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Unsaturated Bicyclic Lactones

Palladium-Catalyzed Carbonylation of 2-(Propargyl)allyl Phosphates Leading to Highly Unsaturated γ-Lactones**

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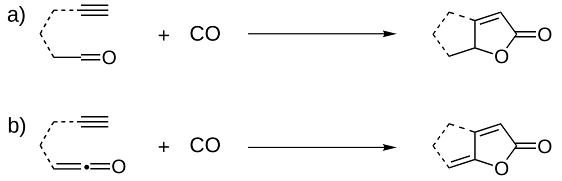
Unsaturated lactones are an intensively studied family of heterocycles, which are important subunits in naturally occurring, as well as biologically active compounds.[1,2] While numerous approaches have been developed for the synthesis of such skeletons,[1] a simple and straightforward method for the construction of highly functionalized γ-lactones continues to be a challenge. We have previously reported on a new method for the construction of γ-lactone skeletons.[3–5] This methodology involves a carbonylative [2+2+1] cycloaddition reaction (Scheme 1 a). If one uses acetylene–ketenes as the substrate in place of acetylene–aldehydes, the formation of γ-alkylidene-α,β-unsaturated lactones would be expected, through the [2+2+1] cycloaddition of alkynes, ketene–carbonyl, and CO (Scheme 1 b). The transformation would provide a new route to unsaturated lactones; however, such a transformation has not been reported thus far.[6] Herein we report on the realization of this approach for the construction of polyunsaturated, fused bicyclic γ-lactones by the Pd-catalyzed carbonylation of 2-(propargyl)allyl phosphates.



Scheme 1. Cycloaddition of alkynes, CO, and carbonyl functionality; see text for details.

Ketenes are versatile, well-known substrates in organic synthesis, but they are most often produced in situ from acid chlorides through dehydrochlorination reactions with tertiary amines.[7] Although various reaction conditions were explored

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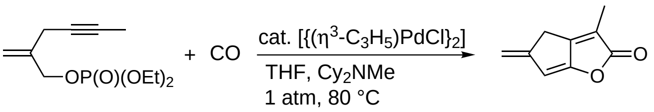
to achieve the reaction of intramolecular acetylene–acid chlorides with CO, the expected lactones were not formed. We then examined π-allyl palladium complexes and CO as the ketene source. Torii et al. reported that the Pd-catalyzed reaction of allyl phosphates with imines led to β-lactams, a reaction in which a [2+2] cycloaddition of in situ generated vinylketenes and imines was proposed as the key step.[8] Negishi et al. also proposed the generation of phenylketene derivatives from the reaction of benzylpalladium complexes and CO.[9] A preliminary screening of potential substrates indicated that 2-(propargy)allyl phosphate provided high reactivity. Thus, treatment of 2-methylene-4-hexyn-1-yl diethyl phosphate (**1a**) (0.5 mmol) with CO (1 atm) in THF (2 mL) in the presence of [{(η^3-allyl)PdCl}$_2$] (0.01 mmol) and Cy$_2$NMe (1 mmol) for 12 h led to the formation of the expected bicyclic lactone **2a**[10] in 52 % yield [Eq. (1)]. Among



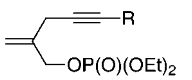
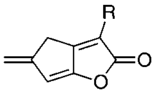
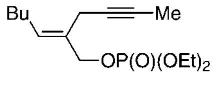
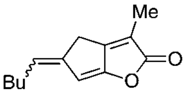
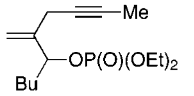
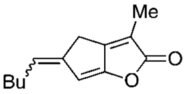
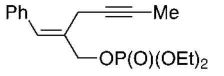
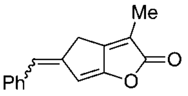
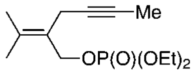
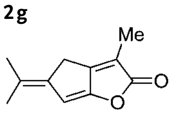
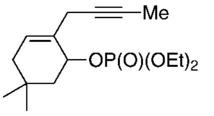
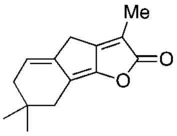
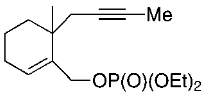
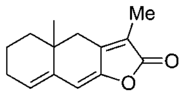
(1)

