CHEMISTRY
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To be cited as: *Chem. Eur. J.* 10.1002/chem.201702045

Link to VoR: http://dx.doi.org/10.1002/chem.201702045

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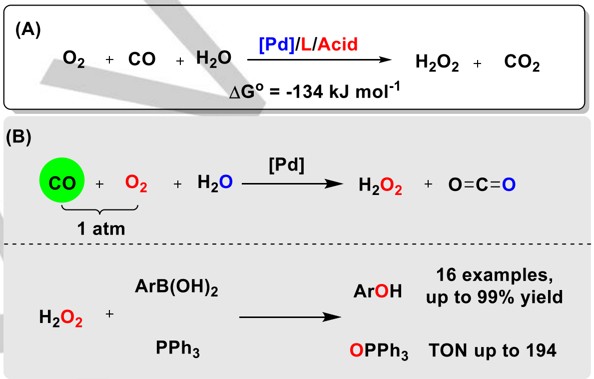
Pd-catalyzed Hydroxylation of Aryl Boronic Acids using *in-situ* Generated Hydrogen Peroxide

Hong Yi, and Aiwen Lei*

***Abstract*:** In this work, we describe a benign and efficient palladium catalyzed *in-situ* generated hydrogen peroxide from carbon monoxide, water and oxygen under mild conditions. This novel methodology combines catalytic hydrogen peroxides production with aerobic oxidation process in a sole reaction system. This system shows good functional group tolerance and provides a benign and efficient access to a variety of functionalized phenols. Furthermore, the *in-situ* generated hydroperoxide can be well used for triphenylphosphine oxidation, in which the TON is up to 194. The isotope labelling studies provides an important mechanistic insight for this process.

Among the many chemical oxidants available to organic chemists, hydrogen peroxide is one of the 'greenest' since the only by-product from it is water. The annual world production of hydrogen peroxide is over 2.2 million tons.[1] It is widely used in most industrial fields, particularly in chemical industry and environment protection. The current manufacture route, anthraquinone oxidation process, is not an ideal method since it generates wastes, consumes significant energy and requires multiple unit operations.[1-2] As a result, the development of novel and environmentally benign method for the production and application of hydrogen peroxide is highly desirable.

One alternative route is the direct synthesis of hydrogen peroxide from hydrogen and oxygen.[3] However, the noticeable side reactions, including the direct formation of water and the decomposition as well as reduction of hydrogen peroxide, are all highly exothermic and thermodynamically favoured.[1] Clearly, direct contact between hydrogen and oxygen also presents an explosion risk. Thus, this process has not yet been put into practice. The production of hydrogen peroxide is also possible from a mixture of oxygen, carbon monoxide and water (Scheme 1A). The feasibility of this concept was first disclosed by using a palladium triphenylphospine catalyst system. Despite the favorable thermodynamics of this transformation ($\Delta G^{\neq} = -134$ kJ mol^{-1}), the reaction efficiency was quite low and a turnover number of only 5 was obtained. The rapid deactivation of the catalyst was mainly due to the oxidation of the phosphine ligand and subsequent precipitation of palladium metal. Researchers at EniChem carried out this reaction in a bi-phase system in the presence of bidentate nitrogen ligand and acid additive to minimize the ligand oxidation. Although this catalysis system showed high stability and catalytic activity,[4] the high CO/O_2 pressure limited the usage in oxidative process.



Scheme 1. **(A)** The production of hydrogen peroxide from a mixture of oxygen, carbon monoxide and water. **(B)** Catalytic hydrogen peroxides production with aerobic oxidation process in a sole reaction system.

