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Green Chemistry

COMMUNICATION

Sustainable oxidations with air mediated by gallic acid: Potential applicability in the reutilization of grape pomace†

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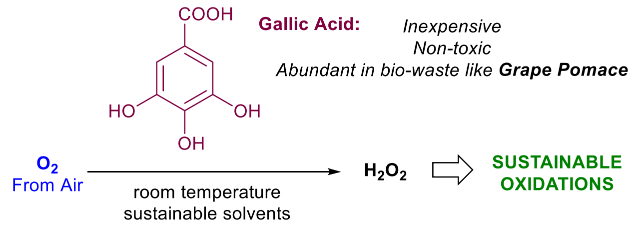
Gallic acid converts atmospheric oxygen into hydrogen peroxide, which is able to oxidize arylboronic acids as a proof of concept of sustainable oxidations. Moreover, tannic acid and grape pomace extract are also able to perform oxidations with air. Therefore this work unleashes an alternative method of reutilization and valorization of bio-waste rich in tannins.

Oxygen from air is certainly the most sustainable and affordable oxidant and oxygen atom source. However oxygen is in a triplet ground state which makes the reaction with singlet organic compounds spin forbidden.[1] Traditionally, such forbiddance is circumvented by using paramagnetic transition catalyst and/or high temperatures or irradiation.[2] In order to walk towards a higher sustainability, metal free methodologies for oxygen activation are highly desirable, particularly if such methodologies are based on non-toxic compounds from renewable sources at room temperature.[3-9] Herein we report an environment friendly solution for oxygen activation by taking advantage of the known auto-oxidation of gallic acid in slightly basic media: Indeed gallic acid can be considered as the simplest prototype of tannin,[10] and it can be extracted from vegetal sources such as oak bark or grape pomace,[11] or synthesized from glucose and microbial catalysis;[12] moreover, it has been reported that gallic acid is able to generate Reactive Oxygen Species (ROS) from oxygen.[13-15] Thus the potential use of gallic acid for atmospheric oxygen activation towards sustainable oxidations has been herein explored and applied (Scheme 1). Additionally, there is an increasing social and legal pressure to develop sustainable processes for the use of natural 'feedstocks' in chemical synthesis as an alternative to hazardous organic reagents or scarce and expensive metal-based catalysts. Particularly attractive is the reutilization and valorisation of the numerous residues generated by agricultural activities.[16,17] Thus, the use of an abundant and underutilized bio-waste such as grape pomace, in sustainable oxidations with air has been also explored herein (Scheme 1).



Scheme 1 Sustainable oxidations with air by gallic acid or with grape pomace extract.

Oxidative hydroxylation of arylboronic acids to phenols (*ipso*-hydroxylation) was chosen as an optimal example to test the effective generation of hydrogen peroxide from air, and to optimize the oxidation conditions. Indeed, it is well known that arylboronic acids react efficiently with ROS. Thus, phenols are expected to be obtained in case that auto-oxidation of gallic acid efficiently generates reactive oxygen species, and no secondary/lateral reactions interfere in any way. Optimization was performed with 4-tertbutyl phenylboronic acid (**1a**, 0.5 mmol). It was dissolved in acetone (2 ml) together with gallic acid (0.5 mmol). Then a 1M solution of sodium bicarbonate (2 ml) was added and the reaction was stirred under air for 24h. Fortunately, 4-tertbutylphenol (**2a**) was obtained in excellent yield, as shown in Table 1 (entry 1).[18] When aqueous phase was neutral or acidic, no oxidation was observed, even after longer reaction times (entries 2 and 3). It is important to highlight that bicarbonate is vital to our process. Using a 1M solution of K_2HPO_4 instead of bicarbonate, the oxidation was unsuccessful, although both salts provide comparable ionic strength and pH (entry 4). Therefore it is very likely that the role of bicarbonate is to activate the peroxide generated, which is proved below. Additionally, the amount of gallic acid could be decreased to 0.55 eq without any detriment on the yield nor in the reaction time (entry 5).[15] Lesser amounts of gallic acid led to incomplete conversions and lower yields (entry 6). Finally, reactions on

