ORGANIC LETTERS

2004
Vol. 6, No. 20
3589−3591

Novel [2 + 2 + 2 + 1] Cycloaddition of Enediynes Catalyzed by Rhodium Complexes

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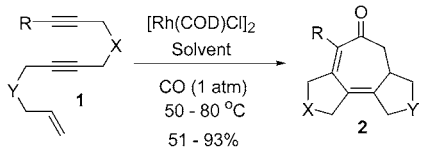
Received July 29, 2004

ABSTRACT



R = TMS, alkyl; X,Y = esters, ethers, O, NR'

The first Rh-catalyzed intramolecular [2 + 2 + 2 + 1] cycloaddition reaction of enediynes and CO is reported. This novel higher order cycloaddition process gives the corresponding 5-7-5 ring systems in high yield and selectivity. This process is another significant addition to the arsenal of cycloaddition-based synthetic methods, which provide powerful tools for rapid and efficient construction of complex polycyclic systems.

It would be ideal if the synthesis of complex target molecules could be achieved quickly, quantitatively, and selectively by simple operations from readily available starting materials.[1] Cycloaddition reactions are among the synthetically most useful processes for rapidly increasing molecular complexity.[2−3] In the past 2 decades, considerable advances have been made in the development of higher order cycloaddition reactions such as [4 + 3],[4] [5 + 2],[5] [6 + 2],[6] [4 + 2 + 2],[7] and [5 + 2 + 1][8] processes. Many of these processes are symmetry-forbidden and impossible or difficult to realize in the absence of proper catalysts. Thus, transition-metal-catalyzed higher order cycloaddition reactions[9] provide powerful methods for the construction of complex polycyclic systems.[10−11] We describe here the first example of a Rh-catalyzed intramolecular [2 + 2 + 2 + 1] cycloaddition process, including CO as the single carbon component.

We previously reported a Rh-catalyzed carbonylative silicon-initiated cascade tricyclization (CO-SiCaT) of dodec-

(1) (a) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, *3*, 765−769 and references therein. (b) Hudlicky, T.; Natchus, M. G. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, 1993; Vol. 2, pp 1−26. (c) Wender, P. A. *Chem. Rev.* **1996**, *96*, 1−2.

(2) *Advances in Cycloaddition*; JAI Press: Greenwich, 1994; Vols. 1−3. (b) Dell, C. P. *Contemp. Org. Synth.* **1997**, *4*, 87−117. (c) Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873−3905.

(3) For examples of metal-catalyzed cycloadditions, see: (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081−1119. (b) Frühauf, H.-W *Chem. Rev.* **1997**, *97*, 523−596. (c) Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579−585.

(4) (a) Harmata, M.; Kahraman, M.; Adenu, G.; Barnes, C. L. *Heterocycles* **2004**, *62*, 583−618. (b) Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694−12695. (c) Harmata, M.; Schreiner, P. R. *Org. Lett.* **2001**, *3*, 3663−3665. (d) Lee, J. C.; Cha, J. K. *Tetrahedron* **2000**, *56*, 10175−10184.

(5) (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721. (b) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976−10977. (c) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164−4165. (d) Wender, P. A.; Barzilay, C. M.; Dyckman, A. J. *J. Am. Chem. Soc.* **2001**, *123*, 179−180. (e) Wender, P. A.; Perdersen, T. M.; Scanio, M. J. C. *J. Am. Chem. Soc.* **2002**, *124*, 15154−15155.

(6) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815−7816.

(7) (a) Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8782−8783. (b) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784−8785.

(8) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876−2877.

(9) For recent reviews, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. (b) Hegedus, L. S. *Coord. Chem. Rev.* **1998**, *168*, 149−175. (c) Haughton, L.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2645−2658.

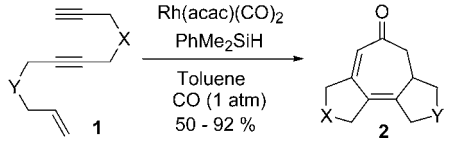
(10) Wender, P. A.; Miller, B. A. *Org. Synth. Theory Appl.* **1993**, *2*, 27−66.

