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Notes

Room Temperature CpCo-Mediated Cyclization of α,*δ*,*ω*-Enediynes to Rearranging Strained Tricylic Dienes. Some Observations of Kinetic versus Thermodynamic Control[†]

J. Kevin Cammack, Satish Jalisatgi, Adam J. Matzger,
Alvin Negrón, and K. Peter C. Vollhardt*

Department of Chemistry, University of California at Berkeley, and Chemical Sciences Division, Lawrence Berkeley Laboratory, Berkeley, California 94720-1460

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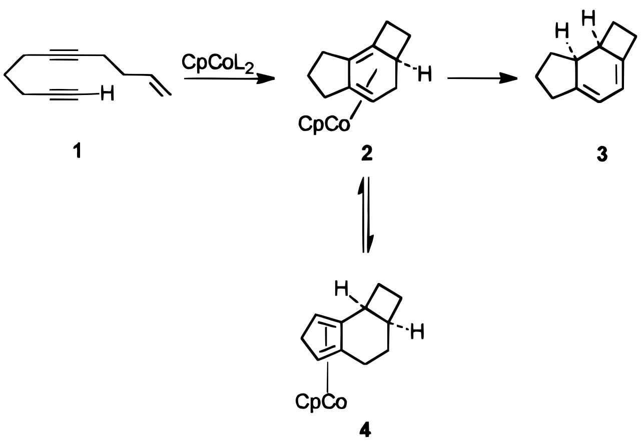
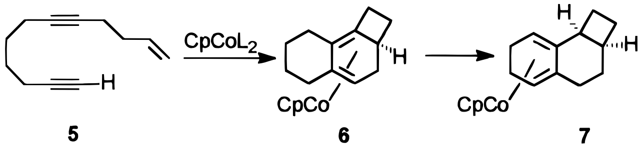
Introduction

As part of a continuing effort to exploit CpCo-mediated [2 + 2 + 2] cycloadditions for the synthesis of complex polycycles of medicinal and theoretical interest,[1] we have reported on unusual cyclizations of the enediynes **1** (Scheme 1) and **5** (Scheme 2) using $CpCo(CO)_2$ in boiling toluene.[2] Under these conditions, the expected cobalt complexes **2** and **6**, respectively, were not isolable, but rather the corresponding rearranged systems **3** (80%) and **7** (88%) were. The former could be shown to be the product of a catalytic conversion of **1**, a facet of the system that was subsequently utilized in a total synthesis of illudol.[3] The double-bond rearrangement of the CpCo-complexed cyclohexadiene units were envisaged to occur via $\eta^4 \rightarrow \eta^2$ shifts followed by *endo*-C−H activation and subsequent regioisomeric hydrogen delivery,[4] in the case of **6** necessitating a transannular CpCo-walk[5] in the intermediate transoid diene before furnishing the evidently thermodynamically more stable **7**. In order to shed further light on these proposed mechanisms, these reactions were repeated at room temperature in the presence of the much more active source of CpCo, $CpCo(CH_2{=}CH_2)_2$.

Scheme 1



Scheme 2



Results and Discussion

The "Jonas catalyst" ($CpCo(CH_2{=}CH_2)_2$), is made by the reductive association of ethene with cobaltocene in the presence of potassium and subsequent crystallization at −78 °C.[6] We have slightly modified this procedure (seeExperimental Section) to provide an alternative for those who find the original purification procedure difficult. When **1** was treated with equimolar amounts of this cobalt complex at room temperature, the originally postulated initial [2 + 2 + 2] cycloaddition product **2** was formed in 90% yield. The efficiency and complete stereoselectivity of this process are remarkable, considering the strain inherent in **2**, the multitude of alternative pathways that are possible,[1,4,7] and the observation that related enediyne cyclizations frequently lead to both stereoisomeric dispositions of the metal relative to the chiral tricyclic diene ligand.[8] The structural assignment of **2** initially relied on the spectral and analytical data. Particularly diagnostic are the NMR spectra.[8] Thus, the four signals at δ 3.06 (bd, $J = 5.1$ Hz, 1H), 1.59 (m, 1H), 1.22 (m, 1H), and −0.43 (dd, $J = 11.7$, 7.5 Hz, 1H) in the ^{1}H NMR measurement are consistent with those of the 2,3,4,5-bis-fused metalated cyclohexadiene center of **2**. This topology is confirmed by the carbon peaks at δ = 95.4, 93.0, 71.3, and 55.2 for the diene unit, a tertiary carbon resonating at δ = 44.1, and the appropriate number of additional signals. However, in light of the mobility of the complexed cyclohexadiene hydrogens in this system, an alternative isomeric structure with a dimethylenecyclobutane subunit could not be excluded on the basis of the available data. Because of this ambiguity, the dearth of structural information in the

