Heterocycles

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Regioselective Syntheses of 1,2-Benzothiazines by Rhodium-Catalyzed Annulation Reactions**

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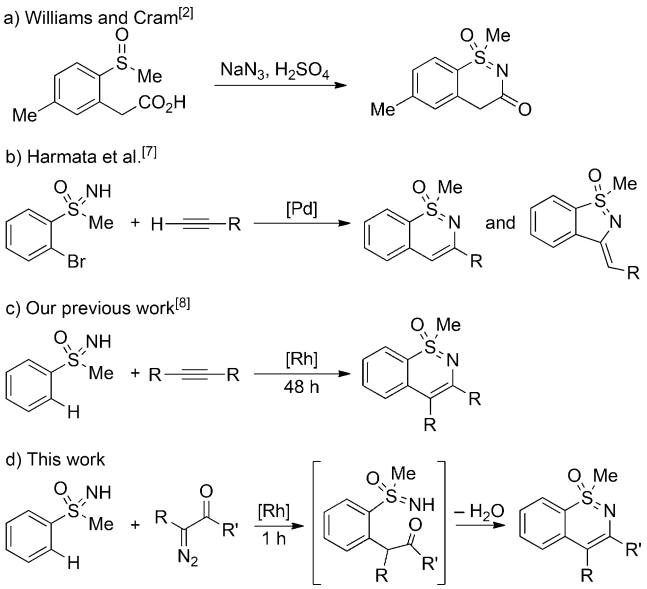
Abstract: *Rhodium-catalyzed directed carbene insertions into aromatic C–H bonds of S-aryl sulfoximines lead to intermediates, which upon dehydration provide 1,2-benzothiazines in excellent yields. The domino-type process is regioselective and shows a high functional-group tolerance. It is scalable, and the only by-products are dinitrogen and water. Three illustrative transformations underscore the synthetic value of the products.*

In 2009, Lovering, Bikker, and Humblet analyzed the structural complexity of molecules considered as drug candidates and entitled their resulting summary "Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success".[1] They found two factors to be most relevant for success in drug discovery: first, a high molecular complexity as revealed by a high degree of carbon bond saturation and, second, the presence of stereogenic atoms. Along these lines, 1,2-benzothiazines represent an interesting scaffold. They have both an all-carbon aromatic fragment and a non-aromatic heterocyclic core with a stereogenic sulfur as the key element.[2] In the light of the pronounced recognition and synthetic use of very related heterocycles,[3,4] it comes as a surprise that 1,2-benzothiazines appear rather neglected in crop protection and medicinal chemistry,[5] where they could be envisaged as key components of bioactive molecules.[6] Preparative challenges contribute to this underrepresentation. In general, three synthetic approaches towards 1,2-benzothiazines can be distinguished. Besides the seminal work by Williams and Cram (Scheme 1a),[2] the findings by Harmata and co-workers are noteworthy (Scheme 1b).[7] While the former developed a sulfoxide imidation/ring-closure reaction sequence, the latter used a Sonogashira-type cross-coupling of an *ortho*-bromo sulfoximine and subsequent intramolecular alkyne amidation. We introduced a rhodium-catalyzed oxidative annulation reaction of sulfoximines and internal alkynes, which led to 1,2-benzothiazines with fully substituted heterocyclic cores (Scheme 1c).[8] Thus, common to all syntheses is that they either require rather elaborate-to-access sulfoximines as starting materials or that specific (unsymmetrical) substitution patterns are difficult to achieve. Herein, we report an unprecedented 1,2-benzothiazine synthesis, which overcomes some of those critical issues by applying rhodium-catalyzed directed migratory carbene insertions into aromatic C–H bonds[9] of standard NH-sulfoximines followed by regioselective dehydrative ring closures (Scheme 1c).



Scheme 1. Syntheses of 1,2-benzothiazines.

