Redox-Click Chemistry for Disulfide Formation from Thiols

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Abstract: The dynamic disulfide linkage plays a vital role in various biological processes as well as drugs and biomaterials. Oxidation of thiols is a widely utilized approach for disulfide synthesis; however, achieving both optimal reactivity and selectivity continues to pose a significant challenge. Here, we report the redox-click chemistry for disulfide formation from thiols by sulfonyl fluorides in both batch and flow-mode. Sulfuryl fluoride is a potent oxidant with exceptional selectivity toward thiols. This reaction's unique characteristics satisfy click chemistry's stringent criteria with its high thermodynamic driving force, simple reaction conditions, wide scope, quantitative yields, exceptional chemoselectivity, and non-chromatographic purification process. Furthermore, the redox click chemistry's ability to joining various modular thiol units was showcased in the synthesis of symmetrical, unsymmetrical and cyclic disulfides, poly(disulfide)s, and the *in vivo* disulfide cross-linked biomedical hydrogels.

One-Sentence Summary: Redox-click chemistry allows simple and reliable construction of disulfide linkages from thiols in complex reaction medium.

Main Text: In nature, disulfide bonds are crucial for protein folding and stability (*1*), as well as a prevalent moiety in drugs and biomaterials (Fig.1). The dynamic nature of disulfide bonds makes them an attractive reversible linkage for on-demand drug delivery (*2-11*). Recently, biodegradable cell-penetrating poly(disulfide)s have been employed to deliver drugs, nucleic acids, and proteins into cells *via* thiol-mediated uptake pathways (Fig. 1B) (*4*, *5*). Moreover, antibody-drug conjugates (ADCs) emerged as a significant class of cancer therapeutics, with disulfides used as the predominant chemically cleavable motifs in ADC linkers (Fig. 1C) (*6*). Disulfide-containing polymers, owing to their inherent biodegradability and biocompatibility, also serve as biomaterials and are extensively utilized in tissue engineering and wound healing applications (Fig. 1D) (*7-11*). Considering the importance of disulfide linkages in drugs, natural products, and biomaterials, it is imperative to develop highly efficient, selective, and biocompatible synthetic methodologies.

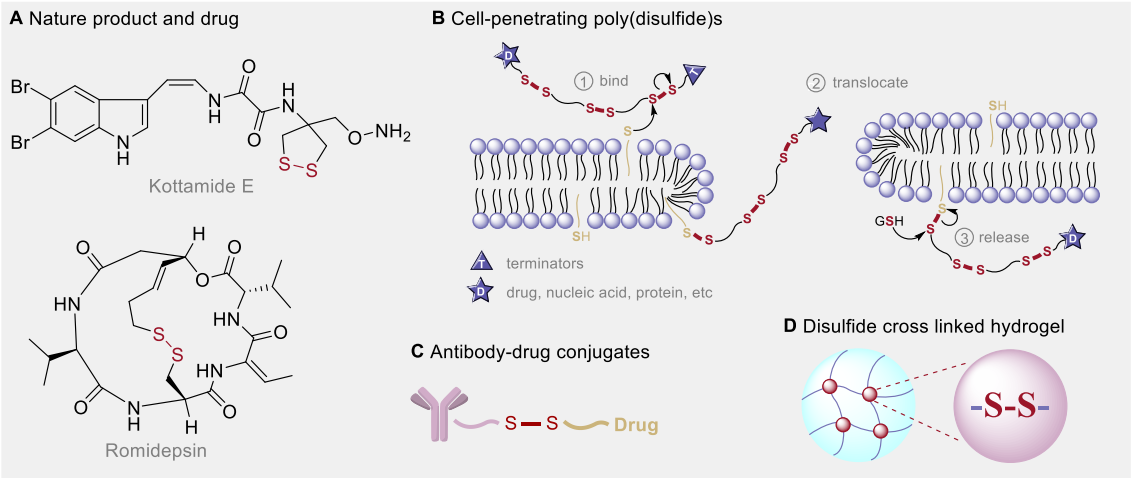


Fig. 1 Applications of disulfides and poly(disulfide)s.