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[†] Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

[1] For reviews, see: (a) Malaska, M.; Vollhardt, K. P. C. In *Advances in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Harwood Academic: Chur, Switzerland, 1992; p 53. (b) Vollhardt, K. P. C. *Lect. Heterocycl. Chem.* **1987**, *9*, 59. (c) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. For most recent work, see: (d) Boese, R.; Matzger, A. J.; Mohler, D. L.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1478. (e) Boese, R.; Harvey, D. F.; Malaska, M. J.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1994**, *116*, 11153. (f) Boese, R.; Van Sickle, A. P.; Vollhardt, K. P. C. *Synthesis* **1994**, 1374. (f) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487.

[2] Duñach, E.; Halterman, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1985**, *107*, 1664.

[3] Johnson, E. P.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381.

[4] For related CpCo-mediated prototropisms, see: (a) King J. A., Jr.; Vollhardt, K. P. C. *J. Organomet. Chem.* **1993**, *460*, 91. (b) (η^4-*exo*-5-Deuterio-1,3-cyclohexadiene)CpCo undergoes exclusive *endo*-H-shifts on thermolysis (King, J. A.,, Jr. Ph.D. Thesis, University of California, Berkeley, 1983).

[5] King Jr., J. A.; Vollhardt, K. P. C. *J. Organomet. Chem.* **1989**, *369*, 245.

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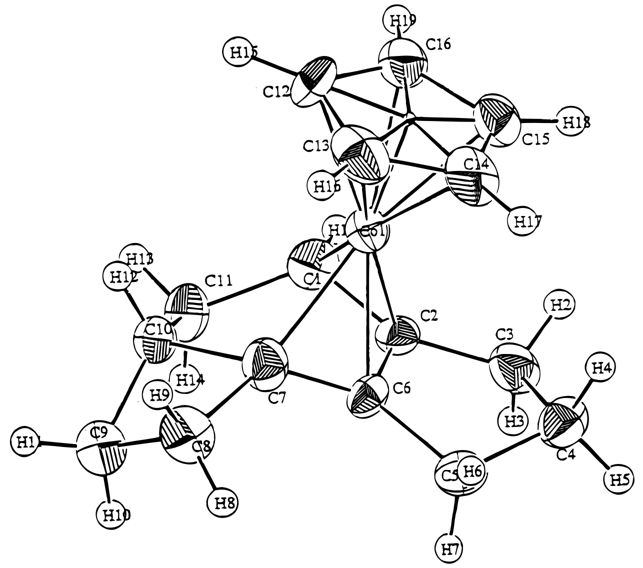
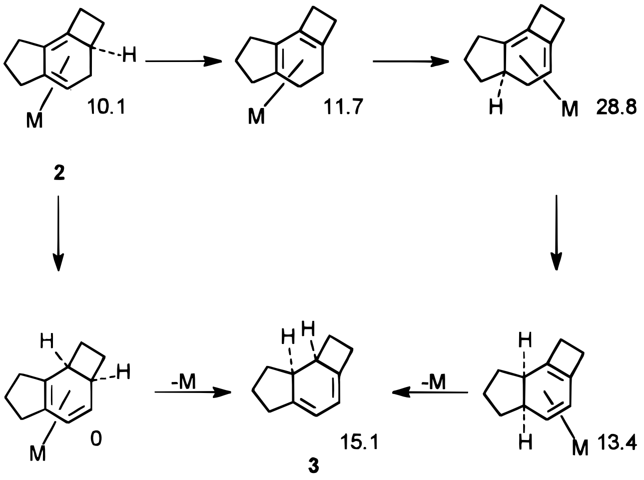


Figure 1. Molecular structure of **2** in the crystal.

