JOC The Journal of Organic Chemistry

Article

Copper-Catalyzed Synthesis of Thiadiazine-1-oxides in Reusable Aqueous Medium Under External [Ag]/Ligand/Base-Free Conditions

Cui Wu, Riting Huang, Ming Zhang, and Zhiyuan Chen

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02828 • Publication Date (Web): 18 Dec 2019

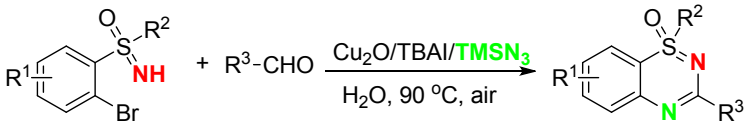
Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Copper-Catalyzed Synthesis of Thiadiazine-1-oxides in Reusable Aqueous Medium Under External [Ag]/Ligand/Base-Free Conditions

Cui Wu, Riting Huang, Ming Zhang, and Zhiyuan Chen*

Key Laboratory of Functional Small Organic Molecules, Ministry of Education, and College of Chemistry & Chemical Engineering, Jiangxi Normal University, 99 Ziyang Road, Nanchang, Jiangxi 330022 (P. R. China). E-mail: zchen@jxnu.edu.cn



40 examples, 35-95% yield.
Hot water as the solvent.
Resuable catalytic system

ABSTRACT: We report herein a copper-catalyzed multicomponent reaction of simple *N*H-sulfoximine with readily available aldehyde and $TMSN_3$ in hot water and aerobic conditions. The reaction tolerated a broad range of functional groups under external [Ag]/ligand/base-free conditions, and can form three C-N bonds in a one-pot transformation, thus represent an extremely cost-effective protocol to biologically active sulfoximine derivatives. This aqueous catalytic system could be circularly utilized in consecutive runs of gram-scale preparations of thiadiazine-1-oxides without extra addition of copper catalyst and PTA. Mechanistically, an "ortho-binding" effect in ortho-bromo *N*H-sulfoximine was proposed to control the chemoselectivity, thus, the other free halides such as bromo- or iodo-atoms in aldehydes **2** were compatible in the reaction.

INTRODUCTION

Biologically active sulfoximine derivatives have attracted noticeable attention recently due to the frequent appearance of the structural motifs in pharmaceutical sciences.[1] Fused heterocyclic benzothiadiazine 1‐oxides bearing a benzene‐fused sulfoximine moiety are particularly relevant to potential medicinal applications (Figure 1).[2] For instance, the bicyclic thiadiazine-1-oxide **A** has been shown to exhibit blood pressure-lowering activity in animal testing as an equipotent to the marketed drug Prazosin.[3] NSC287474 possesses a potential reverse transcriptase inhibitor with inhibition to HIV replication in lymphocytes.[4] Tricyclic fused sulfoximine Gö4962 has displayed significant characteristics as a partial benzodiazepine receptor agonist with excellent anxiolytic and anticonvulsive activities. [5]

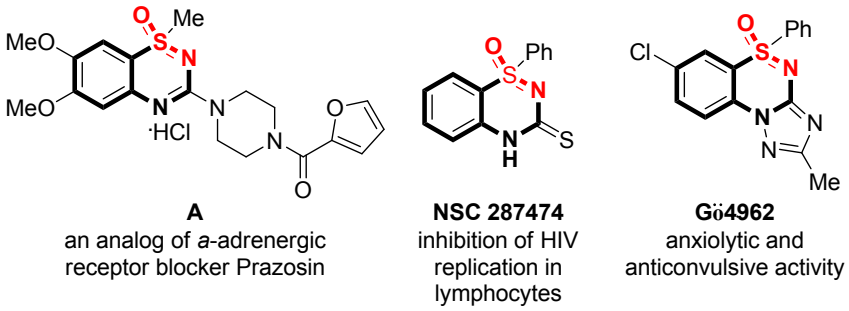


Figure 1. Selected bioactive thiadiazine-1-oxide derivatives.

In spite of the importance of these derivatives, the preparation methods of thiadiazine-1-oxides in organic synthesis are amazingly limted and still need significant development, in efficient synthetic techniques for this structure. The traditional pathways use nitroaryl thioethers or 2-thio-substituted anilines[6] or *N*-protected sulfoxides[7] as the starting materials. Several preparation methods have reportedly utilized *O*-(mesitylenesulfonyl)hydroxylamine (MSH), *n*BuLi/TsN_3,[8] or *tert*-butyl(2,4,6-trichlorobenzoyl)oxycarbamates (Scheme 1, eq. 1),[9] as the key aminating reagents, were reported for cyclic thiadiazine-1-oxide synthesis frameworks. Nevertheless, these methods generally require multiple-step transformations and harsh reaction conditions. To account for these problems, we recently developed a microwave assisted Cp^*Co^{III}-catalyzed one-pot and one-step construction of diverse thiadiazine 1-oxides, starting from *N*H-sulfoximines with 1,4,2-dioxazol-5-ones (Scheme 1, eq. 2).[10] Recently, Dong and co-workers have also disclosed a Cp^*Rh^{III}-catalyzed annulation reaction to build dihydrobenzo thiadiazine 1‐oxide derivatives from *N*H‐sulfoximine and two components of benzyl azides (Scheme 1, eq. 3).[11]

Although these two methods maybe applicable for the preparation of the fused aza-heterocyclic sulfoximines, several limitations still exist: (1) expensive transition-metal catalysts, Cp*M (M = Rh or Co) are needed; and additionally, Ag salts or additional ligands should be added to activate the catalytic species; (2) almost all of the amination reagents are not commercially available, and therefore they must be prepared in advance; (3) stoichiometric excess of external bases or oxidants must be employed; and (4), organic halide solvents are also generally required. These limitations create challenges in high cost and necessary considerations for environmental protection in order to conduct a large-scale synthesis. To further investigate tandem cyclization transformations to polycyclic frameworks or azaheterocyclic molecules,[12] we have proposed a new strategy that would allow for the replacement of the expensive Cp*M complexes with naturally abundant Cu salts as the catalyst. Additionally, if a readily available nitrogen source and commercial aldehyde could be directly employed, a succinct and environment-friendly route to the class of bicyclic sulfoximines could be developed.

Our previous findings revealed that the *N*H-benzoyl-substituted sulfoximine species, a key intermediate to deliver the thiadiazine-1-oxides, could be generated through Cp^*Co^{III}-catalyzed *ortho*-C−H amidation reaction.[10] Therefore, our current report will show an alternative facile synthesis of thiadiazine-1-oxides in an aqueouls solution. The starting materials for the cascade reaction are from readily available azides as the N source and aldehydes as the coupling reagent, thus to highly and efficiently generating diverse thiadiazine-1-oxides with excellent functional group tolerance

under cost-effective copper catalyzed conditions (Scheme 1, eq. 4). It's interesting to note that this aqueous catalytic system could be reused several times upon extraction of the final products when the reaction reaches completion, without affecting the catalytic efficiency of the expected products.

Scheme 1. Reported access to thiadiazine-1-oxides and our design.

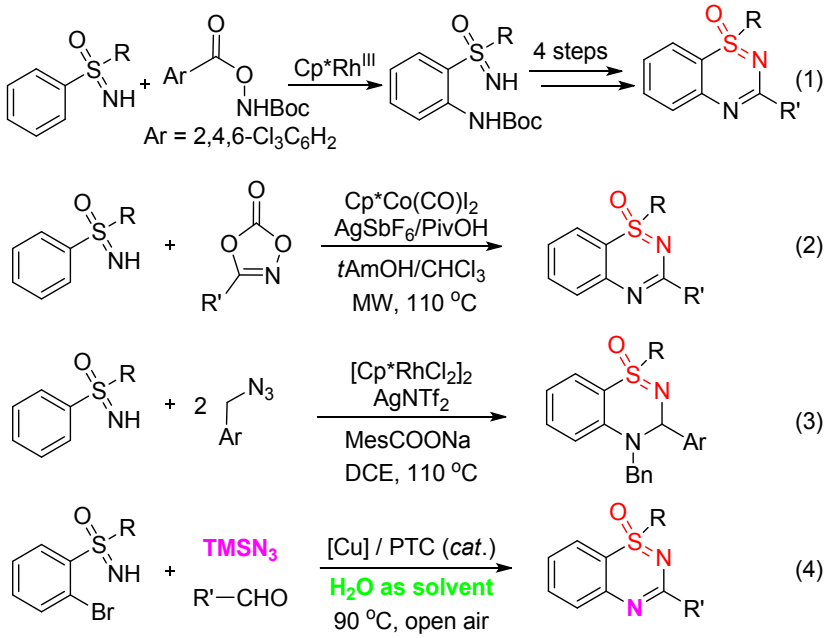
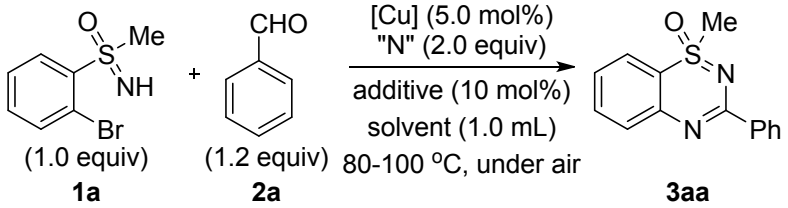


Table 1. Optimization of the reaction conditions.[a]



entry	[Cu]	"**N**"	solvent	additive	**3aa** /%
1	CuI	$NH_3.H_2O$	DMSO	-	n.r.
2	CuI	NaN_3	DMSO	-	10
3	CuI	$TMSN_3$	DMSO	-	29
4	CuI	MsN_3	DMSO	-	trace
5	CuBr	$TMSN_3$	DMSO	-	27
6	CuCl	$TMSN_3$	DMSO	-	26
7	Cu_2O	$TMSN_3$	DMSO	-	55
8	Cu	$TMSN_3$	DMSO	-	19

9	$Cu(OTf)_2$	$TMSN_3$	DMSO	-	22
10	-	$TMSN_3$	DMSO	-	0
11	Cu_2O	$TMSN_3$	DMSO/H_2O	-	46[b]
12	Cu_2O	$TMSN_3$	H_2O	-	65
13	Cu_2O	$TMSN_3$	H_2O	SDS	56
14	Cu_2O	$TMSN_3$	H_2O	$n$$Bu_4OAc$	60
15	Cu_2O	$TMSN_3$	H_2O	TritonX-100	81
16	Cu_2O	$TMSN_3$	H_2O	TBAB	72
17	Cu_2O	$TMSN_3$	H_2O	TBAI	87
18	Cu_2O	$TMSN_3$	H_2O	TBAI	60[c]
19	Cu_2O	$TMSN_3$	H_2O	TBAI	95[d]
20	Cu_2O	$TMSN_3$	H_2O	TBAI	89[e]
21	Cu_2O	NaN_3	H_2O	TBAI	18

[a]Reaction conditions: *N*H-sulfoximine **1a** (0.30 mmol), benzaldehyde **2a** (0.36 mmol) in 1.0 mL of solvent at 80 °C for 12-24 h, isolated yield. [b] DMSO/H_2O = 9 : 1 (*v/v*); [c] TBAI (1.0 equiv); [d] T = 90 °C; [e] T = 100 °C. SDS = sodium dodecanesulfonate; TritonX-100 = polyethylene glycol mono-4-octylphenyl ether (n ≈ 10).

