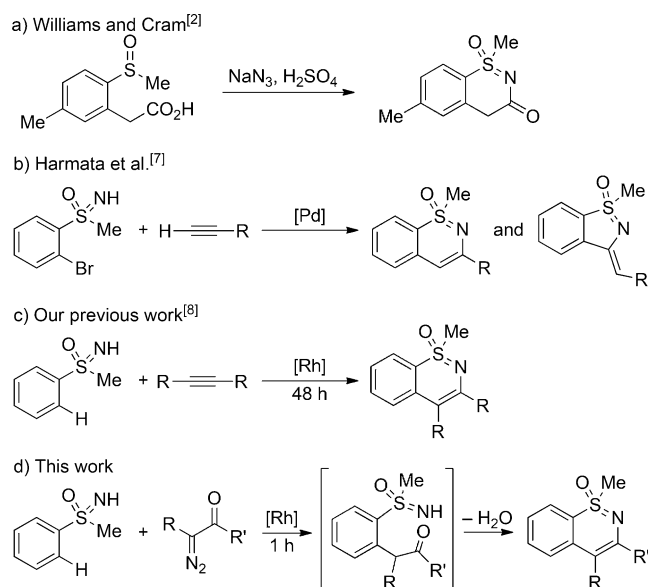


Regioselective Syntheses of 1,2-Benzothiazines by Rhodium-Catalyzed Annulation Reactions**

Ying Cheng and Carsten Bolm*

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



Scheme 1. Syntheses of 1,2-benzothiazines.

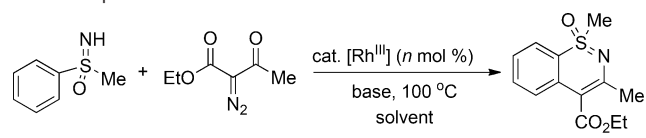
insertions into aromatic C–H bonds^[9] of standard *NH*-sulfoximines followed by regioselective dehydrative ring closures (Scheme 1c).

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 diazoacetate (**2a**) were chosen as representative starting materials. The first attempt, however, remained unsuccessful. Using

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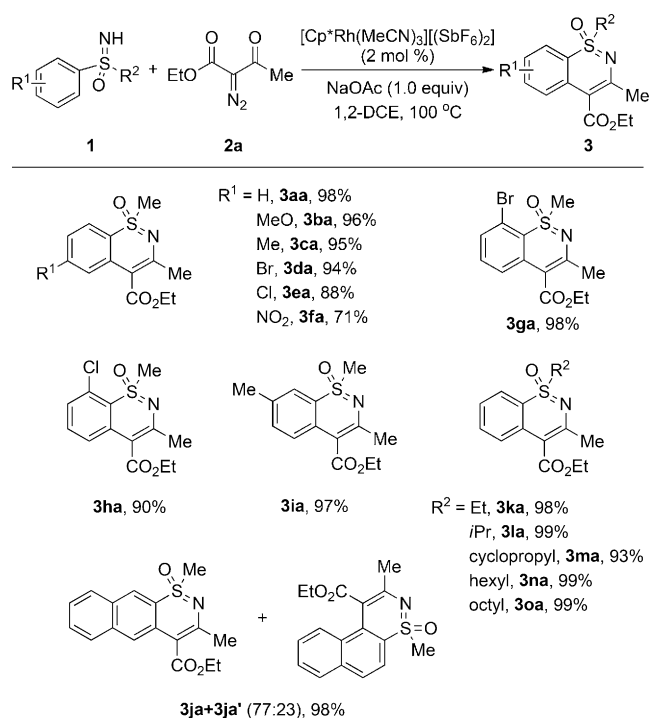
Table 1: Optimization of the reaction conditions.^[a]


Entry	<i>n</i>	Base	Solvent	<i>t</i> [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][SbF₆]₂ (*n* mol %), base (0.30 mmol) and 1,2-DCE (1.5 mL) was stirred at 100 °C under argon. [b] [Cp*RhCl₂]₂ was used as catalyst. Cp* = C₅Me₅.

