentacyclic skeletons and contain a unique bicyclo[4.1.1]octane moiety consisting of ten stereocenters and a cyclobutane containing two quaternary centers. In the total syntheses of (+)-astellatol and (−)-astellatene reported by Xu et al. [141], an intramolecular PKR was exploited to construct the 6,5-bicyclic core embedded in the right-wing scaffold. The desired hydrindane skeleton **67** was generated from enyne **66** with a promising yield and diastereoselectivity at the C7 quaternary carbon center (Scheme 29).



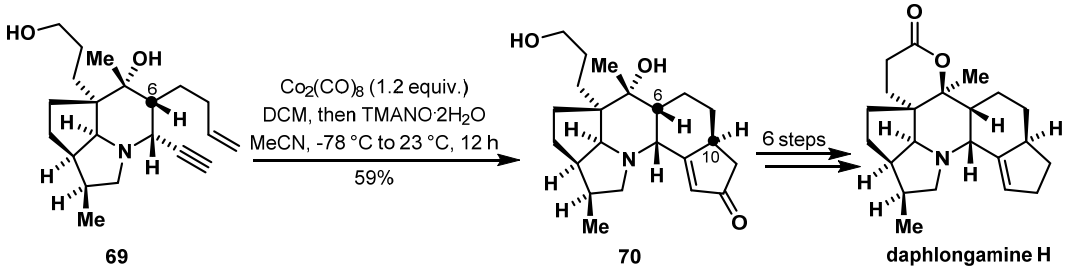
Scheme 29. Xu's asymmetric total synthesis of (+)-astellatol.

Porée et al. reported an elegant synthesis of allosecurinine, utilizing the $W(CO)_6$-promoted oxa-hetero-Pauson–Khand reaction (oxa-hPKR) in the late stage. Despite a low yield, the results constituted the first example of applying the $W(CO)_6$ complex in hPKR, constructing tetracyclic securinega alkaloid featuring an α, β-unsaturated γ-lactone moiety [142] (Scheme 30).



Scheme 30. Porée's enantioselective synthesis of (−)-allosecurinine.

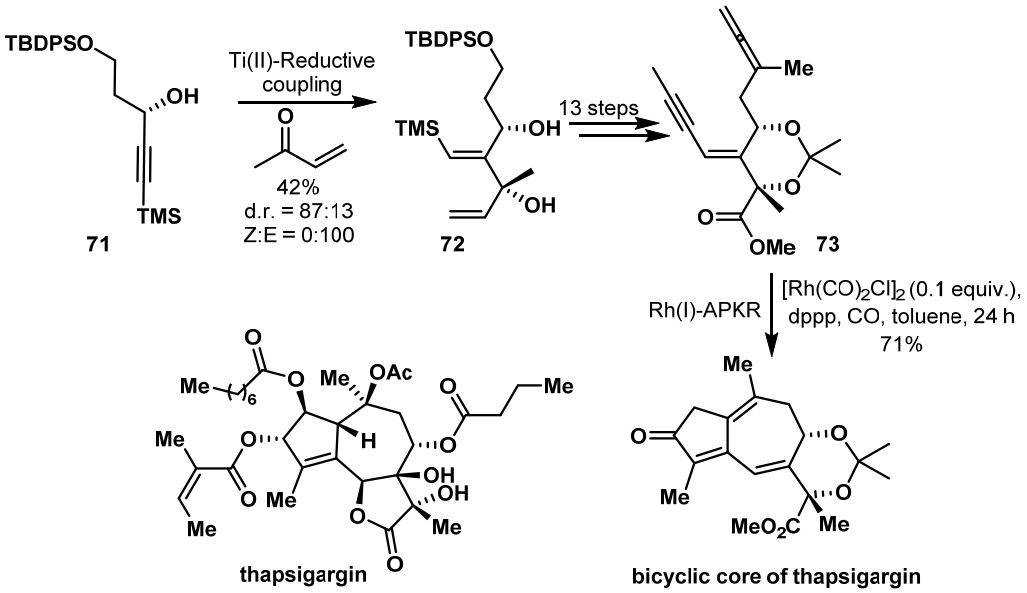
The calyciphylline B-type alkaloids with a unique hexacyclic framework exhibited a variety of important pharmacological potentials. In the synthesis of daphlongamine H, Sarpong et al. used a late-stage cobalt-mediated PKR to accomplish the 6,5-bicyclic segment. The *R* configuration of C6 in the PKR enabled the desired 10-H α orientation in the PK product **70** [143] (Scheme 31).



