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Pd/Norbornene Collaborative Catalysis on the Divergent Preparation of Heterocyclic Sulfoximine Frameworks

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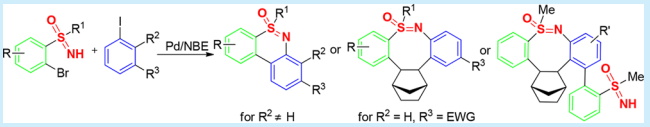
Supporting Information

ABSTRACT: Pd/Norbornene cocatalyzed tandem C−H activation/annulation reactions of free *N*H-sulfoximines with aryl iodides to produce diverse polyheterocyclic sulfoximines in highly chemoselective models are reported. The reaction tolerated a broad range of functional groups under external oxidant-free conditions. The preliminary mechanistic studies using density functional theory (DFT) calculations highlighted the key role of a Pd^{IV} intermediate.

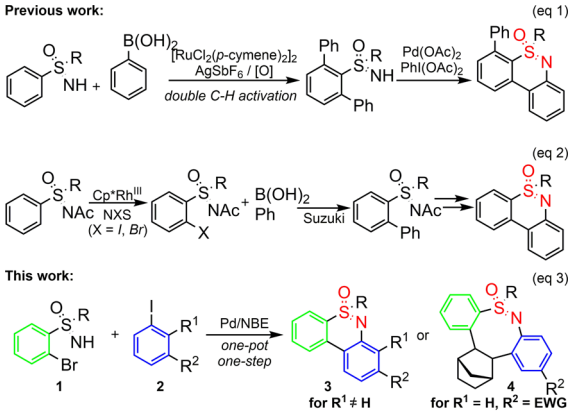


Sulfoximidoyl-based molecules have important biological properties; therefore, they are widely applied in practical pharmaceutical industries, including clinical drugs such as Suloxifen from Gödecke GmbH,[1] Roniciclib (BAY 1000394) from Bayer,[2] AZD-6738 from AstraZeneca,[3] and the insecticide Sulfoxaflor from Dow Chemical Corporation.[4] In organic synthesis, sulfoximine derivatives have been used as key intermediates to prepare biologically active molecules,[5] in directed C−H activations,[6] and asymmetric catalysis.[7]

As a result of intensive efforts in the past decade, novel approaches that employ free *N*H-sulfoximines as readily available starting materials have been developed for the preparation of acyclic sulfoximine derivatives.[8] However, despite the achievements, procedures for the construction of fused heterocyclic sulfoximine frameworks are limited. Several studies have focused on the synthesis of bicyclic sulfoximine derivatives, such as benzothiazines and benzoisothiazines.[9] Our group developed a 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 bicyclic thiadiazine-1-oxides.[10] Based on this result and in connection with our interest in the construction of polycyclic aromatic molecules,[11] we conceived that the fused polycyclic sulfoximines could be prepared in similar C−H activation/C−N bond formation strategies.

A limited number of methods are available for the synthesis of polycyclic sulfoximine derivatives (Scheme 1). For instance, in 2015, Jeganmohan et al. developed the generation of tricyclic dibenzothiazines by Ru-catalyzed *ortho* arylation of *N*H-sulfoximines with aryl boronic acids, followed by Pd-catalyzed intramolecular cyclization sequences in two consecutive steps (eq 1).[12] Later, Bolm and co-workers disclosed the formation of functionalized dibenzothiazines starting from *N*-acylsulfoximines through Rh^{III}-catalyzed *ortho* halogenation, Pd-catalyzed Suzuki coupling reaction, and a subsequent $Pd(OAc)_2$-PhI$(OAc)_2$-mediated oxidative annulation cascade (eq 2).[13] Enlightened by the results, we herein present a facile construction of polycyclic sulfoximine derivatives in a one-pot and one-step annulation reaction, which employs the readily available free *N*H-sulfoximines and aryl iodides as the starting materials, and $Pd(OAc)_2$/norbornene (NBE) as catalysts, to rapidly deliver divergent dibenzothiazines or eight-membered fused heterocyclic sulfoximines (eq 3).

