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Enantioselective C–H amidation of sulfondiimines for the synthesis of 1,2,4-benzothiadiazine-1-imines under cobalt catalysis†

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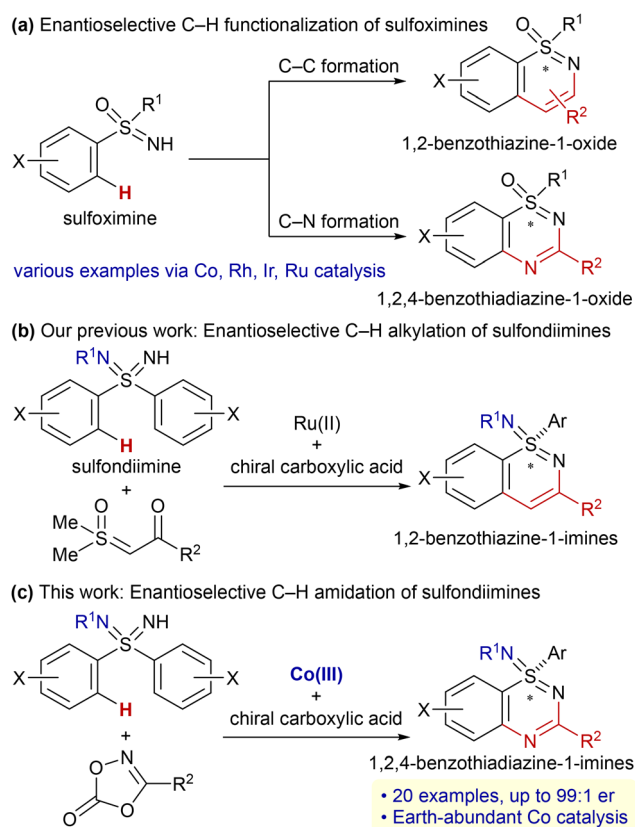
In comparison to the notable recent progress in the derivatization of sulfoximines *via* directed C–H activation, the C–H activation/functionalization of sulfondiimines is underdeveloped. Here, we report C–H amidation/cyclization reactions of sulfondiimines with dioxazolones catalyzed by the combination of a cobalt(III) catalyst and a pseudo C₂-symmetric chiral carboxylic acid, leading to the formation of unprecedented 1,2,4-benzothiadiazine-1-imine structures in high enantioselectivity.

Introduction

Sulfur-containing scaffolds, such as sulfones, sulfoxides, and sulfonamides, are fundamental and important motifs in organic chemistry and related research fields.¹ Sulfoximines, *i.e.*, the mono-aza-analogues of sulfones, are less common than the related hexavalent sulfur compounds, but have recently attracted great attention, particularly in medicinal chemistry.² This surge in interest has led to the development of synthetic and derivatization methods for sulfoximines; in particular, transition-metal-catalyzed directed C–H functionalization reactions have been examined for the derivatization of sulfoximines.^{3–5} Sulfoximines and sulfoximine derivatives that feature different carbon substituents contain a chiral sulfur center, and their stereochemistry can potentially influence their biological properties,⁶ which has motivated the investigation of enantioselective methods for the C–H functionalization of sulfoximines (Scheme 1a). Since the pioneering work by Li^{5a} and Cramer^{5b} using a chiral Cp^{*}Rh(III) catalyst, several catalytic systems have enabled the desymmetrization of diaryl sulfoximines and kinetic resolution to provide chiral 1,2-benzothiazine-1-oxides and 1,2,4-benzothiadiazine-1-oxides in an enantioselective manner.⁵

In contrast to the rapid maturation of the directed C–H functionalization of sulfoximines, sulfondiimines have attracted less attention, despite the fact that they have an

additional substituent that increases the structural diversity and provides new potential sites for interaction with biological target molecules.^{7,8} In 2019, Bolm and co-workers reported



Scheme 1 Enantioselective directed C–H functionalization of sulfoximines and sulfondiimines.

