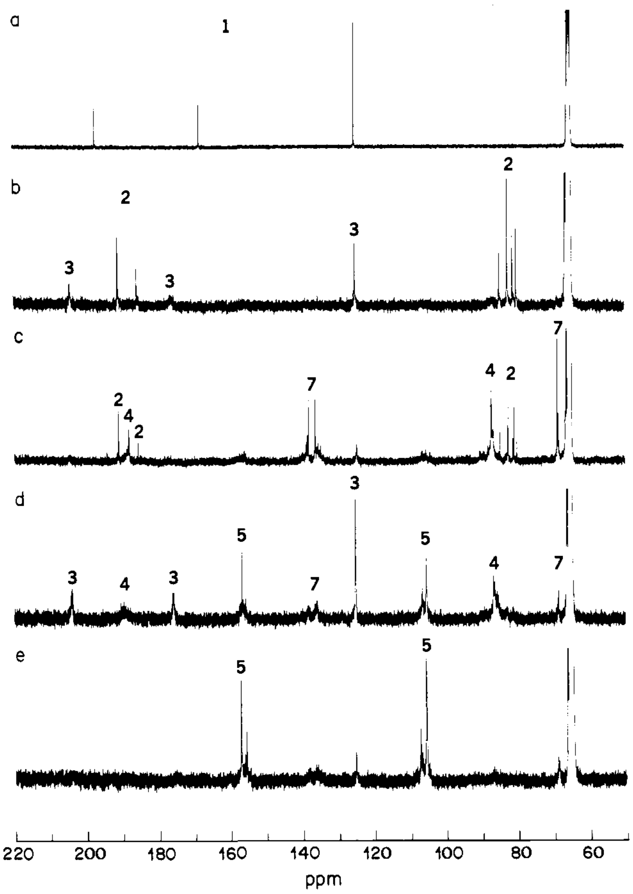
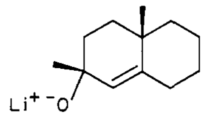


Figure 1. ^{13}C NMR spectra (220 to 50 ppm vs TMS) in diethyl ether-d_{10}: a. 10-methyl-$\Delta^{1,9}$-2-octalone (**1**) (−78 °C); b. $(Me_2CuLi)_2$ + **1** (2 equiv, −78 °C) gives rise to **2** and **3**; c. $(Me_2CuLi)_2$ + **1** (1 equiv, −78 °C) yields **4** and **7** in addition to **2**; d. $(Me_2CuLi)_2$ + **1** (2 equiv, −50 °C for ~0.2 h) shows **3–5** and **7**; e. $Me_2CuLi{\cdot}LiI$ + **1** (1 equiv, −50 °C for 1.5 h) affords **5a** and a minor amount of regioisomeric enolate.

The third new species has olefin resonances at 136.2 (J_{CH} = 148 Hz) and 138.1 ppm and a singlet at 68.9 ppm attributable to a quaternary C bearing an OLi substituent, consistent with 1,2-adduct **7**.[10] Product **7** appears immediately, before the 1,4-adduct **5** appears; therefore, **5** and **7** are not the result of partitioning a π-allylcuprate(III) intermediate such as **8** between alkylation at C-2 and C-9 (octalone numbering).



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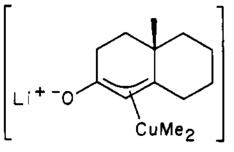

8

With 1 equiv of $Me_2CuLi{\cdot}LiI$, an enolate (157.1, 105.6 ppm, Figure 1e) is observed at −50 °C along with minor amounts of regioisomeric enolate (155.6, 107.2 ppm),[11] since the reaction is slow under our conditions. Following House and Wilkins,[11c] we believe the primary product from $Me_2CuLi{\cdot}LiI$ and **1** to be the Li enolate **5a**; however, its precise nature remains to be established. With 1 equiv of **1** and halide-free $(Me_2CuLi)_2$, the conversion of **4** to enolate mixture **5** occurs at a significant rate when the temperature is increased to −60 °C.[12] Under these conditions **5** increases monotonically at the expense of **3** and **4** (Figure 3, supplementary material). With 2 equiv of **1**, the temperature must be raised to −50 °C for **5** to appear at an appreciable rate.

