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# Natural Gallic Acid Catalyzed Aerobic Oxidative Coupling in Assistance of $Mn(CO_3)_2$ for Synthesis of Disulfanes in Water†

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The formation of S-S bonds have great significance and value in synthetic chemistry and bioscience. To pursue a sustainable approach for such synthesis, an aerobic oxidative coupling method for efficient preparation of organic disulfanes, using a low-toxic natural gallic acid as an organocatalyst and inexpensive $Mn(CO_3)_2$ as a cocatalyst, $O_2$ as the terminal oxidant and water as the solvent, has been successfully developed. The multiple applications of this metal-organic cooperative catalytic protocol access to various symmetrical and unsymmetrical disulfanes in up to 99% yield. Gram scale synthesis with practical convenience and low loading of catalysts further illustrates the practicability of our method.

## Introduction

The disulfide bonds are extremely valuable functional group in abundant natural compounds, biological agents and drugs that display potent reactivity or biological activities.[1-3] With awareness of its biocompatibility, researchers often utilized disulfide bonds as vital motifs in new drugs,[4-6] and also in prodrugs for drug delivery.[7] Furthermore, disulfide group has already played extensively multifaceted roles in functional materials such as biological materials, biological chemosensors, rechargeable batteries and rubber vulcanization accelerator, etc.[8-9] Although there are several less commonly used methods for preparation of disulfanes (the IUPAC recommended nomenclature of organic disulfides) such as thiolysis, reductive dimerization of thiocyanates, alkyl halides substitution with sulfur or polysulfide, reductive coupling of sulfonyl chlorides, etc, the formation of disulfanes most generally occurs via oxidative radical formation and subsequent dimerization of thiols.[10-12] However, the oxidative coupling with stoichiometric oxidants is still used in manufacture of some industrial disulfanes. For example, 2-mercaptobenzothiazole (**1a**) is oxidized with NaClO or $NaNO_2$ for the industrial manufacture of 2,2'-disbenzothiazole disulfide (**2a**), a widely used vulcanization accelerator in the rubber industry and a pharmaceutical intermediate in antibiotics production, which produces large quantities of liquid waste that contains a large percentage of salt and nitrogen oxides, and thus suffers from high cost of disposal.[13] Therefore, many catalysts have been discovered for using molecular oxygen as environmentally friendly oxidant for the oxidative coupling of thiols, which included transition metal-,[14] and organo-[15] and enzyme [16] catalytic models. Unfortunately, while the oxidative self-coupling of thiols results in the formation of symmetrical disulfane, the synthesis of unsymmetrical disulfane via catalytic cross-coupling of different thiols is indeed a subtle methodological challenge. Recent reports gave two an alternative pathway to unsymmetrical disulfane, which were called electro-oxidative cross-coupling [17] and copper-catalyzed oxidative cross-coupling of arylboronic acid and RSSAc,[18-21] respectively. However, the former is only suitable to synthesize aryl alkyl disulfanes, and the latter uses a special disulfurating reagent. Accordingly, the development of the methods for constructing disulfide bond via oxidative coupling has emerged as a research area of significant importance.

While some respectable achievements in synthesis of disulfanes have been made, sustainable technologies are still required with respect to environmental concerns, safety, and cost, facile workup, as well as practical industrial application. Undoubtedly, aqueous aerobic oxidation is a hopeful one because of the using both of the most green and cheap solvent and oxidant.[22-24] These aspects motivated us to pursue a more efficient and practical oxidative coupling for direct catalytic synthesis of disulfanes using molecular oxygen as the terminal oxidant and water as the onefold solvent.[23-28] In consideration of the mechanisms both of aerobic oxidation and thiols coupling, our target catalytic system should be reasonable to deduced two components: 1) a water-soluble redoxable catalyst whose oxidation state could abstract H from thiol to give the thiyl radical, 2) a redoxable metal ion responsible for activating the molecular oxygen and oxidizing the reduction state of catalyst to its oxidation state.

Moreover, the utilization of renewable fedstocks is deemed to be the indicator of chemical sustainability.[29] Phenolic acids,

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especially multihydroxyl ones, are abundant biomass feedstock that can be derived from plant biomass materials. Much of them display antioxidant activities and protective effects against chronic diseases and so on, mainly because of single electron redox property of their hydroxyl moieties.[30-32] So they were thought to be our target redoxable organocatalyst, and their water solubility, readily availability, low toxicity and biodegradability could lead the establishment of greener and cleaner chemical processes for disulfanes preparation in water.

