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Catalytic Asymmetric Synthesis of Chiral Dihydrobenzofurans via A Formal [4+1] Annulation Reaction of Sulfur Ylides and *In Situ*-Generated *ortho*-Quinone Methides

Qing-Qing Yang*[a,b] and Wen-Jing Xiao[b]

Abstract: The first example of catalytic asymmetric formal [4+1] annulation reaction between sulfur ylides and *in situ*-generated *ortho*-quinone methides was reported in this work. A *C*2-symmetric chiral urea was identified to be the best H-bonding catalyst, affording a wide range of chiral dihydrobenzofurans in high yields and moderate enantioselectivities (70-98% yields, up to 89:11 e.r.).

Introduction

Chiral dihydrobenzofurans occupy a very important position in heterocycles due to their prevalence in natural products and synthetic drugs with diverse bioactivities.[1-5] For example, natural product megapodiol can be used as a potential antileukemic agent;[2] (-)-tremetone and (-)-hydroxytremetone, isolated from Eupatorium urticaefolium (Compositae), show insecticidal properties.[3] Moreover, annullatin A exhibits potent agonistic activity toward the cannabinoid receptors CB1 and CB2,[5] and annullatin B displays CB1-agonistic activity and inverse agonistic activity toward CB2 (Figure 1).[5] Given their diverse bioactivities, chiral 2,3-dihydrobenzofurans have drawn increasing research interests from synthetic chemists.[6] Many efficient methods have been developed for the synthesis of chiral dihydrobenzofurans, including the kinetic resolution,[4,7a] asymmetric synthesis from chiral reagents,[7b] or asymmetric catalysis.[7c-l] Despite these advances, the further development of alternative methods to rapidly synthesize chiral 2,3-dihydrobenzofurans is still in demand.

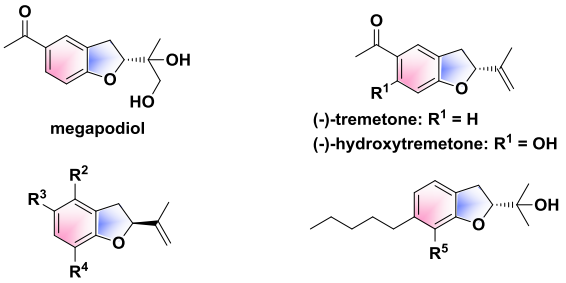
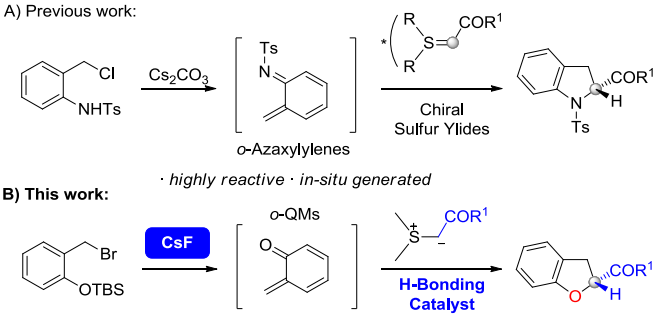


Figure 1. Naturally occurring chiral 2,3-dihydrobenzofurans.

Recently, we disclosed an asymmetric [4+1] annulation of chiral sulfur ylides[8,9] and *in-situ* generated *o*-azaxylylenes, affording chiral indolines in good yields and good enantioselectivities[10d] (Scheme 1A, up to 93% yield, 95.5:4.5 e.r.). Thereafter, we turned our attention to the synthesis of chiral



Scheme 1. Strategies for the enantioselective [4+1] annulations of sulfur ylides and *in situ*-generated highly reactive intermediates.

