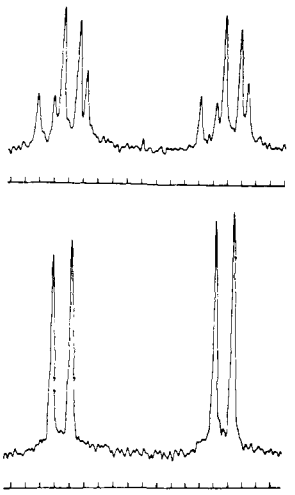

**Figure 2.** $^{31}P$ NMR spectrum of [$^{18}O$]ADP obtained from ($S_P$)-ADP$\alpha$S($\alpha^{18}O_2$). A sample of ($S_P$)-ADP$\alpha$S($\alpha^{18}O_2$) was converted to [$^{18}O$]ADP by reaction with cyanogen bromide in $H_2O$. The proton-spin-decoupled $^{31}P$ NMR spectrum of the resulting [$^{18}O$] ADP was obtained on the Bruker WM-300. The upper pattern of doublets contains the $P_\alpha$ signals and the lower, the $P_\beta$ signals. The chemical shift values and their assignments to $^{18}O$-containing species are given in the text.

containing species in **1**. The signals are assigned to the four species as follows: the signal at 40.962 ppm corresponds to the species lacking $^{18}O$, that at 40.936 ppm to species containing bridging $^{18}O$ and nonbridging $^{16}O$, that at 40.925 ppm to species with bridging $^{16}O$ and nonbridging $^{18}O$, and signal at 40.902 ppm to species with $^{18}O$ in both the bridging and nonbridging positions.

A sample of **1** was reacted with 3 equiv of cyanogen bromide at pH 10.5 in borate buffer. NMR analysis showed that **1** was fully consumed and that about 60% of the product was ADP. The [$^{18}O$]ADP was purified and subjected to analysis by $^{31}P$ NMR with the results illustrated in Figure 2.

The pair of doublets in the lower portion of the figure are the $P_\beta$ region. The signal at −6.199 ppm corresponds to species containing $^{16}O$ in the bridging position and that at −6.220 ppm to species containing bridging $^{18}O$. Note that the [$^{18}O$]ADP is equally populated with briding and nonbridging $^{18}O$, whereas in **1** there was a 3:1 ratio of $^{18}O$:$^{16}O$ in the bridge. The $P_\alpha$ region in further contrast to that of **1** exhibits *five* lines. The least intense and most downfield is the signal for species containing only $^{16}O$ at $\delta$ −10.694. The nearest signal upfield at $\delta$ −10.713 corresponds to species containing bridging $^{18}O$. The next upfield signal at $\delta$ −10.722 corresponds to species containing nonbridging $^{18}O$ and the next at $\delta$ −10.739 to both nonbridging and bridging $^{18}O$. The most upfield signal at $\delta$ −10.749 corresponds to a new species, one containing *two* nonbridging $^{18}O$ and bridging $^{16}O$. This latter can have arisen only from species of **1** that contained both bridging and nonbrdiging $^{18}O$ and reacted by a mechanism leading to the rearrangement of the bridging $^{18}O$ to a nonbridging position and its replacement with $^{16}O$ either from solvent or from another position in the molecule.

Our findings are accounted for by Scheme I, in which adenosine 5′-*cyclo*-diphosphate **3** is the intermediate leading to the transfer of bridging $^{18}O$ to a nonbridging position. In the first step the sulfur in **1** displaces bromide from cyanogen bromide, forming the cyanated intermediate **2**. This has high electrophilic reactivity owing to the absence of electrostatic charge at $P_\alpha$ and to the electron-withdrawing properties of the cyano group, making sulfur a stable leaving group as thiocyanate. Intermediate **2** is partitioned nearly equally between two reaction pathways, the displacement of thiocyanate by $H_2O$ and the internal displacement of thiocyanate by the $\beta$-phosphoryl group. The former pathway leads directly to [$^{18}O$]ADP with $^{18}O$ labeling as in **1**. The internal displacement leads to a second intermediate, adenosine 5′-*cyclo*-diphosphate **3**, in which one of the bridging oxygens is $^{16}O$ and the other is $^{18}O$. Spontaneous hydrolysis of **3** largely by attack at $P_\beta$ leads to two species of [$^{18}O$]ADP, one with bridging $^{18}O$ and a single nonbridging $^{18}O$, and a second with bridging $^{16}O$ and two nonbridging $^{18}O$'s at $P_\alpha$.