Metal-catalyzed carbene insertion is an attractive strategy for the construction C–C bonds.[10] Addressing aromatic C–H bonds proved particularly challenging. Along these lines, the groups of Wang, Satoh, and Miura developed direct alkylations of azoles with *N*-tosylhydrazones using copper, nickel, and cobalt catalysts.[11] Yu and co-workers described rhodium(III)-catalyzed carbenoid insertions into challenging aromatic C–H bonds with diazomalonates,[12] and various formal cycloadducts were obtained by the groups of Rovis,[13] Glorius,[14] and Cui,[15] as well as others using rhodium(III)-catalyzed C–H activations and reactions with diazo compounds. Finally, Wan, Li, and co-workers, as well as Wang and co-workers reported *ortho* alkylations and alkenylations of aromatic C–H bonds with diazo compounds or *N*-tosylhydrazones by rhodium catalysis.[16] On the basis of these findings we wondered if a catalytic activation of a diazo compound could be utilized for the *ortho*-functionalization of an S-aryl sulfoximine, thus leading to an intermediate, which upon dehydration would provide a 1,2-benzothiazine. Rhodium appeared to be the metal of choice for both the carbene formation and the directed C–H insertion. For testing this hypothesis the NH-sulfoximine **1a** and ethyl diazoacetoacetate (**2a**) were chosen as representative starting materials. The first attempt, however, remained unsuccessful. Using

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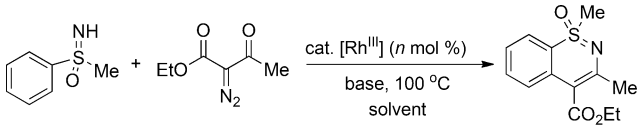
Table 1: Optimization of the reaction conditions.[a]



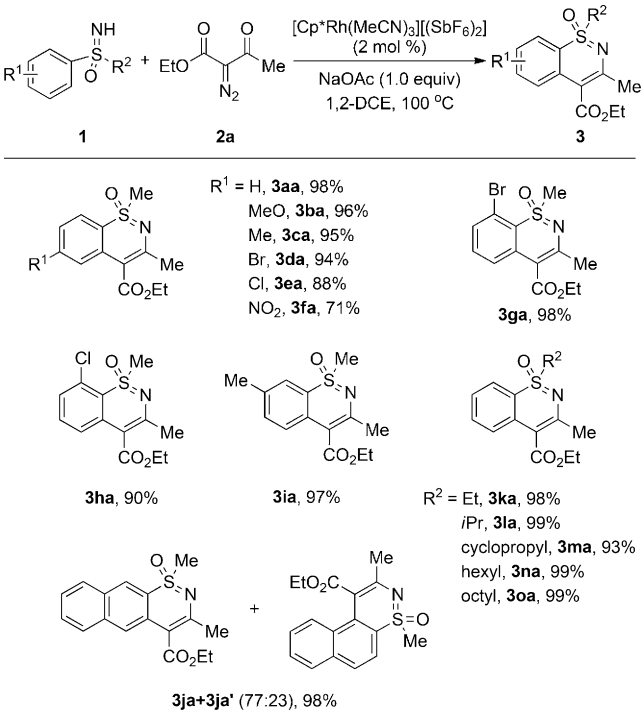
1a **2a** **3aa**

Entry	*n*	Base	Solvent	*t* [h]	Yield [%]
1[b]	2.5	NaOAc	1,2-DCE	3	trace
2	5	NaOAc	1,2-DCE	1	99
3	2	NaOAc	1,2-DCE	1	98
4	1	NaOAc	1,2-DCE	3	82
5	2	CsOAc	1,2-DCE	6	17
6	2	KOAc	1,2-DCE	6	40
7	2	NaOAc	MeOH	6	41
8	2	NaOAc	MeCN	6	82
9	2	NaOAc	toluene	1	91

