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Rh^I-Catalyzed Two-Component [(5+2)+1] Cycloaddition Approach toward [5-8-5] Ring Systems

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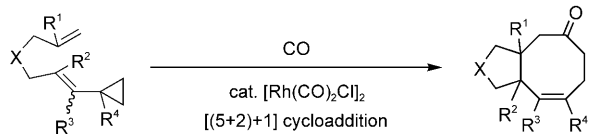
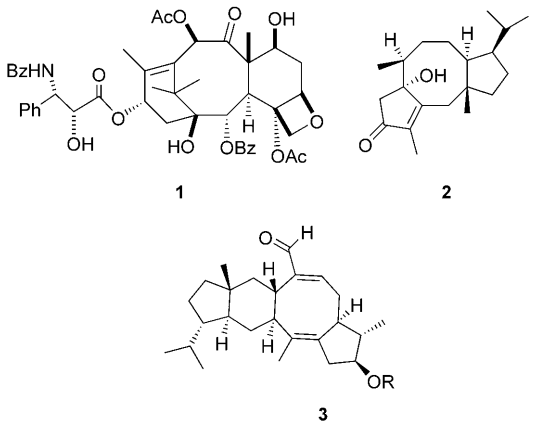
The design and synthesis of complex molecules from simple starting materials in minimum steps is one of the most challenging goals in organic synthesis.[1] As such, cycloaddition reactions catalyzed by transition-metal complexes have been of continuing interest to chemists owing to their efficiency in constructing complicated molecules from much simpler starting materials in atom- and step-economical fashions.[2,3] One representative example in this line is the development of transition-metal-catalyzed cycloadditions for synthesizing cyclooctane ring systems,[4] observed in several classes of natural products, many of which exhibit significant and broad-ranging biological activities. The transition-metal-catalyzed cycloaddition reactions to give cyclooctanes usually take place through many elementary organometallic reaction steps (such as oxidative addition, reductive elimination) so that the unfavorable factors (such as high degree of ring strain, unfavorable transannular interactions, and unfavorable entropy and enthalpy penalties) associated with the classical synthesis of eight-membered carbocycles can be partially or totally circumvented. Several groups have reported elegant transition-metal-catalyzed cycloaddition approaches to eight-membered carbocycles.[5] Recently, we have also developed a two-component [(5+2)+1] cycloaddition of ene-vinylcyclopropanes (ene-VCPs) and CO that provides an efficient way to obtain fused [5-8] and [6-8] ring systems, exemplified by the reactions shown in Scheme 1.[6,7] This method provides a new opportunity for the total synthesis of natural products containing [5-8] and [6-8] bicyclic skeletons.[6b–d]



Scheme 1. Rh^I-catalyzed two-component [(5+2)+1] cycloaddition developed in the Yu group.[6]

It is found that eight-membered carbocycles in many natural products are fused or bridge-fused with one or more five- or six-membered carbocycles. For examples, the diterperne paclitaxel taxol (**1**),[8] fusicoauritone (**2**),[9] and aleurodiscal (**3**)[10] are natural compounds containing [6-8-6] tricyclic, [5-8-5] tricyclic, and [5-6-8-5] tetracyclic cores (Scheme 2), respectively. As a result, one-pot synthesis of the [5-8-5] tricyclic skeleton or a taxol skeleton would be highly demanded from a synthetic point of view. Even though several spectacular strategies applying Cope rearrangement or electrocyclization have been developed for



Scheme 2. Selected polycyclic natural products containing eight-membered carbocycles.

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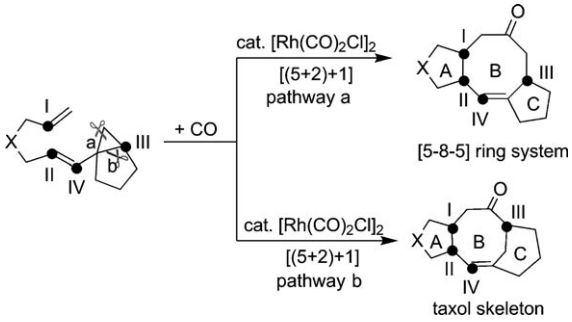
this purpose,[11] no methods by applying transition-metal-catalyzed cycloadditions to construct a [5-8-5] tricyclic skeleton or taxol skeleton in one operation have been reported. Developing such a method could facilitate the total synthesis of the natural products and pharmaceutical compounds with either a [5-8-5] tricyclic skeleton or a taxol skeleton.[12,13]

