Sulfur-sulfur motifs widely occur in vital function and drug design, which yearns for polysulfide construction in an efficient manner. However, it is a great challenge to install desired functional groups on both sides of sulfur-sulfur bonds at liberty. Herein, we designed a mesocyclic bilateral disulfurating reagent for sequential assembly and modular installation of polysulfides. Based on S-O bond dissociation energy imparity (mesocyclic compared to linear imparity is at least 5.34 kcal mol$^{-1}$ higher), diverse types of functional molecules can be bridged via sulfur-sulfur bonds distinctly. With these stable reagents, excellent reactivities with nucleophiles including C, N and S are comprehensively demonstrated, sequentially installing on both sides of sulfur-sulfur motif with various substituents to afford six species of unsymmetrical polysulfides including di-, tri- and even tetra-sulfides. Life-related molecules, natural products and pharmaceuticals can be successively cross-linked with sulfur-sulfur bond. Remarkably, the cyclization of tri- and tetra-peptides affords 15- and 18-membered cyclic disulfide peptides with this reagent, respectively.
Sulfur–sulfur bond has unique and significant roles in biological, pharmaceutical, and material fields. In organism, tertiary structures of proteins are fixed and stabilized via the linkage of sulfur–sulfur bridge among secondary structures, contributing to the versatility of proteins with complex three-dimensional structure (Fig. 1a)1,2. Polysulfides such as trisulfides and tetrakisulfides are primary H2S donors3, signaling of which endogenous gasotransmitter occurs via persulfdation of cysteine residues (RSH) to persulfs (RSSH) in proteins4 with the reduction of glutathione5 (Fig. 1b). As a power linker, sulfur–sulfur bridges cyclized peptide drugs with higher stability, activity, and potency compared with corresponding linear ones (Fig. 1c)6. Given the excellent metabolism of sulfur activity, and potency compared with corresponding linear ones when delivered to the target cells (Fig. 1d)16. Furthermore, grammatically released relying on the reduction of glutathione de30 when application of mesocyclic bilateral disulfide 2f under the assistance of weak base lithium carbonate, affording unsymmetrical diaza-disulfides 3 in Fig. 4. Diverse anilines bearing electron-withdrawing and electron-donating functional groups could be cross-linked with benzyl amines, straight-chain alkylamines, dialkylamine, pyridyl methylamine, tryptamine, and even amino-acid esters at liberty (3a–3j). The unsymmetrical diaza-disulfide structure of 3a was further confirmed through X-ray analysis. Among them, compound 3d was afforded with a yield of 55% with occurrence of the polymerization of vinyl group accelerated by B(C6F5)3 as catalyst (Fig. 3b). As expected, linear disulfurating reagents 1a and 1b resulted in poor selectivities between two S-O/N bonds, bringing mixture when coupling with aniline. Cyclic diaminodisulfide 1c refused to transfer disulfur owing to weak reactivity. Cyclic disulfane 1d and 1e failed to generate mono-coupling product 2 owing to the decomposition of starting material. Mono-aza-disulfide 2f was quantitatively obtained when 10-membered disulfane 1f was employed as a disulfurating reagent (for details, see the Supplementary Table 1).

Since the first S-O cleavage was controllably realized, another nucleophile was subsequently subjected to azadiisulfide 2f under the assistance of weak base lithium carbonate, affording unsymmetrical diaza-disulfides 3 in Fig. 4. Diverse anilines bearing electron-withdrawing and electron-donating functional groups could be cross-linked with benzyl amines, straight-chain alkylamines, dialkylamine, pyridyl methylamine, tryptamine, and even amino-acid esters at liberty (3a–3j). The unsymmetrical diaza-disulfide structure of 3a was further confirmed through X-ray analysis. Among them, compound 3d was afforded with a yield of 55% with occurrence of the polymerization of vinyl group accelerated by B(C6F5)3 as catalyst (Fig. 3b). As expected, linear disulfurating reagents 1a and 1b resulted in poor selectivities between two S-O/N bonds, bringing mixture when coupling with aniline. Cyclic diaminodisulfide 1c refused to transfer disulfur owing to weak reactivity. Cyclic disulfane 1d and 1e failed to generate mono-coupling product 2 owing to the decomposition of starting material. Mono-aza-disulfide 2f was quantitatively obtained when 10-membered disulfane 1f was employed as a disulfurating reagent (for details, see the Supplementary Table 1).

