A bioinspired and biocompatible ortho-sulfiliminyl phenol synthesis

Feng Xiong1, Liang Lu1, Tian-Yu Sun2, Qian Wu2, Dingyuan Yan1, Ying Chen2, Xin Hao Zhang2, Wei Wei1, Yi Lu1, Wei-Yin Sun1, Jie Jack Li3 & Jing Zhao1,2

Synthetic methods inspired by Nature often offer unique advantages including mild conditions and biocompatibility with aqueous media. Inspired by an ergothioneine biosynthesis protein EgtB, a mononuclear non-haem iron enzyme capable of catalysing the C–S bond formation and sulfoxidation, herein, we discovered a mild and metal-free C–H sulfonylation/intramolecular rearrangement cascade reaction employing an internally oxidizing O–N bond as a directing group. Our strategy accommodates a variety of oxyamines with good site selectivity and intrinsic oxidative properties. Combining an O–N bond with an X–S bond generates a C–S bond and an S=N bond rapidly. The newly discovered cascade reaction showed excellent chemoselectivity and a wide substrate scope for both oxyamines and sulfonylation reagents. We demonstrated the biocompatibility of the C–S bond coupling reaction by applying a coumarin-based fluorogenic probe in bacterial lysates. Finally, the C–S bond coupling reaction enabled the first fluorogenic formation of phospholipids, which self-assembled to fluorescent vesicles in situ.

1State Key Laboratory of Coordination Chemistry, Institute of Chemistry and BioMedical Sciences, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China. 2Guangdong Key Laboratory of Nano-Micro Material Research, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, China. 3Department of Chemistry, University of San Francisco, 2130 Fulton Street, San Francisco, California 94117, USA. Correspondence and requests for materials should be addressed to J.Z. (email: jingzhao@nju.edu.cn).
E nzymatic C–S bond formation is a common process in biological systems1–5. For example, ergothioneine is considered as a protectant against oxidative stress67. The key step in its biosynthesis pathway is the mononuclear non-haem iron enzyme EgtB-catalysed sulfonylation formation between γ-glutamyl cysteine and N-α-trimethyl histidine, involving a sulfur transfer step and an oxygen transfer step (Fig. 1a)8,9.

A variety of synthetic methods have been developed to construct the ortho-functionalized phenols which are highly useful in chemical industry10, functional materials11 and medicines12–14. These methods mainly include three kinds of strategies: (a) rearrangement of aromatic O–X bonds15–20, (b) directing group-assisted ortho C–H hydroxylation of arenes21–27; and (c) ortho C–H functionalization of phenols28–32. Although these results have promoted the development of the phenol chemistry, the more efficient, economical and biocompatible methods are still in demand.

Inspired by the sulfur transferases and our previous successes in O–N bond-directed synthesis of ortho-functionalized phenols33–35, we envisioned that ortho-sulfilimyln phenols could be obtained by combining a directing group containing an internally oxidizing O–N bond with a sulfonylation reagent.36,37 The desired sulfonylation reagent and oxidizing X–N bond needs to accomplish the following two tasks (Fig. 1b): (i) sulfur transfer38,39 A well-chosen electrophilic sulfonylation reagent would facilitate the N-sulfonylation of the X–N moiety and lead to the formation of an N–S bond to produce intermediate B; (ii) rearrangement. Pivotal progress was made by Maulide40,41, Procter2,42, Yorimitsu31 and Peng43 who pioneered the directed, metal-free, redox-neutral and ortho-functionalization. These inspiring work suggested that when the substrate captures a suitable partner, the resulting intermediate may undergo a sigmatropic rearrangement and reoration to product D, leading to the formation of a C–X bond with concurrent O–X bond cleavage. Herein, we report a rationally designed and metal-free coupling method to synthesize sulfilimines via an internal oxidant-directing strategy for the cascade formation of C–S and S = N bonds at room temperature.

