Transition Metal Free Sandmeyer-Type Reductive Disulfuration of Anilines

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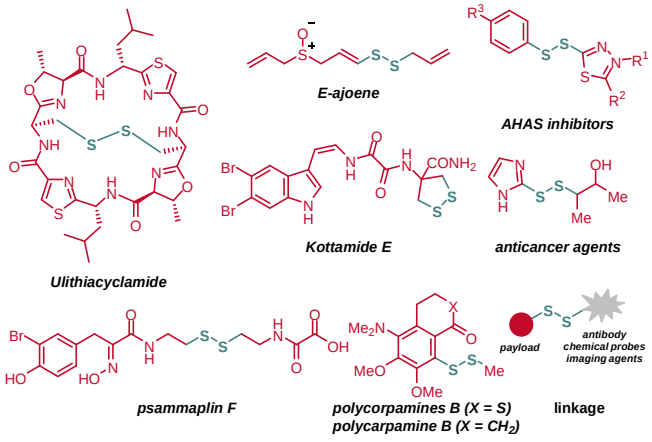
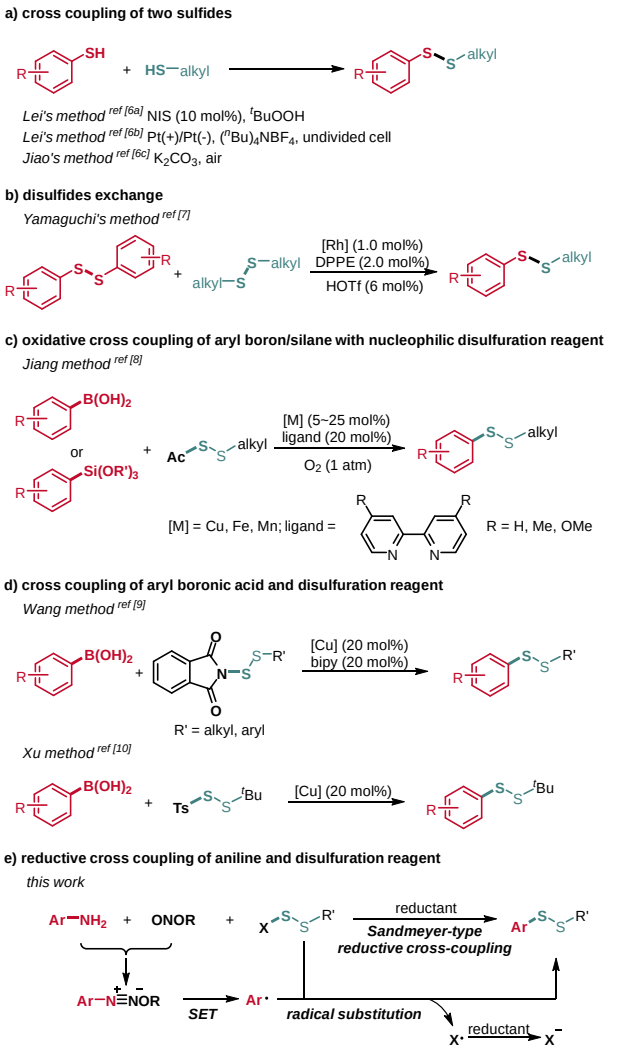
Abstract: A transition metal/ligand free disulfuration of anilines with disulfur transfer reagents (dithiosulfonate or tetrasulfide) is reported herein. The reaction, which can be considered as a reductive disulfuration variation of the classic Sandmeyer reaction, is performed under mild conditions and exhibits broad scope across aniline substrate and disulfur transfer reagent classes. The gram-scale synthesis of disulfides is successfully achieved through this method, rendering the approach highly valuable.

Disulfide scaffolds are ubiquitous structural units in biological molecules. They serve as bridges to add additional stability to the 3D structure of proteins which are required for protein folding and function.[1] In addition to the effect of disulfides in proteins, disulfides enjoy a privileged role in the realm of pharmaceuticals,[2] food chemistry,[3] and natural products (Scheme 1).[4]



Scheme 1. Selected representative disulfides and their applications.