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C–H alkylation/cyclization reactions catalyzed by Rh(III) complexes.⁹ More recently, our group has reported that the combination of a Ru(II) catalyst and a chiral carboxylic acid enables enantioselective C–H alkylation reactions to provide 1,2-benzothiazine-1-imines in high enantioselectivity (Scheme 1b).¹⁰ Nevertheless, no further studies on the directed C–H functionalization of sulfondiimines have been reported. To expand the chemical space of readily available chiral sulfur-containing structures for medicinal chemistry and other biological studies, we envisioned the extension of our chiral carboxylic-acid-assisted enantioselective C–H activation/functionalization strategy^{11,12} to the synthesis of novel chiral scaffolds from sulfondiimines. Here, we report enantioselective C–H amidation and cyclization reactions of sulfondiimines to furnish 1,2,4-benzothiadiazine-1-imines using a Co(III) catalyst¹³ and a chiral carboxylic acid (Scheme 1c). Although the presence of two nitrogen atoms that can potentially act as a directing group in a sulfondiimine makes the stereochemical course of the C–H activation more complicated, the optimal catalytic system achieved high enantioselectivity (up to 99 : 1 er).

Results and discussion

We began our study with an examination of the reaction conditions based on our previous results in the enantioselective C–H amidation of sulfoximines with dioxazolones.^{5g} Gratifyingly, the desired C–H amidation/cyclization reaction proceeded to afford a 1,2,4-benzothiadiazine-1-imine using a catalytic amount of Cp*Co(CO)I₂, AgOTf, and a carboxylic acid in *t*AmOH at 80 °C. No C–H amidation product without cyclization was observed at this reaction temperature. We then evaluated several chiral carboxylic acids (CCAs; **A1**–**A5**) that have previously been investigated in our group^{5g,14} under the optimized reaction conditions with sulfondiimine **1a** and dioxazolone **2a** as model substrates (Table 1, entries 1–5). While amino acid derivative **A1**,^{14b} ferrocene carboxylic acid **A2**,^{14c} and C₁-symmetric binaphthyl carboxylic acid **A3**^{14a} resulted in low enantioselectivity (entries 1–3), pseudo C₂-symmetric binaphthyl carboxylic acid **A4**^{14d} exhibited good reactivity and enantioselectivity (entry 4). Changing the binaphthyl backbone of **A4** to a partially reduced H₈-binaphthyl structure (**A5**)^{5g} further enhanced the reactivity and selectivity, and the desired product was finally obtained in almost quantitative yield and 97 : 3 er (entry 5). The absolute configuration of **3aa** was determined to be *S* by single crystal X-ray diffraction analysis (CCDC 2423806†). With the optimal CCA **A5** in hand, other related piano-stool d⁶ metal catalysts, *i.e.*, [Cp*RhCl₂]₂, [Cp*IrCl₂]₂, and [Ru(*p*-cymene)Cl₂]₂, were also investigated (entries 6–8), but none improved the results relative to Cp*Co(CO)I₂. The combination of a relatively small cobalt catalyst with **A5** was essential for the high enantioselectivity.

We investigated the substrate scope using the combination of Cp*Co(CO)I₂ and **A5** as the catalyst (Scheme 2). To obtain reproducible results for various substrates, including less reac-

Table 1 Effects of chiral carboxylic acids (CCAs) and metal catalysts under the optimized conditions^a

Structures of CCAs

A1

A2

A3

A4

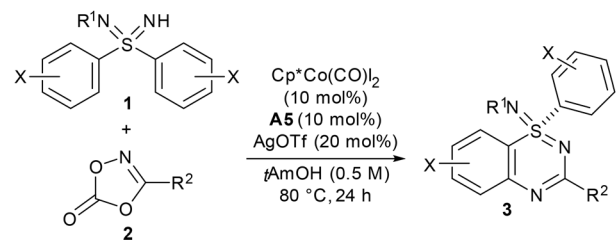
A5

Entry	CCA	Catalyst (mol%)	%yield ^b	er ^c
1	A1	Cp*Co(CO)I ₂ (5)	47	41 : 59
2	A2	Cp*Co(CO)I ₂ (5)	27	69 : 31
3	A3	Cp*Co(CO)I ₂ (5)	24	67 : 33
4	A4	Cp*Co(CO)I ₂ (5)	82	92 : 8
5	A5	Cp*Co(CO)I ₂ (5)	>95	97 : 3
6	A5	[Cp*RhCl ₂] ₂ (2.5)	64	72 : 28
7	A5	[Cp*IrCl ₂] ₂ (2.5)	2	84 : 16
8	A5	[Ru(<i>p</i> -cymene)Cl ₂] ₂ (2.5)	1	80 : 20

