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Silicon-Initiated Carbonylative Carbotricyclization and [2+2+2+1] Cycloaddition of Enediynes Catalyzed by Rhodium Complexes

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Abstract: The reaction of dodec-11-ene-1,6-diynes or their heteroatom congeners with a hydrosilane catalyzed by Rh(acac)(CO)$_2$ at ambient temperature and pressure of CO gives the corresponding fused 5-7-5 tricyclic products, 5-oxo-1,3a,4,5,7,9-hexahydro-3*H*-cyclopenta[*e*]azulenes or their heteroatom congeners, in excellent yields through a unique silicon-initiated cascade carbonylative carbotricyclization (CO−SiCaT) process. It has also been found that the 5-7-5 fused tricyclic products can be obtained from the same type of enediynes and CO through a novel intramolecular [2+2+2+1] cycloaddition process. The characteristics of these two tricyclization processes and the fundamental differences in their reaction mechanisms are discussed. This novel higher-order cycloaddition reaction has also been successfully applied to the tricyclization of undeca-5,10-diyn-1-als, affording the corresponding 5-7-5 fused-ring products bearing a seven-membered lactone moiety. Related [2+2+2] tricyclizations of enediyne and diynal substrates are also discussed. These newly discovered reactions can construct multiple bonds all at once, converting linear starting materials to polycyclic compounds in a single step. Thus, these new processes provide innovative routes to functionalized polycyclic compounds that are useful for the syntheses of natural and unnatural products.

Introduction

It would be ideal if the synthesis of complex target molecules could be achieved quickly, quantitatively, and selectively by a simple operation from readily available starting materials.[1]The transition-metal-catalyzed carbocyclization[2] and cycloaddition[3,4] reactions are among the synthetically most useful processes for rapidly increasing molecular complexity. Many of these processes are symmetry forbidden and impossible or difficult to realize in the absence of proper catalysts. Among various metals, nickel, ruthenium, cobalt, rhodium, and palladium catalysts have been commonly used to promote these two processes.[5−7] Because many bioactive compounds[8] include fused-ring systems in their structures, these polycyclization reactions warrant extensive studies. In fact, various polycyclization processes have been employed for the construction of natural and unnatural fused-ring systems that can be further elaborated into specific targets. For instance, in the last two decades, considerable advances have been made in the development of higher-order cycloaddition reactions such as [4+3],[9] [5+2],[10] [6+2],[11] [4+2+2],[12] and [5+2+1][13] processes. Thus, transition-metal-catalyzed carbocyclization and higher-order cycloaddition reactions[14] provide powerful methods for the construction of complex polycyclic systems.[2c,15−16]

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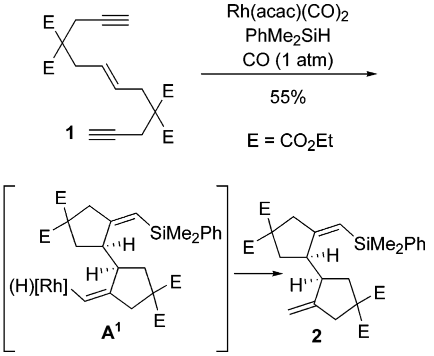
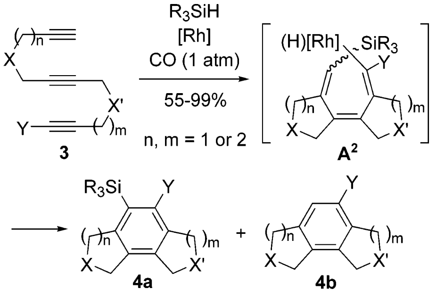
10.1021/ja054221m CCC: $30.25

Scheme 1



Scheme 2

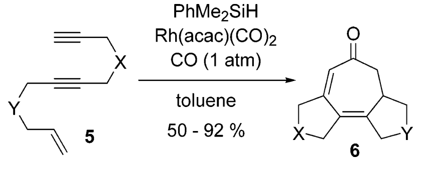


In the course of our investigation into the development of silicon-initiated cyclization processes, intramolecular silylformylation,[7a] silylcyclocarbonylation (SiCCa),[17,18] silylcarbocyclization (SiCaC),[18,19] silylcarbobicyclization (SiCaB),[18d,e] and silylcarbotricyclization (SiCaT)[18c,d] have been discovered. In 1996, we reported a stereospecific cascade SiCaC reaction[20] of dodec-6-ene-1,11-diynes (Scheme 1). In this reaction, although intramolecular carbometalation of the vinylsilane moiety of intermediate **A^1** with the [Rh]−vinyl moiety to form the third ring was conceptually possible, the third cyclization did not take place. Thus, a simple reductive elimination preferentially occurred to give the corresponding bis(cyclopentyl) **2**.

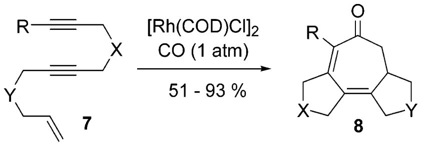
In the case of alkatriynes **3**, however, silylcarbotricyclization (SiCaT) took place to give the fused tricyclic compounds **4a** and **4b** in good to excellent yields (Scheme 2).[21] Reactions catalyzed by rhodium carbonyl clusters showed high selectivity to **4a**.

As a part of our studies on the silicon-initiated cascade carbometalations, we looked at the reaction of dodec-11-ene-1,6-diynes **5**. The reaction of the enediynes **5** with PhMe$_2$SiH in the presence of a rhodium catalyst under ambient pressure of CO afforded, to our surprise, fused 5-7-5 ring products **6** incorporating a CO molecule, and our preliminary study was communicated.[22] This novel silicon-initiated cascade carbonylative carbotricyclization (CO−SiCaT) of enediynes promoted by rhodium catalysts provides a powerful method for the rapid construction of functionalized fused 5-7-5 ring systems (Scheme 3).

Scheme 3



Scheme 4



During our studies on the scope and limitation of the CO−SiCaT reaction, we serendipitously found that the reaction of 1-substituted dodec-11-ene-1,6-diyne **7** catalyzed by [Rh(COD)-Cl]$_2$ in the *absence of* a hydrosilane gave carbonylative tricyclization product **8** in good to excellent yields (Scheme 4). This observation turned out to be the first example of a [2+2+2+1] cycloaddition reaction, and preliminary results were communicated.[23]

Although these two processes, i.e., CO−SiCaT and [2+2+2+1] cycloaddition, lead to the formation of the same type of products, these reactions proceed through fundamentally different mechanisms.[22,23] We describe here a full account of our study on the novel Rh-catalyzed CO−SiCaT and intramolecular [2+2+2+1] cycloaddition processes of enediynes, involving CO as the single carbon component.

Results and Discussion

Silicon-Initiated Carbonylative Carbotricyclization (CO−SiCaT) of Enediynes. The scope of the CO−SiCaT reaction has been investigated systematically by looking at the key elements and reaction variables involved in this process. The enediyne **5a** was used as the substrate for this study (Scheme 5). Results are summarized in Table 1. Reaction of enediyne **5a** with PhMe$_2$SiH (2.0 equiv) catalyzed by Rh(acac)(CO)$_2$ (1 mol %) in toluene under ambient pressure of CO at 70 °C for 1 h gave cyclopenta[*e*]azulene **6a** and bis(cyclopentylidene) **9** as major products and aldehyde **10** as a minor product in 70% overall isolated yield (**6a**/**9**/**10** = 36:43:21) (entry 1). The reaction under higher CO pressure (10 atm) disfavored the formation of **9** (entry 2). Addition of P(OPh)$_3$ completely suppressed the formation of **10** (entry 3), and the use of PPh$_3$ as the additive substantially favored the formation of **10** and reduced the yield of **6a** (entry 4). The use of THF as the solvent

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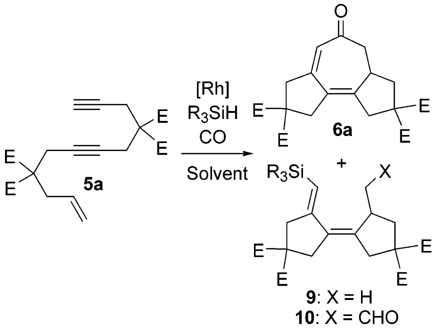
Scheme 5



at a lower temperature (22 °C) gave better product selectivity for **6a** (entry 5). Then, the reaction at a lower concentration (0.015 M) dramatically increased the product selectivity, yielding **6a** as the sole product (entry 6).