Therefore, by selecting a multihydroxyl phenolic acid as the catalyst, we herein investigated a metal-organic cooperative catalytic protocol in aerobic oxidative coupling of thiols for disulfane synthesis. As far as we are aware, phenolic acid as the sole organocatalyst was applied here for the first time to mediate efficiently the aerobic oxidative coupling of thiol.

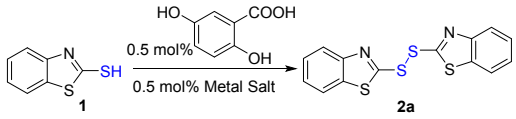
## Results and discussion

### Screening of metal cocatalyst

Our initial attempt at the catalytic synthesis of disulfane explored the performance of common metal salts. Therein, the self-coupling of **1a** was used as the model reaction and 5-Hydroxy-salicylic acid (**HSA**) as the organocatalyst (0.5 mol%) with 0.5 mol% transition metal salts in water under 0.3 MPa $O_2$ at 80 °C for 3 h (Table 1). As can be seen, the aerobic oxidative coupling of **1a** proceeded in all case. However, the different metal salts gave different yields of **2a**. In contrast, Mn salts displayed better than Fe, Cu and Co. And the counterions of Mn ion showed bare influence on the reaction (entries 13-16), whereas Fe, Cu and Co salts with various anions showed different catalytic activities (entries 1-12). Moreover, it was notable imperatively that some amounts of benzothiazole as a byproduct were found in all catalytic reactions of Fe, Cu and Co salts, respectively (as determined by HPLC and GC-MS). Fortunately, such dethiolation of **1a** did not occur in all cases of Mn catalysis, and **HAS**/Mn was found to be a quite effective catalytic system.

It should be notable that Mn is a earth-abundant metal, and $MnCO_3$ exists naturally as the mineral rhodochrosite.[33] Its readily availability and inexpensiveness make this metal-organic cooperative catalytic protocol to have more applicable potential.

**Table 1.** Aerobic oxidative coupling of **1a** with HSA and various metal salts.[a]




| Entry | Metal salt | HPLC Yield (%) |
|---|---|---|
| 1 | $FeSO_4$ | 17 |
| 2 | $Fe_2(SO_4)_3$ | 57 |
| 3 | $NH_4Fe(SO_4)_2$ | 27 |
| 4 | $FeCl_3$ | 19 |
| 5 | $CuCl_2$ | 54 |
| 6 | $CuSO_4$ | 71 |
| 7 | $Cu(OAc)_2$ | 52 |
| 8 | $CuCO_3$ | 44 |
| 9 | $Co(OAc)_2$ | 58 |
| 10 | $CoSO_4$ | 51 |
| 11 | $CoCl_2$ | 56 |
| 12 | $CoCO_3$ | 44 |
| 13 | $MnCl_2$ | 79 |
| 14 | $MnSO_4$ | 75 |
| 15 | $MnCO_3$ | 77 |
| 16 | $Mn(OAc)_2$ | 78 |

[a] Reaction conditions: **1a** (0.5 mmol), HSA (0.5 mol%), metal salt (0.5 mol%), 3 mL $H_2O$, pH = 9, 80 °C, 0.3 MPa $O_2$, 3 h.

### Catalytic abilities of various phenolic acid

Various phenolic acid (0.5 mol%) were employed to catalyzed the aerobic oxidative coupling of **1a** in the present of 0.2 mol% $MnCO_3$ (Table 2). Salicylic acid with sole hydroxyl moiety gave a poor yield (entry 1), but multihydroxyl phenolic acids had higher catalytic activities(entries 2-8). Among them, ones with *para*-dihydroxyls display generally much better catalytic performance than that with two hydroxyls at the *ortho*-, or *meta*-position. And gallic acid (**GA**) and 2,5-dihydroxyterephthalic acid realized excellent yields, respectively (entries 7-8).

**Table 2.** Aerobic oxidative coupling of **1a** with $MnCO_3$ and phenolic acids. [a]

| Entry | Phenolic Acid *or* Quinone | HPLC Yield (%) |
|---|---|---|
| 1 | 2-OH-COOH | 12 |
| 2 | 2,4-di-OH-COOH | 23 |
| 3 | 2,3-di-OH-COOH | 22 |
| 4 | 2,5-di-OH-COOH | 66 |
| 5 | 2,4,6-tri-OH-COOH | 19 |
| 6 | 2,3,4-tri-OH-COOH | 69 |
| 7 | 3,4,5-tri-OH-COOH | 94 |
| 8 | 2,5-di-OH-1,4-di-COOH | 96 |
| 9 | 1,4-benzoquinone | 61 |
| 10 | 1,4-benzenediol | 60 |
| 11 | 1,2-benzenediol | 15 |
| 12 | 1,3-benzenediol | 11 |
| 13 | 1,3,5-benzenetriol | 7 |
| 14 | 2,5-di-OH-1,4-benzoquinone | 18 |
| 15 [b] | 2,5-di-OH-1,4-benzoquinone | 79 |
| 16 [b] | 1,4-benzoquinone | 76 |