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3o). Notably, sulfamethazine and sulfamethoxazole could be successfully linked with different peptides in good yields (3p and 3q), which displayed a great potential for the synthesis of SMDCs drugs. Besides, the antibacterial sulfamethazine and cinacalcet, a kind of calcimimetics, could be connected efficiently in good yield (3r). With this strategy, amines could be cross-linked with mercaptans via disulfur motif, affording aza-trisulfides smoothly. Both electron donor and acceptor substituted anilines were applied in the connection compatibly (4a–4g). Weak nucleophilic thiophenol, straight-chain dodecamercaptan, electron-rich furfuryl mercaptan, electron-deficient 2-mercaptopyrimidine, and even cysteine could be successfully introduced in this connection to afford aza-trisulfides (4h–4m). Tryptamine, peptide, amines with sensitive enamine structure, even sulfonamides like sulfamethazine, sulfacetamide and sulfamethoxazole were cross-linked with thiols by disulfur perfectly (4n–4s), which supplies an efficient protocol for drug-linkage. Interestingly, we successfully synthesized an aza-trisulfide with a long chain of thirty-four-atoms via this method (4t). Tripeptides like H-Ala-Phe-Lys-OMe could be cyclized to form 15-membered cyclic peptides (5a) and tetrapeptides like H-Ala-Phe-Trp-Lys-OMe could be cyclized to form 18-membered cyclic peptides (5b) under the standard conditions (Fig. 5).

### Table: Linear vs. Cyclic Disulfurating Reagents

| Linear disulfurating reagents | Cyclic disulfurating reagents |
|------------------------------|------------------------------|
| $\Delta E_2 - \Delta E_1$ (kcal mol$^{-1}$) | $\Delta E_2 - \Delta E_1$ (kcal mol$^{-1}$) |
| -0.12                         | 9.53                         |
| 5.22                          | 5.22                         |

### Fig. 2 The significance and challenge of bilateral disulfurating reagents.

**a** The significance of bilateral disulfurating reagents. **b** The challenge of bilateral disulfurating reagents. The challenge: how to differentiate two S-O bonds.

### Fig. 3 Screening of bilateral disulfurating reagents.

**a** Conditions of disulfurating reagents synthesis. Yields are based on a 10 or 20 mmol scale reaction after silica gel flash chromatography. **b** Sequent reactivity of disulfurating reagents. Aniline (0.10 mmol), 1 (0.105 mmol), B(C$_6$F$_5$)$_3$ (0.001 mmol, 1 mol%), 1,4-dioxane. Isolated yields.
Fig. 4 Coupling with amines. Amine (0.10 mmol), 1f (0.105 mmol, 1.05 equiv), B(C₆F₅)₃ (0.001 mmol, 1 mol%), dioxane, rt, 4 h, then aliphatic amine or mercaptan (0.11 mmol, 1.1 equiv), Li₂CO₃, 4 h, rt. Isolated yields. Ad Adamantyl. *MeCN instead of dioxane.

Syntheses of aza-disulfides 6, trisulfides 7 and disulfides 8. Furthermore, we established the cross-linkage between carbon and nucleophiles with phenyl boric acid and bilateral disulfurating reagent 1f as coupling partner first (Fig. 6). With the optimized conditions, mono-coupling was obtained in 84% yield (for details see the Supplementary Table 2). Investigating on nucleophiles, diverse aromatic rings were cross-linked with amines, mercaptans, and electron-rich aromatics modularly, affording aza-disulfides, trisulfides, and diaryl disulfides, respectively. The arylboronic acids substituted with electron-withdrawing and donating functional groups afforded the corresponding aza-disulfides readily (6a–6f, 7b–7g, and 8h). Arylboronic acids derived from 1-tyrosine and estrone were compatible in the cross-linkage, affording a pathway to late-stage modification of natural products (6g and 7h), though the slow rate of transmetallation of boric acid with Cu[III] brought about...
Fig. 5 Coupling with linear peptides. Diamine (0.2 mmol), 1f (0.2 mmol), DCM, B(C₆F₅)₃ (0.01 mmol, 5 mol%), 8 h. Isolated yields. Ring sizes are listed with a gray background.