Results

Optimization of the reaction conditions. For direct coupling reactions, especially those catalysed by transition metals, a directing group typically escorts the metal catalyst towards the neighbouring ortho-position and dictates the site selectivity. Directing groups containing N–N bond, S–N bond or O–N bond are redox versatile and could facilitate inter- or intramolecular cyclization44–47. At the outset of this study, compounds 1 with those bonds were firstly screened to couple with a thionating reagent N-ethyliophthalimide 2a under previously reported metal catalysed conditions 48–50 for similar reactions (Fig. 2a). Attempts on substrate 1 with X of N or S yielded no reaction. Gratifyingly, when X was replaced by O, the resulting N-phenoxycetamide 1a concurrently constructed a C–S bond and an S = N bond, giving the desired phenolic sulfinilime product 3aa in 83% yield.

The N–H bond in the O–NHAc moiety was found to be essential for the reaction as no reaction occurred when N–H was methylated (Fig. 2a). The need for an electron-donating phenoxym group as well as an N–H led us to suspect the existence of an ammonium ion as an essential intermediate in promoting the cascade reaction. Therefore, we removed the Rh catalyst and N₂ protection from the reaction system and the reaction could occur smoothly under metal-free conditions. Next, different sulfonylation reagents were screened to explore the cascade strategy (Fig. 2b). Tolyl sulfinides with different leaving groups on the S-atom such as chloride, tosyl and phthalimidoyl coupled with N-phenoxycetamide 1a to afford 3af in 18, 33 and 85% yield, respectively. With benzensulfonyl as the leaving group, however, no reaction took place, suggesting that disulfide remains intact during the course of the coupling reaction. As the coupling reaction was most likely mediated by a base, we tested various bases such as Et₃N, DIPEA, DBU, K₂CO₃, Na₂CO₃, NaOAc and CsOAc, where CsOAc gave the highest yield. Switching the reaction solvent to methanol and using an air atmosphere, the yield of the phenol product 3aa was further improved to 92% (Supplementary Information, Supplementary Table 6).

Substrate scope of the reaction. To probe the scope of the transition metal-free cascade C–S and S = N bond formation, we examined a series of oxamide substrates (Table 1). Replacing the acetyl group with a bulkier pivaloyl or a benzoyl group only slightly decreased the yield to 80% (3ba) and 83% (3ca), respectively. It is worth noting that the sulfinilime substitution occurred exclusively at the ortho-position of the phenoxymide moiety instead of the benzamide moiety (3ca), which indicated the stronger directing ability of the oxamide group for sulfonylation. Substitutions on the phenoxy side of 1 had little impact on the yield. Electron-donating groups (3da, 3ea, 3ia, 3la), electron-withdrawing groups (3ha), as well as halogen groups (3fa, 3ga) were well tolerated, which afforded substituted sulfinilmes in 85% to 92% yield. The C–S bond formation proceeded exclusively at the site ortho to the acetylamino group. Therefore, for substrate 1 with two different ortho-sites, two regioisomers with ratio almost 1:1 were produced (3ja:3ja, 3ka:3ka, 3ma:3ma, 3na:3na). Fusion of a benzene ring as in the substrate of naphthalene did not affect the reaction yield but resulted in high regioselectivity, which only functionalized the ortho C–H at C–1 position, resulting in a 2-naphthol derivative 3oa.

Under optimal conditions, we explored the substrate scope for N-substituted phthalimides (Table 2). The reaction proceeded smoothly for both aliphatic and aromatic thiohiphalimides. Aliphatic groups including trifluoromethyl, linear alkyl and cyclic alkyl gave high yields (3ab–3ad, 76–92%). For aromatic thiohiphalimides, substitutions on the phenyl ring increased the reaction yield (3af–3aj > 3ae). The reaction proceeded well with either electron-donating groups or halogen-containing substrates.

