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Acid-Mediated Sulfonylthiolation of Arenes via Selective Activation of *SS*-Morpholino Dithiosulfonate

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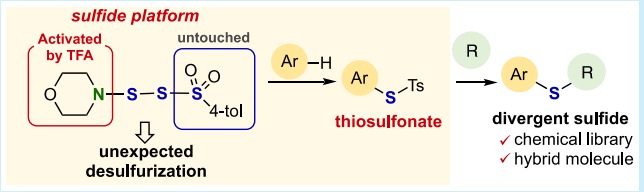
ABSTRACT: A trifluoroacetic-acid-mediated desulfurilative sulfonylthiolation of arenes using *SS*-morpholino dithiosulfonate is described. This system is based on selective activation of the morpholino group over the tosyl group of the doubly transformable sulfur surrogate. Mechanistic studies suggested that the reaction proceeds through electrophilic aromatic substitution followed by sulfur extrusion. The wide substrate scope of this reaction and the transformability of the resulting thiosulfonates enable expeditious access to divergent multifunctionalized sulfides.



Aromatic sulfides have a broad range of applications in fields such as medicinal chemistry[1] and materials science.[2] The double C–S bond formation of doubly transformable sulfur surrogates is a notable approach for efficient access to aromatic sulfides bearing various combinations of substituents (Figure 1A). This approach offers significant advances in the conjugation of functional molecules for the assembly of hybrid molecules[3] or the facile preparation of sulfide libraries from nonsulfur substrates.

Recently, electrophilic sulfur surrogates have attracted increasing attention[4,5] because they are transformable into various organosulfur compounds without giving rise to catalyst poisoning, nucleophilic side reactions, and unpleasant odors due to the electron-withdrawing and masking effect of the leaving group. Therefore, an electrophilic sulfide platform bearing two leaving groups that are selectively transformable in a sequential manner is highly sought-after (Figure 1B). However, despite these potential advantages, only a few examples of studies comparing the relative reactivity of leaving groups with carbon nucleophiles are known.[6,7] For example, *N*-(chlorothio)imide,[6a−c] chlorothiocyanide,[6d,e] and *N*-(thiocyanato)imide[6f−j] are known as doubly transformable thiolating reagents. The applicability of these reagents is limited because of the instability of chloro-containing reagents, the limited transformation of organothiocyanide, and the toxicity of the liberated cyanide.

On the basis of the background and considering the high stability of the S–SO_2R bond, we envisaged that the selective transformation of the S–NR_2 bond over the S–SO_2R bond is possible via protonation (Figure 1D) due to (1) the hard and basic character of the nitrogen atom, (2) the high reactivity of the S–N^+HR_2 bond once activated,[8] and (3) the stability of the liberated ammonium salt.

In addition, despite the excellent transformability of the resulting thiosulfonates[4d,5] through a variety of C–S bond-forming reactions that do not release toxic waste and unpleasant odor, thiosulfonate synthesis via C–S bond formation is rarely reported (Figure 1C),[9,10] except via the S_N2 reaction.[4d] Herein we report the trifluoroacetic acid (TFA)-mediated sulfonylthiolation of arenes using *SS*-morpholino 4-toluene(dithioperoxo)sulfonate (**7**) entailing the selective activation of the morpholino group over the sulfonyl group and an unexpected desulfurization.

To examine the feasibility of selectively transforming the leaving groups, we compared the reactivity of the sulfur-bonded amino and sulfonyl groups. We performed a competitive experiment for the C–S bond-forming reaction using an equimolar mixture of sulfaniylamine **4** and thiosulfonate **3c** with anisole (**1b**) in the presence of TFA (Figure 2A).[8] As a result, sulfanyl amine **4** was completely consumed to afford 4-methoxyphenyl 4-tolyl sulfide (**5a**) in 81% yield, and thiosulfonate **3c** was recovered in 90% yield. This result suggests that the amino group is selectively activated over the sulfonyl group in the presence of a proton source.

