

Figure 2. Plot of the concentration of ATP (O), ADP (Δ), AMP (□), and **2** (▽) vs. time in a solution of 10% D₂O/H₂O at pH 7.6 and at 70 °C containing 0.010 M ATP, 0.015 M [24]-N₆O₂ (**1**), and 0.015 M CaBr₂. The concentrations were calculated from the ³¹P NMR integrals for the various species as described in Table I. Some calcium phosphate precipitated at this pH.

solely to the catalytic effect of the metal ion since the same reaction in the absence of macrocycle has a k_{obsd} of 0.002 min⁻¹.⁶ The presence of Mg(II) had no apparent effect on the overall rate of ATP hydrolysis; however, the addition of Zn(II) to the macrocycle-ATP solution decreased the hydrolysis rate to one-sixth of the control value.

The most striking finding for this model system is the appearance of pyrophosphate. The process occurs readily in the presence of **1** and Ca(II) or Mg(II) at pH 4.5. No pyrophosphate formation was observed in the absence of the metal ions under the same conditions. In a study of the reaction of acetyl phosphate with the macrocycle, Hosseini and Lehn observed a greater yield of pyrophosphate (30%) without the necessity of added metal ion. In the case of ATP hydrolysis, however, there is competition in the approach to the phosphorylated macrocycle between the inorganic phosphate as well as ADP and AMP. The net result is a reduced opportunity for the inorganic phosphate to react at the phosphoramidate site. Furthermore, the rate of hydrolysis of the phosphorylated macrocycle in the absence of other phosphate species in the presence and absence of Ca(II) ion was examined and found to be significantly slower in the latter case. Thus, the role of the metal ion is thought to be twofold. It acts to increase the observed percentage of the intermediate **2** via stabilization of the P-N bond, and, additionally, it is capable of complexation with the nucleotides.

Both ³¹P and ¹³C NMR data for these ternary complexes indicate significant interactions of both Mg(II) and Ca(II) with ATP. While the terminal phosphate of ATP is normally associated strongly with **1**, the addition of Mg(II) and Ca(II) results in a significant upfield shift of the P_β resonance (~1.7 ppm) of ATP, indicating a substantial interaction at that site. That the Ca(II) interactions with ATP may even be strong enough to disrupt the macrocycle-ATP complex is suggested by the ¹³C data for **1**, for which the chemical shifts of the ternary Ca(II)-ATP-macrocycle system are almost identical with those of the free macrocycle, while the binary ATP-macrocycle system differs considerably. The net result is that if the nucleotides are complexed with metal ions, they may more readily dissociate from the macrocyclic cavity, allowing for less restricted association of **2** with inorganic phosphate. Such a macrocyclic-phosphate association is in agreement

with the proposed mechanism for the formation of pyrophosphate via **2** from the reaction of **1** and acetyl phosphate.⁴

These findings serve to accentuate the analogies between ternary metal-ATP-polyammonium macrocycle systems and their biological counterparts, enzymes utilizing ATP, for which the enzyme function is almost invariably mediated by the presence of certain metal ions.

Acknowledgment. We thank M. W. Hosseini and J.-M. Lehn for a preprint of their paper and Linda Maggiora for helpful discussions. This work was supported by a grant from the Institute of General Medical Sciences (GM 33922) of the National Institutes of Health.

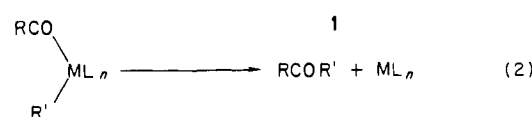
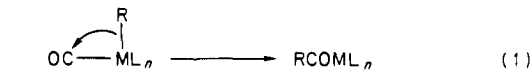
Controlled and Catalytic Acylpalladation. A Novel Route to Cyclopentenone and Cyclohexenone Derivatives¹