[a] Reaction conditions: **1a** (3.34 g, 20 mmol), $MnCO_3$ (0.2 mol%), Phenolic Acid (0.5 mol%), 50 mL $H_2O$, pH = 9, 80 °C, 0.3 MPa $O_2$, 5 h. [b] $CH_3CN$ instead of $H_2O$.

It is well documented that quinones, due to their two single electron redox cycles between itself and its corresponding semiquinone or hydroquinone, could realize oxidations.[34-39] As contrasted with phenolic acids, some quinones, and the corresponding polyphenols were also tested (entries 9-14). 1,4-

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Benzenediol and *p*-benzoquinone obtained similar modest yields (entries 9-10), meaning that the organocatalysts underwent the redox cycles of quinone-(semiquinone-)hydroquinone during the aerobic oxidative coupling of thiol. However, 1,2- and 1,3-Benzenediol as well as 1,3,5-Benzenetriol gave a lower yields (entries 11-13). Surprisingly, the coupling occurred less effectively when 2,5-dihydroxyl-1,4-benzoquinone was used (entries 14). The reason probably is that two intramolecular hydrogen bonds between its hydroxyls and carbonyls restrained its oxidation. The catalytic activities of 2,5-dihydroxyl-1,4-benzoquinone and *p*-benzoquinone increased obviously, albeit in modest yields, when the reactions conducted in $CH_3CN$ instead of $H_2O$ (entries 15-16). This implied that lower aqueous solubility of quinones limited their catalytic performances in water.

As a contrast, the renewable, inexpensive and low-toxic **GA** ($LD_{50\ rat}$ = 5000 mg $kg^{-1}$, the datum has been check with the ChemSpider Database.) had higher aqueous solubilities due to its more than one hydrophilic hydroxyls and one hydrophilic carboxyl moieties, therefore displayed perfect catalytic performances, as expected.

**Reaction conditions optimization**

In the further optimization of the reaction conditions, we evaluated both the loading amounts of **GA** and $MnCO_3$, temperature, $O_2$ pressure, and reaction time (Table 3). As can be seen, the coupled system can work even at as low as *ca* 0.075 mol% loading of **GA**, giving 33% conversions in the course of 5 h (entry 1). It was not unexpected to find that the more loading amounts of both **GA** and $MnCO_3$ resulted in faster rates of coupling (entries 1–8). However, the influence of the loading amount of **GA** on the rate was obviously stronger than that of $MnCO_3$. And 0.15 mol% seemed to be the preferable loading amounts of both **GA** and $MnCO_3$, meaning the ratio of them was 1. The data of entries 6 and 11–13 showed that at 80 °C the coupling proceeded so rapidly that a near complete conversion was obtained after 4 h. Beyond 4 h, there was no significant increase in yield, probably due to the very low concentration of **1a** in the reaction mixture. Increasing the reaction temperature increased the coupling rate, and the preferable temperature was 80 °C (entries 6, 9-10). The pressure of $O_2$ showed a positive influence on the rate below 0.3 MPa (entries 14-16). This suggested that the rate of coupling is controlled by molecular oxygen diffusion and solution in water media under the lower pressure. Moreover, the oxidations barely occurred in the absence of any component under the same conditions (entries 17-19), displaying that two components were indispensable.

Consequently, under the optimal conditions disulfane synthesis could realized perfect efficiency on gram scale, the product **2a** with over 99% purity could be obtained by simple filtration after the reaction accomplishment. The practical convenience and low loading of catalysts of our catalytic method illustrated its practicability.