If a mixture of cuprate and **1** (i.e., **2** and **3**) that has been kept at −78 °C for as long as 1 h is quenched (aqueous NH_4Cl), **1** is recovered quantitatively. Workup of the reaction mixtures after warming yields a single 1,4-addition product, *cis*-9,10-dimethyl-2-octalone and minor amounts of 1,2-product.[10]

House and Umen[13,14] proposed that the reaction of α,β-unsaturated ketones with organocuprates such as $(Me_2CuLi)_2$ proceeds by single electron transfer to give an organic radical anion and an oxidized cuprate cluster, which combine to form a σ-allylcuprate(III) (e.g., **6**) without the intermediacy of copper–olefin complexes. They stated, "Although various π-complexes of the enone and cuprate might be envisioned to precede either process [electron transfer or nucleophilic addition[15]], we are aware of no compelling evidence for their presence...".[13] The ^{13}C NMR observations reported herein constitute compelling evidence for h^2-olefin cuprate and Li-coordinated copper–olefin complexes (**2** and **4**, respectively) on the mechanistic pathway of the conjugate addition reaction of $(Me_2CuLi)_2$ and **1**. Since the reaction conditions used in this study are typical of organocuprate conjugate additions, our results are deemed to be particularly relevant to the general synthetic reaction.

Acknowledgment. We thank Dr. Peter Mirau (AT&T Bell Laboratories) for helpful advice concerning NMR spectroscopy and Dr. J. San Filippo (Rutgers University) for useful suggestions about the preparation of lithium dimethylcuprate.

Supplementary Material Available: Experimental details and figures giving ^{13}C NMR spectra of $(Me_2CuLi)_2$ + **1** in diethyl ether-d_{10} (3 pages). Ordering information is given on any current masthead page.

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(10) The major product from the addition of 1 equiv of MeLi to **1** has peaks at 68.8, 133.9, and 141.3 ppm. Upon quenching (aqueous NH_4Cl) GLC analysis revealed that for a 1:1 ratio of $(Me_2CuLi)_2$:**1**, the yield of 1,2-product was 25%. For a 1:2 ratio of $(Me_2CuLi)_2$:**1** it was 10%, and for a 1:1 ratio of $Me_2CuLi{\cdot}LiI$:**1** it was 5%.

(11) For typical enolate ^{13}C NMR shifts: (a) House, H. O.; Prabhu, A. V.; Phillips, W. V. *J. Org. Chem.* **1976**, *41*, 1209. (b) Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954. (c) For a good model: House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1976**, *41*, 4031.

(12) A number of peaks (104.4, 104.6, 105.2, 157.2, 158.1, and 158.2 ppm) close to those of **5a** are attributable to Cu enolates **5b**, where the Cu atoms are part of different aggregates. Minor peaks in the enolate region (e.g., 105.4, 105.9, 106.6; 156.0, 156.8, and 157.3 ppm) may be due to regioisomeric Cu enolates corresponding to the regioisomeric Li enolate.

(13) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893.

(14) See also: (a) House, H. O.; Fischer, W. F. *J. Org. Chem.* **1968**, *33*, 949. (b) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

(15) Casey, C. P.; Cesa, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4236.

A Highly Efficient Eight-Membered-Ring Cyclization for Construction of the Taxane Carbon Framework

Yoshiaki Horiguchi, Takashi Furukawa, and Isao Kuwajima*

Department of Chemistry
Tokyo Institute of Technology
Meguro, Tokyo 152, Japan

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Members of the taxane family with their unique tricyclo[9.3.1.$0^{3,8}$]pentadecane skeleton[1] and important biological activities[2] have become important targets in synthetic organic chem-

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(1) Review: Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425. Taxusin: (a) Miyazaki, M.; Shimizu, K.; Mishima, N.; Kurabayashi, M. *Chem. Pharm. Bull.* **1968**, *16*, 546. (b) Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W.; Bjamer, K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1966**, 923. Taxol: (c) Wani, M. C.; Taylor, M. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325. (d) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr. *J. Org. Chem.* **1981**, *46*, 1469.