1a **2a**

the solvents examined, THF was found to be the best solvent and gave the highest yield; toluene (47 %), DMF (39 %), cyclohexane (16 %), and CH$_2$Cl$_2$ (no reaction). While tertiary aliphatic amines were effective, *N,N*-dimethylaniline, pyridine, and K$_2$CO$_3$ were not. In place of phosphate, acetate and carbonate did not function as a leaving group, but the use of a chloride gave **2a** in 45 % yield. Some phosphane-free palladium complexes, such as PdCl$_2$ (61 % yield), PdCl$_2$(PhCN)$_2$ (64 %), and Pd(acac)$_2$ (40 %) were active. When the reaction given in Equation (1) was carried out for 40 h, the product yield increased to 73 %.

The reaction was also appplicable to various derivatives of **1** (Table 1). Altering the steric character of an alkyl substituent at the acetylenic carbon atom had little effect on the efficiency of the reaction (Table 1, entries 1–3). However, substitution with trimethylsilyl and H resulted in no observable products, as evidenced by GC and TLC, although the starting materials were completely consumed. The substitution of a phenyl group gave the expected product in only 17 % yield, along with a large variety of impurities (data not shown). The substitution of a butyl group at the olefinic carbon atom, as in **1e**, gave **2e** in 80 % yield (Table 1, entry 4). The stereochemistry of the starting material **1e** was exclusively *E*, but the products obtained were a 2:1 mixture of *E* and *Z* isomers. The reaction of **1e** and **1f** gave the same product **2e**, indicating that the reaction proceeds via a common intermediate (Table 1, entries 4 and 5). Tricyclic lactones **2i** and **2j** were produced in high yield from a cyclic phosphonate (Table 1, entries 8 and 9).

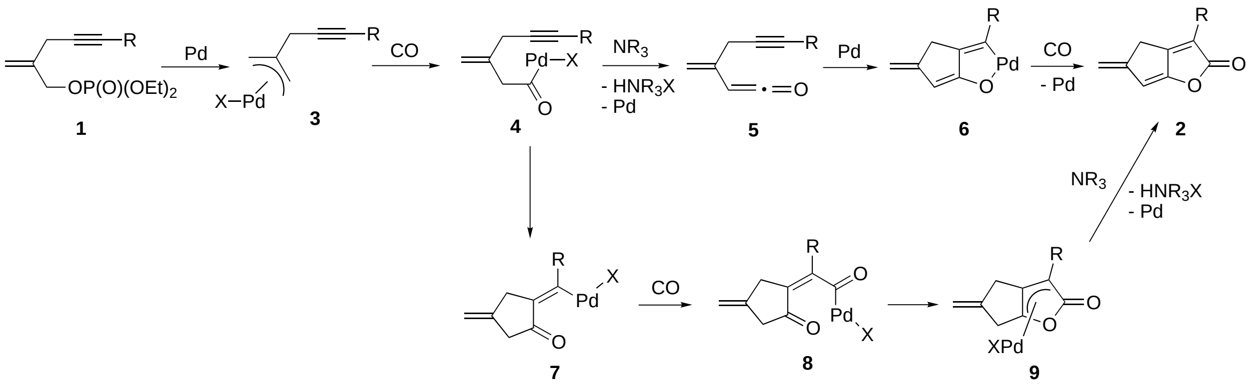
Table 1: Pd-catalyzed reaction of 2-propargylallyl phosphates with CO.[a]

Entry	Allyl phosphate	Product	Yield [%][b]
			
1	**1b** (R = Bu)	**2b**	73
2	**1c** (R = Cy)	**2c**	94
3	**1d** (R = *t*Bu)	**2d**	87
4	 **1e**	 **2e**	80 (*Z*/*E* = 2/1)
5[c]	 **1f**	 **2e**	88 (*Z*/*E* = 2/1)
6	 **1g**	 **2g**	50 (*Z*/*E* = 1/1)
7	 **1h**	 **2h**	73
8[c]	 **1i**	 **2i**	72
9[c,d]	 **1j**	 **2j**	64

[a] Reaction conditions: substrate (0.5 mmol), [{(η^3-C$_3$H$_5$)PdCl}$_2$] (0.01 mmol), Cy$_2$NMe (1 mmol), CO (1 atm), THF (2 mL) at 80 °C for 12 h. [b] Yields of isolated products. The ratio in the parentheses was determined by NMR analysis. [c] 0.025 mmol of catalyst was used. [d] Reaction time 40 h.