Scheme 1. Strategies To Prepare the Polyheterocyclic Sulfoximines



We recently reported Pd/NBE-mediated Catellani-type C−H amination reactions of aryl iodides with *O*-benzoyl hydroxylamines to produce biaryl tertiary amines in a chemoselective-controlled fashion.[14] The Catellani reaction is an effective sequential protocol to construct structurally divergent polycyclic aromatic scaffolds, and the reaction has been optimized through seminal contributions by the groups of Catellani[15] and Lautens[16] among others.[17] Conventionally, the Catellani reaction employs two or more distinct reactive molecules as substrates, such as aryl iodides with alkyl halides or pseudohalides.[18] Nevertheless, the combination of two aryl halides as substrates has been studied,[19] which indicate that the

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inherent competitive chemical selectivity problem could be suppressed when taking the reaction parameters such as substrates, catalyst, ligand, etc. into consideration.

The proposed strategy for the preparation of fused tricyclic dibenzothiazines is depicted in Figure 1. We expected that the

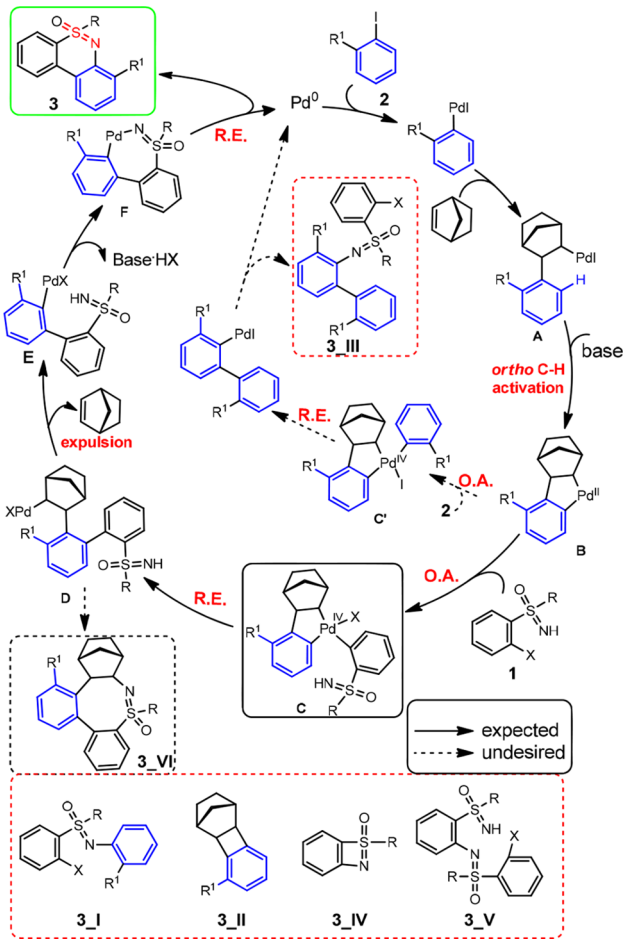

Figure 1. Proposed reaction design to prepare tricyclic dibenzothiazines and possible byproducts.

oxidative addition (O.A.) of Pd^{II} intermediate **B** with a suitable halogenated free *N*H-sulfoximine **1** would selectively generate the Pd^{IV} intermediate **C**,[20] which undergoes reductive elimination (R.E.)/expulsion of norbornene/Buchwald–Hartwig C–N bond formation cascades to give the desired tricyclic product **3**. Nonetheless, we encountered several challenges in this catalytic cycle: (1) Pd-catalyzed direct cross-coupling of *N*H-sulfoximine **1** with aryl iodide or bromide **2** to give *N*-arylated product **3_I** is already known.[21] (2) The oxidative addition of aryl iodide **2** with intermediate **B** to form intermediate **C′** should occur more readily than the formation of aryl bromide analogue **1**. (3) Direct reductive elimination of **B** is possible to give undesired compound **3_II**,[22] and (4) the intramolecular Buchwald–Hartwig cross-couplings may occur to give biaryl sideproducts **3_IV**, **3_V**, and **3_VI**, respectively (Figure 1).

