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Regioselective Synthesis of Phenols and Halophenols from Arylboronic Acids Using Solid Poly(*N*-vinylpyrrolidone)/ Hydrogen Peroxide and Poly(4-vinylpyridine)/Hydrogen Peroxide Complexes

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Abstract: Solid hydrogen peroxide complexes based on poly(*N*-vinylpyrrolidone) and poly(4-vinylpyridine) were prepared and used as solid hydroxylating reagents. These solid hydrogen peroxide equivalents are found to be much safer, convenient and efficient reagent systems for the *ipso*-hydroxylation of arylboronic acids to the corresponding phenols in high yields at a faster rate. The versatility of the reagents has been further expanded for the one-pot synthesis of halophenols. Density functional theory calculations were carried out on hydrogen peroxide complexes of *N*-ethylpyrrolidone and 4-ethylpyridine as models to get a better understanding of structure and behavior of hydrogen peroxide complexes of the polymers poly(*N*-vinylpyrrolidone) and poly(4-vinylpyridine) compared to aqueous hydrogen peroxide.

Keywords: *ab initio* calculations; hydrogen peroxide; hydroxylation; phenols; regioselectivity

Introduction

Hydrogen peroxide is a widely used oxidant and in most cases, dilute solutions (30 wt%) of H_2O_2 are preferred due to the highly oxidative and explosive nature of H_2O_2 at higher concentrations. Many attempts have been made to find a safer way to increase the effective concentration of H_2O_2 in a reagent system. Complexing H_2O_2 with compounds like urea is found to be a very convenient approach, which makes the oxidant safer and a more effective reagent. Realizing the advantages of a safer solid oxidant system, the urea-H_2O_2 1:1 complex (urea hydrogen peroxide, carbamide peroxide) has been extensively explored for various synthetic applications such as epoxidation of alkenes, oxidation of various functional groups such as nitriles, oximes, sulfides, aldehydes, ketones etc., under thermal as well as microwave conditions.[1] Poly(*N*-vinylpyrrolidone) (povidone, PVD) has also been found to form complexes with H_2O_2, which are mainly used for medical and biological applications such as preservation of blood, tissues and biological fluids, treatment of acne vulgaris and in many modern disinfectants.[2–4] The PVD-H_2O_2 complex has been widely used in teeth whitening dentrifices and as a protective coating material in dental bleaching devices.[5]

Urea hydrogen peroxide is an unstable 1:1 combination of urea and hydrogen peroxide in equal amounts. It is soluble in water, alcohol, and ethylene glycol. It decomposes at 75–85 °C or in contact with moisture and is used as a source of water-free hydrogen peroxide. On the other hand, PVD forms a free flowing powdery solid complex with aqueous H_2O_2 (up to 70% H_2O_2) in which the monomer:H_2O_2 composition can reach up to 1:5. Unlike urea, povidone can be easily recovered and recycled. The presence of water in the complex makes it safer and easier to handle. Synthetic applications of this complex have not been well explored. It has been used in organic reactions as a free radical initiator in polymerization processes.[6] Recently, Pourali et al. have used povidone-supported hydrogen peroxide (PVD-H_2O_2) as an efficient reagent for the epoxidation of α,β-unsaturated ketones and the direct iodination of aromatic compounds.[7] *Ab initio* calculations on the PVD-H_2O_2 complex by Panarin et al.[8] showed that H_2O_2 molecules form a stronger H-bond with the carbonyl oxygen of PVD than with hydroxy oxygen in water and therefore a stable complex is formed. Since H_2O_2

is capable of strong self-association due to two hydrogen bonds between adjacent molecules, complexes with a higher H_2O_2 content are possible.

With our continued efforts to develop efficient environmentally friendly polymer-supported reagents, we found that the synthesis of phenols could be achieved in excellent yields by the direct *ipso*-hydroxylation of arylboronic acids, using solid H_2O_2 complexes of poly(*N*-vinylpyrrolidone) (PVD) and poly(4-vinylpyridine) (PVP). Herein, we discuss the efficient *ipso*-hydroxylation of boronic acids achieved using these complexes. The complexes were also used for the one-pot synthesis of halophenols from arylboronic acids. DFT calculations have been carried out on H_2O_2 complexes of *N*-ethylpyrrolidone and 4-ethylpyridine as models to get a better understanding of the greater activity and selectivity of H_2O_2 complexes of the polymers PVD and PVP as compared to aqueous H_2O_2.

