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Synthetic Methods

Palladium-Catalyzed Oxidative Synthesis of Highly Functionalized Ortholactones

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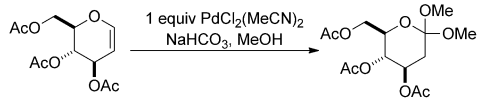
Abstract: A palladium-catalyzed oxidative reaction is reported which converts dihydropyrans to their corresponding ortholactone. The products are formed in good to excellent yields with a very high level of chemoselectivity and functional group tolerance. Mechanistic studies confirm that the reaction proceeds by a Wacker-type mechanism.

Ortholactones are a class of cyclic orthoester which have great potential for synthetic utility. These compounds can act as electrophiles, following Lewis or protic acid activation, allowing for substitution of either one[1] or both of the alcohol leaving groups.[2] A major obstacle to their greater use in synthesis is their formation which generally requires harsh conditions which are not tolerant of a wide range of functionality. These include strongly alkylative conditions such as Meerwein's salt,[3] Lewis acidic conditions analogous to a Noyori ketalization,[4] the substitution of anomeric *gem*-dihalides[5] or by cycloaddition reactions, which only provides specific substitution patterns.[6] Spirocyclic ortholactones can also be formed through the condensation of diols with lactones under acid catalysis[7] or from an addition–elimination strategy using anomeric vinyl sulfides.[8] Although there are many methods available, most require strongly alkylative, acidic or basic conditions that do not tolerate sensitive functionality.

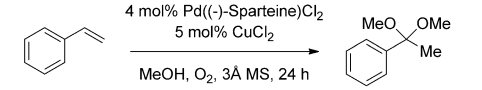
Holzapfel reported an alternative approach whereby ortholactones could be derived from glycals via an oxidative Wacker-type reaction [Eq. (1)].[9] This method provided very high yields, however, one equivalent of a palladium complex was required and all attempts to render this reaction catalytic through the addition of exogenous oxidants failed. Since this report there have been significant advances in Pd^{II}-catalyzed oxidation catalysis.[10] One advance has been the use of ligands which lead to the formation of Pd^{II} complexes that exhibit improved catalytic turnover and high selectivity towards the desired product. A good example of relevant work in this area, is Sigman's oxidation of styrenes in the presence of alcohols to form ketals using a preformed Pd[(−)-sparteine]Cl_2 as catalyst [Eq. (2)].[11] This method used $CuCl_2$ as co-catalyst in an atmosphere of pure oxygen and provided, in most cases, high yield and regioselectivity. We hypothesized that we could build upon Sigman's work to render the oxidative ortholactone formation catalytic and use atmospheric air rather than pure oxygen as the terminal oxidant. Herein, we report the first catalytic ortholactone formation using atmospheric air as the terminal oxidant [Eq. (3)].

Holzapfel (ref. [9]): ortholactone formation with stoiciometric Pd



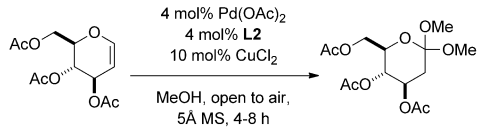
(1)

Sigman (ref. [11]): catalytic Wacker-type oxidation of styrene



(2)

This work: catalytic Wacker-type ortholactone formation



(3)

We began examining the possibility of rendering the ortholactonization catalytic using air as the terminal oxidant (Table 1). We used an in situ prepared Pd^{II}/(−)-sparteine catalyst, similar to the preformed complex used by Sigman, in a reactor with 40 bar of compressed air. Gratifyingly, this provided excellent reactivity with high yields being obtained. Nevertheless, due to the supply problems with sparteine[12] and the issues surrounding the use of pressurized reactors, we began examining more accessible methods. A screen of ligands found that many diamine ligands including both pyridine and basic amine based groups performed well with *N*,*N*,*N*′,*N*′-tetramethyl cyclohexyldiamine (**L2**), providing the highest yields. We were able to lower the palladium loading to 4 mol% and maintain reactivity, however, at lower catalyst loadings the reaction proceeds at a much slower rate leading to reduced yields. The issue of pressurized vessels could be addressed by performing the reaction in an open vessel (a condenser fitted with a drying tube). This allowed for a continuous resupplying of the oxygen levels thus maintaining a constant reaction and preventing the formation of palladium black and provided complete conversion and 85% isolated yield of the ortholac-