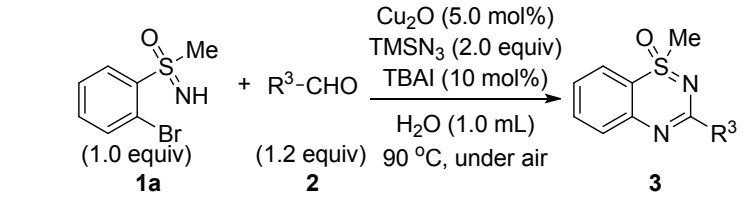
RESULTS AND DISCUSSION

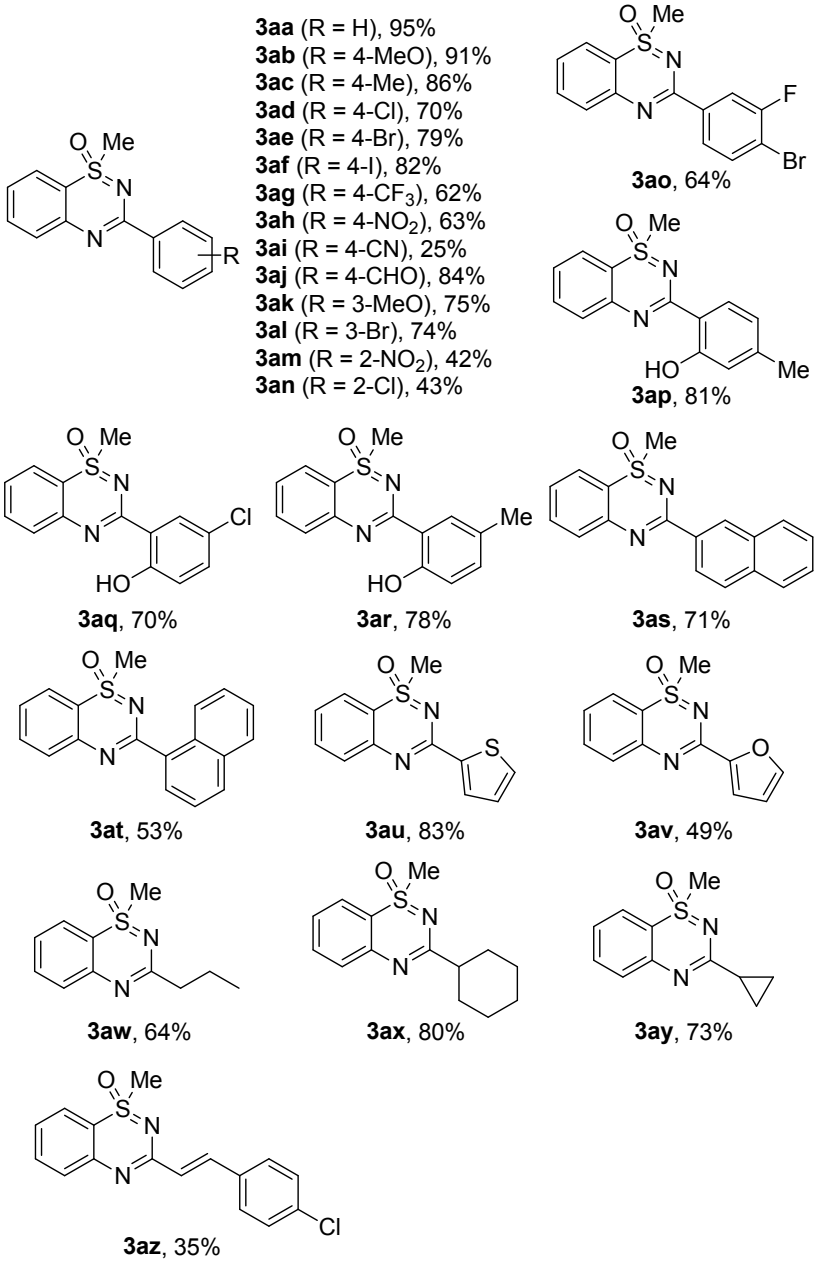
We began the study by using 1-bromo-2-(S-methylsulfonimidoyl)benzene (**1a**) and benzaldehyde (**2a**) as the model substrates in DMSO at 80 °C (Table 1). *N*H-Sulfoximine **1a**, which contained a methyl substitution at the S-linkage, was selected as the starting material in this reaction because the S-alkyl substituted benzothiadiazine 1-oxides were found to be difficult to generate in the previous Cp*M-catalyzed (M = Co, Rh) annulation reactions.[10,11] To explore reaction conditions that would be highly compatible with various functional groups, acidic or basic additives were avoided in the subsequent optimizations. With CuI as the catalyst, different "N" sources were screened, such as $NH_3.H_2O$, NaN_3, azidotrimethylsilane ($TMSN_3$), and methanesulfonyl azide (MsN_3) were screened, which indicated that the desired product **3aa** could be generated in 29% yield when $TMSN_3$ was utilized (entries 1-4). Subsequently, the copper catalysts with varied oxidation states were evaluated. While even Cu powder worked to some extent (entry 8), Cu_2O hold the most optimal results among the [Cu] catalyst examined (entries 5-9). A control experiment also clearly indicated that no reaction occurred when in the absence of any metal catalyst species (entry 10). Water was found to be unprofitable in the previous CuF_2-mediated reductive amination reaction of aryl halides with azides,[13] however, it was observed that the addition of water in no way harmful to this catalytic C-N bond formation reaction. The expected product **3aa** could be isolated in 46% yield when a mixture solvent of DMSO/H_2O (9:1, *v/v*) was utilized (entry 11). This result led us to employ pure water as the reaction medium, which then had an improved yield of 65% (entry 12).[14] The addition of phase-transfer catalyst (PTC) as an additive to this aqueous reaction also proved to be useful. While a good yield was observed when 10 mol% of TritonX-100 was added, screening of different PTCs showed that tetrabutylammonium iodide (TBAI) provided the best result at 87% (entries 13-17). In addition to the

result, the reaction yield decreased when the stoichiometric amount of TBAI was added (entry 18). Furthermore, the reaction time was shortened to about 12 h at reflux temperature, and an excellent yield of 95% was obtained when heating the reaction was set at 90 °C (entries 19-20). However, under this aqueous medium using water as the solvent, NaN_3 was again not a good N source that can be used instead of $TMSN_3$, because the yield of the desired product **3aa** was only 18% under the optimized conditions (entry 21). The aqueous and atmospheric conditions were found to be optimal for this reaction, which suggests that this facile protocol be of probably utmost practical for industrial large-scale applications.

Once we completed optimization for the reaction conditions (Table 1, entry 19), we studied the scope for the Cu_2O-catalyzed protocol for the synthesis of thiadiazine-1-oxide **3**. Initially, we chose *N*H-sulfoximine **1a** as a model substrate and commercially available aryl or alkyl aldehydes **2** to explore the feasibility and efficiency of the desired transformation. As can be seen from Scheme 2, a wide range of aryl aldehydes **2** containing diversified functional groups were well tolerated in the reactions, resulting in the expected bicyclic sulfoximine heterocycles **3aa-3av** in aqueous solution. The benzaldehyde **2**, which bears strong electron-donating 4-MeO or 3-MeO, were tolerated to give the desired products **3ab** and **3ak** in good yields. Aryl aldehydes **2** attached with electron-withdrawing halo-substitutions, such as chloro (**3ad** and **3an**), bromo (**3ae** and **3al**), iodo (**3af**), fluoro (**3ao**), and trifluoromethyl (**3ag**) groups, all were well tolerated without difficulty, regardless of their locations at the *para*-, *meta*- or *ortho*- position of the phenyl moiety. In addition, the strong electron-withdrawing group, such as NO_2 and CN, were also tolerated to give the desired products **3ah** and **3ai** in acceptable yields. The steric effect of the *ortho*-substituted benzaldehydes influenced the efficiency of the reaction dramatically, delivering compounds **3am** and **3an** in only serviceable yields.