(11) (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834.

10.1021/ol048500a CCC: $27.50
Published on Web 09/09/2004

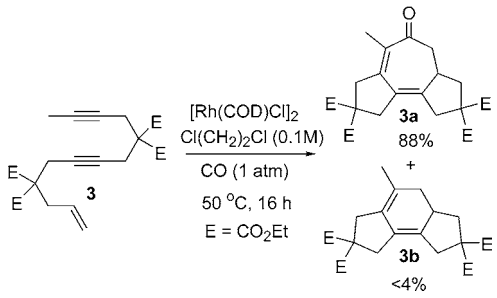
11-ene-1,6-diynes.[12] The reaction of enediynes **1** under CO atomosphere in the presence of a Rh catalyst and $PhMe_2SiH$ (0.5 equiv) afforded the corresponding 5-7-5 ring systems **2** in good to excellent yields. During our studies on

Scheme 1



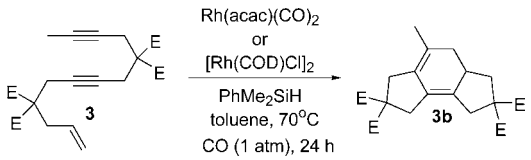
the scope and limitation of the CO-SiCaT reaction, we serendipitously found that the reaction of 1-substituted dodec-11-ene-1,6-diyne **3** catalyzed by $[Rh(COD)Cl]_2$ *in the absence of a hydrosilane* gave carbonylative tricyclization product **3a** in 80% isolated yield accompanied by a small amount of non-carbonylative tricyclization product **3b** (9%). The use of $Cl(CH_2)_2Cl$ as the solvent improved the yield to 88% (with less than 4% of **3b**) (Scheme 2).

Scheme 2



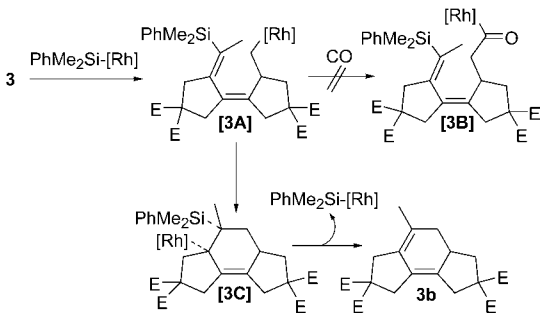
It is worthy of note that the attempted CO-SiCaT reaction of **3** *in the presence of* $PhMe_2SiH$ (0.5 equiv) catalyzed by $[Rh(COD)Cl]_2$ or $Rh(acac)(CO)_2$ afforded the 5−6−5 fused-ring product **3c** exclusively in high isolated yield (70% for $[Rh(COD)Cl]_2$; 96% for $Rh(acac)(CO)_2$) but failed to give **3a**, i.e., no CO insertion (Scheme 3).

Scheme 3



The observed remarkable effects of the terminal methyl group can be ascribed to the substantial steric hindrance in the key intermediate [**3A**], which prevents the CO insertion and promotes the immediate ring closure, followed by β-silylelimination[12] to give **3b**. The results clearly indicate the substantial difference between these two processes, i.e.,

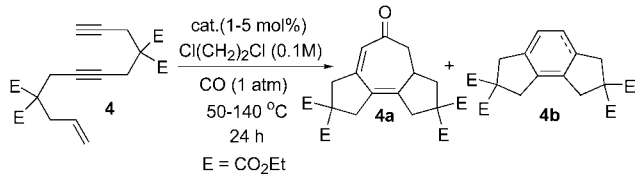
Scheme 4



this $[Rh(COD)Cl]_2$-catalyzed reaction in the absence of a hydrosilane is a novel intramolecular [2 + 2 + 2 + 1] cycloaddition process, which makes a sharp contrast to the CO−SiCaT process, although the same type of products is formed.