We envisioned that if the substrates of the previously developed [(5+2)+1] cycloaddition can be modified by introducing a five-membered carbocycle ring fused with the cyclopropane rings of ene-VCPs, the resulting new ene-VCPs could undergo a [(5+2)+1] cycloaddition to give either a [5-8-5] tricyclic skeleton or a taxol skeleton in one operation, depending on which bond (a or b) in cyclopropane is cleaved (Scheme 3). Cleavage of the external C–C bond of



Scheme 3. Two possible Rh^{I}-catalyzed [(5+2)+1] cycloadditions.

cyclopropyl group (the a bond) via pathway a would furnish a [5-8-5] ring system, whereas cleavage of the internal C–C bond of the VCP (the b bond) via pathway b would give a bridge-fused [6-8] skeleton, presented in taxol and its family (Scheme 3). No matter which pathway of this [(5+2)+1] cycloaddition occurs, the resulting [(5+2)+1] product, either a [5-8-5] ring system or a taxol skeleton, is the privileged skeleton present in many natural products and such endeavor to explore this reaction is worthy considering its potential in total systhesis.[14]

Before testing our hypothesis experimentally, we computed the activation energies for the two cleavage pathways of vinylcyclopropane ring by using the DFT (B3LYP) method (Figure 1).[15] Calculations on the model reaction of **S1**, a complex between VCP and the catalytic species [Rh(CO)Cl],[16] indicated that the activation free energy for external C–C bond cleavage to **S1a** (pathway a, via transition state **TS**) is 9.3 kcal mol^{-1}. In contrary, all efforts to locate an internal C–C bond cleavage (pathway b) transition state proved to be unsuccessful. Calculations indicated that the proposed intermediate **S1b** generated by cleaving the internal

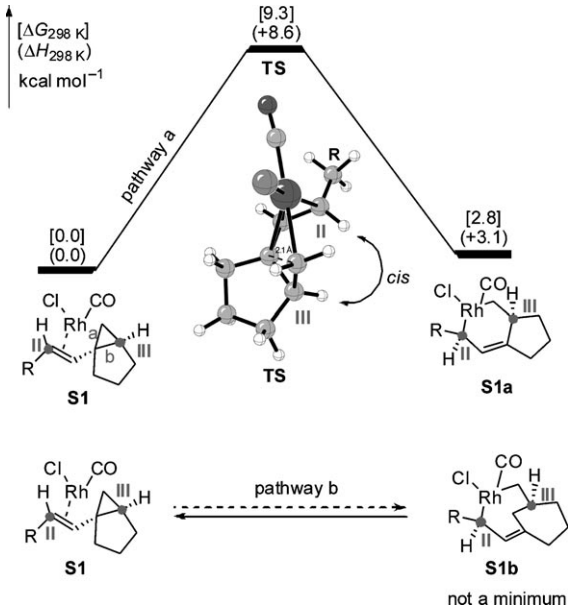
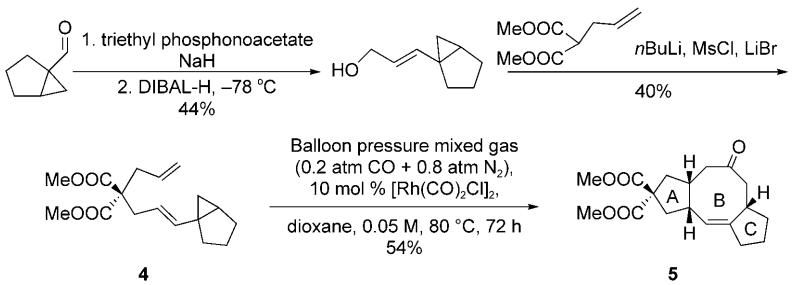


Figure 1. DFT-computed energy surface of the cleavage of vinylcyclopropane ring (R = Me).

