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Article

The Oxidation of Electron-Rich Arenes Using a H_2O_2–Proline System

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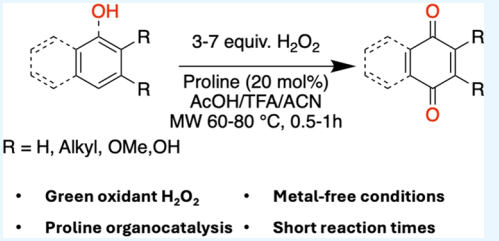
ABSTRACT: This study introduces a novel proline-catalyzed oxidation system employing hydrogen peroxide to synthesize quinones from a diverse range of substrates, including hydroquinones, phenols, resorcinols, aldehydes, and polycyclic aromatics. This approach is well-aligned with green chemistry principles, offering a more environmentally benign approach than earlier studies. Notably, this approach uses cost-effective reagents, proline as a readily available organocatalyst, reduced equivalents of H_2O_2, metal-free conditions, and notably short reaction times to achieve moderate-to-high yields. This promising approach encourages further exploration of the H_2O_2-proline system in oxidation reactions. This study's innovative approach and good results set a strong foundation for future research to expand the scope and efficiency of green oxidation processes.



INTRODUCTION

The quinone motif is a privileged structure in several pharmaceuticals and natural products, as exemplified by the biologically active quinones shown in Figure 1.[1] Accordingly,

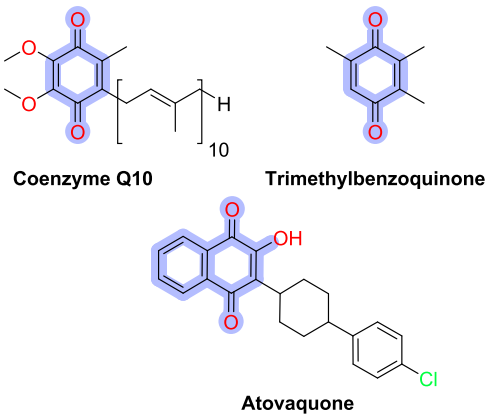


Figure 1. Benzoquinone and naphthoquinone moieties found in natural products and pharmaceuticals.

various approaches have been established for synthesizing these scaffolds,[2] with the most commonly investigated scaffolds being benzoquinone, naphthoquinone, and anthraquinone.[3]

Among the various approaches utilized in synthesizing quinones, the most straightforward approach involves the oxidation of arenes and/or phenols.[4] There are several methods described in the literature. However, most of these methods require the use of oxidants like organic peroxides,[5,6] hypervalent iodine compounds,[6,7] or inorganic salts,[8,9] which results in the generation of a significant amount of waste.[4] Consequently, employing more environmentally benign oxidation methods would be desirable.[10,11]

In this regard, hydrogen peroxide as an oxidant has emerged as a green alternative, as its only byproduct is water. In addition, hydrogen peroxide is both cost-effective and inherently safe.[9] Despite the strong oxidation potential of hydrogen peroxide, it often requires activation due to the high activation barriers required for the oxidation of many organic compounds. This has led to the creation of different catalytic systems to facilitate oxidations using hydrogen peroxide.[12] The electrophilic activation of hydrogen peroxide by hydrogen bond donors has been well-reported in literature.[13−15] However, in literature, the role of proline as a hydrogen bond donor for the activation of hydrogen peroxide is neglected,[15] except for the work by Reddy and co-workers, who reported that a proline-hydrogen peroxide system for the oxidation of sulfides to sulfoxides.[16] As an organocatalyst, proline offers several benefits, including being inexpensive and nontoxic, characteristics that are particularly valuable from the point of view of green chemistry.[17]

Recently, in 2020, Baeza et al. reported the oxidation of electron-rich arenes to quinones using a urea-hydrogen peroxide adduct (UHP) activated by 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) (Scheme 1,A).[10] Additionally, in 2021, Maestri et al. reported the oxidation of phenols and polycyclic aromatics with hydrogen peroxide catalyzed by heterogeneous sulfonic acids

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Scheme 1. Metal-Free Approaches That Utilize H_2O_2 for the Synthesis of 1,4-Quinones