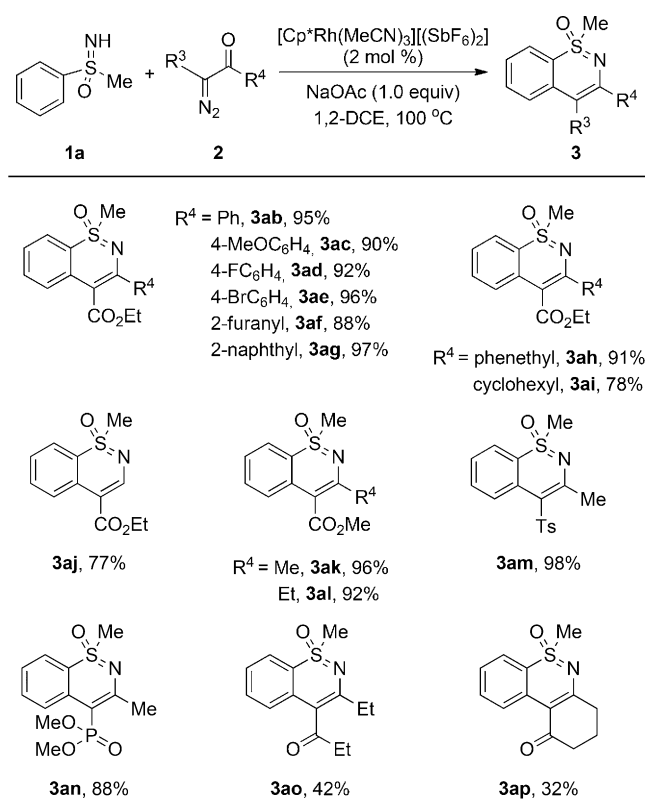
a combination of [Cp*RhCl₂]₂ (2.5 mol %) and NaOAc in 1,2-dichloroethane (1,2-DCE) at 100 °C under an argon atmosphere for 3 hours, provided the desired product **3aa** in only trace amounts (Table 1, entry 1). The situation changed significantly when [Cp*Rh(MeCN)₃][SbF₆]₂ (5 mol %) was used as the catalyst. 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 %.

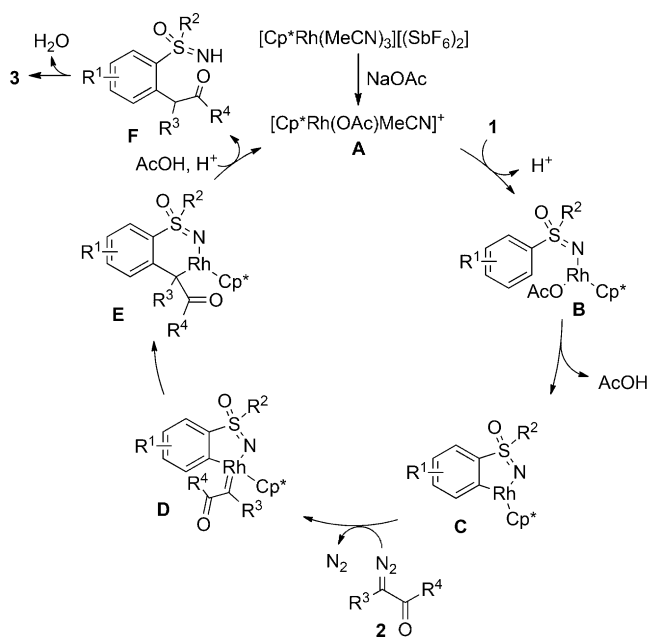

Scheme 2. Reaction scope with respect to sulfoximine component.

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][SbF₆]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.

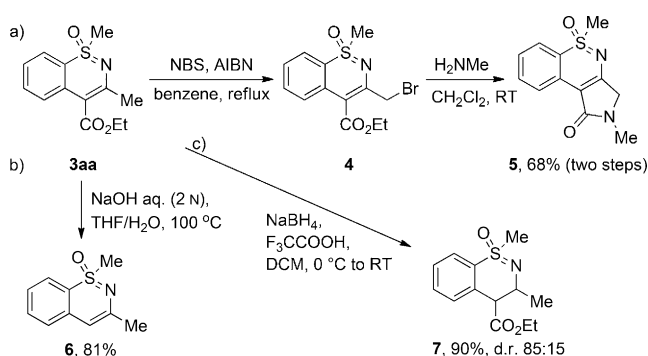


Scheme 4. Plausible mechanism.

A plausible mechanism for the transformation is shown in Scheme 4. First, $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ 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



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

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 NaBH₄ and CF₃COOH 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).

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), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ (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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Angew. Chem. **2015**, *127*, 12526–12529