The observed remarkable dilution effects on the product selectivity appear to be, in part, attributed to the concentration of CO in solution relative to those of the catalyst and hydrosilane; i.e., the relative concentration of CO is higher in dilute solution if the amounts of the catalyst and hydrosilane are kept constant. Also, this observation provides crucial information for the mechanism of this unique reaction. Although the mechanism of this novel carbocyclization process is proposed and discussed later in the text (see Scheme 6), the formations of **9** and **10** should involve a bimolecular process at the final reductive elimination step, whereas that of **6a** should not; i.e., the formation of **6a** is a unimolecular process. Accordingly, the formation of **6a** should be favored at higher dilution, and those of **9** and **10** should be disfavored. In addition, a stoichiometric amount of the hydrosilane should not be necessary for the formation of **6a** because this product does not incorporate the hydrosilane component. This indicates that only a substoichiometric amount of hydrosilane would be sufficient for this reaction to proceed, and such a condition should suppress the formations of **9** and **10**. Thus, we carried out the reaction with a substoichiometric amount of hydrosilane, and indeed, our analysis and prediction was proven correct. Thus, the reaction with 0.5 equiv of $PhMe_2SiH$ at high dilution conditions (0.015 M) gives **6a** exclusively in high overall yield (entries 7, 10, and 11). The reaction with 0.1 equiv of the hydrosilane is 100% selective to the formation of **6a** but does not give complete conversion in 96 h (entry 8). In the absence of $PhMe_2SiH$, no reaction takes place after 96 h, recovering

Table 1. CO−SiCaT of Endiyne **5a**[a]

entry	catalyst	R_3SiH (equiv)	solvent	concn (M)	temp (°C)	CO (atm)	time (h)	yield (%)[b]	product ratio 6a	9	10
1	$Rh(acac)(CO)_2$	$PhMe_2SiH$ (2.0)	toluene	0.2	70	1	1	70	36	43	21
2	$Rh(acac)(CO)_2$	$PhMe_2SiH$ (2.0)	toluene	0.2	60	10	10	55	55	9	36
3[c]	$Rh(acac)(CO)_2$	$PhMe_2SiH$ (1.0)	toluene	0.2	50	1	10	62	65	35	0
4[d]	$Rh(acac)(CO)_2$	$PhMe_2SiH$ (1.0)	toluene	0.2	50	1	10	52	10	32	58
5	$Rh(acac)(CO)_2$	$PhMe_2SiH$ (1.0)	THF	0.2	22	1	12	65	70	15	15
6	$Rh(acac)(CO)_2$	$PhMe_2SiH$ (1.0)	THF	0.15	22	1	24	82	100	0	0
7	$\mathbf{Rh(acac)(CO)_2}$	$\mathbf{PhMe_2SiH}$ **(0.5)**	**THF**	**0.015**	**22**	**1**	**30**	**92**	**100**	**0**	**0**
8	$Rh(acac)(CO)_2$	$PhMe_2SiH$ (0.1)	THF	0.015	22	1	96	33	100	0	0
9	$Rh(acac)(CO)_2$	$PhMe_2SiH$ (0.0)	THF	0.015	22	1	96	0	0	0	0
10	$Rh_4(CO)_{12}$	$PhMe_2SiH$ (0.5)	THF	0.015	22	1	17	78	92	8	0
11	$[Rh(CO)_2Cl]_2$	$PhMe_2SiH$ (0.5)	THF	0.015	22	1	23	80	100	0	0
12	$Rh(acac)(CO)_2$	$PhMe_2SiH$ (0.5)	THF	0.015	22	1	96	42	100	0	0
13	$Rh(acac)(CO)_2$	$(EtO)_3SiH$ (0.5)	THF	0.015	22	1	96	34	100	0	0
14	$Rh(acac)(CO)_2$	Et_3SiH (0.5)	THF	0.015	22	1	96	12	90	10	0
15	$Rh(acac)(CO)_2$	t-$BuMe_2SiH$ (0.5)	THF	0.015	22	1	96	0	0	0	0

[a] Reaction was run with enediyne (0.25−0.5 mmol scale), hydrosilane, and Rh catalyst (1 mol %) in the solvent under CO. [b] Isolated yields. [c] $P(OPh)_3$ (3 equiv to catalyst) was added as a ligand. [d] PPh_3 (3 equiv to catalyst) was added as a ligand.

Scheme 6

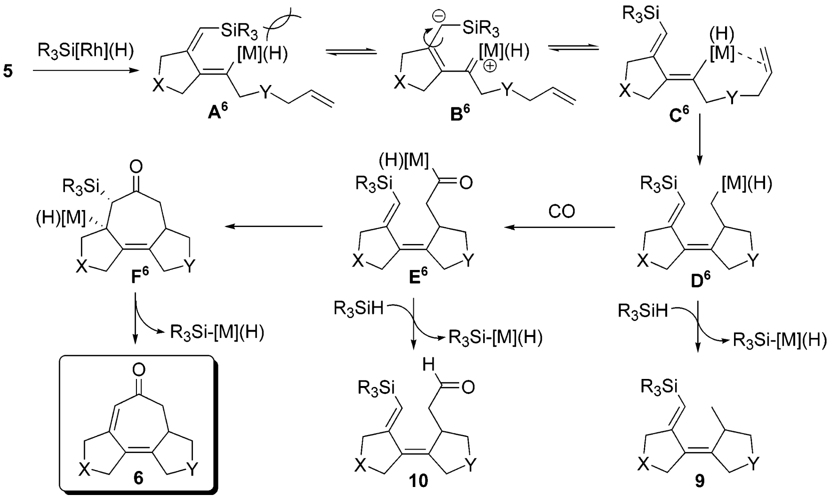
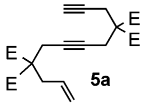
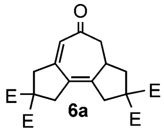
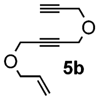
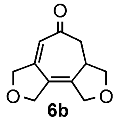
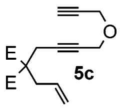
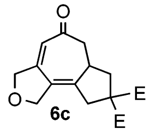
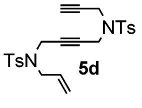
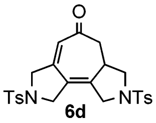
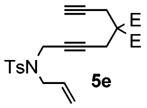
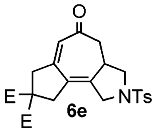
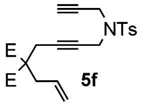
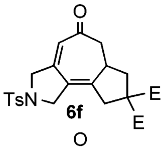
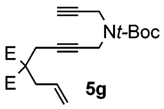
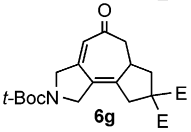
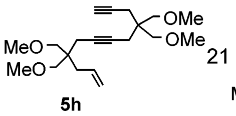
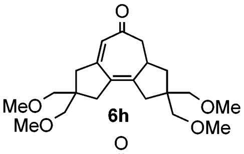
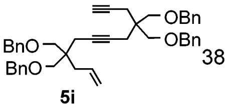
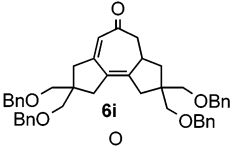
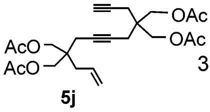
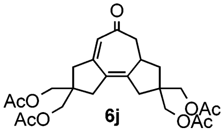
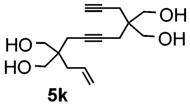
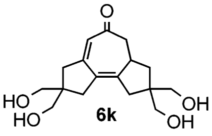
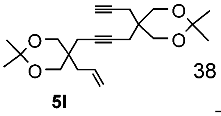
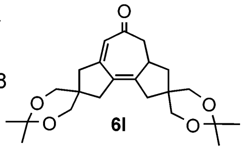


Table 2. CO−SiCaT of Enediynes **5**[a]

entry	substrate	time (h)	product	yield (%)[b]
1	 **5a**	13	 **6a**	88
2	 **5b**	48	 **6b**	50
3	 **5c**	24	 **6c**	91
4	 **5d**	27	 **6d**	85
5	 **5e**	24	 **6e**	84
6	 **5f**	24	 **6f**	82
7	 **5g**	36[c]	 **6g**	86
8	 **5h**	21	 **6h**	89
9	 **5i**	38	 **6i**	87
10	 **5j**	39	 **6j**	81
11	 **5k**	20	 **6k**	62
12	 **5l**	38	 **6l**	65

[a] All reactions were run with 0.25 mmol of enediyne under CO (1 atm) using 1 mol % of Rh(acac)(CO)$_2$ in 17 mL of THF at 22 °C unless otherwise noted. [b] Isolated yields are based on an average of two runs. [c] Reaction was run at 40 °C.

enediyne **5a** (entry 9). Thus, PhMe$_2$SiH is proven necessary for this reaction to occur, although no silyl group is incorporated into product **6a**. The best result is achieved by using 0.5 equiv of PhMe$_2$SiH at 0.015 M concentration, giving **6a** as the single product in 92% isolated yield (entry 7).