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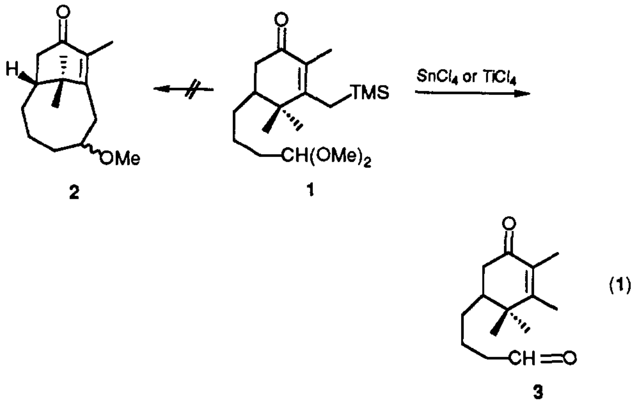
istry.[3] A total synthesis of taxusin has recently been described by Holton et al.[4]

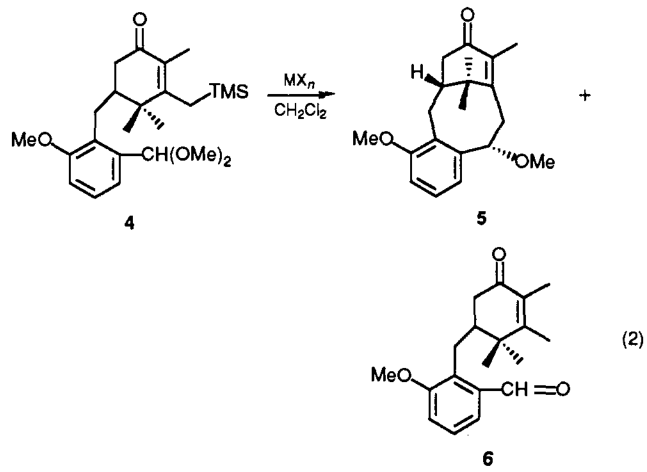
We previously reported the condensation reaction of acetals with cyclic enones bearing (trimethylsilyl)methyl groups at their 3-positions;[5] under the influence of $SnCl_4$, the condensation occurs exclusively at the methylene site bearing the trimethylsilyl (TMS) group. We have investigated an intramolecular version of such a transformation with the hope of developing a useful method for construction of a taxane B ring. Initially, we examined the reaction of substrate **1**[6] under the influence of $SnCl_4$. In order to exclude the possibility of intermolecular condensation, the reaction was attempted under conditions of dilute concentration (0.01 M) at room temperature, but the desired product **2** was not obtained; only the parent aldehyde **3** was formed.



(1)

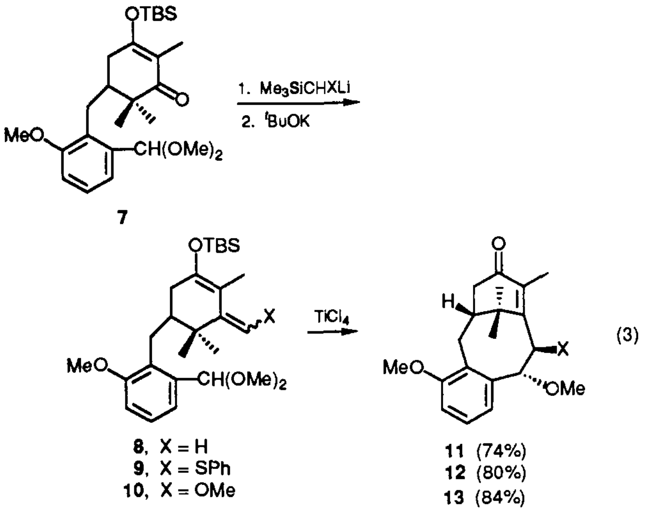
Under similar dilute reaction conditions at room temperature, the cyclization of **4**,[6,7] containing an aromatic ring which corresponds to the C ring of taxane,[8] occurred in the presence of $SnCl_4$ or $TiCl_4$ (CH_2Cl_2, room temperature, 19 h) to give **5**[8] in 15–17% yield, but the major product was the parent aldehyde **6** arising from removal of silyl and acetal groups. Further, a prolonged reaction period or the use of an excess amount of a Lewis acid resulted in the disappearance of **5**, accompanied by the exclusive formation of **6**.