Results and Discussion

Arylboronic acids act as one of the most efficient and versatile synthetic precursors for facile regioselective functional group transformations.[9] We have already reported the *ipso*-halogenation,[10] *ipso*-nitration[11] and *ipso*-hydroxylation[12] of arylboronic acids. An efficient *ipso*-nitration procedure for arylboronoc acids under mild condition has been reported recently.[13] Polymer-supported reagents are also becoming important and very useful tools in synthetic organic chemistry.[14] The polymer support not only makes the reaction simple and environmentally safe, but also helps to modulate the reactivity of the reagents towards various reactions. Furthermore, polymer-supported reagents, after the reaction, can be easily recycled. Recently, we have successfully used the poly(4-vinylpyridine)-SO_2 complex as an effective polymer-supported mild acid catalyst in the three-component Strecker reaction for the synthesis of α-amino nitriles.[15] Based on the amount of H_2O_2 loaded on the polymer, a chromatographic column packed with a definite amount of the complex can be used for several oxidation reactions irrespective of the nature of the substrate (e.g., boronic acid) until substantial drop in the H_2O_2 concentration occurs. The polymer support can be reloaded with H_2O_2 and recycled for further reactions. Products are separated in high yields and purity by simple removal of the solvent. No further work-up or purification is required.

Both PVP- and PVD-H_2O_2 complexes were prepared by the careful addition of cross-linked (with 2% divinylbenzene) PVD or PVP to 50% aqueous H_2O_2 with efficient cooling. Complexes with various compositions were prepared and it was found that the complex remains as a free-flowing wet powder up to a composition of monomer unit and H_2O_2 in a 1:4.5 molar ratio for PVD-H_2O_2 and a 1:3.5 molar ratio for PVP-H_2O_2. Non-cross linked PVD and PVP did not form free-flowing complexes. The hydrogen peroxide content in these complexes was confirmed by quantitative titration with potassium permanganate, thereby ruling out the possibility of any reaction between the polymer support and H_2O_2 which may lead to oxidation products including the formation of *N*-oxides. The change in morphology of the polymer samples due to complex formation was investigated through scanning electron microscopy (Figure 1 and Figure 2). The surface morphology of the complexes changed somewhat uniformly compared to that of the precursor polymer.

In our previous report we have shown that phenols can be obtained from arylboronic acids using aqueous H_2O_2 (30%).[12] This method needs several hours for completion of the reaction and further work-up and

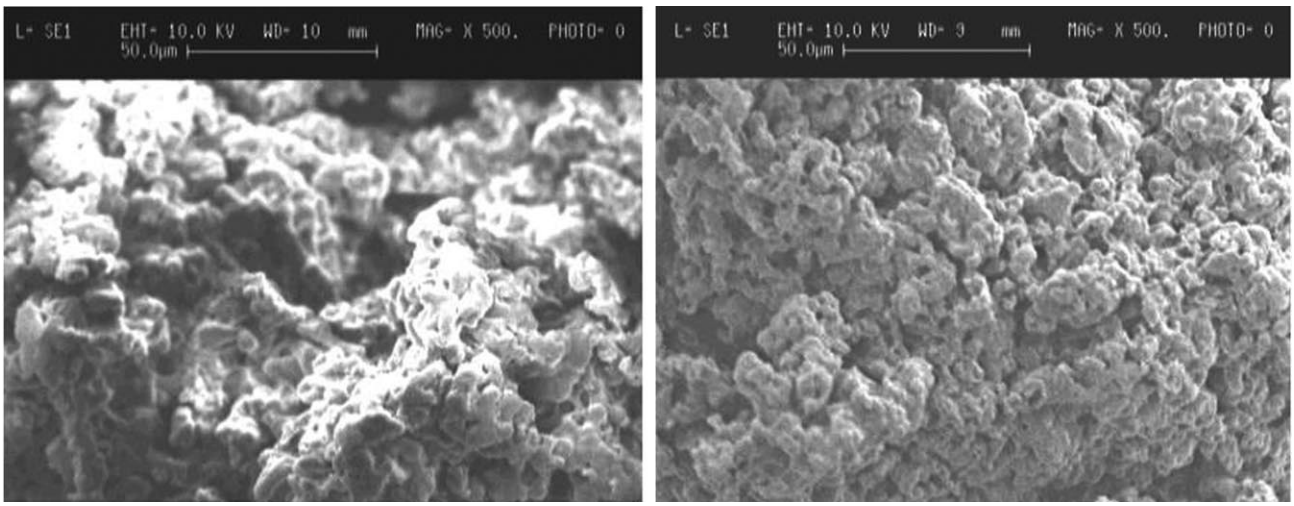


Figure 1. Surface of PVD (*left*) and surface of PVD-H_2O_2 complex (*right*).