*cyclo*-Diphosphates have heretofore not been invoked as intermediates in reactions and have not been described as compounds, although other four-member-ring phosphorus compounds have been described.[4]

In our earlier study ($R_P$)- and ($S_P$)-$\beta$-cyanoethyl-ADP$\alpha$S reacted with cyanogen bromide in $H_2{}^{18}O$ to produce ($S_P$)- and ($R_P$)-$\beta$-cyanoethyl-[$\alpha$-$^{18}O$]ADP with inversion of configuration and high enrichment at $P_\alpha$[5]. That reaction presumably involved a cyanated intermediate analogous to **2** in Scheme I, which reacted essentially exclusively by the pathway involving the direct displacement of thiocyanate by $H_2{}^{18}O$.

**Acknowledgment.** Supported by Grant No. GM30480 from the National Institute of General Medical Sciences. Purchase of the Bruker WP-200 NMR spectrometer was supported by Grant No. GM27431. Spectra were also obtained at the Ohio State University Chemical Instrument Center by using a Bruker WM-300 spectrometer funded in part by NSF Grant No. CHE 7910019.

**Registry No. 1**, 83151-18-2; ADP, 58-64-0; ATPBS, 60478-94-6; [$^{18}O$]ATP, 83115-76-8; cyanogen bromide, 506-68-3.

(4) (a) Michaelis, A.; Schroter, G. *Chem. Ber.* **1894**, *27*, 490–502. (b) Bulloch, G.; Keat, R.; Thompson, D. G. *J. Chem. Soc., Dalton Trans.* **1977**, 1044–1050. (c) Bulloch, G.; Keat, R.; Thompson, D. G., *Ibid.* **1977**, 99–104. (d) DeJeager, R.; Taylor, D. R. *Ibid.* **1980**, 851–853. (e) Gibson, J. A.; Röschenthaler, G.V.; Wray, V. J. *Ibid.* **1977**, 1492–1497. (f) Vilkas, E.; Vilkas, M.; Sainton, J.; Meunier, B.; Pascard, C. *J. Chem. Soc., Perkin Trans.* **1980**, 2136–2140. (g) Kemp, G.; Tripett, S. *Ibid.* **1979**, 879–884.

(5) Sammons, R. D.; Frey, P. A. *J. Biol. Chem.* **1982**, *257*, 1138–1141.

## Mercury(II)-Induced Cyclization of Acetylenic Alcohols: A New Route to Enol Ethers and Substituted Enol Ethers

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Prostacyclin ($PGI_2$) is a potent inhibitor of platelet aggregation and a vasodilator in in vitro experiments.[1] It is, however, an enol ether rapidly deactivated by hydrolysis to give inactive 6-keto-$PGF_{1\alpha}$.[2] Hydrolysis of enol ethers can be slowed by attachment of electron-withdrawing groups, especially to the $\beta$ carbon of the double bond; substitution at positions remote from the double bond has a less dramatic effect on hydrolysis rates.[3] In fact, PGI analogues substituted with electron-withdrawing groups in positions remote from the double bond do show some protolytic stabilization compared with natural PGI;[4] substitution *at the $\beta$ carbon of the enol ether unit*, though, should impart maximum protolytic stability. To date, however, no general methods have been reported for synthesis of $\beta$-halogen enol ethers. An attractive convergent one would involve cyclization of acetylenic alcohols, induced by triple bond coordination to an electrophilic metal center, to give an alkenylmetallic intermediate. This species could undergo cleavage with a range of electrophiles to give a series of desired substituted enol ethers. However, whereas much is known concerning addition of nucleophiles to metal-coordinated *olefins*,[5a]

(1) For example, see: "Prostacyclin"; Vane, J. R., Bergström, S., Eds.; Raven Press: New York, 1979.

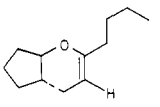
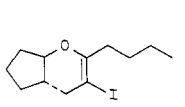
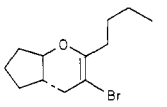
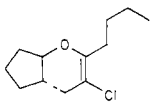
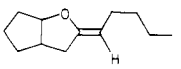
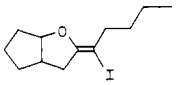
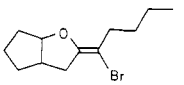
(2) For example, see: Hinman, J. W. *BioScience* **1967**, 779. Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3824.

