Oxidative Cyclization

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Palladium-Catalyzed Oxidative Cyclization of Enynes with Hydrogen Peroxide as the Oxidant**

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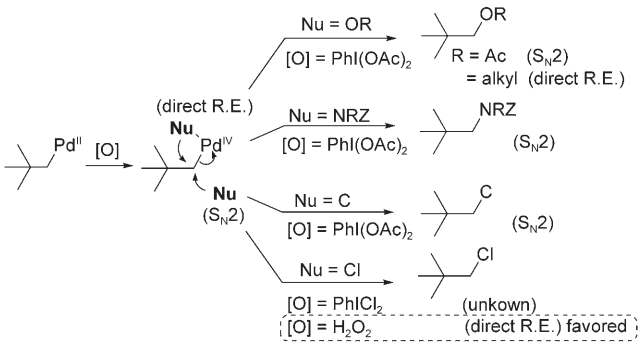
Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday

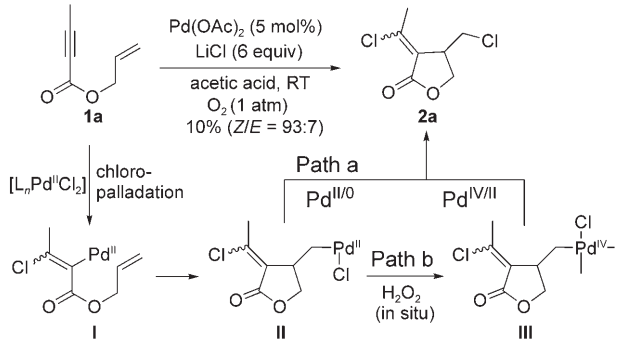
Palladium-catalyzed oxidation reactions are important transformations in organic synthesis.[1] Most of these oxidative reactions proceed through catalytic Pd^{II}/Pd^{0} cycles in the presence of benzoquinone, copper(II) salts, or molecular oxygen as stoichiometric oxidants.[2] Recently, a number of palladium-mediated oxidation reactions have been reported that involve Pd^{IV} complexes as key intermediates.[3] Transformations involving these alkyl–palladium(IV) intermediates are particularly attractive because such complexes can readily undergo reductive elimination reactions to form C–O,[4] C–N,[5] C–C,[6] and C–Cl,[7] bonds, which have proven to be difficult to achieve with catalytic Pd^{II}/Pd^{0} cycles (Scheme 1). Mechanistic studies of these reactions



Scheme 1. Pathways for the oxidative reaction via alkyl–palladium(IV) intermediates. R.E. = reductive elimination, Z = electron-withdrawing group.

indicate that the reductive elimination step in most of these reactions occurs in an S_N2-type fashion.[4b,d,5c,6] One drawback of these reactions is that they usually require strong oxidants, such as $PhI(OAc)_2$, oxone, NXS, or $PhICl_2$, to generate Pd^{IV} complexes, and these oxidants often produce a large amount of by-products. Hydrogen peroxide would be a preferred oxidant because it is inexpensive, environmentally benign, and readily available. Nevertheless, palladium-catalyzed oxidation reactions using hydrogen peroxide as the oxidant are quite rare.[8] In many cases, palladium catalyzes the rapid disproportionation of hydrogen peroxide.[9] Herein, we report an efficient palladium-catalyzed oxidative cyclization of enynes in which H_2O_2 is used as the stoichiometric oxidant at room temperature. These reactions appear to proceed through a mechanism involving the oxidation of $C(sp^3)–Pd^{II}$ species by H_2O_2, and the formation of C–Cl bonds by a direct reductive elimination pathway that leads to the retention of the configuration at the carbon center.[10]

The cyclization of enynes catalyzed by transition-metal complexes is an efficient method for the synthesis of various carbo- and heterocycles. The present study focuses on the Pd-catalyzed oxidative cascade cyclization of enynes, with the terminal oxidant being either molecular oxygen or hydrogen peroxide. During our initial study on palladium-catalyzed aerobic oxidative cyclization of enynes[11] we found that treatment of **1a** with 5 mol% $Pd(OAc)_2$ and 6 equivalents of LiCl under 1 atm of O_2 afforded cyclization products (*Z*)-**2a** and (*E*)-**2a** in low yields (ca. 10%) with a *Z*/*E* ratio of 93:7 at 60 °C (Scheme 2). Although the reaction yield was very low, the formation of **2a** rather than products arising from β-hydride elimination prompted us to examine the mechanism. A plausible reaction mechanism involves chloropalladation of the alkyne followed by cyclization to afford Pd^{II} intermediates **II**,[12] which subsequently undergo reductive elimination to afford **2a**. The reduced Pd^{0} species could be reoxided by O_2 (path a, Scheme 2). However, as formation of a C–Cl bond through reductive elimination from the Pd^{II} intermediate **II** is



Scheme 2. Possible pathways for palladium-catalyzed C–Cl bond formation under oxidation conditions.

