Table I. The Reactions of 1 with Organocuprates

n	X	Cuprate	Pentane-ether ratio	2	3	4	5	6
4	Br	n-Bu	10:1	79	13	1	5	3
4	Br	n-Bu	1:1	33	5	51	3	2
4	Br	n-Bu	1:7	15	4	78	–	–
4	Br	n-Bu	1:1 (THF)	9	2	85	–	–
4	I	n-Bu	1.6:1	91	8	–	–	–
4	Br	Me	Ether	–	–	100	–	–
4	I	Me	6:1	27	22	52	–	–
4	I	t-Bu^a	7:1	90	–	–	2	–
3	Br	n-Bu	7:1	39	9	1	51	–^{b}
				79	7	1	9	–^{c}
5	I	n-Bu	6:1	9	–	7	54	–^{d}
				58	–	11	12	10^e
6	I	n-Bu	7:1	–	–	–	83	13

The columns under "Products (GLPC yields)" are 2, 3, 4, 5, 6. The columns under "1" are n, X, Cuprate.

^{a} Reagent prepared from 1 equiv of CuI(n-Bu$_3$P) and 2 equiv of t-BuLi. ^{b} After 15 min at reflux. ^{c} After 3 hr at reflux. ^{d} After 2 hr at -30°. ^{e} After 1 hr at 24°.

vent components yielded a 2:4 ratio of 15:78. THF was even more effective in promoting the formation of 4 (9:85 ratio of 2:4). The nature of the halogen group is also important as shown by the exclusive conversion of iodide 1 ($n = 4$) to cyclic products 2 (91%) and 3 (8%), even in a less favorable solvent mixture. The organocopper reagent plays a significant role in the cyclization process, since lithium dimethylcuprate and bromide 1 in ether yielded only the linear coupled product 4. (This material predominates even in a 6:1 pentane-ether solvent.) On the other hand, the tert-butyl reagent converted iodide 1 mainly to cyclic product 2. Finally, reaction of iodide 1 with an excess of ethereal n-butylmagnesium bromide containing a catalytic amount of CuI afforded cyclic product 2 (88%), 3 (4%), and 4 (4%). Quenching with D$_2$O led to 85% incorporation of deuterium in 2.

Similar cyclization reactions were also achieved with the appropriate substrates for the formation of cyclobutyl and cyclohexyl derivatives. However, in these instances an acyclic organometallic species accumulates in the reaction mixture and subsequently undergoes cyclization. Thus, reaction of bromide 1 ($n = 3$) with lithium di-n-butylcuprate in pentane-ether (7:1) gave a 39:51 ratio of 2:5 after 15 min at reflux, whereas a 79:9 mixture was obtained upon heating for 3 hr. Hydrolysis with D$_2$O gave 96% incorporation of deuterium in 2. Likewise iodide 1 ($n = 5$) gave a 9:54 ratio of 2 to 5 after 2 hr at −30° and 58:12 after 1 hr at 24°. However, iodide 1 ($n = 6$) could not be induced to cyclize, indicating an upper limit for this process. Preliminary studies of analogues of 1, in which an alkyl group replaces the phenyl substituent, also show cyclization for $n = 3$ and $n = 4$ substrates.[4]

These cyclization reactions probably proceed by metal-halogen exchange leading to the acyclic organocuprate 7 which subsequently cyclizes to vinylic intermediate 8. The latter transformation can actually be observed with the $n = 3$ and $n = 5$ substrates, whereas the acyclic species 7 does not accumulate in the case of $n = 4$, apparently because of a much faster 7 → 8 conversion in this favorable instance. The orientation in the intramolecular addition of the carbon-metal bond of 7 to the remote triple bond is highly regiospecific, with the new carbon-carbon bond being formed exclusively at the nearest acetylenic center. Similar cyclizations have previously been observed in Grignard[5] and other organometallic reactions[6] of compounds of type 1, but these proceed more slowly and often less cleanly. The formation of the acyclic coupled product 4 is probably competitive with the metal-halogen exchange process and the solvent, halogen, and organocopper reagent effects are apparently a

result of changes in the relative efficiencies of these two pathways.