In spite of this impressive achievement, the transport, storage and handling of bulky hydrogen peroxide involve potential safety hazard and extra expense. It is widely recognized that hydrogen peroxide is a strong oxidant, which can oxidize a wide range of substrates under very mild conditions.[5] Therefore, we envisioned that the combination of *in-situ* generation of hydrogen peroxide and an effective oxidation process could avoid the accumulation of hydrogen peroxide in the reaction system, and thus prevent the deactivation of the palladium catalyst. As far as form is concerned, the aerobic oxidation of the substrate was directly achieved using oxygen as the terminal oxidant.[6] Here, we present a palladium catalyzed *in-situ* generated hydrogen peroxide formation from carbon monoxide, water and oxygen (Scheme 1B). This novel methodology combines catalytic hydrogen peroxides production with aerobic oxidation process in a sole reaction system. This transformation shows highly efficiency and tolerance for arylboronic acids oxidation and triphenylphosphine oxidation (PPh$_3$) oxidation.

Phenols are biologically active compounds and widely serve as versatile synthetic intermediates.[7] Meanwhile, the oxidative hydroxylation of arylboronic acids to produce phenols using hydrogen peroxide is a very efficient transformation.[8] Based on the above mentioned strategy, herein we describe a palladium catalyzed aerobic oxidative hydroxylation of arylboronic acids via *in-situ* generated hydrogen peroxide from oxygen, carbon monoxide and water.[9] We initiated our investigation by

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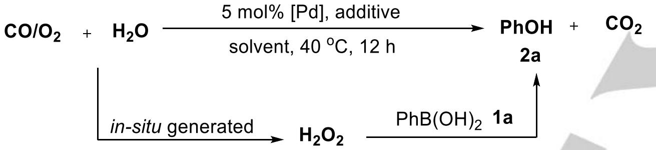
examining the feasibility of the Pd-catalyzed hydroxylation of phenylboronic acid **1a** (Table 1). Representative Pd catalysts, ligands, additives and solvents were examined to boost the efficiency of this transformation (See Supporting Information Table S1-S3 for more detail). The combination of 5 mol% $PdCl_2(PPh_3)_2$/2 equivalents of KF in *t*BuOH under balloon pressure of 3:1 CO/O_2 at 40 °C gave the best result (up to 98% yield) for the oxidative hydroxylation of **1a** (Table 1, entry 1). Among the palladium catalysts examined (Table 1, entries 1-5), only $PdCl_2(PPh_3)_2$ showed high catalytic activity, while other tested bidentate ligands and catalyst precursors gave poor yields for hydroxylated product **2a**. The screening of different additives illustrated that KF also played a key role to facilitate this transformation under these conditions (Table 1, entries 1 and 7-9). Moreover, a survey of the solvent effects revealed that over 90% reaction yields could be obtained in the presence of either *t*BuOH or MeCN as the solvent (Table 1, entries 1, 11 and 12). Finally, the reaction proceeded under O_2 atmosphere without CO afforded 80% yield of the oxidative homo-coupling product instead of hydroxylation product **2a**, which displayed that CO was crucial for the selectivity control (Table 1, entry 10). When using $Pd(PPh_3)_4$ as the catalyst under O_2 atmosphere without CO, 70% diphenyl was achieved.

Table 1. Optimization of Reaction Conditions [a]



Entry	[Pd]	additive	solvent	Yield **2a**[b]
1	**$PdCl_2(PPh_3)_2$**	**KF**	***t*-BuOH**	**98**
2	$PdCl_2(dppf)$	KF	*t*-BuOH	6
3	$Pd(OAc)_2$/bipy	KF	*t*-BuOH	8
4	$Pd(OAc)_2$	KF	*t*-BuOH	12
5	$Pd(MeCN)_2Cl_2$	KF	*t*-BuOH	12
6	none	KF	*t*-BuOH	trace
7	$PdCl_2(PPh_3)_2$	Et_3N	*t*-BuOH	9
8	$PdCl_2(PPh_3)_2$	KOH	*t*-BuOH	41
9	$PdCl_2(PPh_3)_2$	K_3PO_4	*t*-BuOH	11
10[c]	$PdCl_2(PPh_3)_2$	KF	*t*-BuOH	trace
11	$PdCl_2(PPh_3)_2$	KF	DMF	41
12	$PdCl_2(PPh_3)_2$	KF	MeCN	92

[a] Reaction conditions: 1a (0.25 mmol), additive (0.5 mmol), Pd catalyst (0.0125 mmol), CO/O_2 (3:1) at 1 atm pressure in 2.0 mL of solvent and 150 μL H_2O. [b] GC yields. [c] Under 1 atm of O_2 without CO.

