# The First Stereoselective Palladium-Catalyzed Cyclocarbonylation of β,γ-Substituted Allylic Alcohols

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β,γ-Substituted allylic alcohols react with CO in the presence of catalytic quantities of palladium acetate and 1,4-bis(diphenylphosphino)butane affording α,β-substituted-γ-butyrolactones in 42−85% isolated yields. The complete stereoselectivity observed in some cases is a significant feature of the lactonization reaction, with (*E*)-allylic alcohols affording *trans*-disubstituted lactones. Depending on the structure of the allylic alcohol used in the cyclocarbonylation reaction, the formation of the corresponding alkene or the β,γ-unsaturated carboxylic acid was observed as a side or the principal reaction.

## Introduction

Transition metal-catalyzed carbonylation of unsaturated compounds has been a field of great interest, in terms of both academic and industrial applications. The intramolecular cyclization of unsaturated alcohols to lactones, as a special class of carbonylation reaction, represents an elegant route to heterocycles. It has been the subject of several investigations in the last few years.[1−4]

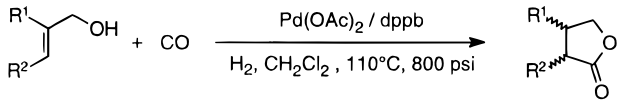
So far, only allylic alcohols with up to two substituents on the C=C bond have been successfully subjected to the cyclocarbonylation reaction. The $Pd(dba)_2$-catalyzed lactonization in the presence of 1,4-bis(diphenylphosphino)-butane (dppb) at 190 °C in DME,[5] and at 100 °C in $CH_2Cl_2$,[2] was applicable to allylic alcohols with a terminal olefinic unit, but no reaction occurred for allylic alcohols bearing an internal double bond. However, palladium(II) chloride could mediate the carbonylation of allylic alcohols, even with internal C=C bonds, when acidic conditions were employed in the presence of oxygen and copper(II) chloride.[6] Nevertheless, this reaction is restricted to disubstituted double bonds.

There are no examples in the literature concerning the cyclocarbonylation of β,γ-substituted allylic alcohols with a 1,1,2-trisubstituted olefinic unit to form α,β-substituted-γ-butyrolactones. Lactones with such a substitution pattern are sometimes difficult to prepare using other classical synthetic methods, and they are potentially useful for the synthesis of biologically active molecules. Bicyclic derivatives of this lactone type including hexahydro-2(3*H*)-benzofuranones and tetrahydro-1*H*-cyclopenta-[*c*]-furan-1,4(3*H*)-dione (cyclosarkomycin) have already been proven to possess high activities as an insect repellent or antitumor agent.[7,8]

We now wish to report the synthesis of α,β-substituted-γ-butyrolactones from β,γ-substituted allylic alcohols by the use of appropriate palladium catalysts and phosphine ligands.

## Results and Discussion

Treatment of allylic alcohols **1** with a 1/1 mixture of carbon monoxide and hydrogen (800 psi) in the presence of a catalytic amount of $Pd(OAc)_2$ and dppb at 110 °C for 18 h resulted in the formation of lactones **2** in modest to good yields (eq 1). The ratio of substrate to palladium catalyst and added ligand was 25/1/1. The results of the cyclocarbonylation of aliphatic and aromatic unsaturated alcohols under these conditions are given in Table 1.




**1** **2**

Other palladium complexes like $Pd(acac)_2$, $Pd_2(dba)_3 \cdot CHCl_3$, or $(PCy_3)_2Pd(H)(H_2O)^+BF_4^-$ in combination with 1 equiv of dppb gave similar results but slightly lower isolated yields of the lactones. $Pd(PPh_3)_4$ with or without dppb was almost inactive, with only 13% of the allylic alcohol **1c** being converted into **2c**. As already demonstrated, reducing the metal-chelate ring size lowers the yield of the obtained lactone.[2] In the case of **1c**, the lactone could be isolated in 63% yield with dppb as the ligand, while dppp (1,3-bis(diphenylphosphino)propane) gave the lactone in only 17% yield, and almost no conversion occurred with dppe (1,2-bis(diphenylphosphino)ethane). An increase of the dppb/metal ratio from 1/1 to 2/1 resulted in a lower yield of the lactone. No carbonylation occurred when the palladium acetate catalyzed reaction was carried out in THF, benzene, DME, or DMF. A reaction temperature of 110 °C was found to be optimal. Lowering the reaction temperature led to the complete suppression of any reaction, while higher temperatures resulted in lower yields of the lactone due to several side reactions. The presence of hydrogen is essential since without hydrogen no lactone was obtained at all.