Aromatic-amine cross-linkage

6a R¹ = H, R² = CH₃
6b R¹ = Cl, R² = tBu
6c (75%) 6d (68%) 6e (83%)
6f (67%)*

Aromatic-mercaptan cross-linkage

7a (75%) 7b (65%) 7c (63%) 7d (80%)
7e (52%) 7f (52%) 7g (60%) 7h (34%)

Aromatic-aromatic cross-linkage

8a (56%) 8b (59%) 8c (76%) 8d (48%)
8e (48%) 8f (65%)

Fig. 6 Mono-coupling with arylboronic acids. Conditions: Arylboronic acid (0.15 mmol, 1.5 equiv), 1f (0.1 mmol), Cu(MeCN)₄PF₆ (0.01 mmol, 10 mol%), 2,2'-bpy (0.02 mmol, 20 mol%), DCM (1 mL), then NuH (0.12 mmol, 1.2 equiv), B(C₆F₅)₃ (0.001 mmol, 1 mol%). Isolated yields. *PhMe (1 mL) as solvent in second step.
insufficient efficiency in the first step. The scope of amine is quite broad when it is served as a nucleophile. Anilines (6a and 6b), aliphatic amines (6c–6e), amino-acid esters (6f and 6g), and antibiotic sulfamethazine (6h) were all efficiently transformed to the corresponding aza-disulﬁdes in moderate yields. Trisulﬁdes could be easily obtained when mercaptans were applied in the cross-coupling. Arylthiophenol like 2-mercaptopyrimidine provided diaryl trisulﬁde (7a). Other thiols even containing hydroxyl (7b) and triethoxysilyl ether (7h) could afforded trisulﬁdes in moderate yields. Sterically bulky aliphatic thiols, such as tert-butylthiol and 1-adamantanethiol, showed great reactivity in this reaction (7e and 7f). Furthermore, cysteine derivatives were successfully converted to trisulﬁde derivatives (7d). Diaryl disulﬁdes were generated when electron-rich aromatics were accommodated under the standard conditions. (+)-8-Tocopherol, a kind of vitamin E, could be disulfurated directly despite of the presence of free hydroxyl group (8b) under nitrogen atmosphere. Indole derivatives were excellent reactants even there is a free amino group (8c). Heterocycles like thiophene could be connected in the reaction as well (8g). The 2-position of N-methyl pyrrole possesses sufﬁcient reactivity in the reaction (8h). The structure of 8f was further conﬁrmed through X-ray analysis.

**Synthesis of tetrathios.** Unsymmetrical tetrathios was a challenging subject in organic synthesis, but the connection between two different mercaptans with 1d as a disulphurating reagent afforded the desired tetrathios highly efﬁciently, owing to large difference between two S-O bonds of eight-membered 1d (9.53 kcal mol−1) (for details see the Supplementary Table 3). The unsymmetrical tetrathios linkage was comprehensively investigated in Fig. 7. Pyrimidine and pyrazine can be easily accommodated under the standard conditions (9a–9c). The structure of 9a was further conﬁrmed through X-ray analysis as a linear tetrathio. Penicillamine and cysteine, two different amino acids, were cross-linked with tetrasulfur fragment via this method (9d). Cysteine (9e), tripeptide (9f), and even glucosinolate (9g) could be cross-linked with 1-adamanthethiol, forming unsymmetrical tetrathios. Sensitive thiols, which even contained hydroxyl and triethoxysilyl ether, could afforded tetrathios (9h). Remarkably, volatile and low-polar allicin analog was modularly provided when propanethiol and allyl mercaptan were used as nucleophiles (9i).

Bilateral reagents 1d and 1f are odorless and stable solid stored at −10°C regardless of air and water. No decomposition was observed even after 5 months, whereas they will deteriorate at room temperature after 24 h. With these designed bilateral reagents, we have established six different kinds of polysulﬁdes, most of which are quite stable under room temperature except aza-trisulﬁdes. They need to be stored in fridge (−10°C) for long-term preservation. Diazasulﬁdes, aza-trisulﬁde, aza-disulﬁde, and tetrathios are fragile to acidic conditions.

