Enantioselective Synthesis of 1,2-Benzothiazine 1-Imines via Ru^{II}/Chiral Carboxylic Acid-Catalyzed C–H Alkylation/Cyclization

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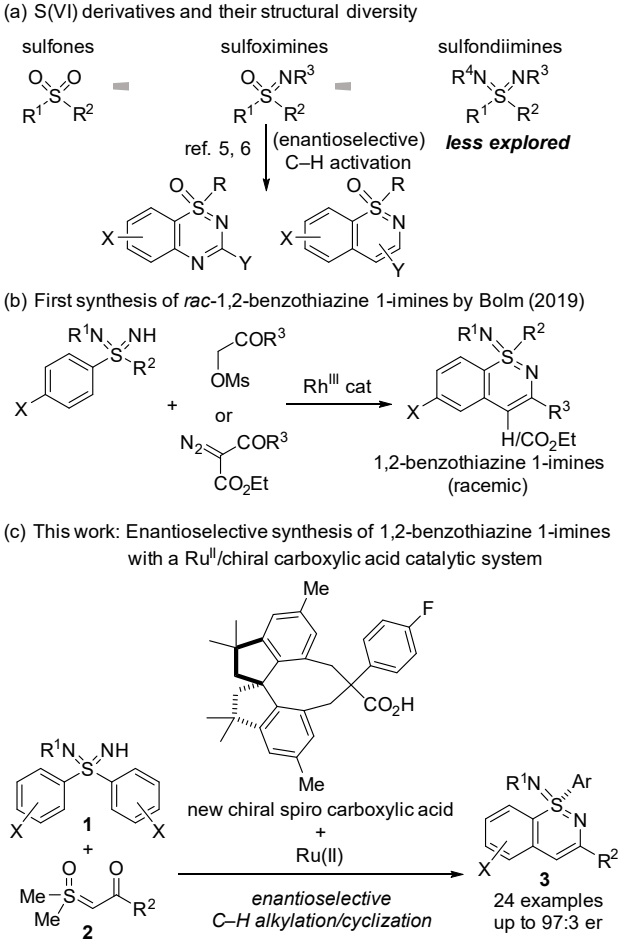
Abstract: Sulfondiimines are diaza-analogues of sulfones with a chiral sulfur center. Compared to sulfones and sulfoximines, their synthesis and transformations have so far been studied to a lesser extent. Here, we report the enantioselective synthesis of 1,2-benzothiazine 1-imines, i.e., cyclic sulfondiimine derivatives from sulfondiimines and sulfoxonium ylides via C–H alkylation/cyclization reactions. The combination of $[Ru(p\text{-cymene})Cl_2]_2$ and a newly developed chiral spiro carboxylic acid is key to achieving high enantioselectivity.

Hexavalent sulfur centers with two S=O bonds, such as sulfones and sulfonamides, are fundamental functional groups in organic chemistry that are widely found in drugs and other biologically active molecules.[1] Replacement of one or two of the oxygen atoms of sulfones with nitrogen substituents results in sulfoximines[2] and sulfondiimines, respectively (Scheme 1a).[3] These aza-analogues of sulfones adopt a tetrahedral chiral sulfur center and provide the opportunity to deploy different substructures in a three-dimensional manner, which significantly increases their structural diversity and complexity. In this context, sulfoximines have attracted great attention, and various synthetic and transformation methods have been developed.[2] Most recently, transition-metal-catalyzed directed C–H functionalizations[4] of sulfoximines have been exploited for the synthesis of cyclic and acyclic derivatives.[5,6] Moreover, enantioselective variants have been developed using chiral metal catalysts or chiral carboxylic acid co-catalysts.[6] Compared to the notable advances in the synthetic chemistry of sulfoximines, the synthesis and transformations of sulfondiimines are much less developed, thus providing an unexplored promising chemical space in which to seek biologically relevant molecules.[3] In 2019, Bolm and co-workers reported Rh^{III}-catalyzed C–H alkylation/cyclization reactions of sulfondiimines for the synthesis of 1,2-benzothiazine 1-imines as unprecedented cyclic organosulfur compounds (Scheme 1b).[7] While 1,2-benzothiazine 1-imines possess *S*-chirality and their stereochemistry can influence their biological properties, enantioselective synthesis of 1,2-benzothiazine 1-imines has not yet been reported.[8]

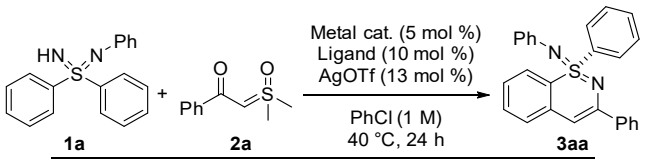


Scheme 1. Various hexavalent organosulfur compounds and synthesis of 1,2-benzothiazine 1-imines.

