N-(*N*-Morpholindithio)phthalimide: A Shelf-Stable, Bilateral Platform Molecule for Accessing Diverse Unsymmetrical Disulfides

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ABSTRACT: A new, shelf-stable, and odorless bilateral disulfurating platform molecule, *N*-(*N*-morpholindithio)phthalimide, was developed. This reagent can be easily prepared in high yields on a gram scale in a single step from the readily available *N*,*N*'-dithiobis(phthalimide). The two leaving groups bound to sulfur were selectively transformed: the morpholino and phthalimide groups were transformed in the presence and absence of H^+, respectively. The platform molecule enabled the facile replacement of the morpholino moiety with various substituents, such as allyl (Csp^3), aryl (Csp^2), and alkynyl (Csp) groups, affording the products in high yields. The wide substrate scope of these transformations and the transformability of the resulting dithiophthalimide moiety provided rapid access to divergent multi-functionalized unsymmetrical disulfides. These results demonstrate the utility of this method for structural expansion in drug discovery and efficient conjugation in linker chemistry.

The disulfide bond is ubiquitous in biological macromolecules and in other molecules relevant to medicinal chemistry, food chemistry, and materials science (Figure 1).[1-13] They are found in a vast array of biologically active natural products,[2] such as metabolites of marine organisms, *Brassicaceae*, and *Allium* plants, and are attracting increasing attention in small molecule drug discovery and preparation of food additives.[3] They also play a crucial role in the regulation of H_2S signaling[4] in the physiological system and are vital for maintaining the three-dimensional structure of proteins.[5] Consequently, disulfides are utilized to form cyclic structures in peptide drug discovery, and the resulting steric constraints can improve the potency, selectivity, and stability of the drug.[6]

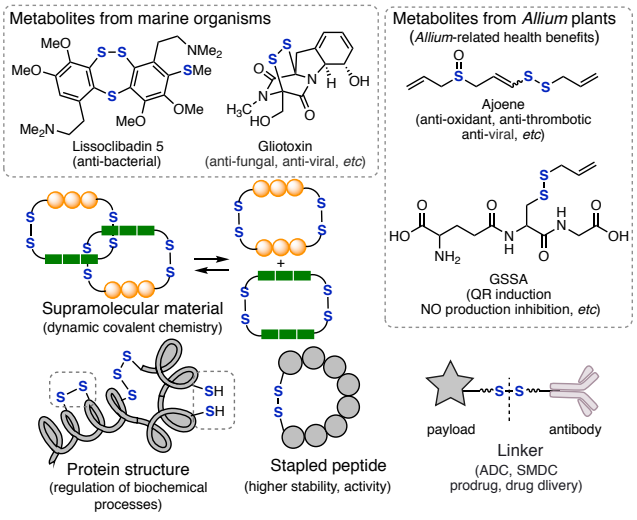


Figure 1. Ubiquity and utility of disulfide bonds.

In organisms, the disulfide bond can undergo reductive cleavage by glutathione, and is an important reversible linker in prodrugs,[7] antibody–drug conjugates (ADCs),[8] and small molecule–drug conjugates (SMDCs).[9] It has also been used for drug delivery to target cells.[10] The reversibility of disulfide bonds[11] has also attracted attention in the field of supramolecular chemistry.[12] Furthermore, owing to their redox properties, they have attracted attention in materials chemistry, particularly for application in lithium-ion batteries.[13] Owing to these vast applications of disulfides, widely-applicable synthetic methods are greatly needed to realize expedient structural optimization in drug discovery, as well as highly-efficient conjugation reactions useful for linker chemistry. Nonetheless, the synthesis of unsymmetrical disulfides is challenging, thereby limiting their applications.[14-20] The conventional methods, such as the oxidation of two thiols[14,15] or substitution reactions of thiols with sulfur electrophiles,[14,16] are unsuitable for controlling the scrambling of substituents. Recently, electrophilic disulfurating reagents bearing a sulfur-bonded leaving group (RSS–LG) have been extensively studied, and reactions introducing a carbon nucleophile into these reagents have been reported (Figure 2A).[17] However, most of these reagents require linear and multistep synthesis from relatively less available thiols, making them unsuitable for accessing various disulfide analogs. To address these issues, a bilateral disulfide platform bearing two selectively transformable leaving groups is desirable (Figure 2B). However, in spite of the synthetic advantages, this strategy is challenging because the relative reactivities of leaving groups are still unexplored.[18,21,22] It is also difficult to control multiple weak bonds (S–S, S–LG^1, S–LG^2) and sulfur extrusion.[22] Recently, in their pioneering work, Jiang *et al.* reported, a novel method for introducing two carbon nucleophiles into a disulfide building block by the virtue of strain release (Figure 2C).[18] However, the carbon nucleophiles that can be used for the first step are limited to arylboronic acids. Thus, a novel method that can be used for the preparation of various disulfides is highly sought after. Herein, we report the development of a disulfide platform molecule bearing amino and imide leaving groups. The developed strategy can introduce various substituents into