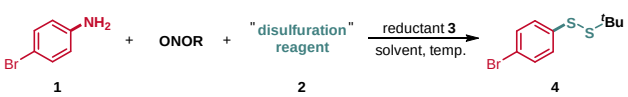
Methods for synthesis of unsymmetric disulfides typically require oxidative activation of one of two different thiol precursors followed by nucleophilic substitution by another thiol.[5] Recent representative progress on oxidative cross-coupling thiophenol and alkylthiol by Lei[6a-b] and Jiao[6c] involved the use of peroxide, air, as well as an electrochemical oxidant (Scheme 2a). Alternatively, Yamaguchi group have disclosed a rhodium-catalyzed disulfide exchange strategy for access to unsymmetric disulfides (Scheme 2b).[7] Although prominent progress has been made to synthesis of unsymmetric disulfides through the construction of S−S bond,[5f] these approaches are often



Scheme 2. Synthetic strategies for access to unsymmetrical aryl disulfides.

limited to a certain extent by at least one of the following points: starting materials are not easily available; homocoupling is unavoidable; overoxidation causes side reactions. In an attempt to overcome these limitations, prefunctionalized disulfur transfer reagents (X-SSR, X = Ac, PhthN, Ts, etc.) have been developed to directly transfer "-SSR" moieties onto substrates through the construction of C−SSR bonds.[8-9] Along these lines, Jiang and co-

Table 1. Reaction optimization.



entry [a]	R	2	3	solvent	yield (%)[b]
1[c]	*tert*-butyl	**2a**	none	MeCN	trace
2	*tert*-butyl	**2b**	none	MeCN	trace
3	*tert*-butyl	**2c**	none	MeCN	trace
4	*tert*-butyl	**2d**	none	MeCN	39
5	*tert*-butyl	**2d**	Na_2S	MeCN	33
6	*tert*-butyl	**2d**	Na_2SO_3	MeCN	46
7	*tert*-butyl	**2d**	$Na_2S_2O_3$	MeCN	26
8	*tert*-butyl	**2d**	S_8	MeCN	25
9	*tert*-butyl	**2d**	**3a**	MeCN	48
10	*tert*-butyl	**2d**	**3b**	MeCN	36
11	*tert*-butyl	**2d**	**3c**	MeCN	51
12	*tert*-butyl	**2d**	**3d**	MeCN	15
13	*n*-butyl	**2d**	**3c**	MeCN	29
14	*iso*-amyl	**2d**	**3c**	MeCN	32
15	*tert*-butyl	**2d**	**3c**	DMF	22
16	*tert*-butyl	**2d**	**3c**	DCM	16
17	*tert*-butyl	**2d**	**3c**	DCE	33
18[d]	***tert*-butyl**	**2d**	**3c**	**MeCN**	**68 (65)**
19[e]	***tert*-butyl**	**2e**	**3c**	**MeCN**	**83**
20[d,f]	*tert*-butyl	**2d**	**3c**	MeCN	50
21[e,f]	*tert*-butyl	**2e**	**3c**	MeCN	69

[a]Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), nitrite (0.26 mmol, 1.3 equiv), **2** (0.40 mmol, 2.0 equiv), **3** (0.40 mmol, 2.0 equiv), solvent (2 mL), N_2, 60 °C, 7 h; [b]Yield determined by GC analysis

using *n*-dodecane as an internal standard. The value in parentheses refers to isolated yield. [c]In the presence of Na_2CO_3 (0.40 mmol, 2.0 equiv). [d]Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), nitrite (0.52 mmol, 2.6 equiv), **2** (0.50 mmol, 2.5 equiv), **3** (0.52 mmol, 2.6 equiv), solvent (2 mL), N_2, 60 °C, 7 h; [e]Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), nitrite (0.36 mmol, 1.8 equiv), **2** (0.50 mmol, 2.5 equiv), **3** (0.52 mmol, 2.6 equiv), solvent (2 mL), N_2, 60 °C, 7 h; [f]The reaction proceeded at room temperature instead of 60 °C.