C–C bond of CP ring is not a minimum. DFT optimization of this hypothetical intermediate led directly to the starting complex **S1**, suggesting that the ring opening of the internal C–C bond is intrinsically disfavored thermodynamically due to the ring strain in the ring-opened intermediate **S1b**, which contains an unfavored bridgehead olefin. DFT calculations can be used to predict the stereochemistry of the [5-8-5] product in Scheme 3. Calculations showed that the relative stereochemistry of substituents in positions II and III in the final [(5+2)+1] cycloadduct is always in a *cis* configuration (see Scheme 3 and Figure 1). The stereochemistry of substituents in positions I and II can have either a *cis* or a *trans* configuration, and this is dependent on the substitution pattern of the substrates (see later discussion of stereochemistry).[6]

To test experimentally whether the reaction in Scheme 3 really takes place via pathway a rather than pathway b, we synthesized an ene-VCP substrate **4** and ran its [(5+2)+1] reaction in the presence of balloon-pressured mixed gas of 0.2 atm CO+0.8 atm N_2, and 10 mol% $[Rh(CO)_2Cl]_2$ catalyst in 1,4-dioxane at 80 °C for 72 h (Scheme 4). Gratifyingly,



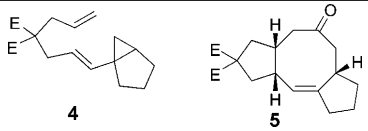
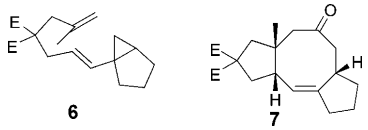
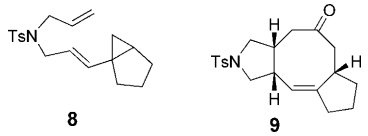
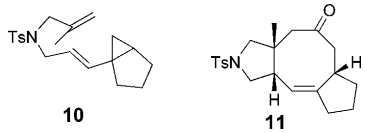
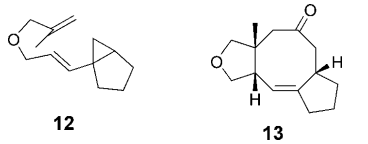
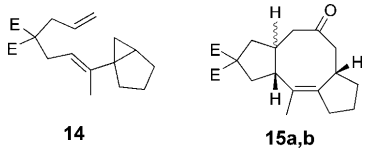
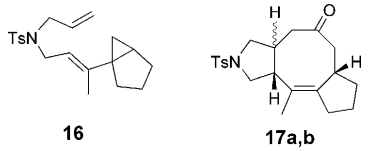
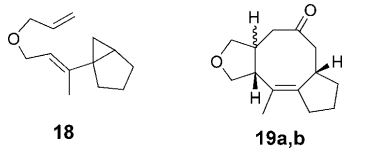
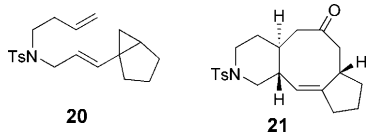
Scheme 4. Preparation and Rh^{I}-catalyzed [(5+2)+1] cycloaddition of ene-vinylcyclopropane **4**.

the [(5+2)+1] reaction occurred to give a [5-8-5] ring cyclooctenone **5**, as a single diastereoisomer with a *cis* configuration for all bridgehead hydrogen atoms, in 54% isolated yield. No compound with a taxol skeleton was observed, agreeing with the DFT predictions.[17]