the platform molecule, thereby facilitating the diverse syntheses of disulfides (Figure 2D).

We began with the design and preparation of novel bilateral disulfide platform molecules (Figure 3) using imide and amino groups as leaving groups. We conceived that the imide group reacts preferentially in the absence of protons because it is electron deficient, while the amino group reacts preferentially in the presence of protons because of the (1) hard and basic character of the amino moiety, (2) high reactivity of the S–N$^+$HR$_2$ bond upon activation,[23] and (3) stability of the liberated ammonium salt (Figure 3A). To examine the feasibility of the selective transformation of the leaving groups, we performed a competitive experiment for C–S bond formation using an equimolar mixture of sulfanyl amine **1** and thioimide **2** (Figure 3B). Consequently, **1** reacted selectively with allyltrimethylsilane (**3a**) in the presence of TFA, whereas **2** reacted selectively with ketoester **4a** in the absence of TFA. Both **1** and **2** afforded the corresponding sulfide in high yield, while the other sulfur reagent was also recovered in high yield, suggesting that the reaction positions can be switched depending on the presence or absence of a proton source.

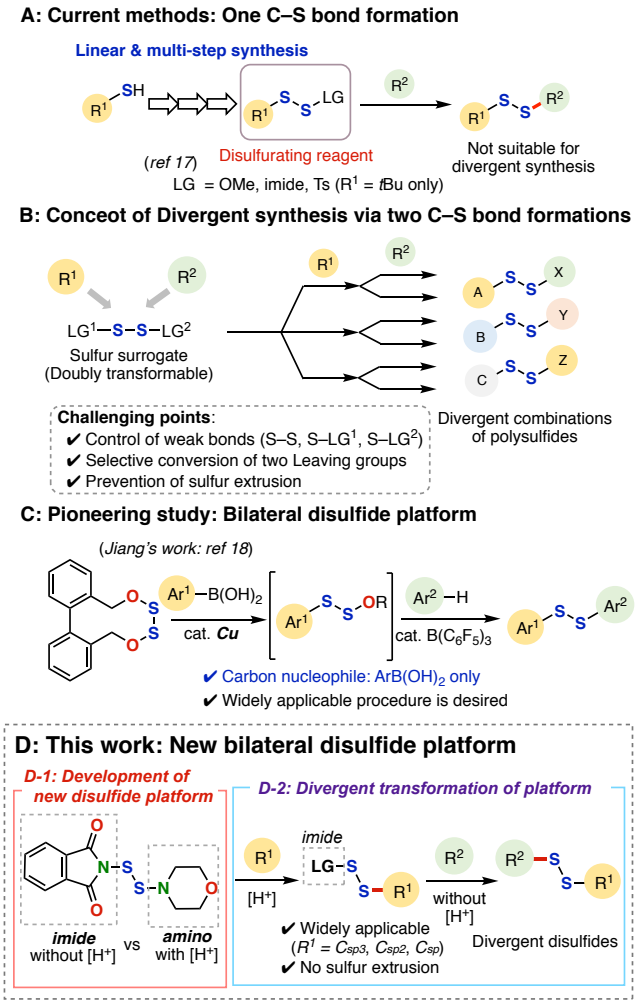


Figure 2. Background and basic concept of this work

In addition to the promising leaving group selectivity, we expected to avoid sulfur extrusion, which was a major concern in our previous study (Figure 3C).[22] DFT calculations showed that the sulfur extrusion was driven by the interaction between the highly polarized S–O bond and the S atom of the disulfide structure. Consequently, we anticipated that sulfur desorption would be prevented owing to the low polarization of the C–O bond in the imide group.

