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Microwave-Assisted Cp*Co^{III}-Catalyzed C−H Activation/Double C−N Bond Formation Reactions to Thiadiazine 1-Oxides

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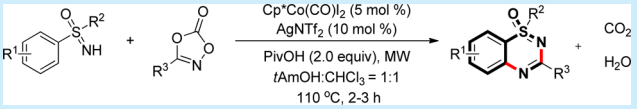
Supporting Information

ABSTRACT: A microwave-assisted, Cp*Co^{III}-catalyzed direct C−H activation/double C−N bond formation reaction of simple *N*H-sulfoximines with 1,4,2-dioxazol-5-ones to produce diverse thiadiazine-1-oxides is reported. The reaction tolerates a broad range of functional groups under external oxidant-free conditions and only releases CO_2 and H_2O as the sole byproducts. The preliminary mechanistic studies revealed an electrophilic metalation pathway is likely involved in the reaction.



Sulfoximines represent an extremely important class of structural motifs in biological natural products and pharmaceutical substances.[1] Thiadiazine 1-oxides that contain a sulfoximine moiety within benzene-fused heterocycles are bioactive compounds with relevance as signicant pharmaceutical agents (Figure 1).[2] For instance, NSC287474 is a potential

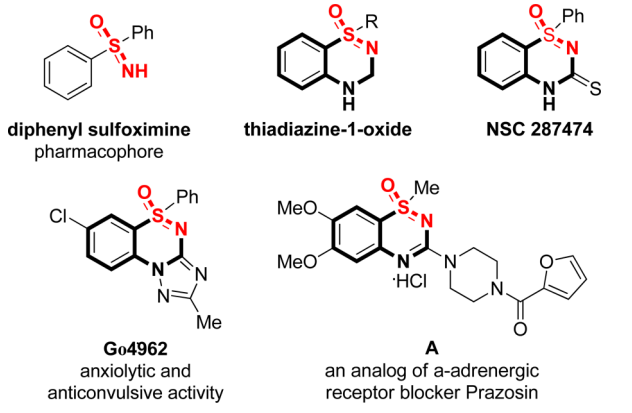
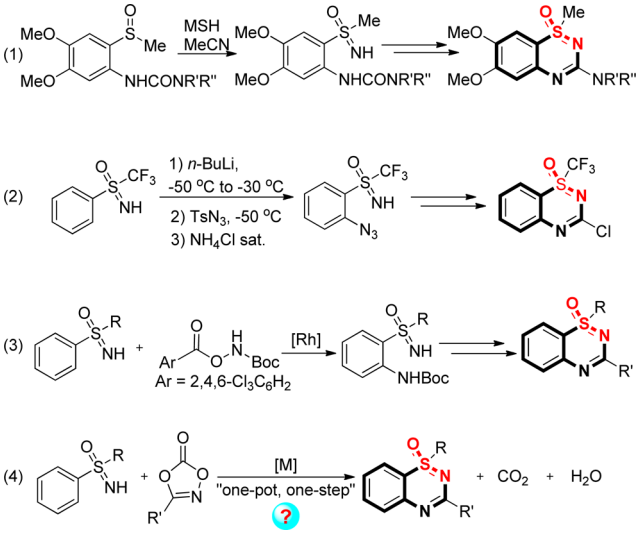


Figure 1. Selected bioactive sulfoximine and thiadiazine 1-oxides.

reverse transcriptase inhibitor with excellent inhibition of HIV replication in lymphocytes.[3] Additionally, the tricyclic fused sulfoximine, Gö4962, is a partial benzodiazepine receptor agonist with excellent anxiolytic and anticonvulsive activities.[4] The functionalized thiadiazine-1-oxide **A** has exhibited blood pressure lowering activity in animal tests equipotent to the marketed drug Prazo.[5]

Over the past decade, many noteworthy advances have been made toward the synthesis of acyclic sulfoximine derivatives, in particular via seminal contributions by Bolm et al.[6] and among others.[7] Nevertheless, methods for the construction of cyclic thiadiazine-1-oxide frameworks are rather limited. Traditional pathways focused on multiple-step transformations starting from nitroaryl thioethers or *N*-protected 2-thio-substituted anilines.[2,8] A typical preparation methodology for thiadiazine 1-oxide begins with the key conversion of *N*-protected sulfoxides into sulfoximines by utilizing *O*-(mesitylenesulfonyl)-hydroxylamine (MSH) as the key aminating reagent (Scheme 1, eq 1).[9] However, the starting sulfoxide material must be

