

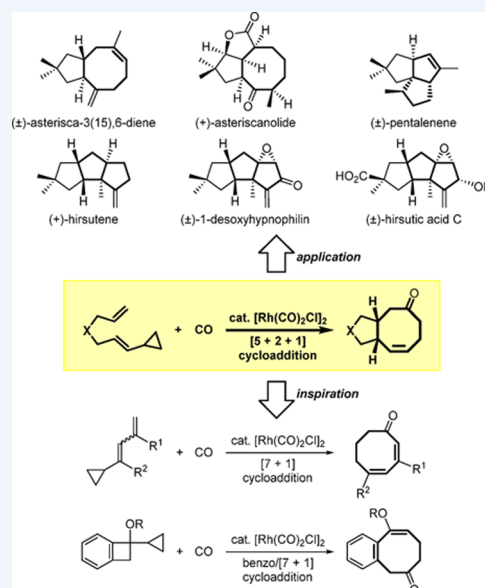
Rhodium-Catalyzed [5 + 2 + 1] Cycloaddition of Ene–Vinylcyclopropanes and CO: Reaction Design, Development, Application in Natural Product Synthesis, and Inspiration for Developing New Reactions for Synthesis of Eight-Membered Carbocycles

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CONSPECTUS: Practical syntheses of natural products and their analogues with eight-membered carbocyclic skeletons are important for medicinal and biological investigations. However, methods and strategies to construct the eight-membered carbocycles are limited. Therefore, developing new methods to synthesize the eight-membered carbocycles is highly desired. In this Account, we describe our development of three rhodium-catalyzed cycloadditions for the construction of the eight-membered carbocycles, which have great potential in addressing the challenges in the synthesis of medium-sized ring systems. The first reaction described in this Account is our computationally designed rhodium-catalyzed two-component [5 + 2 + 1] cycloaddition of ene–vinylcyclopropanes (ene–VCPs) and CO for the diastereoselective construction of bi- and tricyclic cyclooctenones. The design of this reaction is based on the hypothesis that the C(sp³)–C(sp³) reductive elimination of the eight-membered rhodacycle intermediate generated from the rhodium-catalyzed cyclopropane cleavage and alkene insertion, giving Wender’s [5 + 2] cycloaddition, is not easy. Under CO atmosphere, CO insertion may occur rapidly, converting the eight-membered rhodacycle into a nine-membered rhodacycle, which then undergoes an easy C(sp²)–C(sp³) reductive elimination process and furnishes the [5 + 2 + 1] product. This hypothesis was supported by our preliminary DFT studies and also served as inspiration for the development of two [7 + 1] cycloadditions: the [7 + 1] cycloaddition of buta-1,3-dienylcyclopropanes (BDCPs) and CO for the construction of cyclooctadienones, and the benzo/[7 + 1] cycloaddition of cyclopropyl-benzocyclobutenes (CP-BCBs) and CO to synthesize the benzocyclooctenones. The efficiency of these rhodium-catalyzed cycloadditions can be revealed by the application in natural product synthesis. Two eight-membered ring-containing natural products, (±)-asterisca-3(15),6-diene and (+)-asteriscanolide, have been synthesized using the [5 + 2 + 1] cycloaddition as the key step. In the latter case, excellent asymmetric induction was obtained using a chiral substrate. The efficiency of the [5 + 2 + 1] reaction was further demonstrated by the synthesis of four sesquiterpene natural products, (±)-pentalenene, (+)-hirsutene, (±)-1-desoxyhyphnophilin, and (±)-hirsutic acid C, containing linear or branched triquinane skeletons utilizing the tandem or stepwise [5 + 2 + 1] cycloaddition/aldol reaction strategy. With the success of [5 + 2 + 1] cycloaddition in natural product synthesis, application of the [7 + 1] and benzo/[7 + 1] cycloadditions in target- and function-oriented syntheses can be envisioned.



INTRODUCTION

Eight-membered carbocycles are widely found in natural products with impressive biological and medicinal properties. Among these natural products, taxol is one of the most potent anticancer drugs in clinical use.^{1,2} Antibacterial drug retapamulin, which is a C₁₄-sulphonyl-acetate derivative of natural product pleuromutilin, also possesses an eight-membered carbocycle.³ However, methodologies and strategies to

synthesize the eight-membered carbocycles are limited,^{4,5} which greatly constrains the ability of organic synthesis in target-oriented synthesis of these natural products and function-oriented synthesis^{6,7} of their analogues. The challenge for constructing eight-membered carbocycles is partly due to

