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Organocatalysis

Catalytic Asymmetric Conjugate Addition of Tritylthiol to Azadienes with a Bifunctional Organocatalyst

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Abstract: A highly enantioselective sulfa-Michael addition of tritylthiol to azadienes catalyzed by a bifunctional squaramide organocatalyst is described, giving the chiral aminothioethers bearing benzofuran motif with high yields and up to 94% of enantioselectivity. Notably, the aromatization to form the benzofuran is the driving force.

Sulfur is an ubiquitously distributed element that can be found in numerous natural products, pharmaceuticals, and various biological systems (Figure 1), the famous antibiotic penicillin contains the sulfur atom.[1] And further more, owing to importance of the functionalized chiral organic sulfur compounds, the development of efficient methods for their synthesis is still highly desirable starting from the simple materials. To date, some synthetic methods of the optically active organic sulfur compounds have been developed.[1,2]

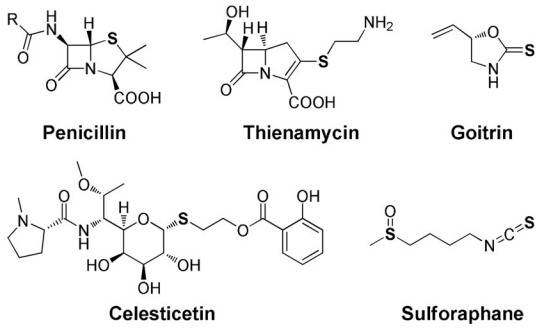

Figure 1. Representative sulfur containing compounds in natural products and pharmaceuticals.

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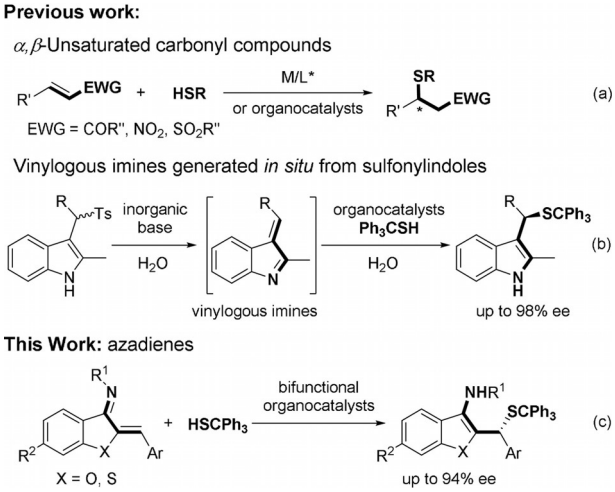
Asymmetric Michael addition is an indispensable and efficient strategy for the construction of C–C or C–X bonds with perfect atom economy.[3] Among them, many effective chiral metal complexes[4] and organocatalysts[4a–b,5–7] have been developed for conjugate addition of sulfur donors to various Michael acceptors. However, C-S bond formation via asymmetric sulfa-Michael addition has been limited to the use of α,β-unsaturated carbonyl compounds,[4,5] nitroolefins[5m,6] and vinyl sulfones[7] (Scheme 1a). To the best of our knowledge, the Michael addition of sulfur donors to α,β-unsaturated imines has only received the limited attention to date. The major problems include the unstability (easy hydrolysis to give α,β-unsaturated ketone) of α,β-unsaturated imines, the relatively low reactivity and the difficult control of enantioselectivity and regioselectivity (1,2 versus 1,4-addition). Not surprisingly, only few examples on Michael addition of sulfur donors to α,β-unsaturated imines was reported. In 2016, Liu and co-workers reported an elegant organocatalytic sulfa-Michael addition to vinylogous imines in situ generated from the sulfonylindoles in a water-compatible system with up to 98% *ee* (Scheme 1b).[8]



Scheme 1. Asymmetric sulfa-Michael addition.