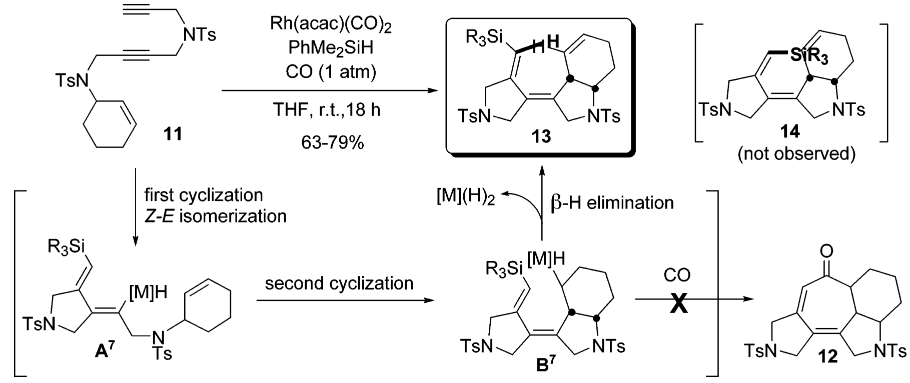
As for the catalyst, Rh(acac)(CO)$_2$, Rh$_4$(CO)$_{12}$, and [Rh(CO)$_2$Cl]$_2$ show similar efficacy. For hydrosilanes in this process, the reactions with Ph$_2$MeSiH and (EtO)$_3$SiH give **6a** exclusively, although the reactions using (EtO)$_3$SiH are slower than those with PhMe$_2$SiH. Trialkylsilanes behave differently; that is, the reaction with Et$_3$SiH gives a 9:1 mixture of **6a** and **9-TES** in low conversion, and that with *t*-BuMe$_2$SiH does not give any conversion after 96 h. Accordingly, PhMe$_2$SiH is the best hydrosilane, so far, for this process.

As described above, the optimal reaction conditions for the CO−SiCaT reaction include the use of Rh(acac)(CO)$_2$, 0.5 equiv of PhMe$_2$SiH at 0.015 M concentration in THF at room temperature, and ambient pressure of CO. To examine the scope and limitations of this reaction for functional group tolerance, a variety of substrates containing ether, ester, hydroxyl, and sulfonamide groups have been subjected to the optimal conditions for the CO−SiCaT process. Results are summarized in Table 2.

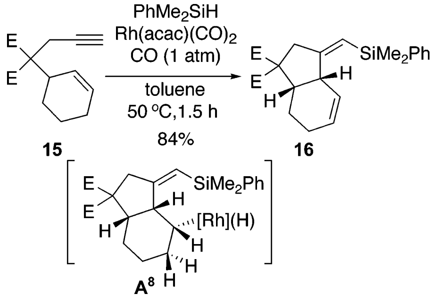
As Table 2 shows, these functional groups and heteroatoms are well tolerated in this reaction to give the corresponding fused 5-7-5 tricyclic compounds **6** in good to excellent isolated yields. The reaction of **5d** gives **6d** that contains two fused pyrrolidine moieties in 85% isolated yield (entry 4), and the reaction of **5b** that contains dipropargyl ether as well as propargyl allyl ether moieties is sluggish to give **6b** in 50% yield after 48 h (entry 2). However, the reactions of unsymmetrical substrates bearing a malonate group as well as a dipropargyl ether or a sulfonamide moiety give the corresponding 5-7-5 products (**6c**,**e**,**f**) in excellent yields (entries 3, 5, and 6). In the case of **5g**, bearing a *tert*-butyl carbamate group, the reaction requires 40 °C to give **6g** in high yield (entry 7). The substrates **5g**−**l** derived from **5a**, bearing ethers, hydroxyl groups, and ketals, are also well tolerated in this reaction, which give the corresponding **6h**−**l** in good to high yields (entries 8−12).

A. Mechansim of the CO−SiCaT Reaction. The most plausible mechanism for this novel carbonylative carbotricyclization, which can accommodate all observed results, is illustrated in Scheme 6. The reaction begins with the insertion of the terminal alkyne moiety into the Si−[Rh] bond of the hydrosilane−Rh oxidative adduct.[22] Carbocyclization then occurs to give (*Z*)-dienyl[Rh](H) intermediate **A^6**. Because of the steric hindrance between the vinylsilane and the vinyl−[Rh] moieties, **A^6** isomerizes to **C^6** via **B^6** through the "Ojima−Crabtree mechanism".[7] Subsequent carbocyclization to **D^6**, followed by reductive elimination, should give **9**. The CO insertion to **D^6** gives acyl−[Rh](H) intermediate **E^6**. Reductive elimination of **E^6** should yield aldehyde **10**. Carbocyclization of **E^6** gives tricyclic intermediate **F^6** that has the silicon and the [Rh] moieties in syn positions. Subsequent β-silyl elimination[18e,21] should take place to afford the fused 5-7-5 tricyclic product **6** and to regenerate the active catalyst species, R$_3$Si-[Rh](H). The proposed mechanism can nicely accommodate the observed three products under nonoptimized conditions, dilution

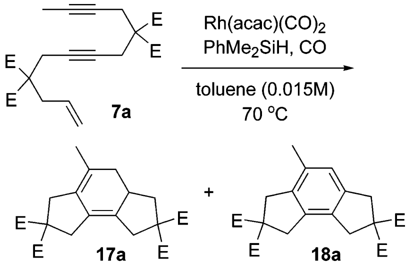
Scheme 7



Scheme 8



Scheme 9



effects, and the fact that only substoichiometric hydrosilane is needed to yield **6**.[24]

Next, we investigated the reaction of enediyne **11** in which the alkene group is a part of a cyclic system (Scheme 7). If the reaction proceeds via CO−SiCaT, fused 5-7-6-5 tetracyclic product **12** should be formed. However, the reaction of **11** under the standard CO−SiCaT conditions did not give **12** but afforded tricyclic product **13** in 63% isolated yield. As Scheme 7 illustrates, the result indicates that after the second carbocyclization, forming intermediate $\mathbf{A^7}$, β-hydride elimination took place exclusively in intermediate $\mathbf{B^7}$ over CO insertion to form the corresponding acyl−[Rh] intermediate. This type of facile β-hydride elimination in the cyclohexyl-containing enyne **15** was previously observed in the SiCaC of a propargyl(cyclohexyl)malonate, wherein the β-hydride elimination was much faster than the reductive elimination to give **16** (Scheme 8).[19] The yield of **13** was improved to 79% when 2 equiv of $PhMe_2SiH$ to **11** were used. The reactions under different conditions, i.e., (i) at higher temperatures (up to 70 °C), (ii) at higher CO pressures (10−30 atm), (iii) use of $Rh_4(CO)_{12}$ as the catalyst, (iv) use of other hydrosilanes (Ph_2MeSiH, Et_3SiH), or (v) addition of $P(OPh)_3$, did not improve the yield of **13** but rather decreased the yield or slowed the reaction (under higher CO pressures). It should be noted that **13** was formed as a single stereoisomer (the stereochemistry was unambiguously determined based on NOE; i.e., **14** was not formed, which is consistent with the proposed mechanism in Scheme 6). This result shows a limitation of the CO−SiCaT process in the substrate type. However, the same result strongly suggests that the formation of the fused 5-7-6-5 tetracyclic product could be achieved by simply blocking the facile β-hydride elimination with the appropriate introduction of a heteroatom or gem disubstitution in the cyclohexyl moiety of enediyne **11**. Accordingly, further studies along this line are actively underway in these laboratories.

B. Attempted CO−SiCaT of Enediyne 7a. We also investigated the reaction of an enediyne **7a**, which bears a 2-butynyl group instead of a propargyl group at one terminal, to examine the effect of this terminal methyl group on the reactivity and mode of the reaction. To our surprise, the attempted CO−SiCaT reaction of **7a** resulted in the formation of SiCaT products **17a** and **18a** without CO insertion (Scheme 9). Results are listed in Table 3. The reaction of **7a** under the standard CO−SiCaT conditions for 24 h did not give any product, and enediyne **7a** was recovered (entry 1). However, when the reaction using 0.3 equiv of $PhMe_2SiH$ was run at 70 °C in toluene for 3 h, SiCaT[21] product **17a** was obtained in 96% yield (entry 3). The reaction using 0.1 equiv of the hydrosilane for 24 h gave a 1:1 mixture of **17a** and **18a** in 90% yield (entry 4). The use of higher CO pressure (25 atm) suppressed the reaction (entry 5). No reaction took place even after 72 h in the absence of the hydrosilane (entry 6), which clearly indicates that the hydrosilane is necessary for the reaction to occur. The reaction using $Rh_4(CO)_{12}$ as the catalyst gave a 2:1 mixture of **17a** and **18a** in only 50% yield (entry 2).

C. Mechanism of the SiCaT Reaction of Enediyne 7a. The proposed mechanism for the formation of SiCaT products **17a** and **18a** is shown in Scheme 10. The reaction begins in the same manner as that of CO−SiCaT (Scheme 6) to form intermediate $\mathbf{A^{10}}$ after the first silylcarbocyclization. However, because of the methyl substituent, the $Z \rightarrow E$ isomerization does not occur, which makes a sharp contrast with the CO−SiCaT mechanism (Scheme 6). Because the silyl group and the [M]-(H) moiety (M = Rh) is very close, a σ-bond metathesis takes place to form metalacycle intermediate $\mathbf{B^{10}}$, liberating a hydrosilane. There are two possible ways that the olefin moiety

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[24] (a) Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* **1998**, 249−250. (b) Jeong, N.; Lee, S.; Sung, B. K. *Organometallics* **1998**, *17*, 3642−3644. (c) Jeong, N.; Sung, B. K.; Choi, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 6771−6772. (d) Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem.* **2001**, *624*, 73−87.

