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COMMUNICATION

Organocatalytic asymmetric [4+2] cyclization of 2-benzothiazolimines with azlactones: access to chiral benzothiazolopyrimidine derivatives†

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Qijian Ni,*[a] Xuyang Wang [a] , Fangfang Xu [a], Xiaoyun Chen [b] and Xiaoxiao Song *[a]

An organocatalytic asymmetric domino Mannich/cyclization reaction between 2-benzothiazolimines with azlactones has been successfully developed. With the bifunctional squaramide catalyst, this formal [4+2] cyclization occurs with good to high yields and excellent stereoselectivities (up to 99% ee, >20:1 dr), providing an efficient and mild access to chiral benzothiazolopyrimidines bearing adjacent tertiary and quaternary stereogenic centers.

Benzothiazolopyrimidine derivatives are widely present in many natural products and bioactive compounds.[1] The typical structural core of isothioureas, especially the chiral homobenzotetramisole (HBTM) has drawn tremendous attention from synthetic chemists because of their prevalence in asymmetric organocatalytic transformations as a Lewis base.[2] Therefore, various synthetic approaches to these heterocycles have been developed in recent years.[3] In 2015, the Enders group disclosed an N-heterocyclic carbene-catalyzed Mannich/lactamization domino reaction of 2-benzothiazolimines with α-chloroaldehydes for the asymmetric synthesis of benzothiazolopyrimidinones with excellent stereoselectivities (Scheme 1a).[4] Very recently, Masson *et al.* developed an elegant strategy to build benzothiazolopyrimidine by chiral phosphoric acid-catalyzed [4+2] cyclization of 2-benzothioazolimines with enecarbamates.[5] As one of the most effective strategies, the asymmetric organocatalytic domino reaction based on 2-benzothiazolimine are still extremely limited.

Azlactones have recently emerged as a type of versatile reactants for the synthesis of nitrogen-containing compounds (Scheme 1) because of their multiple reactive sites.[6] This substrate class possess nucleophilic and electrophilic sites at C4 and C5-positions, respectively, allowing for designing a cascade [n+2] cyclization reaction to build up functionalized lactones or lactams with the use of organocatalyst. For instance, excellent progress has been made on asymmetric [3+2] cyclization[7] of azlactones with 1,3-dipole surrogates, such as oxaziridines,[8] azomethine imines[9] or azonaphthalenes.[10] Meanwhile, considerable attention has been devoted to the asymmetric catalytic [4+2] cyclizations of azlactones with electron-deficient alkenes[11] or quinone methides.[12] In the case of electrophilic imines, the Mannich reactions with azlactones for the asymmetric preparation of diverse synthetic amino acids have been well developed.[13] However, methods for organocatalytic asymmetric cyclization of azlactones with imines to construct heterocycles were not disclosed until a domino reaction of o-hydroxy aromatic aldimines and azlactones reported by Feng group in 2011.[14] They realized the asymmetric synthesis of 3, 4-diaminochroman-2-ones catalyzed by guanidine and bisguanidium salt. Recently, Wang and co-workers disclosed an asymmetric [2+2] cyclization/penicillin-penillonic acid rearrangement by phosphoric acid catalysis affording imidazoline adducts with high diastereo- and enantioselectivity (Scheme 1b).[15] Motivated by the previous work on [n+2] cyclization with azlactones, we envisaged that 2-benzothiazolimines might be suitable substrates for an asymmetric organocatalytic [4+2] cyclization with azlactones by a domino Mannich/cyclization reaction, thus providing highly enantioenriched benzothiazolopyrimidines bearing adjacent tertiary and quaternary stereogenic centers (Scheme 1c). The challenges in this task should

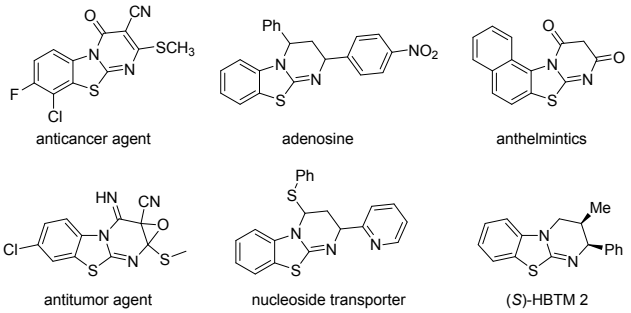

Figure 1 Representative examples of benzothiazolopyrimidine derivatives.

[a] College of Chemistry and Materials Science, Key Laboratory of Functionalized Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials, Anhui Normal University, Wuhu, Anhui 241002, P. R. China. E-mail: qijianni@ahnu.edu.cn, xsong@ahnu.edu.cn.
[b] School of Environmental and Chemical Engineering, Jiangsu University of Science and Technology, Zhenjiang, 212003, P. R. China.