(3) Jones, D. M.; Wood, N. F. *J. Chem. Soc.* **1964**, 5400.

(4) For example, see: Chen, S.-M. L.; Grudzinskas, C. V. *J. Org. Chem.* **1980**, *45*, 2228 and references cited therein.

0002-7863/82/1504-5842$01.25/0 

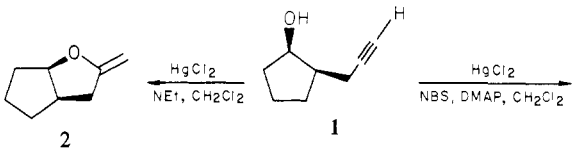
Table I. Hydrolysis of Substituted Enol Ethers[a]

| reaction conditions ($T$ = 25 °C) | | | | | |
|---|---|---|---|---|---|
| acid[b] added ($HClO_4$), mL (N) | $H_2O$,[b] mL | time for disappearance of starting material | | | |
| | |  |  |  |  |
| 1 (0.1) | 1 | 16 min | 7 days (~70% hydr)[c] | 7 days (~5% hydr) | 7 days (no hydr) |
| 1 (1.0) | 1 | ca. 5 min | 19 h | 96 h | 7 days (~50% hydr) |
| | |  |  |  | |
| 1 (0.1) | 1 | ca. 5 min | 70 min | 14 h | |
| 1 (1.0) | 1 | <1 min | 10 min | 50 min | |

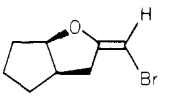
[a] Time for disappearance of starting material (by TLC). [b] Added to 8 mL of dioxane. [c] Hydrolysis.

relatively little is known concerning similar processes involving *acetylenes*.[5b] Furthermore, little is known in general concerning the use of alcohols or alkoxides as nucleophiles in metal-induced addition processes for *any* substrate.[5b,6] In addition, the starting material, an acetylene, is a relatively poor substrate for an electrophilic metal compared with the more electron-rich enol ether *product* of the cyclization reaction.

Mercury(II) species catalyze hydration of acetylenes:[7] derivatives of this metal were examined to activate acetylenic alcohols toward cyclization. We find that for the simple terminal case (**1**, eq 1) a variety of Hg(II) species will suffice ($HgCl_2$, $Hg(OAc)_2$, $Hg(OCOCF_3)_2$). Base that can act as a ligand for Hg(II) is necessary in these cyclization reactions; in its absence only adducts of the acetylenic alcohol and the enol ether are noted. The organomercury intermediate can be intercepted by *N*-halosuccinimides to give β-halo-substituted enol ethers. (If too much base is added, however, the electrophilicity of the mercury is reduced to such a degree that no cyclization reaction occurs.) These procedures are illustrated in eq 1. Cis-acetylenic alcohol **1** (0.12




2 1



3 (1)

mL, 0.9 mmol) was added at room temperature to a mixture of 244 mg (0.9 mmol) of $HgCl_2$ and 0.5 mL (3.6 mmol) of $NEt_3$ in $CH_2Cl_2$ (5 mL). The reaction mixture immediately turned yellow and a white precipitate formed. Workup gave enol ether **2** (100 mg, 0.8 mmol, 89%).[8,9] NBS (89 mg, 0.5 mmol) and alcohol **1** (0.06 mL, 0.45 mmol) were added sequentially at room temperature to a solution of 122 mg (0.45 mmol) of $HgCl_2$ and 110 mg (0.9 mmol) of (dimethylamino)pyridine in $CH_2Cl_2$ (10 mL). After 4 h, the clear solution was concentrated and chromatographed ($SiO_2$, ether/hexanes (1:3, +1% $NEt_3$)) to give bromoenol ether **3** (85 mg, 0.42 mmol, 93%).[10]