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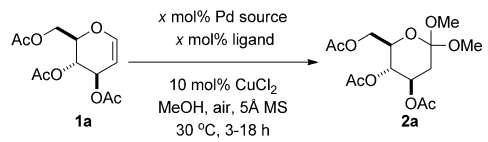
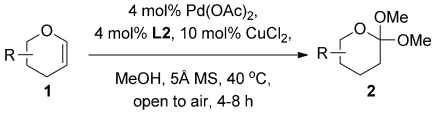
Table 1. Optimization studies.

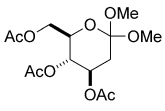
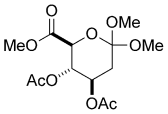
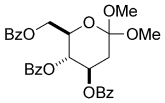
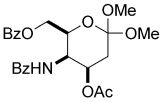
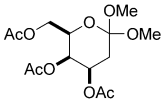
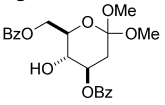
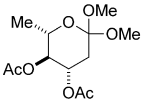
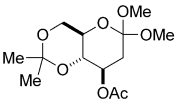
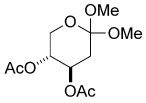


Entry	Pd source ([mol%])	Ligand	*P* [bar]	Yield [%][a,b]
1	$[PdCl_2(MeCN)_2]$ (8)	(−)-sparteine	40	86 (81)
2	$[PdCl_2(MeCN)_2]$ (8)	BiPy	40	69
3	$[PdCl_2(MeCN)_2]$ (8)	**L1**	40	93 (60)
4	$[PdCl_2(MeCN)_2]$ (8)	**L2**	40	100 (75)
5	$[PdCl_2(MeCN)_2]$ (8)	**L3**	40	83
6	$[PdCl_2(MeCN)_2]$ (8)	**L4**	40	93 (60)
7	$PdCl_2$ (8)	**L2**	40	69
8	$Pd(OAc)_2$ (4)	**L2**	40	95 (76)
9	$Pd(OAc)_2$ (2)	**L2**	40	57
10	$Pd(OAc)_2$ (4)	**L2**	10	55
11[c]	**$Pd(OAc)_2$ (4)**	**L2**	**1**	**98 (85)**
12	$Pd(OAc)_2$ (**4**)	**L2**	1 (O_2)[d]	98 (84)

[a] Yields determined by ^1H NMR analysis of the crude using PhCHO as an internal standard (following completion of the reaction). [b] Values in parentheses indicate isolated yields of pure **2a**. [c] Reaction conducted in a flask open to the atmosphere at 40 °C. [d] Performed using a balloon of pure oxygen.

Table 2. Substrate scope.



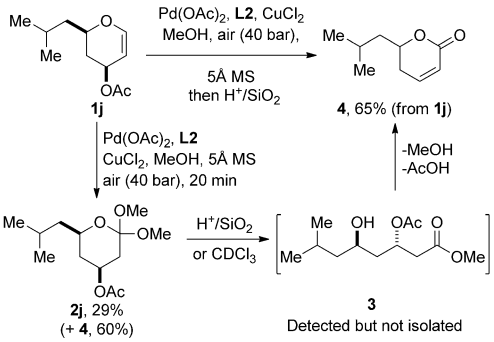
Entry	Product	Entry	Product
1	 **2a**, 85%	6	 **2f**, 60%
2	 **2b**, 69%	7	 **2g**, 45%
3	 **2c**, 65%	8	 **2h**, 54%
4	 **2d**, 54%	9	 **2i**, 68%
5	 **2e**, 29%		

tone **2a**. This was also comparable to when the reaction was run under an atmosphere of pure oxygen which provided similar levels of conversion and isolated yields.[13]

With the optimized conditions in hand (Table 1, entry 11), we began examining the scope of the reaction (Table 2). The ortholactonization was effective for other carbohydrate-derived dihydropyrans including the glucal tribenzoate **2b**, alongside the galactal **2c** and rhamanal **2d** albeit in slightly reduced yields. When the C-5 substituent was removed, as in xylal **2e**, the yield was much reduced due to product decomposition. The reaction was also tolerant of amides **2f**, free alcohols **2h** and ketals **2i** highlighting the very mild conditions.