Thiol-disulfide exchange serves as the basis for most *in vivo* enzyme-catalyzed disulfide linkage formation process (*12*). As for the chemical synthesis of disulfides, the oxidation of thiols is the most straightforward route, because a vast number of thiols are readily available. Thiol oxidation can be accomplished by many oxidants (*2*, *13-23*). However, perfect reactivity and selectivity cannot be achieved simultaneously by any known oxidants (Fig. 2A). The unsatisfactory selectivity was exemplified by the formation of over-oxidized by-products and the oxidation of non-target functional group when strong oxidants and/or excessive oxidants were used (*2*, *13*). In addition, methods for the selective cross-coupling of two different thiols are rare (*18-22*). Conversely, the absence of an extremely reactive oxidizing agent has rendered the oxidation process of tertiary thiols, as well as the oxidative polymerization of dithiols, challenging to achieve (*2*, *13*). In fact, valuable poly(disulfide)s have to be prepared from ring-opening thiol-disulfide exchange polymerization or *via* polymerization of monomers that already contain disulfide moiety (*7*). Due to the lack of reliable synthetic approach, many potentially valuable S-S bond containing small molecules or polymers are yet to be explored. Furthermore, the toxicity of many of the oxidants or catalysts have made the formation of S-S linkage under physiological conditions impossible.

In this work, we aim to develop a redox-click chemistry for the reliable S-S bond formation from thiols. In 2001, click chemistry was articulated by Sharpless and co-workers for the first time (*24*). In order to fulfill the rigorous criteria of click chemistry, a reaction must exhibit exceptional selectivity and efficiency, necessitate straightforward procedures, and generate inoffensive products. Over the last two decades, only a handful of essential click reactions have emerged that

enable the formation of reliable connectivity with unparalleled efficiency. Among these reactions are the sulfur(VI)- fluoride exchange (SuFEx) processes developed by Sharpless, Moses and co-workers (*25-32*). These click chemistries have quickly impacted fields from organic synthesis and material science, to chemical biology and drug discovery.