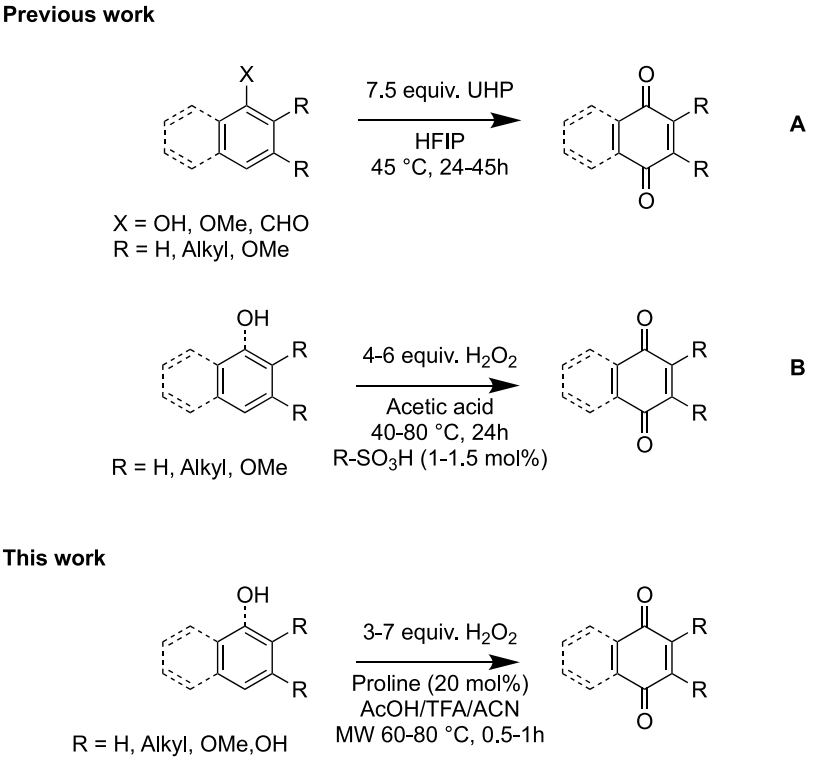
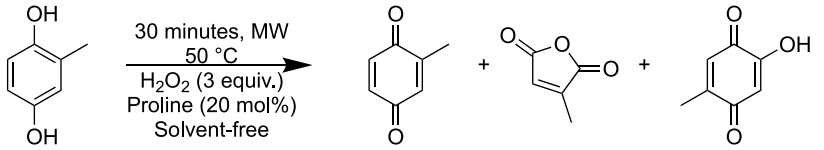


Table 1. Effects of the Solvent on the Oxidation of Methylhydroquinone[a]



entry	solvent	conversion (%)[b]	selectivity (%)[b]
1	neat	36	99
2	acetonitrile	35	99
3	cyclopentyl methyl ether	10	99
4	γ-valerolactone	16	99
5	2-MeTHF	11	99
6	ethyl acetate	12	99
7	dimethyl carbonate	18	99
8	acetone	11	99
9	methanol	20	99
10	ethanol	24	99
11	HFIP	11	99
12	acetic acid	54	99
13	acetic acid	96[c]	99
14	acetic acid	99[d]	86

[a]Reaction conditions: substrates (30 mg), proline (20 mol %), H_2O_2 (3 equiv), 30 min, solvent (0.1 mL), 50 °C. [b]Determined by GC-MS analysis. [c]Reaction performed at 60 °C. [d]Reaction conditions: substrates (30 mg), TFA (20 mol %), H_2O_2 (3 equiv), 30 min, acetic acid (0.1 mL), 60 °C.

(Scheme 1,B).[11] Despite their effectiveness, these methods require expensive reagents and long reaction times.

Subsequently, developing a novel method using readily available and cost-effective reagents is still highly desirable. Herein, we report the proline-catalyzed oxidation of electron-rich arenes and polycyclic aromatics to quinones (Scheme 1).

