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Oxidative Cyclization of β-Hydroxyenones with Palladium(II): A Novel Entry to 2,3-Dihydro-4*H*-pyran-4-ones

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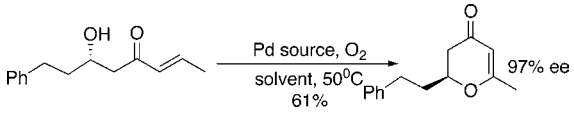
ABSTRACT



A palladium(II)-mediated oxidative cyclization was found to be effective for the preparation of structurally diverse 2,3-dihydro-4*H*-pyran-4-ones from the corresponding β-hydroxyenones. Attractive features of this transformation include the ready availability of the starting enones, the regiocontrol, and the easy access of enantiopure 2,3-dihydro-4*H*-pyran-4-one from the corresponding enantiopure enone.

The oxidation of ethylene to acetaldehyde, the so-called Wacker process, is one of the best-known reactions catalyzed by palladium(II).[1] This transformation has proven to be a versatile method for functionalization of olefins as exemplified by the recently reported asymmetric oxidative Wacker heterocyclization that provides an elegant entry to various enantioenriched heterocycles.[2] All these advances notwithstanding, it is noteworthy that there have been only a few examples of oxidative cyclization involving α,β-unsaturated esters[3] and, to the best of our knowledge, only one paper has reported the palladium(II)-mediated oxidative cyclization of conformationally rigidified 2-hydroxychalcones leading to diverse flavone derivatives.[4] Surprisingly, the process has never been applied to structurally diverse β-hydroxyenones despite the ready availability of these compounds as racemates or in enantiopure form. Given the enormous synthetic potential of the corresponding 2,3-dihydro-4*H*-pyran-4-ones that would be formed upon oxidative cyclization, this lack of work in the area seems even more amazing.[5] Herein we report that the aforementioned palladium(II)-mediated transformation is feasible and that it provides a rapid entry to structurally diverse 2,3-dihydro-4*H*-pyran-4-ones. Our initial studies of this process focused on developing an optimum set of reaction conditions for the oxidative cyclization of the β-hydroxyenone **1a** (Table 1).

The key to success lies in the correct choice of catalyst, solvent, and coreagents to favor the oxidative cyclization

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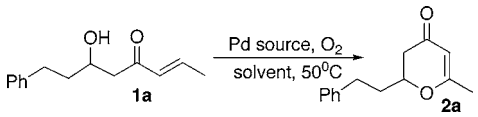
Table 1. Optimization Studies[a]



entry	Pd source (mol %)	co-oxidant (mol %)	additive (10 mol %)	solvent	conversion (%)
1	$PdCl_2$ (10)	CuCl (10)	Na_2HPO_4	DME	100
2	$PdCl_2$ (10)	CuCl (10)	none	DME	90
3	$Pd(TFA)_2$ (5)	CuCl (10)	Na_2HPO_4	DME	50
4	$Pd(OAc)_2$ (5)	CuCl (10)	Na_2HPO_4	DME	20
5	$PdCl_2$ (10)	benzoquinone (400)	Na_2HPO_4	DME	73
6	$Pd(TFA)_2$ (5)	benzoquinone (400)	Na_2HPO_4	DME	7
7	$Pd(TFA)_2$ (5)	benzoquinone (400)	Na_2CO_3[b]	DME	0
8	$PdCl_2$ (10)	none	Na_2HPO_4	DME	60 (89[c])
9	$PdCl_2$ (10)	none	none	DME	1
10	$Pd(TFA)_2$ (5)	none	Na_2CO_3[b] pyridine[d]	toluene	0

[a] All reactions were carried out with 1 atm of O_2 at 50 °C for 20 h. [b] Performed with 200 mol %. [c] Conversion after 40 h. [d] Performed with 20 mol %.