Here, we report the enantioselective synthesis of 1,2-benzothiazine 1-imines **3** from diaryl sulfondiimines **1** and

sulfoxonium ylides **2** via Ru^{II}-catalyzed C–H functionalization reactions (Scheme 1c).[9,10] Even though the desymmetrization-type enantioselective C–H functionalization of diaryl sulfoximines is well established,[6] the straightforward expansion to diaryl sulfondiimines **1** is not trivial because two sterically different nitrogen atoms of **1** can work competitively as the directing group, which can potentially lead to low enantioselectivity. We found that the combination of [Ru(*p*-cymene)Cl_2]$_2$ and a newly developed chiral spiro carboxylic acid is of crucial importance to achieve reasonable yield and high enantioselectivity.

Table 1. Effects of chiral carboxylic acid ligands and metal catalysts.[a]



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

Entry	Metal cat.	Ligand	% Yield[b]	Er[c]
1	[Ru(*p*-cymene)Cl_2]$_2$	**L1**	<5	–
2	[Ru(*p*-cymene)Cl_2]$_2$	**L2**	63	55:45
3	[Ru(*p*-cymene)Cl_2]$_2$	**L3**	66	60:40
4	[Ru(*p*-cymene)Cl_2]$_2$	**L4**	70	77:23
5	[Ru(*p*-cymene)Cl_2]$_2$	**L5**	64	73:27
6	[Ru(*p*-cymene)Cl_2]$_2$	**L6**	44	80:20
7	[Ru(*p*-cymene)Cl_2]$_2$	**L7**	67	95:5
8	[Ru(*p*-cymene)Cl_2]$_2$	**L8**	84	97:3
9	[Ru(*p*-cymene)Cl_2]$_2$	**L9**	68	96:4
10	Ru(*p*-cymene)Cl_2]$_2$	**L10**	36	94:6
11	Ru(*p*-cymene)Cl_2]$_2$	**L11**	88	91:9
12	[Ru(benzene)Cl_2]$_2$	**L8**	20	92:8
13	[Cp*$RhCl_2$]$_2$	**L8**	<5	–
14	[Cp*$IrCl_2$]$_2$	**L8**	<5	–
15	Cp*Co(CO)I_2[d]	**L8**	<5	–

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.055 mmol), metal catalyst (0.0025 mmol), ligand (0.005 mmol), and AgOTf (0.0065 mmol) in PhCl (0.05 mL) at 40 °C for 24 h unless otherwise noted. [b] Determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrabromoethane as the internal standard. [c] Determined by chiral HPLC analysis. [d] 10 mol %.

With previous reports on enantioselective C–H alkylation/cyclization reactions of sulfoximines with sulfoxonium ylides by Shi[6d] and our group[6f] in mind, we investigated the reaction of sulfondiimine **1a** and sulfoxonium ylide **2a** using the combination of a metal catalyst and chiral carboxylic acid, which enables carboxylate-assisted enantioselective C–H activation (Table 1).[11-13] After intensive screening of the reaction conditions, we found that the desired product (**3aa**) was obtained in the presence of [Ru(*p*-cymene)Cl_2]$_2$, AgOTf, and a chiral carboxylic acid ligand. Among the chiral acids **L1**–**L6** (Figure 1), which have been developed in our group,[6g,14] the pseudo-C_2-symmetric acids (**L4**–**L6**)[6g,14d] exhibited moderate enantioselectivity (entries 4–6). Despite these promising results, further improvement by minor tuning was not feasible, which prompted us to develop new chiral spiro carboxylic acids **L7**–**L10**. These acids were successfully synthesized from known compound **4**[15] via double enolate alkylation and subsequent demethylation (Scheme 2). To our delight, **L7**–**L10** significantly improved the enantioselectivity (Table 1, entries 7–10), and we selected **L8** as the best ligand (entry 8, 84% yield, 97:3 er). Although rationalization of the improvement requires further intensive computational studies, we speculate that the conformational rigidity of **L7**–**L10** might be important for high enantioselectivity as the structure of **L4** and **L8** are very similar.[16] A chiral spiro carboxylic acid derived from a simple commercially available SPINOL (**L11**) exhibited enantioselectivity lower than **L8** but much higher than **L6**, which implies that the methyl substituents of **L7** would have a moderate influence on the selectivity (entry 11). When the metal catalyst was changed to [Ru(benzene)Cl_2]$_2$, both reactivity and enantioselectivity dropped (entry 12), indicating that the arene ligand did not dissociate during the catalytic process. As control experiments, Cp*M^{III} catalysts (M = Rh, Ir, Co) were evaluated, albeit that the desired reaction scarcely proceeded (entries 13–15).

