

SCIENTIFIC REPORTS

OPEN

An Unexpected Controlled New Oxidant: $\text{SO}_4^{\cdot-}$

Cui-Bing Bai¹, Nai-Xing Wang¹, Xing-Wang Lan¹, Yan-Jing Wang¹, Yalan Xing², Jia-Long Wen¹, Xue-Wang Gao¹ & Wei Zhang¹

Received: 08 October 2015

Accepted: 22 December 2015

Published: 01 February 2016

A controlled new oxidant sulfate radical anion ($\text{SO}_4^{\cdot-}$) was found and it can be easily prepared by mixing $\text{Na}_2\text{S}_2\text{O}_4$ and TBHP with stirring. In this new metal-free oxidation system ($\text{Na}_2\text{S}_2\text{O}_4/\text{TBHP}$), $\text{SO}_4^{\cdot-}$ can be used as a controllable oxidant to oxidize various aromatic alcohols to the corresponding aldehydes in good yields without any acid formation at room temperature. $\text{SO}_4^{\cdot-}$ was determined by a DMPO (5,5-dimethyl-1-pyrroline-*N*-oxide) spin-trapping EPR method at room temperature on a Bruker E500 spectrometer and the results suggested that $\text{SO}_4^{\cdot-}$ was generated in this transformation.

The selective oxidation of alcohols to the corresponding aldehydes is highly relevant reactions in organic chemistry^{1,2}, and is a fundamental and pivotal transformation for laboratory research and industrial manufacturing³. To date, great efforts have been continuously devoted to the development of excellent oxidation systems for alcohol oxidations⁴⁻⁶. Classically, oxidations of alcohols are performed with inorganic oxidants (notably chromium and manganese oxides), Swern reagents and Dess-Martin reagents (Fig. 1)^{7,8}. However, these stoichiometric oxidants suffer from many drawbacks such as relatively expensive reagents and difficulties in handling heavy-metal wastes⁹. From the viewpoints of environmental concern, more and more attention has been paid towards the development of catalytic aerobic alcohol oxidation methodologies^{10,11}. In the past few decades, transition metal-catalyzed oxidation of alcohols to aldehydes or ketones has been established^{12,13}. For example, the catalytic systems employing different transition metals in combination with TEMPO (2,2,6,6-tetramethyl-piperidyl-1-oxy) or TBHP (*tert*-butyl hydroperoxide)^{14,15}. Although many of these methods were effective for the preparation of the desired products, additional base, transition metals and high reaction temperatures are often needed as shown in Fig. 1⁹.

Recently, a transition-metal-free catalytic system for oxidations catalyzed by TEMPO/ NaNO_2 has attracted special attention due to their outstanding catalytic efficiency^{16,17}. However, these methods have some drawbacks, such as the use of O_2 often requires work in autoclaves¹⁸. And high reaction temperatures are often needed. Despite lots of precedents and advancements in alcohol oxidation strategies recently, there have been few reports on the metal-free oxidation system for oxidation catalyzed by TBHP under mild conditions. Thus, the search for developing highly efficient oxidation system without metals for the oxidation of alcohols remains an area of intensive interest.

As we all know, $\text{Na}_2\text{S}_2\text{O}_4$ (sodium dithionite) is one of the most widely used strong reducing agents in organic chemistry. For example, in the synthesis of the chiral NADH models, $\text{Na}_2\text{S}_2\text{O}_4$ is often used as the most effective reducing agent¹⁹⁻²¹. $\text{Na}_2\text{S}_2\text{O}_4$ is an effective reagent for the reduction of aldehydes and ketones to the corresponding alcohols²². As a continuation of our research on TBHP and $\text{Na}_2\text{S}_2\text{O}_4$ ^{19-21,23}, in an accidental opportunity, we found that TBHP/ $\text{Na}_2\text{S}_2\text{O}_4$ can oxidize aromatic alcohols to corresponding aldehydes without any acid formation.