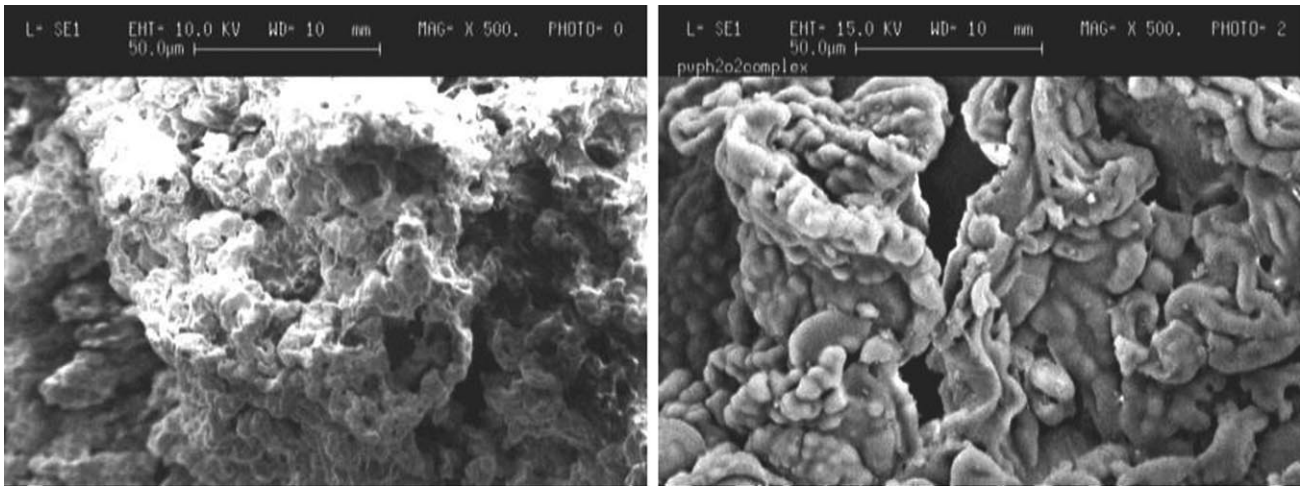
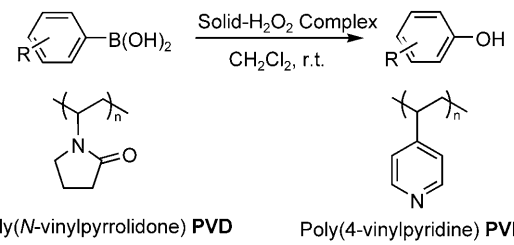


Figure 2. Surface of PVP (*left*) and surface of PVP-H_2O_2 complex (*right*).

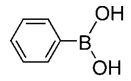
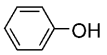
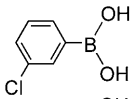
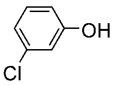
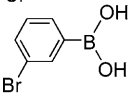
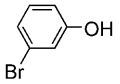
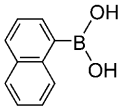
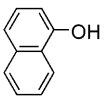
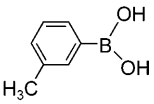
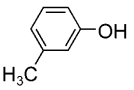
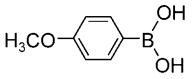
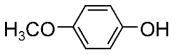
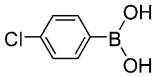
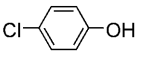
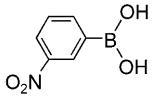
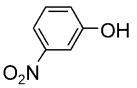
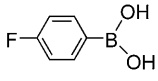
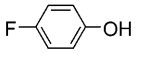
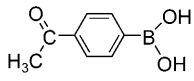
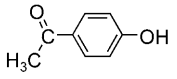
purification is needed. Other methods known for this transformation also have similar limitations.[16] In our new technique using PVD-H_2O_2 and PVP-H_2O_2 complexes, the regioselective hydroxylation of arylboronic acids to the corresponding phenols can be achieved in higher yields at a significantly faster rate (Scheme 1, Table 1) than the earlier methods.