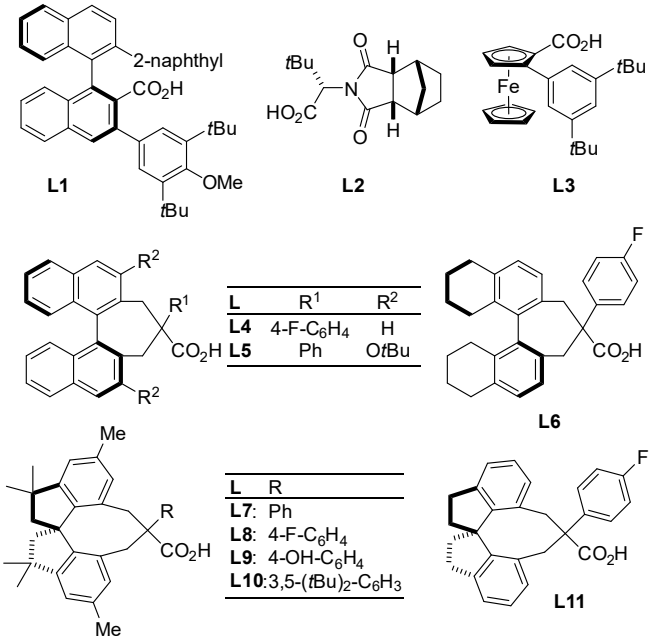
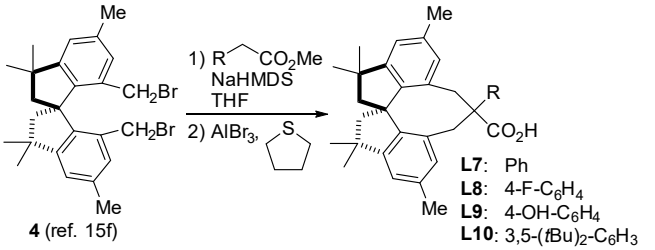


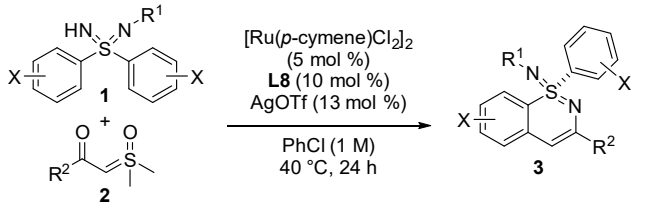
Figure 1. Structures of the chiral carboxylic acids used in this work.

