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Selective Oxidative Hydroxylation of Arylboronic Acids by Colloidal Nanogold Catalyzed in Situ Generation of H_2O_2 from Alcohols Under Aerobic Conditions

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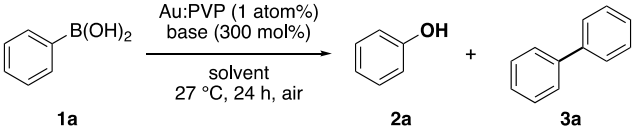
Selective hydroxylation of arylboronic acids were achieved through PVP (polyvinylpyrrolidone)-stabilized nanogold catalyzed *in situ* generated H_2O_2 formed by the oxidation of an alcoholic solvent under aerobic conditions. The synthetic application of *in situ* generated H_2O_2 was investigated through aerobic epoxidation of (*E*)-chalcone.

Since the seminal work by Haruta et al.[1] on the oxidation of CO by nano-sized gold, interest in nanogold as catalysts has exponentially increased over the past few decades. Amongst the myriad of nanogold catalyzed reactions, oxidation reactions remain as a central theme. Previously, we have reported PVP (polyvinylpyrrolidone)-stabilized gold nanoclusters (Au:PVP) catalyzed reactions.[2–6] In all of these cases, nanogold-catalyzed oxidations play a key role. In the Au:PVP catalyzed homocoupling of arylboronic acids, hydroxylation into phenols cannot be avoided under basic conditions.[4] Therefore, several approaches to achieve selective homocoupling were developed, such as employment of chitosan as a stabilizing agent[7] or HAP as a solid support.[8] Selective hydroxylation of arylboronic acids[3] by the Au-catalytic system has also been thoroughly investigated. However, these examples utilize an additional reductant[9–11], electrolytic,[12] or photoredox catalysis.[13,14] In many cases, *in situ* generation of H_2O_2 through the reduction of O_2 by reductant (e.g. H_2,[15] NH_4HCO_3[9]) is involved in the mechanism. We envisioned that as alcohols are readily oxidized by Au:PVP,[5,6] it could act as both solvent and reductant. Here, we report a more selective and simpler alternative to achieve selective hydroxylation through *in situ* generation of H_2O_2 from oxidation of an alcoholic solvent by the Au:PVP catalytic system.

We started our investigation by switching the solvent of Au:PVP catalyzed homocoupling of phenylboronic acid (**1a**) from water to EtOH using K_2CO_3 as a base (Scheme 1). However, this resulted in mediocre conversion with poor selectivity. When the base was changed to KOH, the reaction was completed to afford a phenol (**2a**) and a biphenyl (**3a**) in 89% and 11% yields, respectively.

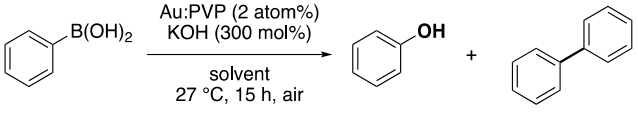


solvent: H_2O, base: K_2CO_3	23%	72%
solvent: EtOH, base: K_2CO_3	21%	22%
solvent: EtOH, base: KOH	89%	11%

Scheme 1. Aerobic Au:PVP catalyzed reaction of phenylboronic acid (**1a**)

To confirm whether alcohol plays a role in determining the selectivity of hydroxylation, EtOH and water at various ratios were employed as solvent (Table 1, entries 1–5). In all cases, quantitative conversion was observed at 27 °C after 15 h, and higher EtOH ratios resulted in higher selectivity towards hydroxylation. When the reaction was carried out without oxygen, no reaction occurred, which was consistent with our previous results[4] that oxygen is indispensable (entry 6). After revealing the effect of EtOH in promoting selective hydroxylation, we tested various alcohols in hope to achieve higher selectivity (entries 7–12). Primary and secondary alcohols were found to be suitable solvents to achieve selective hydroxylation. 2-PrOH provided the highest selectivity, with nearly quantitative hydroxylation (entry 10). The use of MeOH (entry 7) and the highly acidic trifluoroethanol (entry 12) resulted in product yields close to that in water. *t*-BuOH resulted in poor conversion and selectivity (entry 11). These results indicate that the reducing ability of the solvent plays a significant role in the reaction mechanism.