Scheme 31. Sarpong's total synthesis of (−)-daphlongamine H.

2.3. Construction of 5,7 Bicyclic Ring Systems

Thapsigargin (Tg1) and its analogs are biologically important candidates as potent inhibitors of the SERCA-pump protein, with the potential of application in a variety of medicinal areas [144,145]. Numerous attempts have been reported on the total synthesis of this bioactive molecule [146–148]. In 2019, Sorin et al. developed a linear route towards the core of Tg1, which features an allene-yne Rh(I)-catalyzed Pauson-Khand annulation (APKR) as key transformation [149]. The allene-yne precursor was generated from chiral propargylic alcohol **71**, which underwent a Ti(II) mediated reductive coupling to form diol **72**. The allene-yne product **73** was elaborated in several steps. The central feature was identified to be the Rh(I)-catalyzed Pauson-Khand annulation (APKR), resulting in the efficient synthesis of the Tg 1 framework bearing an enol ether moiety in a 71% yield (Scheme 32).

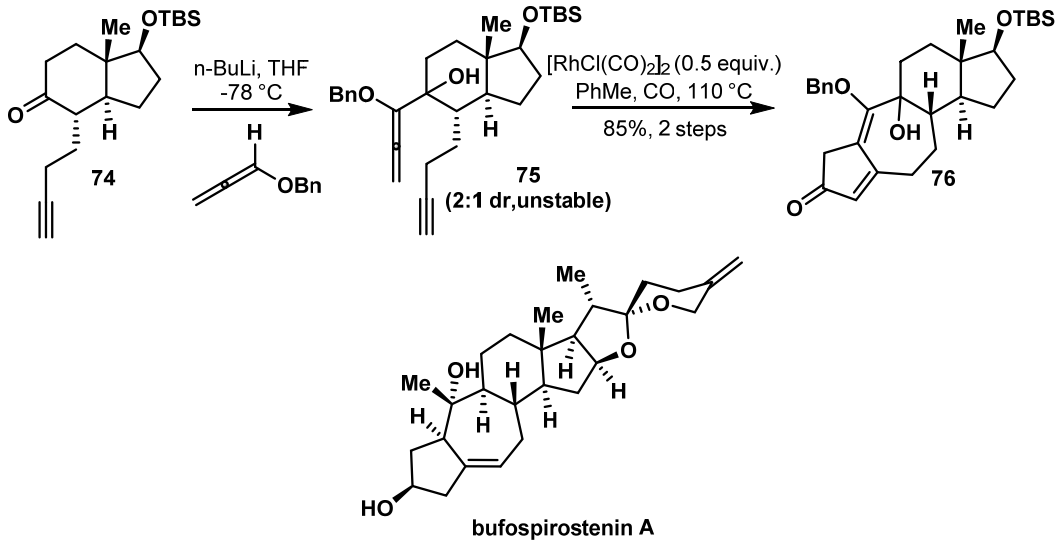


Scheme 32. Sorin's synthesis of a thapsigargin core.

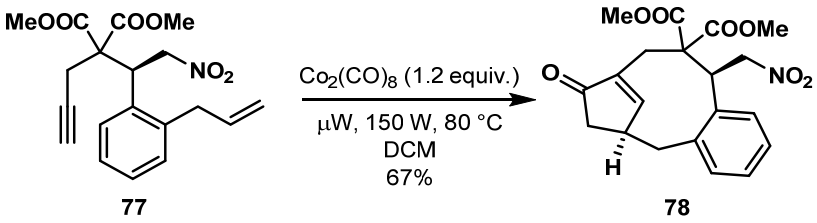
Bufospirostenin A, isolated in 2017 from the toad *Bufo bufo gargarizans*, is an unusual steroid with rearranged A/B rings, possessing a cardioactive effect and promoting blood circulation through causing a 43% inhibition of Na/K ATPase (NKA) at 25 μM [150]. Very recently, a unique intramolecular rhodium-catalyzed PKR of an alkoxyallene-yne substrate was applied to construct the key [5–7] A-B ring system in the first total synthesis of bufospirostenin A reported by Li et al. [151]. Generated from Hajos-Parish ketone, alkyne **74** underwent 1,2-addition to afford precursor **75,** which further yielded tetracyclic product **76** catalyzed by $[RhCl(CO_2)]_2$ in the presence of a balloon pressure of CO in toluene with a high yield (85%). This work represented the first example of an intramolecular Pauson−Khand reaction of an alkoxyallene-yne in natural product synthesis (Scheme 33).