To gain more insights of this reaction, the gas phases was initially detected during the reaction process. CO_2 was found to be generated along with the production of phenol **2a** tested by the clear water solution of $Ca(OH)_2$. To verify where the oxygen in CO_2 came from, isotope labelling experiments were performed utilizing GC-Mass spectroscopy. When using the $H_2{}^{18}O$ as the labeling source, the mass spectrum showed the increase of CO_2 with molecular weight of 46 and the molecular weight of 44 was not detected during the reaction, which indicated that one oxygen in CO_2 came from water (Figure 1A). To further confirm this result, $^{18}O_2$ was also used as the labeling source under the same conditions, the mass spectrum showed the increase CO_2 with molecular weight of 44 and the molecular weight of 46 was not detected during the reaction (Figure 1B). These above results revealed that the formed CO_2 in this oxidative hydroxylation reaction come from water and CO.

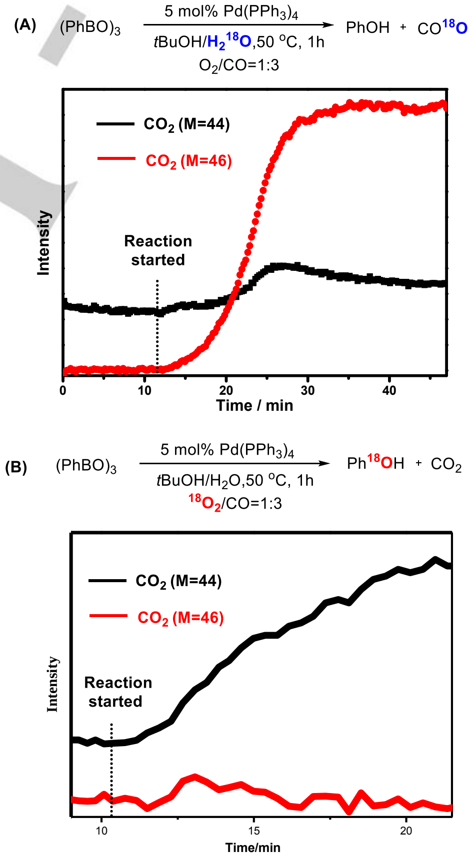
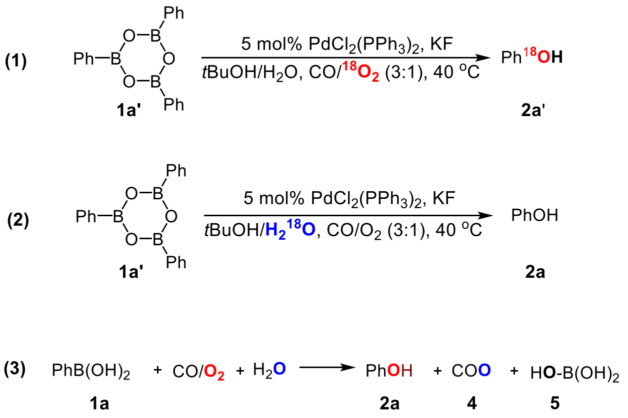


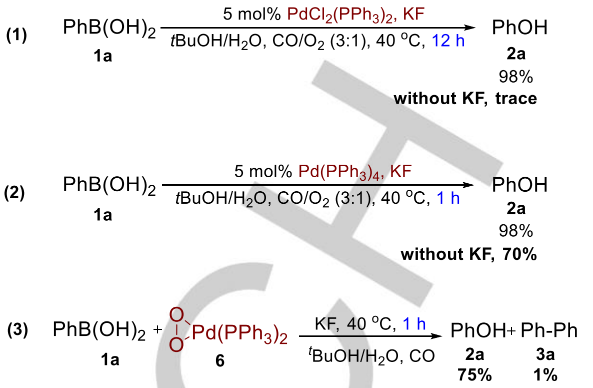
Figure 1. (A) Gas phase detection using isotope labelling experiments. **(B)** Gas phase detection using isotope labelling experiments.