Synthetic application. To further explore the applicability of our method as a useful tool in chemical biology, we conducted the reaction in PBS buffer in air. Gratifyingly, the reaction proceeded well. When the ratio of DMSO to pH 7.4 1 × PBS buffer was 1:19, 81% yield was obtained (Fig. 3a, entry 1). Because of the excellent chemoselectivity under the mild aqeous conditions, we tested the compatibility of the C–S bond coupling reaction with various biomolecules, such as amino acids and proteins. The addition of a stoichiometric amount of amino acids or proteins in standard aqueous conditions did not significantly affect the reaction (Fig. 3a, entry 2–5). Bacterial cell lysates that contained various endogenous biomolecules were also tested and gave product 3aa in 73% yield (Fig. 3a, entry 6). When we started from a non-fluorescent coumarin substrate (1p) to react with 2a under such biomimetic conditions, a fluorescent turn-on process was observed. The fluorescent product 3pa (λex/em = 360/450 nm) was obtained in 80% yield (Fig. 3b).

Finally, we further applied the C–S bond coupling reaction to the first fluorogenic formation of phospholipids. We designed a non-fluorescent coumarin-functionalized analogue of the lysolipid 1-palmitoyl-sn-glycero-3-phosphocholine 1q and a linear alkyl sulfonylation reagent 2k. Phospholipids, which are the major
component of cell membranes, have many important applications such as drug delivery\textsuperscript{51,52}, construction of micro-reactors\textsuperscript{53} and study of protein–membrane interactions\textsuperscript{54}. Pioneered by Devaraj \textit{et al.}, it has been of increasing significance to develop methods for the \textit{de novo} synthesis and assembly of phospholipid membranes\textsuperscript{55–58}. To apply our mild C–S bond coupling reaction to the formation of the lipid vesicle under optimal conditions, we simply mixed compounds 1q and 2k in 0.1 M PBS buffer at pH 7.4 and sonicated the mixture at room temperature for 1h. Blue fluorescent lipid vesicles were observed by the fluorescence microscopy after 3 h at 37°C (Fig. 4c). We confirmed these vesicles were lipid membrane structures by staining with the membrane-staining dye 1,1’-dioctadecyl-3,3’,3’,3’-tetramethylindocarbocyanine perchlorate (DiI), and the orange red fluorescent vesicles were observed, suggesting that fluorescent phospholipid vesicles are lipid membranes (Fig. 4c).

Mechanistic investigation. A combined experimental/computational study was conducted to investigate the reaction mechanism. The cross-over experiment was carried out using a 1:1 mixture of $N$-phenoxyacetamide 1a and its analogue 1a-$d_8$ under the standard conditions, only the intramolecular rearrangement products 3aa and 3aa-$d_8$ were obtained (Supplementary

Figure 1 | Strategy for the formation of ortho-sulfiliminyl phenol derivatives. (a) The mononuclear non-haem iron enzyme EgtB-catalysed sulfonylation formation between $\gamma$-glutamyl cysteine and $N$-$\alpha$-trimethyl histidine. (b) A metal-free approach to ortho-sulfiliminyl phenol via the C–H sulfonylation/intramolecular rearrangement cascade reaction.

Figure 2 | Screening of the X–N functional groups and thiolating reagents. (a) Screening of the multifunctional X–N functional group; reaction conditions: 0.2 mmol substrate 1, $N$-ethylthiophthalimides (1.2 equiv.), $[\text{Cp*RhCl}_2]$\textsubscript{2} (5 mol \%) and CsOAc (0.3 equiv.) in CH$_3$CN (1 ml) at room temperature under N$_2$ for 15 h. (b) Screening of different thiolating reagents with $N$-phenoxyamides. Reaction conditions: 0.2 mmol substrate 1a, 2 (1.2 equiv.) and CsOAc (0.3 equiv.) in MeOH (1 ml) at room temperature for 15 h. Yields are those of isolated products. N.R. = No reaction.
### Table 1 | Substrate scope of aryloxyamides*.