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.33 mmol), [Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (*n* mol%), base (0.30 mmol) and 1,2-DCE (1.5 mL) was stirred at 100°C under argon. [b] [{Cp*RhCl$_2$}$_2$] was used as catalyst. Cp* = C$_5$Me$_5$.

a combination of [{Cp*RhCl$_2$}$_2$](2.5 mol%) and NaOAc in 1,2-dichloroethane (1,2-DCE) at 100°C under an argon atmosphere for 3 hours, provided the desired product **3aa** in only trace amounts (Table 1, entry 1). The situation changed significantly when [Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (5 mol%) was used as the catalyst. Now, **3aa** was obtained in 99% yield after 1 hour (entry 2). Also with only 2 mol% of rhodium, the yield of **3aa** remained excellent (entry 3). Reducing the catalyst loading further to 1 mol% decreased the yield (82%) of **3aa** (entry 4). CsOAc or KOAc instead of NaOAc proved less effective even after 6 hours (entries 5 and 6). Moderate to good yields of **3aa** were observed when the catalyses were run in methanol, acetonitrile, or toluene instead of 1,2-DCE as the solvent (entries 7–9).

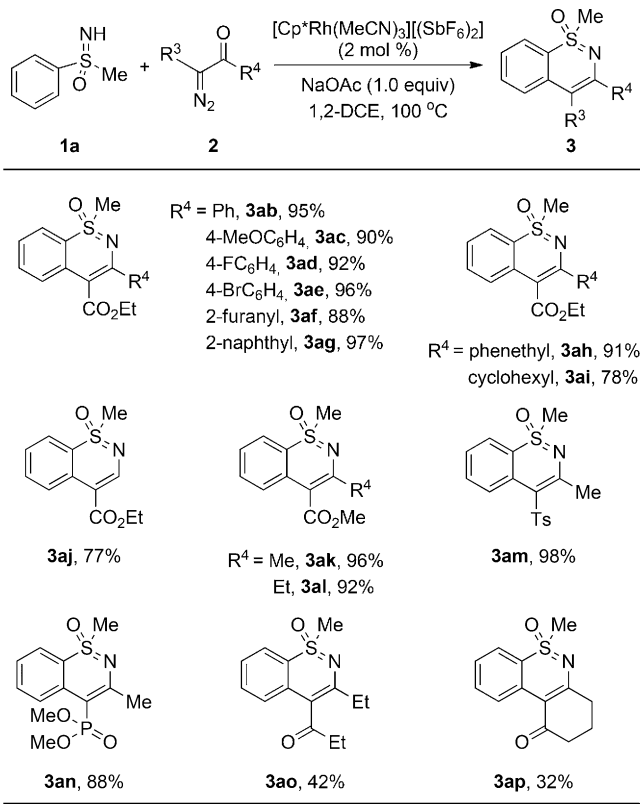
With the optimal reaction conditions in hand, the applicability of a range of diversely substituted NH-sulfoximines was investigated. Ethyl diazoacetoacetate (**2a**) was kept as a representative reaction partner (Scheme 2). In the series of *S*-aryl-*S*-methyl sulfoximines all 1,2-benzothiazines (**3aa–ja**/**3ja′**) were formed in high yields (71–98%) irrespective of the substitution pattern of the sulfoximine arene. Probably as a result of the electrophilic C–H activation process,[12] the sulfoximines bearing electron-withdrawing groups gave the lowest yields. Noteworthy are the results with the sterically compressed 2-bromophenyl- and 2-chlorophenyl-substituted sulfoximines, **1g** and **1h**, respectively, which both reacted well and provided the corresponding 1,2-benzothiazines (**3ga** and **3ha**) in yields of 98 and 90%, respectively. An exclusive site selectivity was observed in the catalysis with the *meta*-methyl-substituted sulfoximine **3i**, which led to a single regioisomeric product (**3ia**) in 97% yield. The analogous transformation of the 2-naphthyl-substituted sulfoximine **1j** showed a lower site selectivity, thus affording the two possible isomeric 1,2-benzothiazines **3ja** and **3ja'** in a ratio of 77:23 (as determined by NMR spectroscopy). Varying the S-alkyl substituent of the S-phenyl sulfoximines led to the 1,2-benzothiazines **3ka–oa** in yields ranging from 93 to 99%.