Scheme 1. Reported Access to Thiadiazine 1-Oxides and Our Methodology



prepared stepwise in advance, and MSH must be handled with extreme caution because it can decompose with explosive violence. Vo-Thanh developed *n*-BuLi-promoted C−H functionalization reaction of free *N*H-trifluoromethyl sulfoximines. Using this reaction, further transformations could be achieved to prepare cyclic fluorinated thiadiazine 1-oxides (Scheme 1, eq

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2).[10] Bolm et al. recently reported Rh-catalyzed *ortho*-amidations using free *NH*-sulfoximines with *tert*-butyl (2,4,6-trichlorobenzoyl)oxycarbamates.[11] Further, a Boc-protected amino group could be easily introduced, and the subsequent ring-closing reactions thereby allow the production of diverse thiadiazine 1-oxides (Scheme 1, eq 3). While the chemoselective synthesis of sulfoximines has been achieved, they also produce stoichiometric amounts of organic wastes, and further manipulations are generally necessary. Thus, the development of atom- and step-economic strategies are still highly sought after.

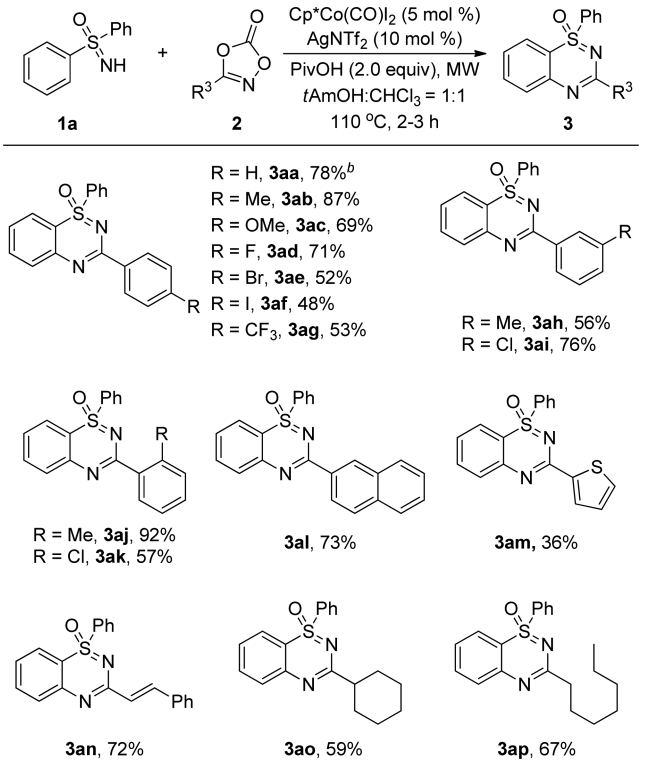
Here, we report our success in the modular one-pot and one-step construction of thiadiazine 1-oxides with good to excellent yields (Scheme 1, eq 4). Employing commercially available free *NH*-sulfoximines **1** as the starting material and 1,4,2-dioxazol-5-ones **2** as the amination reagent, diverse thiadiazine 1-oxide derivatives could be efficiently generated under cobalt(III)-catalyzed and microwave-assisted conditions. 1,4,2-Dioxazol-5-ones are versatile, easy to handle, and have been widely used as amination reagents for the preparation of aza-heterocycles.[12] Only CO_2 and H_2O were generated as chemical wastes during these reactions, which indicates this method is environmentally benign. To our knowledge, this is the first example of transition-metal-catalyzed, robust C−H activation/double C−N bond formation on *NH*-sulfoximines by means of transformable directing group strategy. The method also represents the currently "most concise" approach to generating thiadiazine-1-oxides.

We first screened reaction conditions in the metal-catalyzed cyclization of *NH*-sulfoximine (**1a**) with a "Ph−C═N" source (**2**).[13] The desired product **3aa** was isolated after an extensive survey of reaction conditions when 1,4,2-dioxazol-5-one **2a** was employed as an amination substrate and $[Cp^*RhCl_2]_2/AgSbF_6$ was used as the catalyst, whereas the desired product was only generated in rather low yields (Table S1, entry 1).[14] It should be noted that no reaction occurred when using "Ph−C═N" surrogates such as 5,5-dimethyl-3-phenyl-1,4,2-dioxazole[15] **2a_1** or 5-phenyl-1,3,2,4-dioxathiazole 2-oxide **2a_2** as reagents under the catalysis conditions.[16] No desired product was detected when a first-row metal catalyst, $[Cp^*CoCl_2]_2$ complex, was added instead of [Rh] (Table S1, entry 2). However, significant improvement in product formation was obtained when a $[Cp^*Co(CH_3CN)_3(SbF_6)_2]$ complex was employed (Table S1, entry 4). Further screening revealed that $Cp^*Co(CO)I_2$ was an effective catalyst, and the GC yield of **3aa** could be improved to 50% (Table S1, entry 5). The starting material, **1a**, never reached full consumption under the above-mentioned conventional oil-bath heating conditions. However, rapid conversion was observed when microwave irradiation conditions were used, and the cyclization product **3aa** was formed with 69% yield while the reaction time was shortened to 4 h (Table S1, entry 6).