$$1 \longrightarrow PhC{\equiv}C(CH_2)_nCuBuLi \longrightarrow$$
7

8
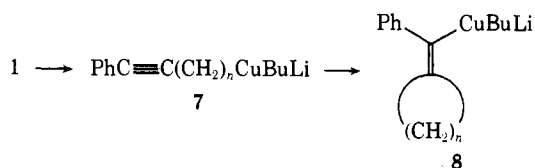
There is substantial synthetic potential in these cyclizations for the construction of cyclic compounds, especially in view of the possibilities for elaboration of the organocopper function of 8. By way of example, the intermediate species 8 ($n = 4$), prepared in the usual fashion, reacts with a variety of reagents XY to give tetrasubstituted olefins 9 as indicated below:[7]

$$8 \xrightarrow{XY}$$

9

Y = CH$_3$ (53% yield) from CH$_3$I
Y = CH$_2$CH=CH$_2$ (66%) from BrCH$_2$CH=CH$_2$
Y = I (83%) from I$_2$
Y = Br (69%) from NBS

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(8) Supported by the Centre Nationale de la Recherche Scientifique of France.

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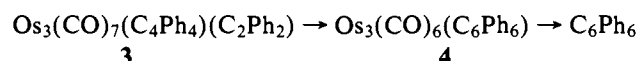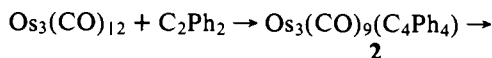Indiana University
Bloomington, Indiana 47401

Synthesis, Reactivity, and Structure of μ3-(η-Diphenylacetylene)-decacarbonyltriosmium. Metallocyclopentadiene Formation in the Triosmium System[1]

Sir:

There is considerable current interest in formation and cleavage of bonds to carbon at the "surface" of a metal cluster complex. Careful work by Cetini, Gambino, and co-workers[2] has revealed a sequence of trinuclear osmium complexes involved in the cyclotrimerization of diphenylacetylene.

$$Os_3(CO)_{12} + C_2Ph_2 \rightarrow Os_3(CO)_9(C_4Ph_4) \rightarrow$$
$$\mathbf{2}$$

$$Os_3(CO)_7(C_4Ph_4)(C_2Ph_2) \rightarrow Os_3(CO)_6(C_6Ph_6) \rightarrow C_6Ph_6$$
$$\mathbf{3} \qquad\qquad\qquad \mathbf{4}$$

Since elevated temperatures (ca. 100°) are necessary to form reactive species from $Os_3(CO)_{12}$, the initial stages of the reaction could not be observed, and the first member (**2**) of the proposed sequence already has two diphenylacetylene units condensed into a metallocyclopentadiene ring.[3] We[1b] (and others)[4,5] have shown previously that organotriosmium species can be formed under milder conditions from the unsaturated complex $H_2Os_3(CO)_{10}$ than from $Os_3(CO)_{12}$. We now wish to report the synthesis of Os_3-$(CO)_{10}(C_2Ph_2)$ (**1**) from $H_2Os_3(CO)_{10}$, some features of its crystal structure, and results that show it to be a precursor to metallocyclic species such as **2**.

Treatment of $H_2Os_3(CO)_{10}$ with 3–4 equiv of diphenylacetylene at room temperature in dichloromethane or hexane rapidly and quantitatively yielded $HOs \; CO)_{10}(C$-$Ph=CHPh)$ (**5**) in which the alkyne is inserted into one of the osmium hydride bonds.[6] Complex **5** is quite stable in solution at room temperature, but in the presence of excess diphenylacetylene at ca. 50°, $Os_3(CO)_{10}(C_2Ph_2)$ (**1**) and stilbene (predominantly cis) were formed. After chromatography complex **1** was isolated in good yield as a yellow crystalline solid and it has been characterized by its ir, NMR, and mass spectra.[7] Direct interaction of **1** with diphenylacetylene at 50–70° cleanly converted it to **2**. Since these temperatures are relatively mild, **1** is a presumptive intermediate between $Os_3(CO)_{12}$ and **2** in the above sequence.[8]