Scheme 2 shows the proposed reaction mechanism. Reaction of **1** with Pd^0 gives a π-allyl palladium complex **3**, in which the insertion of CO followed by deprotonation takes place to generate the ketene **5**. Oxidative cyclization of **5** at a Pd^0 center gives the metallacycle **6**. The insertion of CO[11] in **6** followed by reductive elimination gives the final product **2**. An alternative mechanism, which does not involve the intermediacy of ketene **5**, should also be considered. Here, complex **4** undergoes carbometalation to give the vinyl palladium complex **7**, in which CO is inserted to give an acyl complex **8**. The cyclization of **8** gives the π-allyl palladium complex **9**,[12] which is then deprotonated to give the final product **2**.[13] The loss of stereochemistry at the olefinic part in the starting phosphonates is rationalized by the formation of π-allyl palladium complex **3** (Table 1, entries 4 and 6). The reaction of **1e** and **1f** gave the same product **2e**, indicating that both reactions proceed via the π-allyl palladium complex **3**.

In summary, the present reaction provides a new method for the construction of highly unsaturated bicyclic lactones,[14] which are difficult to access by conventional methods, by the Pd-catalyzed carbonylation of 2-proparygylallyl phosphonates. The reaction proceeds smoothly even under mild



Scheme 2. Proposed reaction mechanism for the formation of **2**.

reaction conditions. Studies of the synthetic applications of these compounds and the reaction mechanism are currently underway.

Experimental Section

Full procedures and chracterization data are given in the Supporting Information.

Representative procedure [Eq. (1)]: A 50-mL resealable Schlenk tube was flame-dried under a stream of nitrogen. The flask was charged with **1a** (0.5 mmol, 123 mg), [{(π-C_3H_5)PdCl}$_2$] (0.01 mmol, 3.7 mg), dicyclohexylmethylamine (1.0 mmol, 0.2 mL), and THF (2 mL), and a three-way stopcock, which was connected to a vacuum line and a balloon filled with carbon monoxide, was attached to the flask. The system was carefully evacuated and refilled with carbon monoxide four times and then filled with carbon monoxide (1 atm). Finally the system was sealed and immersed in an oil bath at 80 °C. After 40 h, the flask was removed from the oil bath and allowed to cool for 1 h, after which the CO was released. The contents were transferred to a 100-mL round-bottomed flask and volatiles were removed in vacuo. The residue was subjected to column chromatography on silica gel (eluent; hexane/EtOAc = 20/1) to give **2a** (54 mg, 73 % yield) as a white solid. Mp 69–73 °C (hexane); $R_f = 0.47$ (hexane/EtOAc = 3/1); ^{1}H NMR (270 MHz, $CDCl_3$, TMS): $\delta = 1.95$ (s, 3H), 3.31 (m, 2H), 5.09 (s, 1H), 5.24 (s, 1H), 6.07 ppm (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$): $\delta = 9.2$, 29.3, 108.6, 112.2, 113.7, 148.2, 157.8, 159.8, 173.4 ppm; IR (KBr): $\tilde{\nu} = 3524$ w, 2936 w, 1944 w, 1922 w, 1770 s, 1660 s, 1614 s, 1498 w, 1406 m, 1374 m, 1306 m, 1246 w, 1232 m, 1184 m, 1106 w, 1050 w, 972 m, 918 w, 858 s, 748 m, 722 w, 674 w, 660 w, 646 cm^{-1} w; MS: m/z (%): 148 (80) [M^+], 120 (26), 91 (100), 67 (49), 65 (15), 53 (25), 51 (24), 50 (16); elemental analysis calcd (%) for $C_9H_8O_2$: C 72.96, H 5.44; found: C 72.72, H 5.55.

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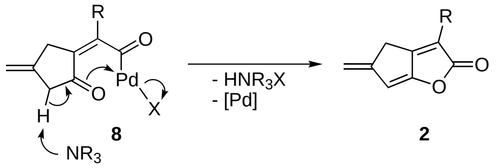

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