RESULTS AND DISCUSSION

We initiated our study by testing various hydrogen-bonding organocatalysts under solvent-free conditions. Preliminary experiments involved stirring methylhydroquinone with 3 equiv of 30% aqueous hydrogen peroxide and 20 mol % of the organocatalyst at 50 °C for 30 min under microwave irradiation. The use of proline afforded promising conversion and selectivity; therefore, further optimization was carried out. The

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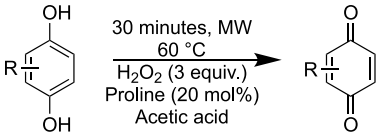
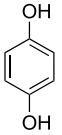
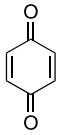
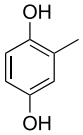
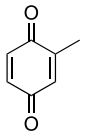
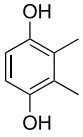
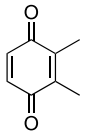
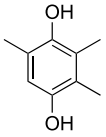
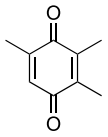
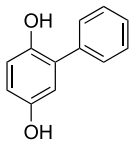
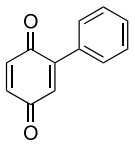
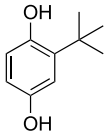
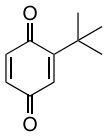
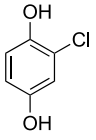
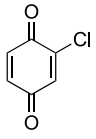
Table 2. Organocatalyzed Oxidation of Various Hydroquinones[a]

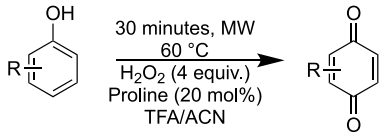


1a-g 2a-g

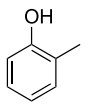
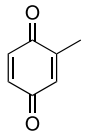
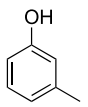
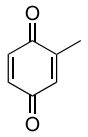
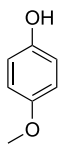
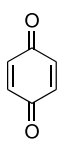
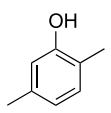
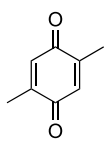
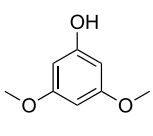
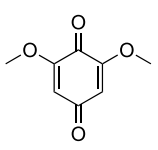
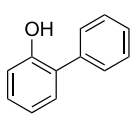
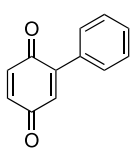
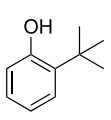
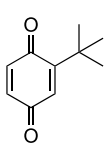
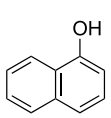
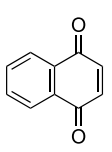
Entry	Substrate	Product	Conversion[b]	Yield[c]
1			65	2a, 58%
2			96	2b, 92%
3			85	2c, 83%
4			99	2d, 83%
5			90	2e, 85%
6			90	2f, 89%
7[d]			60	2g, 55%

[a]Reaction conditions: substrates (30 mg), proline (20 mol %), H_2O_2 (3 equiv), 30 min, acetic acid (0.1 mL), 60 °C. [b]Determined by GC-MS analysis. [c]Isolated yield. [d]Reaction conditions: substrates (30 mg), proline (20 mol %), H_2O_2 (3 equiv), 30 min, trifluoroacetic acid (0.1 mL), 50 °C.

Table 3. Organocatalyzed Oxidation of Various Phenols[a]



3a-i 2a-k

Entry	Substrate	Product	Conversion[b]	Yield[c]
1			30	2b, 18%
2			58	2b, 34%
3			80	2a, 40%
4			93	2h, 74%
5			95	2i, 20%
6			28	2e, 6%
7			55	2f, 36%
8			82	2j, 75%

[a]Reaction conditions: substrates (30 mg), proline (20 mol %), H_2O_2 (4 equiv), 30 min, trifluoroacetic acid (0.1 mL), acetonitrile (0.1 mL), 60 °C. [b]Determined by GC-MS analysis. [c]Isolated yield.

complete optimization can be found in the accompanying Supporting Information (SI) (Table S1).