For less substituted dihydropyran substrates the isolated yields were much lower due to the decomposition of the product prior to the complete consumption of the starting material. We were able to identify and isolate the major decomposition product with lactone **4** being produced in high yields. The ortholactone **2j** could be produced and isolated if the reaction was performed under a high pressure of air and this was observed performing a ring opening to form ester **3** which then underwent a lactonization and elimination to form **4** (Scheme 1). This process is so facile that silica gel and even the residual acid in untreated $CDCl_3$ will promote this pathway.

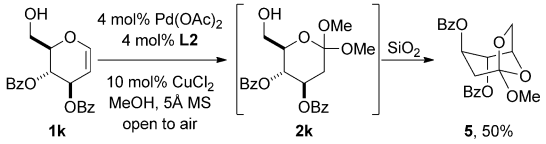
The presence of an unprotected alcohol group was also investigated with C-6 hydroxy substituent **1k** (Scheme 2). In this case, the alcohol does not appear to effect the ortholactone formation with **2k** being formed and isolated; however, the reaction also contained bicyclic ortholactone **5**. The formation of



Scheme 1. Othrolactone decomposition pathway.

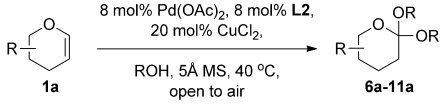
5 was promoted through prolonged exposure of the ortholactone **2k** to silica gel, thus expelling methanol and forming **5**.

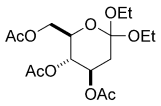
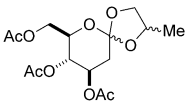
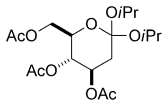
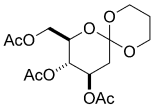
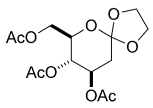
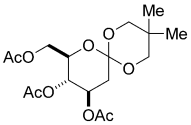
Due to the instability of some of the dimethoxy ortholactones, we began examining the use of alternative alcohols which may provide enhanced stability. We discovered that the reaction of **1a** is very sensitive to sterics. When ethanol is used as solvent, the reaction proceeds much slower and using isopropanol no reaction is observed with quantitative recovery of starting material. The reaction is much more facile when diols are used and excellent yields are obtained when 2,2-dimethylpropan-1,3-diol is used to form spirocyclic product **11a** (Table 3). It was necessary to perform the reaction with the ad-



Scheme 2. Bicyclic ortholactone formation.

Table 3. Alcohol scope.



Entry	Product	Entry	Product
1	 **6a**, 30%	4	 **9a**,[a] 70%, 1:1:1:1 d.r.
2	 **7a**, no reaction	5	 **10a**,[a] 80%
3	 **8a**, 53%	6	 **11a**,[a] 92%

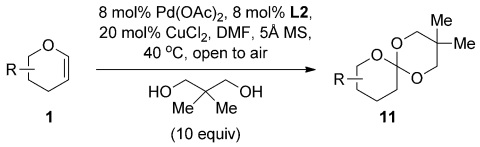
[a] Reaction performed in DMF using 10 equivalents of diol.