Table 3. SiCaT Reaction of Enediyne **7a**

entry	catalyst	$PhMe_2SiH$ (equiv)	solvent	temp (°C)	CO (atm)	time (h)	yield (%)	product ratio[b] **17a**	**18a**
1	$Rh(acac)(CO)_2$	1.0	THF	22	1	24		no reaction	
2	$Rh_4(CO)_{12}$	1.0	toluene	70	1	3	50	67	34
3	$Rh(acac)(CO)_2$	0.3	toluene	70	1	3	96	100	0
4	$Rh(acac)(CO)_2$	0.1	toluene	70	1	24	90	50	50
5	$Rh(acac)(CO)_2$	0.3	toluene	70	25	24		low conversion	
6	$Rh(acac)(CO)_2$	none	toluene	70	1	72		no reaction	

Scheme 10

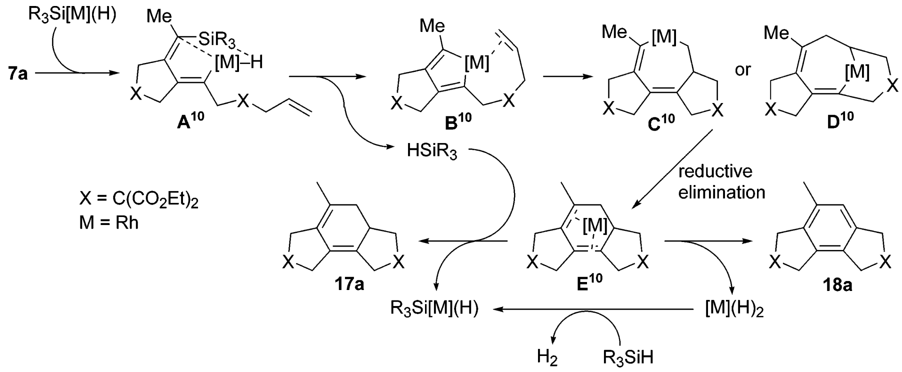


Table 4. Intramolecular [2+2+2+1] Cycloaddition of Enediyne **7a** with CO

entry	catalyst (mol %)	additive (equiv)	solvent	concn (M)	temp (°C)	CO (atm)	time (h)	yield (%)[a] **8**	**17**
1	$Rh(acac)(CO)_2$ (5)	$PhMe_2SiH$ (0.3)	toluene	0.015	70	1	3	0	96
2	$Rh(acac)(CO)_2$ (5)	none	toluene	0.1	50	1	24	49	20
3	$[Rh(COD)Cl]_2$ (5)	$PhMe_2SiH$ (0.5)	toluene	0.1	70	1	24	0	70
4	$[Rh(COD)Cl]_2$ (5)	none	toluene	0.1	50	1	24	77	15
5	$[Rh(COD)Cl]_2$ (5)	none	DMF	0.1	50	1	24	0	38
6	$[Rh(COD)Cl]_2$ (5)	none	EtOH	0.1	50	1	24	0	21
7	$[Rh(COD)Cl]_2$ (5)	none	dioxane	0.1	50	1	24	56	25
8	$[Rh(COD)Cl]_2$ (5)	none	$CHCl_3$	0.1	50	1	20	41	55
9	$[Rh(COD)Cl]_2$ (5)	none	$Cl(CH_2)_2Cl$	0.1	50	1	20	77	15
10[b]	**$[Rh(COD)Cl]_2$ (5)**	**none**	**$Cl(CH_2)_2Cl$**	**0.1**	**50**	**1**	**13**	**88**	**<4**
11[b]	$[Rh(COD)Cl]_2$ (5)	none	toluene	0.1	50	1	16	80	9
12[b]	$[Rh(COD)Cl]_2$ (5)	none	$Cl(CH_2)_2Cl$	0.1	50	4	48	66	30
13[b]	$[Rh(COD)Cl]_2$ (5)	none	$Cl(CH_2)_2Cl$	0.1	50	25	48	38	46
14[b]	$[Rh(CO)_2Cl]_2$ (5)	none	$Cl(CH_2)_2Cl$	0.1	50	1	24	64	19
15[b]	$Co_2(CO)_8$ (5)	mol sieves	$Cl(CH_2)_2Cl$	0.1	65	1	13	0	58
16[b]	$Rh(PPh_3)_3Cl$ (5)	none	toluene	0.1	90	1	16	19	27
17[b]	$Rh_4(CO)_{12}$ (5)	none	toluene	0.1	90	1	16	0	80

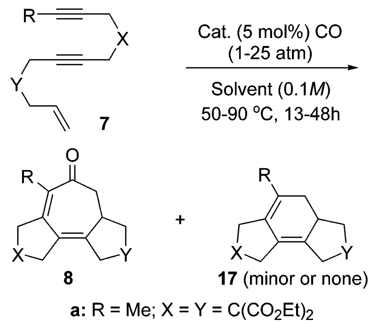
[a] Isolated yields. [b] CO was bubbled into the solution.

inserts into the [M]−C bonds of **B**^{10}, generating 5-7-5 tricyclic metallacycle **C**^{10} or 5-7-6 tricyclic metallacycle **D**^{10}. Reductive elimination of **C**^{10} or **D**^{10} yields fused 5-6-5 tricyclic diene−[M] complex **E**^{10}. When there is sufficient hydrosilane in the system, **E**^{10} reacts with the hydrosilane to form **17a** and regenerate the active catalyst species $R_3Si[Rh](H)$, and aromatization via dehydrogenation competes to give **18a**, generating dihydro−[M] species. Then, the $[M](H)_2$ species reacts with a hydrosilane to liberate molecular hydrogen and regenerate the active species $R_3Si[Rh](H)$.

The proposed mechanism accommodates the results listed in Table 4 very well and explains why CO−SiCaT did not take place for enediyne **7a**. However, it looks possible that an apparent CO−SiCaT product can be obtained from intermediate **C**^{10} via CO insertion, whereas intermediate **D**^{10} would undergo facile reductive elimination. The fact that no CO incorporation took place in this reaction may suggest that this reaction proceeds through **D**^{10} rather than through **C**^{10}.

Intramolecular [2+2+2+1] Cycloaddition of Enediynes with CO. A possible intermediacy of metallacycle **C**^{10} encouraged us to explore hitherto an unknown intramolecular [2+2+2+1] cycloaddition route to fused 5-7-5 tricyclic systems. The formation of metallacycles such as **B**^{10} from 1,6-diynes is a rather common reaction pathway in carbocyclizations.[2] Accordingly, we set out to search for reaction conditions and variables, which might promote the novel intramolecular [2+2+2+1] cycloaddition of enediyne **7** with carbon monoxide. Gratifyingly, we quickly found that the desired fused 5-7-5 tricyclic product **8** was formed through the novel [2+2+2+1] cycloaddition *in the absence of hydrosilane*, although the reaction was accompanied by intramolecular [2+2+2] cycloaddition product **17** (Scheme 11). Thus, we immediately carried

Scheme 11

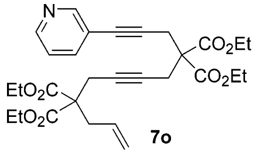


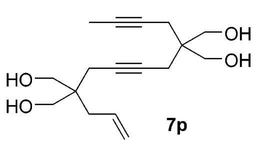
out optimization of this new higher-order cycloaddition process. Results are summarized in Table 4.