Motivated by the above-mentioned challenges, and encouraged by the potential usefulness of the cyclic sulfoximine derivatives in biological evaluations, we aimed toward exploring the possibility of this reaction. Initially, 2-iodotoluene (**2a**) was employed as a substrate, and PPh_3 was selected as a ligand to optimize the reaction. After an extensive study of halogenated sulfoximines, along with metal catalyst, ligands, additives, and solvents, we were pleased to find that 2-bromo-*N*H-sulfoximine **1a**, which is easily available from 2-bromophenyl methyl sulfide,[23] was an optimal substrate for the desired transformation (Table S1). Indeed, in a highly chemoselective conversion in DMF at 105 °C, the expected tricyclic product **3aa** was isolated and identified, albeit in relatively low yield (entry 1). The other 2-bromo substituted substrates, such as 1-bromo-2-(ethylsulfonimidoyl)benzene (**1b**) and 1-bromo-2-(phenylsulfonimidoyl)benzene (**1c**), gave less than desirable results under the reaction conditions, whereas a complex mixture was observed when 1-(methylsulfonimidoyl)-2-iodobenzene was used as a reaction partner.[24]

Once the optimal reaction conditions were established, we defined the scope and limitation of this Pd/norbornene cocatalyzed tandem annulation reaction (Scheme 2). The tandem cyclization reaction of 2-bromo-*N*H-sulfoximine **1a** with various aryl iodides **2a**–**2o** proceeded smoothly to afford products **3aa**–**3ao** in yields ranging from 45% to 95%. Serviceable yields of **3ab**, **3ac**, and **3ae** were obtained when substrate **2** was attached with electron-donating groups, such as MeO– or alkyl groups. A low yield of **3ad** was isolated for the reaction of **1a** with 1-iodo-2-isopropylbenzene **2d**, which should be attributed to the steric hindrance of the starting material. The reaction of 2-bromo-*N*H-sulfoximine **1a** with 1-iodonaphthalene **2f** was successful, affording the tetracyclic framework **3af** in 71% yield. Good to excellent yields were obtained when aryl iodides **2** were attached with electron-withdrawing substituents, as the Cl- and CF_3-substituted tricyclic dibenzothiazines **3ag** and **3ah** were obtained in 90% and 78% yields, respectively. The production results of the methodology was not compromised when reactive electron-withdrawing substituents, such as COOMe or NO_2 groups, were attached, as the corresponding products **3am**, **3an**, and **3ao** were all delivered in up to 95% yields. These results highlighted the possibility that further modulation of these tricyclic heterocycles could be achieved by utilizing the alkyl or reactive substitutions as synthetic handles.

For variation on the *S*-linkage of the *N*H-sulfoximines (Scheme 2, below), the reaction of ethyl substituted 2-bromo-*N*H-sulfoximine substrate **1b** with **2a** and **2f** produced the desired product **3ba** and **3bf** without difficulty in acceptable yields. The tandem cyclization reactions of **1c** with various electron-rich (**2a**) or electron-poor (**2g** and **2m**) aryl iodides all reacted smoothly, resulting in the corresponding dibenzothiazines **3ca**, **3cg**, and **3cm** in 67%–79% yields. A tetracyclic heterocycle **3cf** could be chemoselectively isolated from the reaction of **1c** with 1-iodonaphthalene.

Interestingly, for the aryl iodides **2** bearing an electron-withdrawing substituent located at the meta-position of the phenyl ring, eight-membered bridged heterocycles **4** can be generated (Scheme 3). For instance, the reaction of *N*H-sulfoximine **1a** with methyl 3-iodobenzoate under the standard conditions delivered product **4a** in 86% yield. The structure of compound **4a** was verified unambiguously through X-ray crystallography analysis (CCDC 1819922). Besides the ester group, many synthetically useful substitutions, including nitro (**4b**), cyano (**4c**), and trifluoromethyl (**4d**) groups, were all well tolerated, resulting in corresponding polycyclic sulfoximine derivatives **4** in up to 94% yield. Unfortunately, for the *meta*-MeO substituted electron-rich aryl iodide, the reaction became complex, and the desired product **4e** was not detected, which