Table 1. Optimization of solvent



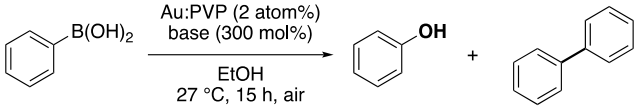
Entry	Solvent	Recovery and Yield (%)[a]		
		1a	2a	3a
1	H_2O	0	31	69
2	H_2O/EtOH (3:1)	0	58	42
3	H_2O/EtOH (1:1)	0	65	35
4	H_2O/EtOH (1:3)	0	73	27
5	EtOH	0	89	11
6[b]	EtOH	>99	0	trace
7	MeOH	0	25	75
8	1-PrOH	0	91	9
9	1-BuOH	0	90	10
10	2-PrOH	0	99	trace
11	*t*-BuOH	88	0	12
12	CF_3CH_2OH	0	24	76

[a]Determined by ^1H NMR analysis using mesitylene as an internal standard. [b]Carried out under vacuum.

Next, the effect of the base was investigated using EtOH as a solvent (Table 2). We first confirmed that base was necessary for the reaction (entry 1). Inorganic hydroxides provided

consistent quantitative conversions, with stronger inorganic hydroxides yielding higher selectivity towards hydroxylation (entries 2–6). In contrast, organic bases were not suitable as it provides very low to zero conversions due to the coordination to the surface of gold nanoclusters, decreasing the catalytic activity (entries 7–9). These results indicate that selective hydroxylation is linked with the strength of base.

Table 2. Optimization of base using EtOH as solvent

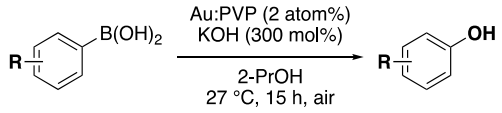


1a 2a 3a

Entry	Base	Recovery and Yield (%)[a]		
		1a	2a	3a
1	None	83	6	11
2	LiOH	0	54	46
3	NaOH	0	85	15
4	KOH	0	89	11
5	CsOH	0	98	trace
6	K_2CO_3	57	21	22
7	Et_3N	88	0	12
8	DBU	100	0	0
9	DMAP	100	0	0

[a]Determined by ^{1}H NMR analysis using mesitylene as an internal standard.

Table 3. Substrate scope



1 2

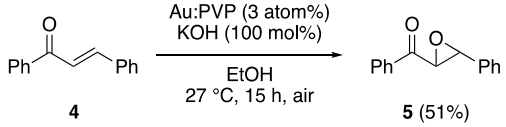
Entry	R	Recovery and Yield (%)[a]	
		1	2
1	*p*-OMe (**1b**)	0	98
2	*p*-F (**1c**)	0	96
3	*p*-Cl (**1d**)	0	99
4	*m*-Cl (**1e**)	46	53
5	*o*-Cl (**1f**)	46	54
6	*p*-Br (**1g**)	11	89
7	*p*-I (**1h**)	0	99
8[b]	*p*-I (**1h**)	84	16
9	*p*-CHO (**1i**)	0	54

[a]Determined by ^{1}H NMR analysis using mesitylene as an internal standard. [b]Performed under EtOH as solvent.

Substrate scope was screened using 2-PrOH as a solvent and KOH as a base (Table 3) because KOH is easier to handle and cheaper than CsOH. We found that *para*-substituted arylboronic acids (**1b–d**, **1g**, **1h**) undergo excellent conversions and hydroxylation selectivity. Although selectivity for hydroxylations were excellent, mediocre conversions were obtained with *meta*- and *ortho*-substituted arylboronic acids (entries 4 and 5). Surprisingly, *para*-iodophenylboronic acid (**1h**) proceeded through the reaction normally. This is in contrary to our expectation, as we previously reported that aryl iodides are strong inhibitors for gold-based nanocluster catalysts.[16] However, low conversion of *para*-iodophenylboronic acid was obtained when EtOH was used as a solvent (entry 8). In the case of *para*-formylphenylboronic acid (**1i**), the desired hydroxylated compound **2i** was obtained in 54% yield along with a significant amount of 4-hydroxybenzylidenacetone, derived through aldol condensation reaction with *in situ* generated acetone (entry 9). This result clearly indicated that 2-PrOH was oxidized under the reaction conditions to afford acetone. Noted that the corresponding isopropyl ester or carboxylic acid, through the oxidation of the formyl group was not observed.[5]

