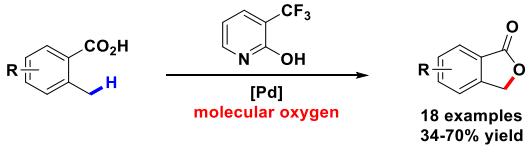
Ligand-Enabled Pd(II)-Catalyzed C(sp^3)–H Lactonization using Molecular oxygen as oxidant

Shaoqun Qian[†], Zi-Qi Li[†], Minyan Li[†], Steven R. Wisniewski[‡], Jennifer X. Qiao[§], Jeremy M. Richter[‖], William R. Ewing[§], Martin D. Eastgate[‡], Jason S. Chen[¶], Jin-Quan Yu[*,†]

[†] Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States
[‡]Chemical & Synthetic Development, Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey 08903, United States
[§]Discovery Chemistry, Bristol-Myers Squibb, PO Box 4000, Princeton, New Jersey 08543, United States
[‖]Research & Development, Bristol-Myers Squibb, Hopewell, New Jersey 08534, United States
[¶]Automated Synthesis Facility, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States
Supporting Information Placeholder



ABSTRACT: Pd(II)-catalyzed C–H lactonization of *o*-methyl benzoic acid substrates has been achieved using molecular oxygen as the oxidant. This finding provides a rare example of C–H oxygenation through Pd(II)/Pd(0) catalysis, as well as a method to construct biologically important benzolactone scaffolds. The use of a gas mixture of 5% oxygen in nitrogen demonstrated the possibility for its application in pharmaceutical manufacturing.

Benzolactones are prominent scaffolds in bioactive natural products and important pharmaceutical compounds(Figure 1).[1] Additionally, the lactone structural motif is a common synthetic intermediate and building block for the synthesis of complex molecules.[2] Traditionally, the benzolactone skeleton is constructed through the cyclization of hydroxy acids or the halolactonization processes.[3] While these methods are well established for the synthesis of such motifs, a direct C–H lactonization would be highly attractive. A number of studies towards C–H lactonization using the Shilov system has been reported.[4] In 2006, Chang reported a platinum(II)-catalyzed lactonization

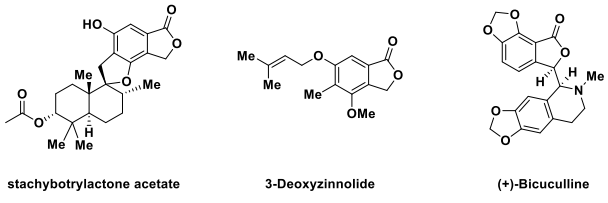
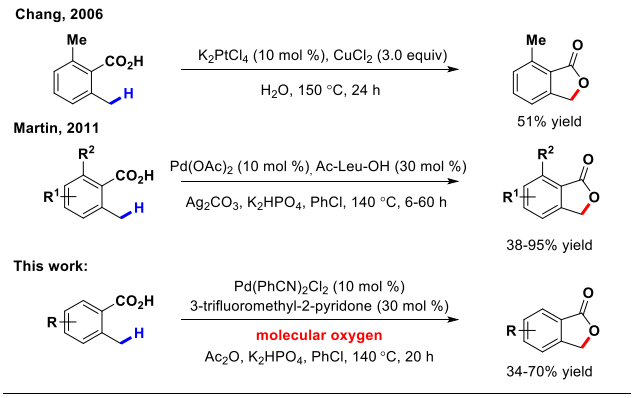


Figure 1. Bioactive and natural benzolactone derivatives

of benzylic C–H bonds affording benzolactones in the presence of 3 equiv. of $CuCl_2$ as the oxidant. Synthetically useful yields can be obtained with a di-*ortho*-methylated benzoic acid substrate (Scheme 1).[4d] In 2011, Martin developed a palladium-catalyzed C(sp^3)–H lactonization with *o*-methyl benzoic acid using MPAA ligand and stoichiometric silver(I) as an oxidant.[4e] Substitution at the 5 or 6-position on the benzoic acid was required to block the C(sp^2)–H bond to prevent the facile *ortho*-C–H activation accelerated by the MPAA ligand. In our search for an efficient route for the preparation of a pharmaceutical ingredient bearing the benzolactone motif, we began to develop new ligands and conditions to achieve such C–H lactonization of simple mono-*o*-methyl benzoic acids in which a ligand will selectively accelerate the activation of the C(sp^3)–H bond over the C(sp^2)–H bond. For potential scaling up to kilograms, the use of expensive oxidant needs to be avoided. To be compatible with safe operation in process, O_2 at low concentration, for example, 5% in N_2, will be the ideal oxidant.