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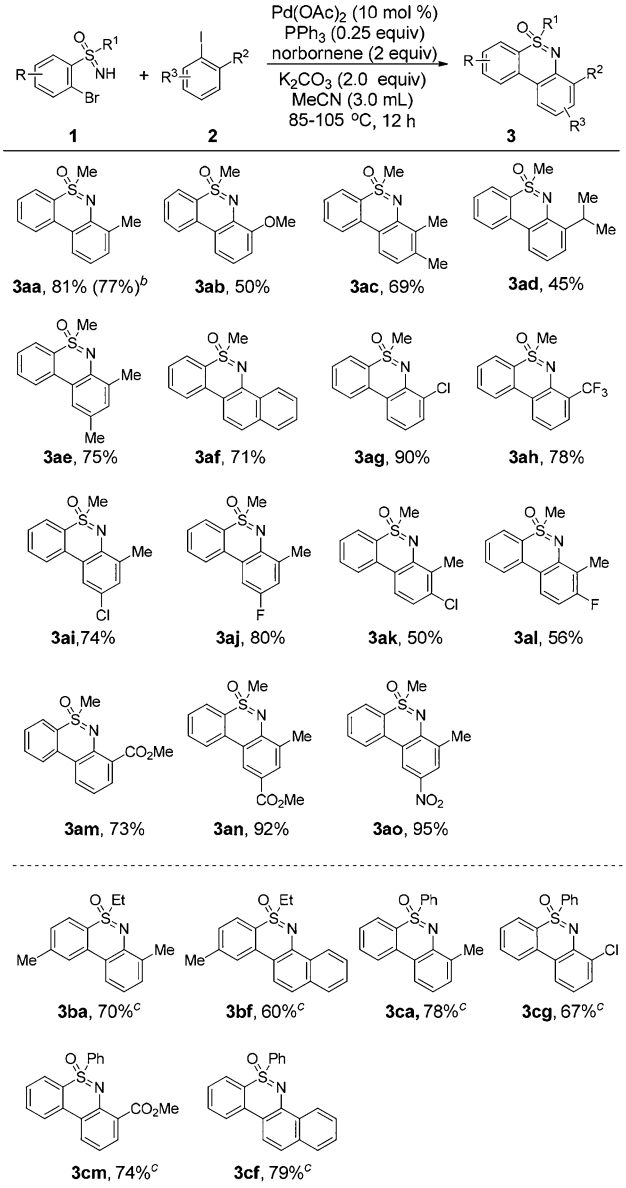
Scheme 2. Substrate Scope Studies[a]

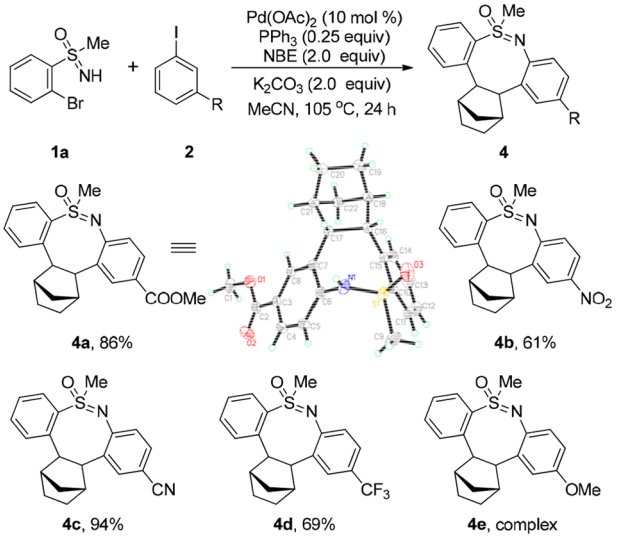


[a]Reaction conditions: Table S1, entry 17, *N*H-sulfoximine **1** (0.30 mmol), arene iodide **2** (0.36 mmol) in 3.0 mL of CH_3CN at 85−105 °C for 12 h. [b]1.0 mmol of **1a** scale reaction. [c]Temp = 105 °C, time = 24 h.

indicated the electronic effect should play a crucial role in the tandem C−H activation/cyclization reaction.