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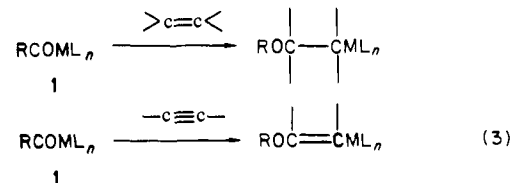
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Carbon-carbon bond formation via transition-metal-catalyzed carbonylation with CO almost invariably involves migratory insertion (eq 1) which is often followed by reductive elimination² (eq 2). In principle, the product of migratory insertion (**1**) can

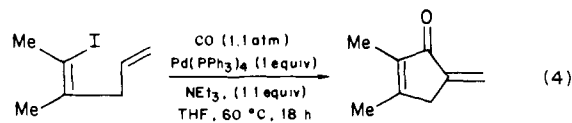


undergo an alternate carbon-carbon bond-forming reaction with alkenes and alkynes as shown in eq 3, i.e., acylmetalation. Al-



though "formal" conjugate addition reactions of acylmetal derivatives to α,β -unsaturated carbonyl compounds,³ reactions involving addition of ROOCML_n to alkenes and alkynes,⁴ and a few examples of the reaction of acylmetalates with ethylene and acetylenes are known,⁵ acylmetalation of unactivated alkenes and alkynes shown in eq 3 remains largely unexplored.⁶

We recently reported the conversion of 1-iodo-1,4-dienes into α -methylene-cyclopentenones represented by eq 4.⁷ This con-



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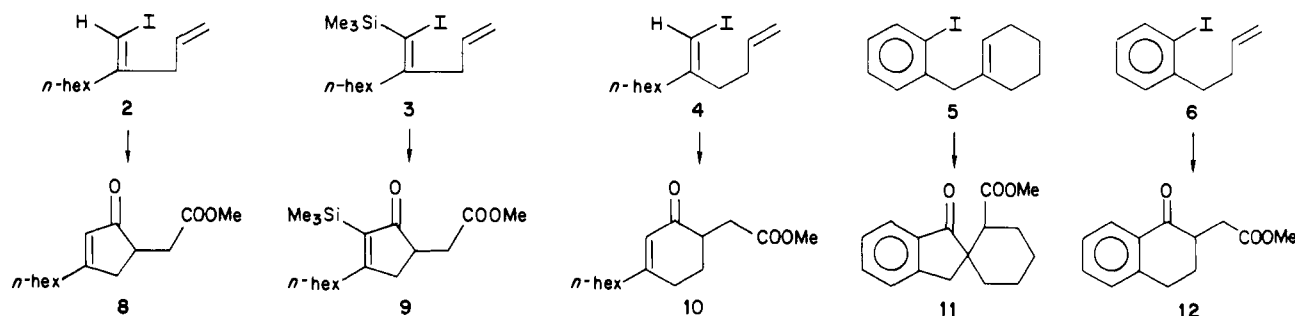
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Scheme I



version most probably involves acylpalladation. Unfortunately, the reaction is only stoichiometric in Pd. In search for a catalytic acylpalladation reaction, we investigated the reaction of 2–6⁵ with CO in the presence of Pd complexes and NEt₃. In reaction of 4 with CO (600 psi) in the presence of 10 mol% of Pd(OAc)₂ and NEt₃ (3 equiv) in CH₃CN at 100 °C for 24 h gave a bicyclic compound 7⁹ in 55% isolated yield.¹⁰ Under the same conditions, however, 2, 3, 5, and 6 did not produce any monomeric products, although the starting compounds were completely consumed. The products in these cases must therefore be polymeric.⁶ Our attempts to observe an intermolecular reaction between iodobenzene and 1-octene under similar reaction conditions also failed to produce any more than traces of monomeric products.