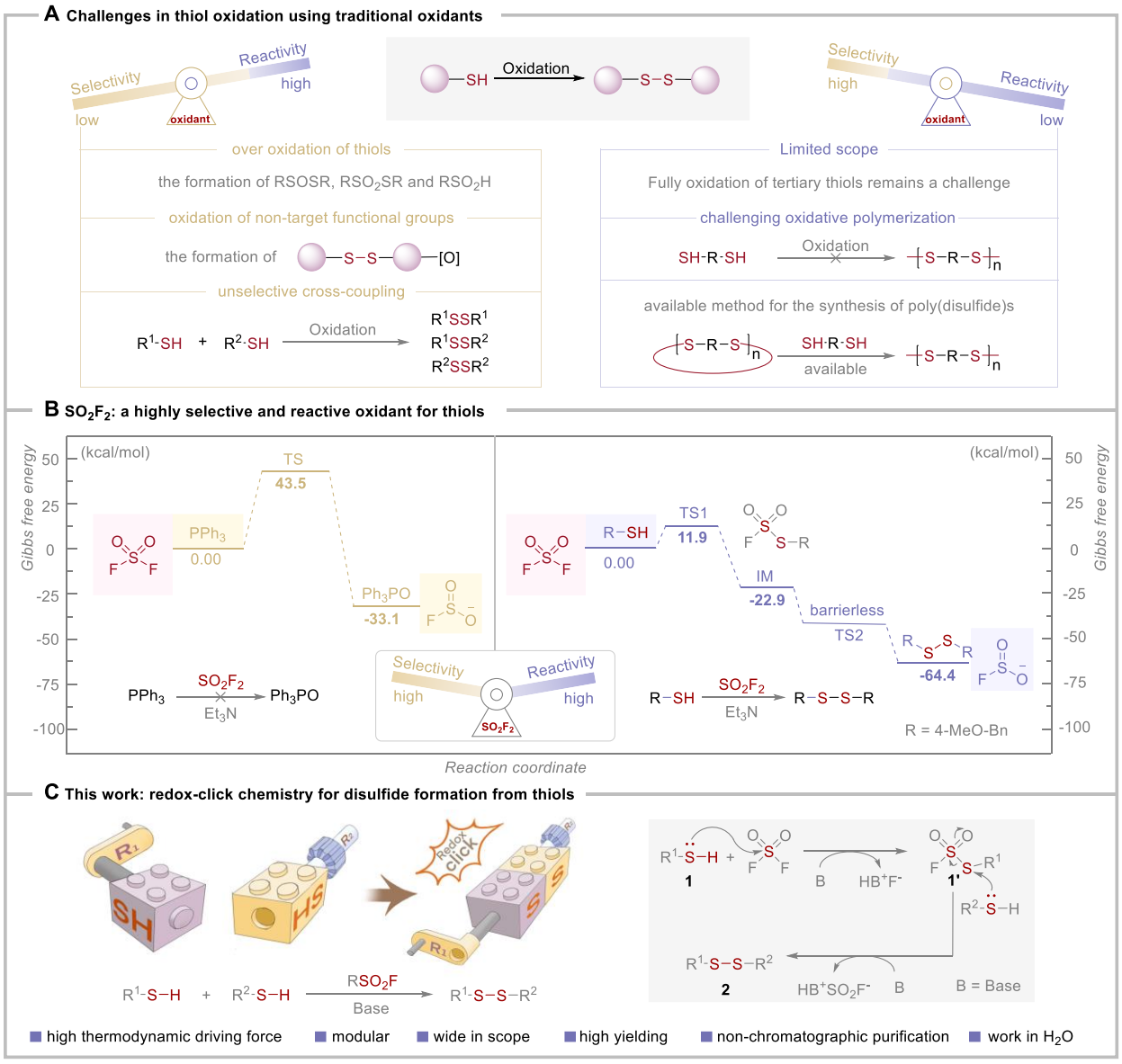


Fig.2 Oxidants for thiol oxidation and redox-click chemistry

Development of Redox-Click Reaction

A redox reaction that meets the criteria of click chemistry is yet to be discovered. The key to developing the redox-click chemistry for S-S linkage formation is a highly reactive and selective oxidant, which should be a potent oxidant with a low kinetic barrier specifically for thiol oxidation. As a high valent sulfur oxidant, SO_2Cl_2 is effective for the oxidation of primary and secondary thiols. However, its low chemoselectivity and high reactivity towards hydrolysis and nucleophilic reaction with non-target functional groups have rendered it less appealing. In contrast, its analogy SO_2F_2, a gaseous S^{VI} compound known as a fumigant and produced on a million-kilogram scale annually (*33*), exhibits remarkable stability and ability to persist in water at 150 °C (*34*). SO_2F_2 is

also an oxidant. However, the S-F bond is much stronger compared with S-Cl bond and its cleavage is almost exclusively heterolytic with the formation of fluoride ion (*35*). Therefore, SO_2F_2 cannot be reduced by most of the known reductant because of the high kinetic barrier. For example, triphenylphosphine, a widely used reductant (*36*), can be oxidized by sulfuryl chloride rapidly at r.t (*37*), but the reaction between sulfuryl fluoride and triphenylphosphine is very slow even at elevated temperature (calculated barrier, 43.5 kcal/mol; Fig 2B) (*38*).

In our study, we intriguingly observed that SO_2F_2 can be quickly reduced by thiol through a two-step process (Fig 2B and 2C). In this thiol oxidation using SO_2F_2, the high thermodynamic driving force, calculated 64.4 kcal/mol, renders the reaction "spring-loaded" for a unidirectional trajectory (Fig. 2C). During the first step (**1→1'**, Fig. 2C), SO_2F_2 was attacked by thiol under basic conditions, resulting in intermediate **1'** (calculated barrier, 11.9 kcal/mol). In the second step, the highly reactive oxidant **1'** was reduced by an additional molecule of thiol, yielding disulfide as the final product. Disulfide is capable of oxidizing triphenylphosphine (*39*); however, triphenylphosphine remains resistant to oxidation by SO_2F_2, a more potent oxidant, as a significant kinetic barrier inhibits the process (calculated barrier, 43.5 kcal/mol). In accordance with theoretical predictions, our experimental findings demonstrated that thiol effectively catalyzed the oxidation of triphenylphosphine by SO_2F_2, thus validating that the oxidation of thiol by SO_2F_2 possesses a considerably lower activation energy in comparison to the oxidation of other species, such as triphenylphosphine (Fig. S2). Owing to the distinctive mechanism of thiol oxidation by SO_2F_2, this reaction exhibits exceptional efficiency and selectivity. The oxidation of other functional groups and any over-oxidation side reactions can be completely prevented.