Scheme 3. Two Pathways of Rearrangement of 2 to 3 and MM2-Calculated Relative Heats of Formation of the Diene Ligands (kcal mol−^{1}, M = CpCo)



series,[8] and the interesting nature of the ligand, an X-ray structural investigation was performed (Figure 1).[9] Apart from confirming the connectivity of the atoms in **2**, it also highlights the distortion of the carbon frame necessary to accommodate the strained link [C7,8,9,10 in Figure 1; torsion angle −22.8(6)°]. The two *endo*-hydrogens (H12 and H13 in Figure 1) which are migrating on route to **3** are at distances of 2.93 and 3.57 Å, respectively, from the metal. To confirm that **2** can indeed function as an intermediate in the catalytic conversion of **1** to **3**, **2** was heated in the presence of CO at 140 °C (C_6H_6, sealed tube) to give **3** (55%) and $CpCo(CO)_2$. Compound **2** also acts as a catalyst in the cyclization of **1** to **3** (72%) under the conditions originally employed with $CpCo(CO)_2$.[2]

The rearrangement of **2** to the free diene **3** can be envisaged to proceed by either or both of the pathways in Scheme 3, in which the relative heats of formation of the diene ligands calculated by MM2 are given below each structure. It is interesting to note that **3** is clearly not the most stable isomer that could be produced from this manifold and that its generation is of kinetic origin. Monitoring the thermolysis of **2** that leads to **3** at lower temperatures by NMR allowed the detection of signals of at least two new sensitive diene complexes, one of which was present almost exclusively after heating **2** at 80 °C for 16 h and was purified by chromatography on alumina. Surprisingly, the NMR data immediately ruled out the generation of any of the topologies depicted in Scheme 3. Thus, there were no signals in the regions diagnostic of internal diene−CH units and the DEPT technique revealed only two quaternary carbons at δ = 97.7 and 96.2, four tertiary carbons at δ = 36.9, 35.3, 35.0, and 33.9 (in addition to the Cp signal at δ = 79.8), and five methylene carbons at δ = 40.8, 29.7, 25.5, 22.1, and 21.8. Indeed, inspection of the ^{1}H NMR spectrum and comparison with that of **7**[2] suggested formation of the lower homolog **4** (Scheme 1), especially when appropriate corrections were made for the chemical shift changes that are expected when replacing cyclohexadiene[8] with cyclopentadiene[10] as the ligand to CpCo. Two-dimensional NMR correlation experiments (COSY and heteronuclear multiple-quantum coherence techniques) confirmed the structure assigned for **4**. In particular, they allowed the identification of the characteristic proton signals for the metal-bound cyclopentadiene segment at δ = 2.37 (m, alkenyl), 2.12 (m, methylene, H_{exo}), and 2.45 (m, methylene, H_{endo}). While **4** extrudes the rearranged ligand **3** under the same conditions that were used to liberate the latter from **2**, it appears reasonable to assign **4** the function of a mechanistic bystander as shown in Scheme 1, being in equilibrium with perhaps the regiochemically more direct precursor of **3**, namely **2**. Relative to its isomers, the ΔH_f of the free cyclopentadiene ligand in **4** is −0.8 kcal mol^{-1}, in accord with the observed results, although the binding energies to the metal could vary sufficiently to make the suggested order of stability tentative, at best.

Reaction of **5** with $CpCo(CH_2{=}CH_2)_2$ under the same conditions that led to **2** from **1** furnished cleanly the complex **6** in 92% yield, thus establishing its potential intermediacy in the higher temperature conversion of **5** to **7**.[2] This was confirmed by heating **6** (C_6H_6, 70 °C, 11h) to result in **7** in 87% yield without any detectable intermediates. The assigned structure of **6** is consistent with its NMR spectra, which are very similar to those of **2**. In particular, the three signals at δ = 2.81 (dd, J = 5.4, 1.2 Hz, 1H), 1.18 (ddd, J = 12.1, 9.4, 5.4 Hz, 1H), and −0.39 (ddd, J = 12.1, 7.8, 1.2 Hz, 1H) in the ^{1}H NMR spectrum are readily recognized as the single vinyl hydrogen and the *endo*- and *exo*-protons of the methylene group in the complexed cyclohexadiene, respectively. The carbon spectrum reveals signals at δ = 90.5, 86.4, 72.6, and 56.1 for the diene moiety and a tertiary carbon resonance at δ 48.2.