Next, the influence of different solvents on the conversion of methylhydroquinone was investigated, and the results are shown in Table 1. In the presence of acetonitrile as a solvent, conversion was comparable to neat conditions (Table 1, entry 2). Employing a range of green solvents decreased conversion (Table 1, entries 3−10). Despite the known role of HFIP in activating hydrogen peroxide, this effect was not observed in our experiments (Table 1, entry 11).[14,18] Notably, using acetic acid as a solvent increased conversion to 54% (Table 1, entry 12). Raising the reaction temperature to 60 °C further enhanced conversion to 96% (Table 1, entry 13). Full conversion was

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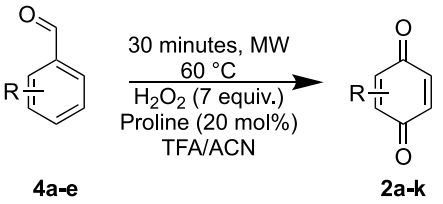
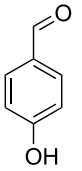
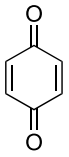
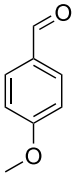
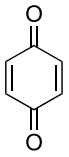
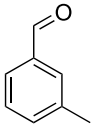
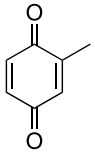
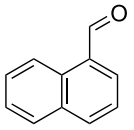
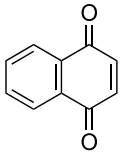
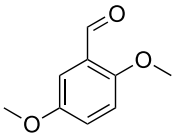
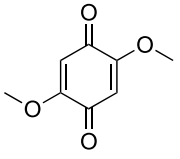
Table 4. Organocatalyzed Dakin Reaction−Oxidation of Various Aldehydes[a]



Entry	Substrate	Product	Conversion[a]	Yield[b]
1			99	2a, 68%
2			99	2a, 28%
3			37	2b, 6%
4			74	2j, 60%
5			95	2k, 40%

[a]Reaction conditions: substrates (30 mg), proline (20 mol %), H_2O_2 (7 equiv), 30 min, trifluoroacetic acid (0.1 mL), acetonitrile (0.5 mL), 60 °C.

achieved when trifluoroacetic acid (TFA) replaced proline with acetic acid as a solvent at 60 °C. However, a reduction in selectivity was observed as 3-methylfuran-2,5-dione and 2-hydroxy-5-methyl-*p*-benzoquinone were obtained as side products. (Table 1, entry 14). Control experiments confirmed the necessity of both proline and acetic acid for effective conversion (Table S2).

Having established the optimal protocol for the reaction, we then explored the electronic and steric properties of hydroquinone substrates to synthesize the corresponding *p*-benzoquinones (Table 2). Hydroquinone (**1a**) affords *p*-benzoquinone (**2a**) in a moderate yield of 58% due to incomplete conversion. Electron-rich hydroquinones (**1b−d**) rendered the corresponding *p*-benzoquinones in good to excellent yields (83−92%). The suboptimal yield obtained in the oxidation of trimethylhydroquinone (**1c**) was due to the formation of 2-hydroxy-3,5,6-trimethyl-*p*-benzoquinone as a side product. Sterically hindered hydroquinones (**1e−f**) afforded the corresponding *p*-benzoquinones in good to excellent yields.

Notably, the oxidation of electron-deficient chlorohydroquinone (**1g**) necessitated the use of TFA, as only trace quantities of the product were detectable when using acetic acid. The corresponding 2-chloro-*p*-benzoquinone (**2g**) was obtained in a moderate yield of 55%. In hydroquinones, the redox potential is influenced by the presence of substituents.[19] Specifically, electron-withdrawing substituents decrease the electron density at the phenoxy group, leading to an increased redox potential. Consequently, this renders electron-deficient hydroquinones more resistant to oxidation.[20] This method provides superior yields compared to the oxidation of hydroquinones with hydrogen peroxide catalyzed by supported sulfonic acids, as reported by Maggi et al. with the exceptions of benzoquinone (**1a**) and chlorohydroquinone (**1g**).[21]

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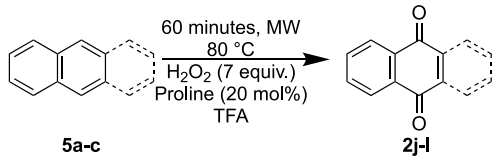
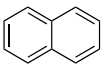
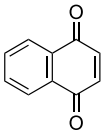
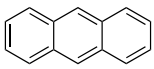
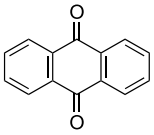
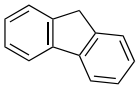
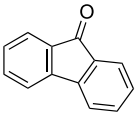
Table 5. Organocatalyzed Oxidation of Various Polycyclic Aromatics[a]