**Table 3.** Conditions Screening of 1a Self-coupling with GA and $MnCO_3$. [a]

| Entry | GA (mol%) | $MnCO_3$ (mol%) | P (MPa) | T (°C) | t (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | 0.075 | 0.2 | 0.3 | 80 | 5 | 33 |
| 2 | 0.125 | 0.2 | 0.3 | 80 | 5 | 72 |
| 3 | 0.15 | 0.2 | 0.3 | 80 | 5 | 98 |
| 4 | 0.25 | 0.2 | 0.3 | 80 | 5 | 98 |
| 5 | 0.5 | 0.2 | 0.3 | 80 | 5 | 99 |
| 6 | 0.15 | 0.15 | 0.3 | 80 | 5 | 98 |
| 7 | 0.15 | 0.125 | 0.3 | 80 | 5 | 82 |
| 8 | 0.15 | 0.1 | 0.3 | 80 | 5 | 69 |
| 9 | 0.15 | 0.15 | 0.3 | 100 | 5 | 98 |
| 10 | 0.15 | 0.15 | 0.3 | 60 | 5 | 65 |
| 11 | 0.15 | 0.15 | 0.3 | 80 | 4 | 98 [c] |
| 12 | 0.15 | 0.15 | 0.3 | 80 | 3 | 78 |
| 13 | 0.15 | 0.15 | 0.3 | 80 | 2 | 14 |
| 14 | 0.15 | 0.15 | 0.2 | 80 | 4 | 64 |
| 15 | 0.15 | 0.15 | 0.1 | 80 | 4 | 49 |
| 16 | 0.15 | 0.15 | 0.3 | 80 | 4 | 96 |
| 17 | 0 | 0.15 | 0.3 | 80 | 4 | 6 |
| 18 | 0.15 | 0 | 0.3 | 80 | 4 | 14 |
| 19 | 0 | 0 | 0.3 | 80 | 4 | 4 |

[a] Reaction conditions: **1a** (3.34 g, 20 mmol), 50 mL $H_2O$, pH = 9. [b] HPLC yield. [c] Isolated yield.

**Self-coupling of various thiols**

The optimal coupled system of **GA** and $MnCO_3$ was employed further to catalyze the aerobic oxidative self-coupling of various thiols to the corresponding symmetric disulfanes (Table 4). As expected, **GA**/$MnCO_3$ displayed exciting catalytic performances. Substituted thiophenols bearing electron-donating groups (**1b-j**), such as amino, acetylamino, methyl, hydroxyl, or methoxyl group, and electron withdrawing groups (**1k-p**), such as chloro, bromo, carboxyl, nitro, or methoxycarbonyl group, gave all desired disulfanes **2b-p** in excellent yields, and substiuents, whatever in the *ortho*-, *meta*- or *para*-position of thiophenols, showed no significant difference effects on the yields. Naphthyldisulfane **2q** was synthesized in 99% yield. Heteroaromatic thiols, such as **1a**, thiophene-2-thiol, pyridine-2-thiol, and pyrimidine-2-thiol, were all oxidized to the corresponding disulfanes **2a** and **2r-t** with good to excellent yields, respectively. And also the oxidation of benzylthiol gave 93 % yield of **2u**. In contrast, the self-coupling of aliphatic thiols proceeded slowly. In the course of 4 h, the oxidative couplings of cyclohexanethiol and *n*-hexanethiol (**1v-w**) gave 39% and 44% yields of the corresponding disulfanes (**2v-w**), respectively. Nevertheless, the yields of **2v-w** can be promoted apparently by merely prolonging the reaction time. Consequently, this oxidative self-coupling of thiols in the aqueous phase is highly versatile and efficient for the synthesis of a large variety of symmetric disulfanes.

**Table 4.** Synthesis of symmetric disulfanes by **GA** and $MnCO_3$.[a,b]

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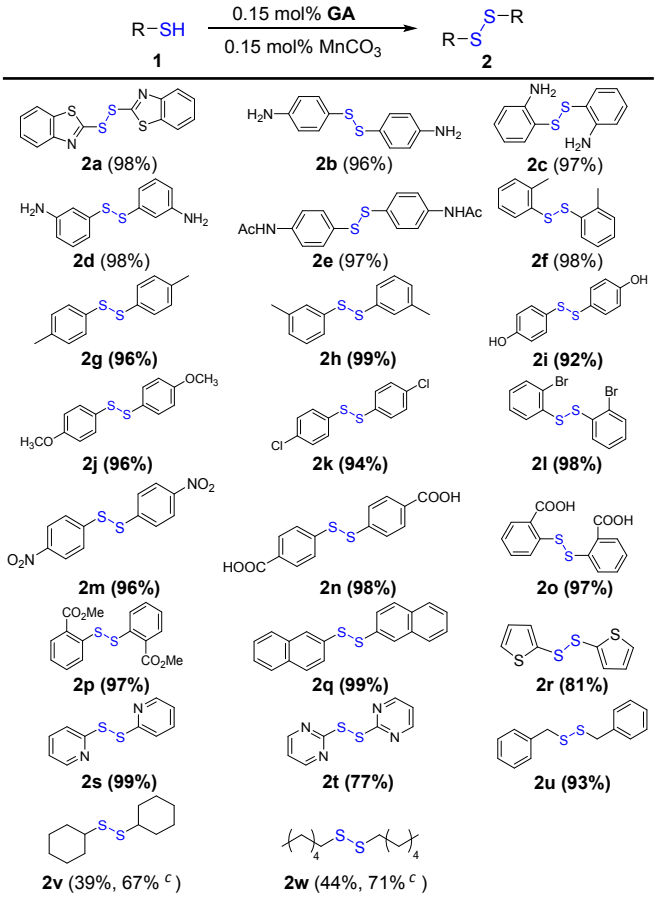