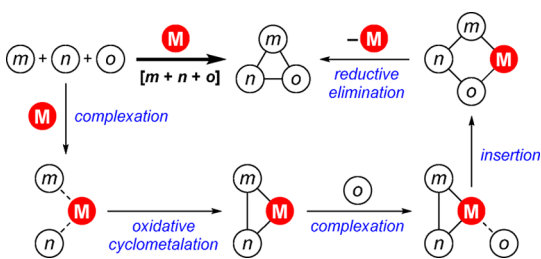
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the reason that the traditional ring closure approaches, such as nucleophilic substitution reactions and aldol condensations, to bring the terminal functional groups together suffer from enthalpic and entropic penalties in the cyclization transition states.^{8,9} Although ring-closing metathesis (RCM) has been widely applied to the formation of eight-membered rings, its success is highly dependent on the geometric feature and reactivities of the substrates used.^{10,11}

To avoid the limitations mentioned above, chemists have designed and developed transition-metal-catalyzed cycloadditions in the past decades to provide efficient, practical, and step-economical ways for the construction of medium-sized ring systems.^{12–18} These reactions usually take place through complexation, oxidative cyclometalation, insertion, and reductive elimination processes, as presented by the transition-metal-catalyzed three-component $[m + n + o]$ cycloaddition shown in Scheme 1. So far, dozens of transition-metal-catalyzed cyclo-

Scheme 1. Transition-Metal-Catalyzed $[m + n + o]$ Cycloaddition

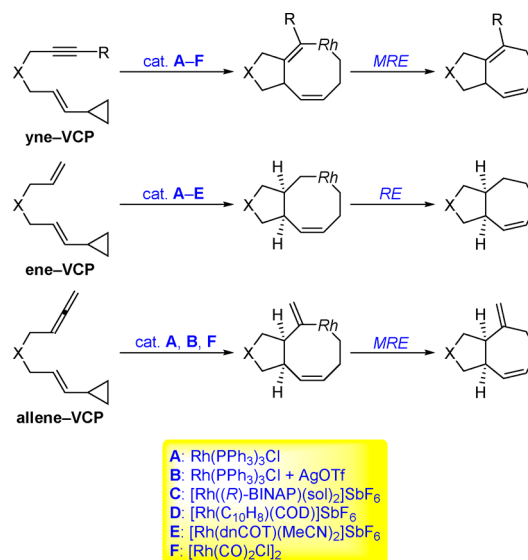


additions to synthesize eight-membered carbocycles have been developed.^{12–25} Among them, rhodium-catalyzed $[5 + 2 + 1]$ cycloaddition of ene–vinylcyclopropanes (ene–VCPs) and CO²³ for the synthesis of bi- and tricyclic cyclooctenones is a powerful reaction and has shown its great potential in addressing challenges of synthesis. In this Account, we describe how this reaction was designed and developed. We also briefly present the application of the $[5 + 2 + 1]$ cycloaddition in natural product synthesis. Furthermore, we show how this $[5 + 2 + 1]$ cycloaddition served as inspiration for the design of two other rhodium-catalyzed cycloadditions, the $[7 + 1]$ cycloaddition of buta-1,3-dienylcyclopropanes (BDCPs) and CO,²⁴ and the benzo/ $[7 + 1]$ cycloaddition of cyclopropylbenzocyclobutenes (CP-BCBs) and CO,²⁵ for the synthesis of eight-membered carbocycles.

REACTION DESIGN AND DEVELOPMENT

Wender's group pioneered the rhodium-catalyzed $[5 + 2]$ cycloaddition of VCPs with alkynes, alkenes, and allenes for the synthesis of seven-membered carbocycles (Scheme 2),^{7,26–36} which are also challenging skeletons in synthesis. Houk's group has performed DFT calculations to understand the detailed reaction mechanism of Wender's $[5 + 2]$ cycloadditions.^{37–42} The reaction pathway for the rhodium-catalyzed $[5 + 2]$ cycloaddition is proposed to consist of catalyst transfer, cyclopropane cleavage, 2π component insertion, and reductive elimination. Asymmetric versions^{43,44} and other variants^{45–47} of the rhodium-catalyzed $[5 + 2]$ cycloaddition have also been developed. $[5 + 2]$ cycloaddition of VCPs and alkynes has also been achieved using other transition-metals, such as ruthenium,^{48,49} nickel,⁵⁰ iron,⁵¹ and iridium.⁵²

Scheme 2. Wender's Rhodium-Catalyzed $[5 + 2]$ Cycloaddition of Yne-, Ene-, and Allene-VCPs