Furthermore, isotope labelling experiments results demonstrated that O_2 participated in this transformation and the oxygen atom transferred into the hydroxylated product **2a'**. On the contrary, ^{18}O labelled water didn't produce any labelled product **2a'** [Scheme 2, Eqs (1) and (2)]. From the above, the overall reaction could be speculated as shown in Scheme 2, Eq (3): oxidative hydroxylation of 1a in the presence of O_2, CO and water produced phenol **2a**, CO_2 4 and boronic acid **5**. The presence of KF as the additive is essential to achieve the $PdCl_2(PPh_3)_2$ catalysed hydroxylation reaction.



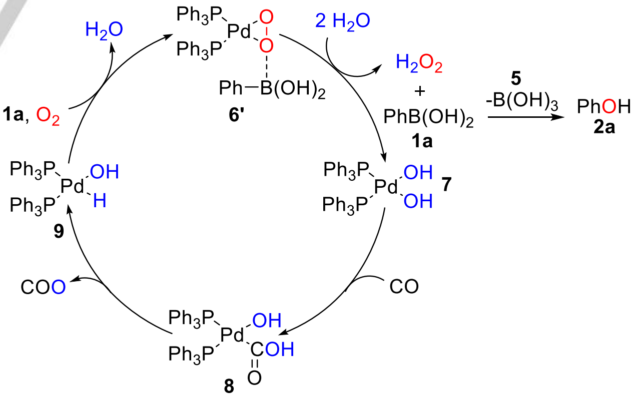
Scheme 2. Isotope labelling experiments.

There is no reaction without the assistance of KF using Pd (II) catalyst [Scheme 3, Eq (1)]. When Pd (0) catalyst was employed as the catalyst in the presence of KF, this transformation afforded excellent yield within a much shorter reaction time comparing to Pd (II) catalyzed reaction. Nevertheless, Pd (0) catalyzed reaction could also proceed smoothly in defect of KF as the additive [Scheme 3, Eq (2)]. As we know, fluoride plays important roles in arylboronic acid derivatives involved coupling reactions.[10] We assumed that it mainly promoted the reduction of Pd (II) catalyst precursor to Pd (0) species in this $PdCl_2(PPh_3)_2$ catalyzed oxidative hydroxylation reaction and the catalyst precursor activation process was probably the rate determined step of this catalytic reaction with Pd(II) catalyst.[11] Moreover, the Pd (0) species is easily to be oxidized to form palladium peroxo complex **6** under the oxygen atmosphere,[12] which is possible catalytic active species of this reaction. To verify this hypothesis, the stoichiometric reaction of **1a** and **6** under the standard conditions was implemented and generated **2a** with high yield [Scheme 3, Eq (3)]. This result further proved palladium peroxo complex **6** was most likely involved in the catalytic cycle. When performing reaction with Pd-oxo complex **6** in MeCN using **1a'** as the substrate, only trace phenol product was detected, which excluded the direct oxidation pathway from Pd-oxo species.



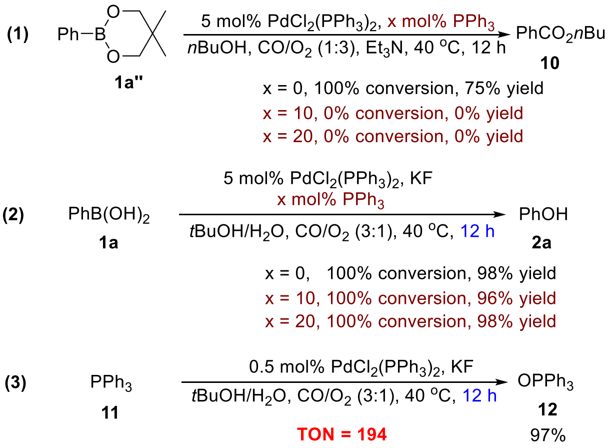
Scheme 3. The KF effects for Pd (II) and Pd (0) catalyzed hydroxylation reactions

