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Mild and Efficient Synthesis of (*Z*)-α-Chloroalkylidene-*β*-lactones via the $PdCl_2$-Catalyzed Cyclocarbonylation of 2-Alkynols

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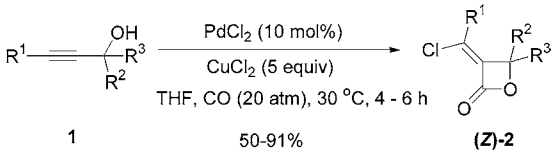
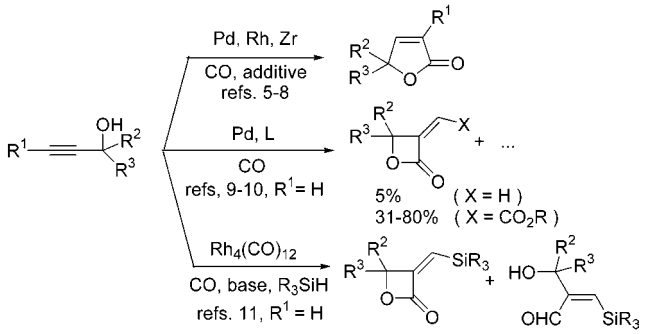
ABSTRACT



A mild and efficient methodology involving $PdCl_2$-catalyzed cyclocarbonylation of 2-alkynols with $CuCl_2$ for the synthesis of (*Z*)-α-chloroalkylidene-*β*-lactones was developed. Using the readily available optically active propargylic alcohols allows convenient synthesis of the corresponding (*Z*)-α-chloroalkylidene-*β*-lactones with high ee values. *cis*-Chloropalladation was observed as the major pathway, which is unique as compared to the reported data.

Propargylic alcohols are readily available compounds of synthetic importance.[1,2] Of particular interest is the transition metal-mediated or -catalyzed carboxylation reaction. Rosenthal et al. reported that the transition metal-catalyzed or -mediated reaction of 2-propynol afforded α-hydroxy (or methoxyl) methyl acrylates together with several other acrylate derivatives.[3,4] For the cyclizative carboxylation reaction of propargylic alcohols, three types of reaction patterns affording butenolides, α-alkylidene-*β*-lactones, or α,*β*-unsaturated enals, respectively, have been demonstrated (Scheme 1).[5−11]

Scheme 1



Usually, *β*-lactones were formed from terminal propargylic alcohols, with the selectivity and the yield depending largely on the structures of the alcohols. [9−11]

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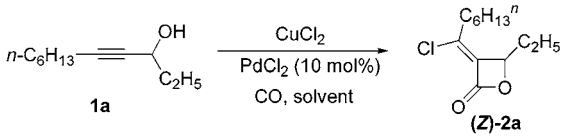
α-Alkylidene-β-lactones are important skeletons in some biologically active natural products[12] and considered as useful building blocks in organic synthesis.[13] Besides the methods described above, α-alkylidene-β-lactones have also been prepared via [2 + 2] cycloaddition of ketenes and carbonyl compounds,[14] lactonization of β-hydroxy carboxylic acids or derivatives,[15] and deoxygenation of β-peroxylactones.[16] However, these known pioneering methods may, in some cases, suffer from lengthy procedures, harsh conditions, or low yields. Thus, new and efficient methodologies for α-alkylidene-β-lactones are still desirable. In this paper, we report a general and high-yielding Pd-catalyzed carbonylation of propargylic alcohols with various structural patterns forming (*Z*)-α-chloroalkylidene-β-lactones selectively.

Our initial observation of achieving (*Z*)-α-chloroalkylidene-β-lactone **2a** involved the reaction of **1a**, 3 equiv of $CuCl_2$, and CO (1 atm) with $PdCl_2$ as the catalyst at 20 °C in PhH, but the yield was only 29% (entry 1, Table 1). With the pressure of CO being 15 atm, the yield was not dramatically improved (entries 2, Table 1). After some trial and error, we found that the solvent, CO pressure, and temperature are crucial factors, and the best reaction conditions are 10 mol % $PdCl_2$, 5 equiv of $CuCl_2$, and CO (20 atm) in THF at 30 °C for 4 h. Under these reaction conditions, (*Z*)-**2a** was isolated in 86% yield (entry 3, Table 1).

Table 1. $PdCl_2$-Catalyzed Cyclocarbonylation of Undec-4-yn-3-ol **1a** with $CuCl_2$

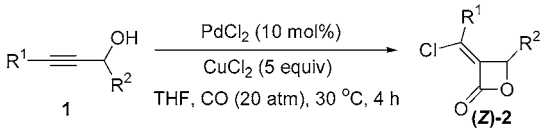


entry	CO (atm)	$CuCl_2$ (equiv)	solvent	temp (°C)	time (h)	yield[a] (%)
1	1	3	PhH	20	18	29
2	15	3	THF	25	17	35
3	**20**	**5**	**THF**	**30**	**4**	**86**
4	20	5	THF	70	4	31

[a] Isolated yield.