In summary, the occurrence of unusually facile H-shifts in the CpCo-mediated cyclizations of enediynes **1** and **5** has been established to proceed via the intermediacy of the expected intramolecular [2 + 2 + 2] cycloaddition products **2** and **6**. The ease of isomerization in these systems relative to others[1,8] suggests that strain activation of the initial tricyclic diene system is responsible for the observed chemistry. The results suggest the exertion of caution in the synthetic planning and interpretation

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[9] The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

[10] Szajek, L. P.; Shapley, J. R. *Organometallics* **1991**, *10*, 2512.

of spectral data obtained in cobalt-mediated enediyne cyclizations. Finally, we note that the “uphill” (with respect to diene ligand) conversion of **2** to **3** is another example of transition-metal-mediated “contrathermodynamic” diene isomerization,[11] obviously driven by the external ligand-induced decomplexation step.

Experimental Section

General. Current experimental standard procedures, descriptions of all analytical instruments, spectral data formats, and calibrations have been summarized recently.[12]

(η^5-Cyclopentadienyl)bis(ethene)cobalt. In a glovebox, thin potassium flakes (453 mg, 11.6 mmol) were cut with a razor blade and placed in a Schlenk flask containing Cp_2Co (1.94 g, 10.3 mmol). The flask was removed from the glovebox and, under an argon atmosphere, cooled to −20 °C using a circulating bath. Freshly distilled ether (40 mL) was added, the stirred mixture was maintained at −20 °C, and the argon was replaced by ethene. A slow constant flow of the latter was maintained for 24 h. Subsequently, the volatiles were removed under high vacuum while the temperature of the solution was kept at −20 °C. The solid residue was triturated with freshly distilled pentane (3 × 20 mL), and the resulting slurry was filtered each time by positive pressure filtration through a syringe needle. The combined extracts were cooled to −20 °C, the volatiles were removed under high vacuum, and the residue was sublimed under high vacuum (10^{-3} mm) on to a cold finger (−15 °C) to give red-orange crystals (1.05 g, 58%): mp 65−67 °C (sealed capillary); ^1H NMR (300 MHz, C_6D_6) δ 4.29 (s, 5H, Cp), 2.53 (6 lines, 2H), 0.66 (6 lines, 2H). Calculated by spectral simulation: $J_{trans} = 14$ Hz, $J_{cis} = 9.5$ Hz, $J_{gem} = 0.4$ Hz.

(Tricyclo[6.3.0.0^{2,5}]-1,7-undecadiene)(cyclopentadienyl)cobalt (2). To a solution of 10-undecene-1,6-diyne (**1**) (82.5 mg, 0.564 mmol) in freshly distilled THF (5 mL) at rt was added, via cannula, a solution of $CpCo(C_2H_4)_2$ (99.4 mg, 0.564 mmol) in freshly distilled THF (5 mL). The resulting mixture was stirred for 1 h, the volatiles were removed in vacuo, and the residue was chromatographed over Al_2O_3 (activity 3, degassed hexanes) under N_2. A fast moving red band gave **2**, which was crystallized from hexane to give red plates (0.137 g, 90%): mp 146−147 °C dec; ^1H NMR (300 MHz, C_6D_6) δ 4.43 (s, 5H, Cp), 3.06 (bd, $J = 5.1$ Hz, 1H, H-7), 1.93−2.68 (m, 10H), 1.58 (m, 1H), 1.22 (m, 1H, H-6 *endo*), −0.43 (dd, 1H, $J = 11.7$, 7.5 Hz, H-6 *exo*); $^{13}C\{^1H\}$ (75 MHz, C_6D_6) δ 95.4, 93.0, 79.7 (Cp), 71.3, 55.2 (C-7), 44.1 (C-5), 33.7, 33.4, 32.4, 29.7, 24.5, 23.3; IR (neat) 3030 (w), 2947 (s), 2922 (s), 2836 (m), 2722 (w), 1428 (w), 1106 (w), 1004 (w), 915 (w), 787 (w) cm^{-1}; MS (EI) *m/z* 270 (M^+, 100), 269 (19), 268 (28), 267 (57), 253 (60), 239 (65), 200 (76), 124 (63); HRMS calcd for $C_{16}H_{19}Co$ 270.0819 found 270.0814. Anal. Calcd for $C_{16}H_{19}Co$: C, 71.11; H, 7.09. Found: C, 70.98; H, 7.40.