On the basis of the results of this competition study, we designed platform molecules **6** and **7** bearing morpholino and tosyl groups on the sulfur and examined the reactivity thereof in an electrophilic substitution reaction (Figure 2B).[11] We found that the treatment of *S*-morpholino 4-toluenethiosulfonate (**6**) with anisole (**1b**) in the presence of TFA provided the desired *S*-(4-methoxyphenyl) 4-toluenethiosulfonate (**3b**)

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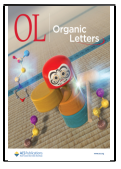

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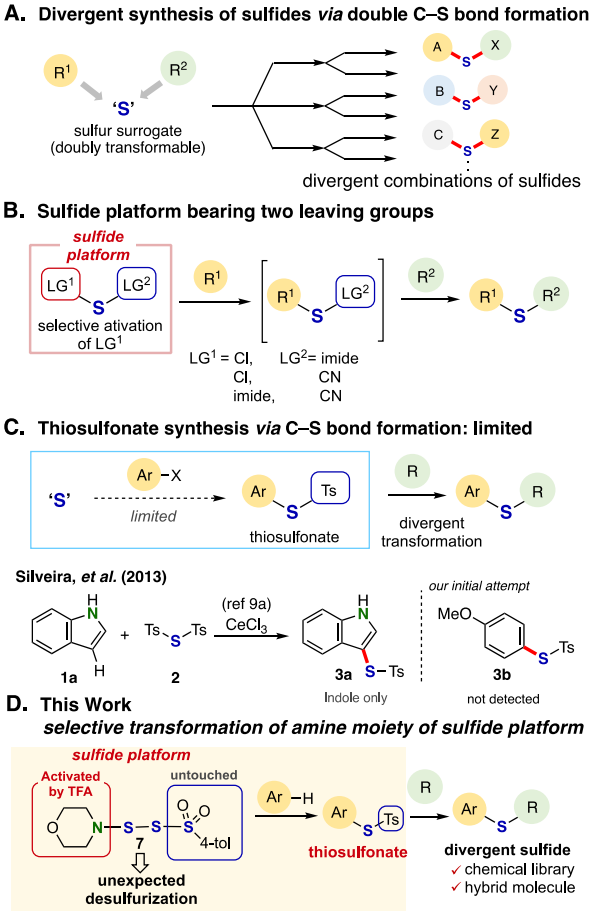


Figure 1. Background and basic concept of this work.

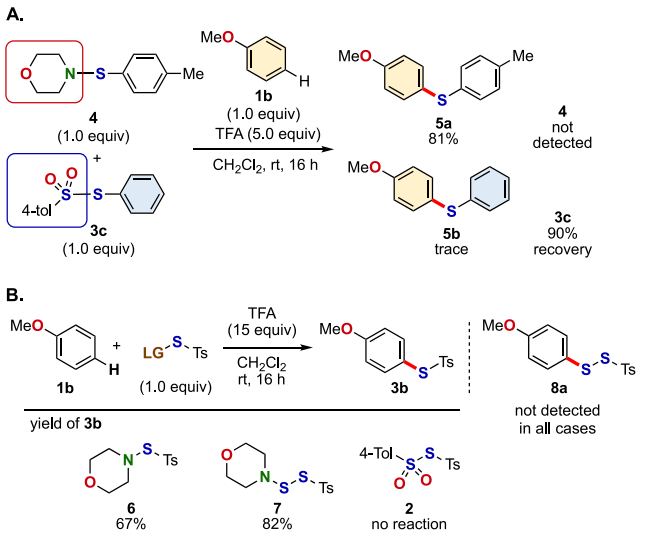
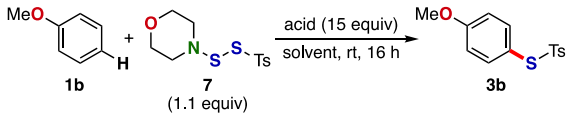


Figure 2. Design of doubly transformable sulfur surrogate. (A) Crossover experiment. (B) Comparison of sulfur reagents. Yields were determined by NMR analysis.

in 67% yield. Surprisingly, the reaction of *SS*-morpholino 4-toluene(dithioperoxo)sulfonate (**7**) under the same conditions afforded the same product, whereas *SS*-(4-methoxyphenyl) 4-toluene(dithioperoxo)sulfonate (**8a**) was not detected.[12] The reaction using di(4-toluenesulfonyl)sulfide (**2**) did not proceed due to the low reactivity of the S–SO_2R bond.