† In memory of Prof. Dieter Enders (1946-2019).

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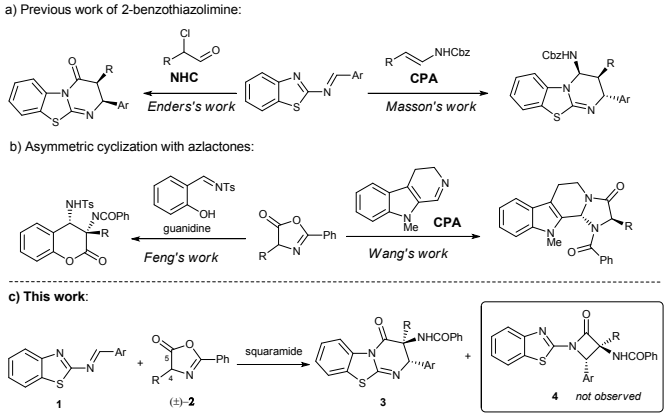
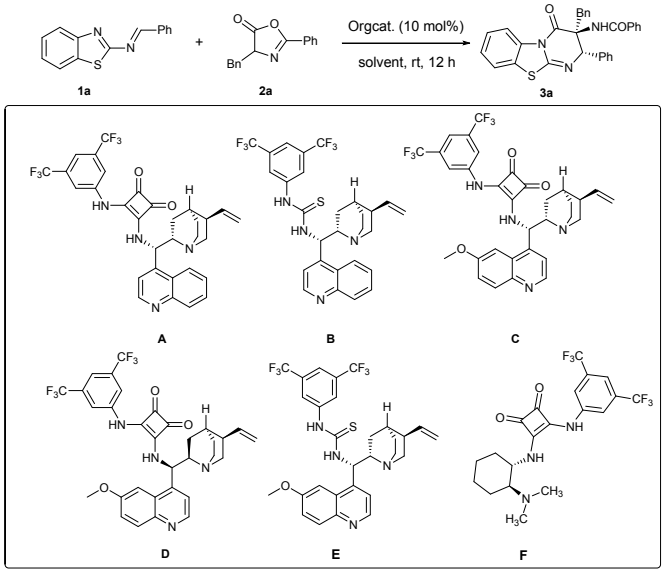
include the dearomatization of the benzothiazole ring[16] and the elusive regioselective control on the ambident N-nucleophiles.



Scheme 1 Research background.

To implement this hypothesis, we commenced our studies by examining the model reaction of 2-benzothiazolimine (**1a**) with racemic phenylalanine-derived azlactones (**2a**). Initially, chiral thioureas or squaramides were chosen as the bifunctional organocatalysts in view of their good performance in stereocontrol. To our delight, this regiospecific reaction delivered the desired product **3a** in 47% yield with excellent diastereoselectivity and enantioselectivity in the presence of 10 mol% of squaramide **A** at room temperature (table 1, entry 1). The [2+2] adduct **4** was not observed. Then a quick screening of catalysts was conducted and the quinidine-derived squaramide catalyst **D** proved to be the best choice for this domino process, with which an excellent efficiency and stereoselectivity were realized (entries 2-6). No further improvements were observed when other solvents, such as dioxane, EtOAc, DCM, PhCl, or toluene were used (entries 7–11). The best reaction conditions are shown in entry 4, and gave **3a** in 70% yield, >20:1 dr and 99% ee.

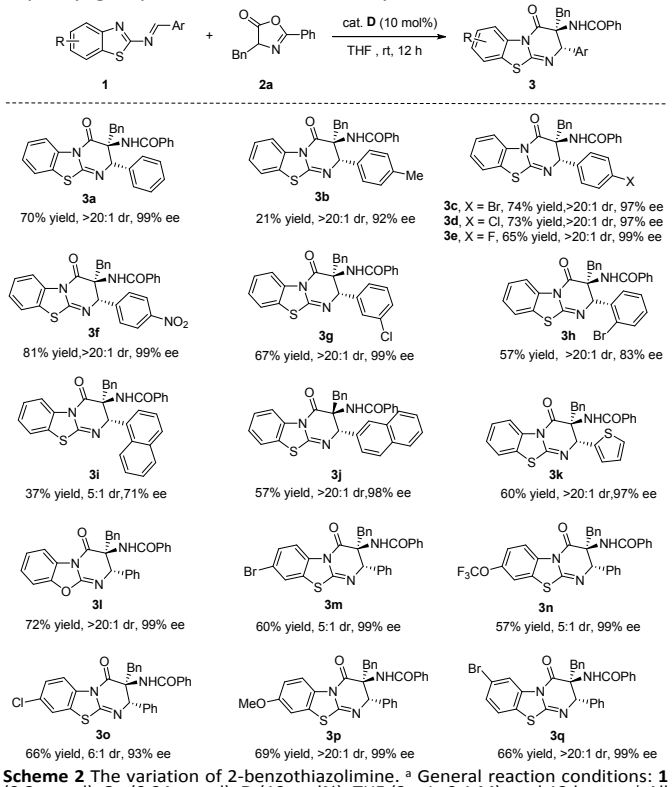
Table 1 Optimization on reaction conditions[a]