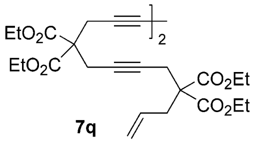
As Table 4 shows, the attempted CO−SiCaT reaction of **7** in the presence of PhMe$_2$SiH catalyzed by Rh(acac)(CO)$_2$ or [Rh(COD)Cl]$_2$ (entries 1 and 3) failed to give **8** but yielded the 5-6-5 fused-ring product **17** exclusively in 70% and 96% isolated yields, respectively. Under the same conditions but without hydrosilane (entries 2 and 4), **8** was formed in 49% yield using Rh(acac)(CO)$_2$ as the catalyst and in 77% yield when [Rh(COD)Cl]$_2$ was used as the catalyst. *These sharply contrasting results in the presence and absence of hydrosilane clearly indicate that the CO−SiCaT and intramolecular [2+2+2+1] cycloaddition processes are fundamentally different*, *although the same type of product is formed*. Because [Rh(COD)Cl]$_2$ was a better catalyst than Rh(acac)(CO)$_2$, we used this catalyst for further optimization. We examined [Rh(COD)Cl]$_2$ as a potentially efficient catalyst for this novel [2+2+2+1] cycloaddition with CO because it has been shown that [Rh(COD)Cl]$_2$ is an efficient catalyst for the catalytic Pauson−Khand reactions of enynes.[24] We looked at the possible effects of concentration by employing 0.015, 0.1, and 0.4 M concentrations and found that 0.1 M was the best substrate concentration, and either lower or higher concentrations decreased the yield and product selectivity of **8**. As for the solvent for this reaction, DMF and EtOH (entries 7 and 8) yielded only **17**. The use of dioxane and chloroform gave a mixture of **8** and **17** (entries 5 and 6). Other solvents such as THF, dimethoxyethane, and dibutyl ether were also examined at different temperatures, but the product selectivity for **8** was more or less in the same range. Accordingly, toluene (entry 4) and dichloroethane (entry 9) gave, so far, the best yield and selectivity for **8** (92% yield and 77% selectivity). However, we found that the bubbling of CO gas into the reaction mixture dramatically increased the selectivity for the formation of **8**; i.e., the reaction gave **8** in 88% isolated yield with less than 4% of the side product **17** (entry 10). This protocol was also effective for the reaction in toluene, giving **8** in 80% isolated yield accompanied by a small amount of **17** (9%). Interestingly, the reactions at higher CO pressures disfavored the formation of carbonylative product **8** (entries 12 and 13). Next, we screened other catalysts for this reaction. The reaction using Co$_2$(CO)$_8$ in the presence of molecular sieves (entry 22) or Rh$_4$(CO)$_{12}$ (entry 24) as the catalyst yielded **17** exclusively. Also, the reaction catalyzed by Co$_2$(CO)$_8$−P(OPh)$_3$ or [Ir(COD)Cl]$_2$ gave only **17**. Other catalysts, [Rh(dppp)(CO)Cl]$_2$, [Cp*RhCl$_2$]$_2$, [Rh(COD)$_2$]SbF$_6$, and Rh(PPh$_3$)$_3$Cl/AgSbF$_6$, strongly favored the formation of **17** accompanied by a minute amount of **8**. The use of [Rh(CO)$_2$Cl]$_2$ (entry 14) and Rh(PPh$_3$)$_3$Cl (entry 16) gave a mixture of **8** and **17**; however, [Rh(CO)$_2$Cl]$_2$ was a much better catalyst than Rh(PPh$_3$)$_3$Cl, although the efficacy was considerably lower than that of [Rh(COD)Cl]$_2$.

A. Scope of the Enediyne Substrates for the [2+2+2+1] Cycloaddition Process. Next, a variety of 1-substituted dodec-11-ene-1,6-diynes were employed to examine the scope of this reaction, especially for its functional group tolerance. Various enediynes **7** containing ether, sulfonamide, carbamate, ester, and ketal groups were examined. In addition, enediynes **7** bearing a methyl, phenyl, or TMS as the substituent of the terminal acetylene moiety were employed as well. Results are summarized in Table 5. These functional groups and heteroatoms are generally well tolerated in this process, affording the corresponding **8b−n** in good to excellent yields. For the substrates **7d** (entry 4), **7h** (entry 8), **7i−l** (entries 9−12), and **7n** (entry 14), [2+2+2+1] adducts **8d**, **8h**, **8i−l**, and **8n** are the exclusive products, respectively. The reactions of **7e−g** having a *p*-toluenesulfonamide moiety gave **8e−g** as predominant products accompanied by **17e−g** as minor products (entries 5−7), and the reaction of **7h** bearing a *t*-Boc-amino moiety afforded **8h** exclusively (entry 8). The reaction of **8m** (R = Ph) gave a ca. 2:1 mixture of **8m** (major) and **17m** (minor), and that of **7n** (R = TMS) yielded **8n** as the sole product. Although Cl(CH$_2$)$_2$Cl is the preferred solvent in most cases, the use of toluene gave better selectivity in some cases. For example, the reaction of **7j** in Cl(CH$_2$)$_2$Cl gave **8j** in 75% isolated yield, but the yield of **8j** was improved to 91% (86% isolated yield) when the solvent was changed to toluene (entry 10). A more drastic solvent effect was observed in the reaction of **7m**. The reaction in Cl(CH$_2$)$_2$Cl gave **8m** in only 27% yield (**17m**: 61% yield), and the same reaction in toluene reversed the product selectivity, affording **8m** and **17m** in 56% and 28% isolated yields, respectively (entry 13). Apparently, the use of toluene in these cases favored the CO insertion process.

When a 3-pyridinyl group was introduced to the 1 position, no reaction took place and the starting material **7o** was recovered intact. No reaction occurred with substrate **7q**, either. A free hydroxyl group in the substrate **7p** was not tolerated in this reaction, resulting in very messy mixtures without a trace of **8p** or **17p**. Accordingly, these enediyne substrates set a limitation in the scope of the Rh-catalyzed [2+2+2+1] cycloaddition process. However, it should be noted that **7o** did undergo the SiCaT reaction (see Scheme 10) to give **17o** in 88% isolated yield, as shown in Scheme 12.

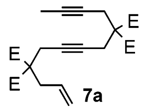
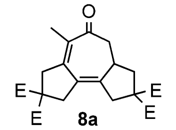
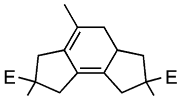
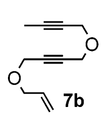
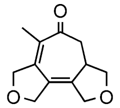
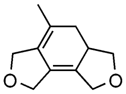
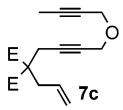
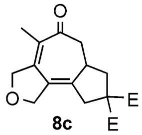
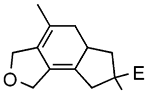
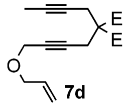
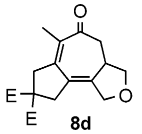
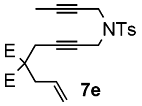
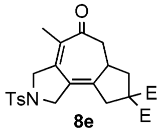
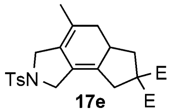
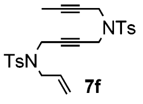
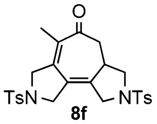
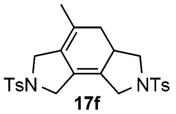
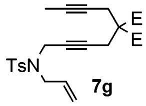
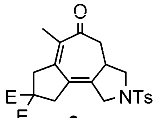
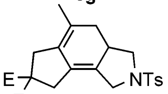
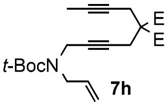
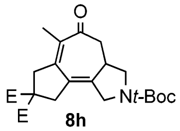
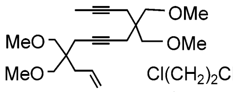
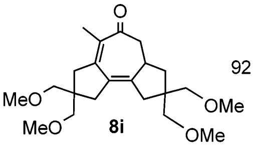
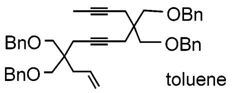
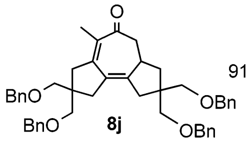
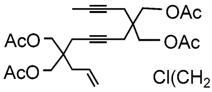
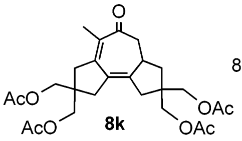
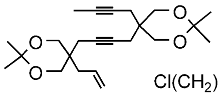
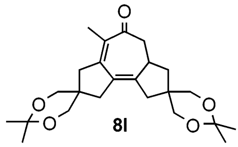
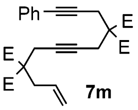
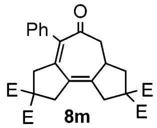
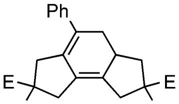
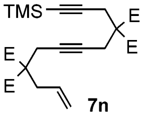
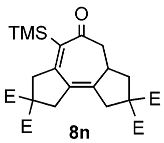

7o


7p


7q

B. Mechanism of Intramolecular [2+2+2+1] Cycloaddition. A proposed mechanism of the novel intramolecular [2+2+2+1] cycloaddition reaction is illustrated in Scheme 13. This reaction is believed to proceed through a series of metallacycles. The proposed mechanism includes (i) selective

Table 5. Rh-Catalyzed Intramolecular [2+2+2+1] Cycloaddition of Enediynes **7** with CO