Scheme 2. Reaction scope studies.[a]



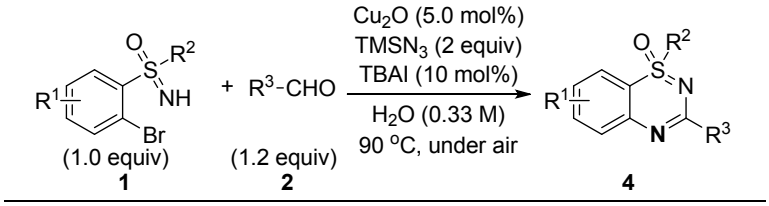


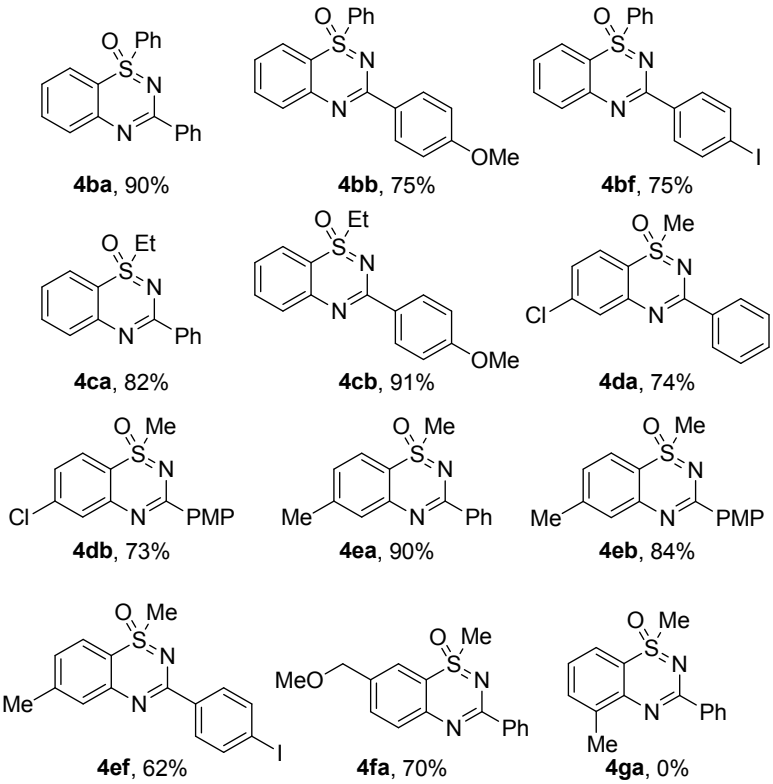
[a]Reaction conditions: *N*H-sulfoximine **1a** (0.30 mmol), aldehyde **2** (0.36 mmol, 1.3 equiv) and TBAI (10 mol%) in 1.0 mL of H_2O at 90 °C under air conditions. Isolated yield.

Interestingly, the terephthalaldehyde **2j** which contained two formyl groups at the para positions of the phenyl ring alsoreacted well to provide the CHO substituted product **3aj** at a 84% yield. The existence of a free formyl substitition in this compound **3aj** indicated its capability to react with another *N*H-sulfoximine under similar conditions. Furthermore, the tolerance of a free hydroxyl group in benzaldehyde **2** was then studied. The reactions occurred smoothly with OH moiety in ortho- position to the formyl group, affording the expected products **3ap**, **3aq**, and **3ar** with good results. The heterocyclic 2-thenaldehyde and 2-furaldehyde also participated in the reaction to give the cyclized products **3au** and **3av** in 83% and 49% yields, respectively.

To our delight, modest to good yields were obtained for the reactions of alkyl or alkenyl aldehydes **2** with *N*H-sulfoximine **1a** in this reaction. For instance, the reactions of butyraldehyde **2w** and cyclohexancarbaldehyde **2x** with **1a** proceeded nicely to produce the desired alkyl-substituted heterocyclic sulfoximine **3aw** and **3ax** in good yields. The strained cyclopropanecarboxaldehyde **3y** participated in the cyclization reaction, giving the cyclopropyl-substituted sulfoximine heterocycle **3ay** in 73% yield. Under the standard conditions, unsaturated 4-chlorocinnamaldehyde also underwent the reaction to give the corresponding product **3az** in synthetically useful yield.

Scheme 3. Reaction scope studies. [a]

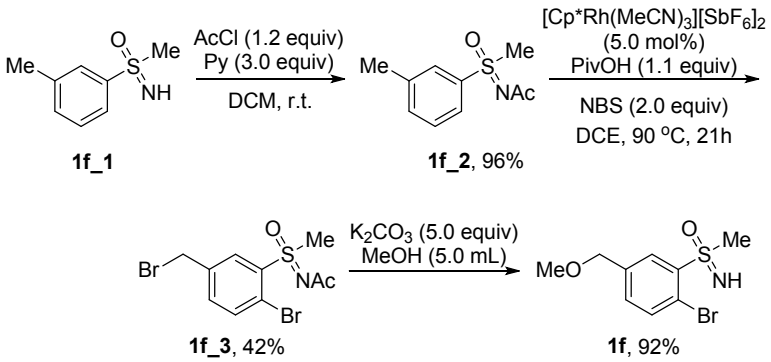




[a]Reaction conditions: *N*H-sulfoximine **1** (0.30 mmol), aldehyde **2** (0.36 mmol, 1.3 equiv) and TBAI (10 mol%) in 1.0 mL of H_2O at 90 °C under air conditions. Isolated yield.

A series of structurally diverse *N*H-sulfoximines **1** with aldehydes **2** were further examined to investigate the generality of the cyclization (Scheme 3). Diphenyl sulfoximine **1b** reacted with free benzaldehyde **2a** to give the desired products **4aa** in 90% yield. The tolerance of an iodo atom from 4-iodobenzaldehyde **2f** could afford the halide-substituted thiadiazine-1-oxide **4bf** in 75% yield. Accordingly, the substitutions which attached to the S atom in *N*H-sulfoximine **1** could be the ethyl group **2c**, which produced the desired products **4ca** and **4cb** in 82% and 91% yields, respectively. Moreover, a series of para-substituted substrates bearing either electron-withdrawing Cl or -donating Me groups could all react smoothly, affording the desired products (**4da**–**4ef**) in good to excellent yields ranging from 62-90%. And the synthetically versatile iodo group in compounds **4bf** and **4ef** indicated their further transformations through transition-metal-catalyzed cross-coupling reactions could be easily achieved.

Scheme 4. Synthesis of **1f**.

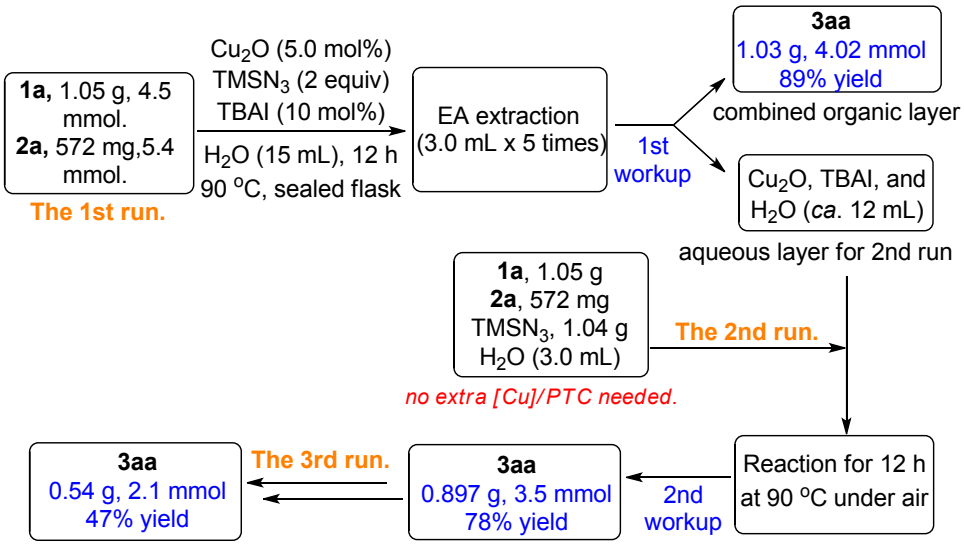


In addition to these results, the 5-$MeOCH_2$-substituted *N*H-sulfoximine **1f** was synthesized according to the protocol as illustrated in Scheme 4. The reaction of **1f** with **2a** was conducted under the standard conditions, the expected product 5-$MeOCH_2$-sustitution thiadiazine-1-oxide **4fa** was isolated in 70% yield. However, a steric effect was obtained for the reaction of 3-Me substituted sulfoximine **1g** with benzaldehyde, the desired product **4ga** could not be obtained under the standard conditions.

The synthetic utility of this Cu_2O-catalyzed synthesis of thiadiazine-1-oxides in H_2O solution could be demonstrated by sequential consecutive runs of gram-scale synthesis of the expected product **3aa** Scheme 5). In the first run of the procedure, the starting materials **1a** (1.05 g, 4.5 mmol) and **2a** (1.2 equiv), $TMSN_3$ (2.0 equiv), Cu_2O (0.225 mmol) and TBAI (0.45 mmol) were mixed in 15 mL of H_2O. The reaction was maintained at 90 °C for 12 h. Upon completion, the reaction was cooled to room temperature and the organic components were extracted with ethyl acetate (EA) for several times; the upper organic layer was partitioned by a burette carefully each time. The combined organic layer was concentrated and isolated to give product **3aa** in 89% yield. The under layer aqueous phase was left in the mother-flask for the second run, in which compounds **1a** (4.5 mmol), **2a** (1.2 equiv), and $TMSN_3$ (2.0 equiv) were added with 3.0 mL of H_2O to the flask in this run, but without the addition of Cu_2O and TBAI. The reaction was

then heated at 90 °C for another 12 h to reach completion. The yield of **3aa** in the second run was 78% yield, which indicated that the method could be applied for the consecutive synthesis of the desired products without any extra addition of a copper catalyst and PTA. Unfortunately, a dramatic decrease in yield of **3aa** was observed in the similar third run, presumably due to the loss of the [Cu] and PTA during the extraction process.

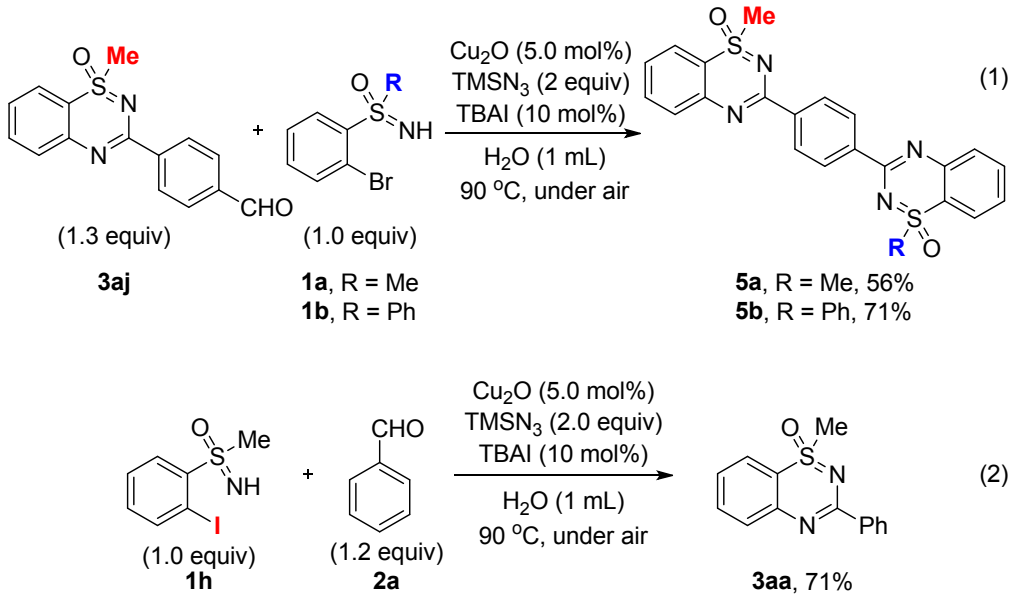
Scheme 5. Gram-scale synthesis of **3aa** in two consecutive runs.