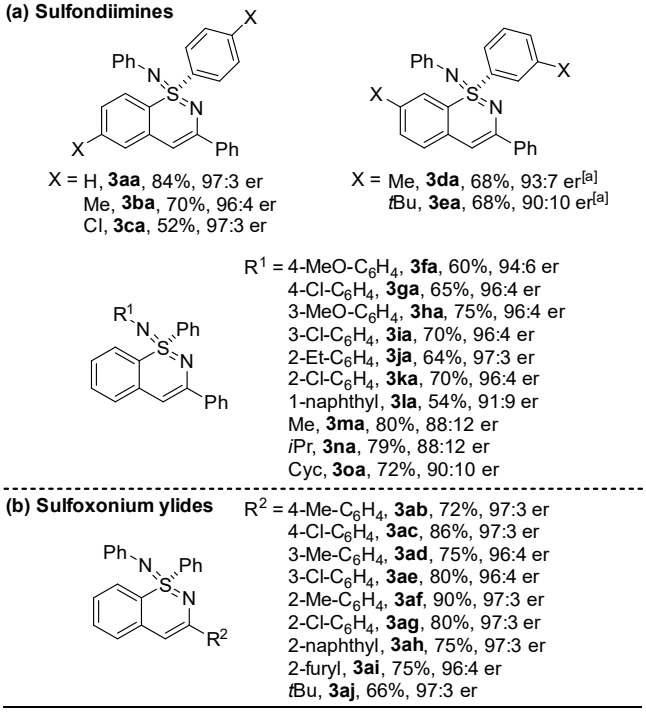


Scheme 2. Synthesis of new chiral spiro carboxylic acids **L7**–**L10**; for details, see the Supporting Information.

We then examined the scope of sulfondiimines (**1**) under the optimized conditions (Table 1, entry 8), and the results are shown in Scheme 3a.[17] In some cases, the use of **L7** afforded slightly improved results. Substituents at the para and meta positions of the S-aryl groups were well tolerated to afford the product in 90:10–97:3 er (**3ba**–**3ea**). In the presence of *meta*-substituents,

the less hindered position was selectively alkylated. As the *N*-substituent, both aryl (**3fa**–**3la**) and alkyl groups (**3ma**–**3oa**) were acceptable, although the enantioselectivity was slightly diminished for the alkyl substituent. The scope of sulfoxonium ylides (**2**) was also investigated (Scheme 3b). Various substituted phenyl groups, as well as 2-naphthyl and 2-furyl groups, were successfully introduced at the 3-position of the product (**3ab**–**3ah**, 96:4–97:3 er) by employing the corresponding sulfoxonium ylide (**2**). Furthermore, *t*Bu-substituted sulfoxonium ylide also provided the product in high enantioselectivity (**3aj**, 97:3 er). We also examined the kinetic resolution of a racemic alkyl-aryl sulfondiimine (Scheme 4; *rac*-**5**), and a reasonably good selectivity factor (*s* = 30) was observed.[18,19]

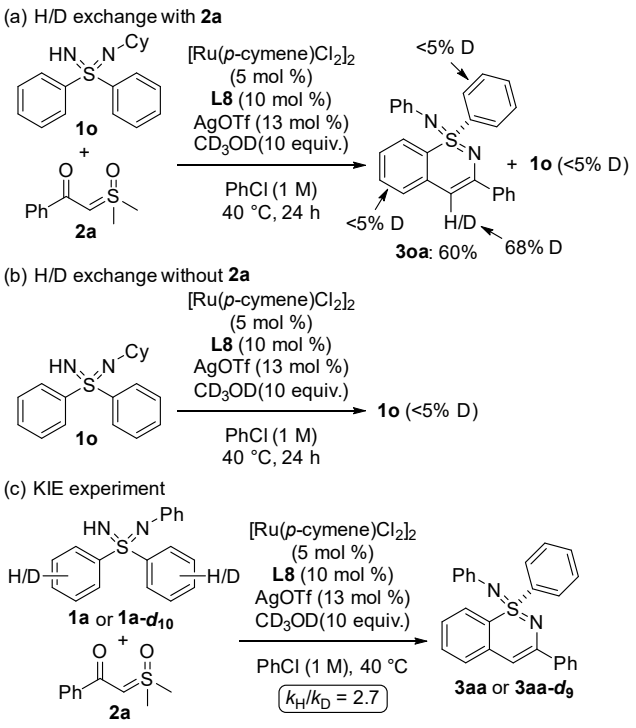




Scheme 3. Substrate scope of the enantioselective C–H alkylation/cyclization of diaryl sulfondiimines. Reaction conditions: **1** (0.05 mmol), **2** (0.055 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.0025 mmol), **L8** (0.005 mmol), and AgOTf (0.0065 mmol) in PhCl (0.05 mL) at 40 °C for 24 h unless otherwise noted. [a] **L7** was used instead of **L8**.