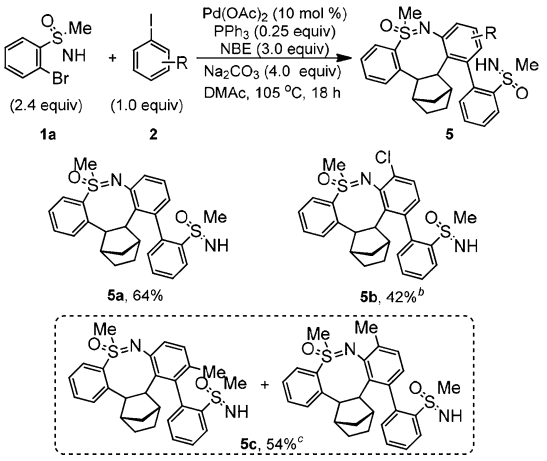
Recently, organic molecules bearing a 3D-type heterocyclic framework have attracted notable attention. Heterocycles containing sp^3-carbon atoms possess explicit spatial configurations, which enable powerful creative applications in porous materials, chemical probes, medicinal drugs, and chiral monomers.[25] When increasing the amount of 2-bromo-*N*H-sulfoximine **1a** to 2.4 equiv, a fused medium-sized polyheterocycle **5**, which bears two sulfoximine moieties, could be isolated under slightly modified conditions (Scheme 4). The Pd/NBE cocatalyzed direct cyclization of **1a** with iodobenzene **2q** reacted smoothly to afford compound **5a** in 64% yield. The structure of compound **5a** was established via 2D NMR. Likewise, the reaction of **1a** with 1-chloro-3-iodobenzene **2r** afforded product **5b** in 42% yield. An inseparable mixture of

Scheme 3. Synthesis of Medium-Sized Sulfoximine Heterocycles[a]



[a]Reaction conditions: *N*H-sulfoximine **1a** (0.30 mmol), aryl iodide **2** (0.36 mmol) in 3.0 mL of CH_3CN at 105 °C for 24 h.

Scheme 4. Synthesis of Medium-Sized Heterocycles Bearing Two Sulfoximine Moieties[a]



[a]Reaction conditions: *N*H-sulfoximine **1** (0.72 mmol, 2.4 equiv), aryl iodide **2** (0.30 mmol, 1.0 equiv) in 3.0 mL of *N*,*N*-dimethylacetamide at 105 °C for 18 h. [b]1-Chloro-3-iodobenzene as the substrate. [c]1-Iodo-3-methylbenzene as the substrate.

constitutional isomers **5c** was formed in 54% yield when **1a** reacted with 1-iodo-3-methylbenzene **2s**.

Based upon these studies and the preliminary DFT calculations on the bond formation Gibbs free energy,[23] we proposed a possible mechanism for the formation of product **5a**. As shown in Scheme 5, the reductive elimination of Pd^{IV}-intermediate **C3** (**C** refer to Figure 1) first occurred to give a biaryl species **H**, which was followed by a C−H activation reaction under the assistance of a base to give the pentapalladacycle **I**. Oxidative addition reaction of **I** with *ortho*-bromo-*N*H-sulfoximine **1a** to give another Pd^{IV}-intermediate **J** occurred, followed by the intramolecular nucleophilic substitution to release HBr and two reductive elimination reactions to deliver the final product **5a**, along with the regeneration of Pd^0 to complete the catalytic cycle.

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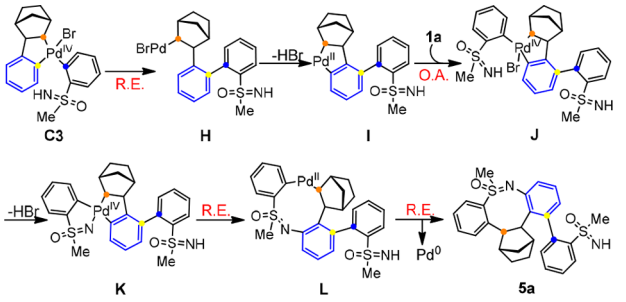
Scheme 5. Proposed Mechanism for the Formation of 5a



In summary, we have described a Pd/NBE cocatalyzed tandem C−H activation/annulation reaction of free *NH*-sulfoximines with aryl iodides, which enables operational convenience with good tolerance of functional groups to tricyclic dibenzothiazines or eight-memberd sulfoximine heterocycles divergently and with excellent selectivity. Considering the availability of the starting materials and the catalytic systems, this one-pot and one-step protocol served as a general and powerful method for the synthesis of fused heterocyclic sulfoximine derivatives. Investigations regarding the mechanism of the reactions through DFT studies were conducted to understand the formation of the two different heterocyclic scaffolds, and the results may provide insight into the development of transition-metal-catalyzed C−H functionalization in sulfoximine chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00776.

Experimental details, characterizations, and copies of ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 1819922 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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