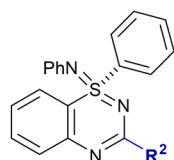
^a Reaction conditions: **1a** (0.060 mmol), **2a** (0.050 mmol), catalyst, CCA (2.5 μmol, 5 mol%), and AgOTf (5.0 μmol, 10 mol%) in *t*AmOH (0.1 mL) at 80 °C for 24 h. ^b Determined by ¹⁹F NMR analysis of the crude reaction mixture using PhCF₃ as the internal standard. ^c Determined by chiral HPLC analysis.

tive ones, we used 10 mol% catalyst under the optimized conditions. We first examined the effects of the structure of dioxazolone **2** (Scheme 2a). A series of *para*-substituted aromatic dioxazolones as well as a *meta*-methyl substituted one resulted in moderate to good product yields with high enantioselectivity (**3aa**–**3aj**; 94 : 6 to 97 : 3 er), except that a *para*-cyano-substituted dioxazolone exhibited very low reactivity (<20%; not shown in Scheme 2) probably due to the competitive coordination of the cyano group. The extended and heteroaryl group substituents (2-naphthyl, 2-furyl, and 2-thienyl) were well tolerated (**3ah**–**3aj**; 97 : 3 er). An alkenyl dioxazolone exhibited slightly lower reactivity but furnished the product in high enantioselectivity (**3ak**; 97 : 3 er). We also examined a methyl-substituted dioxazolone, which gratifyingly provided the corresponding product (**3al**) in good yield and selectivity. Next, we investigated the scope of sulfondiimines (Scheme 2b). The introduction of *para*- and *meta*-substituents at the diaryl



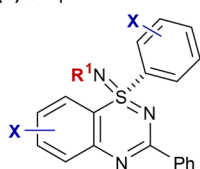


(a) Scope of dioxazolones

 $R^2 =$ 

$pF-C_6H_4$	3aa	76%, 96:4 er
Ph	3ab	71%, 97:3 er
$pMe-C_6H_4$	3ac	67%, 97:3 er
$pOMe-C_6H_4$	3ad	53%, 97:3 er
$pCF_3-C_6H_4$	3ae	98%, 97:3 er
$pMeO_2C-C_6H_4$	3af	61%, 94:6 er
$mMe-C_6H_4$	3ag	65%, 95:5 er
2-naphthyl	3ah	81%, 97:3 er
2-furyl	3ai	51%, 97:3 er
2-thienyl	3aj	60%, 97:3 er
(<i>E</i>)-PhCH=CH	3ak	47%, 97:3 er
Me	3al	68%, 97:3 er

(b) Scope of sulfondiimines

 $R^1 =$ $X =$

Ph	pMe	3bb	74%, 97:3 er
Ph	pCl	3cb	80%, 99:1 er
Ph	pCF_3	3db	89%, 96:4 er
Ph	mMe	3eb	84%, 97:3 er
$pMeO-C_6H_4$	H	3fb	30%, 97:3 er
$pCl-C_6H_4$	H	3gb	35%, 94:6 er
$mCl-C_6H_4$	H	3hb	81%, 97:3 er
$oCl-C_6H_4$	H	3ib	79%, 99:1 er

Scheme 2 Substrate scope. Reaction conditions: **1** (0.24 mmol), **2** (0.20 mmol), $Cp^*Co(CO)I_2$ (0.02 mmol, 10 mol%), **A5** (0.02 mmol, 10 mol%), and AgOTf (0.04 mol, 20 mol%) in tAmOH (0.4 mL) at 80 °C for 24 h.

moieties did not interfere with the desired reactions, leading to products in sufficient yield and high enantioselectivity (**3bb–3eb**; 74–89%, 96:4–99:1 er). Several sulfondiimines with a different aromatic substituent at the nitrogen moiety were also applicable (**3fb–3ib**), although the introduction of a *para*-substituent decreased the reactivity (**3fb** and **3gb**).

To elucidate the origin of the high enantioselectivity achieved using the optimal chiral carboxylic acid (**A5**), we performed DFT calculations on the transition states for the C–H activation step¹⁵ of **1a**, which is generally considered to be the enantio-determining step in chiral-carboxylate-assisted desymmetrization reactions. The sulfondiimine (**1a**) has two coordinating nitrogen atoms, both of which can potentially act as the directing group (DG) for C–H activation. Thus, we carefully performed conformational searches based on several different initial structures to obtain relevant transition states (for details, see the ESI†). We found two transition states for the major (*S*)-product (TS_{major1} and TS_{major2}) and one for the minor (*R*)-product (TS_{minor}) to be energetically feasible (Fig. 1, left). Among these, TS_{major1} was the most stable structure; the energies of TS_{major2} and TS_{minor} are +2.0 kcal mol^{−1} and +2.4 kcal mol^{−1} higher, respectively, which is in reasonably good agreement with the experimental results. The NH moiety acts as the DG in TS_{major1} and TS_{major2}, while the NPh moiety acts as the DG in TS_{minor} (for other energetically higher transition states, see the ESI†), which indicates that both nitrogen