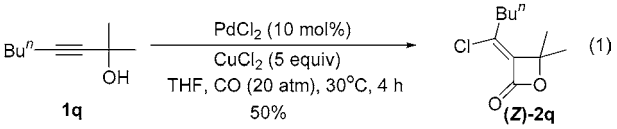
To explore the scope of this reaction, the effect of substituents R^1 and R^2 was investigated. As can be seen from Table 2, R^1 can be an alkyl group or an aryl group, including ^{t}Bu, while the R^2 group should be an alkyl group. The four-membered structures of (Z)-**2** were established by a single-crystal X-ray diffractional study of (Z)-**2k**[17] and (Z)-**2n**[18] (Figure 1). When R^2 was an aryl group, the corresponding carbonylation of 1-(4′-methoxyphenyl)hept-2-yn-1-ol gave only a complex mixture. The cyclocarbonylation of tertary alcohol 2-methyloct-3-yn-2-ol **1q** also gave (*Z*)-α-chloroalkylidene β-lactone (*Z*)-**2q** in 50% yield (eq 1).

Table 2. $PdCl_2$-Catalyzed Cyclocarbonylation of Secondary Propargylic Alcohols with 5 Equiv of $CuCl_2$



entry	R^1	R^2	product	isolated yield (%)
1	*n*-C_6H_{13}	C_2H_5	(*Z*)-**2a**	86
2	*n*-C_5H_{11}	*n*-C_4H_9	(*Z*)-**2b**	76
3	*n*-C_3H_7	*n*-C_4H_9	(*Z*)-**2c**	74
4	*n*-C_4H_9	Me	(*Z*)-**2d**	64
5	*n*-C_4H_9	*n*-C_3H_7	(*Z*)-**2e**	72
6[a]	*n*-C_4H_9	*n*-C_5H_{11}	(*Z*)-**2f**	67
7	*n*-C_4H_9	*i*-Pr	(*Z*)-**2g**	71
8	*n*-C_4H_9	*i*-Bu	(*Z*)-**2h**	90
9	*n*-C_4H_9	cyclohexyl	(*Z*)-**2i**	82
10	*t*-Bu	*n*-C_4H_9	(*Z*)-**2j**	89
11[a]	Ph	*i*-Pr	(*Z*)-**2k**	91
12	Ph	*i*-Bu	(*Z*)-**2l**	81
13[a]	Ph	cyclohexyl	(*Z*)-**2m**	78
14	$PhCH_2CH_2$	*i*-Pr	(*Z*)-**2n**	66
15[a]	$PhCH_2CH_2$	*i*-Bu	(*Z*)-**2o**	52
16[a]	$PhCH_2CH_2$	cyclohexyl	(*Z*)-**2p**	63

[a] Reaction time was 6 h.



A detailed study showed that some amounts of (*E*)-α-chloroalkylidene-β-lactone (*E*)-**2a** and butenolide **3a** were also formed, which were difficult to purify (Figure 2).

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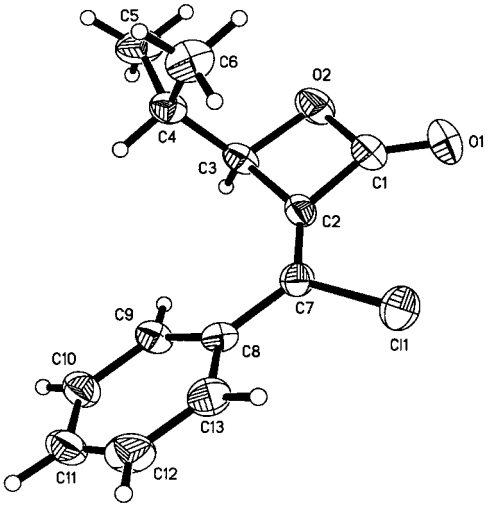
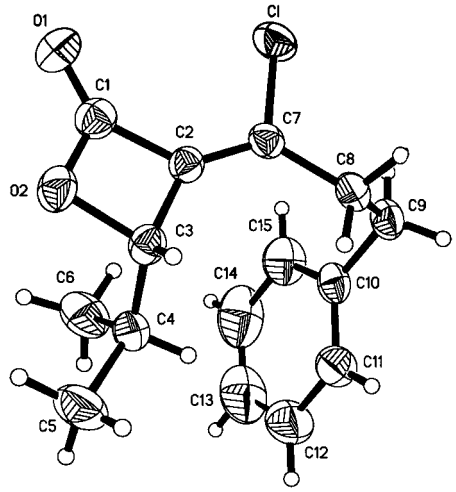


(*Z*)-**2k**

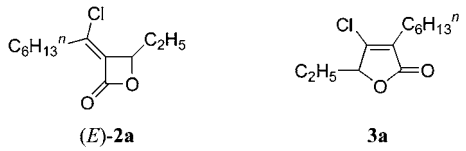


(*Z*)-**2n**

Figure 1.

