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One-step formation of fused tetracyclic skeletons from cyclohexene-diynes and carbon monoxide through Rh(I)-catalyzed [2 + 2 + 2 + 1] cycloaddition reaction†‡

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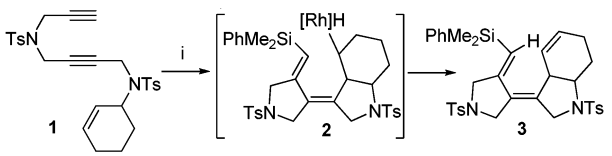
Rapid construction of 5-7-6-5 fused tetracyclic carbocycles and heterocycles from cyclohexene-diynes and CO has been achieved in one step through a Rh(I)-catalyzed [2 + 2 + 2 + 1] cycloaddition process.

Transition metal-catalyzed carbocyclization and cycloaddition reactions have proven to be among the most efficient methods for constructing complex polycyclic systems.[1] A variety of higher order processes have been reported including [2 + 2 + 2 + 1],[2] [4 + 2 + 2],[3] [5 + 1 + 2 + 1],[4] [3 + 3 + 1][5] and [5 + 2 + 1][6] cycloadditions. In addition, transition metal-catalyzed cycloaddition reactions are frequently utilized in the syntheses of complex molecules and natural products.[6,7] Intrigued by naturally occurring 5-7-6-5 fused tetracyclic compounds such as recently discovered Caribenol A,[8] we set out to develop a highly efficient synthetic route to the 5-7-6-5 tetracyclic skeleton *via* a single step process from enediynes. If successful, such a catalytic process will provide rapid access to a library of drug-like carbocycles and heterocycles.

Our first attempt at constructing this skeleton by Rh-catalyzed carbonylative silicon-initiated carbotricyclization (CO-SiCaT)[9] of enediyne **1** bearing a cyclohexenyl group as the olefin moiety resulted in the formation of tricyclic product **3** *via* a facile β-hydride elimination in the key intermediate **2** (Scheme 1).[2a]

In the present work, we have applied our previously developed [2 + 2 + 2 + 1] cycloaddition process[2a,b] to similar cyclohexene-diyne substrates **4**, and found that the reaction



i. $Rh(acac)(CO)_2$ (1 mol%), $PhMe_2SiH$, CO (1 atm), THF, r.t., 18 h, 79%.

Scheme 1 CO-SiCaT of cyclohexene-diyne.

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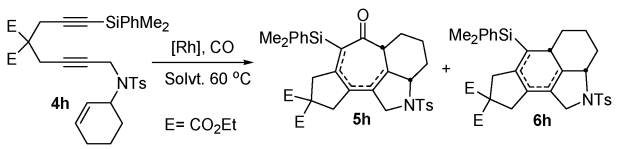
‡ Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b909781c



Scheme 2 [2 + 2 + 2 + 1] cycloaddition of cyclohexene-diyne **4h** with CO.

indeed gives the desired 5-7-6-5 fused tetracyclic products in good to excellent yields and as single diastereomers.

The reaction of **4h** was carried out in the presence of $[Rh(COD)Cl]_2$ (5 mol%); treatment with CO (1 atm) in dichloroethane at 60 °C[2b] for 50 h gave the desired fused tetracyclic product **5h** along with a small amount of the [2 + 2 + 2] cycloadduct **6h** (*ca.* 11.5 : 1) in 89% isolated yield (Scheme 2, Table 1, entry 1).

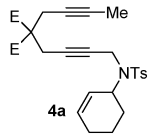
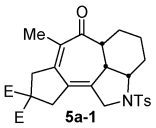
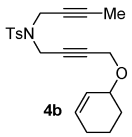
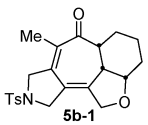
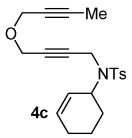
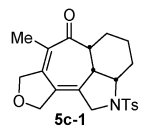
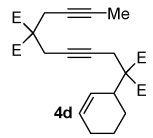
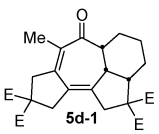
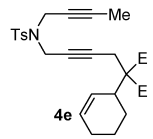
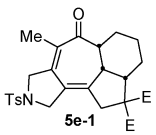
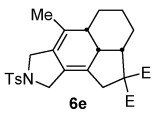
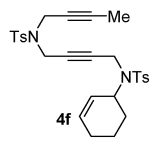
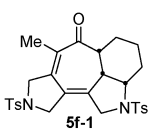
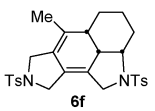
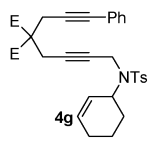
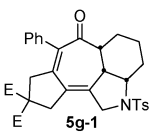
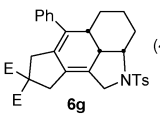
However, we found that these conditions were not generally applicable to other substrates **4** to achieve high selectivity. Thus, the reaction conditions were optimized to improve product selectivity as well as the rate of the reaction (Table 1). The use of $[Rh(CO)_2Cl]_2$ (5 mol%) as the catalyst substantially increased the rate of the reaction (*i.e.*, completion in 20 h) but resulted in somewhat decreased selectivity (Table 1, entry 2). Increase in the CO pressure resulted in lower conversion in 20 h, but with better selectivity (entries 3 and 4). Using trifluoroethanol (TFE) as the solvent[10] under 2 atm of CO, **5h** was obtained exclusively with complete conversion in 20 h, but in 70% yield. The optimal conditions found to date are with $[Rh(CO)_2Cl]_2$ (5 mol%) under 2 atm of CO in DCE–TFE (10 : 1) at 60 °C for 20 h, which gave **5h** exclusively in 92% isolated yield (Table 1, entry 6).