Scheme 4. Kinetic resolution of alkyl-aryl sulfondiimine **5**. The selectivity factor (*s*) was calculated as $s = \ln[(1 - c)(1 - ee_5)] / \ln[(1 - c)(1 + ee_5)]$, where the conversion *c* was calculated as $c = ee_5 / (ee_5 + ee_6)$.[20]

Finally, we performed several experiments to gain insight into the nature of the key enantio-determining C–H activation step. When the reaction using **1o** was performed under the optimized conditions, except for the addition of CD_3OD, deuterium incorporation was observed at the 4-position of product **3oa**, but not at the other positions of **3oa** or recovered **1o** (Scheme 5a). The same experiment without reactant **2a** did not afford deuterium-incorporated **1o** (Scheme 5b). These results indicate that the C–H bond cleavage of **1o** by the Ru^{II}/carboxylic acid catalyst system is irreversible. This irreversibility may explain the independence of the enantioselectivity from the structure of reactant **2** (Scheme 3b)**.** The deuterium incorporation at the 4-position of **3oa** could be feasibly interpreted by the H/D exchange from **2a** or the intermediate of the C–H alkylation before cyclization. We also checked the kinetic isotope effect, and a k_H/k_D value of 2.7 was observed from parallel experiments (Scheme 5c), suggesting that the C–H activation step would be involved in the rate-determining step. This is in line with our experimental observation that the reactivity depends on the structure of the chiral carboxylic acid (Table 1).



Scheme 5. Experimental mechanistic studies.

In summary, we have demonstrated that the combination of [Ru(*p*-cymene)Cl_2]$_2$ and a newly developed chiral spiro carboxylic acid (**L7** or **L8**) enables the enantioselective synthesis of 1,2-benzothiazine 1-imines from sulfondiimines via C–H alkylation/cyclization with a sulfoxonium ylide as the reactant, thus expanding the accessible chemical space with respect to compounds with a chiral S(VI) center. Moreover, the newly developed chiral carboxylic acids will hopefully expand the applicability of the metal/chiral carboxylic acid system for enantioselective C–H functionalization reactions.

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Keywords: asymmetric catalysis • 1,2-benzothiazine 1-imine • C–H activation • ruthenium • sulfondiimine

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J. Yu, S. Zhang, X. Hong, X. Lin, *J. Org. Chem.* **2018**, *83*, 11873; d) W. Sun, H. Gu, X. Lin, *J. Org. Chem.* **2018**, *83*, 4034; e) L. Wang, J. Zhong, X. Lin, *Angew. Chem. Int. Ed.* **2019**, *58*, 15824; *Angew. Chem.* **2019**, *131*, 15971; f) Z. Han, X. Lin, *Synthesis* **2020**, *52*, 1131; g) Z. Han, J. Jin, A. G. Woldegiorgis, X. Lin, *RSC Adv.* **2022**, *12*, 27012; h) L. Yao, A. G. Woldegiorgis, X. Lin, *Tetrahedron Lett.* **2022**, *109*, 154157.

[16] For the calculated structures of **L4** and **L8**, see the Supporting Information.

[17] The absolute configuration of **3ka** was determined via single-crystal X-ray diffraction analysis. Deposition number 2257084 (for **3ka**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[18] The absolute configuration of the major isomer of the recovered sulfondiimine (**5**) was determined by the comparison of its retention time in chiral HPLC analysis and specific rotation with those were previously reported: S. Dong, M. Frings, H. Cheng, J. Wen, D. Zhang, G. Raabe, C. Bolm, *J. Am. Chem. Soc.* **2016**, *138*, 2166 and ref. 3c. See the Supporting Information for details.

[19] For preliminary results of a parallel kinetic resolution of an unsymmetrically substituted diaryl sulfondiimine, see the Supporting Information.

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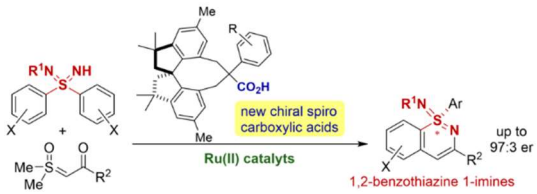

Enantioselective C–H alkylation/cyclization of sulfondiimines with sulfoxonium ylides using a Ru^{II} catalyst and a newly developed chiral spiro carboxylic acid enables the synthesis of 1,2-benzothiazine 1-imines, thus expanding the accessible chemical space of chiral hexavalent organosulfur scaffolds relevant to biologically active compounds.

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