Entry	Cat.	Solvent	Yield of **3a** (%)[b]	dr (**3a**)[c]	ee of **3a** (%)[d]
1	**A**	THF	47	>20:1	99
2	**B**	THF	48	>20:1	99
3	**C**	THF	26	>20:1	99
4	**D**	**THF**	**70**	**>20:1**	**99**
5	**E**	THF	40	>20:1	99
6	**F**	THF	62	>20:1	99
7	**D**	dioxane	51	>20:1	99
8	**D**	ethyl acetate	62	>20:1	99
9	**D**	DCM	39	>20:1	76
10	**D**	PhCl	70	>20:1	97
11	**D**	toluene	38	>20:1	99

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), **D** (0.02 mmol), solvent (2 mL), rt, 12 h. [b] Yield of isolated **3** after flash column chromatography. [c] Determined by ^{1}H NMR. [d] The ee value was determined by HPLC on a chiral stationary phase.

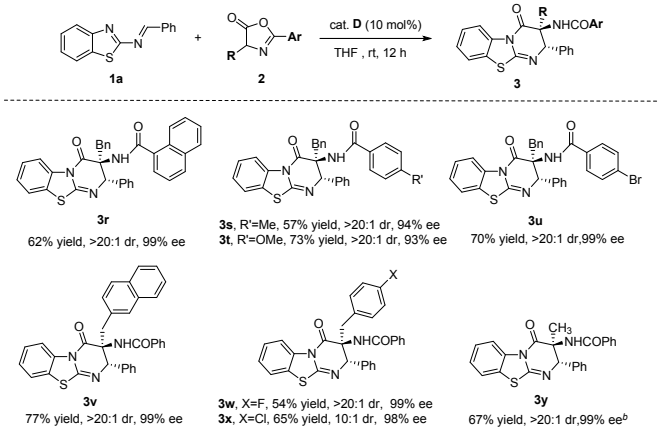
With optimized reaction conditions in hand, the substrate scope of this asymmetric [4+2] cyclization was examined. The reactions of 2-benzothiazolimines **1** with **2a** were first conducted (Scheme 2). In general, the desired benzothiazolopyrimidines were obtained with moderate to excellent yields, excellent diastereo- and enantioselectivities. In contrast to the model substrate (**1a**), the presence of an electron-donating substituent on the aryl ring led to dramatic decreases in the yields of the product **3b**. Substrates bearing electron-withdrawing groups, such as -Br, -Cl, -F and -NO_2 at the *para*-position as well as *meta*-Cl were compatible with the reaction, affording to the corresponding cycloadducts **3c-3g** in 65-81% yield and 97-99% ee. Bromo substituent at the *ortho* position of phenyl ring hindered the Mannich step and resulted in **3h** with a lower yield and stereoselectivity. The 2-benzothiazolimine with α-naphthyl group showed lower reactivity and resulted in the desired



Scheme 2 The variation of 2-benzothiazolimine. [a] General reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), **D** (10 mol%), THF (2 mL, 0.1 M), and 12 h at rt. [b] All yields refer to the isolated yields. [c] The dr values were determined by ^{1}H NMR spectroscopy to be higher than 20:1 in all cases. [d] The ee values were determined by HPLC on a chiral stationary phase.