With the above computational and experimental supports, we then studied the scope and limitation of this one-pot synthesis of [5-8-5] ring skeleton (Table 1). Under the optimal conditions (balloon-pressured mixed gas of 0.2 atm CO and 0.8 atm N_2, 10% $[Rh(CO)_2Cl]_2$ catalyst in dioxane), the new Rh[I]-catalyzed [(5+2)+1] cycloaddition of ene-VCPs tolerates tethers incorporating geminal diester, sulfonamide, and ether functionalities. Cycloadducts of **5, 7, 9, 11**, and **13** have a *cis* configuration for the substituents in positions I, II, and III. If a methyl group is introduced to the IV position of the substrates (**14, 16** and **18**), their corresponding [(5+2)+1] cycloadditions gave mixtures of cycloadducts (**15a,b, 17a,b**, and **19a,b**), in which the bridgehead hydrogen atoms in II and III are *cis*, but the hydrogen atoms in position I of the cycloadducts have both *cis* and *trans* configurations with respect to hydrogen atoms in positions II and III. This is consistent with previous results.[6a,b] Construction of a quaternary carbon atom is very challenging. The present [(5+2)+1] can well establish a quaternary carbon atom in the final cycloadducts when a methyl group is introduced in position I of the substrates, even though the cycloaddition yields are lower in some cases compared to others (see entries 2, 4, and 5 in Table 1). It is important to stress that the present [(5+2)+1] cycloaddition is also applicable in synthesizing a [6-8-5] ring system (**20** to **21**). The A/B ring of **21** has a *trans* configuration. This agrees with our previous result, showing that the [(5+2)+1] cycloadduct of 6/8 prefers a *trans* configuration.[6] The stereochemistry has been determined by 1D and 2D NMR spectroscopies, three cycloadducts (**11**, **17a**, and **21**) have been further confirmed by X-ray analysis (Figure 2). From the above results, we can see that the present method is efficient to generate [5-8-5] systems with reasonable yields (Table 1, entries 1, 3, 7, and 8). Only when quaternary carbon centers are introduced, the yields are not satisfactory (Table 1, entries 4 and 5). Considering the feasibility and facility of the one-pot construction of a [5-8-5] skeleton, the present method has great potential in the synthesis of natural products and their analogues with [5-8-5] skeletons.

As described above, the stereochemistry of substituents in positions II and III of the final [5-8-5] and [6-8-5] cycloadducts is always in a *cis* configuration. This is controlled by the cyclopropane cleavage step (see Figure 1). The stereochemistry in positions I and II , which is controlled by alkene insertion step of the catalytic cycle,[6a] is in either a *cis* or *trans* configuration, depending on whether there is a substitution in position IV of the substrates (entries 1–5 vs. entries 6–8). This suggests that the stereochemistry of position III can be transferred to the stereochemistry in position II, which can be further transferred to position I of the cycloadducts. Therefore, an asymmetric [5-8-5] and [6-8-5] skeletons can be envisioned if a chiral cyclopropanation is used to control the stereochemistry in position III of the substrates.[18]

Table 1. Substrates scope for the Rh[I]-catalyzed [(5+2)+1] cycloaddition.[a,b]

Entry	Substrate	Product	Yield
1	 **4**	**5**	54%
2	 **6**	**7**	61%
3	 **8**	**9**	79%[c]
4	 **10**	**11**	37%
5	 **12**	**13**	44%
6	 **14**	**15a,b**	62%[d,e] *cis*/*trans* = 1:6
7	 **16**	**17a,b**	67%[d,f] *cis*/*trans* = 1:1.3
8	 **18**	**19a,b**	65%[d,f] *cis*/*trans* = 1.5:1
9	 **20**	**21**	30%

[a] E = CO_2Me. Yields of isolated product were reported unless otherwise indicated. [b] All reactions were conducted under a balloon-pressured mixed gas of 0.2 atm CO and 0.8 atm N_2 with 10 mol% $[Rh(CO)_2Cl]_2$ catalyst in 1,4-dioxane at 80°C for 72 h unless otherwise indicated. [c] This yield was based on the recovered starting material. The conversion in this entry was 72%. [d] Total yields of two stereoisomers. [e] Inseparable stereoisomers. [f] Seperable stereoisomers.

In conclusion, we have reported here an efficient and quick approach for diastereoselective synthesis of [5-8-5] and [6-8-5] tricyclic systems in one operation from readily prepared substrates by using atom- and step-economical