As we started to optimize the reaction conditions, we discovered that thiol oxidation by SO_2F_2 required only simple conditions with weak base and exhibited insensitivity towards the reaction medium and oxygen (Table S1 - S3, S5, S8). This reaction preceded well at room temperatures. Both organic base, such as Et_3N, and inorganic base, for instance Na_2CO_3 were appropriately capable to trigger reaction. Excellent yields have been obtained in both water and organic solvents, like CH_3CN. Given that only inoffensive fluoride salt was formed as the byproduct, the product can be purified utilizing simple nonchromatographic method. Apart from SO_2F_2 gas, a range of bench-stable solid surrogates to SO_2F_2, namely, sulfamoyl fluorides **II**, sulfonyl fluorides **III** and **IV**, and fluorosulfates **V** could all successfully convert thiols into the corresponding disulfides, with varied reactivity. Based on extensive experimentations, their order of reactivity was as follows: $SO_2F_2 \approx -NSO_2F > -CSO_2F > -OSO_2F$. This redox click reaction's ability to link various modular thiol units was investigated in the synthesis small-molecule disulfides, poly(disulfide)s and *in vivo* disulfide cross linked hydrogels (Fig. 2-4).

Modular synthesis of small molecules

This method was applied in the synthesis of symmetric, unsymmetrical and cyclic disulfides using SO_2F_2/Et_3N in CH_3CN (Fig. 3). The experimental findings revealed that this reaction exhibited wide scope, quantitative yields and excellent chemoselectivity. All the 31 aliphatic and aromatic thiols surveyed were efficiently converted into the corresponding symmetric disulfides with excellent yields of ≥98% (Fig. 3A), including traditionally challenging substrates such as secondary and tertiary thiols (**2ab**, **2ac**, **2ad**). This method accommodated an array of functional groups, including aniline (**2l**, **2r**), carboxylic acid (**2t**, **2ae**), ketone (**2ac**), halide (**2c**, **2d**, **2i**, **2j**, **2k**, **2p**, **2q**, **2s**), amide (**2n**, **2ae**) and heterocycle (**2u**, **2v**, **2w**, **2x**). Captopril (**2ae**), a medicine, was also smoothly oxidized. Besides, over-oxidized by-product was not observed in any experiment.

The symmetric disulfide synthesis using representative solid state -SO_2F surrogates (**II** - **V**) was also studied (Fig. 3A). The results revealed that all those reagents were as effective as SO_2F_2 for the oxidation of benzyl thiols and thiophenols. Remarkable chemoselectivity over phenol and aniline can be attained through the employment of less reactive reagent **III**. Although phenol and aniline could react with SO_2F_2 under basic conditions, **2l** and **2o** underwent selective oxidation while precluding any undesired interference from the phenol or aniline, which might be attributed to the much faster reaction rate between SO_2F_2 and the thiol. In the context of aliphatic thiols,