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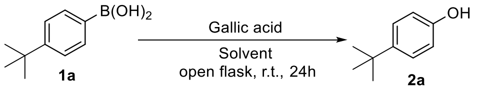
aqueous phase exclusively, gave lower yields (entry 7). Ethanol was chosen as the organic co-solvent, not only because it gave a slightly better yield (entry 8), but also because ethanol is cheaper and has GRAS (generally recognized as safe according to U.S. Food and Drug Administration definition) status. Worth to mention, unchanged yields were obtained when reaction was carried out in the dark (entry 10), ruling out any role of light.[19]

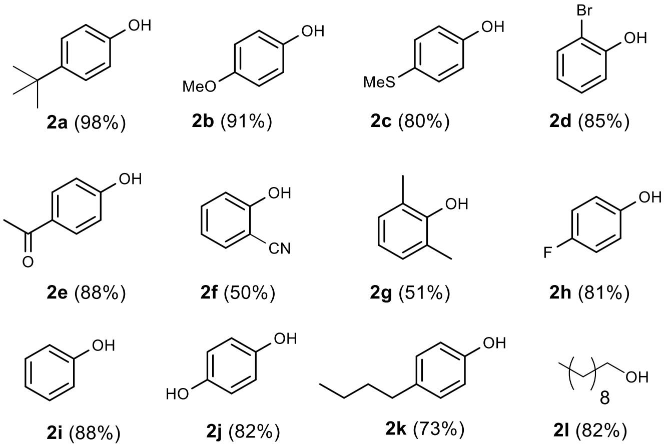
Table 1 Optimization of the conditions for the ipso-hydroxylation of boronic acids[a]



Entry	Gallic acid	Solvent Mixture	Isolated Yield
1	1 eq	Acetone/NaHCO$_3$ (1M)	96
2	1 eq	Acetone/H$_2$O	Traces
3	1 eq	Acetone/TsOH (1M)	Traces
4	1 eq	Acetone/KHPO$_4$ (1M)	16
5	0.55 eq	Acetone/NaHCO$_3$ (1M)	96
6	0.4 eq	Acetone/NaHCO$_3$ (1M)	68
7	0.55 eq	NaHCO$_3$ (1M)	76
8	**0.55 eq**	**Ethanol/NaHCO$_3$ (1M)**	**98**
9	0.55 eq	Isopropanol/NaHCO$_3$ (1M)	97
10[b]	0.55 eq	Ethanol/NaHCO$_3$ (1M)	98

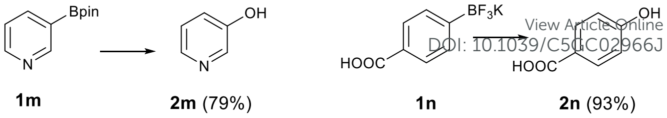
[a] 0.5 mmol of boronic acid used, 24h of reaction. [b] In the dark.

Once the optimal conditions were set up, the scope of the reaction was explored. As it can be seen in Scheme 2, yields were excellent regardless of the nature of the boronic acid employed. Only sterically crowded 2, 6-dimethylphenol (**2g**) and 2-cyanophenol (**2f**) were obtained in moderate yields. We should emphasize that n-decylboronic acid was also efficiently oxidized.



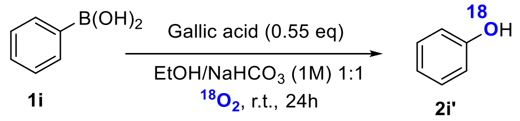
Scheme 2 Scope of *ipso*-hydroxylation of arylboronic acids, under optimized conditions. Conversion was complete in all cases.

On the other hand, arylboronic esters and potassium trifluoroborate salts were also efficiently oxidized with this methodology (Scheme 3).



Scheme 3 *ipso*-hydroxylation of boronic ester and trifluoroborate salt, under optimized conditions for 24h. Conversion was complete in both cases.

A few mechanistic experiments were performed. Firstly, the reaction of oxidation of phenylboronic acid was carried out under $^{18}O_2$ atmosphere, in order to prove that this methodology is indeed activating the atmospheric oxygen and incorporating it into the final products. As it can be seen in Scheme 4, incorporation of such heavier isotope of oxygen in the final compound is detected by MS.



Scheme 4 ^{18}O labelling experiment.