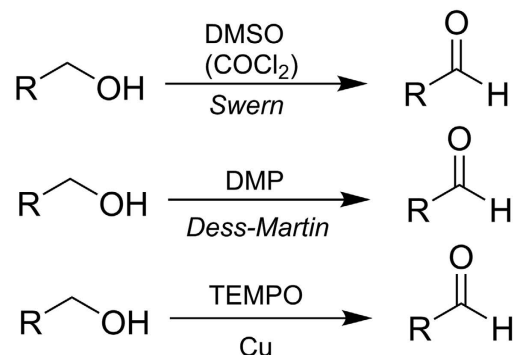
Furthermore, sulfate radical anion ($\text{SO}_4^{\cdot-}$) can be formed by thermal activation, UV photolysis and transition metal catalysis²⁴⁻²⁸. In this paper, a controlled new oxidant sulfate radical anion ($\text{SO}_4^{\cdot-}$) was found and it can be easily prepared by mixing $\text{Na}_2\text{S}_2\text{O}_4$ and TBHP with stirring. To the best of our knowledge, this is first report that sulfate radical anion can be used as controllable oxidant to oxidize various aromatic alcohols to the corresponding aldehydes in good yields without any acid formation.

Results and Discussion

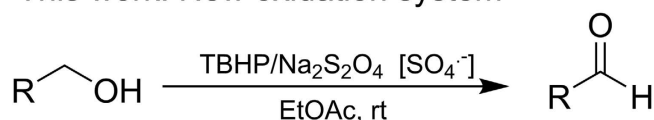
We initially investigated the reaction between 4-methoxybenzyl alcohol (**1a**) with $\text{Na}_2\text{S}_2\text{O}_4$ in the presence of 1 equiv of TBHP in EtOAc at room temperature for 12 h (Table 1, entry 1). To our delight, the $\text{Na}_2\text{S}_2\text{O}_4/\text{TBHP}$ oxidation system showed good catalytic activity for oxidation of **1a** to *p*-anisaldehyde (**2a**) with a good yield of 60% at room temperature (entry 1). Having a promising result in hand, we then optimized the reaction conditions.

¹Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing, 100190, China. ²Department of Chemistry, William Paterson University of New Jersey, 300 Pompton Road, Wayne, New Jersey 07470, United States. Correspondence and requests for materials should be addressed to N.-X.W. (email: nxwang@mail.ipc.ac.cn) or Y.X. (email: xingy@wpunj.edu)

Previous work:



This work: New oxidation system



- 17 examples, up to 91% yield
- controllable oxidation
- SO₄^{·-} was prepared easily
- metal-free and room temperature

Figure 1. Strategies for selective oxidation of primary alcohols to aldehydes.

Entry ^a	Na ₂ S ₂ O ₄ /Additive/Sub.	Additive ^b	Solvent	Yield (%) ^c
1	1/1/1	TBHP	EtOAc	60
2	1/2/1	TBHP	EtOAc	68
3	2/3/1	TBHP	EtOAc	73
4	2/4/1	TBHP	EtOAc	83, 78 ^d
5	2/5/1	TBHP	EtOAc	81
6	2/0/1	-	EtOAc	NR ^e
7	0/4/1	TBHP	EtOAc	NR
8	2/4/1	H ₂ O ₂	EtOAc	NR
9	2/4/1	NBS	EtOAc	15
10	2/4/1	BPO	EtOAc	9
11	2/4/1	DTBP	EtOAc	trace
12	2/4/1	TBHP	CH ₂ Cl ₂	63
13	2/4/1	TBHP	CHCl ₃	57
14	2/4/1	TBHP	CH ₃ CN	55
15	2/4/1	TBHP	THF	41
16	2/4/1	TBHP	cyclohexane	20

Table 1. Optimization of reaction conditions. ^aReaction conditions: alcohol (0.5 mmol), Na₂S₂O₄ and additive in solvent (4 mL) were stirred at room temperature for 12 h. ^bTBHP = *tert*-butyl hydroperoxide, 70% in water, DTBP = di-*tert*-butyl peroxide. ^cIsolated yield. ^dAnhydrous TBHP. ^eNo reaction.

The initial study was carried out using 4-methoxybenzyl alcohol (**1a**) as the model substrate. The results were summarized in Table 1. It was found that the reactivity of the oxidation reaction was the best when molar ratio of Na₂S₂O₄/TBHP/substrate was 2:4:1 (entry 4), while decreasing of the ratio led to lower reactivity (entry 1–3). Increasing the amount of aqueous TBHP or using anhydrous TBHP did not improve the yield of compound **2a**, only 81% and 78%, respectively (entries 4 and 5). Further blank experiments confirmed that the substrates were