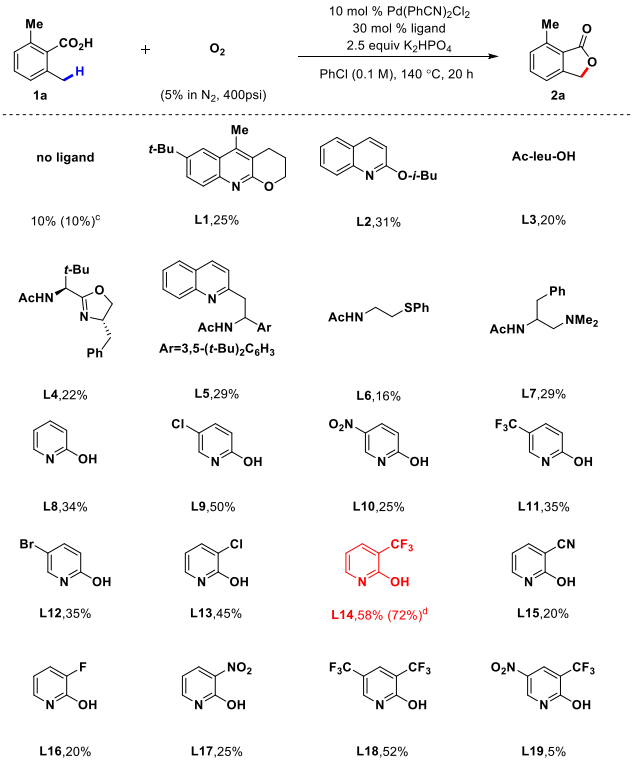
In the past decade, a wide range of palladium-catalyzed C–H functionalization reactions have been realized.[5] While both Pd(II)/Pd(IV) and Pd(II)/Pd(0) redox catalysis have been established for C–C coupling reactions, C–O and C–N formations are largely limited to Pd(IV) catalysis using chalcogenide-type oxidants or by-standing oxidants.[6] For example, TBHP, Ag(I), $CuCl_2$, $K_2S_2O_8$, BQ, and PIDA have been extensively adopted.[6] From the practical viewpoint, it is highly desirable to develop Pd(II)/Pd(0) catalysis using O_2 as the sole oxidant.[7] However, achieving C-H oxygenation *via* Pd(II)/Pd(0) catalysis is challenging due to the lack of a ligand that can promote both C–H activation and C–O reductive elimination from the Pd(II) center. Herein, we report the development of Pd(II)-catalyzed C(sp^3)–H lactonization using molecular oxygen as the oxidant. The absence of oxidants other than oxygen provides a rare example to further investigate the mechanism of C–H oxygenation *via* Pd(II)/Pd(0) catalysis.

Scheme 1. Palladium-catalyzed C–H functionalizations towards the synthesis of benzolactones