In addition, ^{13}C NMR confirmed the abovementioned activation of peroxide by bicarbonate. Such bicarbonate activated peroxide (BAP) is a known method for activating H_2O_2.[20] In such case, the actual oxidant is not hydrogen peroxide, but peroxymonocarbonate ion (HCO_4^-) formed by the equilibrium reaction between bicarbonate ion and H_2O_2 (Figure 1). Peroxymonocarbonate ion is a reactive species but it can be detected by several techniques, such as ^{13}C NMR. We prepared a 1:1 solution of methanol-d_4 and 99% ^{13}C-enriched $NaHCO_3$ (1M) in deuterated water, analogous to the solution used in the reactions. Gallic acid was added and after 10 minutes stirring under air, the ^{13}C NMR experiment at 25 °C was submitted. In the NMR spectrum it is clearly seen three peaks (Figure 1).

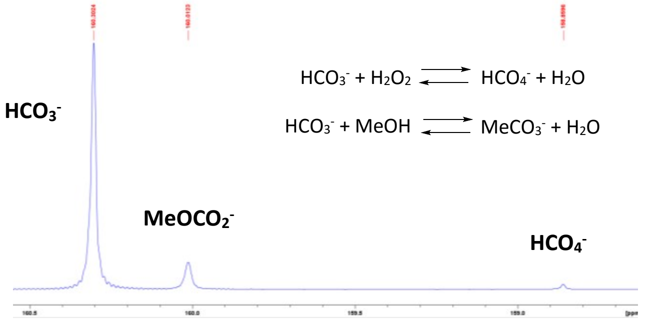


Figure 1 Detection of peroxymonocarbonate by ^{13}C NMR.

The peak at 160.3 ppm is due to HCO_3^-, while the peak at 158.9 ppm corresponds to peroxymonocarbonate HCO_4^-. The third peak observed at 160.0 ppm is due to the known reaction between primary alcohols, such as methanol, with bicarbonate to form alkyl carbonate esters, in this case the methyl carbonate ($MeCO_3^-$). The apparently small peak of peroxymonocarbonate detected is understandable not only due to its intrinsically instable nature, but also because in this case hydrogen peroxide

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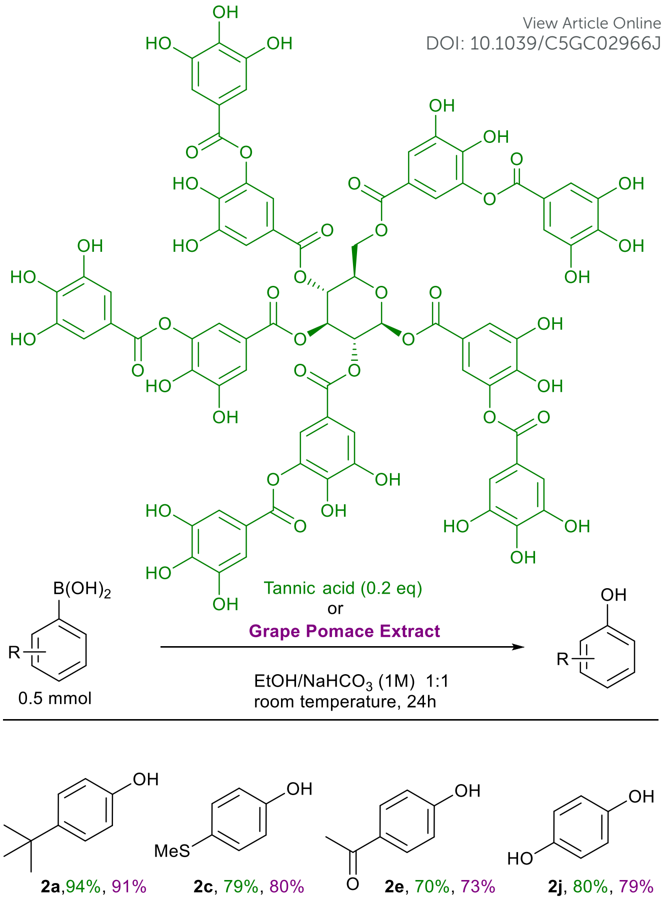
is generated progressively in situ in small amounts, compared to previously reported experiments,[20] where a high concentration of peroxide is employed. Worth to mention, the confirmation of BAP mechanism, paves the way for future combinations of this methodology with sustainable metals or, even better, phytoextracted metals.[21]