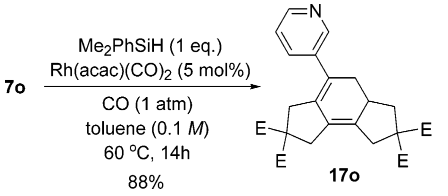
entry	substrate	conditions[a]	product(s)	yield (%)[b,c]
1	 **7a**	Cl(CH$_2$)$_2$Cl 50 °C, 13 h	 **8a**  **17a**	(88) (<4)
2	 **7b**	Cl(CH$_2$)$_2$Cl 50 °C, 21 h	 **8b**  **17b**	53 (52) 46 (43)
3	 **7c**	Cl(CH$_2$)$_2$Cl 50 °C, 21 h	 **8c**  **17c**	79 (77) 20 (17)
4	 **7d**	Cl(CH$_2$)$_2$Cl[d] 50 °C, 24 h	 **8d**	97 (93)
5	 **7e**	Cl(CH$_2$)$_2$Cl 50 °C, 14 h	 **8e**  **17e**	88 (85) 11 (8)
6	 **7f**	Cl(CH$_2$)$_2$Cl 50 °C, 22 h	 **8f**  **17f**	84 (83) 13 (11)
7	 **7g**	Cl(CH$_2$)$_2$Cl 50 °C, 14 h	 **8g**  **17g**	69 (62) 29 (26)
8	 **7h**	Cl(CH$_2$)$_2$Cl 50 °C, 24 h	 **8h**	70 (66)
9	 **7i**	Cl(CH$_2$)$_2$Cl 50 °C, 36 h	 **8i**	92 (87)
10	 **7j**	toluene 80 °C, 22 h	 **8j**	91 (86)
11	 **7k**	Cl(CH$_2$)$_2$Cl 60 °C, 22 h	 **8k**	82 (75)
12	 **7l**	Cl(CH$_2$)$_2$Cl 60 °C, 24 h	 **8l**	78 (72)
13	 **7m**	toluene 50 °C, 32 h	 **8m**  **17m**	59 (56) 32 (28)
14	 **7n**	Cl(CH$_2$)$_2$Cl 50 °C, 21 h	 **8n**	53 (51)

[a] All reactions were run with 50−100 mg of enediyne (C = 0.1 M) and 5 mol % of [Rh(COD)Cl]$_2$ under CO (1 atm). [b] ^{1}H NMR yields using mesitylene as the internal standard. [c] Isolated yields based on an average of two runs. [d] Reaction was run with 2.5 mol % of [Rh(COD)Cl]$_2$.

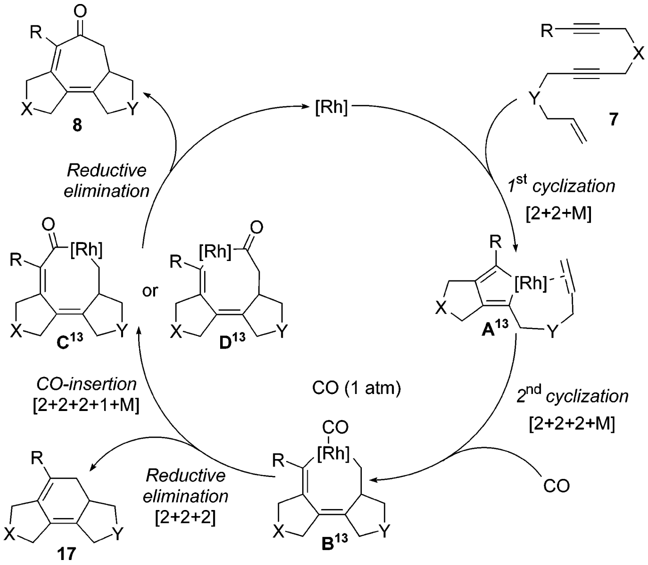
coordination of the diyne moiety of enediyne **7** to the active Rh-catalyst species, forming metallacycle **A**[13] ([2+2+M]); (ii) insertion of the olefin moiety of **7** into the Rh−C bond to form 5-7-5 fused tricyclic rhodacycle **B**[13] ([2+2+2+M]); (iii) coordination of CO to the [Rh] metal followed by migratory insertion of CO into the Rh−C bond to form 5-8-5 rhodacycle **C**[13] or **D**[13] ([2+2+2+1+M]); and (iv) reductive elimination to form [2+2+2+1] cycloadduct **8** and regenerate the active Rh-catalyst species. Reductive elimination from the 5-7-5 rhodacycle **B**[13], prior to the CO insertion, gives [2+2+2] cycloadduct **17**.

C. Characteristics of the CO−SiCaT and [2+2+2+1] Cycloaddition Reactions. As discussed above, we have dis-

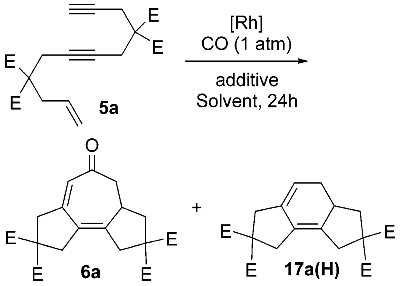
Scheme 12



Scheme 13. Proposed Mechanism of Intramolecular [2+2+2+1] Cycloaddition



Scheme 14



covered two different reactions that give fused 5-7-5 tricyclic products, incorporating carbon monoxide. Although these two reactions yield the same type of products, the mechanisms of these reactions are fundamentally different; i.e., the CO−SiCaT reaction proceeds through sequential carbocyclizations (Scheme 6), and the [2+2+2+1] cycloaddition reaction involves sequential metallacycle formations (Scheme 13). We have shown above a number of compelling cases in which two reaction conditions gave markedly different outcomes. However, those differences were observed for the reactions of enediynes **7** bearing a substituent at the terminal acetylene moiety, wherein the CO−SiCaT reaction did not take place and in most cases the SiCaT reaction occurred to afford the corresponding fused 5-6-5 tricyclic products **17** and/or **18**. Accordingly, a natural question arises; i.e., what will happen when enediynes do not have a substituent at the terminal acetylene moiety for which the CO−SiCaT has taken place? To answer this question and to confirm the fundamental difference between the CO−SiCaT and [2+2+2+1] reactions, we looked at the reactions of enediyne **5a** under the optimized reaction conditions of these two processes (Scheme 14). Results are summarized in Table 6.

As Table 6 shows, the CO−SiCaT reaction of **5a** was carried out with PhMe$_2$SiH (0.5 equiv) at ambient temperature and pressure of CO in THF or toluene in high dilution (0.015 M) for 24 h using Rh(acac)(CO)$_2$ or [Rh(COD)Cl]$_2$ as the catalyst (entries 1 and 3), whereas the [2+2+2+1] reaction of **5a** was performed at 50 °C and ambient pressure of CO in toluene or dichloroethane at 0.1 M concentration for 24 h using [Rh(COD)Cl]$_2$ as the catalyst (entries 6 and 7). The CO−SiCaT reaction of **5a** gave **6a** as the exclusive product without any trace of **17a(H)** (entries 1 and 3), and Rh(acac)(CO)$_2$ in THF is a better catalyst system than [Rh(COD)Cl]$_2$ in toluene (toluene is the best solvent for this catalyst). In the absence of PhMe$_2$SiH, otherwise under the same conditions, no reaction took place at all and **5a** was recovered intact (entries 2 and 4). Thus, it is very clear that the CO−SiCaT reaction requires the hydrosilane. Also, it should be pointed out that the CO−SiCaT reaction proceeds smoothly at ambient temperature. In sharp contrast, the [2+2+2+1] cycloaddition of **5a** requires a much higher concentration (0.1 M) and 50 °C to proceed. Also, the reaction gives a mixture of **6a** (major) and **17a(H)** (minor) (entries 6 and 7). A marked difference in the catalytic activity and selectivity was observed between [Rh(COD)Cl]$_2$ and Rh(acac)(CO)$_2$; i.e., the reaction catalyzed by Rh(acac)(CO)$_2$ needed 90 °C to proceed and resulted in the exclusive formation of **17a(H)** with no trace of **6a** (entry 5).

Scheme 15 summarizes the differences and complementary nature of the CO−SiCaT and [2+2+2+1] cycloaddition reactions. It is confirmed that the mechanisms of these two reactions are fundamentally different. The CO−SiCaT reaction takes place only with 1-terminal free enediynes **5** through silicon-initiative cascade carbocyclization processes. On the other hand, the [2+2+2+1] cycloaddition reaction proceeds with 1-substituted and unsubstituted enediynes **7a** and **5** through sequential metallacycle formations.

The fact that only fairly good product selectivity was observed for this enediyne substrate under the standard conditions for the [2+2+2+1] cycloaddition reaction suggests that the enediynes bearing a free acetylene moiety are not good substrates for this reaction because the reactions with 1-methyl enediyne **7a** gave much better results (see Table 6, entry 1). In fact, the reactions of two other 1-terminus free enediynes, **5b** and **5d**, showed the same tendency (Scheme 16). The reaction of **5b** under the standard [2+2+2+1] cycloaddition conditions proceeded slowly to give **6b** in 51% isolated yield after 3 days at 50 °C. The CO−SiCaC reaction of **5b** gave **6b** in 91% isolated yield after 24 h at 22 °C (see Table 2, entry 2). In a similar manner, the [2+2+2+1] cycloaddition of **5d** afforded **6d** in 52% isolated yield after 24 h at 50 °C, and the CO−SiCaT reaction of **5d** gave **6d** in 84% isolated yield after 24 h at 22 °C (see Table 2, entry 4).