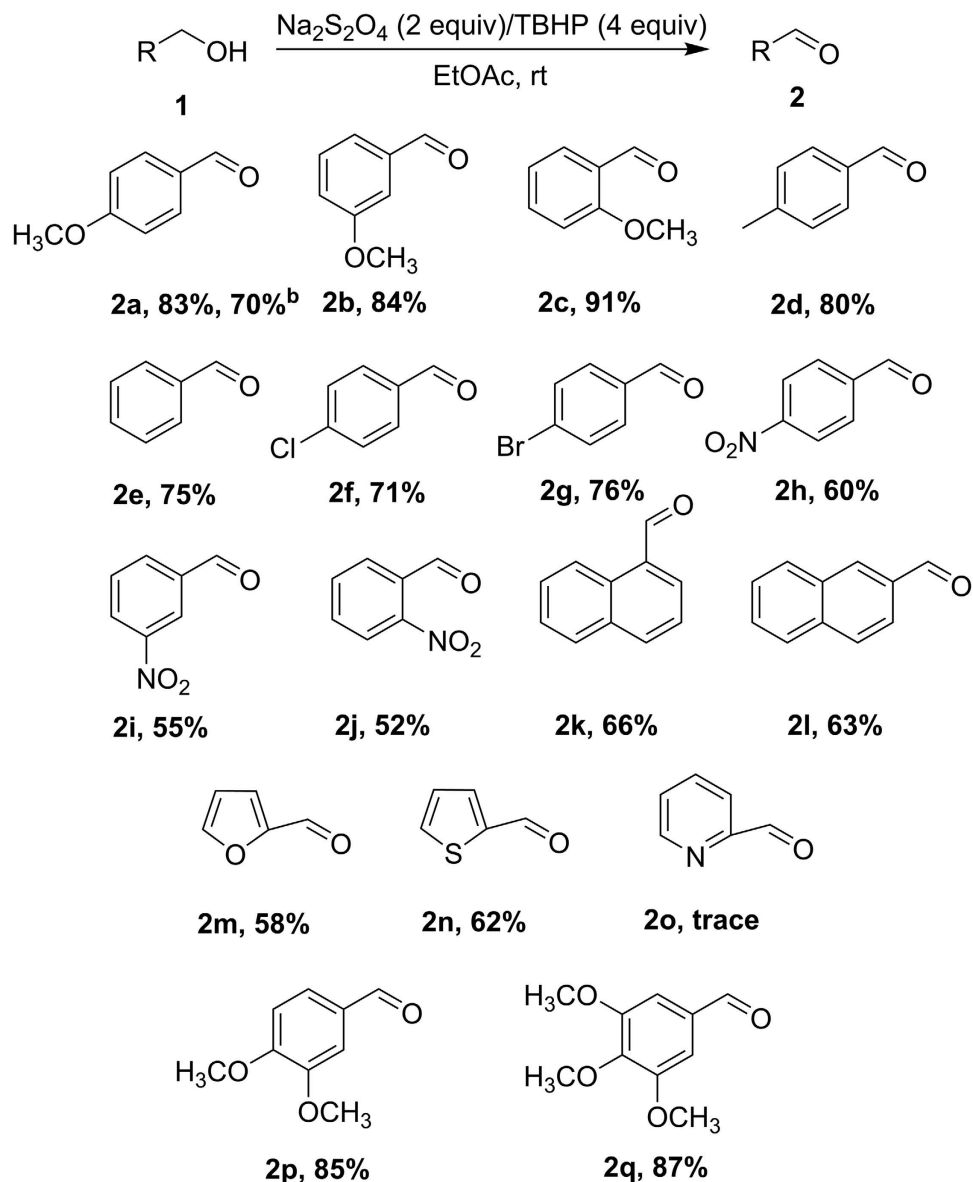


Figure 2. Oxidation of substituted benzylic and other aromatic alcohols.

unreactive in the absence of either TBHP or $\text{Na}_2\text{S}_2\text{O}_4$ (entries 6 and 7). The fact indicated that both TBHP and $\text{Na}_2\text{S}_2\text{O}_4$ were essential for the oxidation. When other different oxidizing agents were used, such as NBS, BPO and DTBP, the yields were not high enough compared with the usage of TBHP (entries 9–11). In addition, no oxidation product was produced when H_2O_2 was used under this condition (entry 8). A profound solvent effect on the reactions was observed (entries 12–16). When the reaction was carried out in various solvents such as CH_3CN , CH_2Cl_2 , CHCl_3 , THF, cyclohexane and EtOAc, the best yield was observed using EtOAc. Hence, EtOAc was considered as an optimal solvent.