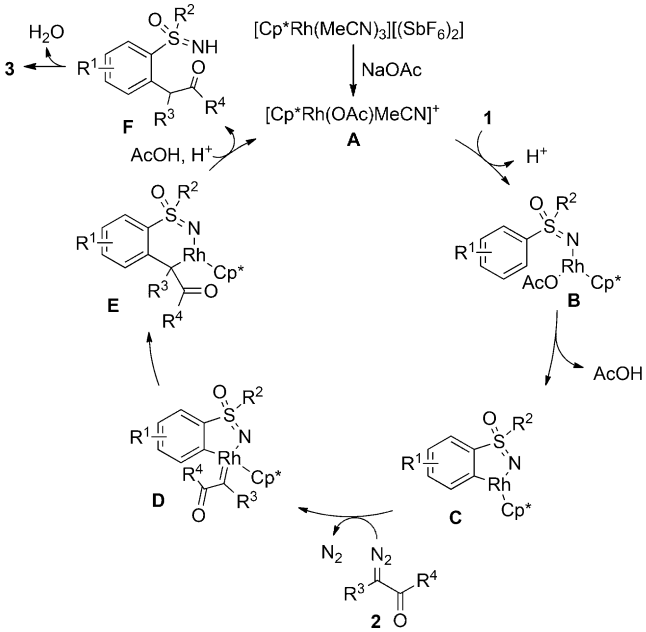
Scheme 2. Reaction scope with respect to sulfoximine component.

Next, structural variations of the diazo compounds were studied (Scheme 3). The NH-sulfoximine **1a** served as a representative coupling partner. Also in these reactions the 1,2-benzothiazine formations were highly regioselective, thus exclusively providing products with the (hetero)carbonyl substituents at the 4-position of the heterocycle. The aryl-containing diazo ethyl esters **2b–e** showed very good reactivities irrespective of the electronic nature of the aryl substituents. Accordingly, the 1,2-benzothiazines **3ab–ag** were obtained in yields ranging from 88 to 97%. Slightly lower yields were observed when alkyl-substituted diazo ethyl esters were applied. While the yield of the phenethyl-substituted 1,2-benzothiazine **3ah** was still good (91%), the sterically more congested product with the cyclohexyl group (**3ai**) was only obtained in 78% yield. Essentially the same result (77% yield) was achieved in the preparation of **3aj** stemming from the annulation of **1a** with the formyl diazo compound **2j**. Methyl diazoacetoacetate (**2k**) and methyl 2-diazo-3-oxopentanoate (**2l**) also underwent coupling with **1a**, thus producing the corresponding 1,2-benzothiazines **3ak** and **3al** in high yields. Extending the chemistry to reactions with the diazosulfone **2m** and diazophosphonate **2n** gave the products **3am** (98%) and **3an** (88%), respectively. Under the same reaction conditions, couplings of the α-diazo-β-diketones **2o** and **2p** with **1a** afforded 1,2-benzothiazines **3ao** and **3ap** in only moderate yields because of low substrate reactivity.

Carrying out the catalysis on a gram scale using 7.0 mmol of **1a** and 7.7 mmol of **2a** in the presence of 2 mol% of [Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ and 1.0 equivalent of NaOAc in 1,2-DCE at 100°C under an argon atmosphere for 1 hour afforded 1,2-benzothiazine **3aa** in 90% yield.