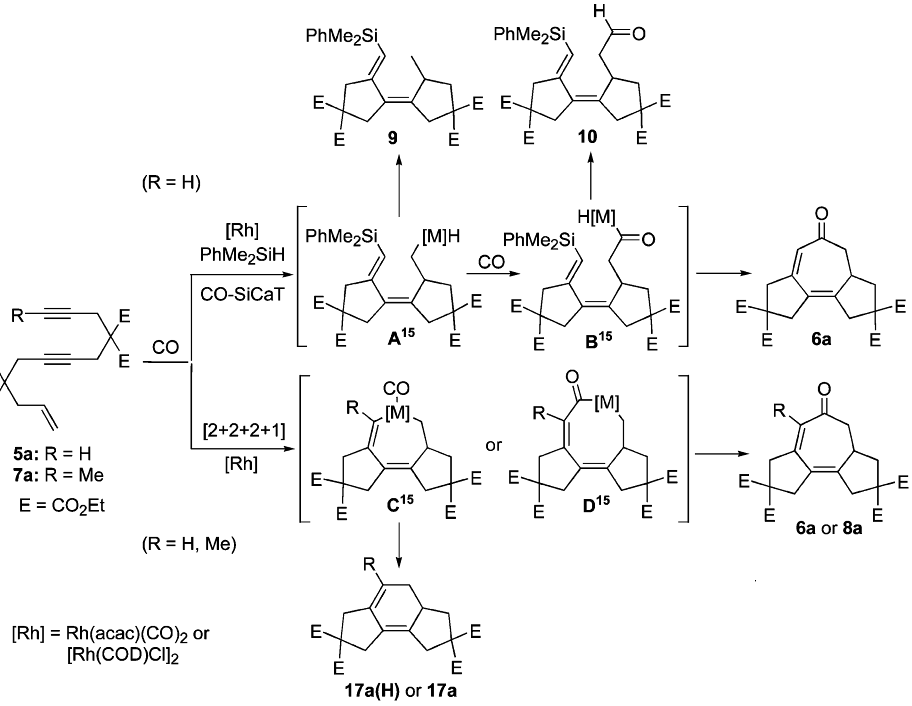
Rh-Catalyzed Tricyclizations of Related Substrates. We also investigated the extension of the CO−SiCaT and [2+2+2+1] cycloaddition reactions of enediynes to related substrates, i.e., allenediyne **19** and diynals **21a,b**. The attempted [2+2+2+1] cycloaddition of allenediyne **19** catalyzed by [Rh(COD)Cl]$_2$ under the standard conditions afforded the fused 5-6-6 tricyclic product **20** exclusively in 97% isolated yield (>98% yield by ^{1}H NMR) through [2+2+2] cycloaddition (Scheme 17). To the best of our knowledge, this presents the first example of

Table 6. Comparison between the CO−SiCaT and [2+2+2+1] Cycloaddition Reactions

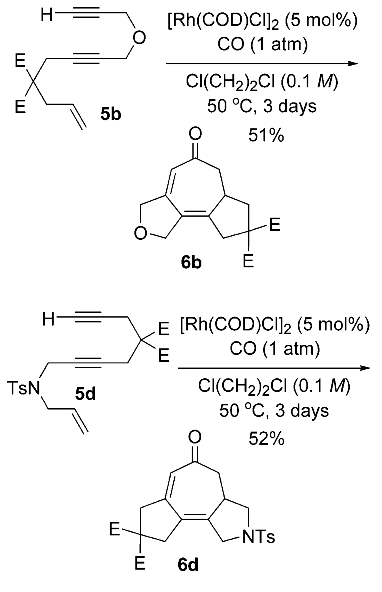
entry	catalyst (mol %)	silane (equiv)	solvent	concn (M)	temp (°C)	yield (%)[a] 6a	17a(H)
1	$Rh(acac)(CO)_2$ (1)	$PhMe_2SiH$ (0.5)	THF	0.015	rt	92	0
2	$Rh(acac)(CO)_2$ (1)	none	THF	0.015	rt	no reaction	
3	$[Rh(COD)Cl]_2$ (5)	$PhMe_2SiH$ (0.5)	toluene	0.015	rt	72	0
4	$[Rh(COD)Cl]_2$ (5)	none	toluene	0.015	rt	no reaction	
5	$Rh(acac)(CO)_2$ (1)	none	toluene	0.1	90	0	47
6	$[Rh(COD)Cl]_2$ (5)	none	toluene	0.1	50	66	30
7	$[Rh(COD)Cl]_2$ (5)	none	$Cl(CH_2)_2Cl$	0.1	50	73	16

[a] Isolated yields.

Scheme 15

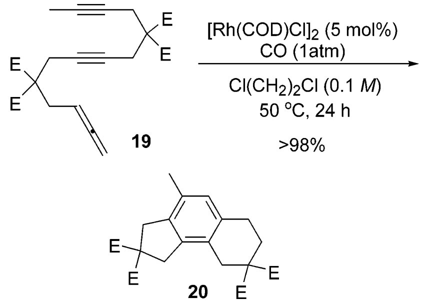


Scheme 16



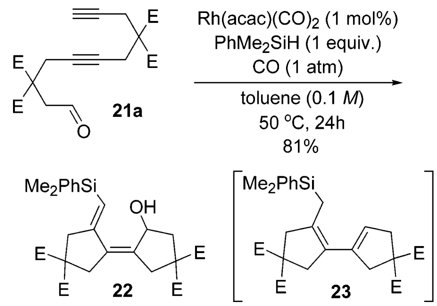
intramolecular [2+2+2] cycloaddition of allenediyne, and further studies on this novel reaction are actively underway in these laboratories.

Scheme 17

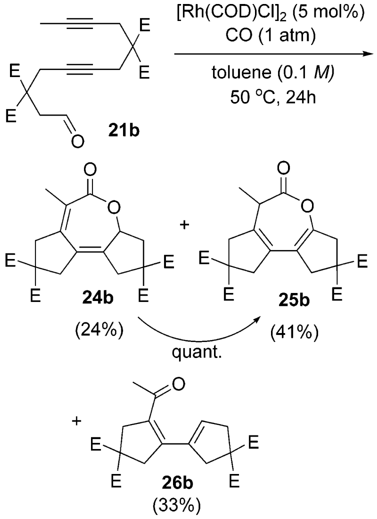


A. Reactions of Diynals under CO−SiCaT and [2+2+2+1] Cycloaddition Conditions. The reaction of undeca-5,10-diyn-1-al (**21a**) catalyzed by $Rh(acac)(CO)_2$ (1 mol %) under the CO−SiCaT conditions with $PhMe_2SiH$ (1 equiv) at high dilution (0.015 M) in THF at 50 °C for 24 h failed to give any CO−SiCaT or SiCaT product but gave the corresponding bicyclization product **22** in 45% isolated yield. The formation of **22**, as the sole product, was improved to 81% isolated yield at a higher concentration (0.1 M) in toluene (Scheme 18). When the same reaction was run in toluene, otherwise under the same conditions, a mixture of **22** (36%) and deoxygenated bicyclization product

Scheme 18



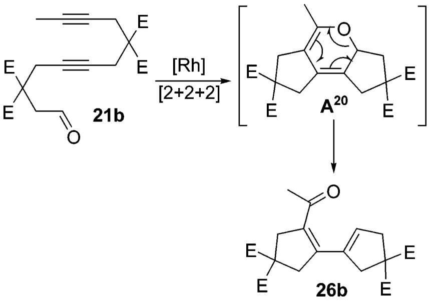
Scheme 19



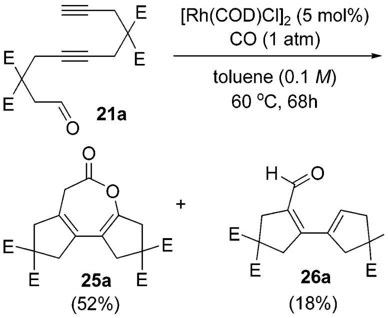
23 (48%) was isolated (Scheme 18). The use of higher CO pressure (20 atm) only slowed the reaction, forming **22**, in toluene.

Because the diynal **21a** did not seem to be suitable for the CO−SiCaT reaction, we examined the [2+2+2+1] cycloaddition conditions. The metal-catalyzed cycloaddition of an aldehyde to diynes has not been extensively studied. Thus, only a few successful examples have been reported for the intermolecular [2+2+2] cycloadditions of 1,7-diynes (no free terminal acetylene moieties) with aldehydes catalyzed by Ni(COD)$_2$−PR$_3$ (R = Bu or Cy). However, no intramolecular version has been reported to date.[25] The reaction of dodeca-5,10-diyn-1-al (**21b**) was carried out with [Rh(COD)Cl]$_2$ (5 mol %) at 50 °C and ambient pressure of CO in toluene (0.1 M) for 24 h. The reaction gave the corresponding [2+2+2+1] cycloaddition products **24b** and **25b** (65% combined yield) as well as an interesting acetylbis(cyclopentenyl) **26b** (33%) in nearly quantitative overall yield (Scheme 19). On monitoring the reaction, it was found that fused 5-7-5 tricyclic lactone **24b** was the kinetic product. Thus, only **24b** and **26b** were formed in the early stage of the reaction. The clean and complete isomerization of **24b**−**25b** was observed by leaving a mixture of **24b** and **25b** in CDCl$_3$ in an NMR tube at ambient temperature for two weeks. The formation of acetylbis(cyclopentenyl) **26b** can be readily explained by assuming the intermediacy of [2+2+2] cycloadduct **A^{20}**, which underwent an electrocyclic ring opening of the central pyrane moiety to form the bicyclic dienone structure of **26b** (Scheme 20).