Table 1 Optimization of [2 + 2 + 2 + 1] cycloaddition of **4h** with CO

Entry	Solvent	[Rh] (5 mol%)	CO/atm	Conv. (%)[a]	**5h** : **6h**[a]	Yield (%)[b]
1	DCE	$[Rh(COD)Cl]_2$	1	100[b]	92 : 8	89
2	DCE	$[Rh(CO)_2Cl]_2$	1	100	90 : 10	86
3	DCE	$[Rh(CO)_2Cl]_2$	2	75	93 : 7	ND[c]
4	DCE	$[Rh(CO)_2Cl]_2$	3	90[d]	93 : 7	ND[c]
5	TFE	$[Rh(CO)_2Cl]_2$	2	100	100 : 0	70
6	DCE–TFE (10 : 1)	$[Rh(CO)_2Cl]_2$	2	100	100 : 0	92

[a] Determined by reverse phase HPLC analysis (Phenomenex, Jupiter 10 μ Proteo 90A) for 20 h reaction. [b] Isolated yield. [c] Not determined. [d] At 50 h.

Table 2 [2 + 2 + 2 + 1] cycloaddition of **4a–g** with CO[a]

Entry	Substrate	**5-1** (Yield %)[b]	**6** (Yield %)[b]
1	 **4a**	 **5a-1** (82)	—
2	 **4b**	 **5b-1** (91)	—
3	 **4c**	 **5c-1** (74)	—
4	 **4d**	 **5d-1** (85)	—
5	 **4e**	 **5e-1** (83)	 **6e** (6)
6	 **4f**	 **5f-1** (85)	 **6f** (5)
7	 **4g**	 **5g-1** (44)	 **6g** (44)

[a] Reactions were run with $[Rh(CO)_2Cl]_2$ (5 mol%) at 60 °C and 2 atm of CO and in DCE–TFE (10 : 1) for 20 h. [b] Averaged isolated yield of analytically pure products based on at least two runs using 50–100 mg of substrates.

Under the optimized conditions, [2 + 2 + 2 + 1] cycloaddition of various cyclohexene-diynes **4** afforded the corresponding 5-7-6-5 fused tetracyclic cycloadducts in good to excellent yields. The reactions of **4a–d**, bearing a methyl group at the terminal ethynyl moiety, gave **5(a–d)-1** exclusively in 74–91% yields (Table 2, entries 1–4).

The reactions of **4(e,f)** also gave **5(e,f)-1** in high yields, but accompanied by small amounts of **6(e,f)** as side products (Table 2, entries 5 and 6). The reaction of **4g**, bearing a phenyl group at the terminal ethynyl moiety, also gave **5g-1**, but an equal amount of **6g** was formed. Thus, further optimization of reaction conditions is underway for this substrate.

As described above (Scheme 2, Table 1, entry 6), the reaction of **4h** proceeded exclusively to give **5h** in excellent yield. However, ^1H and ^{13}C NMR spectra as well as LC-MS of **5h** obtained after flash chromatography indicated that **5h** was a *ca.* 1 : 1 mixture of two isomers, which were isolated by preparative HPLC. Further analysis revealed that one of the isomers was the anticipated product **5h-1**, while the other was its diene-shifted regioisomer **5h-2** (Table 3, entry 1). It should be noted that both **5h-1** and **5h-2** were single diastereomers. Similar results were obtained for the reactions of **4i–k** bearing a $PhMe_2Si$ or Me_3Si group at the terminal ethynyl moiety, affording **5i–k** as a *ca.* 1 : 1 mixture of regioisomers (Table 3, entries 2–4).

Molecular modeling studies (Gaussian; AM1) on **5(h–k)-1** and **5(h–k)-2** indicated that **5(h–k)-2** should be energetically favorable. However, attempted diene isomerization with extended reaction time did not result in any appreciable change in product ratios. Further investigation into the mechanism and suppression of this isomerization is in progress.