On the basis of the initial experiment, we selected dithioperoxosulfonate **7** as a sulfonylthiolating reagent because of its favorable reactivity and availability[13] compared with that of **6** and then extensively screened the conditions for the efficient synthesis of *S*-(4-methoxyphenyl) 4-toluenethiosulfonate (**3b**) from anisole (**1b**) (Table 1). As a result, the desired

Table 1. Optimization of Reaction Conditions



entry	acid	solvent	yield (%)[a]
1	TFA	CH_2Cl_2	82[b]
2	TFA	CH_2Cl_2	96[c]
3	AcOH	CH_2Cl_2	N.D.
4	TsOH	CH_2Cl_2	N.D.
5	TfOH	CH_2Cl_2	N.D.
6	AgOTf	CH_2Cl_2	N.D.
7	$FeCl_3$	CH_2Cl_2	N.D.
8	TFA[d]	CH_2Cl_2	64
9	TFA	$CHCl_3$	79
10	TFA	toluene	94
11	TFA	benzene	72
12	TFA	THF	N.D.
13	TFA	Et_2O	N.D.
14	TFA	DMF	N.D.

[a]Yields were determined by NMR analysis, unless otherwise noted. [b]**7** (1.0 equiv) was used. [c]Isolated yield is shown. [d]TFA (5.0 equiv) was used.

thiosulfonate **3b** was obtained in 96% yield when the reaction was conducted with 1.1 equiv of **7** (entry 2). Interestingly, the use of other acids instead of TFA proved ineffective (entries 3–7). This result indicated that the role of TFA was not only as a proton source but also as a participant in the active species.[14] The desired product was obtained in lower yield when the amount of TFA was reduced to 5 equiv (entry 8). Using other solvents, including $CHCl_3$, toluene, and benzene, instead of CH_2Cl_2 lowered the yield (entries 9–14). Notably, the entire experimental process was free from unpleasant organosulfurous odors.

The optimized conditions (Table 1, entry 2) were successfully applied to the *p*-toluenesulfonylthiolation of a wide range of arenes with **7** (Figure 3) with complete regioselectivity. Various arenes **1** bearing electron-donating groups, including methoxy, methylthio, phenyloxy, phenylthio, hydroxyl, and methyl, underwent *p*-toluenesulfonylthiolation to afford *S*-aryl thiosulfonates **3d–j**, leaving the said groups intact. The *p*-toluenesulfonylthiolation of dopamine derivative **1k** proceeded smoothly to afford the multisubstituted thiosulfonate **3k** in quantitative yield. Moreover, the reaction of substituted naphthalenes also proceeded in good to excellent yields, affording the corresponding thiosulfonates **3l–p**. Notably, substrates containing an electron-withdrawing ester moiety tolerated the reaction. In addition, the sulfonylthiolation of heteroaromatic substrates, such as thiophene, benzothiophene, and dibenzofuran, proceeded smoothly to afford thiosulfonate **3q**, **3r**, and **3s** in good yields. Furthermore, the late-stage sulfonylthiolation of functional molecules such as DTT (**1t**, conductive material), gemfibrozil (hypolipidemic drug) methyl ester **1u**, and metaxalone (**1v**,