For reactions on a 1-mmol scale, a small chromatographic column fitted with a cooling jacket was filled partially with PVD-H_2O_2 complex (5 g, diameter: 2 cm). The arylboronic acids were dissolved in CH_2Cl_2 and passed through this column slowly. For arylboronic acids, which are only partially soluble in CH_2Cl_2, the slurry of the compound in CH_2Cl_2 was prepared and used. The column was continuously eluted with CH_2Cl_2 until TLC showed no product in the eluent. All organic layers were combined and dried over Na_2SO_4 and the solvent was evaporated to obtain the phenol in almost analytically pure form. Both electron-rich and electron-poor arylboronic acids were found to undergo *ipso*-hydroxylation to give phenols in good yields. For example, 4-acetylphenylboronic acid was converted to 4-hydroxyacetophenone (4-acetylphenol) quantitatively.



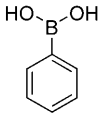
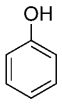
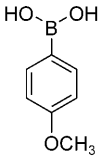
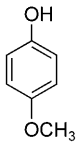
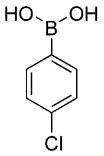
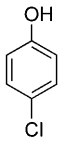
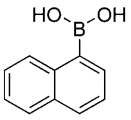
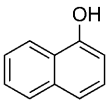
Scheme 1. *ipso*-Hydroxylation of arylboronic acids using solid H_2O_2 complexes of poly(*N*-vinylpyrrolidone) and poly(4-vinylpyridine).

Table 1. Regioselective hydroxylation of arylboronic acids.

Entry	Boronic acids	Phenols	Yield [%][a] A[b]	B[c]
1			97	91
2			95	73
3			85	81
4			95	80
5			97	80
6			99	81
7			94	60
8			90	65
9			93	55
10			80	49

[a] Isolated yields
[b] A: Yield from reaction with PVD-H_2O_2 complex.
[c] B: Yield from reaction with PVP-H_2O_2 complex.

Table 2. Efficiency of PVD-H_2O_2 complex as solid H_2O_2 equivalent and PVD recycling.

Entry	Boronic Acids	Phenols	Yield [%][a] 1st Run	2nd Run	3rd Run	4th Run
1			96	92	89	72
2			99	98	96	90
3			97	94	94	70
4			95	90	92	87

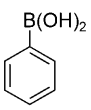
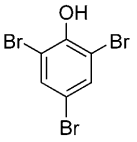
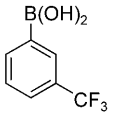
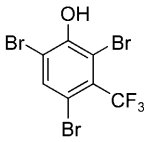
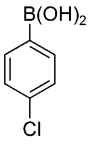
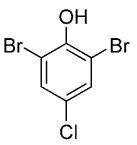
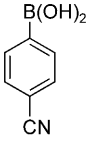
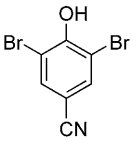
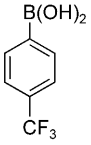
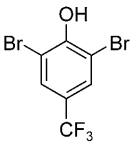
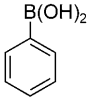
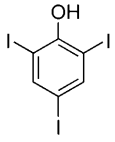
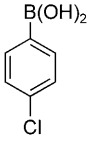
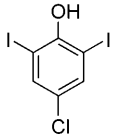
[a] Isolated yield.

We have also investigated the recovery and recycling of the solid hydrogen peroxide complex. After the first reaction, the product is completely eluted out with a sufficient amount of CH_2Cl_2 as eluent. The same column is ready for the subsequent reaction. The procedure was repeated for other substrates. It was observed that the loaded column is very efficient for three successive reactions at the 1-mmol scale. For the forth run the yield was found to drop, but the phenols formed were still very pure. The results are summarized in Table 2. Interestingly in most cases the PVD-H_2O_2 complex is found to be a more efficient oxidant than the corresponding PVP complex, probably due to the higher loading of hydrogen peroxide per monomer unit.