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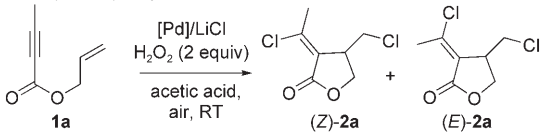
rare,[13] we considered an alternative pathway for the formation of **2a**, in which the intermediate **II** was oxidized by H_2O_2 (formed in situ) to afford Pd^{IV} intermediates **III**, followed by reductive elimination to form a C–Cl bond (path b, Scheme 2). This hypothesis was postulated on the basis that Pt^{IV} complexes can be prepared by treating Pt^{II} complexes with hydrogen peroxide in AcOH.[14,15] It is worth noting that such stable Pt^{IV} adducts are generally considered to be stable model complexes for Pd^{IV} intermediates,[16] thus suggesting that analogous conditions (hydrogen peroxides in AcOH) might be used to generate the key intermediate Pd^{IV} species. Furthermore, Whitfield and Sanford reported that Pd^{IV} complexes synthesized from $PhICl_2$ and Pd^{II} can undergo reductive elimination to form C–Cl bonds.[17]

Based on the above hypothesis, H_2O_2 (30 wt%, aqueous) was used as an oxidant to examine the oxidative cyclization of enynes. Treatment of **1a** with $Pd(OAc)_2$ (5 mol%), LiCl (6 equiv), and H_2O_2 (6×2 equiv) in acetic acid under 1 atm of O_2 afforded a mixture of (*Z*)-**2a** and (*E*)-**2a** in 80% yield with a *Z*/*E* ratio of 88:12 (Table 1, entry 2). Reactions in air or a nitrogen atmosphere gave similar results (Table 1, entries 3 and 4). When the amount of hydrogen peroxide was decreased from 12 equivalents to 2 equivalents, the yield of **2a** did not change significantly (Table 1, entries 2 and 5). In the absence of a palladium catalyst, only a trace amount of **2a** was formed (Table 1, entry 6). Among the Pd sources tested, $[PdCl_2(PhCN)_2]$ was found to be more efficient than $PdCl_2$ and $Pd(OAc)_2$ (Table 1, entries 5, 7, and 8). Solvent screening showed that both acetic acid and Ac_2O were effective (Table 1, entries 8 and 9). The amount of LiCl had little effect on the yields of the reactions, while the ratio of (*Z*)-**2a** and (*E*)-**2a** increased from 70:30 to 97:3 when the amount of LiCl was increased from 2 to 20 equivalents (Table 1, entries 8, 10–14), which suggests that *trans*-chloropalladation is favored at the higher concentration of LiCl.[12]

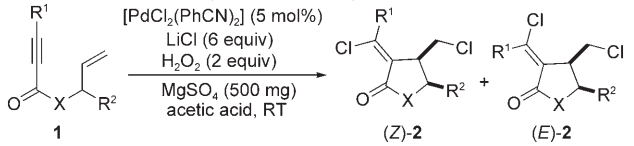
Table 1: Selected screening results of the dichlorination-cyclization of enyne catalyzed by Pd/H_2O_2 in air.[a]



Entry	[Pd]	LiCl [equiv]	H_2O_2 [equiv]	Time [h]	Yield [%] (*Z*/*E*)[b]
1[c,d]	$Pd(OAc)_2$	6	–	5	10 (93:7)
2[c]	$Pd(OAc)_2$	6	6×2	1	80 (88:12)
3	$Pd(OAc)_2$	6	6×2	1	78 (90:10)
4[e]	$Pd(OAc)_2$	6	6×2	1	77 (89:11)
5	$Pd(OAc)_2$	6	2	5	72 (89:11)
6	–	6	2	24	trace
7	$PdCl_2$	6	2	5	75 (90:10)
8	$[PdCl_2(PhCN)_2]$	6	2	5	89 (90:10)
9[f]	$[PdCl_2(PhCN)_2]$	6	2	5	84 (92:8)
10	$[PdCl_2(PhCN)_2]$	2	2	5	84 (70:30)
11	$[PdCl_2(PhCN)_2]$	4	2	5	87 (85:15)
12	$[PdCl_2(PhCN)_2]$	8	2	5	85 (91:9)
13	$[PdCl_2(PhCN)_2]$	10	2	5	91 (93:7)
14	$[PdCl_2(PhCN)_2]$	20	2	5	90 (97:3)

[a] Reaction conditions: **1a** (0.1 mmol), [Pd] 5 mol%, H_2O_2 (30 wt% in water), $MgSO_4$ (100 mg) acetic acid (1 mL) at RT. [b] The yield and *E*/*Z* ratios shown in parentheses were determined by ^1H NMR spectroscopy with tribromobenzene as the internal standard. [c] The reaction was conducted under 1 atm O_2. [d] At 60°C. [e] Under N_2. [f] Ac_2O as solvent.