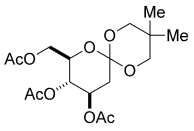
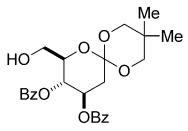
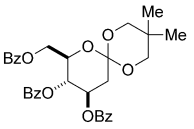
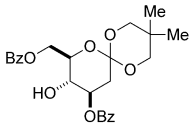
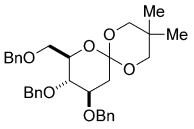
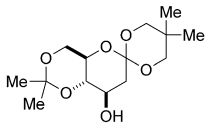
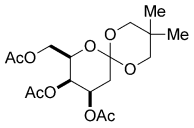
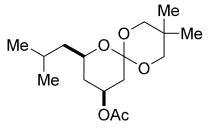
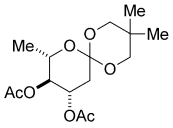
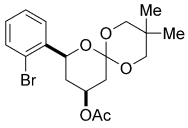
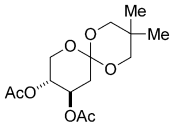
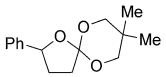
dition of solvent as the diol is a solid, and this also allowed us to lower the stoichiometry of alcohol to 10 equivalents.

We examined the scope of the reaction using 2,2-dimethylpropan-1,3-diol as the alcohol donor. We found that these reactions gave superior yields compared to the methoxy cases due to the enhanced stability of the ortholactone functional groups tolerated, and with little sign of decomposition. The reaction is tolerant of differently protected glucal derivatives **11a**,**b**,**l**, alongside other carbohydrate series including galactal **11c**, rhamanal **11d** and xylal **11e** (Table 4). Free alcohols were tolerated at the C-3, C-4 and C-6 positions **11k**,**m**,**n** with no oxidation observed or side reactions occurring. Non-carbohydrate derived dihydropyrans were also excellent substrates, providing *iso*-butyl **11j** and 2-bromophenyl **11o** ortholactones in high yields. We were also able to demonstrate this method on a five-membered substrate with furan ortholactone **11p** being produced.

To probe the mechanism of the two sets of conditions, deuterium labeling studies were performed.[14] Using C-1 deuterated glycal **12** the reaction was performed firstly with methanol as the alcohol donor. This provided the corresponding ortholactone **13** with 93% deuterium incorporation at the C-2 position [Eq. (4)]. Interestingly, the deuterium transfer occurred with facial selectivity to provide **13** in a 83:17 d.r. We also performed a kinetic isotope effect study and measured a k_H/k_D value of 1.80 which is consistent with proton transfer being rate limiting. In the case of the 2,2-dimethylpropan-1,3-diol conditions, high yields and deuterium transfer were observed with **14** being produced in 90% yield with 97% D incorporation. Again, facial selectivity was observed albeit lower than the methanol case (71:29 d.r.). To our surprise, when the kinetic isotope effect was measured a k_H/k_D value of 0.84 was obtained thus indicating a change in mechanism in comparison with the formation of **13**, and suggesting a change in geometry from sp^2 to sp^3 occurs during the rate-limiting step. When the reaction was performed in [D_4]methanol, no deuterium was incorporated at the C-2 position of **15**.

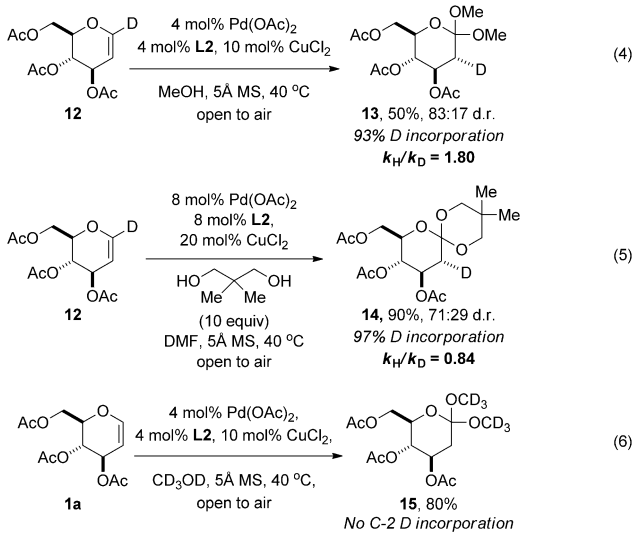
Table 4. 1,3-Diol substrate scope.