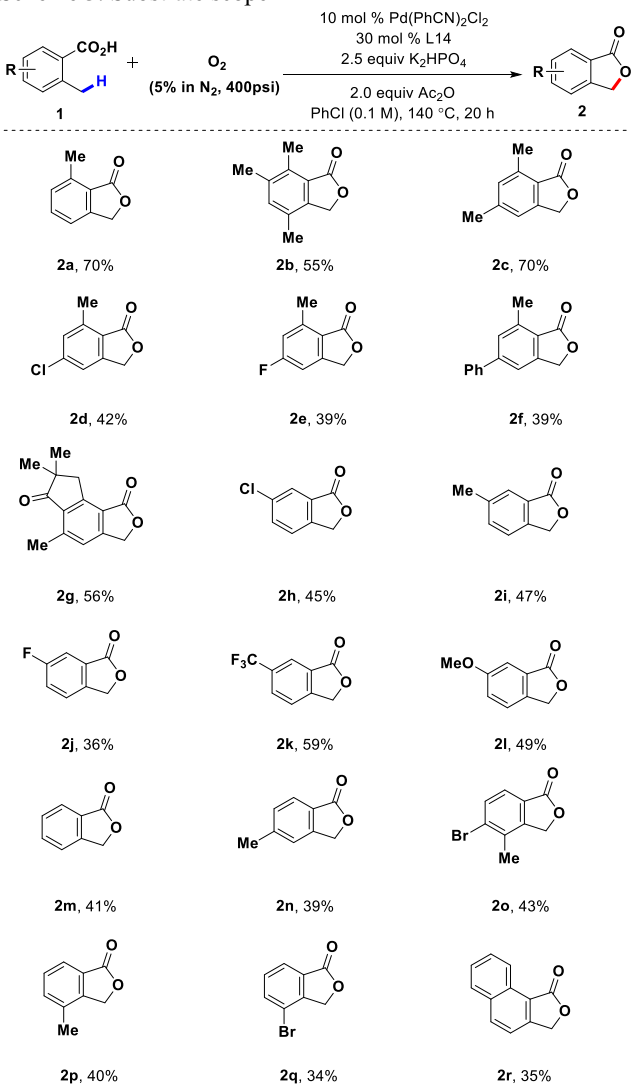
After considerable optimization, we were pleased to observe that using $Pd(PhCN)_2Cl_2$, K_2HPO_4, and chlorobenzene as the solvent in the presence of 1 atm oxygen provided the desired product **2a** in 10% yield (Scheme 2). To ensure safe use of oxygen in process, we attempted to replace pure oxygen with the gas mixture of 5% oxygen in nitrogen which is below the limiting oxygen concentration (LOC) of most organic solvent[8] as the oxygen source. To our delight, the same result was obtained with the gas mixture of 5% oxygen in nitrogen under 400 psi. We next evaluated several mono-dentate pyridine-based ligands (**L1, L2**), which have been shown to promote C–H activation.[9] Interestingly, the yield was improved to 31% by using the pyridine-based ligand (**L2**). Subsequently, we tested Ac-Leu-OH (**L3**) which afforded a remarkable ligand effect in previous Martin's work[4e]. However, ligand **L3** only gave a poor yield of the desired product. We then turned our attention to bidentate ligands (**L4-L7**) developed in our laboratory.[10] Unfortunately, no further improvement was observed. Guided by our recent finding that 2-pyridone ligands can accelerate C–H activation,[11] we turned to investigate this type of ligand. Encouragingly, the yield increased to 34% with a simple 2-pyridone ligand (**L8**). Based on our previous successes with electron-deficient 2-pyridones,[12] we set out to extensively screen 2-pyridone ligands with electron-withdrawing substituents. To our delight, the use of 5-chloro-2-pyridone (**L9**) increased the yield to 50%. Further tuning the substitution at the 5-position did not enhance the reactivity (**L10-L12**). We next evaluated 2-pyridone ligands bearing 3-substituents (**L13-L17**). Intriguingly, the yield increased

Scheme 2. Ligand optimization [a,b]



[a]Reaction conditions: substrate **1a** (0.1 mmol), $Pd(PhCN)_2Cl_2$ (10 mol %), ligand (30 mol %), K_2HPO_4 (2.5 equiv), PhCl (1.0 mL), 140 °C, 20 h. [b]The yields were determined by 1H NMR analysis of the crude product using 1,3,5-Trimethoxybenzene as the internal standard. [c]1 atm O_2. [d]Ac_2O (2.0 equiv) were used.