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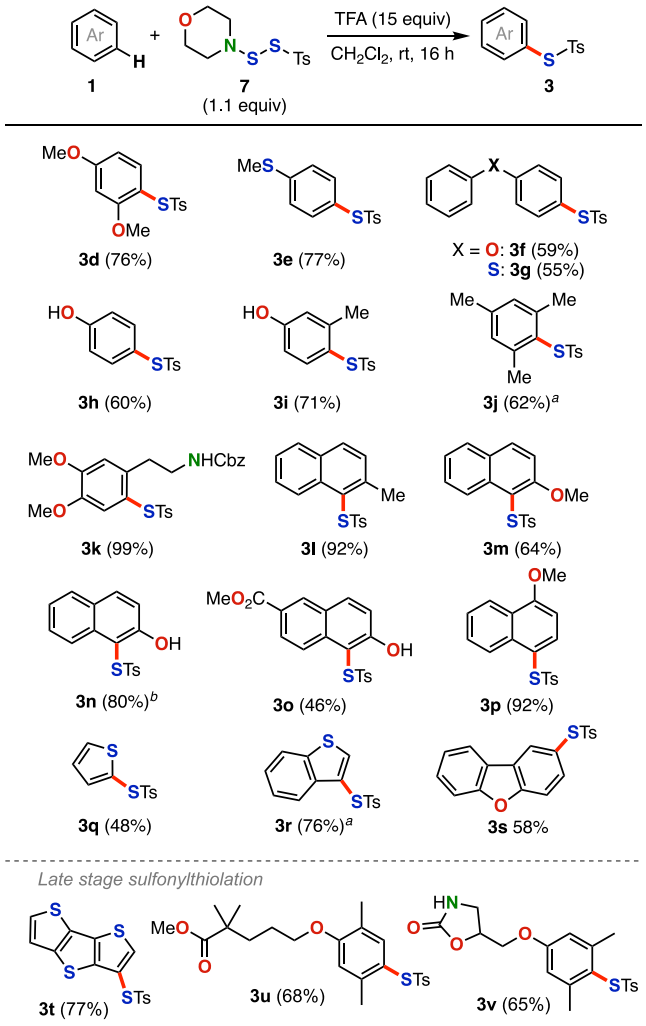

Figure 3. Substrate scope. Isolated yields are shown. [a]Toluene was used instead of CH_2Cl_2. [b]TFA (5.0 equiv) was used.

muscle relaxant) afforded the corresponding thiosulfonates **3t**–**3v** in good yield. It should be noted that all of the transformations exclusively gave monothiolated products due to the strong electron-withdrawing effect of the sulfonyl group. This result is in contrast with some previously reported C–S bond formations.[15]

As shown in Figure 1A, the wide substrate scope of the sulfonylthiolation and the remarkable transformability of the resulting thiosulfonate enable rapid access to divergent combinations of aryl sulfides via double C–S bond formation (Figure 4). For example, papaverine (**1w**, an antispasmodic drug) and a glycine fragment were sequentially assembled into platform molecule **7** to afford the hybrid molecule **5c** in good yield (Figure 4A).[16] The rapid expansion of the ring system of 6-bromo-2-naphthol (**1x**) was also accomplished via TFA-mediated sulfonylthiolation and subsequent C–S/C–O bond formation with benzyne (Figure 4B).[17,5e] Furthermore, an advantage of this direct mono C–S bond formation was showcased by the sequential introduction of multiple different sulfanyl groups on one molecule (Figure 4C).[15] These results clearly demonstrated the utility of platform molecule **7** for combining nonsulfur carbon nucleophiles to afford functionalized sulfides.

To gain insights into the mechanism of the TFA-mediated sulfonylthiolation, we conducted several control experiments