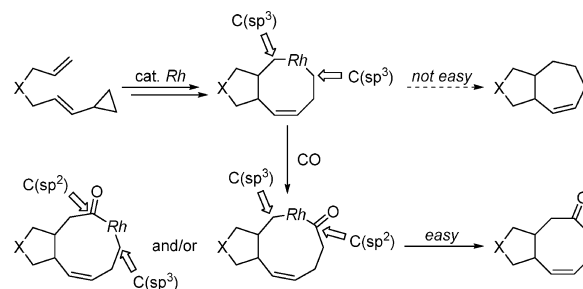


Our mechanistic curiosity to understand the observations that $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ can catalyze the $[5 + 2]$ cycloaddition of yne- and allene-VCPs but not that of ene-VCPs (Scheme 2)^{30,38} prompted our design of the $[5 + 2 + 1]$ cycloaddition.²³ We hypothesized that the $\text{C}(\text{sp}^3)\text{--}\text{C}(\text{sp}^3)$ reductive elimination (RE) in the $[5 + 2]$ cycloaddition of ene-VCPs is much slower than the $\text{C}(\text{sp}^2)\text{--}\text{C}(\text{sp}^3)$ migratory reductive elimination (MRE) in the $[5 + 2]$ cycloaddition of yne- and allene-VCPs (Scheme 2). Therefore, ene-VCPs were inferior substrates for the $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ -catalyzed intramolecular $[5 + 2]$ cycloaddition.

Inspired by Wender's three-component $[5 + 2 + 1]$ cycloaddition of VCPs, alkynes⁵³ (or allenes³⁴), and CO, we wondered whether a new reaction, the two-component $[5 + 2 + 1]$ cycloaddition of ene-VCPs and CO, can be achieved if CO gas was introduced into the reaction system. In this case, CO insertion and the subsequent reductive elimination between a carbonyl carbon and an sp^3 carbon may become easier than the $\text{C}(\text{sp}^3)\text{--}\text{C}(\text{sp}^3)$ reductive elimination in the $[5 + 2]$ pathway, as indicated by our preliminary DFT calculations (Scheme 3).²³ In-depth understanding of the reaction mechanism, reactivities, and stereoselectivities is ongoing in our lab and will be published in due course.

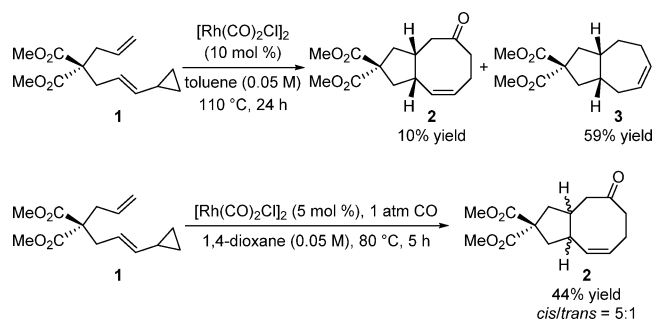
To our delight, ene-VCP **1** can indeed undergo the designed $[5 + 2 + 1]$ cycloaddition using 10 mol % $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ as the catalyst under N_2 atmosphere to give

Scheme 3. Design of the Two-Component $[5 + 2 + 1]$ Cycloaddition of Ene-VCPs and CO



bicyclic cyclooctenone **2** in 10% yield (Scheme 4). The CO participating in the [5 + 2 + 1] cycloaddition came from the

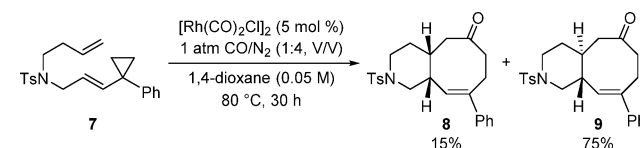
Scheme 4. Initial Results



catalyst. The double-bond-isomerized [5 + 2] cycloadduct, bicyclic cycloheptene **3**, was also obtained in 59% yield. Under CO atmosphere, the yield of [5 + 2 + 1] cycloadduct **2** was increased to 44% and 5:1 diastereomeric ratio (dr) was observed (Scheme 4). Further optimization studies showed that lower CO pressure can facilitate the reaction. When a balloon pressured (labeled as 1 atm in this Account) mixed gas of CO and N₂ (1:4, V/V) was used, 70% isolated yield and >20:1 dr were obtained (Table 1, entry 1). The two-component [5 + 2 + 1] cycloaddition of ene–VCPs and CO has a broad scope, furnishing the bicyclic cyclooctenones in high yields and excellent diastereoselectivities (Table 1). Carbon-, nitrogen-, and oxygen-tethered ene–VCPs can all undergo the [5 + 2 + 1] cycloaddition, but ene–VCP tethered by an ester moiety failed to give the desired [5 + 2 + 1] cycloadduct.⁵⁴ When R⁴ = H, the [5 + 2 + 1] cycloaddition gave *cis*-fused 5–8 bicyclic ring system as the major product. However, when R⁴ = Me, the bicyclic cyclooctenone provides either a *cis* (when *Z*-ene–VCP was used) or *trans* (when *E*-ene–VCP was used) configuration (Table 1, entries 9–12). The [5 + 2 + 1] cycloaddition has also been used to synthesize the fused 6–8 bicyclic ring system, in

which case, the *trans*-fused product **9** was observed as the major product (Scheme 5).