Other rhodium, ruthenium, iridium, and cobalt complexes were examined for their catalytic activity using **4** as the substrate in the hope of improving the selectivity (Scheme 5). However, it has turned out that $[Rh(COD)Cl]_2$ is the best

Scheme 5



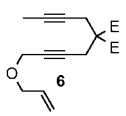
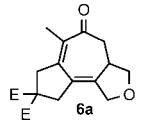
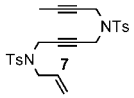
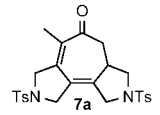
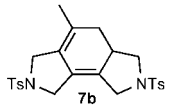
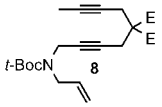
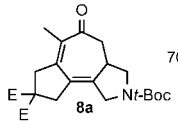
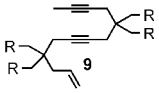
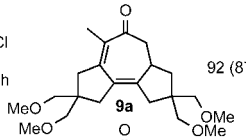
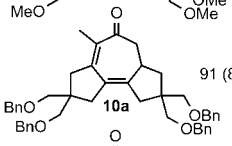
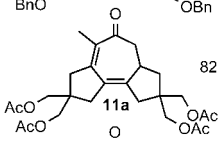
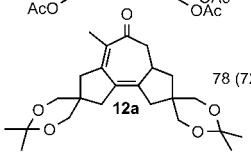
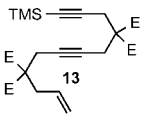
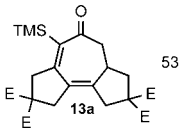
catalyst among those examined so far to date, followed by $[Rh(NBD)Cl]_2$ and $[Rh(CO)_2Cl]_2$. Rh catalysts such as Rh_4CO_{12}, $Rh(acac)(CO)_2$, $[Rh(dppp)(CO)Cl]_2$, $[Cp^*RhCl_2]_2$, $[Rh(COD)_2]SbF_6$, and $Rh(PPh_3)Cl/AgSbF_6$ strongly favored the formation of **4b** accompanied by a small amount of **4a**. Other catalysts, $Co_2(CO)_8-P(OPh)_3$ and $[Ir(COD)Cl]_2$, yielded **4b** exclusively without a trace of **4a**, and $Ru_3(CO)_{12}$ gave a messy mixture.

Scheme 6 illustrates the proposed mechanism of this novel [2 + 2 + 2 + 1] cycloaddition reaction. This reaction is believed to proceed through a series of metallacycles. Thus, the mechanism is clearly different from that of the CO-SiCaT reaction, which is a stepwise process including sequential carbocyclizations.[12]

The proposed mechanism includes (i) selective coordination of the diyne moiety of enediyne **5** to active Rh catalyst species, forming a metallacycle **I** ([2 + 2 + M]), (ii) insertion of the olefin moiety of **5** into the Rh−C bond to form 5-7-5 fused tricyclic rhodacycle **II** ([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 rhoda-

(12) Ojima, I.; Lee, S.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 2385−2386.