S2Cl2, a common disulphur structure, hardly achieves multiple heteroatom hybrid connection on account of its fractious activity and strong acidity. Taking synthesis of 9a as an example, the selectivity of 9a to 9a-S3 is 2.5:1 when S2Cl2 was involved, much lower than 15:1 afforded by our reagent 1d. Besides, there is a huge gap between the efficiency afforded by S2Cl2 and 1d (8% vs 70%) (Fig. 8a). Di(1-phthalimidyl)disulfane (1b) reagent developed by Harpp’s group which avoids the disadvantage of acidity with S2Cl2, still remains less selective and efﬁcient owing to the non-distinctive S-N bonds. For instance, Harpp’s reagent gave a mono-coupling product only in 30% and a bis-coupling byproduct in 60% in the ﬁrst step coupling with aniline. Optimistically, quantitative yield of 2f could be obtained with our reagent 1f (Fig. 8b).

**Discussion**

In summary, based on S-O bond dissociation energy nuance, a series of mesocyclic bilateral disulphurating reagents were designed for constructing six species of unsymmetrical polysulﬁdes. Disulphides, tetrathios and trisulﬁdes can be accurately achieved with amines, mercaptans, arylboronic acids, and electron-rich aromatic molecules. A considerable range of signiﬁcant life-related molecules, such as sulfonamides, amino acids, peptides, glucosinolate, vitamin E, and estrene could be cross-linked at will with disulphur bridge to form varieties of diverse functional molecules, which showcases great potential for application of SMDCs and ADCs. Readily available linear
peptide precursors can be tied up with disulfur fragment to form unique cyclic peptides with a tetraheteroatomic motif. Drug discovery with polysulfides is undergoing in our laboratory.

**Methods**

**General procedure for syntheses of diaza-disulfides 3 and azaa-disulﬁdes 4.** To a Schlenk tube were added amine (0.1 mmol, 1.0 equiv), B(C₆F₅)₃ (0.5 mg, 1 mol%), and Li₂CO₃ (7.4 mg, 0.1 mmol) were added to the mixture at r.t. for 4 h to obtain 4f. After amine was consumed, another amine (0.12 mmol, 1.2 equiv) or thiol (0.11 mmol, 1.1 equiv) and Li₂CO₃ (7.4 mg, 0.1 mmol) were added to the mixture. The mixture was stirred at r.t. for 8–24 h before it was concentrated under vacuum. Purification by column chromatography afforded the desired product 3 or 4.

**General procedure for syntheses of aza-disulfides 6, trisulfides 7, and disulfides 8.** To a Schlenk tube were added arylboronic acid (0.15 mmol, 1.5 equiv), Cu(MeCN)₂PF₆ (3.7 mg, 10 mol%), bpy (3.1 mg, 20 mol%), and redistilled CH₂Cl₂ (1 mL), the mixture was stirred at r.t. for 10 h under N₂ atmosphere. After 8f was consumed, another nucleophile (0.12 mmol, 1.2 equiv) was added to the mixture. The mixture was stirred at r.t. for 8 h under air before it was concentrated under vacuum. Purification by column chromatography afforded the desired product 6, 7, or 8.

**General procedure for syntheses of tetrasulfides 9.** To a solution of 1d (24.0 mg, 0.12 mmol) in MeOH (1 mL) was added thiol (0.1 mmol, 1.0 equiv) in MeOH (1 mL) dropwise at ~78 °C, then the mixture was stirred at ~78 °C for 30 min before MeOH was removed under vacuum. CH₂Cl₂ (1 mL), another thiol (0.11 mmol, 1.1 equiv) and B(C₆F₅)₃ (0.5 mg, 0.001 mmol, 1 mol%) was added to the mixture at r.t. for 4 h under air before it was concentrated under vacuum. Purification by column chromatography afforded the desired product 9.

**Data availability**

The X-ray crystallographic coordinates for the structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC-1941481 (1f), 1941479 (3a), 1941480 (4d), 1941478 (8f), and 1941482 (9a). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Source data are provided with this paper.

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Author contributions

X.J. conceived the idea and supervised the whole project. I.X. designed and carried out the experiments. X.J. and I.X. discussed the results, contributed to writing the manuscript, and commented on the manuscript. All authors approved the final version of the manuscript for submission.

Competing interests

The authors declare no competing interests.

Additional information

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