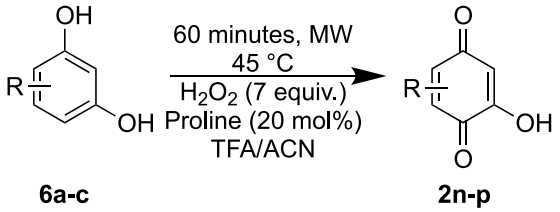
Entry	Substrate	Product	Conversion	Yield
1[b]			40	2j, 19%
2			72	2l, 61%
3			5	Trace

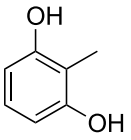
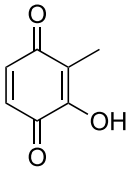
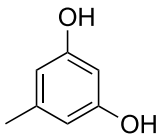
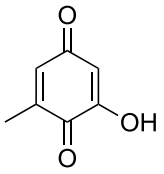
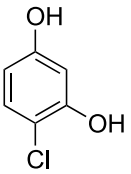
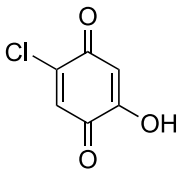
[a]Reaction conditions: substrates (30 mg), proline (20 mol %), H_2O_2 (7 equiv), 60 min, trifluoroacetic acid (0.1 mL), 80 °C. [b]Reaction conditions: substrates (30 mg), proline (20 mol %), H_2O_2 (7 equiv), 60 min, trifluoroacetic acid (0.1 mL), acetonitrile (0.25 mL), 80 °C.

Encouraged by the preceding results, we proceeded to investigate the oxidation of less reactive phenol substrates (Table 3). Initial experimental data indicated that effective conversion required 4 equiv of hydrogen peroxide and the use of TFA. This is anticipated because phenolic substrates are more challenging to oxidize compared to the corresponding hydroquinones.[22] Furthermore, acetonitrile was added as a cosolvent to increase selectivity by promoting the reaction to the desired quinone product from the partial oxidation hydroquinone intermediate.

We began our investigation by expanding on the substrate scope previously reported in the literature, which focused primarily on electron-rich substrates.[10,11] *o*-Cresol (**3a**) and *m*-cresol (**3b**) were utilized to synthesize the corresponding *p*-benzoquinone (**2b**), achieving yields of 18% and 34%, respectively. The oxidation of mequinol (**3c**) resulted in benzoquinone (**2a**) forming with a 40% yield due to the incomplete oxidation of the hydroquinone intermediate. Employing 2,5-dimethylphenol (**3d**) led to the synthesis of 2,5-dimethyl-*p*-benzoquinone (**2h**) with a yield of 74%. The use of 3,5-dimethoxyphenol (**3e**) produced 2,6-dimethoxy-*p*-benzoquinone (**2i**) with a yield of 20% due to the incomplete oxidation of the hydroquinone intermediate. Sterically hindered phenols (**3f**–**g**) afforded the corresponding *p*-benzoquinones (**2e**–**f**) in poor yields of 6–36%. The reaction of 1-naphthol (**3h**) produced *p*-naphthoquinone (**2j**) with a yield of 74%. The results indicate an enhanced reactivity for electron-donating substituents, with naphthol exhibiting greater reactivity than phenols, which is in agreement with the existing literature.[10] The suboptimal yields are attributed to incomplete conversion and partial oxidation to the corresponding hydroquinones in less reactive substrates. Increasing the equivalence of hydrogen peroxide did not result in an increased yield. Additionally, the corresponding furan-2,5-diones and 2-hydroxy-*p*-benzoquinones were obtained as side products along with the desired quinone. The reaction methodology proved unsuitable for phenol, 2-bromophenol, and *p*-cresol, as the corresponding quinones were only detectable in trace amounts.

Table 6. Organocatalyzed Oxidation of Various Resorcinols[a]



Entry	Substrate	Product	Conversion
1			2m, 67%
2			2n, 51%
3[b]			2o, 15%

[a]Not purely isolated; estimated conversion by GC-MS. Reaction conditions: substrates (30 mg), proline (20 mol %), H_2O_2 (7 equiv), 60 min, trifluoroacetic acid (0.1 mL), acetonitrile (0.5 mL), 45 °C. [b]Reaction conditions: substrates (30 mg), proline (20 mol %), H_2O_2 (7 equiv), 30 min, trifluoroacetic acid (0.1 mL), acetonitrile (0.5 mL), 50 °C.