This role is supported by other reactions observed for **1**. Thus, the complexes $Os_3(CO)_9(C_2Ph_2-C_2HPh)$ (**6**), Os_3-$(CO)_9(C_2Ph_2-C_2HEt)$ (**7**), and $Os_3(CO)_9(C_2Ph_2-$$C_2(CO_2Me)_2)$ (**8**) were formed from **1** and the appropriate alkyne under the same conditions as for **2**. These compounds have been characterized as osmiacyclopentadiene analogues of **2** on the basis of their ir, NMR, visible, and mass spectra and represent the first mixed-alkyne metallocyclic cluster complexes to be reported.[11] Furthermore, **1** reacted with molecular hydrogen to give H_2Os_3-$(CO)_9(C_2Ph_2)$ (**9**) and with trimethylphosphite or triphenylphosphine to yield $Os_3(CO)_9P(OMe)_3(C_2Ph_2)$ (**10**) or $Os_3(CO)_9PPh_3(C_2Ph_2)$ (**11**), respectively. Interestingly, **11** also reacted further with diphenylacetylene to produce the derivative of **2**, $Os_3(CO)_8PPh_3(C_4Ph_4)$. This was prepared previously by substitution *after* metallocycle formation.[2b]

Two reasonable pathways could be considered for the creation in **1** of a vacant electrophilic site: dissociation of a carbonyl or a rearrangement such that the bound alkyne becomes a two-electron donor. In fact, complexes with formulas analogous to both possible intermediates in the conversion of **1** into **2**, $Os_3(CO)_{10}(alkyne)_2$ or $Os_3(CO)_9(alkyne)$, have been reported.[2d,5] However, preliminary observations concerning the reactivity of **1** suggest a dissociative mechanism. Thus, conversion of **1** into **2** was strongly inhibited under an atmosphere of carbon monoxide. Furthermore, an argon-flushed solution of **1** in dry cyclohexane heated under reflux for 10 hr changed color from yellow to reddish orange. An infrared spectrum of this solution suggested ca. 40% of **1** had been converted into a new species with major bands at 2091 m, 2048s, 2005s, and 1992 m. *At room temperature* exposure of the solution to carbon monoxide instantly regenerated **1**, whereas addition of triphenylphosphine, trimethylphosphite, or molecular hydrogen rapidly afforded **11**, **10**, and **9**, respectively, mixed with unreacted **1**. Thus, the probable formula of the red species is $Os_3(CO)_9(C_2Ph_2)$, although purification has been hindered

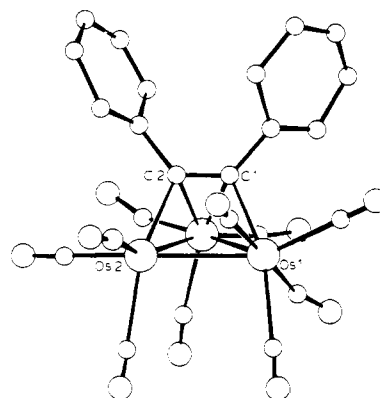Figure 1. Perspective view of the $Os_3(CO)_{10}(C_2Ph_2)$ molecule. Separations between osmium atoms are: $Os(1)-Os(2) = 2.884$ (5) Å, $Os(1)-$$Os(3) = 2.855$ (5) Å, $Os(2)-Os(3) = 2.717$ (5) Å. Osmium–acetylene carbon distances are: $Os(1)-C(1) = 2.27$ (3) Å, $Os(2)-C(2) = 2.14$ (3) Å, $Os(3)-C(1) = 2.14$ (3) Å, $Os(3)-C(2) = 2.33$ (3) Å, and $C(1)-C(2) = 1.29$ (5) Å.

by its extreme reactivity (it is destroyed instantly upon application to a chromatography plate). Treatment of this species with diphenylacetylene or phenylacetylene at room temperature yielded a brown or a pink complex, which could be isolated by chromatography. With slight warming each was cleanly converted to the metallocyclic product, **2** or **6**, respectively. These complexes must each have two alkyne moieties bound to the triosmium framework, but we do not yet know the extent of C–C bond formation.