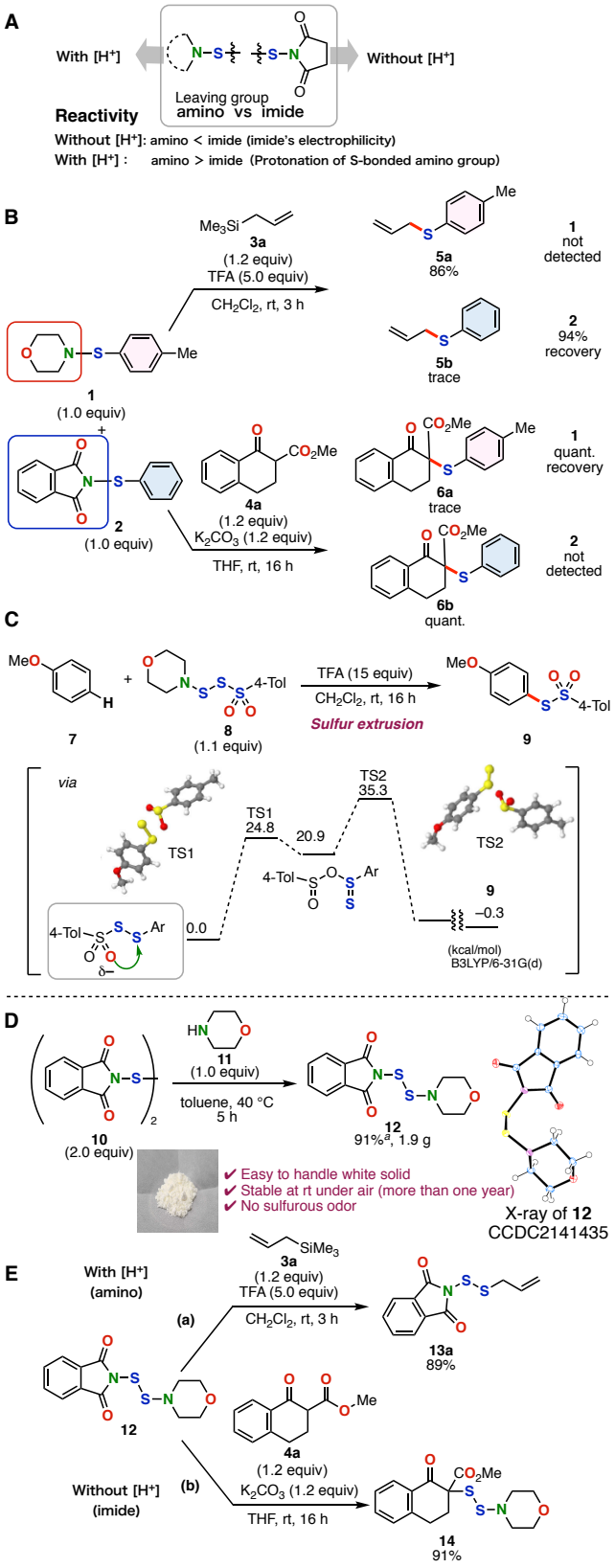
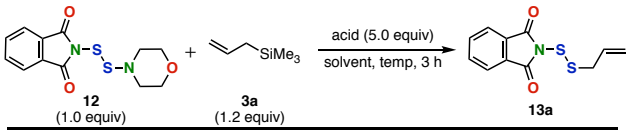


Figure 3. Design and development of a bilateral disulfide platform. (A) Design of two leaving groups. (B) Crossover experiment. (C) Design for avoiding sulfur extrusion. (D) Synthesis of platform

molecule. (E) Evaluation of selectivity. Yields were determined by NMR analysis. [a]Isolated yield.