These results suggest that the cyclization initially takes place to yield **5**, but it readily undergoes ring opening to give **6** under the reaction conditions. Indeed, on treatment with $TiCl_4$ in CH_2Cl_2, **5** was quickly converted to **6** at room temperature. We found that when the reaction was conducted at 0.1 M and at a reaction temperature as low as possible, the desired cyclization could be effected in good yield. Thus, the reaction of **4** with $TiCl_4$ (1.1 equiv) at −23 °C for 2 h gave **5** in 40% NMR yield, whereas $SnCl_4$ failed to induce the cyclization at that temperature. Interestingly, use of a mixture of $TiCl_4$ (1.1 equiv) and $SnCl_4$ (1.1 equiv) greatly improved the yield of **5** (73% NMR and 58% isolated yield). Further, ^1H NMR spectra indicated that **5** is obtained as a single stereoisomer. The structure has been reasonably assigned as **5**, bearing a methoxy group below the face of the eight-membered ring, on the basis of the comparison of two transition states as well as the thermodynamic stability[9] of each isomer.



(2)

For introduction of another requisite oxygen functional group on the position corresponding to C-10, enol silyl ethers **8**–**10** were prepared from **7**, and their cyclization reactions were also investigated. On treatment with $TiCl_4$ (1.1 equiv) at low temperature, these dienol silyl ethers readily underwent cyclization to afford the corresponding eight-membered products **11**–**13** in excellent isolated yields. Remarkable stereocontrol has been observed in these cyclization reactions also: Peterson reaction of siloxy enone **7** gave **9** as a 1:1 mixture of *E* and *Z* isomers, but cyclization of this mixture resulted in the formation of **12** as a single stereoisomer.[10] Further, the reaction of **10**[11] at −78 °C initially gave a mixture of two stereoisomers,[12] but when the reaction temperature was raised to −25 °C, the cis isomer disappeared and the trans isomer **13**[13] was obtained as a single product in 84% isolated yield. The stereochemical relationships between the vicinal methoxy and X groups of **12** and **13** have been confirmed as trans configurations by their ^1H NMR spectra.[10,12] Furthermore, X-ray crystallographic analysis has verified the structure of **12**.



(3)

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[4] Holton, R. A.; Kim, J. H.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

[5] Hatanaka, Y.; Kuwajima, I. *J. Org. Chem.* **1986**, *51*, 1932.

[6] Both **1** and **4** were prepared in good yields from the corresponding cyclohexane-1,3-diones by the method recently developed in our laboratory. Horiguchi, Y.; Kataoka, Y.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 3327.

[7] The requisite 5-substituted 4,4-dimethylcyclohexane-1,3-dione was prepared in good overall yield by the following procedures: (1) a cross-coupling of ortho-lithiated *m*-methoxybenzaldehyde dimethyl acetal with 6-bromo-4-hexen-3-yl acetate, (2) hydrolysis (K_2CO_3 in aqueous MeOH) and oxidation (PCC/NaOAc), (3) conjugate addition of lithiated isobutyric ester, and (4) cyclization with KO^{t}Bu.

[8] Synthesis and conformation studies of C-aromatic taxanes: Shea, K. J.; Gilman, J. W. *Tetrahedron Lett.* **1984**, *25*, 2451; *J. Am. Chem. Soc.* **1985**, *107*, 4791. Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953.