In contrast to other $Os_3(CO)_{10}(alkyne)$ species,[2d,4,5,10] for which a structural model such as I appears satisfactory, **1** displays no infrared evidence for a bridging carbonyl.
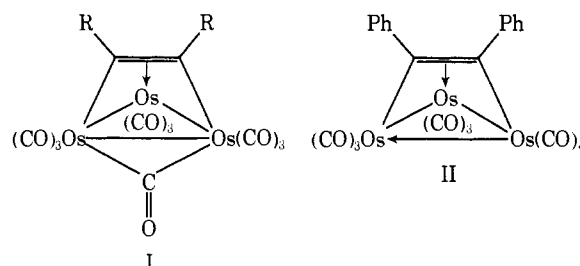
Therefore, a single-crystal x-ray study of **1** was undertaken in order to reveal the mode of binding between alkyne and metal triangle.[12] The molecular geometry determined for **1** is depicted in Figure 1; the composition of the complex and the absence of bridging carbonyls[13] are confirmed. The acetylenic moiety is bound unsymmetrically with respect to the metal triangle and displays bonding contacts with each osmium atom. In formal terms this configuration provides only Os(3) with the optimum 18 valence electrons, whereas Os(1) and Os(2) have 19 and 17 electrons, respectively. For bookkeeping purposes conformity to the 18-electron rule can be achieved by considering the Os(1)–Os(2) interaction as a donor–acceptor bond and representing the alkyne binding by the usual $2\sigma + \pi$ localized model (see II). However, it should be emphasized that this is only a formal device. The considerable variety of Os–Os and Os–C bond distances observed for **1** indicates that the four electrons contributed by the bound alkyne actually must be delocalized over the whole metal triangle.[15] Nevertheless, the obvious relationship between models I and II may be useful in considering a mechanism for the intramolecular rearrangement exhibited by $Os_3(CO)_{10}(alkyne)$ complexes.[10] This point is under further investigation.

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(6) HOs₃(CO)₁₀(CPh=CHPh): ir (ν_{CO}, C_6H_{12}), 2102 m, 2062 s, 2050 m, 2024 s, 2005 m, 1994 m, 1982 w, 1955 vw; ¹H NMR (CDCl₃), τ 25.18 s (1), 2.6–3.3 m (10), 3.00 (1), position of vinylic hydrogen determined by difference from comparison with product from D₂Os₃(CO)₁₀; mass spectrum (field desorption), *m/e* 1036 (¹⁹²Os) plus fragment ions due to successive loss of ten carbonyls.
(7) Os₃(CO)₁₀(C₂Ph₂): mp 118–119°; ir (ν_{CO}, C_6H_{12}), 2100 w, 2066 vs, 2047 s, 2028 s, 2011 s, 1996 m, 1982 sh, 1965 w; ¹H NMR (CDCl₃), τ 2.8–3.3 m; mass spectrum, *m/e* 1034 (¹⁹²Os) plus ion multiplets corresponding to loss of ten carbonyls.
(8) Johnson and co-workers have recently reported⁹ that a metallocyclohexadienone complex, Os₃(CO)₉((C₂HPh)₂CO) (A), derived from H₂Os₃(CO)₁₀ and excess phenylacetylene provided an osmiacyclopentadiene species after brief heating at 130°. A similar intermediate was proposed for the formation of **2**. We have independently isolated complexes of type A from reactions of H₂Os₃(CO)₁₀ with terminal alkynes and have observed that they rearrange through intervening stages to analogues of **2**.¹⁰ However, the temperatures required for this transformation are uniformly higher than for metallocyclopentadiene formation from Os₃(CO)₁₀(alkyne) complexes. Furthermore, the latter are not converted into type A species with excess alkyne nor has a complex related to A been observed for diphenylacetylene.
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(10) M. Tachikawa and J. R. Shapley, unpublished results.
(11) Two isomers are possible for **6** and **7** but only one was observed in each case. The NMR data obtained did not establish the configuration selected.
(12) Crystallographic data are: C_i^1–P_1; ρ_{calcd} = 2.653, ρ_{exptl} = 2.62 (2) g/cm³; Z = 2 for Os₃(CO)₁₀(C₂(C₆H₅)₂); a = 16.044 (3), b = 8.947 (3), c = 9.734 (3) Å; α = 113.99 (5)°, β = 87.39 (5)°, γ = 92.03 (5)°. The conventional R factor obtained from the full-matrix least-squares refinement of 2165 reflections measured on a Picker diffractometer is currently 0.082.
(13) It is interesting that the excess formal charge on Os(1) is not relieved by formation of semibridging carbonyls.¹⁴ Nonbonding contacts for the trans (173°) carbonyls on Os(1) are not less than 2.88 Å.
(14) F. A. Cotton and J. M. Troup, *J. Am. Chem. Soc.*, **96**, 1233 (1974).
(15) A similar disposition of the diphenylacetylene moiety relative to the metal triangle was observed in the crystal structure of **3**.³ᵇ Therefore, it apparently does not result from specific steric interactions or the presence of a bridging metallocyclopentadiene group.
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Diphenyl Phosphorazidate (DPPA) and Diethyl Phosphorocyanidate (DEPC). Two New Reagents for Solid-Phase Peptide Synthesis and Their Application to the Synthesis of Porcine Motilin