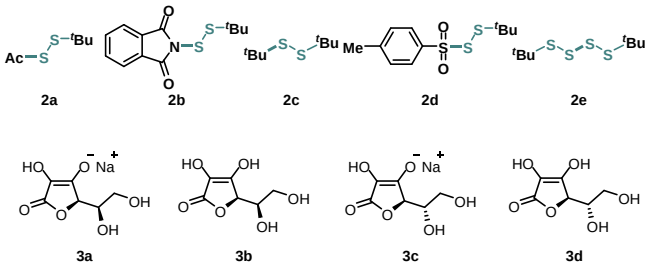


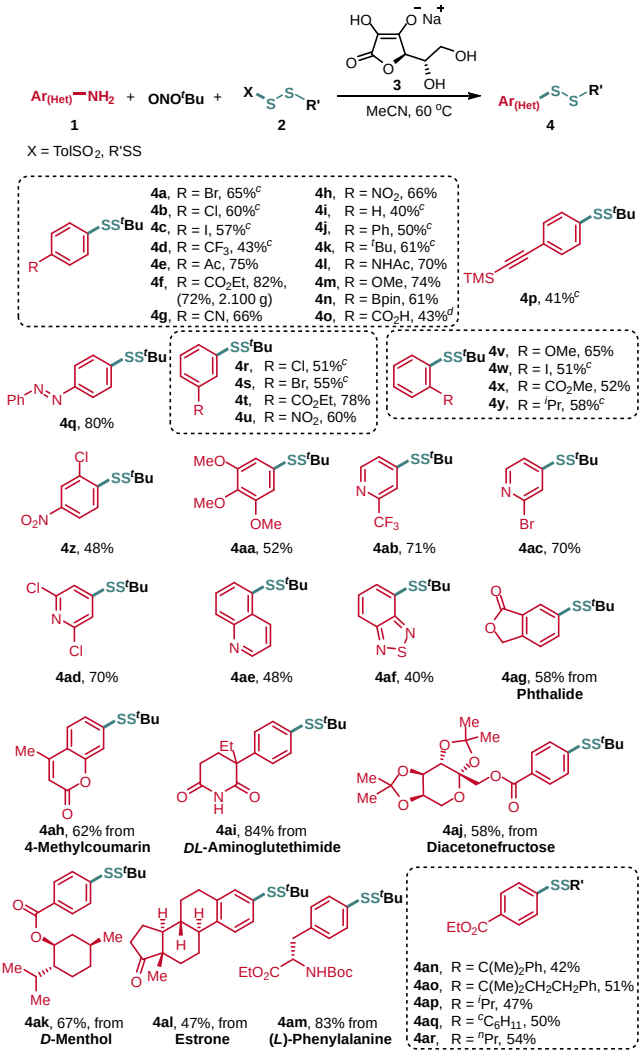
Figure 1. Disulfuration reagents and reductants tested.