The lactonization of the allylic alcohols **1a**, **1c**, **1d**, **1e**, and **1g** proceeded with complete stereoselectivity, with (*E*)-allylic alcohols affording *trans*-lactones. The *trans*-stereochemistry of the obtained lactones was established on the basis of a crystallographic study of **2c** (see Supporting Information).

A mixture of five- and six-membered ring lactones was formed as an inseparable mixture by the cyclocarbonylation reaction of **1b**. Nevertheless, the $^1H$, $^{13}C$, and COSY NMR spectral data indicated that the five- as well as the six-membered rings exist as a mixture of *cis*- and

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(5) El Ali, B.; Alper, H. *J. Org. Chem.* **1991**, *56*, 5357.
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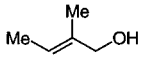
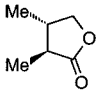
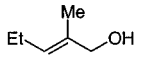
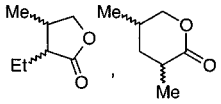
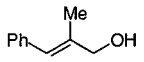
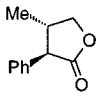
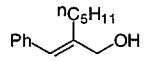
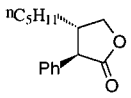
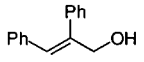
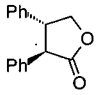
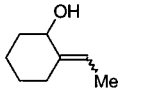
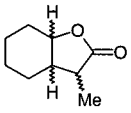
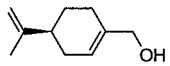
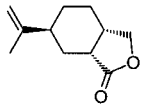
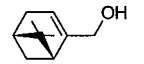
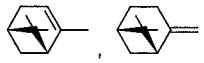
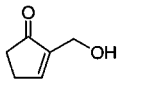
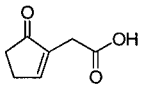
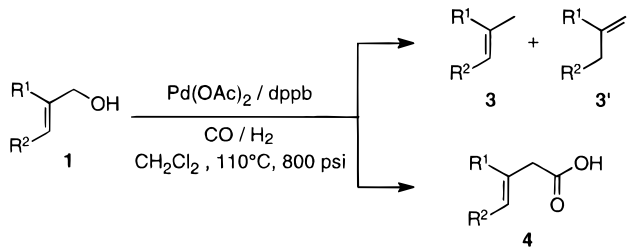
**Table 1. Cyclocarbonylation of *β,γ*-Substituted Allylic Alcohols Catalyzed by Pd(OAc)$_2$/dppb**

| entry | allylic alcohol | | product | | yield [%][a] |
|---|---|---|---|---|---|
| 1 |  | **1a** |  | (±)-**2a** | 68 |
| 2 |  | **1b** |  | **2b**, **2'b** | 53[b] |
| 3 |  | **1c** |  | (±)-**2c** | 63 |
| 4 |  | **1d** |  | (±)-**2d** | 65 |
| 5 |  | **1e** |  | (±)-**2e** | 42 |
| 6 |  | **1f**[c] |  | **2f** | 85 |
| 7 |  | **1g** |  | **2g** | 56 |
| 8 |  | **1h** |  | **3a**, **3'a** | 100 |
| 9 |  | **1i**[d] |  | **4a** | 70 |

Reaction conditions: 1 mmol substrate, 0.04 mmol Pd(OAc)$_2$, 0.04 mmol dppb, 10 ml $CH_2Cl_2$, 800 psi CO/$H_2$ (1/1), 110°C, 18 h. [a] isolated yields. [b] lactone isomers could not be separated; calculated by NMR, the mixture contained 48% of *trans*-**2b**. [c] (*E*)/(*Z*): 2/1. [d] reaction time: 48 h.