- [1] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.
- [2] For the seminal discovery of this heterocyclic scaffold, see: T. R. Williams, D. J. Cram, *J. Org. Chem.* **1973**, *38*, 20–26.
- [3] a) G. J. Wells, M. Tao, K. A. Josef, R. Bihovsky, *J. Med. Chem.* **2001**, *44*, 3488–3503; b) R. Bihovsky, M. Tao, J. P. Mallamo, G. J. Wells, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1035–1038; c) X. Chen, S. Zhang, Y. Yang, S. Hussain, M. He, D. Gui, B. Ma, C. Jing, Z. Qiao, C. Zhu, Q. Yu, *Bioorg. Med. Chem.* **2011**, *19*, 7262–7269; d) O. O. Ajani, *Arch. Pharm. Chem. Life Sci.* **2012**, *345*, 841–851.
- [4] For the use of the isomeric 2,1-benzothiazines in synthetic work, see: a) M. Harmata, M. Kahraman, D. E. Jones, N. Pavri, S. E. Weatherwax, *Tetrahedron* **1998**, *54*, 9995–10006; b) M. Harmata, N. Pavri, *Angew. Chem. Int. Ed.* **1999**, *38*, 2419–2421; *Angew. Chem.* **1999**, *111*, 2577–2579; c) M. Harmata, S. K. Ghosh, *Org. Lett.* **2001**, *3*, 3321–3323; d) M. Harmata, X. Hong, C. L. Barnes, *Tetrahedron Lett.* **2003**, *44*, 7261–7264; e) M. Harmata, S. K. Ghosh, C. L. Barnes, *J. Supramol. Chem.* **2002**, *2*, 349–351; f) M. Harmata, X. Hong, *J. Am. Chem. Soc.* **2003**, *125*, 5754–5756; g) M. Harmata, X. Hong, C. L. Barnes, *Org. Lett.* **2004**, *6*, 2201–2203; h) M. Harmata, X. Hong, *Tetrahedron Lett.* **2005**, *46*, 3847–3849; i) M. Harmata, N. L. Calkins, R. G. Banghman, C. L. Barnes, *J. Org. Chem.* **2006**, *71*, 3650–3652.
- [5] J. G. Lombardino, D. E. Kuhla, *Adv. Heterocycl. Chem.* **1981**, *28*, 73–126.
- [6] Note the analogy to the chemistry of sulfoximines, which recently experienced a renaissance. For an excellent review highlighting this development, see: U. Lücking, *Angew. Chem. Int. Ed.* **2013**, *52*, 9399–9408; *Angew. Chem.* **2013**, *125*, 9570–9580.
- [7] a) M. Harmata, K. Rayanil, M. G. Gomes, P. Zheng, N. L. Calkins, S.-Y. Kim, Y. Fan, V. Bumbu, D. R. Lee, S. Wacharasinth, X. Hong, *Org. Lett.* **2005**, *7*, 143–145; b) see also in A. Garimallaprabhakaran, X. Hong, M. Harmata, *ARKIVOC* **2012**, 119–128.
- [8] W. Dong, L. Wang, K. Parthasarathy, F. Pan, C. Bolm, *Angew. Chem. Int. Ed.* **2013**, *52*, 11573–11576; *Angew. Chem.* **2013**, *125*, 11787–11790.
- [9] For a synopsis highlighting the concept of metal–carbene migratory insertions, see: Z. Liu, J. Wang, *J. Org. Chem.* **2013**, *78*, 10024–10030.
- [10] For reviews on catalytic carbene insertions into C–H bonds, see: a) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724; b) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417–424; c) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2903.
- [11] a) X. Zhao, G. Wu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 3296–3299; b) T. Yao, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2012**, *51*, 775–779; *Angew. Chem.* **2012**, *124*, 799–803; c) Q. Xiao, L. Ling, F. Ye, R. Tan, L. Tian, Y. Zhang, Y. Li, J. Wang, *J. Org. Chem.* **2013**, *78*, 3879–3885; d) for dirhodium(II)-catalyzed intramolecular carbenoid insertions into aryl C–H bonds, see: C. P. Park, A. Nagle, C. H. Yoon, C. Chen, K. W. Jung, *J. Org. Chem.* **2009**, *74*, 6231–6236.
- [12] W.-W. Chan, S.-F. Lo, Z. Zhou, W.-Y. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 13565–13568.
- [13] a) T. K. Hyster, K. E. Ruhl, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 5364–5367; b) for an asymmetric version, see: B. Ye, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 7896–7899; *Angew. Chem.* **2014**, *126*, 8030–8033.
- [14] a) Z. Shi, D. C. Koester, M. Bouladakis-Arapinis, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 12204–12207; b) Y. Liang, K. Yu, B. Li, S. Xu, H. Song, B. Wang, *Chem. Commun.* **2014**, *50*, 6130–6133.
- [15] S. Cui, Y. Zhang, D. Wang, Q. Wu, *Chem. Sci.* **2013**, *4*, 3912–3916.
- [16] a) X. Yu, S. Yu, J. Xiao, B. Wan, X. Li, *J. Org. Chem.* **2013**, *78*, 5444–5452; b) F. Hu, Y. Xia, F. Ye, Z. Liu, C. Ma, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 1364–1367; *Angew. Chem.* **2014**, *126*, 1388–1391.
- [17] T. K. Hyster, T. Rovis, *Chem. Sci.* **2011**, *2*, 1606–1610.
- [18] Alternatively, the process can involve an intramolecular 1,2-aryl shift of an intermediate formed by association of the rhodacycle **C** and **2**. For details, see Ref. [12].
- [19] Taking into account the low nucleophilicity of the sulfoximine nitrogen atom we assume that the dehydrative ring-closing process leading to the final products is also accelerated by either a metal or a protonic catalyst.
- [20] For an analogous reaction sequence, see: Y. H. Kim, H. Lee, Y. J. Kim, B. T. Kim, J.-N. Heo, *J. Org. Chem.* **2008**, *73*, 495–501.

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