Table 1. Optimization of reaction conditions



12 (1.0 equiv) + **3a** (1.2 equiv) → **13a**

Entry	Acid	Solvent	Temp.	Yield (%)[a]
1	TFA	CH_2Cl_2	r.t.	89
2	AcOH	CH_2Cl_2	r.t.	N.D.
3	$TsOH \cdot H_2O$	CH_2Cl_2	r.t.	35
4	$BF_3 \cdot Et_2O$	CH_2Cl_2	r.t.	56
5	Tf_2O	CH_2Cl_2	r.t.	62
6	TFAA	CH_2Cl_2	r.t.	32
7	TFA	$CHCl_3$	r.t.	70
8	TFA	toluene	r.t.	55
9	TFA	THF	r.t.	N.D.
10	TFA	CH_2Cl_2	–20 °C	99[b], (99)[b-d]

[a]NMR Yield. [b]Reaction time of 1 h. [c]**3a** (3.0 equiv) was used. [d]Isolated yield.

Based on these observations, we designed a disulfide platform molecule **12** bearing a morpholino and phthalimide moiety on the sulfur atoms. The compound can be easily prepared in excellent yield on a gram scale from readily available *N*,*N*'-dithiobis(phthalimide) (**10**) using morpholine (**11**) (Figure 3D). Platform molecule **12** is a stable (more than 1 year at rt) and easy-to-handle solid without any sulfurous odor.

With this new reagent in hand, we next investigated its selectivity. The TFA-mediated allylation using allyltrimethylsilane (**3a**) proceeded selectively at the morpholine moiety to afford **13a** in 89% yield, and the base-mediated reaction with cyclic ketoester (**4a**) at the phthalimide moiety afforded **14** in 91% yield (Figure 3E). Thus, we successfully developed a platform molecule whose reaction sites could be switched, depending on the presence or absence of a proton source, to afford desired compounds without desulfurization.

We further optimized the reaction conditions for the efficient acid-mediated allylation of **12** with allyltrimethylsilane (**3a**) to afford the products in quantitative yield (Table 1).[24] Among the acids and acid anhydrides examined (entries 1–6), excellent results were obtained using TFA (entry 1). Although the reaction proceeded efficiently in nonpolar solvents, such as $CHCl_3$ and toluene, it did not proceed in ether solvents (entries 7–9). The yield drastically increased to 99% upon lowering the reaction temperature to –20 °C (entry 10).