*trans*-diastereomers. It is very likely that **1b** was first partially isomerized to 2-methyl-3-penten-1-ol before being carbonylated. By integration of the NMR signals as well as GLC analysis it was determined that the lactone mixture consisted of one major compound (48%) which could be assigned structure *cis*-**2b**. The lactonization of **1f** led directly to **2f**, which is an insect repellent.[7] Compared to the literature data, lactone **2f** consisted of a mixture of *cis*- and *trans*-fused hexahydro-2(3*H*)-benzofuranones, each with an *exo*- or *endo*-methyl group. Subjecting (*S*)-perillyl alcohol (**1g**) to the catalytic reaction resulted in the exclusive formation of one diastereomer of the bicyclic furanone **2g**. The stereochemistry of **2g** was not determined, but it is very conceivable that the isopropylidene substituent is in the *trans*-position to the furanone ring. Force field calculations showed that this diastereomer possesses the lower energy.[9]

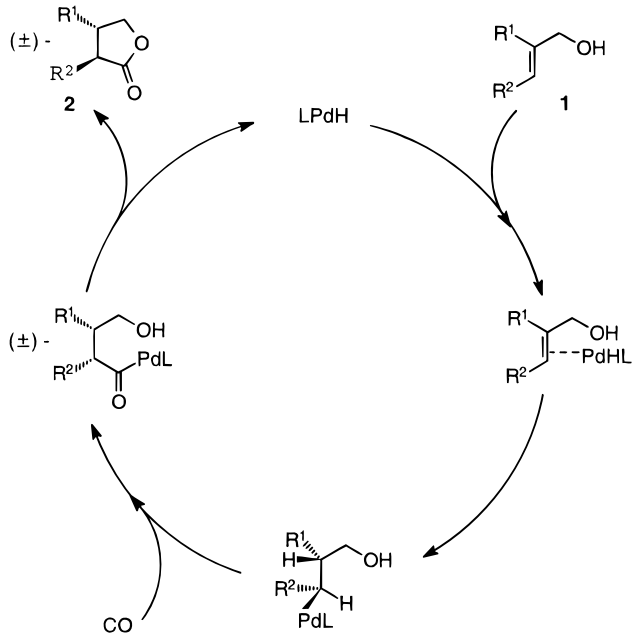
It is noteworthy that under the chosen reaction conditions the conversion of the allylic alcohols **1a**−**g** was always 100%. After the reaction time, no starting material could be detected by GLC analysis. In the case of **1c**−**e**, the side products were isolated and could be identified as the alkenes **3** and **3′** (eq 2).



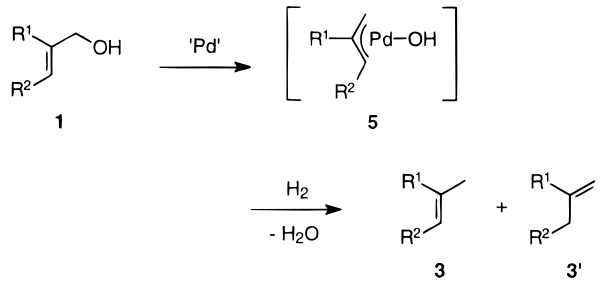

The structures of these alkenes were determined by comparison of the spectral data with literature data or authentic samples. Subjecting (1*R*)-myrtenol (**1h**) to the carbonylation conditions afforded (1*R*)-α- and *β*-pinene but no carbonylation products. This type of transformation was also observed with other palladium catalysts mentioned previously. The production of alkenes *via* decarboxylation of the corresponding lactone can be ruled out. No lactone decomposition was observed by treating the heterocycles with the palladium catalyst under the standard reaction conditions for 72 h—the lactones were fully recovered. Therefore we assume that a hydroxyallyl palladium complex was involved which reacts with the hydrogen present to form $H_2O$ and thereby releasing the alkenes (eq 3). In an additional experiment the hydrogen pressure was reduced to 100 psi. Although the conversion of the allylic alcohol was not complete after 18 h,

(9) The energies of the possible diastereomers were compared by MM2 calculations using the Spartan SGI 4.04.GL software.

**Scheme 1. Proposed Mechanism of the Pd-Catalyzed Cyclocarbonylation**




lactone and alkenes were nevertheless formed in the same ratio.