The key to the successful rapid construction of the 5-7-6-5 fused tetracyclic skeleton in one step from enediynes **4** and CO lies in the mechanism of the [2 + 2 + 2 + 1] cycloaddition process. As illustrated in Scheme 3, the reaction proceeds through (i) selective coordination of the diyne moiety of enediyne **4** to the active Rh-catalyst species to give metallacycle **A** ([2 + 2 + M]); (ii) insertion of the olefin moiety of **4** into the Rh–C bond to yield 5-7-6-5 fused-tetracyclic rhodacycle **B** ([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 5-8-6-5 rhodacycle **C** or **C′** ([2 + 2 + 2 + 1 + M]); and (iv) reductive elimination to give [2 + 2 + 2 + 1] cycloadduct **5-1** and regenerate the active Rh-catalyst species. Reductive elimination from rhodacycle **B** prior to CO insertion gives [2 + 2 + 2] cycloadduct **6**.[2a,c] The observed exclusive formation of **5-1** and **6** as a single diastereomer is ascribed to the exclusive *endo* insertion of the olefin moiety of the cyclohexene group into the Rh–C bond to form rhodacycle **B**, which is energetically the only feasible pathway.

It should be noted that intermediate **B** has already installed the Rh–C bond with the sp^2 carbon, which was originally the terminal ethynyl group. This metallacycle structure prevents the β-hydride elimination which took place in **2** (Scheme 1) as the most facile pathway. This newly found feature has significantly expanded the scope of the [2 + 2 + 2 + 1] cycloaddition process.

It is clear that this novel [2 + 2 + 2 + 1] cycloaddition process has opened an avenue for possible rapid construction of a library of fused tetracyclic compounds using unsaturated carbocycles and heterocycles as the ene component. Further studies on the scope and application of this unique process are actively underway in these laboratories.

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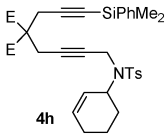
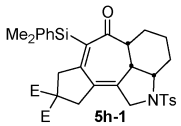
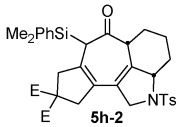
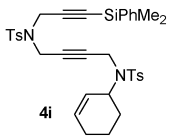
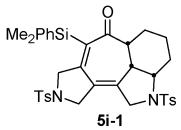
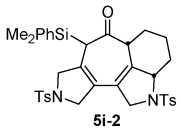
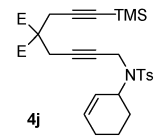
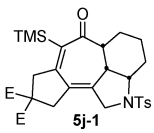
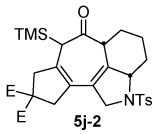
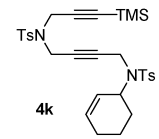
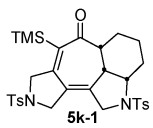
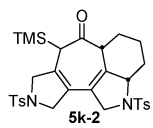
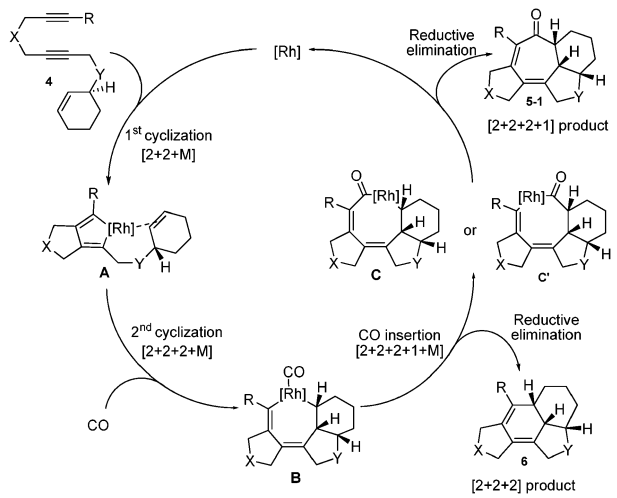
Table 3 [2 + 2 + 2 + 1] cycloaddition of **4h–k** with CO[a]

Entry	Substrate	5-1	5-2	Yield (%)[b]
1	 **4h**	 **5h-1**	 **5h-2**	92
2	 **4i**	 **5i-1**	 **5i-2**	77
3	 **4j**	 **5j-1**	 **5j-2**	92
4	 **4k**	 **5k-1**	 **5k-2**	87[c]

[a] See footnote *a* of Table 2. [b] Isolated yield. Isomers were isolated by preparative HPLC (Phenomenex, Jupiter 10μ Proteo 90A). [c] **6k** was formed in 6% yield.



Scheme 3 Mechanism for [2 + 2 + 2 + 1] cycloaddition.

Notes and references

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