Based on above experiment observations, the proposed mechanism was listed in Scheme 4. As above mentioned, the Pd(II) catalyst precursor was initially transformed to palladium peroxo complex **6**, which could be coordinated by phenylboronic acid **1a** to form a new Pd complex **6'**.[13] Hydrolysis of **6'** would generate palladium hydroxide species **7** and the adduct of hydrogen peroxide and phenylboronic acid. The latter would undergo a fast oxidative hydroxylation process affording phenol **2a** and boric acid **5**. Then CO insertion into the intermediate **7** afforded acyl palladium complex **8**, which proceeded β-hydrogen elimination to create palladium hydride species **9** and liberate carbon dioxide. Finally, reductive elimination of **9** produced water and Pd(0) species, which was oxidized to palladium peroxo complex **6'** in the presence of oxygen and **1a**. Agreeably, this reaction mechanism accorded with the above isotope labelling experiment results, in which the oxygen atom involved in phenol comes from oxygen. In the meanwhile, CO_2 could be also formed along with the production of phenol.



Scheme 4. Proposed mechanism.

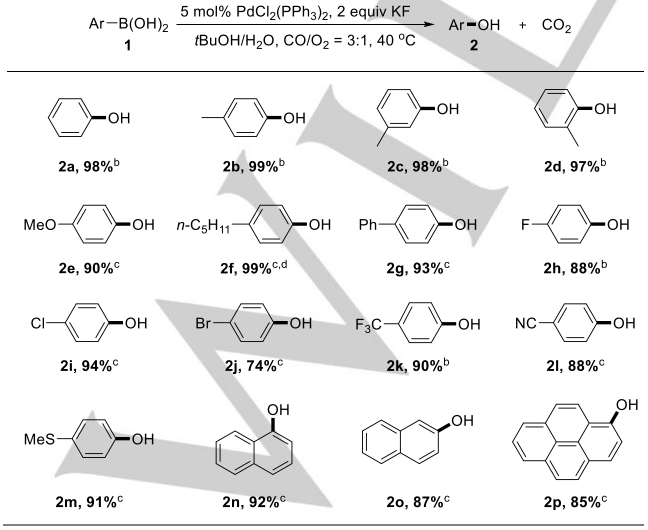
Previously, we have reported a palladium catalyzed oxidative carbonylation reaction under similar reaction conditions.[14] In that case, additional 10 mol% PPh_3 can completely shut down the reaction [Scheme 5, Eq (1)]. It might be due to the excess PPh_3 constrain the CO coordination and insertion steps. Conversely, no ligand inhibition effect was observed when excess PPh_3 was added in this oxidative hydroxylation reaction [Scheme 5, Eq (2)]. As we know, PPh_3 can be oxidized by hydrogen peroxide very fast. As hydrogen peroxide is generated during the reaction process, the excess PPh_3 can be oxidized to triphenyl phosphine oxide and thus do not inhibit this transformation. Actually, the catalytic aerobic oxidation of triphenyl phosphine could be achieved proficiently under the standard conditions with 194 turnover number (TON) [Scheme 5, Eq (3)], which further approved our proposed mechanism.



Scheme 5. PPh_3 effect on oxidative hydroxylation of arylboronic acids and PPh_3 oxidation

With the optimized reaction conditions in hand, we examined the substrate scope of the palladium catalyzed aerobic oxidative hydroxylation of arylboronic acids (Scheme 6). A variety of arylboronic acids were smoothly oxidized to the corresponding phenols in good to excellent yields. Electron-neutral, electron-donating, and electron-withdrawing functional groups were all well tolerated in this transformation. The reactions of steric hindered substrates provided excellent results as well (Scheme 6, **2d**, **2n,** **2o** and **2p**). More importantly, the electron-rich and bromo- substituted phenols, which are difficult to obtain from the traditional nucleophilic substitution and transition-metal catalyzed hydroxylation of aryl halides,[15] could be straightforwardly synthesized using this catalytic oxidative hydroxylation protocol (Scheme 6, **2e**, **2j** and **2m**).