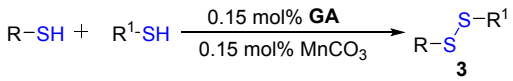

[a] Reaction conditions: **1a** (0.5 mmol), 3 mL $H_2O$, pH = 9, 80 °C, 0.3 MPa $O_2$, 4 h. [b] Isolated yield. [c] For 18 h.

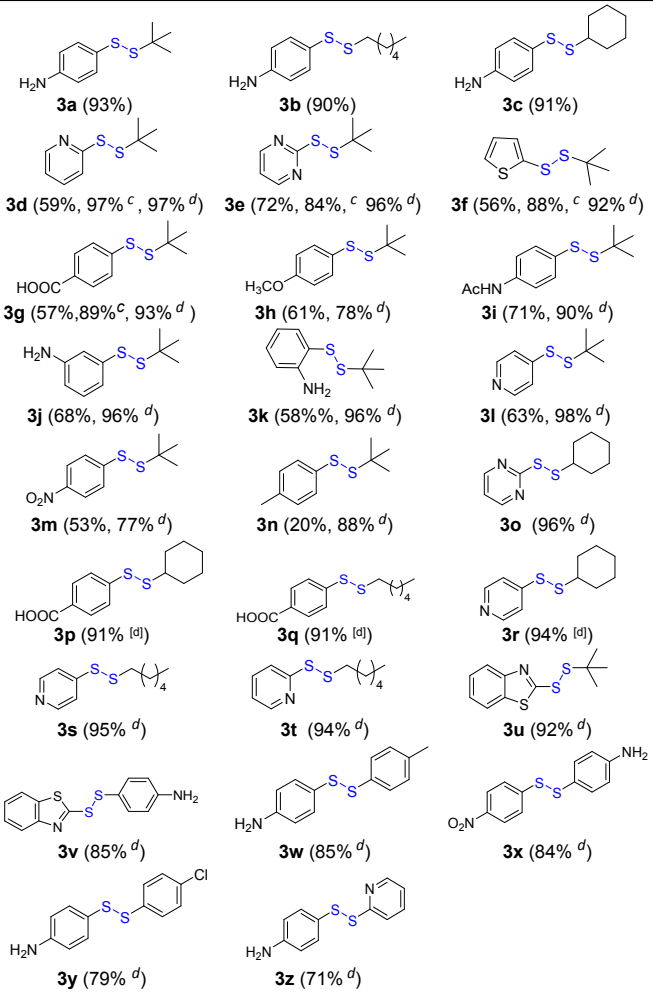
### Cross-coupling of various thiols

Although there are many different methods for the preparation of symmetrical disulfanes, most of them are not suitable to the synthesis of unsymmetrical disulfanes, due to the formation of symmetrical side products form self-coupling. The stoichiometric oxidation of mixtures of thiols, and thiol-disulfane exchange reactions are the most common approaches to obtain unsymmetrical disulfanes.[40] An interesting oxidation method used dichlorodicyanoquinone (**DDQ**, 1 eqiv.) as oxidant, which afforded moderate to high yields of unsymmetrical disulfanes with equimolar loading amounts of different thiols, but it did not tolerated the presence of amino group at thiol probably due to reaction with carbonyl of **DDQ**, and failed to oxidize the tertiary thiol possibly due to steric hindrance.[38, 41] To expand the generality of **GA**/$MnCO_3$ method for cross coupling, a series of mixtures of different thiols were tested (Table 5). It was delightful to find that, in the course of 4 h the cross couplings of *p*-aminophenthiol with *t*-butylthiol, *n*-hexylthiol, and cyclohexylthiol in equimolar amounts realized 93%, 90%, 91% isolated yield (**3a-c**), respectively. This meant that **GA**/$MnCO_3$ tolerated amino thiol and the tertiary thiol oxidation. Furthermore, the cross couplings of *t*-butylthiol with various aryl thiols obtained good yields of unsymmetrical disulfanes (**3d-n**), respectively.