In the last few years, azadienes have been identified as an effective reactants for addition reactions owing to the driving force of aromatization.[9] Recently, our laboratory has developed an effective catalytic asymmetric 1,4-addition of phosphites to azadienes with a bifunctional organocatalyst, giving the chiral products with high enantioselectivity.[9f] We envision

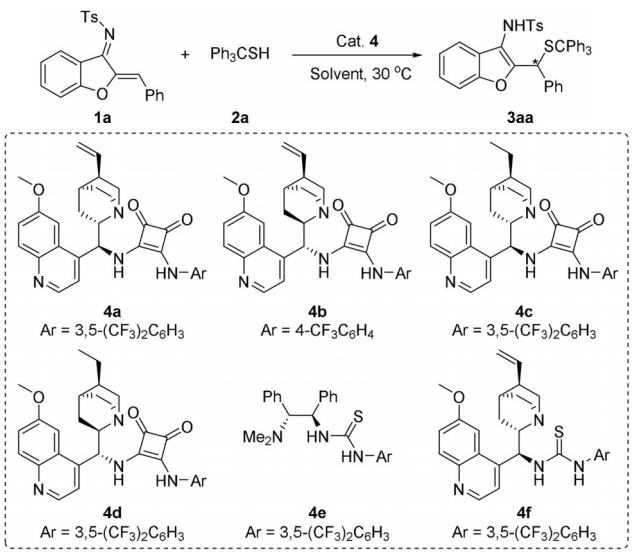
that this bifunctional orgnocatalyst might be applied to a sulfa-Michael addition of sulfur donors to the azadienes. This strategy, if successfully realized, would provide a facile access to the chiral aminothioethers containing the benzofuran motif. Herein, we report an organocatalytic asymmetric conjugate addition of tritylthiol to azadienes with up to 94% of enantioselectivity (Scheme 1c). Notably, the aromatization to form the benzofuran is the driving force.

To validate the feasibility of our proposed transformation, the initial reaction development was conducted with azadiene (**1a**) and tritylthiol (**2a**) in the presence of cinchona alkaloid based bifunctional squaramide catalyst (**4a**) in DCM at 30 °C. Fortunately, the reaction proceeded smoothly, affording the anticipated product **3a** in 96% yield with moderate 72% *ee* after being stirred for 3 hours (Table 1, entry 1). This promising result confirmed our hypothesis and encouraged us to further investigate the effect of different bifunctional organocatalysts on the reactivity and enantioselelctivity (Table 1, entries 2–6). Organocatalyst (**4c**) displayed the best result in terms of the yield (98%) and enantioselectivity (84% *ee*) (Table 1, entry 3). Then, we examined the effect of solvents such as DCE, toluene, THF, and 1,4-dioxane (Table 1, entries 7–10). Among the different kinds of solvents, DCM was proved to be more suitable in terms of enantioselectivity. Slight decrease in enantioselectivity was observed when the catalyst loading was reduced to 5 mol% (Table 1, entry 11 vs. entry 3). Conducting the reaction at different temperatures provided the desired improvement in enantioselectivity (Table 1, entries 12–13), the best enantioselectivity was obtained at −20 °C (Table 1, entry 13). Thus, the optimized conditions were established as: organocatalyst (**4c**) (10 mol%), DCM, −20 °C.

Having optimized the reaction conditions, the substrate scope of the organocatalytic asymmetric sulfa-Michael addition reaction was investigated; the results were shown in Table 2. Firstly, aryl substituents of the azadienes were examined; the reaction could proceed smoothly, providing the corresponding products in excellent yields with 89–94% of enantioselectivities (Table 2, entries 1–12). It's obvious that the electronic and steric properties of the substituents on the aromatic ring Ar had marginal effect on the reactivity and enantioselectivity. Gratifyingly, the methyl substituted substrate (**1m**) was also a suitable reaction partner and the reaction performed well with 92% yield and 88% *ee* (Table 2, entry 13). Next, the effect of substituents on the nitrogen atom was investigated. Various azadienes with different substituents on the nitrogen performed smoothly with good enantioselectivities and high yields (84–89% *ee*, 94–99% yield) (Table 2, entries 14–16).