As mentioned above, the compound **3aj** that contained a free formyl group (CHO) group indicated that this product could be utilized as a starting material to react with *N*H-sulfoximine **1a** or **1b** under the standard conditions to give the products **5**, which contains two thiadiazine-1-oxide moieties in the molecule (Scheme 6, eq 1.). For the reaction of **1a** with **3aj**, the expected product **5a** could be isolated in 56% yield; however, in the reaction of **1b** with **3aj**, the desired product **5b** was isolated in 71% yield.

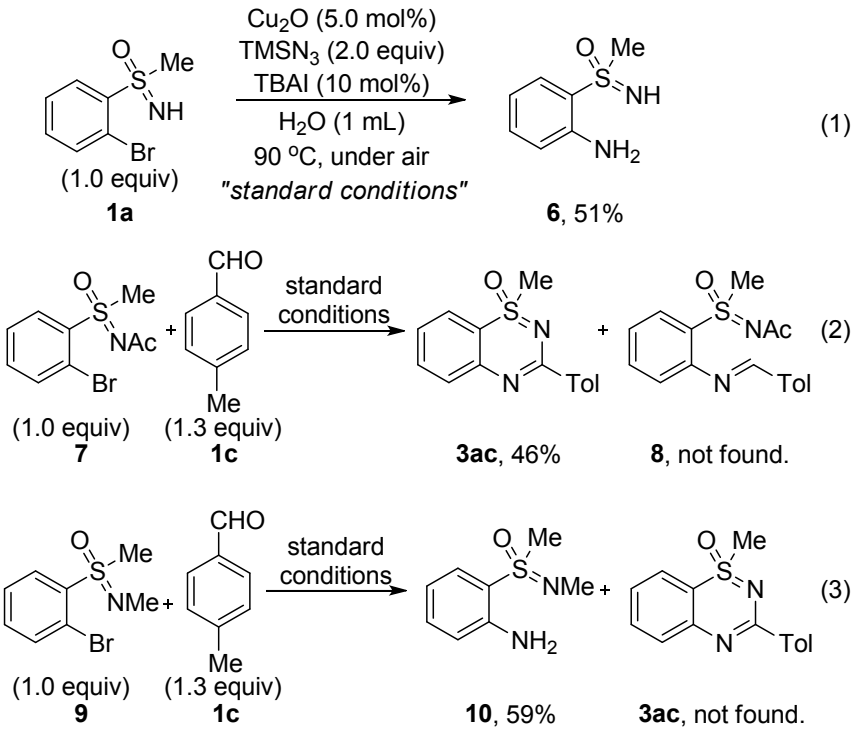
We have also tried the reaction of the other *ortho*-halide substituted ***N***H-sulfoximine **1** with benzaldehyde **2a**. Good yield of **3aa** was obtained for the reaction of aryl iodide **1h** with **2a** (Scheme 6, eq 2). However, only <10 yield of **3aa** was observed in the reaction of *ortho*-chloride substituted ***N***H-sulfoximine with **2a**.

Scheme 6. Extension reactions from **3aj** and the reaction of *ortho*-iodide substituted ***N***H-sulfoximine **1h**.

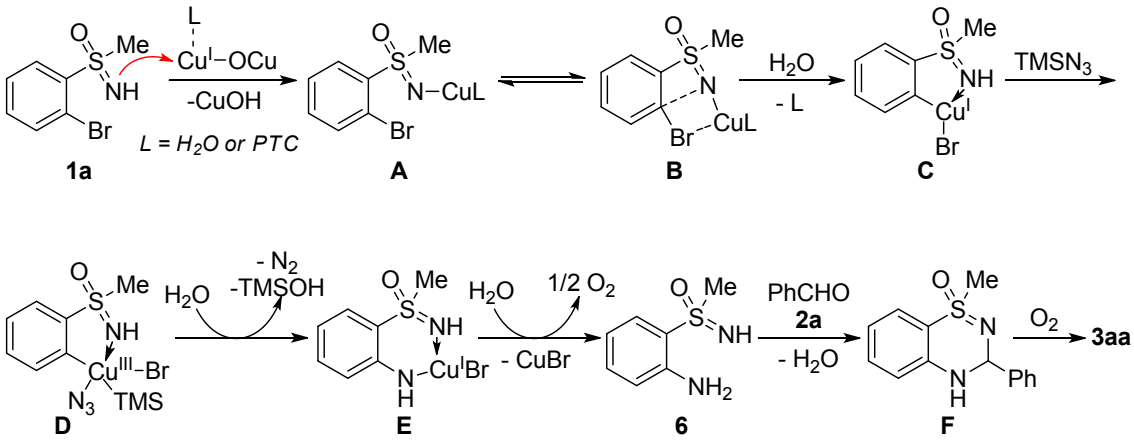


To further shed light on the reaction mechanism, several extention reactions were studied (Scheme 7). For the Cu_2O-catalyzed reaction of *N*H-sulfoximine **1a** with $TMSN_3$ without the addition of aldehyde, the *ortho*-amino sulfoximine **6** was isolated in 51% yield under the standard conditions (eq. 1). This result indicated that a copper-catalyzed C-Br amination reaction should be involved as a key step in the reaction sequence. This result was further supported by the reactions of *N*-protected sulfoximine **7** or **9** with 4-methylbenzaldehyde **1c**. In the reaction of NAc-sulfoximine **7** with **1c**, the cyclization product **3ac** could be isolated in moderate yield while the putative imine side product **8** could not be detected (eq. 2), due to the hydrolysis ability of the amide bond in compound **7**. However, when NMe-sulfoximine **9** was employed under the standard conditions, the amino-substituted intermediate **10** was formed because N-Me bond was stable in aqueous condition, whilst **3ac** cannot be detected (eq. 3).

Scheme 7. Control experiments.



Scheme 8. Proposed mechanism**.**



Inspired by our current results and the previous reports on the copper-catalyzed cross-coupling reactions of aryl bromide with azides,[13,15] we proposed a possible mechanism for this reaction as outlined in Scheme 8. Initial nucleophilic metallation reaction of substrate **1a** with Cu_2O could be expected to form a low-valent copper species **A.** The ortho-C-Br bond in intermediate **B** could be selectively activated through "ortho-binding" effect, thus to efficiently control the chemoselectivity of this reaction. Note that the other free halides, such as Br or I in aldehydes **2**, could be compatible in this reaction without difficulty. The next oxidative addition reaction with aryl bromide under the assistance of H_2O or PTC as a ligand to give the complex **C**. The subsequent oxidative addition of **C** with $TMSN_3$ to generate a copper-azide complex **D**, followed by a denitrogenative reductive elimination reaction with H_2O to give

complex **E**. Hydrolysis decomposition of **E** would give rise the ortho-amino sulfoximine intermediate **6** and regenerate the active low valent copper species to complete the catalytic cycle. The final condensation reaction followed by aromatization would deliver the observed product **3aa**.

In summary, we have developed a copper-catalyzed multicomponent reaction of simple *N*H-sulfoximine with aldehyde and $TMSN_3$, to selectively produce diverse thiadiazine-1-oxides in good to excellent yields. The readily available $TMSN_3$ was found to be a suitable N source and common aldehydes were employed as the annulation substrates, thus resulting in no external Ag salt, ligand, or base was required, and only hot water was employed as the neat solvent under aerobic conditions. An "ortho-binding" effect in substrate **1** was proposed in this reaction to control the chemoselectivity, thus, the other free bromo- or iodo-atoms in aldehydes **2** were found to be well tolerated. This novel methodology represents an environmentally benign and inexpensive avenue to deliver medicinally significant thiadiazine-1-oxides. In addition, this aqueous catalytic system could be circularly utilized in consecutive runs of scaled-up preparations of the bicyclic heterocyclic sulfoximines. Further applications of this facile and more sustainable method to synthesize useful heterocyclic sulfoximines are currently underway.

EXPERIMENTAL SECTION

General information. Unless otherwise noted, commercial reagents were purchased from the commercial suppliers, and were used as received. Reactions were conducted under air. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Flash column chromatography was performed using silica gel (60-Å pore size, 32-63 μm, standard grade). Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25-35 °C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million (ppm) from internal standard tetramethylsilane (TMS) on the δ scale. High resolution mass spectrometry (HRMS) spectra analysis was performed by electrospray ionization (ESI-micrOTOF). Most of the starting *N*H-Sulfoximines **1**, **7** and **9** were purchased from commercal source in this project. Except for *N*H-Sulfoximine **1f**, which was prepared in our lab following the literature method.[16]

General procedure for the preparation of NH-sulfoximine 1f.

To an ice-cold stirred solutuon of **1f_1** (960 mg, 5.68 mmol) and Py (1.34 g, 17 mmol) in 10 mL of dichloromethane (DCM) was added acetyl chloride (531 mg, 6.82 mmol) dropwise at 0 °C. The resulting solution was stirrred under N_2 for 3 h. Upon completion, water (10 mL) was added to quench the reaction, and extracted with DCM (5.0 mL x 3). The combined solvent was washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified through column chromatography to give the desired product 1-methyl-3-(S-methylsulfonimidoyl)benzene **1f_2** (1.12 g, 96%) as a yellow oil.

***N*-(Methyl(oxo)(m-tolyl)-l6-sulfanylidene)acetamide 1f_2**

Yield 1.12 g, 96%; yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.47 (m, 2H), 3.35-3.29 (m, 3H), 2.46 (d, *J* = 3.0 Hz, 3H), 2.21-2.11 (m, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 180.3, 140.1, 138.6, 134.6, 129.5, 127.3, 124, 44.2, 26.8, 21.4. **HRMS** calcd. for $C_{10}H_{14}NO_2S$ $(M+H)^+$: 212.0740, found: 212.0746.