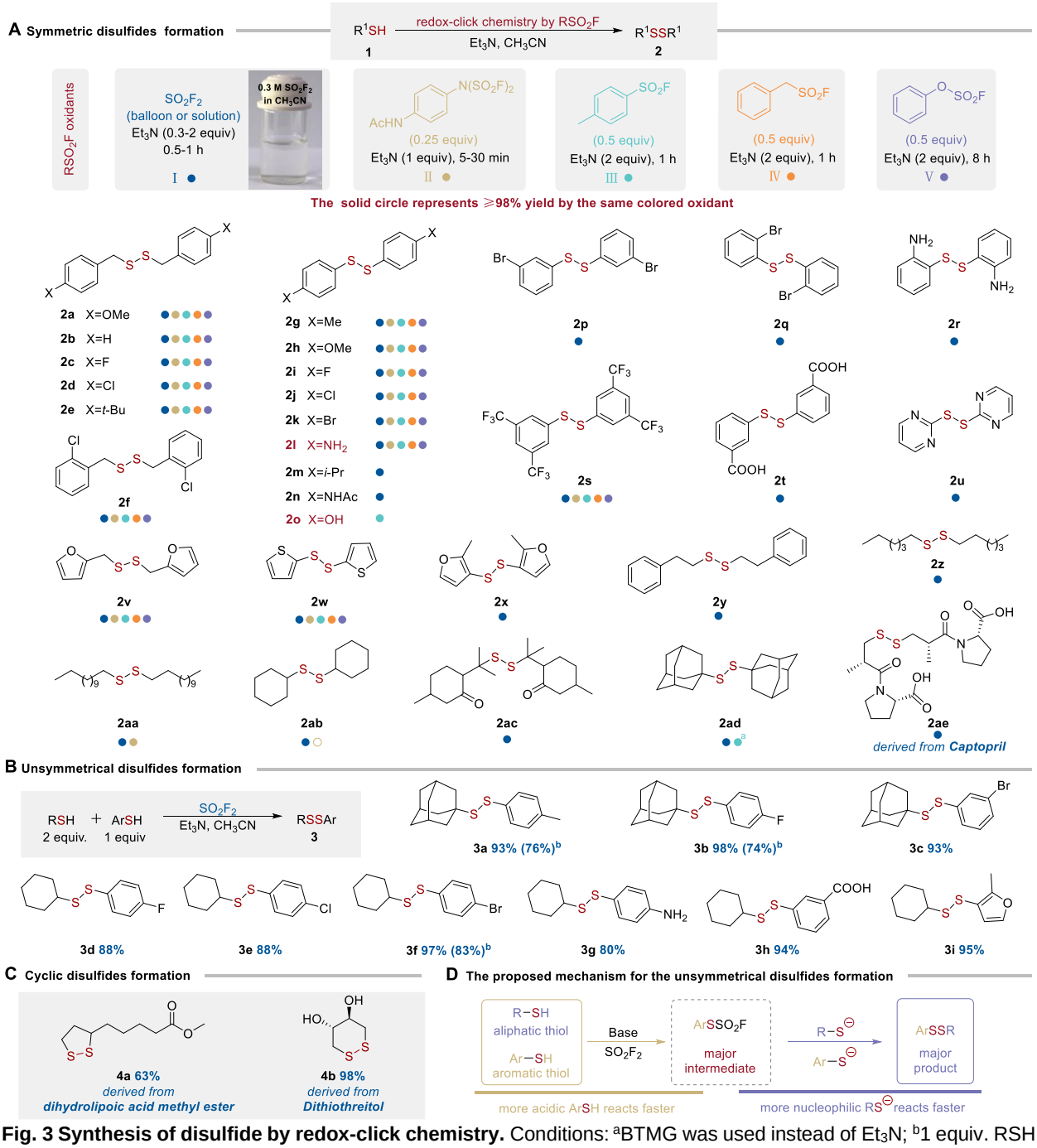


Fig. 3 Synthesis of disulfide by redox-click chemistry. Conditions: [a]BTMG was used instead of Et_3N; [b]1 equiv. RSH was used instead of 2 equiv.

particularly tertiary thiols, quantitative yields were not achieved employing solid state -SO_2F surrogates and Et_3N, as the residual mass balance consisted of unreacted starting materials. However, by substituting Et_3N with a stronger base, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG), the yields can be significantly enhanced. For example, 98% yield of **2ad** was obtained by using oxidant **III** and BTMG.

This redox-click reaction's ability to link two different modules was studied in the direct synthesis of unsymmetrical disulfide using equimolar amount of aromatic thiol and aliphatic thiol as the precursors (Fig. 3B). The reaction between the same amount of **1g** and **1ad** gave 76% of the cross-coupling product with only <15% symmetrical disulfide formed from the competitive homo-coupling reaction. By increasing the amount of the aliphatic thiols to 2 equiv., good yields can be obtained for a range of aromatic thiols (**1g**, **1i-1l**, **1p**, **1t**, **1x**) and aliphatic thiols (**1ab**, **1ad**). To explain the unusual selectivity of this cross-coupling reaction, a series of controlled reaction were conducted (see SI 13 for details). The findings indicated that, in the sulfonylation step, the comparatively more acidic aromatic thiols exhibited a swifter reaction with SO_2F_2 as opposed to aliphatic thiols. Therefore, $ArSSO_2F$ was formed as the major intermediate. During the second step, the reaction rate between $ArSSO_2F$ and the thiolate anion was dominated by the nucleophilicity of thiolate anion. Thiolate anion derived from the aliphatic thiol was more nucleophilic than that derived from the aromatic thiol, which led to the formation of ArSSR as the major final product (Fig. 3D).

In addition, the oxidation of unsymmetrical 1,3- and 1,4-dithiols (dihydrolipoic acid methyl ester and dithiothreitol) was also examined, which gave five- and six-membered cyclic disulfides (**4a** and **4b**) with 63% and 98% yields, respectively (Fig. 3C).