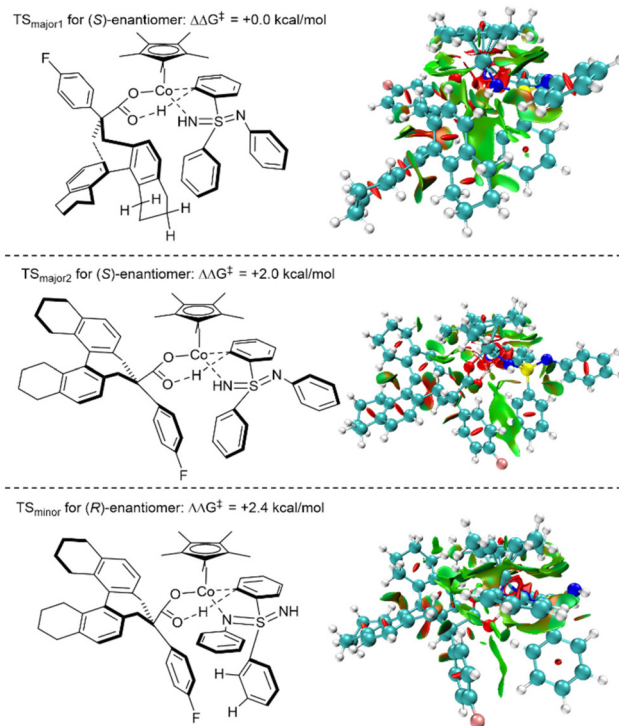


Fig. 1 Transition-state structures and relative Gibbs energies for C–H bond cleavage (left) and non-covalent interaction plots (right) calculated at the M06/def2-TZVPP+SMD(tBuOH)//M06L/def2-SVP level of theory.^{17–20} The NCI plots were generated with Multiwfn 3.7²¹ and visualized by VMD 1.9.4²² (isosurface = 0.5; color scale from −0.04 to 0.02).

atoms function competitively as DGs, and that the pathway is controlled by the carboxylate ligand. Additionally, a non-covalent interaction (NCI) plot¹⁶ was produced to visualize the weak interactions contributing to the high enantioselectivity (Fig. 1, right). TS_{major1} involves π – π and C–H/ π interactions between the H₈-binaphthyl moiety of **A5** and the phenyl group of **1a**, and TS_{major2} involves π – π interactions around the α -aryl group of **A5**. On the other hand, TS_{minor} shows only minor C–H/ π interactions between the α -aryl group of **A5** and the phenyl group of **1a**. These DFT calculations suggest that the high selectivity with **A5** might be enhanced by the weak π – π and C–H/ π interactions in TS_{major1}. The improvement of the selectivity upon changing the binaphthyl to the H₈-binaphthyl backbone (Table 1, **A4** vs. **A5**) might be due to the slight enhancement of such interactions by the increased dihedral angle of the backbone of **A5**.

Conclusions

In summary, we have developed enantioselective C–H amidation/cyclization reactions of sulfondiimines with dioxazolones using an earth-abundant and readily available cobalt catalyst and a chiral carboxylic acid. This catalytic transformation enables convenient and highly enantioselective access to unprecedented chiral 1,2,4-benzothiadiazine-1-imine derivatives,



which would further facilitate biological and medicinal research on chiral-sulfur-containing heterocyclic compounds.

Author contributions

A.M. and T.E. performed the experiments and analyzed the data. A.M. and Y.H. performed the DFT calculations. A.M. and K.H. performed SC-XRD analysis. A.M., T.E., Y.H., and T.Y. prepared, reviewed, and edited the ESI.† T.Y. and S.M. conceptualized and supervised the project. Y.H., K.H., T.Y., and S.M. contributed to the preparation of the manuscript and all authors contributed to reviewing and editing the manuscript.

Data availability

A part of the data supporting this article have been included as part of the ESI.† Crystallographic data for **3aa** has been deposited at the CCDC under deposition number 2423806.†

Conflicts of interest

There are no conflicts to declare.

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