2.4. Construction of Macrocycles

The synthesis of macrocyclic natural products and related structures through a direct C-C bond formation is challenging. Widely applied methodologies include ring-closing metathesis (RCM), Nozaki-Hiyama-Kishi (NHK) reaction, and intramolecular Diels-Alder reactions. PKR has been used and confined in the synthesis of medium-sized rings (up to 11 atoms) [152,153], thus not yet been extended to macrocycles (Scheme 34).

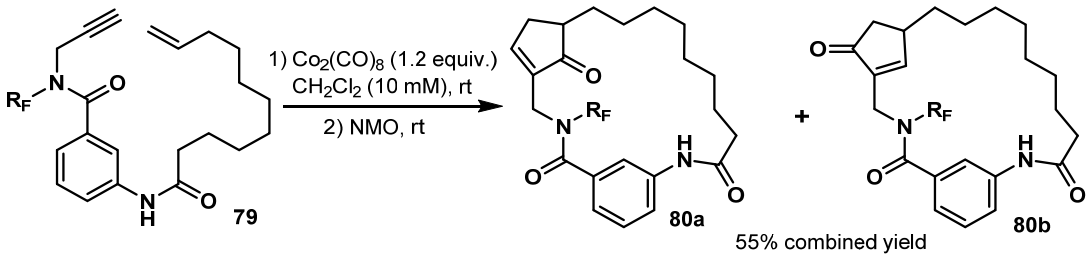


Scheme 33. Li's asymmetric total synthesis of bufospirostenin A.



Scheme 34. Synthetic strategy for medium-sized rings.

Spring et al. reported their investigation of PKR for macrocyclization of a template substrate **79** [154]. After fluorous solid-phase extraction (F-SPE), optimized PKR conditions produced a mixture of structurally unusual macrocycles containing a cyclopentenone motif; these can be separated by HPLC, but they used the mixture in the modified phase (Scheme 35).



Scheme 35. Spring's synthetic strategy for structurally diverse and complex macrocycles.

3. Summary and Outlook

The extraordinary impact of the Pauson-Khand reaction on synthetic methods is still recognized nowadays, and attempts are currently undertaken to further extend the use of various metal-assisted chemistry to environmentally friendly processes within the strongly invoked green chemistry paradigm. The PKR, especially when conducted in an intramolecular fashion, has been widely used as a convenient and powerful tool for the construction of cyclopentenone structural units in natural product synthesis. Though the classical PK cycloaddition has the shortcoming that requires high temperatures and a long reaction time, chemists have developed a range of promoters (TMTU/NMO/TMAO = trimethylamine *N*-oxide, etc.) to circumvent this situation. Moreover, PKR has the merit of well tolerance to a broad variety of functional groups, such as alcohols, ethers, thioethers, esters, nitriles, amines, amides, sulfonamides, etc. With the impressive developments in the catalytic version of

the Pauson–Khand reaction, the application will be more facilitated. Additionally, 4,5-fused bicycles afforded by intermolecular PKR patterns are still called for intensive studies.

Author Contributions: Conceptualization, S.C. and C.J.; data collection S.C. and C.J.; writing—original draft preparation, S.C. and C.J.; writing—review and editing, S.C., C.J., N.Z., Z.Y. and L.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Key Research and Development Program of China (grant no. 2018YFC0310905); National Science Foundation of China (grant nos. 21632002 and 21801123); and Shenzhen Basic Research Program (grant nos. 2019SHIBS0004, JCYJ20170818090044432, and JCYJ20180302180215524).

Acknowledgments: Research activities in related areas in Yang's lab are financially supported by the National Key Research and Development Program of China (grant no. 2018YFC0310905); National Science Foundation of China (grant nos. 21632002 and 21801123); and Shenzhen Basic Research Program (grant nos. 2019SHIBS0004, JCYJ20170818090044432, and JCYJ20180302180215524).

Conflicts of Interest: The authors declare no conflict of interest.

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