Table 2: Palladium-catalyzed oxidative cyclization.[a]



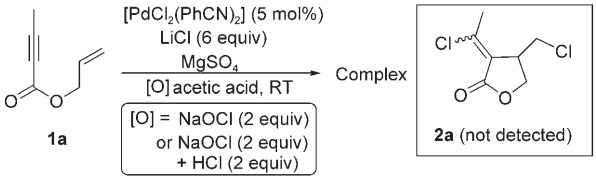
Entry	**1**	X	R^1	R^2	**2**	Yield [%][b]	*Z*/*E*[c]
1	**1a**	O	Me	H	**2a**	85	90:10
2	**1b**	O	*n*Bu	H	**2b**	69	76:24
3	**1c**	O	CH_2OMe	H	**2c**	84	88:12
4	**1d**	O	Ph	H	**2d**	80	63:37
5[d]	**1e**	O	Me	Me	**2e**	60	86:14
6[d]	**1f**	O	Me	Ph	**2f**	58	88:12
7	**1g**	NTs	Me	H	**2g**	82	64:36
8	**1h**	NBn	Me	H	**2h**	67	95:5

[a] Reaction conditions: **1** (0.5 mmol), $[PdCl_2(PhCN)_2]$ (5 mol%), LiCl (6 equiv), H_2O_2 (2 equiv), and $MgSO_4$ (500 mg) in acetic acid (5 mL) at room temperature and in air for 5–7 h. [b] Yield of isolated product. [c] The ratios were determined by ^1H NMR spectroscopy, *E*/*Z* correspond to the exocyclic double bond. [d] Only the cis isomer of β,γ-substituents lactone was obtained. Ts = toluene-4-sulfonyl, Bn = benzyl.

reaction is compatible with various esters and amides to afford different lactones and lactams. Aryl, alkyl, and ether substituents are well tolerated on the alkyne component. The ratios of the *Z*/*E* isomers varied slightly with different substituents (R^1). The reactions of **1a** (R^1 = Me) and **1c** (R^1 = methoxymethyl) gave better selectivity than **1b** (R^1 = *n*Bu) and **1d** (R^1 = Ph; Table 2, entries 1–4). It is notable that the reactions of **1e** and **1f**, which bear substituents on the allylic positions, yielded the *cis* isomer of β,γ-substituted lactones exclusively (Table 2, entries 5 and 6). Imide **1g** and amide **1h** afforded the cyclization products **2g** and **2h**, respectively (Table 2, entries 7 and 8).

With the above results in hand, we turned our attention to mechanistic studies. The first question we wanted to address was whether HOCl, which could potentially form in situ from H_2O_2 and LiCl in acetic acid, could serve as the oxidant. The addition of two equivalents of NaOCl (or combined with 2 equiv HCl) to the reaction mixture failed to yield **2a** [Eq. (1)], thus indicating that HOCl is not the active oxidant in the reaction.

To address the stereochemistry of the C–Cl bond formation, pure (*E*)-**3** and (*Z*)-**3** were used in two separate



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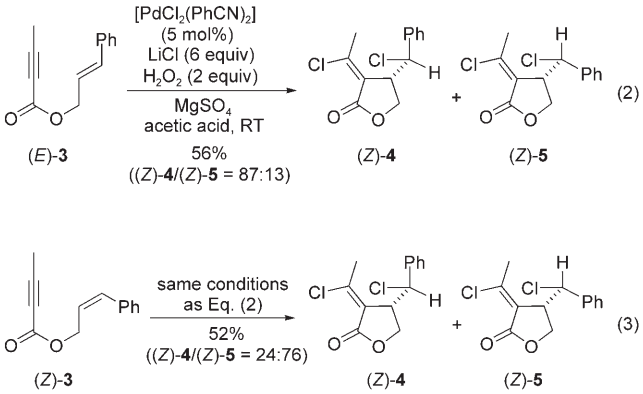
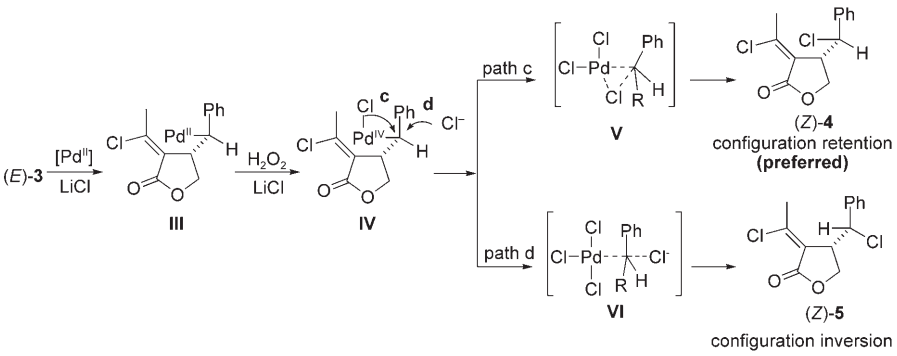
cyclization experiments. In the case of olefin (*E*)-**3**, products (*Z*)-**4** and (*Z*)-**5** were obtained in 56% yield and in a ratio of 87:13 at room temperature [Eq. (2)]. The reaction of (*Z*)-**3** also afforded (*Z*)-**4** and (*Z*)-**5** in 52% combined yield, but in a ratio of 24:76 [Eq. (3)]. These results ruled out a radical