To adjust the electrophilicity of Hg(II) through selective ligation becomes critical when cyclizations are attempted for internal acetylenes: since the sterically larger substrate is less reactive toward cyclization, more strongly electrophilic metal centers are necessary to effect this transformation. For prostacyclin models, another factor complicates the creation of a successful cyclization procedure: although steric hindrance at carbon of a secondary alcohol can slow down polycondensation, the kinetic, exocyclic product of cyclization is susceptible to double bond isomerization to give the more stable endocyclic enol ether. Indeed, with use of highly electrophilic mercuric compounds, only double-bond-isomerized products result.[11] Their appearance seems to be correlated with the presence of electrophilic Hg(II) residues of cyclization/cleavage. Fast cyclization to a reactive organomercury compound that could undergo selective cleavage to a desired organic product and a mercuric byproduct *incapable* of effecting organic product isomerization could be accomplished by using two different ligand modification schemes. In the first, cyclization was effected at low temperature by using a highly electrophilic Hg(II) species; at low temperature, ligand replacement was effected in which a poor donor ligand was replaced by a better one. This both activated the organomercuric compound toward electrophilic cleavage (for example, protonation) and also gave rise to a Hg(II) species which, upon such cleavage, was not an isomerization catalyst. In the second, cyclization was carried out at low temperature by using an electrophilic Hg(II) complex in the presence of ca. 1 equiv of a base. The organomercury compound thus formed was intercepted by an *N*-halosuccinimide; workup was preceded by addition of excess base to quench reactivity of the Hg(II) residues thus formed. These procedures are illustrated below.

At −78 °C 0.05 mL (0.26 mmol) of cis-acetylenic alcohol **4** (eq 2) was added to a solution of 110 mg (0.25 mmol) of $Hg(O_2CCF_3)_2$ and 0.037 mL (0.27 mmol) of $NEt_3$ in $CH_2Cl_2$ (10 mL). After 10 h, 130 mg (0.97 mL) LiI in ether (5 mL) was added, and the reaction mixture was warmed to room temperature.

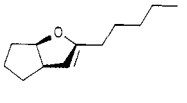
(5) (a) For example, for olefins, see: Eisenstein, O.; Hoffmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4308 and references cited therein. (b) For acetylenes, see: Chisholm, M. H.; Clark, H. C. *J. Am. Chem. Soc.* **1972**, *94*, 1532. Marten, D. F.; *J. Chem. Soc., Chem. Commun.* **1980**, 341.

(6) James, D. E.; Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1806.

(7) Stacy, G. W.; Mikulec, R. A. "Organic Synthesis"; Wiley: New York, 1963; Collect. Vol. IV, 13.

(8) $^1H$ NMR ($C_6D_6$) δ 4.47 (br s + m, 2), 3.83 (m, 1), 2.2–1.0 (m, 9).

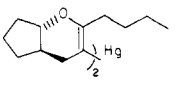
(9) Cyclization could be effected by using a catalytic amount of $HgCl_2$ in the presence of $NEt_3$; **2** and **2-endo** were obtained in a ratio of 3:2. $Pd(OAc)_2$ catalysis (in $CH_2Cl_2$) yielded only **2-endo**.



8

(10) $^1H$ NMR ($C_6D_6$) δ 4.61 (br s, 1), 4.45 (m, 1), 2.4–0.9 (m, 9); $^{13}C\{^1H\}$ 159.1, 89.9, 70.4, 41.2, 36.8, 34.0, 32.4, 24.2.

(11) **8**: $^1H$ NMR ($C_6D_6$) δ 4.97 (m, 1), 3.22 (m, 1), 2.20–0.91, (m, 15), 0.84 (t, 3); $^{13}C\{^1H\}$ δ 159.8, 97.6, 86.9, 47.6, 36.0, 34.1, 31.8, 28.3, 26.9, 23.5, 22.8, 14.1.