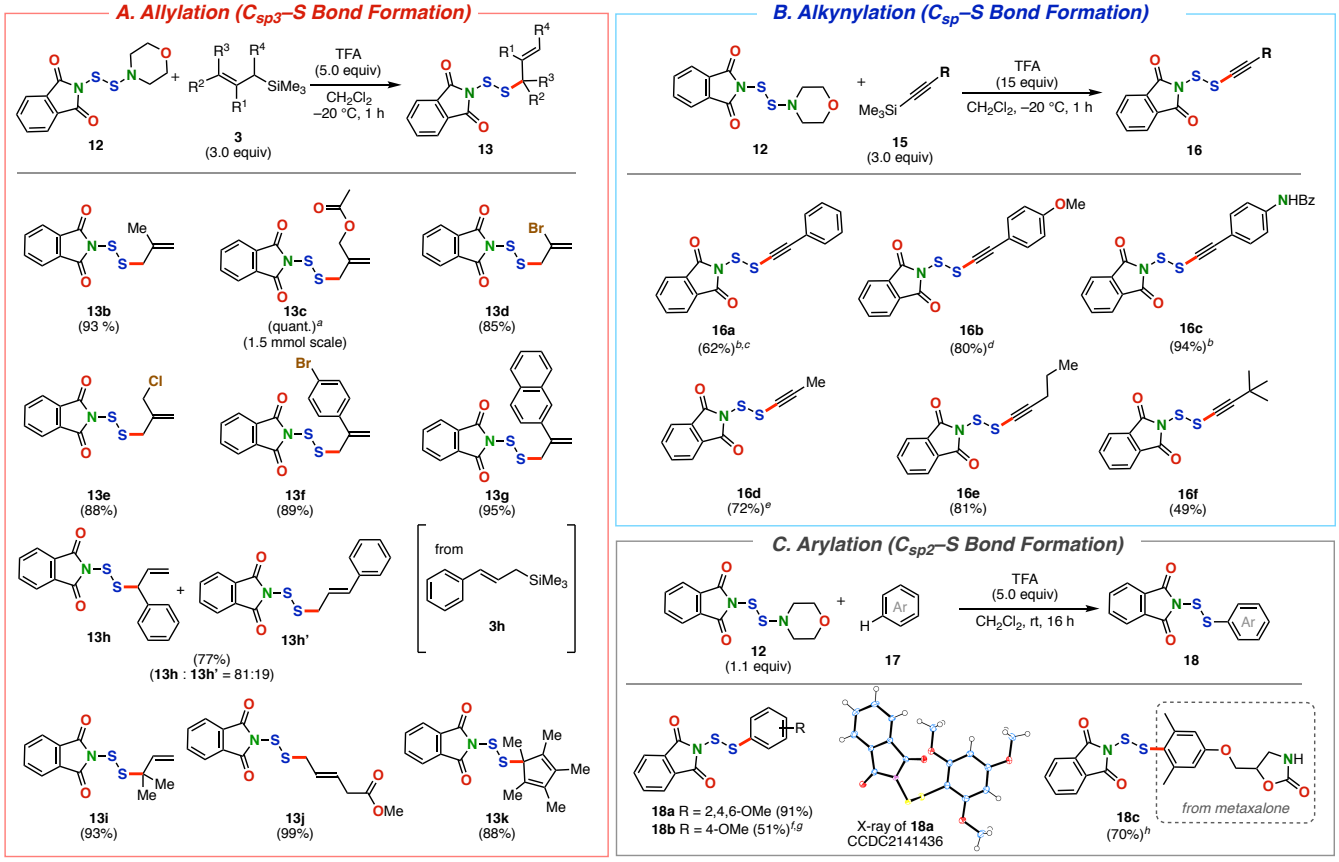


Figure 4. Transformations of **12**. (A) Allylation with allyltrimethylsilanes **3**. (B) Alkynylation with alkynyltrimethylsilanes **15**. (C) Arylation with electron-rich arenes **17**. Isolated yields are shown. [a]Reaction time of 1.5 h. [b]TFA (10 equiv) was used. [c]Conducted at 10 °C. [d]TFA (5.0 equiv) was used. [e]Conducted at –40 °C. [f]anisole (3.0 equiv) was used. [g]NMR yield. [h]TFA (15 equiv) was used.

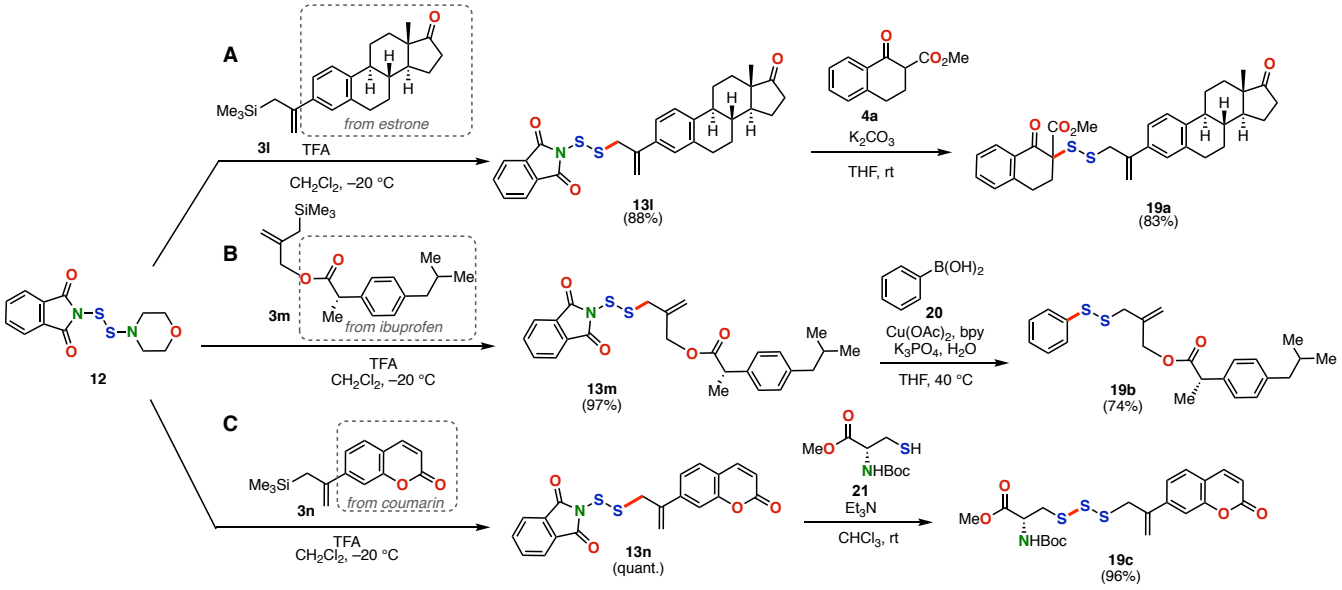


Figure 5. Synthesis of diverse polysulfides from **12**. See the Supporting Information for details.