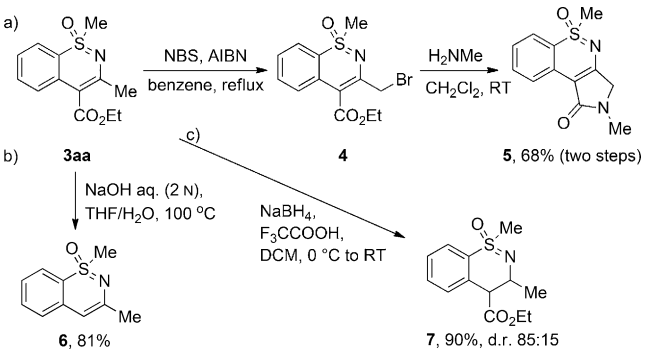
Scheme 3. Reaction scope with respect to the diazo component.



Scheme 4. Plausible mechanism.

A plausible mechanism for the transformation is shown in Scheme 4. First, $[Cp^*Rh(MeCN)_3][SbF_6]_2$ reacts with NaOAc and upon concomitant decoordination of acetonitrile the acetate-ligated cationic rhodium(III) complex **A** is formed.[17] Reaction of **A** with the sulfoximine **1** leads to the intermediate **B** by deprotonation. Electrophilic C–H bond cleavage of **B** and loss of acetic acid provides the five-membered rhodacycle **C**,[8] which reacts with the diazo compound **2**, thus forming the rhodium-carbene **D** upon extrusion of dinitrogen. Migratory insertion of the carbene into the rhodium–carbon bond generates the intermediate **E**.[18] Protonolysis of **E** leads to the intermediate **F** and allows the rhodium complex to start a new catalytic cycle. The 1,2-benzothiazine formation is terminated by ring-closing elimination of water, thus converting **F** to the final product **3**.[19]

To demonstrate the synthetic potential of the products, a few chemical modifications were explored using **3aa** as a representative starting material. Treatment of **3aa** with NBS/AIBN in benzene gave the methyl bromide **4** (Scheme 5a), which was subsequently reacted with methyl amine in dichloromethane at room temperature, thus affording the tricyclic lactam **5** in 68% yield in two steps.[20] The hydrolysis of the ethyl ester group of **3aa** with NaOH at 100°C and subsequent decarboxylation provided the 1,2-benzothiazine **6** in 81% yield (Scheme 5b). This transformation is noteworthy because it opens access to 4-unsubstituted 1,2-benzothiazines, which are difficult to prepare by alternative methods. Finally, the double bond in the heterocyclic core of **3aa** was reduced by applying a mixture of $NaBH_4$ and CF_3COOH in dichloromethane. As a result, the product **7** (with a d.r. value of 85:15 as determined by NMR spectroscopy of the crude reaction mixture) was obtained in 90% yield (Scheme 5c).



Scheme 5. Selected transformations of **3aa**.

In summary, we have developed a rhodium-catalyzed domino C–H activation/cyclization/condensation process starting from NH-sulfoximines and diazo compounds, thus providing specifically substituted 1,2-benzothiazines in high yields. A mechanistic scheme has been proposed, and initial functionalization reactions illustrate the synthetic value of the products.

Experimental Section

General procedure for the rhodium-catalyzed synthesis of 1,2-benzothiazines: A Schlenk tube (25 mL) was charged with the sulfoximine **1** (0.30 mmol), diazo compound **2** (0.33 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0 mg, 0.006 mmol, 2 mol%), and NaOAc (24.6 mg, 0.30 mmol). Under an argon atmosphere, dry 1,2-dichloroethane (1.5 mL) was added by syringe. After stirring the reaction mixture at 100°C for 1 h, it was cooled to room temperature and diluted with dichloromethane (10 mL). The mixture was filtered

through a Celite pad and washed with dichloromethane (3 × 20 mL). The filtrate was concentrated, and the product was purified by column chromatography on silica gel with *n*-pentane/ethyl acetate (10:1 to 1:2) as eluent to afford **3** as a pure product.

Keywords: C–H activation · carbenes · diazo compounds · heterocycles · rhodium

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