To a screw-capped test tube were added 1-methyl-3-(S-methylsulfonimidoyl)benzene **1f_2** (600 mg, 2.84 mmol), NBS (1.01 g, 5.68 mmol),$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (118 mg, 0.14 mmol), PivOH (332 mg, 3.12 mmol) and 1,2-DCE (8.0 mL). The mixture was stirred at 90 °C oil bath for 21 h. The reaction was monitored by TLC. The mixture was then cooled to room temperature, diluted with EtOAc (10 mL), and washed with saturated $Na_2S_2O_3$ solution (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The product was purified by flash chromatography on silica gel to give the desired product **1f_3** (417 mg, 42% yield) as a yellow solid.

***N*-((2-Bromo-5-(bromomethyl)phenyl)(methyl)(oxo)-l6-sulfanylidene)acetamide 1f_3**

Yield 412 mg, 42%; yellow solid, mp: 154-155°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.49 (m, 2H), 3.45 (s, 3H), 2.12 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 179.5, 139.0, 138.4, 136.2, 135.1, 132.1, 118.8, 41.6, 30.7, 26.2. **HRMS** calcd. for $C_{10}H_{12}Br_2NO_2S$ $(M+H)^+$: 367.8950, found: 367.8956.

To a stirred solution of NAc-Sulfoximine **1f_3** (210 mg, 0.57 mmol) and K_2CO_3 (395 mg, 2.86 mmol) were stirred in MeOH (5.0 mL) at room temperature for 2 h. Upon the completion of the reaction as determined by TLC, the solvent was removed in vacuo. The product was purified by flash chromatographyon silica gel to give the expect product 1-bromo-4-(methoxymethyl)-2-(S-methylsulfonimidoyl)benzene **1f** (146 mg, 92%) as a yellow oil.

(2-Bromo-5-(methoxymethyl)phenyl)(imino)(methyl)-l6-sulfanone 1f.

Yield 146 mg, 92%; yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.74 (m, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 4.47 (s, 2H), 3.43 (d, *J* = 1.2 Hz, 3H), 3.32 (d, *J* = 1.2 Hz, 3H), 2.91 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 142.5, 139.1, 135.7, 132.8, 129.8, 119.4, 73.2, 58.6, 43.1. **HRMS** calcd. for $C_9H_{13}BrNO_2S$ $(M+H)^+$: 277.9845, found: 277.9851.

General procedure for the preparation of thiadiazine-1-oxides 3 or 4.

To a vigorous stirred mixture of *N*H-Sulfoximine **1** (0.30 mmol), aldehyde **2** (0.36 mmol), Cu_2O (0.015 mmol), and TBAI (0.03 mmol) in H_2O (1.0 mL) was added $TMSN_3$ (0.60 mmol) under an air atmosphere. The reaction was heated at 90 °C oil bath for about 12 h. Upon completion of the reaction as indicated by TLC, the reaction was allowed to cool to room temperature, and diluted with water (2.0 mL) and saturated aqueous $NaHCO_3$ (2.0 mL), then extracted with ethyl acetate (3.0 mL×4). The combined organic layer was dried over Na_2SO_4, and concentrated to give the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to afford the expected thiadiazine-1-oxides **3** or **4**, as a white solid.

1-Methyl-3-phenyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3aa)

Yield 73 mg, 95%; white solid, mp: 132-133 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.37 (m, 2H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.46-7.44 (m, 3H), 7.38 (t, *J* = 7.4 Hz, 1H), 3.52 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.9, 147.5, 137.4,

135.0, 131.0, 128.9, 128.5, 128.2, 126.2, 123.5, 113.1, 47.1. **HRMS** calcd. for $C_{14}H_{13}N_2OS$ $(M+H)^+$: 257.0743, found: 257.0741.

3-(4-Methoxyphenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide(3ab)

Yield 78 mg, 91%; white solid, mp: 151-152 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35-8.33 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.70-7.63 (m, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.36-7.32 (m, 1H), 6.96-6.93 (m, 2H), 3.85 (s, 3H), 3.51 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 162.2, 157.6, 147.9, 134.9, 130.3, 129.9, 128.7, 125.7, 123.5, 113.5, 112.8, 55.4, 47.1. HRMS calcd. for $C_{15}H_{14}N_2NaO_2S$ $(M+Na)^+$: 309.0668, found: 309.0661.

1-Methyl-3-(p-tolyl)-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3ac)

Yield 70 mg, 86%; white solid, mp: 163-164°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.25 (m, 2H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.74 -7.65 (m, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.26-7.24 (m, 2H), 3.52 (s, 3H), 2.40 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.9, 147.6, 141.4, 134.9, 134.6, 128.9, 128.9, 128.5, 126.0, 123.5, 113.0, 47.1, 21.5. **HRMS** calcd. for $C_{15}H_{14}N_2NaOS$ $(M+Na)^+$: 293.0719, found: 293.0713.

3-(4-Chlorophenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3ad)

Yield 61 mg, 70%; white solid, mp: 176-177 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33-8.31 (m, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.42-7.40 (m, 3H), 3.54 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 156.8, 147.3, 137.2, 135.9, 135.1, 129.9, 128.9, 128.3, 126.4, 123.6, 113.0, 47.1. **HRMS** calcd. for $C_{14}H_{12}ClN_2OS$ $(M+H)^+$: 291.0353, found: 291.0354.

3-(4-Bromophenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3ae)

Yield 79 mg, 79%; white solid, mp: 170-171°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.24 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.72 (m, 1H), 7.59 (m, 3H), 7.42 (t, *J* = 7.4 Hz, 1H), 3.55 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 156.9, 147.3, 136.3, 135.1, 131.3, 130.1, 128.9, 126.4, 125.8, 123.6, 113.1, 47.2. **HRMS** calcd. for $C_{14}H_{12}BrN_2OS$ $(M+H)^+$: 334.9848, found: 334.9850.

3-(4-Iodophenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3af)

Yield 94 mg, 82%; white solid, mp: 169-170 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.09 (m, 2H), 7.80 (m, 3H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 3.55 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.1, 147.3, 137.3, 136.9, 135.1, 130.2, 129.0, 126.4, 123.6, 113.1, 98.2, 47.2. **HRMS** calcd. for $C_{14}H_{12}IN_2OS$ $(M+H)^+$: 382.9710, found: 382.9715.

1-Methyl-3-(4-(trifluoromethyl)phenyl)-1l4-benzo[*e*][1,2,4]thiadiazine1-oxide(3ag)

Yield 60 mg, 62%; white solid, mp: 153-154 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50-8.48 (m, 2H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.75-7.69 (m, 3H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 3.57 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 156.4, 147.1, 140.7, 135.1, 132.5, 129.1, 128.8, 126.8, 125.0, 124.1 (q, *J* = 270 Hz), 123.6, 113.2, 47.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -62.67.**HRMS** calcd. for $C_{15}H_{12}F_3N_2OS$ $(M+H)^+$: 325.0617, found: 325.0623.

1-Methyl-3-(4-nitrophenyl)-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3ah)

Yield 57 mg, 63%; yellow solid, mp: 193-194 °C.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.52-8.50 (m, 2H), 8.36-8.33 (m, 2H), 8.28 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.63-7.58 (m, 2H), 3.98 (s, 3H). **^{13}C{^{1}H} NMR**(100 MHz, DMSO-*d6*) δ 154.9, 149.3, 145.8, 143.6, 135.6, 129.5, 128.6, 127.8, 125.0, 124.0, 114.5, 45.7. **HRMS** calcd. for $C_{14}H_{11}N_3NaO_3S$ $(M+Na)^+$: 324.0413, found: 324.0410.

4-(1-Methyl-1-oxido-1l4-benzo[*e*][1,2,4]thiadiazin-3-yl)benzonitrile (3ai)

Yield 21 mg, 25%; yellow solid, mp: 191-192 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42-8.40 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.69-7.65 (m, 3H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 3.51 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 155.8, 146.9, 141.5, 135.2, 131.9, 129.1, 129.0, 127.1, 123.6, 118.8, 114.1, 113.2, 47.1. **HRMS** calcd. for $C_{15}H_{11}N_3NaOS$ $(M+Na)^+$: 304.0515, found: 304.0512.

4-(1-Methyl-1-oxido-1l4-benzo[*e*][1,2,4]thiadiazin-3-yl)benzaldehyde (3aj)

Yield 72 mg, 84%; yellow solid, mp: 196-197 °C.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.10 (s, 1H), 8.51-8.49 (m, 2H), 8.27 (d, *J* = 7.6 Hz, 1H), 8.05-8.03 (m, 2H), 7.83 (t, *J* = 7.4 Hz, 1H), 7.62-7.56 (m, 2H), 3.97 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-*d6*) δ 193.4, 155.7, 146.0, 142.9, 138.1, 135.5, 129.9, 129.0, 128.6, 127.5, 124.9, 114.5, 45.6. **HRMS** calcd. for $C_{15}H_{13}N_2O_2S$ $(M+H)^+$: 285.0692, found: 285.0704.

3-(3-Methoxyphenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3ak)

Yield 64 mg, 75%; white solid, mp: 130-131°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.6 Hz, 1H), 7.93 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.43-7.32 (m, 2H), 7.04-7.01 (m, 1H), 3.90 (s, 3H), 3.54 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 159.6, 157.7, 147.4, 138.9, 135.0, 129.1, 129.0, 126.2, 123.5, 121.1, 117.6, 113.1, 113.0, 55.5, 47.1. **HRMS** calcd. for $C_{15}H_{14}N_2NaO_2S$ $(M+Na)^+$: 309.0668, found: 309.0664.

3-(3-Bromophenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3al)

Yield 74 mg, 74%; yellow solid, mp: 152-153 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.64-7.56 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 3.56 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 156.3, 147.1, 139.4, 135.1, 133.8, 131.5, 129.7, 129.0, 127.1, 126.6, 123.6, 122.4, 113.2, 47.1. **HRMS** calcd. for $C_{14}H_{12}BrN_2OS$ $(M+H)^+$: 334.9848, found: 334.9853.