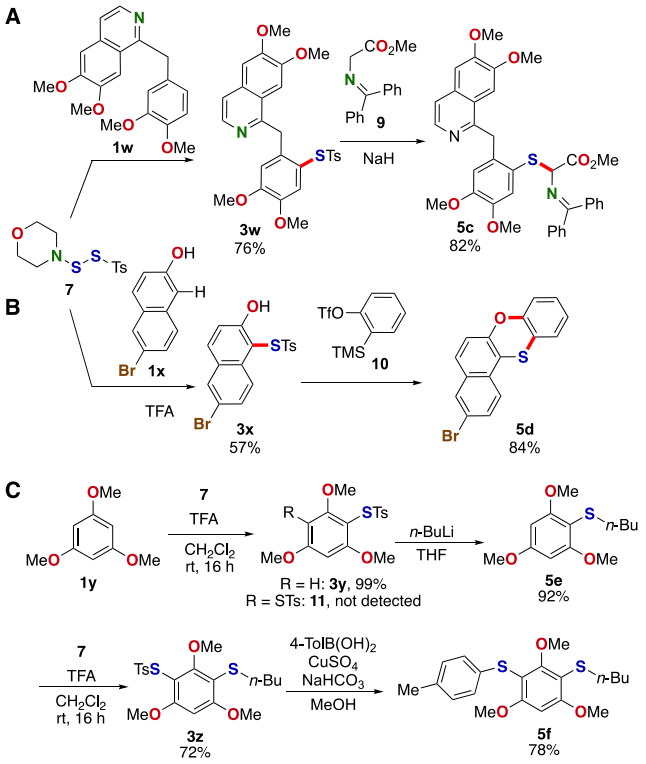

Figure 4. Synthesis of diverse sulfides via the double C–S bond formations of **7**. (A) Conjugation of papaverine (**1w**) and glycine imino ester **9**. (B) Preparation of phenoxathiin derivative **5d** via the aryne reaction. (C) Sequential multisulfanylation of **1y**. See the Supporting Information for details.

(Figure 5). The reaction of anisole (**1b**) with **7** in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO)

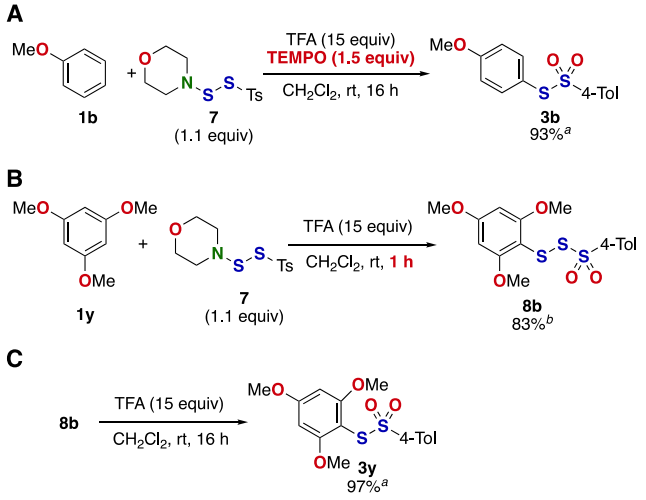

Figure 5. Mechanistic studies. (A) Sulfonylthiolation of anisole (**1b**) in the presence of TEMPO. (B) Isolation of intermediate **8b** before desulfurization. (C) Desulfurization of **8b** to **3y**. [a]Yields were determined by NMR analysis. [b]Isolated yield is shown.

did not significantly affect the formation of thiosulfonate **3b**, suggesting that radical intermediates are not involved (Figure 5A). Furthermore, treatment of 1,3,5-trimethoxybenzene (**1y**) with **7** under standard conditions for 1 h afforded *SS*-aryl 4-toluene(dithioperoxo)sulfonate **8b**, the expected desulfuriza-