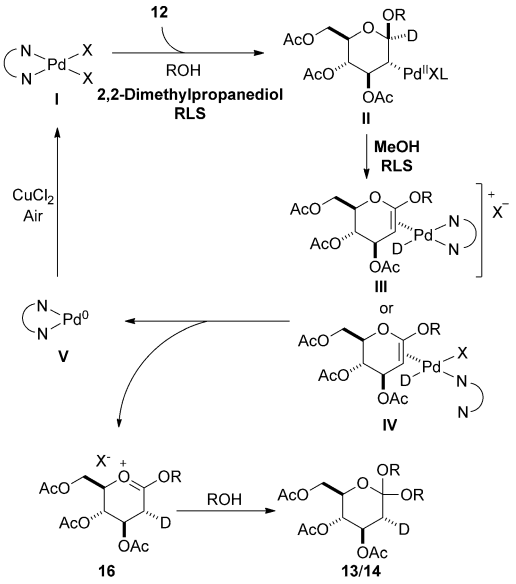


Entry	Product	Entry	Product
1	 **11a**, 92%	7	 **11k**, 52%
2	 **11b**, 80%	8	 **11m**, 80%
3	 **11l**, 90%	9	 **11n**, 88%
4	 **11c**, 70%	10	 **11j**, 72%
5	 **11d**, 98%	11	 **11o**, 75%
6	 **11e**, 52%	12	 **11p**, 47%

With our mechanistic data in hand we can propose a mechanism which accounts for all the observations and data (Scheme 3).[15]

The electron-rich dihydropyran **12** undergoes *trans*-oxypalladation to form acetal complex **II**. β-Hydride elimination pro-





Scheme 3. Proposed mechanism.

vides a ketene acetal with the palladium–deuteride complex coordinated to one face. This can exist either as a cationic complex **III** or via the decomplexation of one of the amine ligands **IV**.[16] Deprotonation of the palladium complex leads to palladium(0) complex **V** and oxocarbenium ion **16** which is trapped by a second equivalent of alcohol to form ortholactone **13** and **14**. The coordination–deprotonation event leads to the facial selectivity of the deuterium transfer. The diastereomeric ratio in **13**/**14** can be obtained either from the facial selectivity of the initial oxypalladation or via a decomplexation pathway. **V** is then oxidized back to Pd^{II} using the $CuCl_2$ and air to regenerate the original catalyst **I**. When methanol is used as the nucleophile, β-hydride elimination appears rate limiting whereas the inverse secondary effect when dimethylpropane diol is used, suggests oxypalladation is rate limiting, presumeably due to the much more sterically demanding nucleophile.

In conclusion, we have developed robust and high yielding methods for the formation of highly functionalized 2-deoxyortholactones. These reactions are performed under neutral conditions from readily available substrates using atmospheric air as the terminal oxidant. In particular, the spirocyclic derivatives are the most effective due to their stability relative to the dimethoxy variant. We have discovered some interesting side reactions to form bicyclic systems and highlighted the major decomposition pathway. Finally, our mechanistic studies have elucidated the pathways involved, including the difference in rate-limiting step for the two sets of conditions developed. The use of these compounds in synthesis is currently being investigated.

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Keywords: aerobic oxidation · ortholactone · palladium · synthetic methods · Wacker-type reaction

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Synthetic Methods

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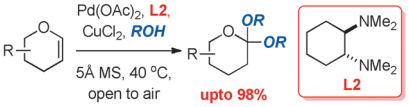
Palladium-Catalyzed Oxidative Synthesis of Highly Functionalized Ortholactones



A breath of fresh air: A palladium-catalyzed oxidative reaction is reported which converts dihydropyrans to their corresponding ortholactone. The products are formed in good to excellent yields with a very high level of chemoselectivity and functional group tolerance (see scheme). Mechanistic studies confirm that the reaction proceeds by a Wacker-type mechanism.