1-Methyl-3-(2-nitrophenyl)-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3am)

Yield 40 mg, 42%; yellow solid, mp: 185-186 °C.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.27 (d, *J* = 8.0 Hz, 1H), 7.98-7.92 (m, 2H), 7.84-7.77 (m, 2H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-*d6*) δ 155.8, 149.8, 145.7, 135.6, 132.8, 131.4, 131.0, 128.1, 127.7, 125.0, 124.3, 114.1, 45.6. **HRMS** calcd. for $C_{14}H_{11}N_3NaO_3S$ $(M+Na)^+$: 324.0413, found: 324.0419.

3-(2-Chlorophenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3an)

Yield 38 mg, 43%; yellow solid, mp: 133-134°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.6 Hz, 1H), 7.76-7.66 (m, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.51-7.39 (m, 2H), 7.38-7.29 (m, 2H), 3.57 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 158.8, 146.8, 138.0, 135.2, 132.4, 130.43, 130.41, 130.3, 128.8, 127.0, 126.7, 123.5, 112.8, 47.0. **HRMS** calcd. for $C_{14}H_{11}ClN_2NaOS$ $(M+Na)^+$: 313.0173, found: 313.0180.

3-(4-Bromo-3-fluorophenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine1-oxide(3ao)

Yield 68 mg, 64%; yellow solid, mp: 173-174 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 10.0 Hz, 1.6 Hz, 1H), 8.06 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.65-7.57 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 3.56 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 158.9 (d, ^1J = 245 Hz), 155.7, 147.0, 139.0, 135.2, 133.1, 129.0, 126.7, 125.1 (d, ^3J= 4 Hz), 123.6, 116.3 (d, ^2J = 25 Hz), 113.2, 112.1 (d, ^2J = 21 Hz), 47.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -107.62. **HRMS** calcd. for $C_{14}H_{11}BrFN_2OS$ $(M+H)^+$: 352.9754, found: 352.9763.

3-(2-Hydroxy-4-methylphenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3ap)

Yield 70 mg, 81%; yellow solid, mp: 174-175 °C.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.52 (br, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.82 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 2H), 6.74 (s, 2H), 3.97 (s, 3H), 2.31 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-*d6*) δ 161.7, 159.3, 144.4, 143.5, 135.9, 129.4, 127.2, 126.5, 125.2, 119.9, 118.0, 115.6, 114.7, 45.5, 21.7. **HRMS** calcd. for $C_{15}H_{15}N_2O_2S$ $(M+H)^+$: 287.0849, found: 287.0850.

3-(5-Chloro-2-hydroxyphenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3aq)

Yield 64 mg, 70%; yellow solid, mp: 149-150 °C.

^{1}H NMR (400 MHz, DMSO) δ 14.65 (br, 1H), 8.29 (d, *J* = 7.4 Hz, 1H), 8.09 (d, *J* = 2.6 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.67-7.55 (m, 2H), 7.42 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 4.02 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 160.4, 158.0, 143.0, 136.0, 133.4, 128.3, 127.8, 126.6, 125.3, 122.3, 119.9, 119.2, 114.8, 45.5. **HRMS** calcd. for $C_{14}H_{12}ClN_2O_2S$ $(M+H)^+$: 307.0303, found: 307.0308.

3-(2-Hydroxy-5-methylphenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3ar)

Yield 67 mg, 78%; yellow solid, mp: 185-186 °C.

^{1}H NMR(400 MHz, DMSO-*d6*) δ 14.33 (br, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.61-7.50 (m, 2H), 7.21 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 3.99 (s, 3H), 2.29 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-*d6*) δ 159.6, 159.3, 143.5, 135.9, 134.7, 129.3, 127.4, 127.2, 126.6, 125.2, 117.7, 117.7, 114.7, 45.6, 20.6. **HRMS** calcd. for $C_{15}H_{14}N_2NaO_2S$ $(M+Na)^+$: 309.0668, found: 309.0669.

1-Methyl-3-(naphthalen-2-yl)-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3as)

Yield 65 mg, 71%; yellow solid, mp: 168-169 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.50 (d, *J* = 8.6 Hz, 1H), 7.98 (d, *J* = 6.8 Hz, 1H), 7.90-7.85 (m, 2H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.71-7.65 (m, 2H), 7.55-7.46 (m, 2H), 7.37 (t, *J* = 7.0 Hz, 1H), 3.54 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.8, 147.5, 135.0, 134.9, 134.7, 133.0, 129.3, 129.2, 129.0, 127.74, 127.69, 127.2, 126.3, 126.2, 125.3, 123.6, 113.1, 47.1. **HRMS** calcd. for $C_{18}H_{15}N_2OS$ $(M+H)^+$: 307.0900, found: 307.0899.

1-Methyl-3-(naphthalen-1-yl)-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3at)

Yield 49 mg, 53%; yellow solid, mp: 135-136 °C.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.79-8.73 (m, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 8.07-7.93 (m, 3H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.63-7.53 (m, 5H), 3.98 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-*d6*) δ 159.4, 146.2, 136.4, 135.4, 133.9, 130.9, 130.6, 128.8, 128.4, 128.3, 127.2, 126.9, 126.4, 126.3, 125.5, 124.8, 114.1, 45.4. **HRMS** calcd. for $C_{18}H_{15}N_2OS$ $(M+H)^+$: 307.0900, found: 307.0908.

1-Methyl-3-(thiophen-2-yl)-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3au)

Yield 65 mg, 83%; white solid, mp: 151-152 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 3.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 4.8 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.16-7.05 (m, 1H), 3.53 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 154.1, 147.3, 143.3, 135.0, 130.4, 129.9, 128.5, 127.8, 125.9, 123.6, 113.1, 47.1. **HRMS** calcd. for $C_{12}H_{11}N_2OS_2$ $(M+H)^+$: 263.0307, found: 263.0304.

3-(Furan-2-yl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3av)

Yield 36 mg, 49%; yellow solid, mp: 195-196 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 1H), 7.64-7.59 (m, 1H), 7.58-7.53 (m, 2H), 7.34-7.29 (m, 1H), 7.18 (d, *J* = 3.2 Hz, 1H), 6.46 (m, 1H), 3.48 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 151.3, 150.3, 147.0, 145.3, 135.1, 128.9, 126.2, 123.6, 114.8, 113.5, 112.0, 47.0. **HRMS** calcd. for $C_{12}H_{10}N_2NaO_2S$ $(M+Na)^+$: 269.0355, found: 269.0350.

1-Methyl-3-propyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3aw)

Yield 43 mg, 64%; yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 3.38 (s, 3H), 2.54-2.42 (m, 2H), 1.73 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 165.1, 147.1, 134.9, 128.1, 125.9, 123.4, 112.6, 46.9, 42.7, 21.0, 13.8. **HRMS** calcd. for $C_{11}H_{15}N_2OS$ $(M+H)^+$: 223.0900, found: 223.0907.

3-Cyclohexyl-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3ax)

Yield 63 mg, 80%; yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 3.45 (s, 3H), 2.56-2.44 (m, 1H), 1.96 (d, *J* = 12.8 Hz, 2H), 1.82 (d, *J* = 12.8 Hz, 2H), 1.64-1.56 (m, 2H), 1.45-1.20 (m, 4H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.5, 147.4, 134.8, 128.2, 125.8, 123.4, 112.8, 48.8, 46.9, 30.8, 30.7, 26.0, 25.9. **HRMS** calcd. for $C_{14}H_{19}N_2OS$ $(M+H)^+$: 263.1213, found: 263.1219.

3-Cyclopropyl-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3ay)

Yield 48 mg, 73%; white solid, mp: 105-106 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 3.41 (s, 3H), 1.99-1.85 (m, 1H), 1.21-1.08 (m, 2H), 0.94-0.89 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 166.1, 147.2, 134.9, 127.6, 125.3, 123.48, 112.9, 46.9, 19.2, 9.2, 8.4. **HRMS** calcd. for $C_{11}H_{13}N_2OS$ $(M+H)^+$: 221.0743, found: 221.0741.

(E)-3-(4-Chlorostyryl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (3az)

Yield 33 mg, 35%; yellow solid, mp: 183-184 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.65 (m, 3H), 7.58-7.47 (m, 3H), 7.45-7.31 (m, 3H), 6.89 (d, *J* = 15.6 Hz, 1H), 3.54 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.9, 147.2, 138.1, 135.1, 135.0, 134.4, 129.0, 128.9 128.5, 128.2, 126.4, 123.7, 113.7, 47.1. **HRMS** calcd. for $C_{16}H_{14}ClN_2OS$ $(M+H)^+$: 317.0510, found: 317.0513.

1,3-Diphenylbenzo[*e*][1,2,4]thiadiazine 1-oxide (4ba)

Yield 98 mg, 90%; white solid, mp: 146-147 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-8.43 (m, 2H), 7.89-7.87 (m, 2H), 7.68-7.59 (m, 3H), 7.57-7.53 (m, 2H), 7.46-7.43 (m, 4H), 7.25 (t, *J* = 7.4 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 158.1, 147.3, 140.8, 137.6, 134.4, 133.9, 131.0, 129.3, 128.7, 128.7, 128.6, 128.2, 126.3, 124.8, 113.8. **HRMS** calcd. for $C_{19}H_{15}N_2OS$ $(M+H)^+$: 319.0900, found: 319.0904.

3-(4-Methoxyphenyl)-1-phenylbenzo[*e*][1,2,4]thiadiazine 1-oxide (4bb)

Yield 78 mg, 75%; white solid, 52-54 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41-8.38 (m, 2H), 7.89-7.87 (m, 2H), 7.65-7.60 (m 3H), 7.58-7.54 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.17-7.09 (m, 1H), 6.97-6.94 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 162.2, 157.8, 147.6, 141.0, 134.3, 133.7, 130.4, 130.2, 130.0, 128.6, 128.5, 125.8, 124.8, 113.6, 113.5, 55.4. **HRMS** calcd. for $C_{20}H_{17}N_2O_2S$ $(M+H)^+$: 349.1005, found: 349.1006.