Scheme 5. Two-Component [5 + 2 + 1] Cycloaddition for the Construction of Fused 6–8 Bicyclic Ring System



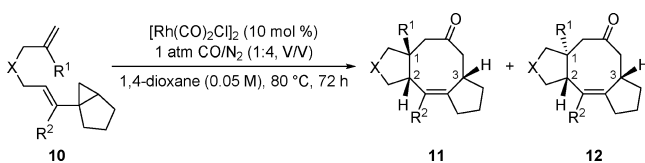
The [5 + 2 + 1] cycloaddition is also effective for the construction of fused 5–8–5 tricyclic ring systems if the cyclopropane ring of the ene–VCP substrate is replaced by a bicyclo[3.1.0]hexane moiety (Table 2).⁵⁵ It was found that, in all cases, the bridgehead hydrogens at C2 and C3 positions are in a *cis* relationship in the tricyclic products **11** and **12**. When R² = H, the relative configuration of the bridgehead C1 was *cis* with respect to C2 (Table 2, entries 1–5). However, when R² = Me, the bridgehead C1 and C2 carbons are in either *cis* or *trans* relationship (Table 2, entries 6–8). The fused 6–8–5 tricyclic compound **14** has also been synthesized using the [5 + 2 + 1] cycloaddition in 30% yield as a single diastereomer (Scheme 6).

Inspired by Wender's tandem [5 + 2 + 1] cycloaddition/aldol reaction,^{34,53} we found that an aldol reaction in tandem with the rhodium-catalyzed two-component [5 + 2 + 1] cycloaddition of ene–VCPs and CO can furnish the linear triquinane skeleton in a novel way.⁵⁶ As shown in Table 3, our tandem [5 + 2 + 1] cycloaddition/aldol reaction is very efficient and four stereogenic centers, including one or two quaternary centers, are formed in a highly diastereoselective manner. Considering that only the *cis*-fused 5–8 bicyclic system can undergo the aldol condensation, when R = Me, *Z*-ene–VCP substrate **16**, which gives the *cis*-fused [5 + 2 + 1] cycloadduct, is used for the tandem reaction. The [5 + 2 + 1] cycloaddition of the corresponding *E*-counterpart **15** leads to the *trans*-fused

Table 1. Scope for Two-Component [5 + 2 + 1] Cycloaddition of Ene–VCPs and CO

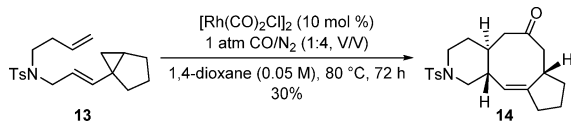
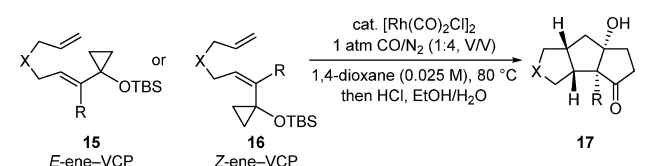
entry	X	Z/E of 4	R ¹	R ²	R ³	R ⁴	R ⁵	isolated yield, S/6
1	C(CO ₂ Me) ₂	only <i>E</i>	H	H	H	H	H	70%, >20:1
2	NTs	only <i>E</i>	H	H	H	H	H	81%, >20:1
3	O	only <i>E</i>	H	H	H	H	H	44%, ^a >20:1
4	C(CO ₂ Me) ₂	only <i>E</i>	Me	H	H	H	H	29%, >20:1
5	NTs	only <i>E</i>	Me	H	H	H	H	71%, >20:1
6	O	only <i>E</i>	Me	H	H	H	Ph	78%, >20:1
7 ^b	NTs	only <i>E</i>	H	Me	H	H	H	40%, >20:1
8	O	only <i>E</i>	H	H	Me	H	Ph	83%, >20:1
9	C(CO ₂ Me) ₂	Z/E = 1:3	H	H	H	Me	H	66%, 1:3
10	C(CO ₂ Me) ₂	Z/E = 3:1	H	H	H	Me	H	69%, 3:1
11	NTs	Z/E = 1:3	H	H	H	Me	H	59%, 1:3
12	NTs	Z/E = 3:1	H	H	H	Me	H	41%, 3:1
13	NTs	only <i>E</i>	H	H	H	H	Ph	92%, >20:1
14	O	only <i>E</i>	H	H	H	H	Ph	73%, >20:1

^a90% GC yield. Isolated yield is 44% because of the volatility of the product. ^bThe reaction was performed at 90 °C in 1,4-dioxane (0.015 M).