Tribromophenol (TBP) and its derivatives are used as flame retardants for plastics, paper and textiles. These compounds also find applications in wood preservation and as general fungicides.[17] Triiodophenol, known as Bobel-24, has been found to have anti-inflammatory properties in various animal models and also is a 5-lipoxygenase inhibitor.[18] Triiodophenol and its derivatives are potential candidates in developing therapy for leukemia.[19] Realizing the importance of halophenols, we further expanded the versatility of this reagent for the one-pot synthesis of halophenols directly from arylboronic acids. When boronic acids with free *ortho*- and *para*-positions were treated with a bromine solution (in dicholoromethane) and PVD-H_2O_2 at room temperature, the corresponding tribromophenols were obtained in high yields (Table 3, entries 1 and 2). When the *para*-position was blocked by other groups, bromination occured at the free *ortho*-positions and the corresponding dibromophenols were formed (Table 3, entries 3–5). Similar results were obtained when an iodine solution was used in place of the bromine solution (Table 3, entries 6 and 7).

Our attempt to synthesize various fluorophenols using electrophilic fluorinating agents such as Selectfluor®, Synfluor® and *N*-fluorobenzenesulfonamide along with PVD-H_2O_2 under various conditions was, however, not successful. The *p*-methoxyboronic acid (electron-rich boronic acid) when stirred in bromine solution (in dicholoromethane) with PVD-H_2O_2 underwent *ipso*-bromination instead of *ipso*-hydroxyl-

Table 3. Synthesis of halophenols from boronic acids.

Entry	Boronic acids	Products	Yields [%][a]
1			90
2			77
3			88
4			85
5			85
6			80
7			79

[a] Yield calculated by NMR.

ation followed by bromination to give a mixture of 4-bromoanisole and 2,4-dibromoanisole.

Density Functional Theory (DFT) Study of *N*-Ethylpyrrolidone-H_2O_2 Complexes and Comparison with 4-Ethylpyridine-H_2O_2 Complexes as Models for the Polymer-H_2O_2 Complexes

We were also interested in studying the nature of the H_2O_2-complexes using DFT calculations. The complexes of *N*-ethylpyrrolidone [used as model for poly(*N*-vinylpyrrolidone)] with H_2O_2 were calculated using density functional theory method (DFT) at the B3LYP/6-311+G** level. For a 1:4 complex of *N*-ethylpyrrolidone and H_2O_2, two minimum energy structures, **1a** and **1b**, were found (Figure 3). Structures **1a** and **1b** are hydrogen-bonded structures with C=O···H bond distances of 1.672 Å and 1.591 Å, respectively. Energetically **1b** was found to be 3.7 kcal mol^{-1} more stable than **1a** at the B3LYP/6-311+G**//B3LYP/6-311+G**+ZPE level (Table 4). The complexation energy of *N*-ethylpyrrolidone and four H_2O_2 molecules was calculated to be exothermic by 36.4 kcal mol^{-1}.

For comparison we have also calculated the complexation of 4-ethylpyridine [used as model for poly(4-vinylpyridine)] with H_2O_2 at the B3LYP/6-311+G** level. Similar to *N*-ethylpyrrolidone complexes, the 1:4 complex of 4-ethylpyridine and H_2O_2