It should be pointed that under the above optimal conditions the occurrence of self-coupling was not prevented completely and a few of symmetrical disulfanes often existed. So, variations on the reaction conditions had been conducted. When 2 equiv. $R^1SH$ was used without the other conditions

**Table 5.** Synthesis of unsymmetric disulfanes with GA and $MnCO_3$. [a,b]




[a] Reaction conditions: RSH (0.5 mmol), $R^1SH$ (0.5 mmol), **GA** (0.28 mg, 0.15 mol%), $MnCO_3$ (0.172 mg, 0.15 mol%), 3 mL $H_2O$, pH = 9, 80 °C, 0.3 MPa $O_2$, 4 h. [b] Isolated yield. [c] 1.0 mmol $R^1SH$ was used. [d] 1.0 mmol $Na_2CO_3$ was used.

change, the cross-coupling became the main reaction (3d-g). Excitingly, 2-Pyridyl *t*-butyl disulfanes was obtained in 97% yield (3d). The cross-couplings of *t*-butylthiol with pyrimidine-2-thiol and thiophene-2-thiol gave 84% and 88% yields, respectively (**3e-f**). Further conditions screening indicated that alkalinity shown positive effect markedly on formation of unsymmetrical disulfanes. When 1 equiv. $Na_2CO_3$ was added into the reaction mixture instead of pH 9 adjustment, the yields of unsymmetrical disulfanes promoted

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tremendously. The cross-couplings of heteroaromatic thiols, arylthiols and alkylthiols gave over 90% yields of the corresponding unsymmetrical disulfanes (**3d-u**), respectively, where the symmetrical disulfanes were barely found. Good yields were realized in the cross-couplings between the different arylthiols (**3v-z**). Although the reason of the alkalinity effect should be further studied, it didn't make any difference to the conclusion that a novel and simple method of unsymmetrical disulfanes synthesis was developed.

**Studies of aerobic oxidative coupling routes**

Recognizing the successful performance of the first combination of **GA** and $MnCO_3$, we sought to find the route which both of phenolic acids and Mn ion went through in the oxidative coupling.

It is well documented that hydroquinone oxidation featured two readily accessible oxidation states: one-electron-oxidized semiquinone, and two-electron-oxidized quinone.[36] Both of them could oxidize other substrate via single electron transfer and converted to their reducing states. In-situ UV investigation indicated clearly that *p*-benzoquinone was reduced to 1,4-hydroquinone during its reaction with *t*-butylthiol under $N_2$ atmosphere (Blue line, Figure 1). Being identical to the reference samples, the shoulder peak at 239 nm was assigned to the absorption band of *p*-benzoquinone, and its absorbance decline meant that *p*-benzoquinone was somewhat reduced during its reaction with *t*-butylthiol.

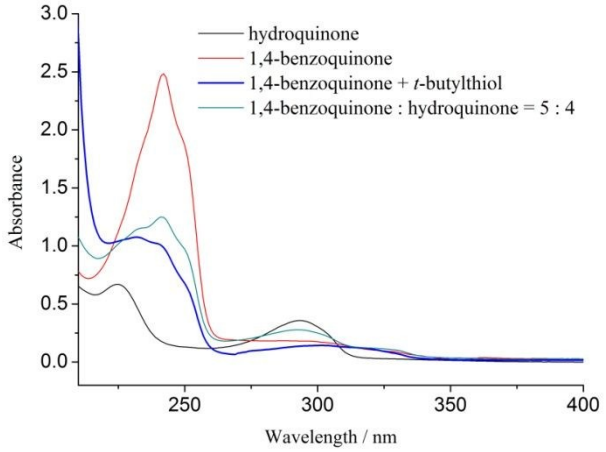


**Figure 1.** In-situ UV investigation on reaction of 1,4-benzoquinone and *t*-butylthiol in $CH_3CN$ at 70 °C under $N_2$ atmosphere for 3 h, all concentrations were $1\times10^{-7}$ mol/ml except for the mixture of 1,4-benzoquinone ($5\times10^{-8}$ mol/ml) and 1,4-hydroquinone ($4\times10^{-8}$ mol/ml).