We reasoned that the anion counterpart of the silver salt should be essential for activation of the Co-complex. Indeed, use of $AgNTf_2$ offered a slight improvement (Table S1, entries 7 vs 6), whereas use of AgOTf was deleterious, possibly due to the weak acidity of AgOTf (Table S1, entry 8). Subsequent solvent screening demonstrated that a mixture solvent of *t*-AmOH/$CHCl_3$ = 1:1 (v/v) was optimal, led an acceptance reaction rate in only 2 h and 79% isolated yield (Table S1, entry 9). No reaction occurred when PivOK was used in place of PivOH, indicating that the acid additive was vital for the transformation (Table S1, entry 10). Furthermore, we found that the reaction was easily handled and not very sensitive to moisture- or oxygen-atmosphere conditions. Thus, our results suggest that the method may be potentially useful for industrial applications.

The reaction scope for this convenient preparation of thiadiazine 1-oxide **3** was next studied (Scheme 2). The

Scheme 2. Reaction Scope Studies[a]



[a]Reaction conditions: *NH*-sulfoximine **1a** (0.20 mmol), 1,4,2-dioxazol-5-one **2** (0.40 mmol) in 2.0 mL of solvent at 110 °C under microwave heating conditions. Isolated yield. [b]On 1.0 mmol scale.

reaction of **1a** with **2a** could be easily scaled up to 1.0 mmol, and the product **3aa** could be isolated in 78% yield. The cyclization reactions of various 3-aryl-1,4,2-dioxazol-5-ones **2** bearing para electron-donating and -withdrawing groups all reacted smoothly with **1a**, resulting in moderate to high yields (**3aa**−**ag**). Synthetically useful halo substitutions including chloro (**3ai** and **3ak**), bromo (**3ae**), and iodo (**3af**) groups were all tolerated without difficulty. The production of fluoro- (**3ad**) and trifluoromethyl-substituted (**3ag**) thiadiazine 1-oxides through this microwave-assisted Cp^*Co^{III}-catalyzed cyclization reaction methodology indicates a potential utility in generating fluorine-containing compounds. An excellent yield of 92% (**3aj**) was obtained for the reaction of **1a** with *o*-methyl substituted 3-aryl-1,4,2-dioxazol-5-one **2j**. The substrate **2l**, which contains a 2-naphthyl group, underwent the reaction smoothly to give **3al** in serviceable yield, whereas the 2-thienyl heterocycle furnished the desired product **3am** with only moderate yield. Notably, the reaction displayed excellent functional group compatibility for alkenyl, cyclohexyl, and alkyl groups, and the corresponding products **3an**−**ap** were produced in good yields.

For various substitutions affiliated on the aromatic ring of *NH*-sulfoximine **1**, good to excellent yields of the corresponding products **3** were obtained whenever the substitutions on the