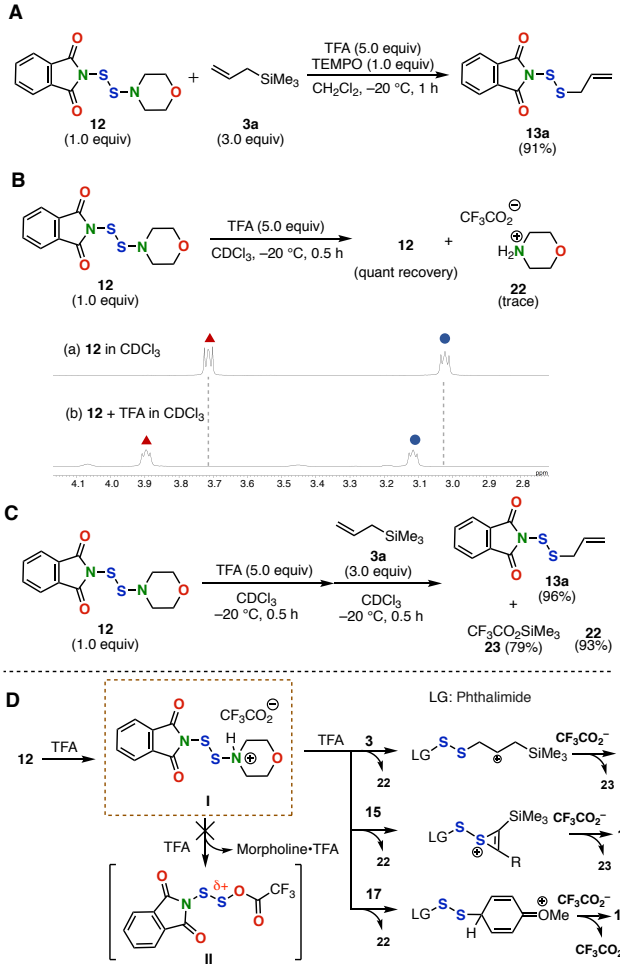


Figure 6. Mechanistic studies. (A) Allylation of **12** in the presence of TEMPO. (B) NMR observation of the mixture of **12** and TFA in $CDCl_3$. (C) NMR observation after the addition of allyltrimethylsilane (**3a**) to a mixture of **12** and TFA in $CDCl_3$. (D) Plausible reaction mechanisms. Yields were determined by NMR analysis.

The reaction of various functionalized allylsilanes **3** with platform molecule **12** (Figure 4A) was conducted under the optimized conditions (Table 1, entry 10). Various allylsilane derivatives bearing methyl, acetoxymethyl, bromo, chrolomethyl, and aryl groups at the 2-position participated in the allylation to afford **13b**–**13g** in excellent yields. The reaction of 1- or 3-substituted allylsilane derivatives proceeded smoothly to afford **13h**–**13k** in excellent yields with complete γ-selectivity except for the reaction of *E*-cinnamyltrimethylsilane (**3h**).

Encouraged by these results, we next studied the reactions with other nucleophiles such as alkynylsilanes[25] and electron-rich arenes.[23a,b,d] The alkynylation reaction proceeded under similar reaction conditions as those used for the reactions with allylsilanes (Figure 4B). The reactions with alkynylsilanes bearing a methoxy or carbamate moiety on the benzene ring afforded the desired disulfides **16a**–**16c** in good yields. The disulfuration of alkynylsilanes with alkyl substituents also proceeded, affording **16d**–**16f**. Furthermore, various aromatic disulfides possessing functional groups were synthesized through the disulfuration of electron-rich arenes (Figure 4C). For instance, **18a** and **18b** were efficiently prepared by treating **12** with 1,3,5-trimethoxybenzene and anisole, respectively. Furthermore, late-stage disulfuration of functional molecules was demonstrated using metaxalone (muscle relaxant), affording the corresponding disulfide **18c** in good yield. All of the transformations exclusively gave mono-substituted products,[26] and the entire experimental process was free from unpleasant odors. Thus, **12** could be efficiently utilized to replace the morpholino moiety with various carbon substituents, such as allyl (Csp^3), aryl (Csp^2), and alkynyl (Csp) groups.