To probe the efficiency of the $\text{Na}_2\text{S}_2\text{O}_4$ /TBHP oxidation system, the oxidation of various aromatic alcohols to the corresponding aldehydes was studied under the optimized conditions as summarized in Fig. 2. By the comparison of spectral data (^1H and ^{13}C NMR) with the authentic samples, all the aldehydes were well characterized. Benzylic alcohols with electron-donating substituents (e.g., methoxy) can be oxidized into corresponding aldehydes in excellent yields. However, in case of nitro-substituted benzylic alcohols, the yield was comparatively less than that of the electron-donating counterparts (**2h**). Under the same conditions, for aromatic alcohols with methoxy-substituted (**2a–2c**) and nitro-substituted (**2h–2j**) benzene ring, *para*-, *ortho*- and *meta*- aromatic alcohols could be converted into the corresponding products with good yields, respectively. Aromatic alcohols substituted with halogen gave satisfactory yields under the optimized conditions (**2f** and **2g**). Some other aromatic substrates such as furfural and 2-thiophene methanol were readily oxidized to furfural and 2-thiophenecarboxaldehyde, respectively (**2m**, **2n**). However, only trace oxidation product was obtained with pyridin-2-ylmethanol (**2o**). In addition, we conducted a large-scale (10 mmol) reaction, and the results showed that this new oxidation system was also very effective even on the gram scale (**2a^b**). In fact, we have previously