Redox-click chemistry in water

Upon investigating the scope of this redox-click reaction in organic solvent, we subsequently established its efficacy under aqueous and more complex physiological conditions (Fig. 4). Primarily, for water-soluble substrates, like poly(ethylene glycol) methyl ether thiol (mPEG-SH), water may serve as an appropriate solvent in conjunction with water-soluble inorganic bases. For example, mPEG-SH was converted into **2ah** with 98% yield using SO_2F_2/Na_2CO_3 in water. Given the importance of organic reactions compatible with biological media for numerous biological and medical applications, we further assessed the reaction in intricate biological media and under physiological pH conditions. Our findings revealed that, in the medium of bovine serum albumin, mPEG-SH could be oxidized to the corresponding disulfide with a 98% yield, utilizing SO_2F_2/Na_2CO_3. Moreover, under physiological pH conditions maintained by a borax buffer, boc-*L*-cysteine and glutathione were successfully converted to the corresponding disulfides **2af** and **2ag**, achieving yields of 85% and 98%, respectively, when mediated by SO_2F_2/Et_3N.

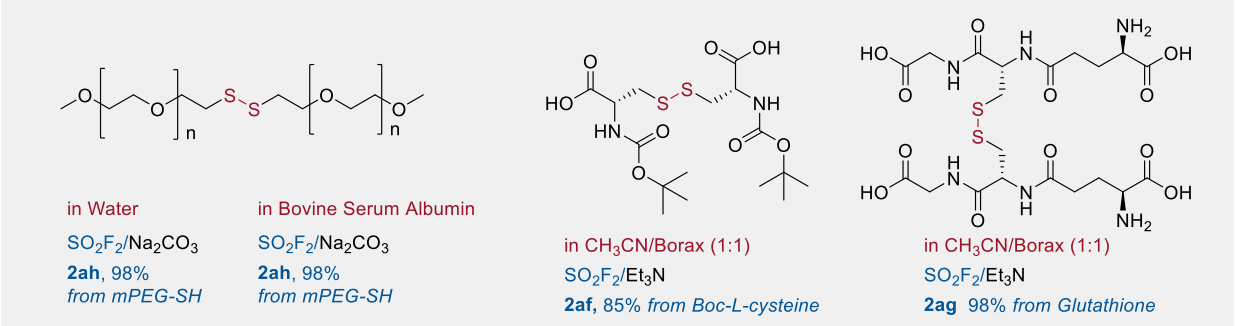


Fig. 4 Application of the redox-click chemistry in various reaction medium

Flow-click chemistry

To enhance the prospective industrial applicability of this reaction and facilitate its large-scale implementation, we have devised a tube-in-tube flow-click chemistry apparatus tailored for the efficient synthesis of disulfides (Fig. 5). In this apparatus, the inner tube was filled with SO_2F_2, which diffused through the inner tube's wall into the solution of the thiol and base situated between the inner and outer tubes, thereby triggering the oxidation of thiols. The outer tube was fabricated with Teflon, while the inner tube was constructed from a polyvinylidene fluoride microporous hollow fiber membrane. The hollow fiber membrane, an inexpensive and readily accessible semipermeable material, is commonly employed in water treatment processes. Owing to its high specific surface area and exceptional mass-transfer properties, the hollow fiber membrane effectively facilitated the mixing of gaseous SO_2F_2 within the inner tube and the liquid reaction mixture present in the outer tube. This work represented the first application of the hollow fiber membrane in gas-liquid flow chemistry (*40*). By sealing the inner tube's terminus with a balloon, the potential leakage of SO_2F_2 was effectively circumvented. The reactor shown in Fig. 5 has been used in the oxidation of captopril and glutathione which gave >95% yields and a production rate of 5 mmoL/h. The potential for further scale-up of this reactor can be efficiently realized by implementing multiple parallel tubes in the design. Additionally, the reactor demonstrates versatility as it is well-suited for the scale-up of other gas-liquid reactions (see SI 14 for details).