Another type of catalytic transformation was observed when **1i** was subjected to the same conditions for the palladium-mediated carbonylation reaction. In this case, the β,γ-unsaturated acid **4a** was obtained in 70% yield. Surprisingly, the acid was formed without isomerization to the complete conjugated system. This type of double bond migration has been described for the carbonylation of allylic alcohols to carboxylic acids using a catalytic system based on palladium chloride and 2 equiv of $PPh_3$ at 80 °C under very high CO pressure (3500 psi).[10] However, it has recently been observed that the conversion of allylic alcohols into β,γ-unsaturated carboxylic acids can occur without isomerization using a palladium clay catalyst in the presence of an acid.[11]

A possible mechanism for the cyclocarbonylation is given in Scheme 1. It is conceivable that under the reaction conditions Pd(II) is reduced to Pd(0). Indeed both Pd(II) and Pd(0) catalysts gave similar results. Furthermore, a palladium hydride complex can be assumed to be the active species as lactone formation only occurs in the presence of hydrogen. Coordination of the allylic alcohol to the metal complex followed by *cis*-addition of the palladium hydride to the allylic C=C bond and subsequent CO insertion into the Pd−C bond would lead to an acylpalladium complex. Rotation about the central C−C bond followed by ring closure affords the *trans*-substituted lactone with regeneration of palladium hydride. An alternative pathway would involve initial oxidative addition of palladium(0) to the OH bond of the allylic alcohol to generate a palladium hydride.

In conclusion, we have demonstrated a catalytic method allowing the synthesis of α,β-substituted-γ-butyrolactones from β,γ-substituted allylic alcohols in modest to good yields. In most cases, this transformation occurred with complete stereoselectivity since (*E*)-allylic alcohols were exclusively converted into the *trans*-lactones. Although many approaches for the synthesis of lactones have been reported, the present strategy is potentially useful as an attractive complementary methodology, especially considering the obtained substitution pattern of the lactones. Depending on the structure of the allylic alcohol, alkenes or carboxylic acids could be formed in a side reaction which became in some cases the main reaction pathway. The asymmetric cyclocarbonylation of β,γ-substituted allylic alcohols is currently under investigation.

## Experimental Section

**General.** Gas chromatography was performed on the HP 5890 series II gas chromatograph containing an OV-17 column connected to a HP 3396 series II integrator. For preparative HPLC a JAI LC-908 instrument equipped with a JAIGEL 2H column was used. Melting points are uncorrected.

**Materials.** Solvents were dried by standard methods and distilled under $N_2$. Metal catalysts and phosphine ligands were purchased from commercial sources or prepared according to literature procedures ($Pd_2(dba)_3$·$CHCl_3$[12] and $(PCy_3)_2$-$Pd(H)(H_2O)^+BF_4^-$ [13]). 2-Methyl-3-phenyl-2-propen-1-ol (**1c**), (*S*)-perillyl alcohol (**1g**), and (1*R*)-myrtenol (**1h**) are commercially available. The allylic alcohols **1a,b,d** were prepared from the reduction of the corresponding aldehydes with $NaBH_4$ in $EtOH/H_2O$.[14] **1e** was prepared from the reduction of the acyl chloride with $NaBH_4$ under similar conditions. The synthesis of the allylic alcohol **1f** followed the standard Wittig conditions. The ylide was reacted with the TBDMS-protected α-hydroxy-ketone in the presence of $(Me_3Si)_2NK$.[15] **1i** was prepared according to a literature procedure.[16] All the alcohols were further purified by vacuum distillation or flash column chromatography prior to use. The following allylic alcohols are known compounds and have spectral data in accord with the literature data: **1a**, **1b**,[17] **1d**,[18] **1f**,[19] and **1i**.[20]

**(*E*)-2,3-Diphenyl-2-propen-1-ol (1e).** Colorless crystals, mp 68 °C. $^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.37−6.98 (m, 10H), 6.70 (br s, 1H), 4.44 br s, 2H), 2.14 (br s, 1H). $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ = 141.4, 138.5, 136.4, 129.1, 128.7, 126.7, 126.3, 68.3. MS (70 eV, EI) 210 [$M^+$]. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.53; H, 6.72.