We noticed that the colorless aqueous solution of 1,4-benzenediol became red at once when its pH was adjusted to 9 at room temperature. After stirring for 10 min *ca* 10% *p*-benzoquinone was found in the solution by HPLC detections, and the amount of 1,4-benzenediol continuously decreased when the time prolonged (A, Figure 2), showing that the 1,4-benzenediol was converted to the corresponding phenolic anion and then readily susceptible to oxidation to benzoquinone and over-oxidation products. In sharp contrast, any changes both of solution color and the amount of 1,4-benzenediol were not observed when thiol was added into 1,4-benzenediol solution (d, A, Figure 2), meaning 1,4-benzenediol oxidation was restrained completely. The similar phenomenon also was observed in the HPLC tracing tests on interactions of **GA** and 4-methoxy-phenthiol (B, Figure 2). Along with the amount of 4-methoxy-phenthiol decreased, the corresponding disulfane (5.80 min) increased, but any **GA** oxidation was not found (d-e, B, Figure 2). These meant that thiol could immediately reduce the inchoate oxidation product of

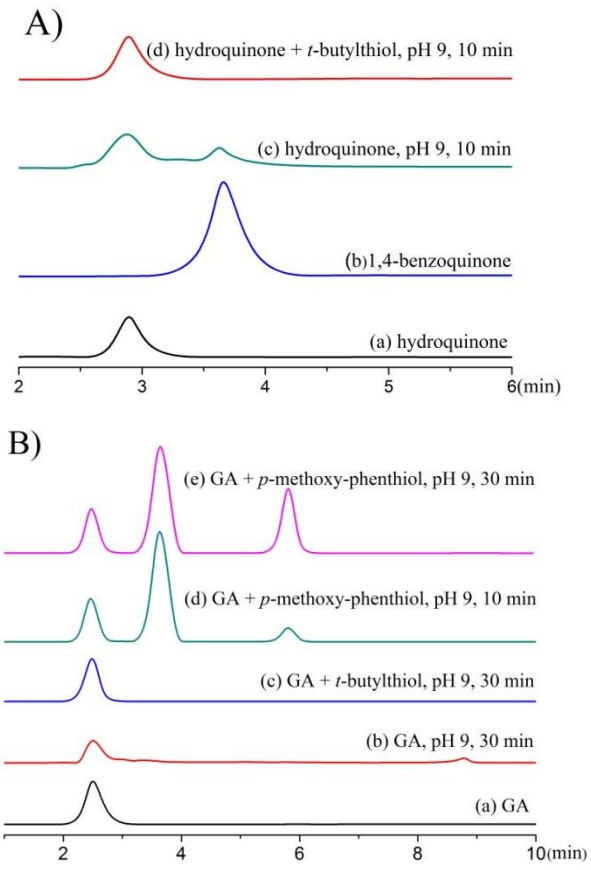


**Figure 2.** HPLC tracing tests on interactions of 1,4-hydroquinone and **GA** with thiols at room temperature. A) 1,4-Hydroquinone (**2**$\times10^{-6}$ mol/ml) and *t*-butylthiol ($2\times10^{-5}$ mol/ml), the flow phase $CH_3OH/H_2O$ (v:v = 1:1), the detection wavelength 230 nm; *p*-Benzoquinone ($2\times10^{-6}$ mol/ml). B) **GA** ($1.3\times10^{-6}$ mol/ml) and 4-methoxy-phenthiol ($1.3\times10^{-5}$ mol/ml), the flow phase $CH_3OH/H_2O$ (v:v = 9:1), the detection wavelength 254 nm.

phenolic acid as long as it formed. So it may be speculated that in phenolic acid catalysis the reciprocal transformation between hydroquinone and semiquinone was the main redox cycle, quinone barely existed.

Inorder to understand why unsymmetrical disulfanes were the major products one when 1 equiv. $Na_2CO_3$ was used, HPLC tracing tests on reactions between equimolar **2t** and *t*-butylthiol was operated under the optimal conditions (Figure 3). The results clearly clarified that the formation of unsymmetrical disulfanes followed the formation of symmetrical disulfanes,

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meaning that unsymmetrical disulfane was produced by thiolate-disulfane exchanged reaction.[41-42] In comparison of the results of reaction at pH9 (a - c, Figure 3) and using 1 equiv. $Na_2CO_3$ (d - e, Figure 3), it could be concluded that alkalinity accelerated this thiolate-disulfane exchanged reaction.