Table 2. Two-Component [5 + 2 + 1] Cycloaddition of Ene-VCPs and CO for the Construction of Fused 5–8–5 Tricyclic Ring Systems


entry	X	R ¹	R ²	yield of 11	yield of 12
1	C(CO ₂ Me) ₂	H	H	54%	
2	NTs	H	H	79% ^a	
3	C(CO ₂ Me) ₂	Me	H	61%	
4	NTs	Me	H	37%	
5	O	Me	H	44%	
6	C(CO ₂ Me) ₂	H	Me	9% ^b	53% ^b
7	NTs	H	Me	29%	38%
8	O	H	Me	39%	26%

^aYield based on the recovered starting material. 72% conversion was obtained. ^bInseparable diastereomers, the yields were calculated according to the combined isolated yield and diastereomeric ratio (dr), which was determined by ¹H NMR.

Scheme 6. Two-Component [5 + 2 + 1] Cycloaddition for the Construction of Fused 6–8–5 Tricyclic Ring System**Table 3. Scope for Tandem [5 + 2 + 1] Cycloaddition/Aldol Reaction**


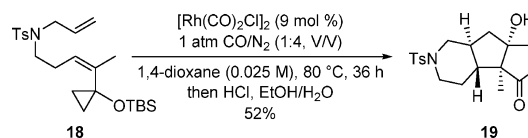
entry	substrate	X	R	time (h)	yield
1	15	CMe ₂	H	24	19%
2	15	C(CO ₂ Et) ₂	H	20	28%
3	15	NTs	H	18	22%
4	16	CH ₂	Me	36	26%
5	16	CMe ₂	Me	48	62%
6	16	C(CO ₂ Et) ₂	Me	48	67%
7	16	NTs	Me	48	50% ^a

^aBased on the recovered starting material.

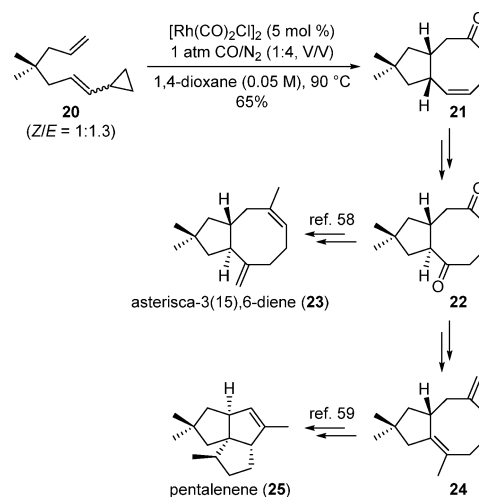
[5 + 2 + 1] cycloadduct; however, it can not undergo the subsequent aldol condensation. When R = H, [5 + 2 + 1] cycloaddition of *E*-ene-VCP substrate **15** gives *cis*-fused cycloadduct; therefore, the subsequent aldol condensation can take place, giving the desired tricyclic product **17**. The tandem [5 + 2 + 1] cycloaddition/aldol reaction has also been used to furnish the fused 6–5–5 tricyclic compound **19** as shown in Scheme 7.

■ SYNTHETIC APPLICATIONS

In the course of our studies, the rhodium-catalyzed [5 + 2 + 1] cycloaddition has been used as a key step in the synthesis of six natural products. The formal synthesis of asterisca-3(15),6-

Scheme 7. Tandem [5 + 2 + 1] Cycloaddition/Aldol Reaction for the Construction of Fused 6–5–5 Tricyclic Ring System

diene, **23**, is representative (Scheme 8). Asterisca-3(15),6-diene, which owns the bicyclo[6.3.0]undecane skeleton,

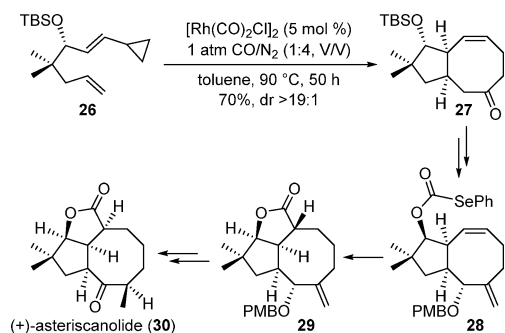
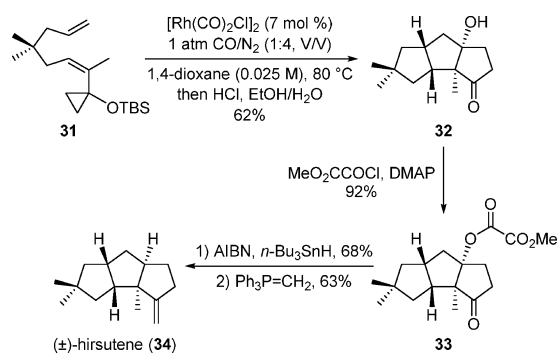
Scheme 8. Formal Syntheses of Asterisca-3(15),6-diene and Pentalenene