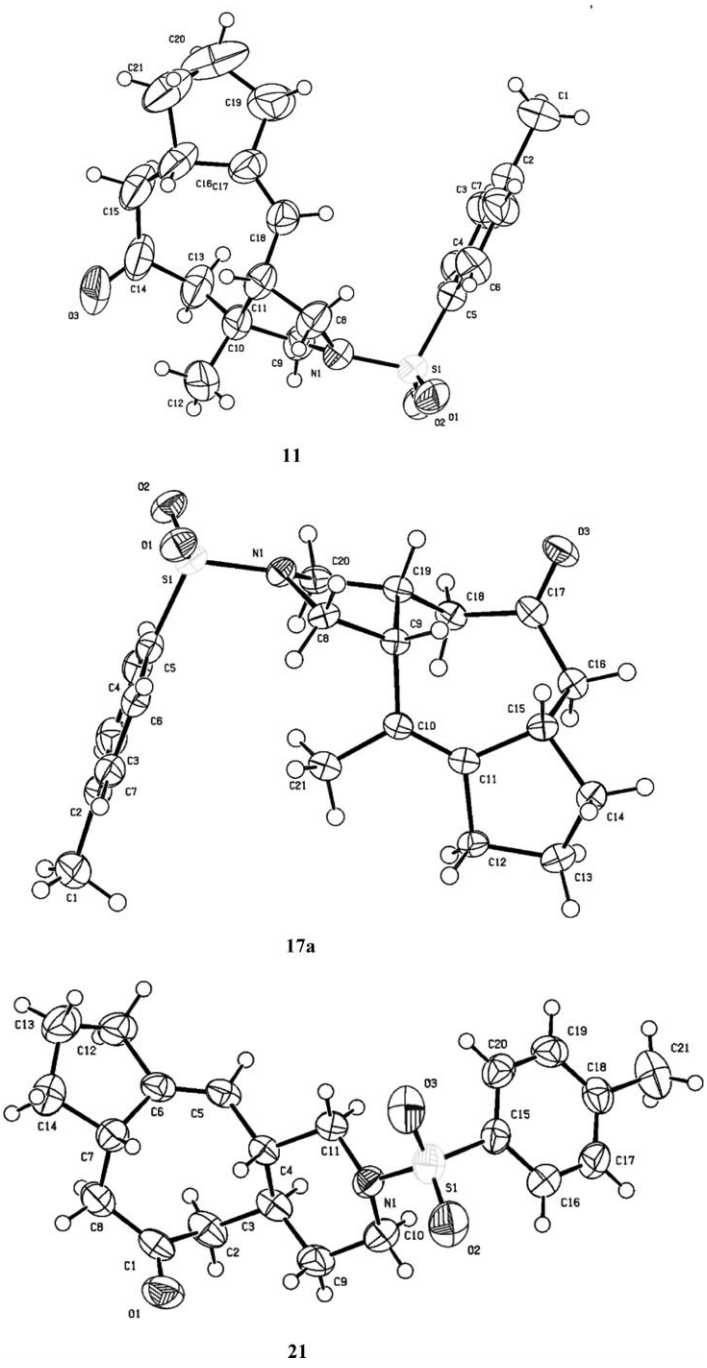


Figure 2. X-ray crystal structures of compounds **11**, **17a**, and **21**.

Rh^{I}-catalyzed [(5+2)+1] cycloaddition. Quaternary carbon centers can also be introduced in the cycloadducts. Further extension of this chemistry and its application are underway.

Experimental Section

General procedure for the [(5+2)+1] cycloaddition reactions: $[Rh(CO)_2Cl]_2$ (10 mol% to the substrate) was charged in a base-washed, oven-dried Schlenk flask under an atmosphere of nitrogen, and then a solution of the ene-VCP substrate in degassed dioxane (0.05 M) was added. The solution was bubbled with mixed CO (0.2 atm CO+0.8 atm N_2) for 5 min. The reaction mixture was stirred at 80 °C under the balloon-pressured mixed gas of CO (0.2 atm) and N_2 (0.8 atm) for 72 h. After being cooled to room temperature, the mixture was concentrated and the residue was purified by flash column chromatography with silica gel to afford the cycloaddition products.

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Keywords: cycloaddition · density functional calculations · fused-ring systems · homogeneous catalysis · rhodium

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[7] We suggest here a new nomenclature system for transition-catalyzed cycloaddition reactions. For three-component cycloaddition of vinylcyclopropanes, alkynes, and CO, this is named as a [5+2+1] cycloaddition.[5b] For the two-component cycloaddition of ene-VCPs and CO,[6] this is named as a [(5+2)+1] cycloaddition, where the (5+2) part comes from one molecule, ene-VCP.

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