| Reaction | Product | yield [%] | Remarks |
|----------|---------|-----------|---------|
| $\text{R}_1 - \text{O} - \text{N} - \text{R}_2$ | $\text{R}^1 - \text{S} - \text{N} - \text{R}_2$ | $\text{R}^1 - \text{S} - \text{N} - \text{R}_2$ | CsOAc (0.5 eq.), MeOH, r.t., air, 3h |
| $3\text{aa}$ | 92% | CsOAc (0.5 eq.) | MeOH, r.t., air, 3h | Yields are those of isolated products. |
| $3\text{ba}$ | 80% |  |  |
| $3\text{ca}$ | 83% |  |  |
| $3\text{da}$ | 90% |  |  |
| $3\text{ea}$ | 85% |  |  |
| $3\text{fa}$ | 85% |  |  |
| $3\text{ga}$ | 86% |  |  |
| $3\text{ha}$ | 89% |  |  |
| $3\text{oa}$ | 90% |  |  |
| $3\text{ia}$ | 89% |  |  |
| $3\text{ia}$ | 89% |  |  |
| $3\text{ka}$ | 90% |  |  |
| $3\text{ka}$ | 85% |  |  |
| $3\text{ka}$ | 84% (1.05:1) |  |  |
| $3\text{ma}$ | 85% (1.1:1) |  |  |
| $3\text{ma}$ | 85% (1.1:1) |  |  |
| $3\text{na}$ | 86% (1:1) |  |  |
| $3\text{na}$ | 86% (1:1) |  |  |
| $3\text{la}$ | 88% |  |  |
| $3\text{la}$ | 88% |  |  |
| $3\text{la}$ | 88% |  |  |
| $3\text{lb}$ | 88% |  |  |
| $3\text{lb}$ | 88% |  |  |
| $3\text{lb}$ | 88% |  |  |

*Reaction conditions: 0.2 mmol oxyamide, N-ethylthiophthalimides (1.2 equiv.) and CsOAc (0.5 equiv.) in MeOH (1 ml) at room temperature for 3 h. Yields are those of isolated products.

### Table 2 | Substrate scope of $N$-substituted thiophthalimides*.

| Reaction | Product | yield [%] | Remarks |
|----------|---------|-----------|---------|
| $\text{R} - \text{NHAc}$ | $\text{R} - \text{S} - \text{N} - \text{Ac}$ | $\text{R} - \text{S} - \text{N} - \text{Ac}$ | CsOAc (0.5 eq.), MeOH, r.t., air, 3h |
| $3\text{ac}$ | 85% |  |  |
| $3\text{ad}$ | 76% |  |  |
| $3\text{ae}$ | 67% |  |  |
| $3\text{af}$ | 85% |  |  |
| $3\text{ag}$ | 80% |  |  |
| $3\text{ah}$ | 75% |  |  |
| $3\text{ai}$ | 70% |  |  |
| $3\text{aj}$ | 68% |  |  |

*Reaction conditions: 0.2 mmol 1a, $N$-substituted thiophthalimides (1.2 equiv.) and CsOAc (0.5 equiv.) in MeOH (1 ml) at room temperature for 3 h. Yields are those of isolated products.
of oxyacetamides was converted into the corresponding phenols. Functionality tolerance of the reaction conditions, a wide range and efficient method enabled the simultaneous construction of C–S bond coupling reaction in aqueous conditions and in the presence of biomolecules. Conditions: 1a (0.075 mmol), 2a (0.09 mmol), CsOAc (0.5 equiv.), DMSO/PBS buffer = 1:19 (5 ml); the yield was determined by 1H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard. The temperature was RT. (b) Reaction of 1p with 2a in aqueous conditions. Conditions: 1p (0.2 mmol), 2a (0.24 mmol), CsOAc (0.5 equiv.), DMSO/PBS buffer = 1:19 (10 ml); isolated yield. The temperature was RT. (c) Fluorescence spectra of reaction b in aqueous conditions. (d) Photograph showing the visual fluorescence of 1p and 3pa under a 365 nm ultraviolet lamp.