(Tricyclo[6.3.0.0^{2,5}]-8,11(1)-undecadiene)(cyclopentadienyl)cobalt (4). A solution of complex **2** (310 mg, 1.14 mmol) in C_6H_6 (20 mL) was heated to reflux for 16 h. The solvent was removed, and the resulting oil was subjected to chromatography on neutral alumina (activity 4, hexanes) to yield **4** (205 mg, 66%) as a red oil: ^1H NMR (300 MHz, C_6D_6) δ 4.48 (s, 5H, Cp), 2.75 (m, 2H, H-7, H-10), 2.58 (dt, $J = 13.0$, 2.3 Hz, 1H, H-6 *exo*), 2.45 (m, 1H, H-10 *endo*), 2.13−2.42 (m, 4H), 2.0−2.12 (m, 3H), 1.6−1.9 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, C_6D_6) δ 97.7, 96.2, 79.8 (Cp), 36.9, 35.3, 35.0, 33.9, 29.7, 25.5, 22.1, 21.8; IR (neat) 3096 (w), 2921 (s), 2837 (m), 2727 (s), 1623 (w), 1436 (m), 1358 (m), 796 (s) cm^{-1}; MS (EI) *m/z* 270 (M^+, 89), 269 (100), 241 (79), 215 (62), 202 (32), 175 (32), 174 (32), 124 (47), 115 (38); HRMS calcd for $C_{16}H_{19}Co$ Found 270.0808. Anal. Calcd for $C_{16}H_{19}Co$: C, 71.11; H, 7.09. Found: C, 71.07, H, 7.38.

(Tricyclo[6.4.0.0^{2,5}]-1,7-dodecadiene)(cyclopentadienyl)cobalt (6). To a solution of 11-dodecene-1,7-diyne (**4**) (60.3 mg, 0.376 mmol) in freshly distilled THF (5 mL) at rt was added, via cannula, a solution of $CpCo(C_2H_4)_2$ (66.3 mg, 0.376 mmol) in freshly distilled THF (5 mL). The resulting mixture was treated as in the preparation of **2** to give a red oil of **6** (98 mg, 92%): ^1H NMR (300 MHz, C_6D_6) δ 4.45 (s, 5H, Cp), 2.81 (dd, $J = 5.4$, 1.2 Hz, 1H, H-7), 2.68 (m, 1H), 2.56 (dd, $J = 9.3$, 5.4 Hz, 1H), 2.38 (m, 2H), 1.71−2.17 (m, 7H), 1.58 (m, 2H), 1.18 (ddd, $J = 12.1$, 9.4, 5.4 Hz, 1H, H-6 *endo*), −0.39 (ddd, $J = 12.1$, 7.8, 1.2 Hz, 1H, H-6 *exo*); $^{13}C\{^1H\}$ NMR (75 MHz, C_6D_6) δ 90.5, 86.4, 80.4 (Cp), 72.6, 56.1 (C-7), 48.2 (C-6), 32.9, 32.3, 29.9, 25.6, 24.2, 23.5, 22.7; IR (neat) 3030 (w), 2923 (s), 2840 (m), 1432 (w), 1106 (w), 1002 (w), 788 (w) cm^{-1}; MS (EI) *m/z* 284 (M^+, 100), 282 (21), 280 (45), 252 (40), 214 (57), 187 (67), 124 (60); HRMS calcd for $C_{17}H_{21}Co$: 284.0975, Found 284.0976. Anal. Calcd for $C_{17}H_{21}Co$: C, 71.82; H, 7.45, Found: C, 71.57; H, 7.15.

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