rather than the direct Michael addition.[6] The effect of various reaction parameters (catalyst, solvent, co-oxidant, additives such as base or salts, solvent) on the conversion of a representative enone into the corresponding adduct was examined (Table 1). The oxidative cyclization of enone **1a**, readily prepared by an aldol reaction of 3-penten-2-one with hydrocinnamaldehyde in 79% isolated yield, was first attempted under the conditions traditionally applied for a Wacker-type oxidation using palladium(II) chloride/copper(I) chloride/oxygen in DME. Under these conditions, all the starting material was converted into the desired product **2a** (entry 1). The absence of Na_2HPO_4 resulted in slightly lower conversion (90%) (entry 2). Substituting $PdCl_2$ for $Pd(TFA)_2$ or $Pd(OAc)_2$ while keeping all other parameters constant induced a marked decrease in the conversion (entries 3 and 4). It was also found that the use of the organic oxidant benzoquinone in place of CuCl was not beneficial, independent of the Pd source and the additive (entries 5−7). A catalytic Pd(II) oxidation using O_2 as the sole stoichiometric oxidant was also attempted (entry 8). Gratifyingly, this reaction delivered the desired product albeit with reduced conversion (60%) after 20 h. The conversion could be improved to 89% by leaving the reaction for 40 h. For this transformation, the presence of 10 mol % Na_2HPO_4 was essential (entry 9). Finally, we investigated the possibility of promoting the cyclization of **1a** into **2a** using the reaction conditions applied by Stoltz *et al.* for the Pd-catalyzed aerobic cyclization of phenol-alkenes.[2i] We found that under these conditions, no product was formed (entry 10).

Under our optimized conditions, the oxidative cyclization of various substituted β-hydroxyenones now occurs smoothly (Table 2).

It became quickly apparent that the reaction times could be significantly reduced for some substrates such as the enone (*E*)-**1a**, which was completely converted into the desired product **2a** after only 4 h at 50 °C. After purification, **2a** was isolated in 79% yield (entry 1). Changing the geometry of the enone did not affect the transformation, as **2a** could also be obtained from the enone (*Z*)-**1a** with a chemical yield of 59% (entry 2). The reaction does not tolerate the presence of a substituent on the vinylic carbon adjacent to the carbonyl group. Indeed, the presence of a methyl group on this position is sufficient to suppress the reaction, with only starting material being recovered after 20 h at 50 or 80 °C (entry 3). This result is in agreement with the lack of reactivity observed for $MeCOCMe{=}CH_2$ toward the intermolecular palladium(II)-catalyzed acetalization with alcohols or diols.[7] In contrast, the preparation of 1-substituted 2,3-dihydro-4*H*-pyran-4-ones such as **2a** and **2c**−**f** was successful, the isolated yields typically ranging from 43 to 86%. In this series, the phenyl-substituted β-hydroxy enone **1e** was the least reactive since the initial stage of this transformation involves disruption of the conjugated system between the carbonyl and phenyl group; this reaction therefore required an extended reaction time to afford **2e** in an isolated chemical yield of 43% (entry 6). In contrast, the 1-alkyl 2,3-dihydro-4*H*-pyran-4-ones were all prepared with chemical yields superior to 75%. For substrate **1g** possessing an unsubstituted terminal enone functionality, a side product identified as the acyclic reduced enone **3** was also formed (entry 8). A similar side product has not been observed with the other substrates.

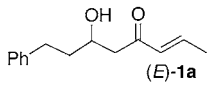
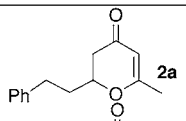
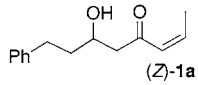
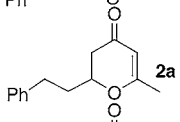
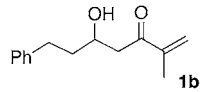
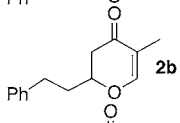
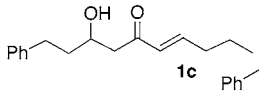
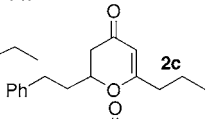
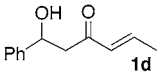
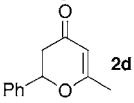
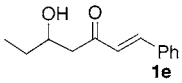
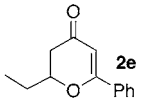
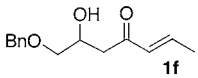
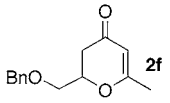
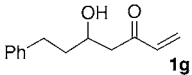
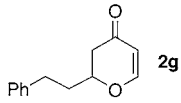
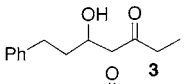
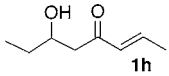
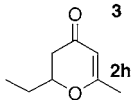
We have also successfully applied the methodology for the preparation of hepialone (±)-**2h**, a natural pheromonal component of the male moth, isolated from *Hepialus hecta L.* (entry 9).[8] Interestingly, we have not detected the formation of a Michael adduct for any of the substrates studied herein. With the success of the oxidative cyclization on