workers have developed a novel nucleophilic reagent Ac-SSR applied in aryl unsymmetric disulfides synthesis via transition metal catalyzed (transition metal = Cu, Fe, Mn) oxidative cross-coupling of arylboronic acid and Ac-SSR under oxygen atmosphere.[8a] Similarly, the same group also reported the oxidative cross-coupling of aryl silane and Ac-SSR (Scheme 2c).[8b] In the absence of oxidants, the direct copper-catalyzed disulfuration of aryl boronic acids with electrophilic disulfurating reagents PhthN-SSR[9] or Ts-SSR[10] have been reported by Wang and Xu, independently (Scheme 2d). Though very useful, these appoaches commonly require transition metal catalyst (5~25 mol%) and ligand (20 mol%). Moreover, poly-substituted aryl and heteroaryl boronic acids could be rather expansive or even challenging to access. The development of novel and practical disulfuration transformation using other types of common and readily available aryl precursors would thus be of high value. Anilines as relatively cheap and readily available aryl sources, are commonly used in all sorts of coupling reactions through *in situ* generated aryl diazonium salts, which have been established as a series of classic methods for amino group converstion.[11-13] Besides, anilines and protected anline derivatives, are easily functionalized via electrophilic aromatic substitution and C-H functionalization strategies.[14] The reductive cross-coupling of two electrophilic counterparts[15, 16] to form unsymmetric disulfides is less studied by far, with the differentiation of the two electrophiles being a key challenge. In our proposed strategy, we envisioned that the aryl diazonium salt and the electrophilic disulfuration reagent could be effectively differentiated, where the aryl radical would be first generated through preferential SET (single electron transfer) reduction of the more oxidizing aryl diazonium salt,[17] followed by radical substitution on the electrophilic disulfuration reagent to form the aryl disulfide product. Subsequently, the resulting radical X· would be further reduced by an excess amount of reductants. In this communication, we show a general and practical disulfuration of aniline under mild conditions without requiring any transition metal catalyst, ligand, and oxidant. Moreover, the amino group on anilines can be readily protected and deprotected, rendering this approach suitable for late-stage introduction of disulfide moieties onto an aromatic structure. The reaction is also a very rare example of reductive cross coupling in both Sandmeyer-type reactions[17b, 18] and disulfuration reactions (Scheme 2e).

We evaluated the feasibility of the proposed scheme in the reaction of 4-bromoaniline **1a**, nitrite,[19] and disulfuration reagent (Table 1). An initial screening of disulfuration reagents, including nucleophilic reagent **2a** in combination with sodium carbonate as the base[8a] and other reagents[20] **2b** and **2c** proved discouraging (Table 1, entries 1-3), only Ts-SS^{t}Bu **2d**[10] giving the desired product **4** in a promising 39% yield (entry 4). Concerning the electrophilicity of both aryl diazonium salt and Ts-SS^{t}Bu, we turned to screen reductants to promote the reductive cross coupling process. The efficiency was not conspicuously improved with inorganic reductants, such as sodium sulphide, sodium sulfite, sodium thiosulfate, and elemental sulfur (entries 5-8). To be gratified, organic reductants such as sodium erythorbate **3a** and sodium ascorbate **3c** provided positive results, whereas the homologous erythorbic acid **3b** and vitamin C **3d** did not (entries 9-12). A careful screen revealed that sodium ascorbate **3c** led to a significant improvement on yield of aryl disulfide **4** (entry 11). Next, we conducted a screen of nitrites, which demonstrated *tert*-butyl nitrite still to be the most effective diazotization reagent for the conversion (entries 13 and 14). Other solvents were tested. However, in all cases a substantial loss in yield was noted (entries 15-17). Pleasingly, a distinct improvement of the yield to 68% (65% isolated yield) was observed by further optimizing the amount and the ratio of *tert*-butyl nitrite, disulfuration reagent **2d**, and reductant **3c** (entry 18). Additionally, the reagent tetrasulfide **2e** remarkably enhanced the reactivity, providing the desired **4** in 83% yield based on GC analysis. However, we failed to obtain the isolated yield of **4** because the resulting disulfide **4** and the remaining **2e** are mixed and inseparable by TLC (thin-layer chromatography) and column chromatography (entry 19). Ultimately, disulfuration at room temperature provided disulfide **4** with a lower efficiency (entries 20-21).

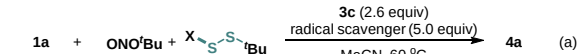
With optimized conditions identified, we explored the scope of the anilines **1** and disulfur transfer reagents **2** in reductive disulfuration (Table 2). The protocol succeeded with a variety of anilines bearing *para*-substituents, whereas the electronic perturbation of substituents had a distinct influence on the reaction efficiency. The conversion of 4-halogeno anilines and 4-trifluomethyl aniline with **2d** proceeded smoothly, delivering disulfides **4a**-**4d** in moderate isolated yield. The anilines bearing the stronger electron withdrawing groups including acetyl, ester, cyano, nitro groups at *para*-position reacted with tetrasulfide **2e**, affording products **4e**-**4h** in higher yields. To document the practicability, the disulfuration of aniline **1f** on gram-scale gave desired product **4f** in comparable yield as the small-scale experiment. Aniline, 4-phenyl aniline, and 4-*tert*-butyl aniline engaged in reactivity by using Ts-SS^{t}Bu **2d**, as the desired disulfides **4i-4k** were formed in 40~61% isolated yield. In this protocol, as the same as the strong electron withdrawing groups, the electron donating groups, such as