[9] Severe steric repulsion of the methoxy group with both methyl and methylene groups may greatly disfavor the cyclization leading to the stereoisomer bearing a methoxy group above an eight-membered ring. Further, MM2 calculation has shown **5** to be more stable than the isomer by ca. 2.3 kcal/mol. Thus, on both kinetic and thermodynamic grounds, the formation of **5** should predominate over the other.

[10] Two methine protons appear at 4.53 and 4.86 ppm with coupling constant J = 10.9 Hz.

We suggest that the cyclization of **9** and **10** may initially form two stereoisomers, but the less stable cis product undergoes ring opening, and the thermodynamically more stable **12** and **13** are formed exclusively[14] through equilibration.

The present reaction has provided a powerful method to resolve two of the most challenging problems for taxane synthesis: (1) an efficient cyclization of an eight-membered-ring system and (2) complete stereocontrol of two functional groups corresponding to the C-9 and C-10 positions. We are currently pursuing a total synthesis of taxusin and taxinine by applying this methodology.

Acknowledgment. This work was partially supported by grants from the Ministry of Education, Science, and Culture of the Japanese Government. We are also indebted to Prof. H. Suzuki of this Institute for the X-ray crystallographic analysis of **12**.

Supplementary Material Available: Preparation of the starting materials, discussions on the transition states which control the stereochemistry, experimental details on cyclization reactions, and an ORTEP drawing and bond lengths and dihedral angles of typical parts of **12** (9 pages). Ordering information is given on any current masthead page.

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(11) A subsequent treatment of the siloxy enone **7** with $Me_3SiCH(OMe)Li$ and with ^tBuOK gave **10** (Z:E = 82:18), which, on treatment with $TiCl_4$ at −78 °C for 15 min, gave a mixture of **13** and its cis isomer in 64 and 16% yields, respectively, but when a similar reaction was performed at −78 °C for 45 min and then at −25 °C for 45 min, **13** was obtained exclusively.

(12) Two protons corresponding to C-9 and C-10: **13**, 4.52 and 4.83 (J = 10.0 Hz); the cis isomer, 4.60 and 4.80 (J = 5.8 Hz).

(13) Overall yield of **13** from *m*-methoxybenzaldehyde dimethyl acetal was about 35%.

(14) It has been confirmed by a separate experiment that the cis isomer undergoes isomerization to **13** under similar reaction conditions. By MM2 calculation, the trans isomer **13** has been estimated to be ca. 2.2 kcal/mol more stable than the cis isomer.

A New Coordination Mode for CO. Synthesis and Structure of $Cp_4Mo_2Ni_2S_2(\eta^1,\mu_4\text{-}CO)$

Ping Li and M. David Curtis*

Department of Chemistry
The University of Michigan
Ann Arbor, Michigan 48109-1055

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Coordination modes of CO in organometallic compounds have long served as models of catalytic activation of CO and of coordination of CO on metal surfaces.[1-3] A variety of CO coordination types (η^{1-2},μ_{1-3}) have been recognized either in organometallic compounds or on surfaces of catalysts. However, the only μ_4-CO ligands known are also bonded to the metal framework through the oxygen atom (μ_4,η^2-CO).[4]

In this paper, we report a new sulfido bimetallic cluster, $Cp_4Mo_2Ni_2S_2(CO)$ (**2**), which contains an unprecedented η^1,μ_4-CO ligand, which may serve as a model of CO coordinated in the 4-fold hollows of the 110 surfaces of face-centered cubic (fcc) metals. EHMO calculations support the η^1,μ_4-coordination assignment.