**General Procedure for the Carbonylation of the Allylic Alcohols.** All catalytic reactions were carried out using standard Schlenk technique in a $N_2$ atmosphere. A solution of $Pd(OAc)_2$ (0.04 mmol) and dppb (0.04 mmol) in 5 mL of $CH_2$-

(10) Himmele, W.; Hoffmann, W.; Janitschke, L. U.S. Pat. 4 585 594, 1988.
(11) Naigre, R.; Alper, H. *J. Mol. Cat. A* **1996**, *111*, 11.
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(13) Leoni, P.; Sommovigo, M.; Pasquali, M.; Midollini, S.; Braga, D.; Sabatino, P. *Organometallics* **1991**, *10*, 1038.
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(16) Smith, A. B., III; Dorsey, B. D.; Ohba, M.; Lupo, A. T., Jr.; Malamas, M. S. *J. Org. Chem.* **1988**, *53*, 4314.
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$Cl_2$ was stirred at room temperature for 20 min. After addition of the allylic alcohol (1.0 mmol) dissolved in 5 mL of $CH_2Cl_2$, the solution was transferred to a 45 mL of Parr autoclave equipped with a glass liner. The reactor was flushed three times with carbon monoxide and pressurized to 400 psi of CO. The delivery line connecting the reactor and the hydrogen tank were purged with hydrogen, and the autoclave was charged with hydrogen to a total pressure of 800 psi. The autoclave was immersed in a preheated oil bath, and the reaction mixture was stirred for 18 h at 110 °C. The pressure was released after the reactor was cooled down to room temperature. The catalyst was removed by filtration over Florisil. The consumption of the reactant allylic alcohol was monitored by gas chromatography. The mixture was evaporated, and the product was isolated by preparative TLC, HPLC, or vacuum distillation. The following lactones are known compounds and have spectral data in accord with the literature data: **2a**,[21] **2′b**,[22] **2c**,[23] **2e**,[24] and **2f**.[25]

**Dihydro-3-ethyl-4-methyl-2(3*H*)-furanone (*trans*-2b).**[26] $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 4.29 (dd, 1H, $^2J$ = 9.0 Hz, $^3J$ = 7.7 Hz), 3.66 (dd, 1H, $^2J$ = 9.0, $^3J$ = 9.0 Hz), 2.28 (m, 1H), 2.11 (m, 1H), 1.09 (d, 3H, $^3J$ = 6.6 Hz), 0.97 (tr, 3H, $^3J$ = 6.6 Hz). $^{13}$C NMR (125.8 MHz, $CDCl_3$): $\delta$ = 179.0, 72.4, 47.9, 35.3, 21.5, 16.7, 10.9.

**Dihydro-4-pentyl-3-phenyl-2(3*H*)-furanone (*trans*-2d).** Colorless crystals, mp 31 °C. IR (KBr): 1775 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 7.36−7.17 (m, 5H), 4.50 (dd, 1H, $^2J$ = 9.1 Hz, $^3J$ = 7.7 Hz), 3.94 (dd, 1H, $^2J$ = 9.1 Hz, $^3J$ = 9.1 Hz), 3.35 (d, 1H, $^3J$ = 11.0 Hz), 2.62 (m, 1H), 1.67−1.19 (m, 8H), 0.82 (tr, 3H, $^3J$ = 6.5 Hz). $^{13}$C NMR (50.3 MHz, $CDCl_3$): $\delta$ = 177.4, 136.2, 128.9, 128.5, 127.6, 71.7, 52.8, 45.1, 31.9, 26.6, 22.3, 13.9 ppm. MS (70 eV, EI): 232 [M$^+$]. HRMS (70 eV, EI): calcd for $C_{15}H_{20}O_2$: 232.14633, found 232.14664. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.62; H, 8.84.

**Hexahydro-(6*S*)-isopropenyl-1(3*H*)-isobenzofuranone (2g).** Colorless oil. IR (KBr): 1776 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 4.68 (br s, 2H), 4.32 (dd, 1H, $^2J$ = 8.3 Hz, $^3J$ = 6.7 Hz), 3.82 (dd, 1H, $^2J$ = 8.3, $^3J$ = 6.6 Hz), 2.19−1.84 (m, 6H), 1.68 (s, 3H), 1.31−1.19 (m, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): $\delta$ = 177.2, 148.3, 109.4, 72.0, 45.1, 44.6, 43.2, 30.2, 29.5, 27.4, 20.8 ppm. MS (70 eV, EI): 180 [M$^+$]. HRMS (70 eV, EI): calcd for $C_{11}H_{16}O_2$: 180.11503, found 180.11467.

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**Supporting Information Available:** ORTEP crystal data, coordinates bond lengths and angles, and experimental protocol for X-ray of **2c**; $^1$H and $^{13}$C NMR spectra of lactone **2g** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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