3-(4-Iodophenyl)-1-phenylbenzo[*e*][1,2,4]thiadiazine 1-oxide (4bf)

Yield 100 mg, 75%; yellow solid, mp: 175-176 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.06 (m, 2H), 7.78-7.77(m, 2H), 7.70-7.67 (m, 2H), 7.56-7.50 (m, 3H), 7.49-7.45 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.20-7.13 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.2, 147.1, 140.6, 137.4, 137.2, 134.5, 134.0, 130.4, 129.4, 128.7, 128.6, 126.5, 124.9, 113.9, 98.2. **HRMS** calcd. for $C_{19}H_{14}IN_2OS$ $(M+H)^+$: 444.9866, found: 444.9864.

1-Ethyl-3-phenyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (4ca)

Yield 67 mg, 82%; viscid liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.25 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.43-7.33 (m, 3H), 7.27 (t, *J* = 7.4 Hz, 1H), 3.63-3.54 (m, 1H), 3.49-3.40 (m, 1H), 1.08 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 158.5, 148.7, 137.5, 135.0, 131.0, 128.8, 128.5, 128.2, 126.2, 123.7, 110.0, 52.6, 8.1. **HRMS** calcd. for $C_{15}H_{14}N_2NaOS$ $(M+H)^+$: 293.0719, found: 293.0717.

1-Ethyl-3-(4-methoxyphenyl)-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (4cb)

Yield 79 mg, 91%; white solid, mp: 120-121 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.25 (m, 2H), 7.65-7.54 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.88-6.85 (m, 2H), 3.76 (s, 3H), 3.62-3.52 (m, 1H), 3.48-3.38 (m, 1H), 1.08 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 162.2, 158.2, 148.9, 134.9, 130.3, 130.0, 128.6, 125.7, 123.7, 113.5, 109.8, 55.4, 52.6, 8.1. **HRMS** calcd. for $C_{16}H_{17}N_2O_2S$ $(M+H)^+$: 301.1005, found: 301.1006.

6-Chloro-1-methyl-3-phenyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (4da)

Yield 64 mg, 74%; white solid, mp: 164-165 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.26 (m, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.54 (s, 1H), 7.45-7.32 (m, 3H), 7.25 (d, *J* = 8.8 Hz, 1H), 3.44 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 158.8, 148.8, 141.1, 136.9, 131.4, 128.7, 128.3, 128.2, 126.6, 124.9, 111.3, 47.2. **HRMS** calcd. for $C_{14}H_{12}ClN_2OS$ $(M+H)^+$: 291.0353, found: 291.0353.

6-Chloro-3-(4-methoxyphenyl)-1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (4db)

Yield 70 mg, 73%; white solid, mp : 143-144 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.19 (m, 2H), 7.65-7.59 (m, 1H), 7.50 (s, 1H), 7.24-7.17 (m, 1H), 6.91-6.82 (m, 2H), 3.78 (s, 3H), 3.42 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 162.5, 158.6, 149.1, 141.0, 130.5, 129.4, 128.0, 126.1, 124.9, 113.5, 111.0, 55.4, 47.2. **HRMS** calcd. for $C_{15}H_{14}ClN_2O_2S$ $(M+H)^+$: 321.0459, found: 321.0461.

1,6-Dimethyl-3-phenyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (4ea)

Yield 98 mg, 90%; white solid, mp: 159-160 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.27 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.38-7.28 (m, 4H), 7.10 (d, *J* = 8.0 Hz, 1H), 3.40 (s, 3H), 2.36 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.9, 147.5, 146.1, 137.5, 130.9, 128.5, 128.5, 128.1, 127.6, 123.4, 110.4, 47.2, 21.9. **HRMS** calcd. for $C_{15}H_{15}N_2OS$ $(M+H)^+$: 271.0900, found: 271.0894.

3-(4-Methoxyphenyl)-1,6-dimethyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (4eb)

Yield 76 mg, 84%; white solid, mp: 115-116 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33-8.31 (m, 2H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.38 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.95-6.93 (m, 2H), 3.85 (s, 3H), 3.47 (s, 3H), 2.44 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 162.1, 157.7, 147.8, 146.0, 130.2, 130.0, 128.3, 127.2, 123.4, 113.4, 110.2, 55.4, 47.2, 21.9. **HRMS** calcd. for $C_{16}H_{17}N_2O_2S$ $(M+H)^+$: 301.1005, found: 301.1006.

3-(4-Iodophenyl)-1,6-dimethyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (4ef)

Yield 74 mg, 62%; yellow solid, mp: 132-133 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.07 (m, 2H), 7.78-7.76 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 3.50 (s, 3H), 2.46 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.1, 147.3, 146.2, 137.3, 137.1, 130.2, 128.5, 127.9, 123.4, 110.4, 98.1, 47.3, 21.9. **HRMS** calcd. for $C_{15}H_{14}IN_2OS$ $(M+H)^+$: 396.9866, found: 396.9868.

7-(Methoxymethyl)-1-methyl-3-phenyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (4fa)

Yield 54.9 mg, 61%; white solid, mp: 143-144°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (m, 2H), 7.73 (s, 1H), 7.56 (m, 2H), 7.42-7.34 (m, 3H), 4.45 (s, 2H), 3.48 (s, 3H), 3.38 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.8, 146.9, 137.3, 136.9, 134.1, 131.0, 129.0, 128.5, 128.2, 121.9, 112.8, 73.5, 58.6, 47.1. **HRMS** calcd. for $C_{16}H_{17}N_2O_2S(M+H)^+$: 301.1005, found: 301.1007.

Gram-scale synthesis of 3aa in two consecutive runs.

The 1st run: To a mixture of *N*H-Sulfoximine **1a** (1.05 g, 4.50 mmol), benzaldehyde **2a** (572 mg, 5.40 mmol), Cu_2O (0.225 mmol), and TBAI (0.45 mmol) in H_2O (15.0 mL) was added $TMSN_3$ (1.04 g, 9.0 mmol) in a round bottle flask under air. The reaction was heated at 90 °C oil bath for 12 h. After completion of the reaction as monitored by TLC, the reaction was allowed to cool to room temperature and extracted with ethyl acetate (10.0 mL × 4). The combined organic layers was dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product, which

was further purified by column chromatography (silica; petroleum ether/ethyl acetate 5:1) to afford thiadiazine-1-oxide **3aa** (1.03 g, 89%) as a white solid.

The aqueous layer in the mother flask was collected for the 2nd run of the reaction, without additional Cu_2O and TBAI.

The 2nd run: The aqueous layer in the mother flask was diluted with H_2O (3.0 mL) to ca. 15 mL, then the substrates *N*H-Sulfoximine **1a** (1.05 g), benzaldehyde **2a** (572 mg) and $TMSN_3$ (1.04 g, 9.0 mmol) were added subsequently. The reaction was heated at 90 °C oil bath for 12 h. After completion of the reaction as monitored by TLC, the reaction was allowed to cool to room temperature and extracted with ethyl acetate (10.0 mL × 3). The combined organic layers was dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product, which was further purified by column chromatography (silica; petroleum ether/ethyl acetate 5:1) to afford thiadiazine-1-oxide **3aa** (0.897 g, 78%) as a white solid.

General procedure for the reaction of 3aj to 5a and 5b.

To a mixture of aldehyde **3aj** (0.39 mmol), and *N*H-Sulfoximine **1a** or **1b** (0.30 mmol), Cu_2O (0.015 mmol), and TBAI (0.03 mmol) in H_2O (1.0 mL) was added $TMSN_3$ (0.60 mmol) under an air atmosphere. After that, the tube was sealed, and the reaction was heated at 90 °C oil bath for 12 h. After completion of the reaction as monitored by TLC, the reaction was allowed to cool to room temperature, diluted with water (2 mL) and saturated $KHCO_3$ aqueous solution, extracted with ethyl acetate (3.0 mL×4). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to give the crude product, which was further purified by column chromatography (silica; petroleum ether/ethyl acetate 5:1) to afford thiadiazine-1-oxides **5a** or **5b**.

3,3'-(1,4-Phenylene)bis(1-methyl-1l4-benzo[*e*][1,2,4]thiadiazine 1-oxide (5a)

Yield 73 mg, 56%; yellow solid, mp: 297-298 °C.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.42 (s, 4H), 8.27-8.25 (m, 2H), 7.84-7.80 (m, 2H), 7.62-7.60 (m, 2H), 7.57-7.54(m, 2H), 3.96 (s, 6H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-*d6*) δ 156.3, 146.2, 139.9, 135.4, 128.4, 128.2, 127.1, 124.9, 114.5, 45.6. **HRMS** calcd. for $C_{22}H_{19}N_4O_2S_2$ $(M+H)^+$: 435.0944, found: 435.0947.

1-Methyl-3-(4-(1-oxido-1-phenyl-1l4-benzo[*e*][1,2,4]thiadiazin-3-yl)phenyl)-1l4-benzo[e][1,2,4]thiadiazine 1-oxide (5b)

Yield 65 mg, 71%; yellow solid, mp: 144-145 °C.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.48-8.43 (m, 4H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.99-7.97 (m, 2H), 7.85-7.80 (m, 3H), 7.78-7.69 (m, 3H), 7.65-7.61 (m, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 3.97 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-*d6*) δ 156.6, 156.3, 146.5, 146.2, 140.1, 139.8, 139.7, 135.6, 135.4, 135.1, 130.4, 129.1, 128.7, 128.5, 128.4, 127.8, 127.1, 125.5, 124.9, 114.5, 114.1, 45.6. **HRMS** calcd. for $C_{27}H_{21}N_4O_2S_2$ $(M+H)^+$: 497.1100, found: 497.1101.

General procedure for the reation of ortho-iodide *N*H-sulfoximine 1h with benzaldehyde 2a.

To a vigorous stirred mixture of *N*H-Sulfoximine **1h** (84 mg, 0.30 mmol), aldehyde **2a** (38 mg, 0.36 mmol), Cu_2O (0.015 mmol), and TBAI (0.03 mmol) in H_2O (1.0 mL) was added $TMSN_3$ (0.60 mmol) under an air atmosphere. The reaction was heated at 90 °C oil bath for about 12 h. Upon completion of the reaction as indicated by TLC, the reaction

was allowed to cool to room temperature, and diluted with water (2.0 mL) and saturated aqueous $NaHCO_3$ (2.0 mL), then extracted with ethyl acetate (3.0 mL × 3). The combined organic layer was dried over Na_2SO_4, and concentrated to give the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to afford the expected thiadiazine-1-oxide **3aa** (55 mg, 0.21 mmol, 71%) as a white solid.