Platform molecule **12** is suitable for various transformations, and the transformability of the resulting dithiophthalimides[17d-f,27] provides rapid access to divergent disulfides bearing complex substituents via the formation of two C–S bonds (Figure 5). For example, the reaction of functionalized allylsilanes **3l**–**3n** with estrone (steroid hormone), ibuprofen (anti-inflammatory drug), and coumarin (fluorescent molecule) framework successfully proceeded to afford **13l**–**13n** in excellent yields. Subsequent diversification of **13l** and **13m** upon the reaction with carbon nucleophiles such as ketoester **7a**[17e] or phenylboronic acid (**20**)[17d] enabled rapid access to divergent disulfides via the formation of two C–S bonds. Furthermore, a CySSA derivative,

which has attracted attention because of its *Allium*-related health benefits, was rapidly prepared by the base-mediated substitution reaction with protected cysteine **21** (Figure 5C).[27] These results clearly demonstrated that **12** could be successfully used to access divergent multi-functionalized unsymmetrical disulfides and trisulfides using reactants bearing appropriate substituents. As shown in Figure 1, disulfide derivatives play an important role in linker chemistry as well as in small molecule drug discovery, thereby demonstrating the utility of **12** for the rapid structural expansion for structure-activity relationship studies in drug discovery and for developing reliable conjugation methods for linker chemistry.

To gain insights into the mechanism of the acid-mediated reaction using **12**, we conducted several control experiments (Figure 6). The reaction between **3a** and **12** in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO) did not affect the formation of **13a**, suggesting that radical intermediates were not involved (Figure 6A). The treatment of **12** with TFA (5.0 equiv) in $CDCl_3$ at –20 °C for 0.5 h led to the complete recovery of **12**, with the formation of only trace amounts of morpholine salt **22**, confirming that the S–N bond was not cleaved (Figure 6B). The subsequent addition of allyltrimethylsilane (**3a**) to this mixture, followed by stirring for 0.5 h, afforded the desired product **13a** (96%), along with morpholine salt **22** (93%) and $CF_3CO_2SiMe_3$ (**23**; 79%) (Figure 6C). In addition, the NMR signal of the proton adjacent to the nitrogen of the morpholine moiety was shifted upfield before the addition of **3a** (Figure 6B), indicating that the nitrogen atom of morpholine was activated through protonation. These observations suggested that the reaction was probably initiated by the protonation of **12** to generate **I**, followed by a reaction with the corresponding nucleophile to afforded disulfides **13**, **16**, and **18** (Figure 6D). NMR spectral analysis suggested that intermediate **II**, which was generated via C–N bond cleavage upon the exchange of the morpholine moiety with TFA, was not likely to be an active species.[28]

In summary, we developed a novel, shelf-stable, bilateral disulfurating platform molecule, *N*-(*N*-morpholindithio)phthalimide (**12**). This reagent was easily prepared as a stable and easy-to-handle odorless solid. The two leaving groups bound to sulfur were transformed selectively: the morpholino and phthalimide groups were transformed in the presence and absence of H^+, respectively, without any undesirable sulfur extrusion. Thus, the platform molecule **12** was efficiently utilized to replace the morpholino moiety with various carbon substituents, such as allyl (Csp^3), aryl (Csp^2), and alkynyl (Csp) groups. The wide substrate scope of these transformations and the transformability of the resulting dithiophthalimide moiety provided rapid access to divergent multi-functionalized unsymmetrical disulfides. This strategy will open a new avenue for rapid structural expansion in drug discovery, as well as for introducing effective conjugation in linker chemistry. Studies on the synthesis of bioactive disulfide-containing molecules and SMDCs are currently underway.

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Notes

The authors declare no competing financial interest.

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