belongs to sesquiterpene natural products. Our [5 + 2 + 1] cycloaddition provides a very efficient approach to construct the fused 5–8 bicyclic ring system in asterisca-3(15),6-diene.⁵⁷ Ene-VCP substrate **20** can be easily prepared from commercially available starting materials in two steps. The [5 + 2 + 1] cycloaddition of **20** and CO gave the bicyclic cyclooctenone **21** as a single *cis*-diastereomer in 65% isolated yield. Further functionalizations including acetal protection, a hydroboration–oxidation reaction, PCC oxidation, and a one-pot deprotection–isomerization process yielded the Mehta's intermediate **22**,⁵⁸ which has been used to synthesize asterisca-3(15),6-diene in three steps. Compound **22** can also be used to furnish Pattenden's intermediate **24**⁵⁹ in three steps, which provides a formal synthesis of tricyclic sesquiterpene natural product pentalenene, **25**.⁵⁷

Another example for the application of [5 + 2 + 1] cycloaddition is the total synthesis of (+)-asteriscanolid, **30** (Scheme 9).^{54,60} There are two key reactions in our synthetic route. One is the rhodium-catalyzed [5 + 2 + 1] cycloaddition of a chiral ene-VCP substrate **26** and CO, which efficiently constructs the bicyclo[6.3.0]undecane skeleton with excellent asymmetric induction and diastereoselectivity. The other is an alkoxy carbonyl radical annulation which builds the bridging lactone ring with high efficiency.

The tandem [5 + 2 + 1] cycloaddition/aldol reaction strategy has been successfully applied to the synthesis of linear triquinane natural products. The total synthesis of (±)-hirsutene, (±)-**34**, is very concise (Scheme 10).⁵⁶ Tandem [5 + 2 + 1] cycloaddition/aldol reaction of ene-VCP substrate **31** gave the fused tricyclic carbocycle **32** as a single diastereomer in 62%

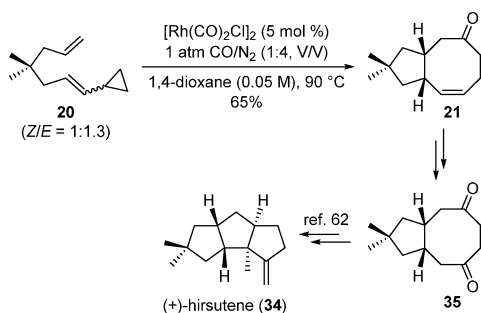
Scheme 9. Total Synthesis of (+)-Asteriscanolide

Scheme 10. Total Synthesis of (\pm)-Hirsutene

yield. Deoxygenation followed by a Wittig reaction accomplished the total synthesis of (\pm)-hirsutene.

A stepwise [5 + 2 + 1] cycloaddition/aldol reaction strategy was also used to achieve the formal synthesis of (+)-hirsutene (Scheme 11).⁶¹ Bicyclic cyclooctenone **21** was converted into a

Scheme 11. Formal Synthesis of (+)-Hirsutene

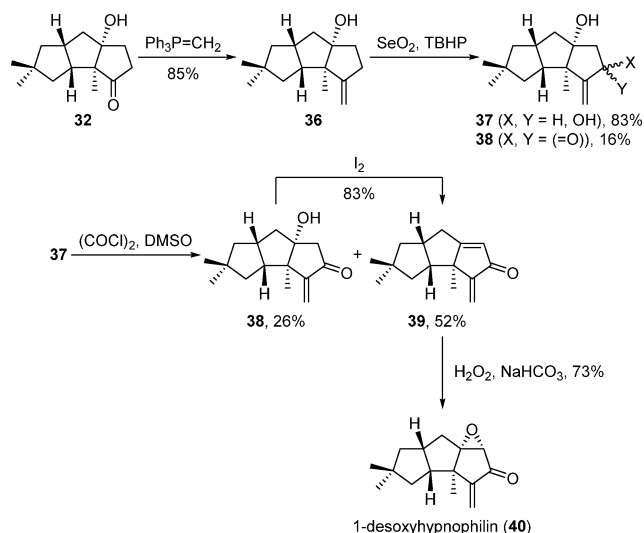


symmetric diketone **35** with excellent yield in three steps. Compound **35** can undergo the organocatalytic asymmetric transannular aldol condensation and three more steps to furnish (+)-hirsutene as reported by Chandler and List.⁶²