General procedure for the synthesis of *ortho*-amino sulfoximine 6.

To a stirred mixture of *N*H-Sulfoximine **1a** (0.30 mmol), Cu_2O (0.015 mmol), and TBAI (0.03 mmol) in H_2O (1.0 mL) was added $TMSN_3$ (0.60 mmol) in a tube under an air atmosphere. The reaction tube was sealed and heated at 90 °C oil bath for 12 h. After completion of the reaction as monitored by TLC, the reaction was allowed to cool to room temperature, diluted with water (2.0 mL) and saturated $NaHCO_3$ aqueous solution, then extracted with ethyl acetate (3.0 mL×4). The combined organic layer was dried over Na_2SO_4, the crude residue was purified by flash column chromatography to yield **6** (26 mg, 51% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.81 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.36 (br, 2H), 3.12 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 146.3, 134.6, 129.6, 124.0, 117.7, 117.5, 43.0. **HRMS** calcd. for $C_7H_{11}N_2OS$ $(M+H)^+$: 171.0587, found: 171.0589.

General procedure for the reaction of *N*Ac-sulfoximine 7.

To a stirred mixture of *N*Ac-Sulfoximine **7** (0.30 mmol), 4-methylbenzaldehyde **1c** (0.39 mmol), Cu_2O (0.015 mmol), and TBAI (0.03 mmol) in H_2O (1.0 mL) was added $TMSN_3$ (0.60 mmol) in a tube under an air atmosphere. The reaction tube was sealed and heated at 90 °C oil bath for 12 h. After completion of the reaction as monitored by TLC, the reaction was allowed to cool to room temperature, diluted with water (2.0 mL) and saturated $KHCO_3$ aqueous solution, then extracted with ethyl acetate (3.0 mL×4). The combined organic layer was dried over Na_2SO_4, the crude residue was purified by flash column chromatography to yield **3ac** (37 mg, 46% yield), as a white solid. Compound **8** was not detected in this reaction.

General procedure for the reaction of *N*Me-sulfoximine 9.

To a stirred mixture of *N*Me-Sulfoximine **9** (0.30 mmol), 4-methylbenzaldehyde **1c** (0.39 mmol), Cu_2O (0.015 mmol), and TBAI (0.03 mmol) in H_2O (1.0 mL) was added $TMSN_3$ (0.60 mmol) in a tube under an air atmosphere. The reaction tube was sealed and heated at 90 °C oil bath for 12 h. After completion of the reaction as monitored by TLC, the reaction was allowed to cool to room temperature, diluted with water (2.0 mL) and saturated $KHCO_3$ aqueous solution, then extracted with ethyl acetate (3.0 mL×4). The combined organic layer was dried over Na_2SO_4, the crude residue was purified by flash column chromatography to yield **10** (33 mg, 59% yield), as a viscous solid. Compound **3ac** was not detected in this reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 1H), 7.29-7.26 (m, 1H), 6.76-6.66 (m, 2H), 5.24 (br, 2H), 3.00 (s, 3H), 2.62 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 146.5, 134.5, 131.3, 117.8, 117.1, 41.7. 29.6. **HRMS** calcd. for $C_8H_{13}N_2OS$ $(M+H)^+$: 185.0743, found: 185.0749.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/ acs.joc-2019-02828c.

Copies of ^{1}H and ^{13}C NMR spectra (PDF).

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zchen@jxnu.edu.cn

ORCID

Zhiyuan Chen: 0000-0002-5159-7287

■ ACKNOWLEDGMENT

We thank the National Natural Science Foundation of China (21672085, 21961015) and the Talented Youth Project of Jiangxi Province (20171BCB23038) for financial support. Z.C was grateful for theopen project program of Polymer Engineering Research Center, Jiangxi Science&Technology Normal University (KFGJ18014).

REFERENCES

1 For reviews, see: (a) Lücking, U. Sulfoximines: a neglected opportunity in medicinal chemistry. *Angew. Chem. Int. Ed*. **2013**, *52*, 9399. (b) Bull, J. A.; Degennaro, L.; Luisi, R. Straightforward Strategies for the Preparation of *N*H-Sulfoximines: A Serendipitous Story. *Synlett* **2017**, *28*, 2525. (c) Lücking, U. Neglected sulfur(VI) pharmacophoresin drug discovery: exploration of novel chemical space by the interplay of drug design and method development *Org. Chem. Front*. **2019**, 6, 1319-1324. (d) Gupta, S.; Baranwal, S.; Chaudhary, P.; Kandasamy, J. Copper-promoted dehydrogenative cross coupling reaction of dialkylphosphites with sulfoximines. *Org. Chem. Front.* **2019**, 6, 2260. (e) Wiezorek, S.; Lamers, P.; Bolm, C. Conversion and degradation pathways of sulfoximines. *Chem. Soc. Rev*. **2019**, 48, 5408. (f) Zhou, H.; Chen, Z. Recent Achievements in the Synthesis of Sulfoximine Derivatives. *Chin. J. Org. Chem*. **2018**, *38*, 719.

2 Wagner, A.; Reinöhl, G. Heterocycles with endocyclic sulfur-nitrogen double bond. II. 1-Substituted 3,4-dihydro-1*H*-1,2,4-benzothiadiazin-3-ones and 1-substituted 3,4-dihydro-1*H*-1,2,4-benzothiadiazin-3-one 1-oxides. *Liebigs Ann. Chem*. **1964**, *675*, 189.

3 Dillard, R.; Yen, T.; Stark, P.; Pavey, D. Synthesis and blood pressure lowering activity of 3-(substituted-amino)-1,2,4-benzothiadiazine 1-oxide derivatives. *J. Med. Chem*. **1980**, *23*, 717.

4 Robert, W.; Fliakas-Boltz, V.; Decker, W.; Roberson, J.; Pyle, C.; White, B.; Bowdon, B.; McMahon, J.; Michael, R.; John, P.; David, G.; Hubert, B.; Tammy, K. Biological and biochemical anti-HIV activity of the benzothiadiazine class of nonnucleoside reverse transcriptase inhibitors. *Antiviral Res*. **1994**, *1*, 43.

5 Bartoszyk, G.; Dooley, D.; Barth, H.; Hartenstein, J.; Satzinger, G. Stereoselective pharmacological effects and benzodiazepine receptor affinity of the enantiomers of Go 4962. *J. Pharm. Pharmacol*. **1987**, *39*, 407.

6 Williams, T.; Cram, D. New ring systems of carbon, nitrogen, and chiral sulfur. *J. Am. Chem. Soc*. **1971**, *93*, 7333.

7 Dillard, R.; Yen, T.; Stark P.; Pavey, D. Synthesis and blood pressure lowering activity of 3-(substituted-amino)-1, 2,4-benzothiadiazine 1-oxide derivatives. *J. Med. Chem*. **1980**, *23*, 717.

8 Le, T.; Diter, P.; Pégot, B.; Bournaud, C.; Toffano, M.; Guillot, R.; Vo-Thanh, G.; Magnier, E. S-Trifluoromethyl Sulfoximine as a Directing Group in *Ortho*-Lithiation Reaction toward Structural Complexity. *Org. Lett*. **2016**, *18*, 5102.

9 Cheng, Y.; Dong, W.; Wang, H.; Bolm, C. Rhodium-Catalyzed ortho-Amidations in the Preparation of Thiadiazine 1-Oxides. *Chem. Eur. J*. **2016**, *22*, 10821.

10 Huang, J.; Huang, Y.; Wang, T.; Huang, Q.; Wang, Z.; Chen, Z. Microwave-Assisted Cp*Co^{III}-Catalyzed C-H Activation/Double C-N Bond Formation Reactions to Thiadiazine 1-Oxides. *Org. Lett*. **2017**, *19*, 1128.

11 Li, Y.; Liu, C.-F.; Liu, X.-Y.; Xu, Y.-J.; Dong. L. Rhodium(III)-catalyzed tandem reaction: efficient synthesis of dihydrobenzothiadiazine 1-oxide derivatives. *Org. Chem. Front*. **2019**, *6*, 1458.

12 (a) Zhou, H.; Chen, W.; Chen, Z. Pd/Norbornene Collaborative Catalysis on the Divergent Preparation of Heterocyclic Sulfoximine Frameworks. *Org. Lett.* **2018**, *20*, 2590. (b) Huang, J.; Chen, Z.; Wang. Z. Transition-Metal-Catalyzed Hydrosulfoximination and Oxidation Reaction for the Synthesis of Sulfoximine Derivatives. *J. Org. Chem.* **2016**, *81*, 9308. (c) Chen, X.; Zhou, H.; Chen. Z. Pd/P/dba-Promoted cascade annulations to produce fused medium-sized sulfoximine polyheterocycles. *Org. Chem. Front.* **2019**, *6*, 3415.

13 Monguchi, Y.; Maejima, T.; Mori, S.; Maegawa, T.; Sajiki, H. Copper-Mediated Reductive Amination of Aryl Halides with Trimethylsilyl Azide. *Chem. Eur. J.* **2010**, *16*, 7372.

14 For a review of organic reactions in H_2O, see: Li, C.-J.; Chan, T.-H. *Comprehensive Organic Reactions in Aqueous Media*, Wiley-Interscience, 2nd edn, **2007**.

15 (a) Upadhyaya, K.; Thakur, R. K.; Shukla, S.; Tripathi, R. One-Pot Copper(I)-Catalyzed Ligand/Base-Free Tandem Cyclooxidative Synthesis of Quinazolinones. *J. Org. Chem*. **2016**, *81*, 5046. (b) Maejima, T.; Shimoda, Y.; Nozaki, K.; Mori, S.; Sawama, Y.; Monguchi, Y.; Sajiki, H. One-pot aromatic amination based on carbonenitrogen coupling reaction between aryl halides and azido compounds. *Tetrahedron*, **2012**, *68*, 1712.

16 Cheng, Y.; Dong, W.; Parthasarathy, K.; Bolm, C. Rhodium(III)-Catalyzed Ortho Halogenations of *N*-Acylsulfoximines and Synthetic Applications toward Functionalized Sulfoximine Derivatives. *Org. Lett*. **2017**, *19*, 726.