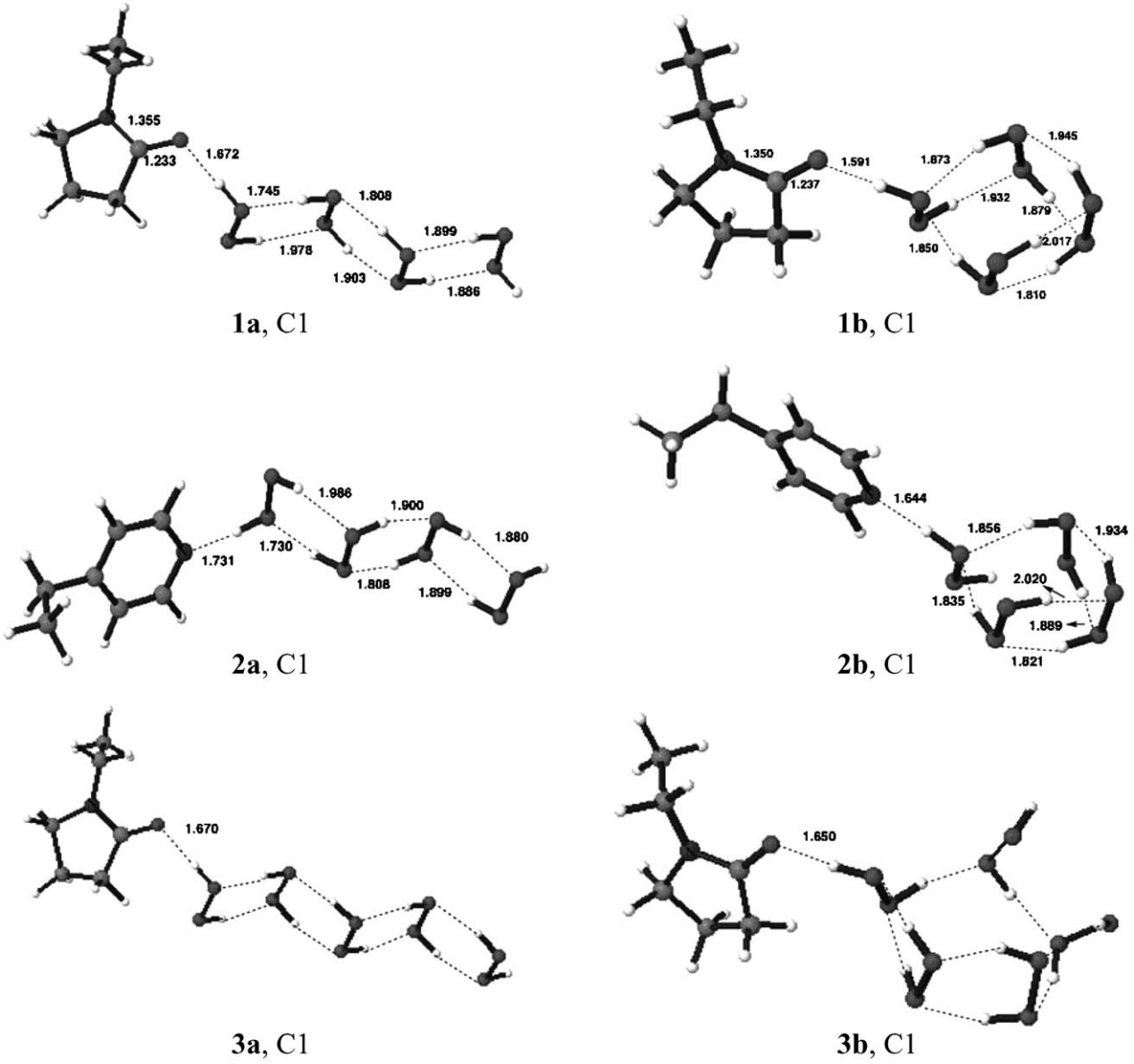


Figure 3. B3LYP/6-311+G** calculated structures of **1–3**.

Table 4. Total energies (−au), ZPE[a] and relative energies (kcal mol^{-1}).[b]

Entry	B3LYP/6-31G**// B3LYP /6-31G**	ZPE	B3LYP /6-311+G B3LYP /6-311+G**	rel. energy [kcal/mol]
1a	971.53182	172.3	971.83846	3.7
1b	971.54263	173.0	971.84545	0.0
2a	933.18599	158.7	933.47640	3.9
2b	933.19721	159.4	933.48378	0.0
3a	1123.09605	190.3	1123.45604	0.0
3b	1123.09608	190.0	1123.45436	0.7
Pyrrolidone	365.27530	101.1	365.36589	
Pyridine	326.93086	87.6	327.00441	
H_2O_2	151.54319	15.9	151.60206	

[a] Zero point vibrational energies (ZPE) at B3LYP/6-31G**//B3LYP/6-31G** scaled by a factor of 0.96.
[b] At B3LYP/6-311+G**//B3LYP/6-311+G**+ZPE level.

also has two minimum energy structures **2a** and **2b** (Figure 3).