The catalytic mechanism for the homocoupling of arylboronic acids has been thoroughly studied.[7,17] It is also well established that oxygen is readily adsorbed on nano-sized gold surfaces.[18,19] This results in the formation of superoxo-like species,[20] which generates Lewis acidic sites on the gold surface[21] to facilitate adsorption of substrates such as arylborates[4,17] and alcohols.[22,23] Under the basic aqueous conditions, formation of HOO^- reduced from O_2 is unavoidable,[17] which is then responsible for arylboronic acid hydroxylation. As alcohols are readily adsorbed[18,19] and oxidized by nano-sized gold surfaces,[5,6] oxygen-promoted oxidation of alcohols on the gold surface could directly form H_2O_2. First, oxygen is adsorbed on the gold surface, followed by adsorption of alkoxide more predominant than that of arylboronate. At the same time, hydrogen atom expelled during alkoxide formation and oxygen could interact to form a peroxide. Subsequent β-hydride elimination then results in the formation of either an aldehyde or ketone and H_2O_2. This proposed mechanism is supported by the fact that 1) oxygen is necessary, 2) non-reducing alcohols does not promote selective hydroxylation, and 3) stronger bases promote higher selectivity, probably due to the formation of highly nucleophilic peroxide anion under the reaction conditions. The drastic change of chemoselectivity would attribute to the preferential adsorption of the solvent alcohols, which undergo the degradative production of H_2O_2 under the reaction conditions. It is also assumed that the generation of transmetallation-active borate intermediate may be suppressed in alcoholic solvents, impeding the homocoupling catalytic cycle. MeOH did not promote selective hydroxylation as it is less readily oxidized compared to EtOH and 2-PrOH.[24] In fact, we have previously demonstrated that Au:PVP catalyzed oxidation of MeOH occurs only at elevated temperatures.[25] When non-reducing alcohols are utilized, only dissolved residual water participates in the reaction.

Since *in situ* formation of H_2O_2 is likely to occur under the aerobic Au:PVP catalyzed, alcoholic, and basic system, we sought to apply this catalytic system into other oxidation reactions. We chose (*E*)-chalcone (**4**) as our model substrate. The corresponding epoxide product (**5**) was obtained in 51% isolated yield and total conversion of the starting material when the reaction was carried out in EtOH at 27 °C under air in the presence of 3 atom% of Au:PVP with a stoichiometric amount of KOH (Scheme 3).[26] This highlights the potential to apply the *in situ* generated H_2O_2 by the Au:PVP catalytic system to other oxidation reactions.



4 **5** (51%)

Scheme 2. Aerobic epoxidation of (*E*)-chalcone (**4**) catalyzed by

Au:PVP.

In summary, by utilizing an alcoholic solvent and Au:PVP as catalyst, we were able to generate H_2O_2 *in situ*, which could be utilized for selective hydroxylation of arylboronic acids and aerobic oxidations. We have successfully demonstrated one example by achieving aerobic epoxidation of (*E*)-chalcone.

2. Experimental

Preparation of Au:PVP. The preparation of Au:PVP(K-30) was carried out following our previously reported method.[4]

General procedure for hydroxylation of arylboronic acids.[26] To a 15 mL test tube was added 0.200 mmol of arylboronic acid, 33.7 mg KOH, and 2 atom% of Au:PVP catalyst before addition of 5 mL solvent. The reaction mixture was stirred at 27 °C for 15 h under air, then quenched by ca. 1 mL of 1 M HCl solution. The products were extracted with EtOAc (ca. 20 mL × 3) and the combined organic layer was dried over Na_2SO_4 and evaporated in vacuo. The mixture was then analyzed by ^{1}H NMR.

Aerobic Epoxidation of (*E*)-chalcone. To a 15 mL test tube was added 0.200 mmol of (*E*)-chalcone, 11.2 mg KOH, and 3 atom% of Au:PVP catalyst before addition of 5 mL EtOH. The reaction mixture was stirred at 27 °C for 15 h under air, then quenched by ca. 1 mL of 1 M HCl solution. The products were extracted with EtOAc (ca. 20 mL × 3) and the combined organic layer was dried over Na_2SO_4 and evaporated in vacuo. The product was purified using preparative TLC with an eluent system consisting 1:1:6 ratio of EtOAc, CH_2Cl_2, and *n*-hexane, respectively.

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26. Since the H_2O_2 generated in situ was consumed by reacting with Au:PVP catalyst itself (this phenomenon was also explained in ref. 5), it is intrinsically difficult to keep the generated H_2O_2 untouched during the H_2O_2 generation step. Therefore, the reaction is necessary to be conducted through the *in-situ* generation of H_2O_2 in the presence of the substrates such as arylboronic acids and chalcone. We appreciate one of the reviewers for the helpful discussion.