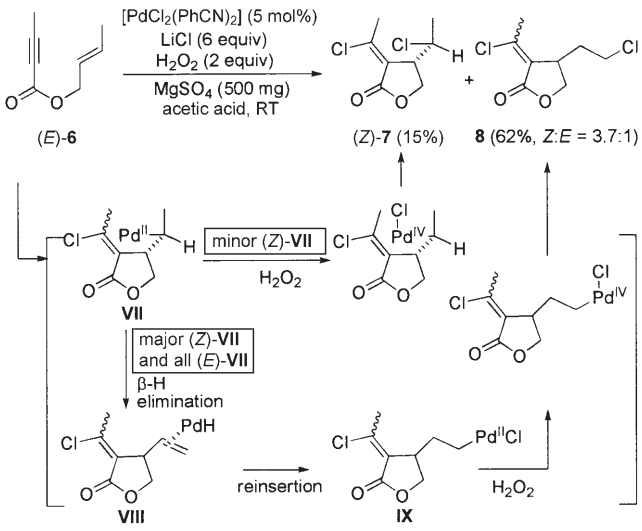
pathway, as the same ratio of (*Z*)-**4** and (*Z*)-**5** would be expected for these two reactions. The formation of (*Z*)-**4** as the major product from (*E*)-**3** suggested that a direct reductive elimination pathway of the proposed C(sp^3)–Pd^{IV} intermediate, which leads to the retention of the C(sp^3) center (path c, Scheme 3),[10,18] is favored over the S_N2-type reductive



Scheme 3. Possible Pd^{II}/Pd^{IV} mechanisms for the formation of a C–Cl bond.

elimination pathway. In the latter mechanism for reductive elimination, the C(sp^3)–Pd^{IV} intermediate is attacked by an external Cl^- ion, which leads to inversion of the C(sp^3) center (path d, Scheme 3).[4b,d,5c,6] The reaction of (*E*)-**6** afforded (*Z*)-**7** in 15% yield and **8** in 62% yield (Scheme 4). The fact that only isomer (*Z*)-**7**, generated from minor intermediate (*Z*)-**VII**, was observed strongly supported our hypothesis of a direct reductive elimination pathway from a C(sp^3)–Pd^{IV} species (path c, Scheme 3). The formation of **8** is likely to proceed through β-H elimination of the major intermediate (*Z*)-**VII** and all the (*E*)-**VII**, followed by reinsertion of the alkene to form a new C(sp^3)–Pd^{II} intermediate **IX**, which is then oxidized by H_2O_2 and undergoes reductive elimination to generate the C–Cl bond and the Pd^{II} species.[6a]

In summary, we have reported a palladium-catalyzed oxidative cyclization of enynes in which hydrogen peroxide is



Scheme 4. Palladium-catalyzed oxidative cyclization of (*E*)-**6**.

used as a simple, inexpensive, and environmentally benign oxidant. The reaction is proposed to proceed through a Pd^{II}/Pd^{IV} cycle in which the key C–Cl bond-forming step involves the formation of a Pd^{IV} intermediate from the oxidation of a Pd^{II} species by H_2O_2, followed by a direct reductive elimination to generate C–Cl bonds and leads to the retention of the configuration at the C(sp^3) center. We are currently investigating new types of palladium-catalyzed oxidative reaction in which hydrogen peroxide is used as the terminal oxidant.

Experimental Section

General procedure: In a glass tube, enyne **1** (0.5 mmol), $[PdCl_2(PhCN)_2]$ (0.025 mmol, 5 mol%), LiCl (3 mmol), and anhydrous $MgSO_4$ (500 mg) were added to HOAc (5 mL). Then, 30 wt% aqueous H_2O_2 (115 μL, 1.0 mmol) was added and the mixture stirred at room temperature. The reaction was monitored by thin-layer chromatography. After the reaction was complete, diethyl ether (25 mL) was added, and the mixture was filtered through a plug of celite (to remove $MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography on silica gel to give the corresponding dichlorolactone **2**.

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