We have now found that the above difficulty can be overcome by running the Pd-catalyzed carbonylation reaction of 2–6 in the presence of MeOH. In each case, the reaction cleanly yielded a single product in a predictable manner. It is highly likely that MeOH prevents undesirable polymerization processes through methanolysis. The experimental data summarized in Table I indicate that both Pd(0) and Pd(II) catalysts, such as Pd(PPh₃)₄,

Table I. Synthesis of Cyclopentenone and Cyclohexenone Derivatives via Palladium-Catalyzed Carbonylation^a

iodide	catalyst	NEt ₃ , equiv	MeOH, equiv	time, h	product	yield, ^b %
2	Cl ₂ Pd(PPh ₃) ₂	1.5	4	20	8 ^c	100 (90)
3	Cl ₂ Pd(PPh ₃) ₂	1.5	4	24	9	89 (75)
4	Cl ₂ Pd(PPh ₃) ₂	1.5	4	24	10	73 (66)
4	Pd(OAc) ₂ ^d	3	0	24	7	(55)
5	Cl ₂ Pd(PPh ₃) ₂	1.5	4	24	11	84 (67)
6	Cl ₂ Pd(PPh ₃) ₂	1.5	4	11	12	90 (58)
6	PdCl ₂ + 10% PPh ₃	1.2	2	18	12	52
6	Pd(PPh ₃) ₄	1.2	2	24	12	40
6	Pd(dba) ₂	1	1	24	12	53
6	Pd(dba) ₂	1.1	2	36	12	80 (73)
6	Pd(dba) ₂	TMEDA (2x)	2	24	e	
6	Cl ₂ Ni(PPh ₃) ₂	1.5	4	18	12	10

^a Unless otherwise mentioned, the carbonylation reaction was carried out in the presence of 5 mol % of a Pd catalyst under 600 psi of CO in a 1:1 mixture of CH₃CN–benzene at 100 °C. ^b By GLC (SE-30). The numbers in parentheses are isolated yields. ^c Both 2 and 8 contained their regioisomers (up to 7%) formed during allylaluminum–iodinolysis. ^d 10 mol %. ^e Seven unidentified products were detected by GLC.

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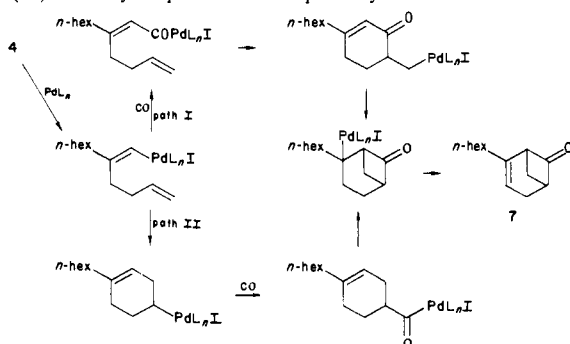
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(8) The compounds 2 and 3 were prepared via Zr-catalyzed allylaluminum (Miller, J. A.; Negishi, E. *Tetrahedron Lett.* **1984**, *25*, 5863) and allylzincation⁷ of the corresponding alkynes, respectively, followed by iodinolysis. The compound 4 was prepared as reported previously (Boardman, L. D.; Bagheri, V.; Sawada, H.; Negishi, E. *J. Am. Chem. Soc.* **1984**, *106*, 6105) by treating 1-octyne with CH₂=CH(CH₂)₂Cu–MgBr₂ followed by iodinolysis (Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841). The preparation of 19 was analogously achieved with CH₂=CH(CH₂)₃Cu–MgBr₂. The compounds 5 and 6 were prepared by the reaction of α-bromo-2-iodotoluene with lithium (1-cyclohexenyl)trimethylaluminum and allylmagnesium bromide, respectively. The former reagent (Baba, S.; Van Horn, D. E.; Negishi, E. *Tetrahedron Lett.* **1976**, 1927) was generated by the reaction of 1-cyclohexenyllithium (Braude, E. A.; Coles, J. A. *J. Chem. Soc.* **1950**, 2014) with Me₃Al. The direct use of alkenyllithium or alkenylmagnesium reagents led to an extensive formation of 0,0'-diiodobiphenyl.

(9) All isolated cyclic ketones yielded satisfactory ¹H and ¹³C NMR, IR, and high-resolution MS spectra.