Finally, we pondered the application of this methodology as an alternative way for the reutilization and valorization of bio-waste,[22,23] such as grape pomace, which is known to be rich in gallic acid and other tannins.[11] Grape pomace is an abundant agricultural residue: The wine industry generates a huge amount of grape by-products called pomaces, which account for about 20% of the weight of the grapes used to make wine.[23] Considering that grape is one of the world's largest fruit crops,[24] grape pomace represents a waste management issue both ecologically and economically. Thus, we decided to explore a grape pomace extract to carry out oxidations with air.[25]

As a first approach, tannic acid was employed instead of gallic acid. Tannic acid is present in considerable amounts in wine byproducts.[11] The aim of this preliminary approach is to evaluate if complex derivatives of gallate behave similarly. Indeed, tannic acid displays a glucose bearing five digallates (Scheme 5). The optimal amount of tannic acid required for a complete oxidation in 24h was studied, being 0.2 eq. As it is seen in Scheme 5, oxidation of several boronic acids was successful.

Subsequently, we tested the oxidation of arylboronic acids directly with grape pomace extract. For this experiment, grape pomace from a local winery was employed (E. Páez winery). The red grapes *Vitis vinifera* (*Listan Negro*, a local cultivar) were cultivated in the Canary Islands, specifically in the north of Tenerife (Finca Los Angostos, La Cruz Santa, Los Realejos) and harvested at the beginning of October 2015. The grapes were pressed right after the harvest and left in contact with the grape juice for one week, while fermentation was going on. Grape seeds and skins were pressed and dried at air for two days. The extraction method chosen was analogous to other previously reported,[26] and it was not optimized. The grape pomace was left with ethanol/water/HCl (37%) (7:2.9:0.1) (3ml per g of pomace), for 3 days, and then filtered. To 2ml of such extract, boronic acid was added (0.1mmol), and finally 2ml of 1M solution of sodium bicarbonate (2 ml) was added and the reaction was stirred under air for 24h. These results are shown in Scheme 5 (purple). As it can be seen, yields were excellent considering the complex mixture present in the extract, and the non-optimized conditions employed. Further experiments on this and other reactions are being carried out in our lab.



Scheme 5 Yield of the oxidation of boronic acids by tannic acid (in green) and grape pomace extract (in purple). The latter oxidations were carried out in 0.1 mmol scale. Conversion was complete in all cases.

Conclusions

In summary, auto-oxidation of gallic acid in slightly basic media has proven to be an inexpensive and sustainable way to generate hydrogen peroxide in situ from air, which acts efficiently as an oxidant of arylboronic acids. The relevance of bicarbonate in the reaction media has proved to be related not to the pH, but to the activation of the peroxide, to produce the reactive peroxymonocarbonate. More importantly, other tannins such as tannic acid, and even grape pomace extract are able to carry out the oxidation reactions with air successfully. Therefore, these results unleash an alternative method for the reutilization of certain bio-wastes like grape pomace, which is rich in gallic acid and its derivatives: This work shows the potential utilization of the reactivity of compounds present in bio-waste, rather than the compounds themselves. Such an approach, therefore, could complement other traditional waste reutilization methods. Indeed, once the extraction of grape pomace has been performed, other traditional treatments of such waste can still be applied (biogas, fertilizer, etc.). Additionally, there are great environmental and economic advantages in substituting conventional chemical reagents for bio-waste, thus avoiding compounds which are very likely to be

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more expensive or more toxic, or which simply have to be manufactured, causing additional costs and waste.

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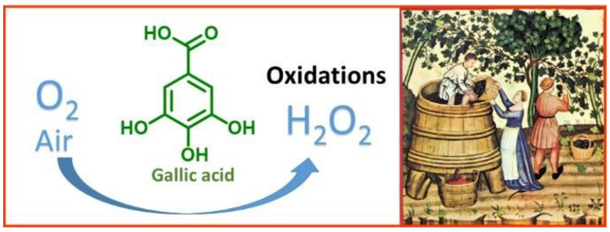

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