(6) For conversion of enones into β-benzyloxy ketones or β-amido ketones, see: Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S. *Chem. Lett.* **1989**, *11*, 2001−2004. Gaunt, M. J.; Spencer, J. B. *Org. Lett.* **2001**, *3*, 25−28.

(7) Hosokawa, T.; Ohta, T.; Kanayama, S.; Murahashi, S. *J. Org. Chem.* **1987**, *52*, 1758−1764.

(8) For other multistep syntheses of **2h**, see for example: (a) Dreeβen, S.; Schabbert, S.; Schaumann, E. *Eur. J. Org. Chem.* **2001**, 245−251. (b) Uchino, K.; Yamagiwa, Y.; Kamikawa, T.; Kubo, I. *Tetrahedron Lett.* **1985**, *26*, 1319−1320.

Table 2. Oxidative Cyclization of β-Hydroxy Enones

entry	starting material	product	time, temp. yield
1	 (*E*)-**1a**	 **2a**	4h, 50°C 79%
2	 (*Z*)-**1a**	 **2a**	4h, 50°C 59%[a]
3	 **1b**	 **2b**	20h, 50°C 0%
4	 **1c**	 **2c**	20h, 50°C 76%
5	 **1d**	 **2d**	8h, 50°C 86%
6	 **1e**	 **2e**	8 days, 50°C 43%
7	 **1f**	 **2f**	20h, 50°C 75%
	 **1g**	 **2g**	20h, 50°C 60% ratio **2g**/**3** = 4/1
8		 **3**	
9	 **1h**	 **2h**	10h, 50°C 52%

[a] Unoptimized yield.

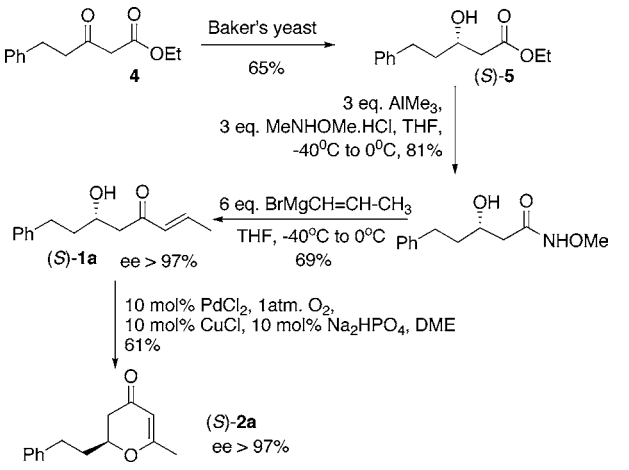
racemic β-hydroxyenones, we could then investigate the stereochemical integrity of enantiopure enone **1a** upon oxidative cyclization into the corresponding 2,3-dihydro-4*H*-pyran-4-one **2a** (Scheme 1).

Enone **1a** was prepared in three steps from the ketoester **4** using as the key step a Baker's yeast-mediated catalytic asymmetric reduction to afford the β-hydroxy ester (*S*)-**5**.[9] Functional group manipulation of (*S*)-**5** afforded the enone (*S*)-**1a** with an overall yield of 56% and an enantiomeric excess of 97%. Under our optimized cyclization conditions, we found that the desired product was formed with an enantiomeric excess of 97% thereby proving that this palladium(II)-mediated oxidative cyclization occurs with no detectable racemization.