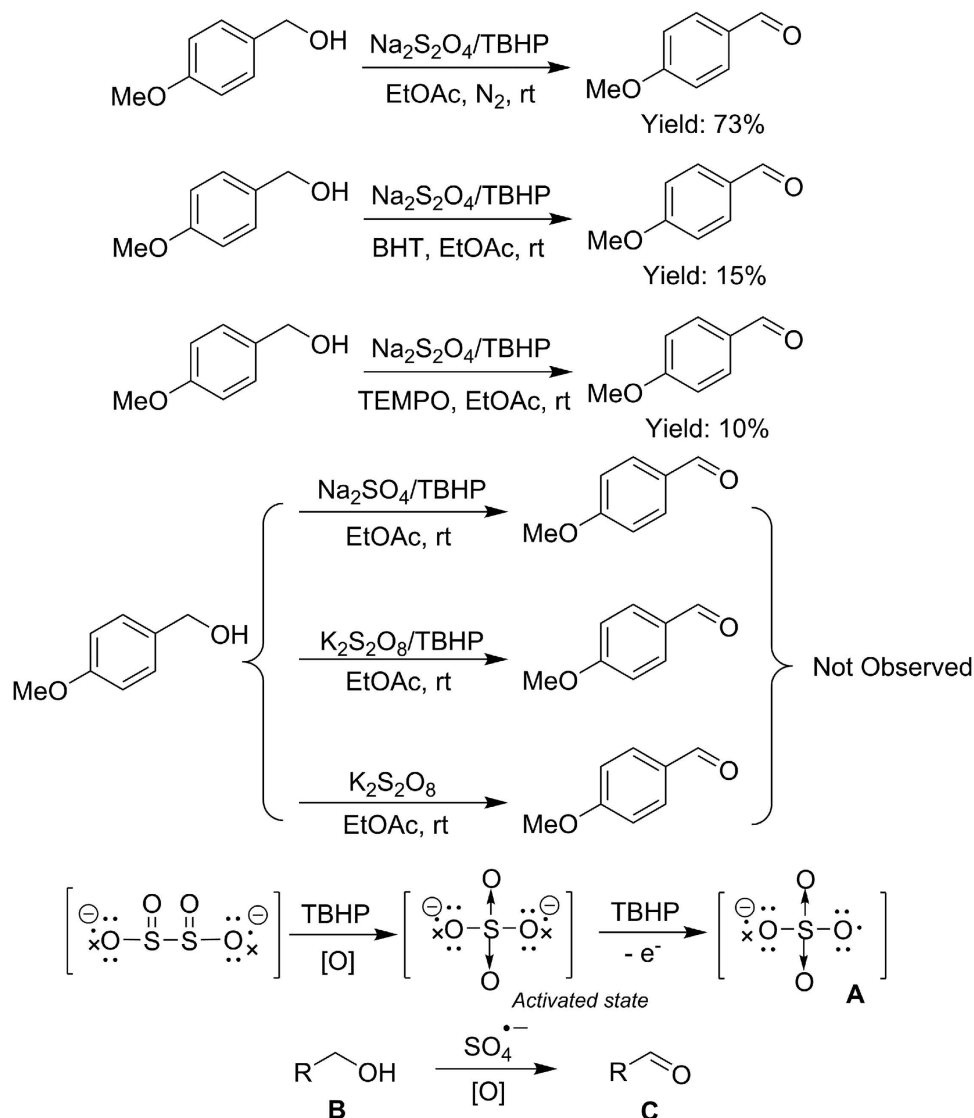


Figure 3. Plausible reaction mechanism.

studied some substrates with 2° aromatic alcohols. We found that the desired product acetophenone can be obtained in 53% yield. Unfortunately, this system is not good for controllable oxidation of fatty alcohols to their corresponding aldehydes.

The reaction was performed in the presence of $\text{Na}_2\text{S}_2\text{O}_4/\text{TBHP}$ under N_2 atmosphere (Fig. 3) and the results showed that TBHP as the terminal oxidant in this reaction. Furthermore, the reaction yield dropped when radical inhibitor BHT (butylated hydroxytoluene) and TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxy) was added, respectively (Fig. 3). It indicated that the reaction should undergo a radical process. EPR spin trapping using the commonly used spin trap, 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), has been employed in the detection of $\text{SO}_4^{\cdot-}$ (see Supplementary Figs S1 and S2 online). A quartet of signals were detected during the reaction process, and the results suggested that $\text{SO}_4^{\cdot-}$ was generated in this transformation²⁹. As shown in Fig. S1 and Fig. S2, with the prolonged reaction time, the concentration of $\text{SO}_4^{\cdot-}$ was also gradually increasing in ethyl acetate or acetonitrile.

In fact, we have used sodium sulfate (Na_2SO_4) in place of dithionate ($\text{Na}_2\text{S}_2\text{O}_4$) to drive the reaction and further prolonged the reaction time, but no reaction was observed (Fig. 3). In this reaction, nascent state SO_4^{2-} should be an activated species, which generated and consumed to form $\text{SO}_4^{\cdot-}$ very quickly in the reaction. Furthermore, we have considered the formation of persulfate ($\text{S}_2\text{O}_8^{2-}$) from sulfate by TBHP (Fig. 3). We also tried to test the intermediate reaction by mixing $\text{K}_2\text{S}_2\text{O}_8$ and TBHP under the optimized conditions. However, we found that the desired product **2a** could not be obtained. The result shows that $\text{SO}_4^{\cdot-}$ can not be generated from $\text{S}_2\text{O}_8^{2-}$ under this conditions. Besides, we tested the mass spectra. A signal at $m/z = 96.9600$ was observed (see Supplementary online). That was assigned to $[\text{SO}_4^{2-} + \text{H}]^-$ (calculated: 96.9596) species. The results suggested that SO_4^{2-} was only generated in the process of forming product.

On the basis of previous studies and the results of our experiments^{30,31}, a plausible reaction mechanism of the oxidation of aromatic alcohols to aldehydes is proposed. A radical anion **A** (sulfate radical anion) could be generated by action of TBHP and Na₂S₂O₈ in this reaction. **A** was found to be an excellent controllable oxidant for oxidation of aromatic alcohols **B** to aldehydes **C** under this reaction conditions.

Conclusion

In conclusion, we have developed a new metal-free oxidation system, which was applied to oxidize various primary aromatic alcohols to corresponding aldehydes in good yields at room temperature. This is a new way to produce SO₄^{•-} by the new oxidation system. The present protocol provides a new tool for alcohol controllable oxidation under mild conditions, and also could be used widely in general organic synthesis. Detailed mechanistic studies and other applications of the new oxidation system in organic reactions are under way in our laboratory.

Methods

Full experimental details and characterization of the compounds can be found in the Supplementary Information.