Cluster **2** was synthesized in ca. 20% yield from the reaction of a 1:1 molar ratio of *trans*-$Cp_2Mo_2(SMe)_2(CO)_2$ (**1**) and Cp_2Ni in a refluxing toluene solution (eq 1). The reaction is similar to those we have recently reported for sulfido Mo/late-transition-metal carbonyl clusters, $Cp_2Mo_2M'_{2-3}S_{2-4}(CO)_x$.[5] Compound **2** was characterized by X-ray crystallographic analysis[6] and other spectroscopic methods. ^1H NMR spectra gave two equal-intensity peaks for Mo and Ni cyclopentadienyl (Cp) rings at 6.00 and 5.05 ppm in $CDCl_3$. Mass spectra obtained by electron-impact ionization displayed peaks at 662 $[P]^+$ and 634 $[P-CO]^+$. Anal. ($C_{21}H_{20}Mo_2Ni_2OS_2$) C, H, S. Calcd: 38.11, 3.05, 9.69. Found: 38.19, 3.14, 10.21.

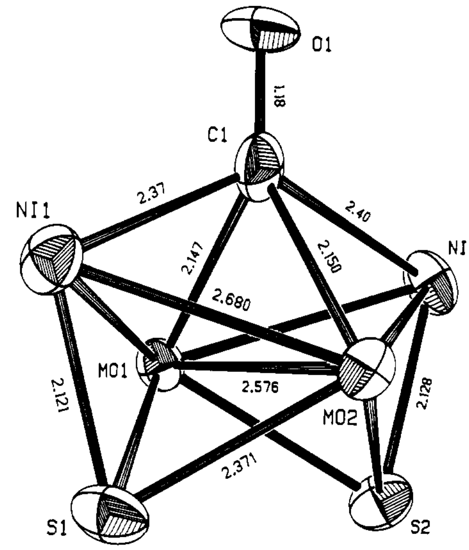
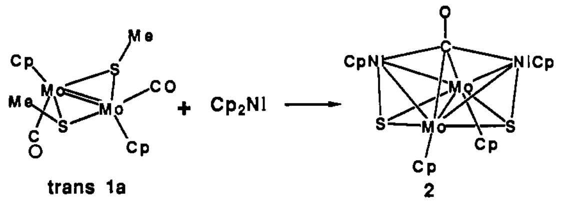


Figure 1. ORTEP plot (50% probability thermal ellipsoids) for the framework structure of $Cp_4Mo_2Ni_2S_2(CO)$.



(1)

The geometrical arrangement of the core (see Figure 1) may be described either as a bicapped trigonal bipyramid with Ni atoms at apex positions and Mo and C atoms in equatorial positions (the carbonyl carbon is regarded as a normal vertex member) or as a butterfly cluster with the carbonyl group bonded to the hinge Mo and wingtip Ni atoms. The Mo–Mo bond distance, 2.576 Å, is shorter than those (2.64–2.67 Å) found in geometrically similar clusters.[5,7,8] The CO ligand is equidistant from both Ni atoms within experimental error. The η^1-CO model is supported by the long Ni–O distances ($d_{Ni-O} > 3.03$ Å) and the unbent CO: the angle between O, C, and the centroid of the Mo–Mo bond is approximately 180°.

The η^1,μ_4-CO assignment is indicated also by the extremely low CO stretching frequency in both the solid state (1654 cm^{-1} in a KBr pellet) and in solution (1653 cm^{-1} in THF) (cf. ν(CO) $\sim$ 1850 cm^{-1} for μ_2-CO and $\sim$1740–1720 cm^{-1} for μ_3-CO). However, the long Ni–CO distances (average 2.39 Å) suggest only a small bonding interaction between the Ni atoms and the carbonyl group. In related cyclopentadienyl Ni dimers and trimers,[9,10] Ni–CO distances average 1.85–1.87 Å for μ_2-CO and 1.93–2.03 Å for μ_3-CO. Since the Ni–CO distance increases with increasing connectivity of the μ_n-CO, a Ni–μ_4-CO distance of 2.39 Å is reasonable. A very long Fe–CO distance (2.63 Å) was also observed in an η^1,μ_3-CO coordination mode.[7,11]

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(6) Crystallographic data for **2**: orthorhombic space group $P2_12_12_1$; a = 9.811 (2) Å, b = 16.106 (5) Å, c = 13.417 (2) Å; Z = 4; R = 0.033.

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