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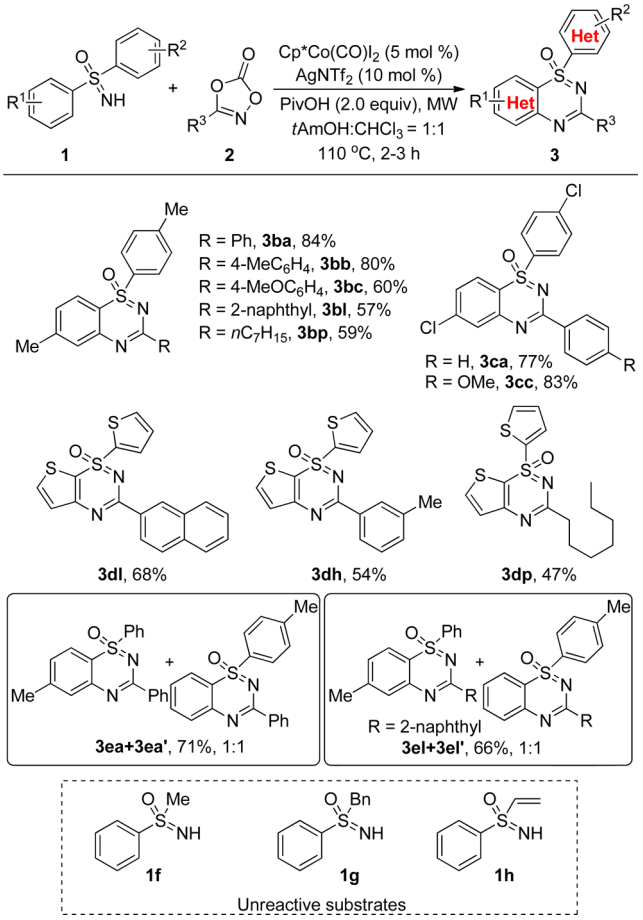
aromatic ring of **1** had electron-donating (**3bb**–**bp**) or -withdrawing properties (**3ca** and **3cc**, Scheme 3). Thieno-

Scheme 3. Reaction Scope Studies[a]



[a]Reaction conditions: *NH*-sulfoximine **1** (0.20 mmol), 1,4,2-dioxazol-5-one **2** (0.40 mmol) in 2.0 mL of solvent at 110 °C under microwave heating conditions. Isolated yield.

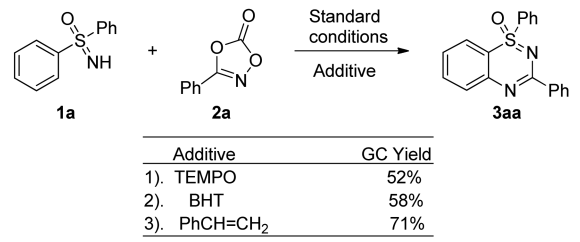
1,2,4-thiadiazine derivatives were found to be potent openers of Kir 6.2/SUR1 K_{ATP} channels in the suppression of glucose-stimulated insulin release from rat islets.[17] Interestingly, the products **3dl**, **3dh**, and **3dp**, which contain thieno[3,2-*e*][1,2,4]thiadiazine 1-oxide heterocyclic scaffolds, were isolated in moderate to good yields in the reaction of 2,2′-sulfonimidoyldithiophene **1d** with 1,4,2-dioxazol-5-ones **2**. In the reaction of 1-methyl-4-(phenylsulfonimidoyl)benzene **1e** with 3-phenyl-1,4,2-dioxazol-5-one **2a**, two isomer products **3ea** + **3ea′** were isolated with 71% yield with molecular ratio of 1:1. Likewise, the reaction of **1e** with **2l** produced **3el** + **3el′** in 66% yield.

Limitations became clear when *NH*-sulfoximines **1** contained a nonaromatic moiety (Scheme 3). No reaction occurred for the methyl- (**1f**) or benzyl-functionalized (**1g**) *NH*-sulfoximines with **2a**. The vinyl-substituted *NH*-sulfoximine **1h** was found to decompose to fragment species in the cyclization reaction.

We conducted several control experiments to understand the possible mechanism of this microwave-assisted, Cp*Co^{III}-catalyzed C–H activation/double C–N bond formation reaction (Scheme 4). Moderate to good yields were observed for the reaction of **1a** with **2a** while in the presence of typical radical scavengers (TEMPO, BHT and styrene) (Scheme 4a).