Motivated by the limited existing research, we applied our novel method to the direct oxidation of aromatic aldehydes, which are among the most widely available starting materials, to yield the corresponding quinones (Table 4).[10,23] It is proposed that the reaction proceeds via an acid-catalyzed Dakin oxidation, which produces the corresponding hydroquinone.[24] Thereafter, further oxidation occurs, yielding the corresponding *p*-benzoquinone. Preliminary method optimization indicated that effective conversion required 7 equiv of hydrogen peroxide and the use of additional acetonitrile to dilute the reaction mixture to improve selectivity.

p-Hydroxybenzaldehyde (**4a**) and *p*-anisaldehyde (**4b**) were employed to synthesize the corresponding *p*-benzoquinone (**2a**), resulting in yields of 68 and 28%, respectively. Although the oxidation of *p*-anisaldehyde (**4b**) was low yielding due to partial oxidation to 4-methoxyphenol and hydroquinone, Baeza et al., reported that the oxidation of *p*-anisaldehyde (**4b**) resulted

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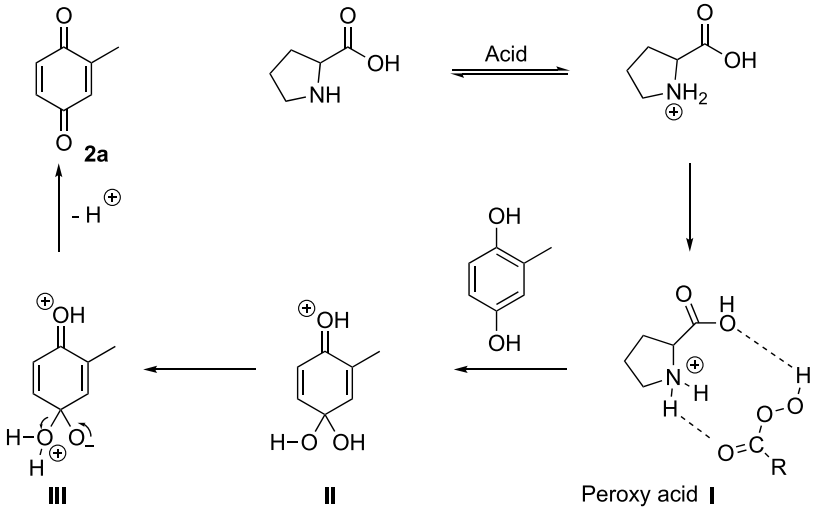
Scheme 2. Possible Reaction Mechanism (Peroxycarboxylic Acid Generated In Situ from Acid and H_2O_2)[a]



[a]Control experiments demonstrate the importance of the proline carboxylic acid functionality.

exclusively in the formation of 4-methoxyphenol. The oxidation of *m*-tolualdehyde (**4c**) led to the formation of 2-methyl-*p*-benzoquinone (**2b**), achieving a poor yield of 6%. The reduced yield is attributed to the poor conversion of *m*-tolualdehyde (**4c**) and the formation of 3-methylbenzoic acid as the major oxidation product. The oxidation of 1-naphthaldehyde (**4d**) led to the synthesis of *p*-naphthoquinone (**2j**) with a yield of 60%. Employing 2,5-dimethoxybenzaldehyde (**4e**) produced 2,5-dimethoxy-*p*-benzoquinone (**2k**) with a yield of 40%. The moderate yield is attributed to the formation of 2,5-dimethoxyphenol and 2,5-dimethoxyhydroquinone as side products. Consistent with the previously observed trend, naphthyl demonstrates greater reactivity compared to phenyl substrates. The unsatisfactory yields for the oxidation of aldehydes result from the partial oxidation to phenol and hydroquinone derivatives. Additionally, the formation of benzoic acid derivatives was observed across all substrates in varying amounts. In accordance with the findings reported by Baeza et al., *o*-anisaldehyde was converted quantitatively to *o*-methoxyphenol.[10]

It should be noted that our investigation into the reactivity of anisol derivatives revealed that the reaction was unsuitable for anisol and *p*-methoxyanisole.[10]

Thereafter, we applied our established method to the oxidation of unsubstituted naphthalene and anthracene, motivated by the scarcity of practically feasible and environmentally benign methods (Table 5).[11] The oxidation of naphthalene (**5a**) led to the formation of *p*-naphthoquinone (**2j**), achieving a yield of 19%. The low yield is due to poor conversion and the formation of phthalic anhydride and phthalide as side products. The addition of acetonitrile increased selectivity for the desired quinone.