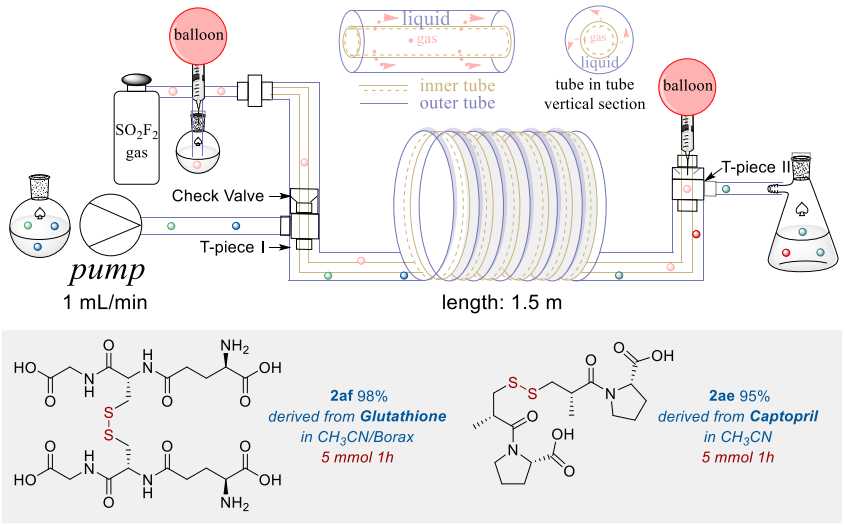


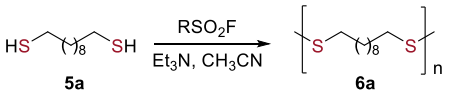
Fig. 5 Tube-in-tube flow-click chemistry for large scale disulfide synthesis

Modular synthesis of poly(disulfide)s

Subsequently, this reaction's ability to link modular thiols was further demonstrated in the synthesis of polymers (Tables 1 and 2). Traditionally, oxidative polymerization of dithiols was very challenging. In this study, the oxidative polymerization was investigated using a hydrophobic monomer **5a** and a hydrophilic monomer **5b** as models. Monomer **5a** underwent complete polymerization within a duration of 0.5 hours by employing SO_2F_2/Et_3N or reagent **II**/Et_3N in organic solvent (Table 1). In the case of **5b**, the utilization of either organic base/solvent or inorganic base/water was feasible (Table 2). It was noteworthy that crucial parameters, including average molecular weight and the polydispersity index (PDI), exhibited a decrease in correlation to the increment of Et_3N concentration (entries 1-3, Table 1). Replacing SO_2F_2 with reagent **II** resulted in smaller average molecular weight and larger polydispersity index (entry 4, Table 1). Under the aqueous polymerization conditions, the utilization of a stronger base NaOH instead of

a weaker base Na_2CO_3 resulted in a higher average molecular weight and smaller polydispersity index of the polymer (entries 3-4, Table 2). The rapid and controllable oxidative polymerization of dithiols accomplished by our redox-click reaction will enable the preparation of various poly(disulfide)s to meet the different requirements for drug delivery and biomaterial synthesis.

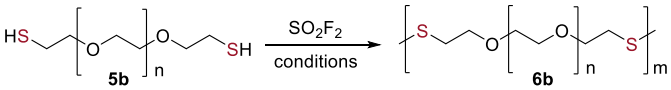
Table 1. Oxidative polymerization of 5a



5a 6a

Entry	RSO_2F	Base/equiv	Mn^{ps}/ kDa	PDI
1	SO_2F_2	Et_3N/4	13.6	1.44
2	SO_2F_2	Et_3N/6	22.1	1.25
3	SO_2F_2	Et_3N/8	26.6	1.16
4	II	Et_3N/6	4.68	1.43

Table 2. Oxidative polymerization of 6a



5b 6b

Entry	Base/equiv	Solvent	Mn^{ps}/ kDa	PDI
1	Et_3N/6	CH_3CN	14.5	1.09
2	Et_3N/6	H_2O	9.90	1.23
3	Na_2CO_3/10	H_2O	5.78	1.46
4	NaOH/10	H_2O	17.0	1.06