Structures **2a** and **2b** are hydrogen-bonded structures with C=O···H bond distances of 1.731 Å and 1.644 Å, respectively. Energetically **1b** was also found to be 3.9 kcal mol^{-1} more stable than **2a** at the B3LYP/6-311+G**//B3LYP/6-311+G**+ZPE level (Table 4). The complexation energy of pyridine and four H_2O_2 molecules was calculated to be exothermic by 36.5 kcal mol^{-1}. Two structures, **3a** and **3b**, were also found as minima for the 1:5 complex of *N*-ethylpyrrolidone and H_2O_2. However, unlike 1:4 complexes, energetically **3b** was found to be 0.7 kcal mol^{-1} less stable than **3a** at the B3LYP/6-311+G**//B3LYP/6-311+G**+ZPE level (Table 4). The complexation energy of *N*-ethylpyrrolidone and five molecules of H_2O_2 was calculated to be exothermic by 40.4 kcal mol^{-1}. These studies suggest that strong hydrogen bonding stabilizes the PVD-H_2O_2 and PVP-H_2O_2 complexes.

Computational Methods

Calculations were performed using the Gaussian 03 program.[20] The geometry optimizations and vibrational frequency calculations were performed using density functional theory (DFT) method[21] at the B3LYP/6-311+G** level.[22] Vibrational frequencies were used to characterize stationary points as minima (number of imaginary frequency, NIMAG=0) and to evaluate zero point vibrational energies (ZPE) which were scaled by a factor of 0.96. Final energies were calculated at the B3LYP/6-311+G**//B3LYP/6-311+G**+ZPE level. Calculated energies are given in Table 4.

Conclusions

In summary, we have successfully developed a milder new technique to transform arylboronic acids to the corresponding phenols regioselectively in excellent yields and high purity, using a solid PVD-H_2O_2 complex which can be reused further for several runs. The solid PVP-H_2O_2 complex was also prepared and its efficacy was studied for the same reaction. Furthermore, we have demonstrated that this methodology can be successfully applied for the preparation of halophenols from boronic acids in a one-pot fashion. High level DFT calculations were also performed on model systems to understand the nature of these complexes. Studies on the application of these complexes in various other oxidation reactions are currently underway.

Experimental Section

Preparation of PVD-H_2O_2 and PVP-H_2O_2 Complexes

To a 50% H_2O_2 (34 g, 0.5 mol) aqueous solution in a Nalgene container was added 2% cross-linked poly(*N*-vinylpyrrolidone) (PVD) slowly with vigorous shaking and efficient cooling using a dry ice-acetone bath (***Caution! exothermic***). The morphology of the polymer complex changed during the course of the addition and formed a fine wet powder until the ratio of PVD monomer to H_2O_2 went up to 1:4.5. The complex was kept under cool (−20 °C) and dry conditions. The PVP-H_2O_2 complex was also prepared in a similar way using 2% cross-linked poly(4-vinylpyridine) and 50% H_2O_2 (1:3.5 molar ratio).

Typical Procedure for *ipso*-Hydroxylation of Arylboronic Acids

The solid complex (5.4 g) was loaded into a small chromatographic column having a water jacket. A solution of arylboronic acid (1 mmol) in CH_2Cl_2 (10 mL) was slowly poured in from the top of the column (keeping the temperature constant by passing water through the water jacket). The solution was kept in the column in contact with the solid complex for two minutes and then slowly passed through and collected in a flask at the bottom. The column was then eluted with excess CH_2Cl_2 and the eluant was monitored continuously by TLC for any remaining product. The solvent fractions were combined and dried over anhydrous sodium sulfate. The solvent was evaporated to give the phenols in analytically pure form. After rinsing the column with CH_2Cl_2, the same column can be used for the next run (three consecutive runs at a 1-mmol scale of the reactant).

Typical Procedure for the Synthesis of Halophenols from Arylboronic Acids

The respective arylboronic acid (1 mmol) was charged in a 100-mL round-bottom flask and dissolved in CH_2Cl_2 (10 mL). To this solution, 5 equivalents of bromine in CH_2Cl_2 were added slowly along with 2 g of the solid H_2O_2

complex. The whole mixture was stirred at room temperature and the reaction was monitored using TLC. When the starting material was completely consumed, the solid complex was separated by filtration. The filtrate was washed three times with sodium thiosulfate solution followed by water. The organic phase was separated and dried over anhydrous sodium sulfate. The solvent was evaporated to give the halophenols in analytically pure form. In some cases, the halophenols were passed through a flash column using CH_2Cl_2 as eluent to separate any impurities present.

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