General. All solvents and chemicals are used directly from commercial sources without further purification. Analytical Thin Layer Chromatography was carried out on precoated plates (silica gel 60), visualized with UV light. NMR spectra was performed on a Bruker DPX-400 spectrometer operating at 400 MHz (¹H NMR). All spectra were recorded in CDCl₃ and the chemical shifts (δ) are reported in ppm relative to tetramethylsilane referenced to the residual solvent peaks. High-resolution mass spectral analyses (HRMS) were measured using ESI ionization. Sulfate radical anion were determined by a DMPO spin-trapping EPR method at room temperature on a Bruker E500 spectrometer. Instrument settings were modulation frequency: 100.00 KHz; modulation amplitude: 2.00 G; sweep width: 100.00 G; time constant: 40.960 ms; conversion: 40.000 ms; sweep time: 40.96 s. The microwave power was 10.03 mW, and the frequency was 9.857 GHz.

General Procedure for the Synthesis of Products 2. To a mixture of alcohol (0.5 mmol) and Na₂S₂O₈ (174 mg, 1.0 mmol) in ethyl acetate (4 mL) was slowly added *tert*-butyl hydroperoxide (257 mg, 2.0 mmol, 70% in water). The mixture was stirred at room temperature for 12 h. After evaporation of ethyl acetate under reduced pressure, the residue was separated on a silica gel column by using petroleum ether and ethyl acetate as eluent.

References

- Shin, K. *et al.* Photoinduced oxidation of secondary alcohols using 4-benzoylpyridine as an oxidant. *Org. Lett.* **17**, 3326–3329 (2015).
- Doi, R. *et al.* Development of an azanoradamantane-type nitroxyl radical catalyst for class-selective oxidation of alcohols. *J. Org. Chem.* **80**, 401–413 (2015).
- Tang, L. *et al.* Pt, Pd and Au nanoparticles supported on a DNA–MMT hybrid: efficient catalysts for highly selective oxidation of primary alcohols to aldehydes, acids and esters. *Chem. Commun.* **49**, 5213–5215 (2013).
- Enache, D. I. *et al.* Solvent-Free oxidation of primary alcohols to aldehydes using Au–Pd/TiO₂ catalysts. *Science* **311**, 362–365 (2006).
- Uyanik, M., Akakura, M. & Ishihara, K. 2-Iodoxybenzenesulfonic acid as an extremely active catalyst for the selective oxidation of alcohols to aldehydes, ketones, carboxylic acids, and enones with oxone. *J. Am. Chem. Soc.* **131**, 251–262 (2009).
- Feng, X. *et al.* Aerobic oxidation of alcohols and the synthesis of benzoxazoles catalyzed by a cuprocupric coordination polymer (Cu⁺-CP) assisted by TEMPO. *Inorg. Chem.* **54**, 2088–2090 (2015).
- Corey, E. J. & Suggs, J. W. Pyridinium chlorochromate. An efficient reagent for oxidation of primary and secondary alcohols to carbonyl compounds. *Tetrahedron Lett.* **16**, 2647–2650 (1975).
- Taylor, R. J. K. *et al.* Tandem oxidation processes using manganese dioxide: discovery, applications, and current studies. *Acc. Chem. Res.* **38**, 851–869 (2005).
- Liu, X.-L. *et al.* Cu-NHC-TEMPO catalyzed aerobic oxidation of primary alcohols to aldehydes. *J. Org. Chem.* **78**, 8531–8536 (2013).
- Xu, B., Lumb, J.-P. & Arndtsen, B. A. A TEMPO-free copper-catalyzed aerobic oxidation of alcohols. *Angew. Chem. Int. Ed.* **54**, 4208–4211 (2015).
- Chen, B.-T. *et al.* Enzyme-Inspired functional surfactant for aerobic oxidation of activated alcohols to aldehydes in water. *ACS Catal.* **5**, 1313–1317 (2015).
- Gartshore, C. J. & Lupton, D. W. Readily Accessible oxazolidine nitroxyl radicals: bifunctional cocatalysts for simplified copper based aerobic oxidation. *Adv. Synth. Catal.* **352**, 3321–3328 (2010).
- Zhu, Y., Zhao, B. & Shi, Y. Highly efficient Cu(I)-catalyzed oxidation of alcohols to ketones and aldehydes with diaziridinone. *Org. Lett.* **15**, 992–995 (2013).
- McCann, S. D. & Stahl, S. S. Copper-catalyzed aerobic oxidations of organic molecules: pathways for two-electron oxidation with a four-electron oxidant and a one-electron redox-active catalyst. *Acc. Chem. Res.* **48**, 1756–1766 (2015).
- Burange, A. S. *et al.* Oxidation of benzylic alcohols to carbonyls using *tert*-butyl hydroperoxide over pure phase nanocrystalline CeCrO₃. *Catal. Commun.* **40**, 27–31 (2013).
- Miao, C. X. *et al.* Self-neutralizing *in situ* acidic CO₂/H₂O system for aerobic oxidation of alcohols catalyzed by TEMPO functionalized imidazolium salt/NaNO₂. *J. Org. Chem.* **75**, 257–260 (2010).
- Miao, C. X. *et al.* Synthesis of bimagnetic ionic liquid and application for selective aerobic oxidation of aromatic alcohols under mild conditions. *Chem. Commun.* **47**, 2697–2699 (2011).
- Holan, M. & Jahn, U. Anaerobic nitroxide-catalyzed oxidation of alcohols using the NO⁺/NO[•] redox pair. *Org. Lett.* **16**, 58–61 (2014).
- Wang, N.-X. & Zhao, J. A novel NADH model: design, synthesis, and its chiral reduction and fluorescent emission. *Adv. Synth. Catal.* **351**, 3045–3050 (2009).
- Wang, N.-X. & Zhao, J. Progress in coenzyme NADH model compounds and asymmetric reduction of benzoylformate. *Synlett.* **18**, 2785–2791 (2007).
- Zhao, J. *et al.* A new type of NADH model compound: synthesis and enantioselective reduction of benzoylformates to the corresponding mandelates. *Molecules*, **12**, 979–987 (2007).
- de Vries, J. G. & Kellogg, R. M. Reduction of aldehydes and ketones by sodium dithionite. *J. Org. Chem.* **45**, 4126–4129 (1980).
- Zhang, J.-X. *et al.* Selective nickel- and manganese-catalyzed decarboxylative cross coupling of some α,β-unsaturated carboxylic acids with cyclic ethers. *Sci. Rep.* **4**, 7446–7450 (2014).
- Liang, C. J. & Bruell, C. J. Thermally activated persulfate oxidation of trichloroethylene: experimental investigation of reaction orders. *Ind. Eng. Chem. Res.* **47**, 2912–2918 (2008).