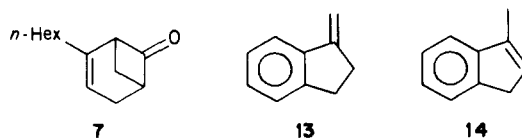
(10) The bicyclic product 7 most probably was formed either via acyl-



palladation–alkenylpalladation (path I) or via alkenylpalladation–acylpalladation (path II). Although unclear, some of the organopalladium intermediates, especially acylpalladium intermediates, can, in principle, undergo addition to the C=C bond of 4 or other intermediates leading to polymers.⁶

Pd(dba)₂, where dba is dibenzylideneacetone, Cl₂Pd(PPh₃)₂, Pd(OAc)₂, and even PdCl₂, may be used. After several experiments for optimizing the yield of 12, we chose 5 mol% of Cl₂Pd(PPh₃)₂, 600 psi of CO, 1.5 equiv of NEt₃, and 4 equiv of MeOH in CH₃CN–benzene (ca. 1 mL each per mmol of an iodide) as a standard set of reagents and ran the reaction in an autoclave at 100 °C for 18–24 h. Under these conditions 8–12⁹ were obtained in 58–90% yields after the usual extractive workup and Kugelrohr distillation.

The following points are noteworthy. First, the uniformly observed mode of cyclization is “exo” rather than “endo”. Second, no products formed via the intramolecular Heck-type alkenylpalladation and arylpalladation¹¹ were detected in the above carbonylation reaction. When 6 was treated with 5 mol % of Cl₂Pd(PPh₃)₂ and NEt₃ (1.5 equiv) in CH₃CN–benzene (1/1) in the absence of CO under an atmosphere of nitrogen at 100 °C for 12 h, however, two isomeric bicyclic products 13¹² and 14¹³



were obtained in a ratio of 60:40 in 89% combined yield. These results clearly indicate that the carbonylation reaction is considerably faster than the alkenyl- or arylpalladation process.

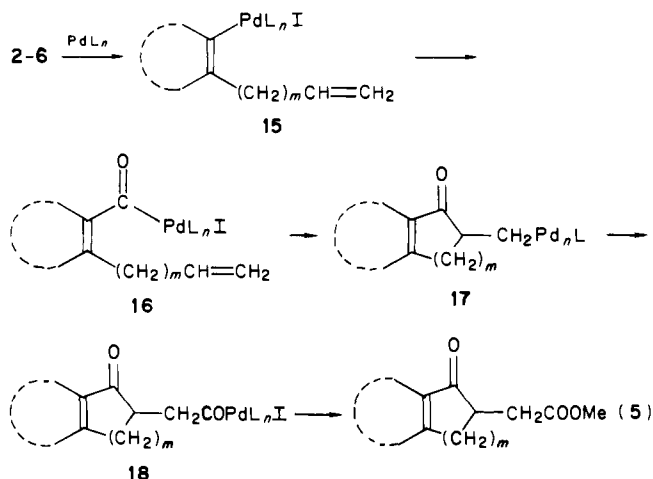
Third, the reaction must be initiated by oxidative addition of the iodides 2–6 with a Pd(0) complex to form 15, which can then undergo CO insertion to produce 16. This intermediate must then undergo intramolecular acylpalladation to produce 17 much faster

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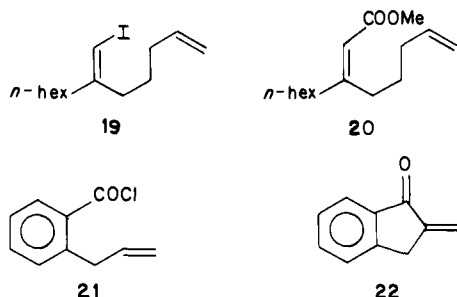
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than methanolysis. The intermediate **17** must then undergo the second CO insertion to give **18** faster than dehydropalladation. Unlike **16**, the intermediate **18** evidently prefers methanolysis to intramolecular or intermolecular acylpalladation (eq 5). After



the initial oxidative addition step, each of the presumed intermediates has at least one alternate and plausible path to follow, as discussed above. And yet none of these alternate steps appears to be competitive in the reaction. Especially noteworthy is that neither carbopalladation involving aryl- and alkenylpalladium species nor dehydropalladation, two key microsteps in the Heck-type reaction, occurs in the presence of CO.