Scheme 3. Substrate scope [a, b]



[a]Reaction conditions: substrate **1a** (0.2 mmol), $Pd(PhCN)_2Cl_2$ (10 mol %), **L8** (30 mol %), K_2HPO_4 (2.5 equiv), Ac_2O (2.0 equiv) PhCl (2.0 mL), 140 °C, 20 h. [b]isolated yield

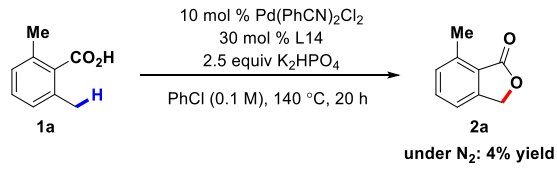
to 58% when 3-trifluoromethyl-2-pyridone (**L14**) was used. Installing another trifluoromethyl group on **L14** gave slightly lower yield (**L18**). And the use of 5-nitro-3-trifluoromethyl-2-pyridone (**L19**) resulted in loss of reactivity. These results indicated that this lactonization is highly sensitive to the electronic and steric environments of the 2-pyridone ligands. With **L14** as the top performing ligand, we next investigated the effect of additives towards Pd(II)-catalyzed C(sp^3)–H lactonization. To our delight, the addition of acetic anhydride was found to be beneficial to the reaction, and the yield was further increased to 72%. The acetic anhydride could act as a transient protecting group for benzoic acid and prevent the decarboxylation of the starting material.

With the optimal conditions in hand, the scope of benzoic acids was evaluated. As shown in Scheme 3, a wide range of functional groups are well accommodated in this transformation. Benzoic acids bearing electron-donating groups, such as methyl (**2a-2f, 2i** and **2n**), methoxy (**2l**) and phenyl (**2f**) gave the desired lactones in moderate to excellent yield. Electron deficient

benzoic acids, such as fluoro (**2e** and **2j**), trifluoromethyl (**2k**) and ketone (**2g**) are also well tolerated. Furthermore, our methodology can react with C(sp^3)–H bonds selectively over C(sp^2)–H (**2h**-**2r**). More interestingly, the selectivity is not determined by steric effects since benzoic acids without 5-substitution (**2m**-**2q**) still gave the desired product, while previous method[4e] only tolerated 5-substituted benzoic acids. Moreover, aryl halides (**2d**, **2h**, **2o** and **2q**) were well tolerate in the reaction, which enabled further transformations with classical cross-coupling reactions. Besides benzoic acid derivatives, the desired lactone product was formed with naphthenic acid, albeit with slightly lower yield (**2r**). This result showed the potential of employing our methodology with more complex aromatic ring system.

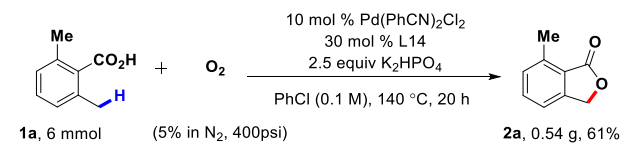
In order to gain experimental data in support of the involvement of Pd(II)/Pd(0) redox catalysis, a control experiment under nitrogen atmosphere was conducted and 4% yield of the desired product was observed (Scheme 4). This result indicated that the reductive elimination still occurred in the absence of any oxidant, hence suggesting that the reaction is more likely to proceed through a Pd(II)/Pd(0) catalytic cycle.

Scheme 4. Control experiment with N_2



To demonstrate the scalability of this protocol, a gram-scale reaction was conducted under the standard lactonization conditions affording desired lactone product **2a** in 61% yield (Scheme 5).

Scheme 5. Gram scale reaction



In conclusion, Pd(II)-catalyzed C(sp^3)–H lactonizations of a range of benzoic acids using molecular oxygen as the oxidant have been developed with a broad functional group tolerance. The reaction is conducted under pressurized gas mixture of 5% oxygen in nitrogen (below the limiting oxygen concentration for most organic solvents) which meets the safety requirement in process chemistry. This rare example of catalytic C–H oxygenation reaction via Pd(II)/Pd(0) catalysis using O_2 as the sole oxidant also provides a valuable example for probing the mechanism of the C–O reductive elimination from a Pd(II) center in C–H activation reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and characterization of new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

* yu200@scripps.edu

Notes

The authors declare no competing financial interest.

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