Scheme 6. Palladium catalyzed aerobic oxidative hydroxylation of arylboronic acids.[a]



[a] Reaction conditions: $ArB(OH)_2$ (0.25 mmol), KF (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.0125 mmol), CO/O_2 (3:1) at 1 atm pressure in 2 mL of *t*BuOH and 150 μL H_2O. [b] GC yields. [c] Isolated yields. [d] $PdCl_2(PPh_3)_2$ (0.019 mmol) was used.

In summary, we have developed a mild condition for hydrogen peroxide generation from carbon monoxide, water and oxygen by Pd catalyst. This methodology combines catalytic hydrogen peroxides production with aerobic oxidation process in one system. This transformation shows highly efficiency and widely tolerance for arylboronic acids oxidation and triphenylphosphine oxidation (PPh_3) oxidation. A serial of investigations indicated that the *in-situ* generation of hydrogen peroxide along with carbon dioxide, and that both oxygen and water contributed in this transformation and the oxygen atom in the hydroxylated product originated from oxygen. Further synthetic application of this catalytic hydrogen peroxide formation reaction system and more detailed mechanistic studies are the subjects of on-going in our lab.

Experimental Section

General procedure: In a schlenk tube equipped with a stir-bar, Pd catalyst (0.0125 mmol), additive (0.5 mmol) and phenyl boronic acid (0.25 mmol) were combined. A balloon filled with CO and O_2（CO: O_2 = 3:1）was connected to the Schlenk tube via the side tube. The reaction tube was purged with the mixed gas for 1 minute. *t*-Butanol (2 mL) and 150 μL H_2O were then added to the reaction tube via a syringe. The Schlenk tube was placed in an oil-bath and heated to 40 ℃ for 12 hours and then cooled to room temperature. The yields of product were determined by GC.

Acknowledgements

This work was supported by the 973 Program (2012CB725302), the National Natural Science Foundation of China (21390400, 21520102003, 21272180 and 21302148), the Hubei Province Natural Science Foundation of China (2013CFA081), the Research Fund for the Doctoral Program of Higher Education of China (20120141130002), and the Ministry of Science and Technology of China (2012YQ120060). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated. We thank Prof Qiang Liu and Dr Jie Liu for the contribution and discussion of this work.

Keywords: palladium catalysis • aerobic oxidation • hydroperoxide • dioxygen activation • oxidative coupling

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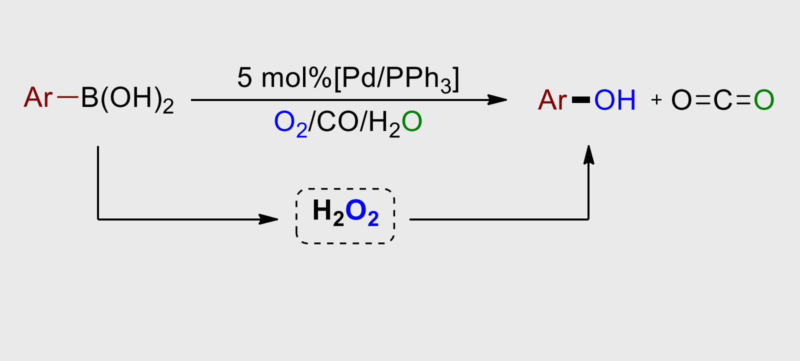

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A benign and efficient palladium catalyzed *in-situ* generated hydrogen peroxide from carbon monoxide, water and oxygen under mild conditions is developed in this work. This system shows good functional group tolerance and provides a new route to a variety of functionalized phenols.