Unfortunately, if thiophenol (**2b**) was used as nucleophile instead of tritylthiol (**2a**), the reaction proceeded smoothly and afforded the desired product (**3ab**) in excellent yield, albeit

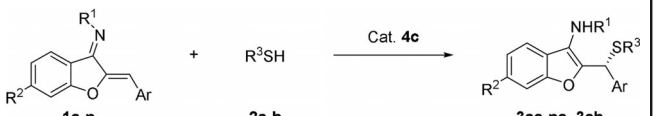
Table 1. The evaluation of reaction parameters.[a]



Entry	Cat. 4	Solvent	Yield [%][b]	*ee* [%][c]
1	**4a**	DCM	96	72 (*R*)
2	**4b**	DCM	97	83 (*R*)
3	**4c**	DCM	98	84 (*R*)
4	**4d**	DCM	96	58 (*S*)
5	**4e**	DCM	95	8 (*S*)
6	**4f**	DCM	94	47 (*R*)
7	**4c**	DCE	97	82 (*R*)
8	**4c**	toluene	96	69 (*R*)
9	**4c**	THF	97	76 (*R*)
10	**4c**	1,4-dioxane	98	72 (*R*)
11[d]	**4c**	DCM	97	83 (*R*)
12[e]	**4c**	DCM	98	90 (*R*)
13[f]	**4c**	DCM	98	93 (*R*)

[a] Reaction condition: azadiene **1a** (0.15 mmol), **2a** (0.18 mmol), cat. **4** (0.015 mmol), solvent (2.0 mL), 30 °C, 3–48 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Catalyst loading was reduced to 5 mol%. [e] The reaction was carried out at 0 °C. [f] The reaction was carried out at −20 °C.

Table 2. The Evaluation of Reaction Parameters.[a]

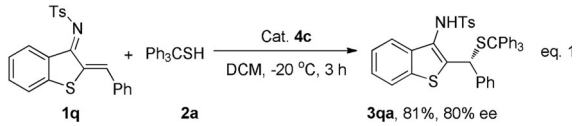


Entry	R^1	R^2	R^3	Ar	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ts	H	Ph_3C	Ph	3	98 (**3aa**)	93 (*R*)
2	Ts	H	Ph_3C	2-MeC_6H_4	3	99 (**3ba**)	92 (*R*)
3	Ts	H	Ph_3C	3-MeC_6H_4	3	98 (**3ca**)	92 (*R*)
4	Ts	H	Ph_3C	4-MeC_6H_4	5	96 (**3da**)	93 (*R*)
5	Ts	H	Ph_3C	4-*i*PrC_6H_4	5	83 (**3ea**)	90 (*R*)
6	Ts	H	Ph_3C	4-*t*BuC_6H_4	5	97 (**3fa**)	91 (*R*)
7	Ts	H	Ph_3C	4-$MeOC_6H_4$	3	98 (**3ga**)	89 (*R*)
8	Ts	H	Ph_3C	4-PhC_6H_4	4	96 (**3ha**)	90 (*R*)
9	Ts	H	Ph_3C	2-naphthyl	3	99 (**3ia**)	93 (*R*)
10	Ts	H	Ph_3C	3-ClC_6H_4	3	98 (**3ja**)	93 (*R*)
11	Ts	H	Ph_3C	4-ClC_6H_4	5	98 (**3ka**)	92 (*R*)
12	Ts	H	Ph_3C	3-BrC_6H_4	3	89 (**3la**)	94 (*R*)
13	Ts	Me	Ph_3C	Ph	5	92 (**3ma**)	88 (*R*)
14	$MesSO_2$	H	Ph_3C	Ph	48	94 (**3na**)	84 (*R*)
15	Ns	H	Ph_3C	Ph	3	99 (**3oa**)	89 (*R*)
16	Ms	H	Ph_3C	Ph	24	98 (**3pa**)	86 (*R*)
17	Ts	H	Ph	Ph	3	98 (**3ab**)	1