Scheme 20



Scheme 21



The preferential formations of **25b** and **26b** indicate that the two endo-double-bond system is substantially more favorable than the two exo-double-bond system. In fact, the tricyclization reaction of **21a**, which does not have a methyl substituent at the terminal acetylene moiety, at 60 °C for 68 h gave fused 5-7-5 tricyclic lactone **25a** (major) and **26a** (minor); i.e., the kinetic product **24a** was not isolated at all in this reaction (Scheme 21).

The overall results on the reactions of diynals **21** show that the intramolecular tricyclization involving diyne and aldehyde components is ready to occur by the catalysis of [Rh(COD)-Cl]$_2$, and the novel [2+2+2+1] cycloaddition of diynal with CO was achieved for the first time. However, the [2+2+2+1] cycloaddition and [2+2+2] cycloaddition processes are competing. Thus, further optimization of the [2+2+2+1] cycloaddition process is necessary for this reaction to be synthetically useful. Nevertheless, it is worth mentioning that unique fused 5-7-5 tricyclic lactones **25** can be obtained in fairly good isolated yields even at this discovery stage. Further studies on this novel higher-order cycloaddition reaction are actively underway in these laboratories.

In summary, we reported here the full account of the novel silicon-initiated carbonylative carbotricyclization (CO−SiCaT) as well as higher-order [2+2+2+1] cycloaddition reactions of enediynes with CO catalyzed by rhodium complexes. The most plausible mechanisms for these two reactions, which are fundamentally different from each other, were proposed and discussed. Another mechanism for the formation of fused 5-6-5 tricyclic products from 1-substituted enediynes under CO−SiCaT conditions was proposed. The scope and limitations of these unique processes were described. These newly discovered reactions allow us to construct multiple bonds all at once, converting linear starting materials to polycyclic compounds in one single step. Thus, these new processes have high synthetic potential to provide innovative routes to appropriately functionalized polycyclic intermediates for the syntheses of natural and unnatural products of medicinal and/or biological interests.

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[25] Tsuda, T.; Kiyoi, T.; Miyane, T.; Saegusa, T. *J. Am. Chem. Soc.* **1988**, *110*, 8570−8572.

We also reported the first examples of intramolecular tricyclization of diynals, including the formation of fused 5-7-5 tricyclic lactones through [2+2+2+1] cycloaddition with CO as one carbon unit. In addition, the first [2+2+2] cycloaddition of an allenediyne, yielding the corresponding fused 5-6-6 tricyclic product was reported. These novel polycyclization processes clearly warrant further investigations.

Experimental Section

General Method and Materials. See Supporting Information.

General Procedure for the Catalytic CO−SiCaT Reaction. A typical procedure is described for the reaction of 4,4,9,9-tetra(carbethoxy)dodec-11-ene-1,6-diyne (**5a**). A reaction vessel equipped with a stirring bar and a CO inlet was charged with Rh(acac)(CO)$_2$ (0.6 mg, 1 mol %). After purging the reaction vessel with CO, THF (14.6 mL) was added to dissolve the catalyst. Dimethylphenylsilane (38 μL, 0.5 equiv) was then added, and the mixture was stirred at 22 °C. After 1 min, a solution of substrate **5a** (112 mg, 0.25 mmol) in THF (2 mL) was added, and the reaction mixture was stirred under CO (1 atm) for 30 h. All volatiles were removed under reduced pressure. The crude products were purified by column chromatography on silica gel using hexanes/EtOAc (5:1) as eluent to give 2,2,8,8-tetra(carbethoxy)-5-oxo-1,3a,4,5,7,9-hexahydro-3*H*-cyclopenta[*e*]azulene (**6a**) as a colorless oil (109 mg, 92%): TLC (SiO$_2$, hexanes/EtOAc = 5:1, R_f = 0.17); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.24 (t, 6 H, J = 7.2 Hz), 1.25 (t, 6 H, J = 7.2 Hz), 1.96 (dd, 1 H, J = 11.7 Hz/J = 12.9 Hz), 2.51 (bd, 1 H, J = 12.9 Hz), 2.72 (m, 3 H), 3.01(m, 1 H), 3.13 (m, 4 H), 3.25 (dd, 1 H, J = 2.1 Hz/J = 17.4 Hz), 4.19 (q, 4 H, J = 7.2 Hz), 4.20 (q, 4 H, J = 7.2 Hz), 6.03 (s, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.90 (2C), 13.9 (2C), 37.7, 39.5, 40.5, 41.0, 43.6, 44.7, 57.5, 58.8, 61.7, 61.8, 61.8 (2C), 124.0, 129.4, 150.1, 154.1, 170.4, 170.6, 170.7 (2C), 197.5; IR (neat, cm^{-1}) 2981 (m), 2938 (w), 1731 (s), 1646 (s), 1603 (w), 1465 (w), 1447 (m), 1366 (m), 1288 (s), 1252 (s), 1193 (s), 1159 (s), 1099 (m), 1070 (s), 1018 (m), 861 (w); HRMS (FAB) m/z calcd for $C_{25}H_{33}O_9$ (M + 1)$^+$ 477.2125, found 477.2124 (Δ = −0.2 ppm).

General Procedure for the [2+2+2+1] Cycloaddition Reaction. A typical procedure is described for the reaction of enediyne **7a**. All other reactions are run following the same procedure unless otherwise noted. Enediyne **7a** (100 mg, 0.216 mmol) was introduced to a Schlenck tube, followed by Cl(CH$_2$)$_2$Cl (2.16 mL) under argon, and then CO was bubbled into the solution at room temperature. After 15 min, [Rh(COD)Cl]$_2$ (5.3 mg, 0.0108 mmol, 5 mol %) was added under CO and the resulting mixture was stirred at room temperature for an additional 5 min. Then, the reaction mixture was heated to 50 °C with stirring and kept for 16 h under CO (ambient pressure, bubbled into the solution). All volatiles were removed from the reaction mixture under reduced pressure, and the crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:9−3:7) affording **8a** as a light yellow oil (92.5% yield by ^{1}H NMR; 93 mg, 88% isolated yield) and **17a** as a colorless oil (5.5% yield by ^{1}H NMR; <4 mg, <4% isolated yield).

6-Methyl-2,2,8,8-tetra(carbethoxy)-5-oxo-1,3a,4,5,7,9-hexahydro-3*H*-cyclopenta[*e*]azulene (8a): colorless oil; TLC (SiO$_2$, EtOAc/hexanes = 1:4, R_f = 0.30); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.25 (m, 12 H), 1.90 (s, 3 H), 1.96 (m, 1 H), 2.61−3.20 (m, 10 H), 4.22 (m, 8 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.0, 15.8, 37.4, 39.9, 40.3, 40.9, 42.4, 45.7, 56.9, 59.1, 61.7, 129.7, 130.8, 147.3, 149.5, 170.7, 170.8, 170.9, 171.0, 197.3; IR (neat, cm^{-1}) 2910 (s), 1731 (s), 1644 (s), 1367 (m), 1289 (m), 1068 (m); HRMS (EI) m/z calcd for $C_{26}H_{34}O_9$ (M$^+$) 490.2203, found 490.2205 (Δ = 0.4 ppm).

5-Methyl-2,2,7,7-tetra(carbethoxy)-1,3,3a,4,6,8-hexahydro-*as*-indacene (17a): colorless oil; TLC (SiO$_2$, EtOAc/hexanes = 1:4, R_f = 0.56); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.22 (m, 12 H), 1.70 (s, 3 H), 1.82 (m, 1 H), 1.84 (m, 1 H), 2.13 (m, 1 H), 2.60−3.07 (m, 8 H), 4.18 (m, 8 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.9, 14.0, 19.4, 35.9, 36.1, 36.7, 36.8, 39.7, 41.3, 59.4, 59.7, 61.4, 123.5, 128.2, 128.9, 131.1, 171.6, 171.7, 171.9; HRMS (EI) m/z calcd for $C_{25}H_{35}O_8$ (M + H)$^+$ 463.2332, found 463.2325 (Δ = −1.5 ppm).

For other reactions and their products, see Supporting Information.

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Supporting Information Available: Experimental procedures and complete characterization data for all new substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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