Table 2. Substrate scope of reductive disulfuration.[a, b]



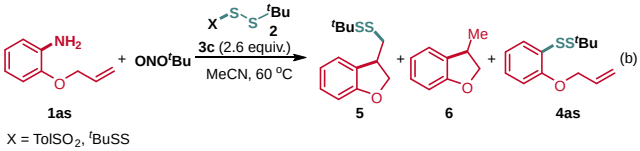
[a]Reaction condition **A**: **1** (0.20 mmol, 1.0 equiv), *tert*-butyl nitrite (0.36 mmol, 1.8 equiv), **2e** (0.50 mmol, 2.5 equiv), **3c** (0.52 mmol, 2.6 equiv), MeCN, N_2, 60 °C, 7 h. [b]Isolated yield. [c]Reaction condition **B**: **1** (0.20 mmol, 1.0 equiv), *tert*-butyl nitrite (0.52 mmol, 2.6 equiv), **2d** (0.50 mmol, 2.5 equiv), **3c** (0.52 mmol, 2.6 equiv), MeCN, N_2, 60 °C, 7 h. [d]4-Aminobenzoic acid sodium salt was employed as the substrate.

acetamino and methoxy groups, also worked well to give **4l** and **4m** in good yields, respectively. Significantly, the mild conditions were tolerant of vulnerable functionalities, such as boronic ester, benzoate, alkynyl, phenylazo, delivering products **4n**-**4q**. Gratifyingly, these success results were mirrored with other anilines bearing *meta*-substituents (**4r**-**4u**). We next interrogated the electronic and steric effect of substitution on *ortho*-position of anilines. Electronic and steric modulations of the *ortho*-substituents have no obvious effect on the reactivity of the transformation. Methoxy, iodo, ester, and *iso*-propyl groups were tolerated, providing disulfides **4v**-**4y** in moderate yield. Furthermore, di- and multi-substituted disulfides **4z** and **4aa** were accessed in synthetically useful yield from extreme electron-poor and electron-rich anilines. Notably, the approach promoted the smooth synthesis of various Lewis basic *N*-heterocyclic motifs with satisfactory yields (**4ab**-**4af**). To demonstrate the generality and practicability of this novel method applied in more complex molecules, we successfully converted the amino groups embedded in phthalide, 4-methylcoumarin, *DL*-aminoglutethimide, diacetonefructose, *D*-menthol, estrone and *L*-phenylalanine framework into disulfide groups (**4ag**-**4am**). Finally, with respect to disulfur transfer reagents as the coupling partners, both more bulky -C(Me)$_2$Ph and -C(Me)$_2$CH$_2$CH$_2$Ph and less bulky ^{c}C$_6$H$_{11}$, ^{i}Pr, ^{n}Pr substituted reagents behaved well, affording the anticipated products **4an**-**4ar** in moderate yields.