To probe the intermediacy of **16**, we prepared **19**⁸ and subjected it to the standard carbonylation conditions described above. After



24 h, the major product formed in ca. 50% yield was **20**.⁹ The results not only indicate that, in this case, methanolysis of the presumed acylpalladium intermediate is faster than its intramolecular acylpalladation reaction to produce a seven-membered ring but also support the assumption that **16** must be intermediate in the cyclization reaction.

Finally, that the intramolecular acylpalladation process is indeed feasible has been indicated by the reaction of **21** with Pd(PPh₃)₄ (1 equiv) and NEt₃ (1.5 equiv) in CH₃CN-benzene (1/1) at 55 °C for 1 h to give **22**⁹ in 50% isolated yield. Unfortunately, **21** is incompatible with MeOH so that the development of a catalytic process via methanolysis is not feasible in this case.

Further transformations of the cyclic ketone products as well as the development of asymmetric cyclization procedures are under investigation.

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Supplementary Material Available: Experimental section including experimental procedures and spectral data for products (7 pages). Ordering information is given on any current masthead page.

Nature of the Migrating Group in 1,5-Sigmatropic Hydrogen Shifts

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Sigmatropic rearrangements, in particular suprafacial 1,5-hydrogen shifts, have recently found use in synthetic methodology.² Systematized and analyzed by Woodward and Hoffmann³ these symmetry-allowed processes have been shown by numerous experimental⁴ and theoretical studies^{5,6} to occur in a concerted manner. Less well established is the nature of the migrating group or the factors which influence its character. The formal molecular orbital analysis treats the transition state for the 1,5-shift in 1,3-pentadiene in terms of interaction of a hydrogen atom and a pentadienyl free radical. On the other hand, it has been suggested that the transition state for [1,5]-sigmatropic migration in cyclopentadiene is such that the migrating hydrogen is "protonic" while the underlying carbon skeleton resembles an "aromatic" cyclopentadienyl anion.⁷

Electron density surfaces corresponding to $\psi^2 = 0.002$ electron/bohr³⁸ have been obtained from 3-21G wavefunctions^{9,10} for the transition structures for [1,5] migration in 1,3-pentadiene, cyclopentadiene, and 3-cyano-1,3-pentadiene.¹¹ Radii for the migrating hydrogens, obtained from least-squares fitting the electron density surface to nuclear-centered spheres,⁸ are provided in Table I. An example showing the relationship between the

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- (11) All transition structures have been constrained to C_s symmetry. 3-21G level transition structures for 1,3-pentadiene⁹ and for cyclopentadiene¹⁰ have already been published. Geometrical parameters for the transition structure for [1,5] migration in 3-cyano-1,3-pentadiene are as follows: bond lengths in angstroms, C₁C₂ = 1.403, C₂C₃ = 1.391, C₃C₆ = 1.429, C₆N = 1.141, C₁H_{in} = 1.075, C₁H_{out} = 1.077, C₁H_{mig} = 1.452, C₂H = 1.075; bond angles in degrees, C₁C₂C₃ = 123.0, C₂C₃C₄ = 121.3, C₂C₃C₆ = 119.3, C₂C₁H_{in} = 118.7, C₂C₁H_{out} = 116.4, C₂C₁H_{mig} = 98.3, C₃C₂H = 116.2; dihedral angles in degrees, C₁C₂C₃C₄ = 9.2, C₁C₂C₃C₆ = 170.8, C₆C₃C₂H = 24.4, C₃C₂C₁H_{in} = 64.4, C₃C₂C₁H_{out} = 156.5, C₃C₂C₁H_{mig} = -27.0.