Table 1. Rh-Catalyzed Intramolecular [2 + 2 + 2 + 1] Cycloaddition Reactions

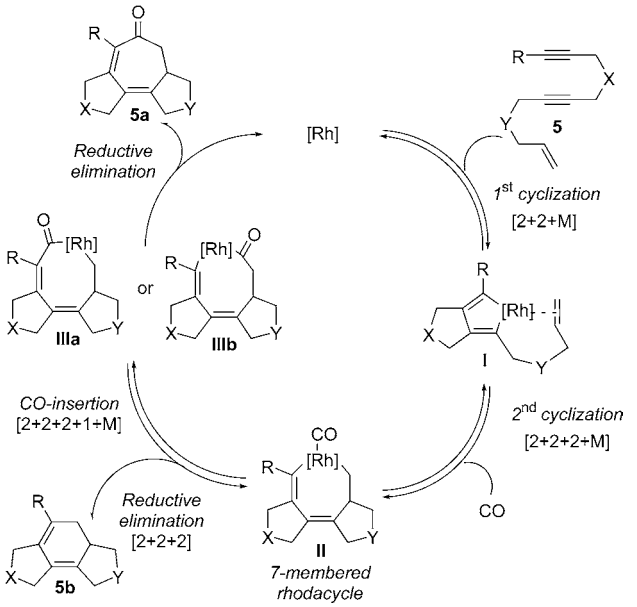
entry	substrate	conditions[1]	product	yield (%)[2,3]
1	 **6**	$Cl(CH_2)_2Cl$[4] 50 °C, 24 h	 **6a**	97 (93)
2	 **7**	$Cl(CH_2)_2Cl$ 50 °C, 22 h	 **7a**  **7b**	84 (83) 13 (11)
3	 **8**	$Cl(CH_2)_2Cl$ 50 °C, 24 h	 **8a**	70 (66)
4	 **9** R = OMe	$Cl(CH_2)_2Cl$ 50 °C, 36 h	 **9a**	92 (87)
5	R = OBn **10**	Toluene 80 °C, 22 h	 **10a**	91 (86)
6	R = OAc **11**	$Cl(CH_2)_2Cl$ 60 °C, 22 h	 **11a**	82 (75)
7	 $OC(CH_3)_2O$ **12**	$Cl(CH_2)_2Cl$ 60 °C, 24 h	 **12a**	78 (72)
8	 **13**	$Cl(CH_2)_2Cl$ 50 °C, 21 h	 **13a**	53 (51)

[1] All reactions were run with 50−100 mg of enediyne ($C = 0.1$ M) under CO (1 atm) using 5 mol % of $[Rh(COD)Cl]_2$. [2] 1H NMR yields using mesitylene as internal standard. [3] Isolated yields based on an average of two runs. [4] Reaction run using 2.5 mol % of $[Rh(COD)Cl]_2$.

cycle **IIIa** or **IIIb** ([2 + 2 + 2 + 1 + M]), and (iv) reductive elimination to form [2 + 2 + 2 + 1] cycloadduct **5a** and regenerate the active Rh catalyst species. Reductive elimination from the 5-7-5 rhodacycle **II**, prior to the CO insertion, gives [2 + 2 + 2] cycloadduct **5b**.

Next, we looked at the heteroatom and functional group tolerance of this novel process. Various enediyne substrates containing ether, sulfonamide, carbamate, ester, and ketal groups were examined. Also, enediynes bearing a methyl and TMS as the substituent of the terminal acetylene moiety were employed. Results are summarized in Table 1.

Scheme 6



These functional groups and heteroatoms are generally well tolerated in this process, affording the desired 5-7-5 fused tricyclic cycloadducts **6a**−**13a** in good to excellent yields. For all tested substrates except for **7** (entry 2) the corresponding [2 + 2 + 2 + 1] adducts are the exclusive products. The reaction of **8** bearing a *t*-Boc-protected amine afforded only 5-7-5 product **8a** with no trace of [2 + 2 + 2] cycloaddition product (entry 3), whereas the reaction of **7** having a *p*-toluenesulfonamide moiety gave a mixture of 5-7-5 (83%) and 5-6-5 (11%) products (entry 2). Although $Cl(CH_2)_2Cl$ is the preferred solvent in most cases, the use of toluene gave better selectivity in some cases. For example, the reaction of **10** in $Cl(CH_2)_2Cl$ gave **10a** in 75% isolated yield, but the yield was improved to 86% when the solvent was changed to toluene (entry 5). Apparently the use of toluene in this case favored the CO insertion process. It was found that free alcohol functionality was not tolerated in this reaction, resulting in very messy mixtures with no trace of the 5-7-5 or 5-6-5 products.

Further studies on the scope of this novel process and its application to organic synthesis are actively underway in these laboratories.

Acknowledgment. This research was supported by grants from the National Institutes of Health (NIGMS) and the National Science Foundation.

Supporting Information Available: Complete characterization data for all new compounds **3**, **6**−**13**, **3a**, **6a**−**13a**, **3b** and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048500A