The use of anthracene (**5b**) led to the synthesis of anthraquinone (**2l**) with a yield of 61%. In addition to the desired quinone, phthalic anhydride, 1,8-naphthalic anhydride, 1-hydroxyanthraquinone, and anthrone were observed as side products. These observations imply that the significant energetic stabilization due to aromaticity was too energetically disfavored to be overcome in the case of naphthalene.[11] Employing fluorene (**5c**) produced fluorenone in trace amounts due to poor conversion.

In light of the observations made by Baeza et al., who reported on the incompatibility of the UHP-HFIP system with resorcinols, the focus was then directed to explore the oxidation of resorcinol substrates with our method.[10] We were pleased to discover that the reaction was compatible with substrates **6a−c**, as confirmed by GC-MS (Table 6). Unfortunately, efforts to isolate these compounds were consistently met with degradation to unknown products as determined by GC-MS. It should be noted that the reaction was incompatible with resorcinol and 2,6-dihydroxybenzaldehyde, as these substrates underwent complete conversion to unidentified oxidation products. Interestingly, employing 2-bromoresorcinol as a substrate resulted in the formation of dibromoresorcinol. Additionally, when acetonitrile was omitted from the reaction conditions, 2-bromoresorcinol and 4-chlororesorcinol yielded a mixture of dihalogenated and trihalogenated resorcinols. Further, no reaction occurred when phloroglucinol was used as a substrate.

To enhance conversions, reaction times were extended, and temperatures were increased for the various substrates. However, no improvement was observed. Regarding the reaction mechanism, one possibility based on previous literature reports is depicted in Scheme 2.[16,25] Acetic acid and trifluoroacetic acid generate their corresponding peroxycarboxylic acids *in situ* with hydrogen peroxide.[26] The peroxycarboxylic acid is activated by the protonated proline acid complex (**I**). Thereafter, intermediate **II** is formed, an electrophilic attack of the peracid in the π system of the hydroquinone. Finally, through intermediate **III**, the corresponding quinone is formed (**2a**). Control experiments illustrated that the carboxylic acid group of proline is essential for activation, as pyrrolidine and proline tetrazole exhibited no activity. In addition, Fmoc-Pro-OH displayed lower activity than unprotected proline (Tables S3−S4). The reduced activity might be attributed either to the steric hindrance imposed by the Fmoc group or the protection of the free NH, which potentially limits hydrogen bonding interactions. Additionally, control experiments demonstrated that the reaction proceeds when peracetic is used directly. However, it is also possible that proline activates hydrogen peroxide, thereby initiating the oxidation process.

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CONCLUSIONS

In conclusion, in this study we report an effective, novel proline-catalyzed oxidation system using hydrogen peroxide to synthesize quinones from a diverse range of substrates, including hydroquinones, phenols, resorcinols, aldehydes, and polycyclic aromatics. It can be asserted that under the specified reaction conditions, naphthalene derivatives and electron-rich arenes demonstrated enhanced performance. This approach is well-aligned with the principles of green chemistry, offering a more environmentally benign approach compared to earlier studies. Notably, this approach uses cost-effective reagents, proline as a readily available organocatalyst, reduced equivalents of reagents, metal-free conditions, and notably short reaction times to achieve moderate-to-high yields. Furthermore, the successful application of the H_2O_2-proline system in oxidation reactions, particularly compared with the UHP/H_2O_2−HFIP systems, underscores its potential as a versatile and sustainable oxidation system for organic synthesis.[27] This study's innovative approach and promising results set a strong foundation for future research to expand the scope and efficiency of green oxidation processes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c04383.

Optimization details; general procedure for the synthesis; preliminary mechanistic studies, and NMR spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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