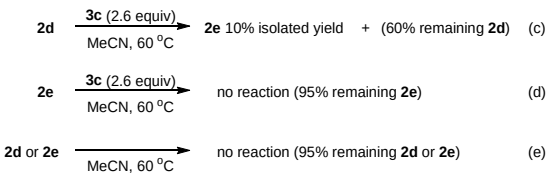
X = TolSO$_2$, ^{t}BuSS

radical scavenger	2	4a
TEMPO	**2d**	trace
BHT	**2d**	trace
TEMPO	**2e**	trace
BHT	**2e**	trace



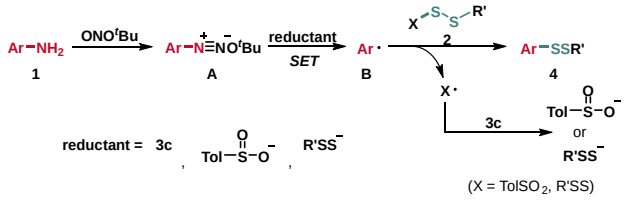
X = TolSO$_2$, ^{t}BuSS

2	3	5	6	4as
2d	**3c**	30% isolated yield	ND.	ND.
2e	**3c**	48% isolated yield	ND.	ND.



Scheme 3. Mechanistic studies.

A set of experiments contributed to our current in-depth understanding of the reaction mechanism as well as the reactivity of the disulfuration reagents. Initially, the disulfurations of aniline **1a** with **2d** and **2e** were shut down by addition of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) under standard conditions. The similar result was obtained by addition of another well-known radical trapping agent BHT (butylated hydroxytoluene) (Scheme 3a). To verify whether aryl radical is generated in the current reductive disulfuration process, a radical clock probe was introduced by using 2-(allyloxy)aniline **1as** as the substrate. Under standard reaction conditions, the product **5** was formed in 30% and 48% isolated yield through the radical cyclization/disulfuration sequence by using Ts-SS^{t}Bu **2d** and ^{t}BuSSSS^{t}Bu **2e** respectively, whereas the hydroarylation product **6** and the normal aryl disulfuration product **4as** were not detected (Scheme 3b). Next, the control experiments showed that in the presence of the reductant **3c**, the reagent Ts-SS^{t}Bu **2d** was partly decomposed and converted (60% remaining **2d**), resulting in formation of tetrasulfide **2e** in 10% isolated yield (Scheme 3c). However, reductant **3c** was not able to reduce the reagent ^{t}BuSSSS^{t}Bu **2e** (>95% remaining **2e**) under the same condition (Scheme 3d). In addition, both dithiosulfonate **2d** or tetrasulfide **2e** were thermally stable at reaction temperature in the absence of reductant **3** (Scheme 3d and 3e). These results demonstrate that SET reduction of aryl diazonium salt to generate aryl radical is involved in the mechanism. Sodium ascorbate **3c** acts as a reductive promoter to facilitate the formation of aryl radical and slow release of ^{t}BuSSSS^{t}Bu from Ts-SS^{t}Bu. It is possible that aryl radical undergoes radical substition with Ts-SS^{t}Bu to form the disulfide **4**.



Scheme 4. Proposed mechanism.

The mechanism of the reductive disulfuration is proposed to begin with SET reduction of *in situ* generated aryl diazonium salt **A** from aniline **1.** The process was promoted by sodium ascorbate **3** and also by possible reductant *p*-tolylsulfinate (Ts$^-$) or disulfane anion (R'SS$^-$) to form the corresponding aryl radical **B** (Ar·), which subsequently undergoes radical substitution with dithiosulfonate or tetrasulfide to afford the disulfide **4**. Meanwhile the radical substitution generates the corresponding *p*-tolylsulfonyl radical (Ts·) or disulfane radical (R'SS·),[21, 22] which is subsequently further reduced by sodium ascorbate **3c** to generate the reductive *p*-tolylsulfinate or disulfane anion (Scheme 4).

In conclusion, we have developed a novel reductive Sandmeyer-type disulfuration of anilines using sodium ascorbate as a reductive promoter. Aryl and heteroaryl unsymmetric disulfides with a variety of substitution patterns can be accessed from readily available anilines under transition metal/ligand free and oxidant free conditions. The value of the method has been further proved by the compatibility with various complex structures and the feasibility of gram-scale synthesis. Expansion of substrate scope, synthetic application, and thorough mechanistic investigation will be of value to our group's ongoing efforts.

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Keywords: Sandmeyer-type reaction • diazonium salts • radical • disulfuration • reductive coupling

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