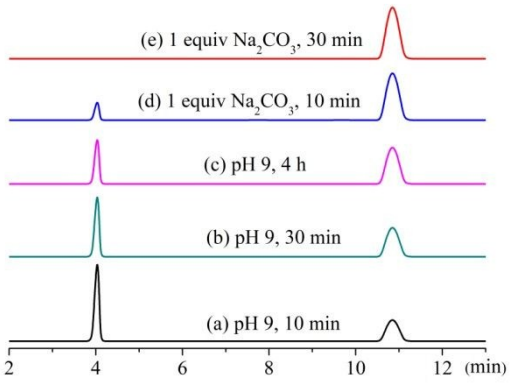
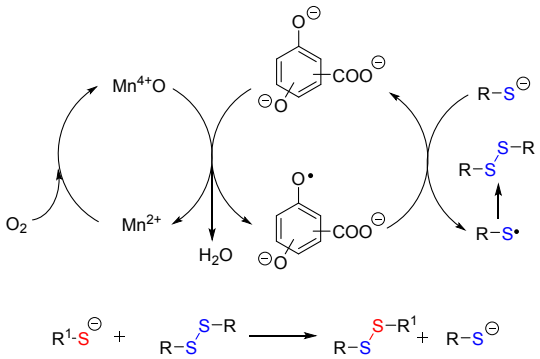



**Figure 3.** HPLC tracing tests on the reactions between equimolar **2t** and *t*-butylthiol at 80 °C. 4.02 min, **2t**; 10.81 min, **3e**. The flow phase $CH_3OH/H_2O$ (v:v = 6:4), the detection wavelength 254 nm.

Since there are easy redox transformations during the multivalence states, Mn and its oxides have been extensively employed as a component in the oxidation catalysts.[43-46] In our catalytic system, $Mn^{2+}$ combined affinitively with dioxygen to form the active MnO species that was responsible for activation of dioxygen and transmit oxidizability to the oxidation of phenolic acid.

As a consequence, although MnO species are not known in detail, the general mechanism of this new catalytic oxidative coupling can be described possibly as in Scheme 1. Under basic condition, thiol converted to the corresponding thiolate anion. During the reaction, phenolic anion was oxidized to its semiquinone radical by MnO species. The transformation of semiquinone radical to hydroquinone anion converted the thiolate anion easily to the thiyl radical which then coupled to symmetrical disulfane. Another thiolate anion reacted with symmetrical disulfane to give unsymmetrical one.




**Scheme 1.** The proposed route of Mn-mediated phenolic acids-catalyzed aerobic oxidative coupling of thiols under basic condition.

## Conclusions

We successfully developed a novel, highly efficient and versatile methodology to prepare disulfanes that used firstly a natural renewable gallic acid as an organocatalyst, inexpensive $Mn(CO_3)_2$ as a cocatalyst, dioxygen as the terminal oxidant and water as the onefold solvent. Mechanistically, the reciprocal transformation between hydroquinone and semiquinone of phenolic acid was possibly the key catalytic redox cycle that lead thiol more easily to thiyl radical and then coupled to disulfane. Such aerobic oxidative coupling method was suitable to synthesize various disulfanes from aromatic, alkyl, and heterocyclic thiols under mild condition, and tolerated amino thiol and the tertiary thiol. Importantly, unsymmetrical disulfanes were prepared with high yields from directly the corresponding mixture of two different thiols in equimolar amounts. The reaction can be conducted on a gram scale with good reaction efficiency, which gives a practicable protocol from both an economic and an environmental point of view as well as for operational ease of not handling organic solvents, toxic and expensive reagents. Further application of this general, straightforward and sustainable approach in other useful transformations is under way in our laboratory.

## Experimental Section

### General Procedure for the Aerobic Oxidative Self-Coupling

The catalytic reactions were performed in a 25-mL Schlenk tube and the general procedure is described typically with self-coupling of 2-mercaptobenzothiazole (**1a**) as follows: **1a** (0.5 mmol), gallic acid (**GA**) (0.15 mol%), $MnCO_3$ (0.15 mol%), and $H_2O$ (3 mL) was added into the reactor and adjusted pH to 9 by $Na_2CO_3$ solution under stirring. Subsequently, the reaction mixture was stirred under 0.3 MPa $O_2$ at 80 °C and monitored by thin layer chromatography (TLC). After cooling to room temperature, the end reaction mixture was added 10 mL water to and extracted with ethyl acetate (10 mL×3). The combined organic extract phase was dried over $Na_2SO_4$, and after filtration, the solvent was removed on rotovap under reduced pressure. The resulting residue was purified by flash chromatography on silica gel to give the desired product.

### General Procedure for the Aerobic Oxidative Corss-Coupling

RSH (0.5 mmol), $R^1SH$ (0.5 mmol), **GA** (0.15 mol%), $MnCO_3$ (0.15 mol%), $Na_2CO_3$ (1.0 mmol) and $H_2O$ (3 mL) was added into a 25-mL Schlenk tube. Other subsequent operations were in keeping with the above procedure of self-coupling.

## Conflicts of interest

There are no conflicts to declare.

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