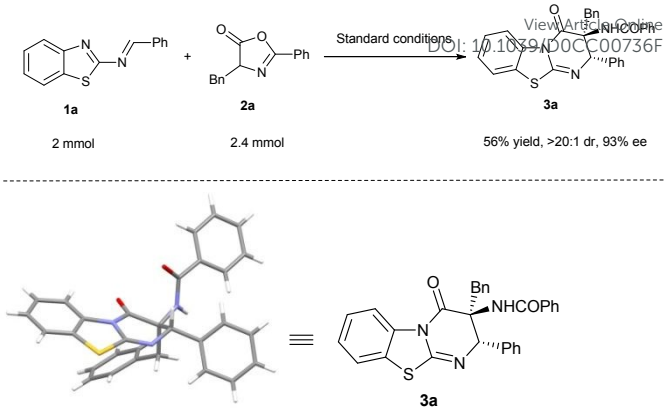
product **3i** in 37% yield with 71% ee. However, the naphthyl group in *beta* position was well tolerated by this reaction, affording the corresponding **3j** in 57% yield and 98% ee under the standard reaction conditions. It was noteworthy that the introduction of a heterocyclic thienyl group on benzothiazolimine gave the desired product **3k** in good yield with excellent asymmetric induction. Additionally, the [4+2] adduct **3l** was also obtained in 99% ee with 72% yield when benzoxazolimine was used as a substrate. Meanwhile, substrates **1** bearing substituents on C5 or C6 positions of benzothiazole rings were successfully applied in the reaction, and the cycloadducts **3m-3q** were obtained in good yields (57-69%) with excellent enantioselectivities (93-99% ee).

Subsequently, the transformations of 2-benzothiazolimines **1a** with azlactones **2** were carried out under the established reaction conditions. As shown in Scheme 3, the reaction tolerated a wide range of azlactones with diverse substituents on the aromatic rings regardless of their electronic properties and substitution patterns, and the corresponding products **3r-u** were generated in good yields with excellent diastereo- and enantioselectivities.. Furthermore, we found that the benzyl group with various substituents had almost no effect on the stereoselectivity, and the products **3v-x** were isolated in 54-77% yields, ≥10:1 dr and 98-99% ee. In addition, we also tested azlactones linked methyl group instead of the benzyl group, which delivered the desired **3y** in 67% yield, >20:1 dr and 99% ee at 0 °C for 20 h.



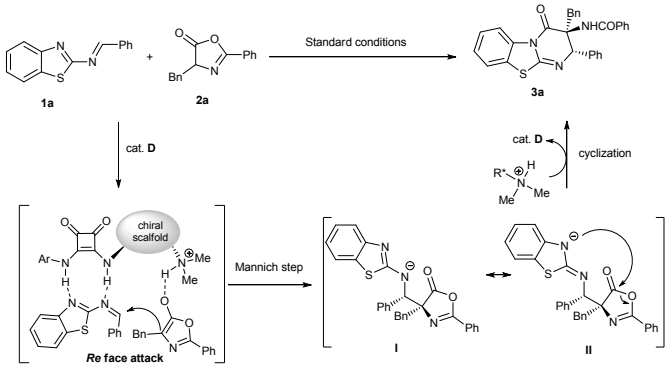
Scheme 3 The variation of azlactones. [a] General reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), **D** (10 mol%), THF (2 mL, 0.1 M), and 12 h at rt. All yields refer to the isolated yields. The dr values were determined by ^{1}H NMR spectroscopy. The ee values were determined by HPLC on a chiral stationary phase. [b] Performed at 0 °C for 20 h.

To demonstrate the practicality of this catalytic system, a large-scale synthesis of product **3a** (2 mmol) was conducted. Under the optimized condition, the reaction of **1a** (2 mmol) with azlactone **2a** (2.4 mmol) worked smoothly and the desired adduct **3a** was isolated in 56% yield, >20:1 dr and 93% ee. Moreover, the absolute configuration of the product **3a** was unambiguously determined by X-ray crystallographic analysis (CCDC 1934497), which revealed a sterically unfavourable *cis*-configuration between benzyl and phenyl groups. The configurations of the other adducts **3b-3t** were assigned by analogy.



Scheme 4 The large-scale reaction and X-ray structure[χ_{abs} = 0.009(14)] of **3a**.

On the basis of previous reports and stereochemical outcome, a possible reaction mechanism was proposed. As shown in Scheme 5, the bifunctional squaramide catalyst **D** that serves as dual-role. The azlactone **2a** was deprotonated by the tertiary amine moiety of catalyst **D** to provide enolate species. Meanwhile, 2-benzothiazolimine **1a** was activated by the H-bonding interactions between the nitrogen atoms and the squaramide. Subsequently, nucleophilic attack of the azlactone enolate on its *Si*-face *via* Mannich reaction leads to two possible intermediates **I** and **II**. Finally, the intramolecular lactamization of the intermediate **II** produces the desired product **3a** and regenerates the catalyst **D**.



Scheme 5 Proposed reaction mechanism.

In summary, we have developed an asymmetric domino Mannich/cyclization reaction between 2-benzothiazolimines with azlactones derivatives using a quinidine-derived squaramide organocatalyst. A series of optically active benzothiazolopyrimidines with contiguous quaternary and tertiary stereogenic centers were constructed in moderate to good yields with excellent diastereo and enantioselectivities. Further studies on the extension of this protocol to the synthetic application and new cyclizations are currently ongoing in our laboratory and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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