[a] Reaction condition: azadiene **1** (0.15 mmol), **2** (0.18 mmol), cat. **4c** (0.015 mmol), DCM (2.0 mL), −20 °C. [b] Isolated yields. [c] Determined by chiral HPLC.

with very low enantioselectivity (1% *ee*) (Table 2, entry 17). For simple benzyl mercaptan, 96% yield and 41% *ee* were obtained under the above standard conditions and the corresponding product had poor stability. The results demonstrated that a bulky moiety on the thiol plays an important role on enantioselectivity.

Furthermore, to demonstrate the versatility of our method, the benzothiophene-derived substrate **1p** was also investigated, and moderate 80% of enantioselectivity was obtained under the above standard conditions [Eq. (1)].



The absolute configuration of the addition product (−)-**3aa** was unambiguously assigned to be *R* by X-ray single crystallographic analysis after a simple recrystallization with ethyl acetate and *n*-hexane (See the Supporting Information for detailed operation) (Figure 2).

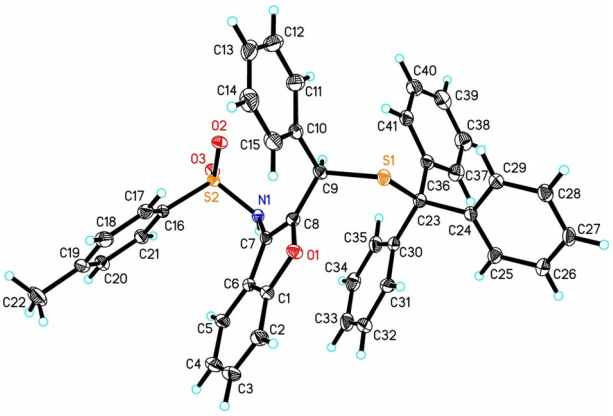


Figure 2. X-ray crystal structure of compound (−)-**3aa**. the solvent (ethyl acetate) has been omitted for clarity.

Based on the literature reports[10] and the above results, we proposed a plausible transition state for the organocatalytic asymmetric conjugate addition of tritylthiol (**2a**) to azadiene (**1a**), as shown in Figure 3. Deprotonation of the tritylthiol (**2a**) gives a protonated amine that activates the electrophile azadiene (**1a**) by Brønsted acid catalysis, while the squaramide moiety binds the nucleophilic thiolate by hydrogen bonding. Subsequent delivery of the proton from the quinuclidine nitrogen to the nitrogen of azadiene (**1a**) gives the product, and complete the catalytic cycle. Notably, the aromatization to form the benzofuran is the driving force.

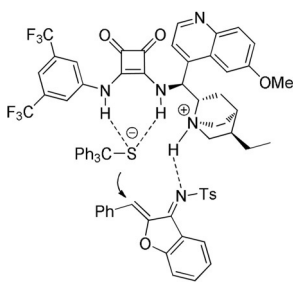


Figure 3. Proposed transition state.

In conclusion, we have successfully developed an effective catalytic asymmetric sulfa-Michael addition of azadienes using the bifunctional cinchona alkaloid derived squaramide catalysts. Excellent yields and up to 94% of enantioselectivity were achieved. Highlights of this method involve the mild conditions, short operation and wide substrate scope. Further investigations on application of this methodology in organic synthesis are ongoing in our laboratory.

Experimental Section

Preparation of 3: A reaction mixture of azadiens **1** (0.15 mmol), thiols **2** (0.18 mmol) and bifunctional squaramide organocatalyst **4c** (0.015 mmol, 9.5 mg) in dichloromethane (2.0 mL) was stirred at −20 °C for 3–48 hours. Then the crude product was directly purified by flash chromatography on silica gel using hexanes and ethyl acetate as eluent to give the corresponding addition products **3**.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: azadienes · organocatalysis · enantioselectivity · sulfa-Michael addition · thiols

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