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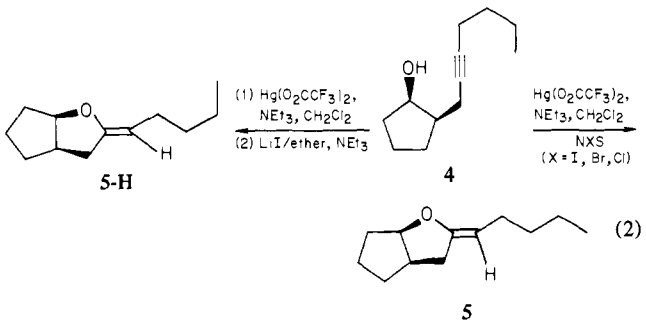
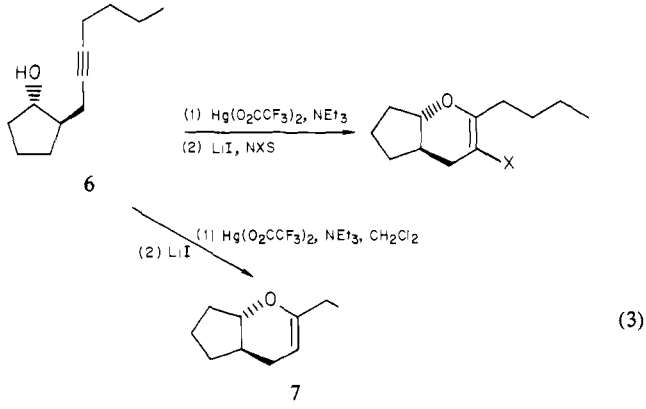



After an additional 3 h, 0.1 mL (0.72 mmol) of $NEt_3$ was added. Workup and separation by LC ($SiO_2$, ether/hexanes (15:85, +4% $NEt_3$)) gave product **5-H**[12] (21 mg, 0.12 mmol, 45%, purity by GC = 99%) and recovered starting material (24 mg, 0.13 mmol, 50%). At -78 °C 0.05 mL (0.25 mmol) of cis-acetylenic alcohol **4** was added to a solution of 110 mg (0.25 mmol) of $Hg(O_2CCF_3)_2$, 0.038 mL (0.27 mmol) of $NEt_3$, and 58 mg (0.26 mmol) of NIS. The reaction was stopped after 15 min by addition of 0.2 mL (1.44 mmol) of $NEt_3$ and warming to room temperature. Concentration and separation by LC ($SiO_2$, ether/hexanes (15:85, +4% $NEt_3$)) yielded 67 mg (0.22 mmol, (87%) of cis-iodoenol ether **5** (X = I).[13] Similar procedures gave the β-bromo- (88%)[14,15] or β-chloroenol (32%)[16] ethers. The β-halo compounds were subjected to hydrolysis conditions more vigorous than physiological ones: as the electron-withdrawing ability of the halogen substituent increased, stability toward hydrolysis also *increased* (see Table I).

Mercury-induced cyclization of the trans isomer occurred at a rate slower than that noted for the cis isomer and gave the thermodynamically favored endocyclic product (**7**, eq 3) directly




(86% after chromatograhy on silica, based on **6**).[17,18] Here, the intermediary organomercury compound could by isolated.[19] The iodo-, bromo-, and chloroenol ethers were obtained in 88%, 76%, and 82% yields, respectively, based on **6**, after chromatography on silica) and were subjected to hydrolysis conditions (see Table I).

It may be for the prostacyclin series, as in the model cases noted above, in which a cis fusion of the bicyclic enol ether moiety is a requirement, that formation of the 5,5-bicyclic species is *kinetically* preferred. In the corresponding trans-fused case such a ring system may not be feasible on strain grounds, and therefore, only slower cyclization to give the 5,6-endocyclic species can occur. General rules for acetylenic alcohol cyclization remain to be elucidated.

**Acknowledgment.** We acknowledge support for this work provided by the National Institutes of Health (Grant No. HL22612).

**Registry No. 1**, 83096-84-8; **2**, 83096-85-9; **2**-endo, 83096-95-1; **3**, 83114-94-7; **4**, 83096-86-0; **5**-H, 83096-87-1; **5** (X = I), 83096-88-2; **5** (X = Br), 83096-89-3; **5** (X = Cl), 83096-90-6; **6**, 83096-91-7; **7**, 83096-92-8; $HgCl_2$, 7487-94-7; $Hg(O_2CCF_3)_2$, 13257-51-7; *trans* 2-butyl-3-iodo-4,4a,5,6,7,7a-hexahydrocyclopenta[*b*]pyran, 83114-95-8; *trans*-3-bromo-2-butyl-4,4a,5,6,7,7a-hexahydrocyclopenta[*b*]pyran, 83096-93-9; *trans*-2-butyl-3-chloro-4,4a,5,6,7,7a-hexahydrocyclopenta-[*b*]pyran, 83096-94-0.