![Diagram](https://example.com/diagram.png)

**Figure 3** | Application of the C-S bond coupling reaction in biocompatible conditions. (a) C-S bond coupling reaction in aqueous conditions and in the presence of biomolecules. Conditions: 1a (0.075 mmol), 2a (0.09 mmol), CsOAc (0.5 equiv.), DMSO/PBS buffer = 1:19 (5 ml); the yield was determined by 1H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard. The temperature was RT. (b) Reaction of 1p with 2a in aqueous conditions. Conditions: 1p (0.2 mmol), 2a (0.24 mmol), CsOAc (0.5 equiv.), DMSO/PBS buffer = 1:19 (10 ml); isolated yield. The temperature was RT. (c) Fluorescence spectra of reaction b in aqueous conditions. (d) Photograph showing the visual fluorescence of 1p and 3pa under a 365 nm ultraviolet lamp.

In summary, we have developed a bioinspired strategy for the synthesis of ortho-sulfyliminyl phenols by internal oxidation-induced sulfur transfer under mild conditions. This efficient method enabled the simultaneous construction of C–S and S=N bonds. Thanks to the mild nature and good functionality tolerance of the reaction conditions, a wide range of oxacyanamides was converted into the corresponding phenols. For the sulfur donors, not only trifluoromethyliothio group (CF3S-) but also a variety of sulfur-containing groups were able to participate in C–H sulfenylation. The sulfur donors included N-substituted thiophalalmides with S-substituted aromatic and aliphatic groups. Moreover, the method utilized the leaving acetamide moiety of the internal oxidant/directing oxacyanamide group to construct a sulfilimine functional group. Our method was successfully applied to the *in situ* formation of fluorogenic phospholipid membranes. To the best of our knowledge, this is the first fluorogenic phospholipid membranes formation. Further applications of the fluorogenic phospholipid membranes are under investigation and will be reported in due course.

**Methods**

**Materials.** For NMR spectra of compounds in this manuscript, see Supplementary Figs 1–32. For the crystallographic data of compound 3aa and 3ab, see Supplementary Figs 33 and 34 and Supplementary Tables 1–5. For the representative experimental procedures and analytic data of compounds synthesized, see Supplementary Methods.

**General procedure of C-S bond coupling reaction.** Aryloxyamide (1) (0.2 mmol), N-substituted thiophalalmides (2) (0.24 mmol) and CsOAc (0.06 mmol or 0.10 mol) were weighed into a 10 ml pressure tube, to which was added MeOH (1 ml). The reaction vessel was stirred at room temperature for 3 h in air. Then the mixture was concentrated under vacuum and the residue was purified by column chromatography on silica gel with a gradient eluent of petroleum ether and ethyl acetate to afford the corresponding product.

**In situ self-assembly of fluorescent vesicles.** An aliquot of 10.0 μl of a 4 mM coumarin-functionalized analogue of the lysolipid 1-palmitoyl-sn-glycero-3-phosphocholine 1q solution in 100 mM PBS buffer pH 7.4 was added to 2.0 μl of a 20 mM solution of sulfenylation reagent 2k in CHCl3. Then, 28 μl of a 100 mM PBS buffer pH 7.4 solution was added, and the mixture was sonicated at room temperature (RT) for 1 h. After 3 h standing at 37 °C, stained with membrane-staining dye DiI, 10 min later, the corresponding mixture was observed by fluorescence microscopy.
**Figure 4 | Synthesis of fluorogenic phospholipids by C–S bond coupling reaction.** (a) Reaction conditions: 1q (4 mM in PBS buffer, 10 μl) and 2k (20 mM in CHCl₃, 2 μl) in PBS buffer PH 7.4 (28 μl) was sonicated at RT for 1 h; (b) Model of spontaneous fluorescent vesicle assembly induced by C–S bond coupling reaction; (c) Fluorescent microscopic images of phospholipid vesicles. Conditions: 1q (4 mM in PBS buffer), 10 μl and 2k (20 mM in CHCl₃, 2 μl) in PBS buffer PH 7.4 (28 μl) was sonicated at RT for 1 h, after 3 h standing at 37 °C, stained with Dil before being imaged on the fluorescence microscopy. Scale bar, 20 μm.

**Data availability.** The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC1041436 and CCDC983618. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The authors declare that all other data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author upon reasonable request.

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