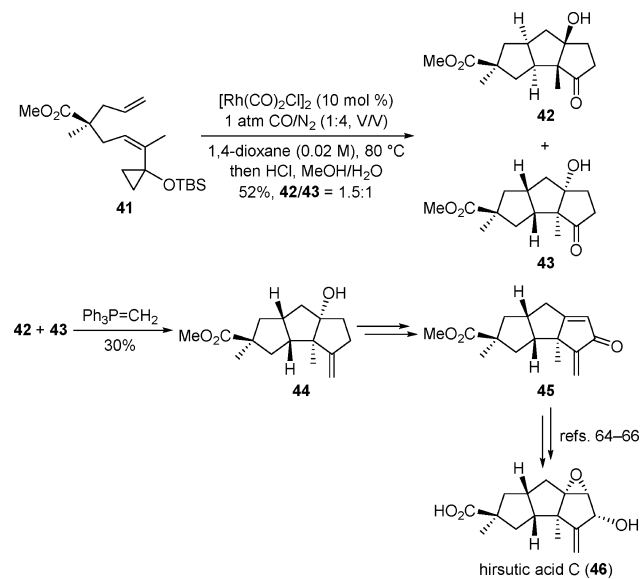
The fused tricyclic carbocycle **32**, which was synthesized by the tandem [5 + 2 + 1] cycloaddition/aldol reaction shown in Scheme 10, can also be used to synthesize natural product 1-desoxyhyphnophilin, **40** (Scheme 12).⁵⁶ Compound **32** can be converted into diol **37** by a Wittig reaction and the subsequent SeO_2 oxidation. Swern oxidation of **37**, followed by an epoxidation gave the target natural product **40** in good yields.

A similar strategy has also been applied to the formal synthesis of hirsutic acid **C**, **46** (Scheme 13).⁶³ Tandem [5 + 2 + 1] cycloaddition/aldol reaction of ene-VCP substrate **41** gave two inseparable diastereomers **42** and **43**. Wittig reaction of the mixture of **42** and **43**, followed by oxidations and

Scheme 12. Total Synthesis of 1-Desoxyhyphnophilin



Scheme 13. Formal Synthesis of Hirsutic Acid C

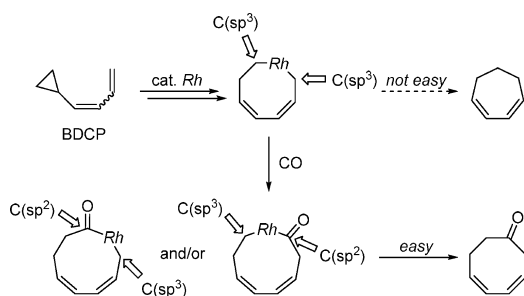


dehydration gave compound **45**, which has been used in the total synthesis of hirsutic acid **C** by Schuda et al.,⁶⁴ Ikegami et al.,⁶⁵ and Banwell et al.⁶⁶

INSPIRATIONS FOR DEVELOPING NEW REACTIONS FOR SYNTHESIS OF EIGHT-MEMBERED CARBOCYCLES: [7 + 1] AND BENZO/[7 + 1] CYCLOADDITIONS

The rhodium-catalyzed [5 + 2 + 1] cycloaddition of ene-VCPs and CO was designed and developed by the hypothesis that the CO insertion and the $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ reductive elimination of rhodacyclononene in the [5 + 2 + 1] pathway are faster than the $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ reductive elimination of rhodacyclooctene in the [5 + 2] pathway. Inspired by this, we then replaced the ene-VCP substrate by a seven-carbon unit, buta-1,3-dienylcyclopropane (BDCP) to test whether a [7 + 1] cycloaddition can be realized.²⁴ In the presence of $[\text{Rh}(\text{CO})_2\text{Cl}]_2$, a rhodacyclooctadiene intermediate may be formed (Scheme 14). We hypothesized that the $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ reductive elimination of the rhodacyclooctadiene is slow.

Scheme 14. Design of the [7 + 1] Cycloaddition of BDCPs and CO



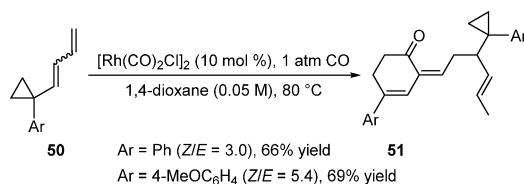
Through introducing CO gas into the reaction system, CO insertion and the subsequent C(sp²)-C(sp³) migratory reductive elimination of the rhodacyclonadiene may occur, giving the [7 + 1] product cyclooctadienone as the final product. To our delight, when BDCP was treated with [Rh(CO)₂Cl]₂ under CO atmosphere, the [7 + 1] cycloaddition indeed occurred (Table 4). However, 1-substituted BDCP **50** can not give the desired [7 + 1] cycloadduct; only compound **51** with a newly formed six-membered ring was obtained (Scheme 15).