(12) $^1H$ NMR ($C_6D_6$) δ 4.96 (t × t, $J$ = 7.2 × 1.8 Hz), 4.49 (m, 1), 2.6-1.1 (m, 15), 0.93 (t, 3, $J$ = 6.3 Hz). Exact mass: calcd, 180.1514; found, 180.1522 ± 0.0018.

(13) $^1H$ NMR ($C_6D_6$) δ 4.52 (m, 1), 2.8-1.0 (m, 15), 0.90 (t, 3, $J$ = 6.4 Hz); $^{13}C\{^1H\}$ δ 155.6, 81.5, 68.1, 43.3, 42.6, 37.9, 29.7, 28.7, 27.1, 22.6, 20.0, 14.1. Exact mass: calcd, 306.0482; found, 306.0454 ± 0.003.

(14) $^1H$ NMR ($C_6D_6$) δ 4.51 (m, 1), 2.8-1.0 (m, 15), 0.90 (t, 3, $J$ = 6.4 Hz); $^{13}C\{^1H\}$ δ 155.0, 97.9, 90.1, 41.2, 38.7, 34.5, 33.6, 33.3, 30.7, 24.2, 21.9, 14.0. Exact mass: calcd, 258.0620; found, 258.0603 ± 0.0025.

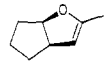
(15) In the absence of mercuric salts, the reaction between 4 and NBS gave only polybrominated products, as did treatment of 4 simultaneously with Hg(II) and NBS.

(16) The chloro compound could not be purified satisfactorily by chromatography. The $^1H$ NMR spectrum was similar to that of the β-bromo analogue. Exact mass: calcd, 214.1124; found, 214.1106 ± 0.002.

(17) **7**: $^1H$ NMR ($C_6D_6$) δ 4.52 (m, 1), 3.46 (m, 1), 2.24-1.14 (m, 15), 0.89 (t, 3, $J$ = 6.4 Hz); $^{13}C\{^1H\}$ δ 156.0, 95.3, 81.7, 39.9, 34.3, 29.9, 29.0, 28.3, 27.8, 22.6, 19.9, 14.1. Exact mass: calcd, 180.1514; found, 180.1514 ± 0.0018.

(18) Cyclization to **7** could be effected successfully by using a catalytic amount of Hg(II) salts either in the presence (slowly) or absence (rapidly) of base or with $Pd(OAc)_2$ in $CH_2Cl_2$ (slowly).

(19) In the presence of 2 equiv of $NEt_3$, the di(alkenyl)mercury derivative **9** could be isolated (15%, after chromatography on silica): $^1H$ NMR ($C_6D_6$) δ 3.26 (m, 1), 2.0-1.0 (m, 15), 0.85 (t, 3, $J$ = 6 Hz). This species could be converted to the corresponding β-halogen enol ethers in high yield.



2-endo

## Palladium-Catalyzed Decarboxylation-Dehydrogenation of Allyl β-Keto Carboxylates and Allyl Enol Carbonates as a Novel Synthetic Method for α-Substituted α,β-Unsaturated Ketones

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β-Keto esters are important intermediates for selective alkylation of ketones. Usually after the alkylation, the ester group as the activating group of the ketone is removed by hydrolysis and subsequent decarboxylation. If the ester group is removed oxidatively, instead of by simple decarboxylation, such a method would be very useful for further transformation. In this communication, we report the facile formation of α,β-unsaturated ketones from β-keto esters under very mild conditions.

In a previous paper, we have reported the palladium-catalyzed rearrangement of allylic esters of acetoacetic acid to form γ,δ-unsaturated methyl ketones (the Pd-catalyzed Carroll rearrangement).[1,2] In the course of further studies on this reaction with cyclohexanone derivatives, we found a profound effect of the ligand: the decarboxylation-dehydrogenation took place to give 2-alkyl-2-cyclohexenones (**2**, Scheme I) from allyl 2-alkylcyclohexanone-2-carboxylates (**1**) by using 1,2-bis(diphenylphosphino)ethane (dppe), instead of $PPh_3$, as the ligand. In a typical example, allyl 2-methylcyclohexanone-2-carboxylate (**1a**) (1 mmol) in $CH_3CN$ was refluxed for 30 min in the presence of

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(2) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381-6384.

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