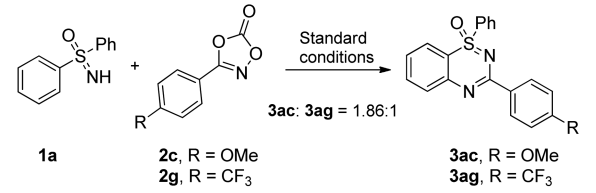
Scheme 4. Control Experiments

(a) Radical scavengers experiments

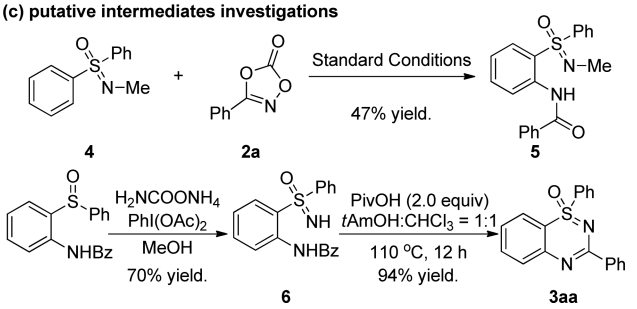


Additive	GC Yield
1). TEMPO	52%
2). BHT	58%
3). $PhCH=CH_2$	71%

(b) Intermolecular competition experiments



(c) putative intermediates investigations



Thus, a radical process can be excluded from the transformations, which are quite different from recent theoretical DFT calculations on Co^{III}-catalyzed C(sp^2)–H oxygenation reactions.[18] Intermolecular competition reactions between *NH*-sulfoximine **1a** and the differently functionalized substrates **2c** and **2g** were conducted (Scheme 4b). The results suggested that substrate **2c**, which contains an electron-donating MeO group, preferentially participated in the cyclization, thus indicating an intermolecular electrophilic substitution-type C–H cobaltation event likely be involved in the key C–H activation step.[19]

To investigate the possible reaction intermediates, N-Me substituted sulfoximine **4** was synthesized. The reaction of compound **4** with **2a** produced the *NH*-benzoyl-substituted sulfoximine **5** in 47% yield (Scheme 4c). This indicates that a high-valent cobalt(III)-catalyzed *ortho*-C–H amidation reaction should be involved in the reaction.[20] Moreover, *NH*-benzoyl-substituted sulfoximine **6** was synthesized following Luisi's procedure.[21] Treatment of this compound with 2.0 equiv of PivOH in *t*-AmylOH/$CHCl_3$ delivered product **3aa** in 94% yield (Scheme 4c).

On the basis of the aforementioned mechanistic studies, we propose a plausible catalytic cycle for the reaction depicted in Scheme 5. The reaction of neutral complex Cp*$Co(CO)I_2$ with $AgNTf_2$ in the presence of PivOH first generates a reactive cationic species **A**, which then undergoes electrophilic metalation with **1a** to give a five-membered cobaltacyle **B** upon release of PivOH and $HNTf_2$. Coordination of the amidating reagent **2a** with cobaltacycle **B** to produce a dioxazolone-bound cobaltacyle **C** is assumed, followed by subsequent amido insertion to produce amido complex species **D**.[22] Proto-

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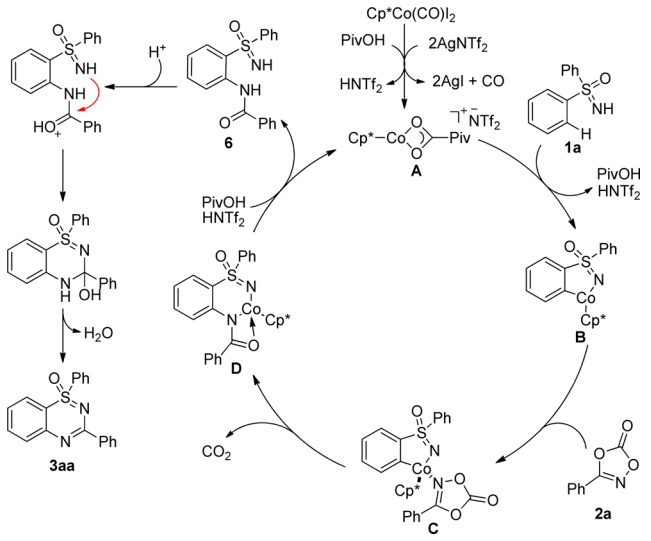
Scheme 5. Proposed Mechanism



decobaltation of **D** delivers the key intermediate **6**, along with the regeneration of the reactive metal catalyst **A** to complete the catalytic cycle. Finally, dehydration and cyclization reaction of compound **6** which is facilitated by PivOH would produce the product **3aa**.

In summary, we have developed a novel, microwave-assisted, Cp^*Co^{III}-catalyzed C−H activation/double C−N bond formation reaction of free *N*H-sulfoximines with 1,4,2-dioxazol-5-ones to produce diverse thiadiazine 1-oxides in moderate to excellent yields. No external oxidants were required, and only stoichiometric CO_2 and H_2O were generated as the major chemical wastes. This novel methodology thus represents an environmentally benign and straightforward avenue to synthesize medicinally significant thiadiazine 1-oxides. The reaction mechanism has been proposed based on control experiments. Further applications of this air- and moisture-tolerant reaction and more detailed mechanistic investigations are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00120.

Experimental details, characterization data, and ^1H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(13) See the Supporting Information for details.
(14) CCDC 1517010 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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