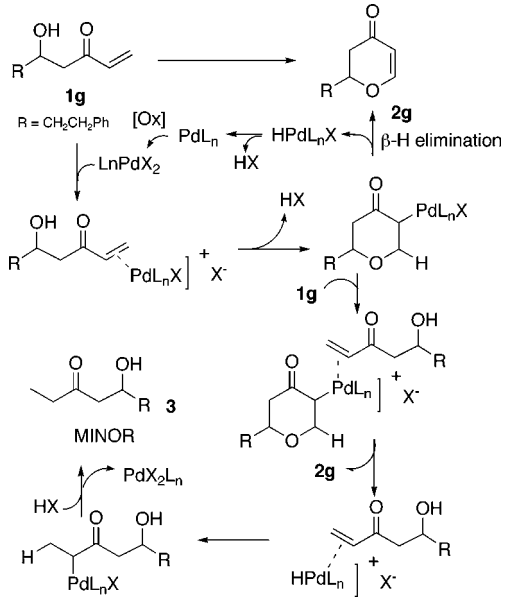
Although the exact details of the mechanism are unclear, a plausible proposal for the oxidative cyclizations reported herein is presented in Scheme 2.

Initial alkene binding to the electrophilic $PdCl_2$ could lead to a π-alkene−palladium complex, which could activate the

Scheme 1. Preparation and Oxidative Cyclization of (*S*)-**1a** into (*S*)-**2a**



Scheme 2. Proposed Mechanism for the Cyclization of **1g**



enone toward intramolecular nucleophilic attack. The latter process would lead to a palladium(II) enolate being formed, which could coordinate to palladium either through the carbon atom (σ-alkyl) or through the oxygen (η^3-oxoallyl).[10] Subsequent β-hydride elimination would produce HPdX, which would eliminate HX and allow Pd^0 to reenter the catalytic cycle after oxidation by molecular oxygen and CuCl. The dibasic disodium hydrogen phosphate probably acts as a proton scavenger. We did not observe the formation of a Michael adduct. Such a species could be formed by proto-

(9) Athanasiou, N.; Smallridge, A. J.; Trewhella, M. A. *J. Mol. Catal. B: Enzym.* **2001**, *11*, 893−896.

(10) (a) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494−496. (b) Albeniz, A. C.; Catalina, N. M.; Espinet, P.; Redon, R. *Organometallics* **1999**, *18*, 5571−5576. (c) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648−2649. (d) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463−466. (e) Vicente, J.; Abad, J. A.; Chicote, M. T.; Abrisqueta, M. D.; Lorca, J. A.; Ramirez de Arellano, M. C. *Organometallics* **1998**, *17*, 1564−1568.

nolysis of the cyclic palladium enolate. In this catalytic cycle, it is possible that ligand exchange can occur prior to β-hydride elimination, allowing transfer of a palladium-hydride species onto the starting enone upon reductive elimination. This new C-bound palladium enolate can undergo protonolysis to afford the reduced acyclic enone **3**. This second pathway can account for the formation of the side product **3** observed upon cyclization of enone **1g** and could be regarded as a palladium-catalyzed disproportionation of the reactant **1g**.

In conclusion, we have developed a palladium-mediated route to structurally diverse 2,3-dihydro-4*H*-pyran-4-ones. These compounds are more often prepared using a concerted or stepwise hetero-Diels−Alder (HDA) reaction of aldehydes with Danishefsky's dienes catalyzed by various Lewis acids. The stepwise HDA reactions of carbonyl compounds present similarities with our approach, as both strategies involve a β-hydroxyenone as the key intermediate. Interestingly, the oxidation state of carbons 2 and 3 within the products is established within the starting dienes for the HDA route, whereas in our approach, the oxidation state of these two carbons is addressed in the cyclization step. Therefore, with this novel palladium(II)-mediated cyclization process in hand, β-hydroxy-enones such as **1a**−**h** can now be regarded as common precursors for the preparation of both the corresponding tetrahydro-4*H*-pyrano-4-ones via a Michael addition process and the 2,3-dihydro-4*H*-pyran-ones using a Wacker-type oxidative cyclization. Efforts to expand the scope of the process to other heterocycles are ongoing in our laboratory.

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Supporting Information Available: Experimental details for all substrates **1a**−**h** and reaction products **2a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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