Sir:

Solid-phase peptide synthesis ingeniously launched by Merrifield[1] has received great attention since it has now

Table I. Comparisons of the Reactivities of DCCD, DPPA, and DEPC in DMF and Methylene Chloride

coupling agent	Rate of coupling, %ᵃ		
	5 min	30 min	60 min
DCCD	12 (95)	20 (98.5)	32 (99)
DPPAᵇ	40 (3)	72 (12)	80 (21)
DEPCᵇ	98 (55)	98 (70.5)	99 (82)

ᵃ Rates of coupling of Boc-Ile·½H₂O (1.5 equiv) and Gly-resin with 1.5 equiv of each coupling agent in dimethylformamide. Numbers in parentheses represent rates of coupling in methylene chloride. ᵇTogether with triethylamine (1.5 equiv).

been automated and makes possible the very rapid preparation of peptides. Although many reagents for peptide bond formation are known,[2] N,N'-dicyclohexylcarbodiimide (DCCD) is the sole coupling reagent widely used for solid-phase synthesis.

We have previously disclosed that two O,O'-disubstituted phosphoropseudohalidates, diphenyl phosphorazidate (N₃PO(OPh)₂, DPPA)[3] and diethyl phosphorocyanidate (NCPO(OEt)₂, DEPC),[4] in combination with triethylamine are very efficient coupling reagents for racemization-free conventional (solution) peptide synthesis. We here report that these two reagents may also be useful for solid-phase peptide synthesis in both the stepwise and fragment condensation approaches and were successfully applied to the synthesis of porcine motilin, a gastrointestinal hormone exhibiting gastric motor stimulating activity.[5]

First, comparisons of DCCD with DPPA and DEPC were conducted by the coupling of Boc-Ile[6] with Gly-polystyrene-resin according to the general procedure described by Stewart and Young.[7] When DPPA and DEPC were the coupling reagents, they were added after the addition of Boc-Ile·½H₂O, followed by the addition of triethylamine. The reaction was followed by determining the unreacted amino group of the Gly-resin according to the Porath method.[8] When methylene chloride was used as the solvent, the reactivity of DCCD was higher than that of DPPA or DEPC. However, with dimethylformamide DPPA and DEPC were much more reactive than DCCD as shown in Table I.

The DPPA and DEPC methods were applied to the synthesis of Boc-Pro-Leu-Gly-NH₂, the amino acid sequence of which corresponds to the melanocyte release inhibiting hormone.[9] The synthesis[10] started from Boc-Gly-resin (1 equiv). Stepwise attachment of Boc-Leu (3 equiv) and Boc-Pro (3 equiv) using either DPPA or DEPC (3 equiv) in the presence of triethylamine (3 equiv) in dimethylformamide (each coupling reaction time was 2 hr, room temperature) gave Boc-Pro-Leu-Gly-resin. Treatment of the resin with ammonia in methanol afforded Boc-Pro-Leu-Gly-NH₂ in a 70% (DPPA) or a 76% (DEPC) yield. The sample of Boc-Pro-Leu-Gly-NH₂·½H₂O, mp 136–138°, $[\alpha]^{25}$ D −72° (c = 1.64, MeOH)[11] was identical with that similarly prepared from Gly-OMe by the solution method using DEPC.

To check racemization during fragment coupling on a solid support we adopted the Izumiya test[12] involving condensation of Boc-Gly-Ala with Leu-resin. Three equivalents of Boc-Gly-Ala and DPPA or DEPC were used together with triethylamine (3 × 0.95 equiv) in dimethylformamide. After the coupling reaction, the resin was treated with hydrogen bromide in trifluoroacetic acid to give Gly-Ala-Leu. The extent of racemization was determined with an amino acid analyzer. The coupling reaction proceeded almost quantitatively during 2 hr with little racemization: the extent of racemization = [D,L/(D,L + L,L)] × 100%; DPPA 2.5% at 20°, 2% at 0°; DEPC 1% at 20°, <0.5% at 0°. These values are considerably lower in the solid-phase method than are those for other coupling reagents.[13] Thus,