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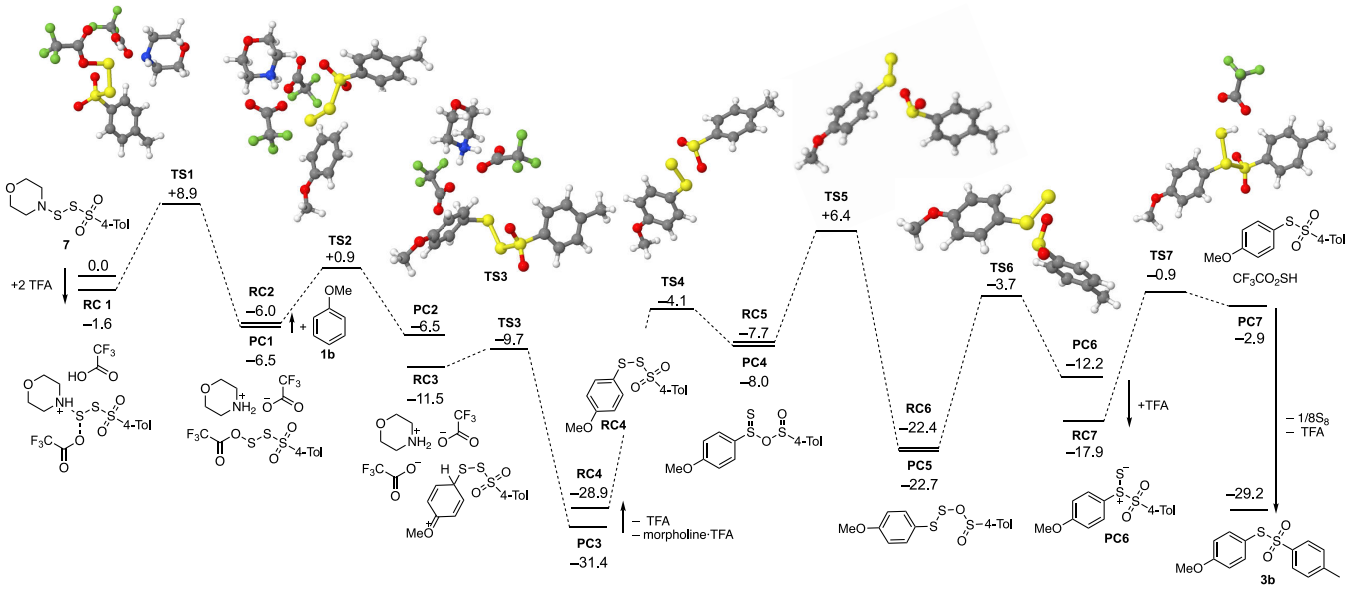

Figure 6. Calculated potential energy diagram (in kcal mol^{-1}) obtained by the B3LYP/6-31+G(d,p) level of theory for the reaction of anisole (**1b**) with *SS*-morpholino 4-toluene(dithioperoxo)sulfonate (**7**) to afford thiosulfonate **3b**. Color code of atoms: hydrogen, white; carbon, gray; nitrogen, blue; oxygen, red; fluorine, green; sulfur, yellow.

tion precursor intermediate, in 83% yield (Figure 5B). In addition, the desulfurization of **8b** to thiosulfonate **3y** was confirmed after the conversion of **8b** in the presence of TFA for 16 h (Figure 5C). The results obtained from the control experiments (Figure 5) and crossover experiment (Figure 2A) indicated that the reaction proceeds via selective transformation of the morpholino group over the tosyl group to afford *SS*-aryl 4-toluene(dithioperoxo)sulfonate[18] followed by sulfur extrusion.[12a]

This mechanistic insight was supported by density functional theory (DFT) calculations. On the basis of the reaction mechanism previously proposed,[12b] we performed geometry optimizations and vibrational frequency calculations at the B3LYP/6-31+G(d,p) level of theory to obtain the structures of intermediates **RC1**−**PC7** and those of transition states **TS1**−**TS7** (Figure 6). The results indicated that the activation of the morpholino group occurs to form **PC1**, which subsequently reacts with anisole (**1b**) in an electrophilic aromatic substitution reaction to afford *SS*-aryl 4-toluene(dithioperoxo)-sulfonate (**PC3**). Sulfur extrusion of **PC3** via thiosulfoxide **PC6** affords thiosulfonate **3b**. These results suggest the possibility of a pathway from **7** to **3b**, which involves C−S bond formation and desulfurization.

In conclusion, we have developed a TFA-mediated desulfurilative sulfonylthiolation of arenes using *SS*-morpholino 4-toluene(dithioperoxo)sulfonate (**7**) as a doubly transformable sulfur platform. The wide substrate scope of this reaction and the ability to transform the resulting thiosulfonates enables rapid access to various combinations of sulfides or the conjugation of functional molecules via double C−S bond formation. Control experiments and theoretical calculations suggested that the reaction proceeds via the electrophilic aromatic substitution mechanism and subsequent sulfur extrusion with selective activation of the morpholino group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04289.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(10) The known methods suffer from practical limitations. For example, the $CeCl_3$-mediated sulfonylthiolation[9a] of anisole (**1b**) with TsSTs (**2**) resulted in no reaction due to the low reactivity of **2** (Figure 1C).

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