25. Dogliotti, L. & Hayon, E. Flash photolysis of per[oxydi]sulfate ions in aqueous solutions. The sulfate and ozonide radical anions. *J. Phys. Chem.* **71**, 2511–2516 (1967).
26. Furman, O. S., Teel, A. L. & Watts, R. J. Mechanism of base activation of persulfate. *Environ. Sci. Technol.* **44**, 6423–6428 (2010).
27. Furholz, U. & Haim, A. Kinetics and mechanisms of the reactions of mononuclear and binuclear ruthenium(II) ammine complexes with peroxydisulfate. *Inorg. Chem.* **26**, 3243–3248 (1987).
28. Anipsitakis, G. P. & Dionysiou, D. D. Radical generation by the interaction of transition metals with common oxidants. *Environ. Sci. Technol.* **38**, 3705–3712 (2004).
29. Zamora, P. L. & Villamena, F. A. Theoretical and experimental studies of the spin trapping of inorganic radicals by 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO). 3. Sulfur dioxide, sulfite, and sulfate radical anions. *J. Phys. Chem. A* **116**, 7210–7218 (2012).
30. Hoover, J. M., Ryland, B. L. & Stahl, S. S. Mechanism of Copper(I)/TEMPO-catalyzed aerobic alcohol oxidation. *J. Am. Chem. Soc.* **135**, 2357–2367 (2013).
31. Ghosh, P. P. & Mukherjee, P. & Das, A. R. Triton-X-100 catalyzed synthesis of 1,4-dihydropyridines and their aromatization to pyridines and a new one pot synthesis of pyridines using visible light in aqueous media. *RSC Adv.* **3**, 8220–8226 (2013).

Acknowledgements

This work was supported financially by the Natural Science Foundation of China (21172227).

Author Contributions

C.B.B., N.X.W. and Y.X. wrote the main manuscript text. X.W.L., Y.J.W. and W.Z. prepared Figures 2 and 3. J.L.W. prepared NMR spectra. X.W.G. prepared EPR spectra. All authors discussed the results and commented on the manuscript.

Additional Information

Supplementary information accompanies this paper at <http://www.nature.com/srep>

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Bai, C.-B. *et al.* An Unexpected Controlled New Oxidant: $\text{SO}_4^{\cdot-}$. *Sci. Rep.* **6**, 20163; doi: 10.1038/srep20163 (2016).



This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>