***In situ* gelation by redox-click reaction**

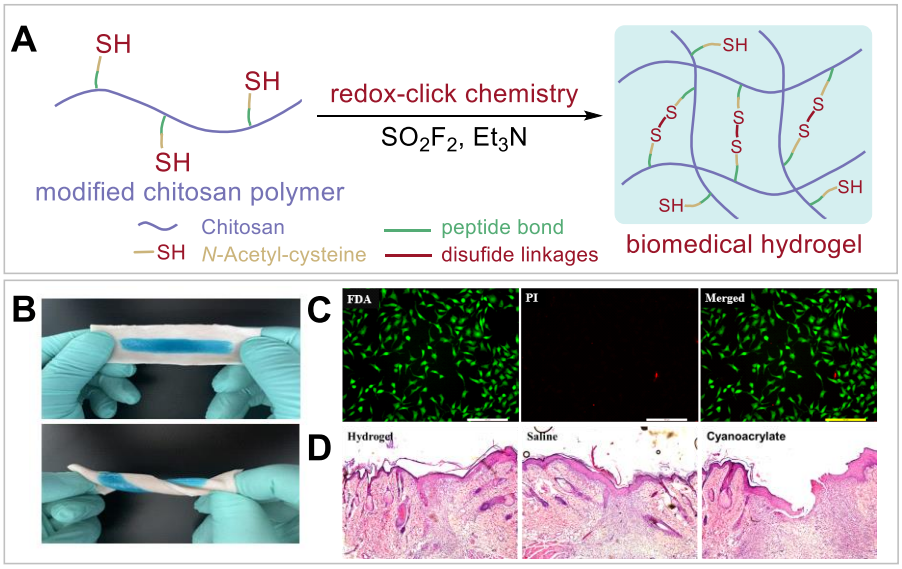


Fig. 6 The redox-click chemistry as a new cross-linking method for the *in-situ* gelling of hydrogels. (**A**) *In-situ* gelation by click chemistry. (**B**) Torsion test of the hydrogel. (**C**) The cytotoxicity of the hydrogel. (**D**) Histological analysis of the rat skin wound model and treatment.

This redox-click reaction was applied as a new cross-linking method for the *in-situ* gelation of hydrogels (Fig. 6). Hydrogel scaffold, *N*-acetyl-*L*-cysteine modified chitosan, was selected for investigation. The results showed that rapid hydrogel formation could be achieved by mixing an aqueous solution of *N*-acetyl-*L*-cysteine modified chitosan and Et_3N, and a solution of SO_2F_2 in CH_3CN (Fig. 6A). The dynamic time sweep rheological experiment revealed an immediate cross-over of G′ and G″ (Fig. S11), signifying the swift formation of a 3D network through disulfide cross-linkers. When the freshly mixed *in-situ* gel was applied to porcine skin, a tissue adhesive strength of 42.5 kPa was observed after 16 h, which was comparable to that of other *in-situ* hydrogels cured by UV radiation (Table S11). In a separate experiment, a colored *in situ* gel was applied to fresh porcine skin. Even after stretching and twisting the skin tissue, there were no signs of breakage or detachment of the adhesive hydrogel (Fig. 6B). Considering the paramount importance of biocompatibility for biomaterials, an *in vitro* cytotoxicity evaluation of the *in-situ* gel was performed utilizing the CCK-8 assay on L929 cells (Fig. 6C). The results revealed a high cell viability exceeding 98% at the hydrogel concentration of 25000 ug/mL after 24 h incubation

period. Furthermore, to test the performance of this redox-click reaction *in vivo*, the *in-situ* gel was administered on a tissue defect model. This model entailed the generation of a dorsal wound, measuring 1.5 cm in length and 3 mm in depth, on Sprague Dawley rat dorsal skin (Fig. S13). The hydrogel exhibited rapid curing upon application to the wound, thus indicating the effectiveness of the redox-click reaction as a cross-linking method for *in-situ* gelling. Subsequent histological analysis conducted after seven days revealed favorable biocompatibility for the hydrogel cross-linked by redox-click reaction (Fig. 6D). Neither fibrosis nor necrosis was detected in the wounds treated with the hydrogel, which demonstrated a significantly superior result compared to the cyanoacrylate treated group. In comparison to the CK group, the wounds treated with the hydrogel exhibited enhanced healing. These findings indicated the potential for future applications of redox-click chemistry in the field of biomaterial.

In conclusion, we have successfully designed and developed a redox reaction for the reliable construction of disulfide linkage from thiols that meets the rigorous criteria of click chemistry. This redox-click reaction is poised to enable the development of novel drugs, drug delivery systems, and innovative polymeric biomaterials, paving the way for enhanced therapeutic solutions and novel material technologies.

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Supplementary Materials

Materials and Methods

Supplementary Text

Figs. S1 to S16

Tables S1 to S13

References (*41*–*88*)