In addition, the results for the cyclocarbonylation of the optically active secondary propargylic alcohols[19] are summarized in Table 3. From Table 3, it can be seen that racemization of the chiral center in **1** was not observed. The yields range from 63 to 89%.

A plausible mechanism is shown in Scheme 2. The coordination of the triple bond of **1** with $PdCl_2$ gave complex **4**, which was followed by *cis*-chloropalladation to give **5**. The subsequent coordination and insertion of CO gave complex **6**, which was followed by reductive elimination to afford the major product (*Z*)-**2**. $PdCl_2$ was regenerated by the oxidation reaction of the in situ-generated Pd(0) with $CuCl_2$. It is interesting to note that here, even with a nonterminal C−C triple bond, *cis*-halometalation is the major pathway.[20]

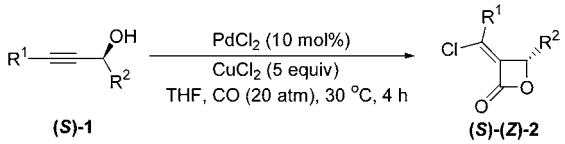


(*E*)-**2a**

3a

Figure 2.

Table 3. Synthesis of Optically Active (*Z*)-α-Chloroalkylidene-*β*-lactones

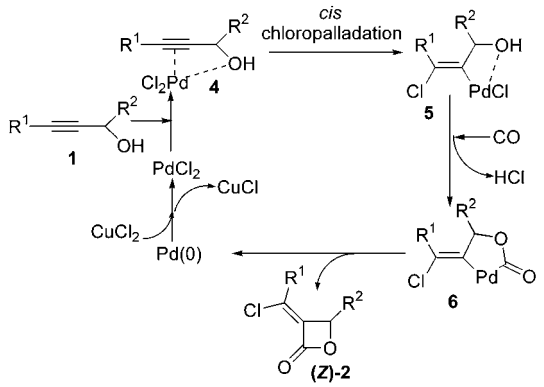


(*S*)-**1** (*S*)-(*Z*)-**2**

	(*S*)-**1**[a]		(*S*)-(*Z*)-**2**	
entry	R^1	R^2	% ee	yield[b] (%), ee (%)[c]
1[d]	Ph	*i*-Pr	>91	89 (*S*)-(*Z*)-**2k**, 92
2	Ph	*i*-Bu	>83	63 (*S*)-(*Z*)-**2l**, 85
3[d]	Ph	cyclohexyl	96	83 (*S*)-(*Z*)-**2m**, 96
4	$PhCH_2CH_2$	*i*-Pr	97	68 (*S*)-(*Z*)-**2n**, 97
5	$PhCH_2CH_2$	*i*-Bu	95	64 (*S*)-(*Z*)-**2o**, 92
6	$PhCH_2CH_2$	cyclohexyl	98	63 (*S*)-(*Z*)-**2p**, 98

[a] Absolute stereochemistry was established by comparison with the literature data.[19b] Enantiomeric excess was determined by HPLC on a chiralcel OD column. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC on a chiralcel OD-H or AS column. [d] Reaction time was 6 h.

Scheme 2



(17) Crystal data for compound **2k**: $C_{13}H_{13}O_2Cl$, MW = 236.68, monoclinic, space group *P*2(1)/*n*, Mo Kα, final *R* indices [$I > 2\sigma(I)$], *R*1 = 0.0502, w*R*2 = 0.0963, a = 9.8786 (13) Å, b = 18.626 (2) Å, c = 13.5620 (17) Å, α = 90°, β = 101.777 (3)°, γ = 90°, V = 2442.9 (5) Å^3, T = 293 (2) K, Z = 8, reflections collected/unique: 14691/5663 (R_{int} = 0.0761), no observation [$I > 2\sigma(I)$] 2497, parameters 393.

(18) Crystal data for compound **2n**: $C_{15}H_{17}O_2Cl$, MW = 264.74, monoclinic, space group *C*2/*c*, Mo Kα, final *R* indices [$I > 2\sigma(I)$], *R*1 = 0.0613, w*R*2 = 0.1314, a = 30.575 (4) Å, b = 6.3076 (9) Å, c = 16.685 (2) Å, α = 90°, β = 115.390 (3)°, γ = 90°, V = 2907.0 (7) Å^3, T = 293 (2) K, Z = 8, reflections collected/unique: 7296/2712 (R_{int} = 0.1504), no observation [$I > 2\sigma(I)$] 1514, parameters 212.

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In conclusion, (1) we have developed a mild, good-yielding, and efficient methodology for the synthesis of (*Z*)-α-chloroalkylidene-*β*-lactones; (2) using the readily available chiral propargylic alcohols allows synthesis of the corresponding (*Z*)-α-chloroalkylidene-*β*-lactones with high ee values; (3) and *cis*-chloropalladation was observed as the major reaction pathway. Further studies in this area are being pursued in our laboratory.

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Supporting Information Available: Typical experimental procedure and analytical data for all products, including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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