Table 4. Scope for [7 + 1] Cycloaddition

entry	R ¹	R ²	Z/E of 47 ^a	conversion ^b	yield, ^c 48/49
1	H	4-MeOC ₆ H ₄	2.5	81%	74%, 6:1
2	Me	4-MeOC ₆ H ₄	2.0	76%	55%, 10:1
3	H	Ph	2.9	85%	77%, 6:1
4	H	4-FC ₆ H ₄	3.0	86%	55%, 6:1
5	H	4- <i>t</i> -BuC ₆ H ₄	1.9	83%	59%, 6:1
6	H	2-thienyl	4.0	77%	47%, 8:1
7	H	2-naphthyl	2.2	72%	70%, 19:1
8	H	Bn	0.8	96%	85%, 15:1
9	H	<i>c</i> -C ₃ H ₅		94%	63%, 4:1
10	H	Me	0.3	90%	12%, - ^d

^aDetermined by ¹H NMR. ^bBased on the recovered starting material. ^cCombined isolated yield. ^dOnly **48** was isolated.

Scheme 15. Unexpected Reactions of BDCPs and CO



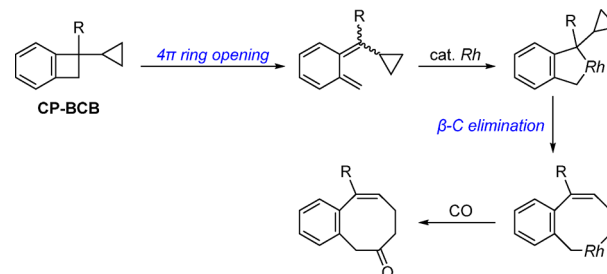
With the [7 + 1] cycloaddition of BDCPs and CO in hand, we further developed the benzo/[7 + 1] cycloaddition of cyclopropyl-benzocyclobutenes (CP-BCBs) and CO by merging thermal and rhodium-catalyzed C-C bond cleavages (Scheme 16).²⁵ This reaction provides a novel way to synthesize benzo-fused eight-membered carbocycles. Under thermal conditions, ring opening of the benzocyclobutene ring in CP-BCB would generate a BDCP intermediate, which then

Table 5. Scope for Benzo/[7 + 1] Cycloaddition^a

entry	substrate	product	time (h)	yield
1			4	84%
2			20	79%
3			20	84%
4			24	73%
5 ^b			20	74%
6			24	81%
7			24	50%
8 ^{c,d}			10	55%
9 ^c			24	51%
10 ^c			20	62%

^aReaction conditions: 0.2 mmol substrate, 2.5 mol % [Rh(CO)₂Cl]₂, 1 atm CO, 4 mL of *p*-xylene, 140 °C. ^bInseparable isomers with phenyl at C1 and C2 positions. ^c5 mol % [Rh(CO)₂Cl]₂ was used. ^dSeparable isomers with methyl at C1 and C2 positions (C1/C2 = 1.6:1).

Scheme 16. Proposed Catalytic Cycle for Benzo/[7 + 1] Cycloaddition



undergoes the rhodium-catalyzed [7 + 1] cycloaddition to furnish the benzocyclooctenone product. The reaction is efficient with high yields (Table 5). Fused 6–8–5 and 6–8–6 tricyclic ring systems can also be generated in moderate yields via the benzo/[7 + 1] cycloaddition (Table 5, entries 9 and 10).

CONCLUSION AND PERSPECTIVES

A computationally designed and experimentally verified [5 + 2 + 1] cycloaddition of ene–VCPs and CO has been realized to synthesize bi- and tricyclic cyclooctenones. Application to natural product synthesis has further demonstrated the power of this reaction. Inspired by the success of this reaction, two new reactions, [7 + 1] and benzo/[7 + 1] cycloadditions, have been developed to synthesize the eight-membered carbocycles. These three reactions provide new approaches for the synthesis of eight-membered ring-containing molecules of interest. Further development of the reaction may include developing the asymmetric version of the present [5 + 2 + 1] cycloaddition, which is challenging because CO may serve as a ligand and it can replace the chiral ligands used, and consequently, no asymmetric induction can be achieved. We are still working on this issue. Using other catalysts instead of rhodium catalyst is another consideration worth future investigation. Also more applications of these reactions to solve problems in synthesis are needed, and we also hope more chemists can use these reactions in their synthetic works.

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Notes

The authors declare no competing financial interest.

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