dihydrobenzofurans from sulfur ylides and *ortho*-quinone methides (*o*-QMs), which can be *in-situ* generated from phenol derivatives.[11] Notably, *o*-QMs are recognized as highly useful intermediates which were widely used in the synthesis of 5-, 6- or 7-membered oxa-heterocyles.[12] During our research, the group of Zhou, Osyanin and Sun reported a formal [4+1] annulation reaction of *o*-QMs intermediates and sulfur ylides, affording the 2,3-dihydrobenzofuran products.[13,14] However, the known camphor derived chiral sulfonium salts were used to realize the enantioselective synthesis of the corresponding products.[13b,d] And three results were obtained, in which 63% ee was the best but only in 25% yield.[13d] Herein, for the first time, we developed the enantioselective synthesis of 2,3-dihydrobenzofuran via an asymmetric [4+1] annulation reaction of acyl-substituted sulfur ylides and *o*-QMs intermediates (Scheme 1B). This success lied on the cooperative catalysis strategy of multiple H-bonding catalysts,[15] which has been well developed in our previous work on the annulation reactions of sulfur ylides with unsaturated keto-esters[10a] and nitroolefins.[10c]

Results and Discussion

The feasibility of this planned [4+1] annulation reaction was examined using TBS-protected phenol substrates **1a** (1.0 equiv.) and sulfur ylide **2a** (1.2 equiv.) in toluene at room temperature, providing the desired product in 90% yield (Table 1, Entry 1).[16]

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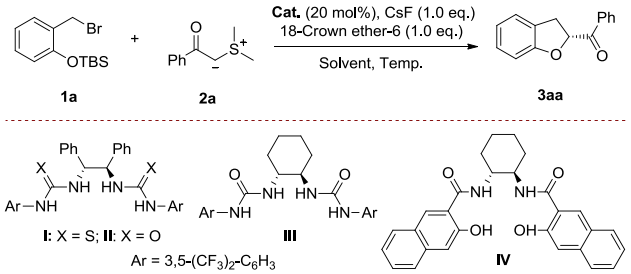
Then we turned our attention to the asymmetric catalysis. As shown in Table 1, our investigation started with the screening of chiral multiple H-bonding catalysts (entries 2-5) at 20 mol% catalyst loading in toluene for the reaction of *tert*-butyldimethylsilyl (TBS)-protected phenol substrate **1a** and sulfur ylide **2a** in the presence of CsF (1.0 equiv.) and 18-Crown ether-6 (1.0 equiv.). As highlighted in Table 1, the urea catalyst **III** induced the chiral cycloadduct **3aa** in excellent yield with promising enantiomeric ratio (93% yield, 60:20 e.r., Table 1, entry 4). Further optimization of the reaction media revealed that toluene was still the best solvent (Table 1, entries 6-7 vs entry 4). Additional efforts to improve the enantioselectivity were made by lowering the reaction temperature (Table 1, entries 8-9 vs entry 4). When the reaction was implemented at -20 ^{o}C, the enatiomeric ratio of **3aa** was significantly increased to 85:15 (Table 1, entry 9). Finally, carrying out the reaction under higher dilution[16] can further increase the enantiomeric ratio to 89:11 (Table 1, entry 10).

Table 1. Optimisation of reaction conditions.[a]



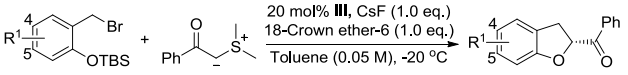
Entry	**Cat.**	Solvent	Temp.	*t*	Yield[b]	e.r.[c]
1	-	Toluene	25 ^{o}C	2 h	90%	-
2	**I**	Toluene	25 ^{o}C	1.5 h	60%	51:49
3	**II**	Toluene	25 ^{o}C	1.5 h	95%	50:50
4	**III**	Toluene	25 ^{o}C	1.5 h	93%	60:40
5	**IV**	Toluene	25 ^{o}C	2.5 h	94%	54:46
6	**III**	CH_2Cl_2	25 ^{o}C	1.5 h	96%	59:41
7	**III**	THF	25 ^{o}C	1.5 h	95%	54:46
8	**III**	Toluene	0 ^{o}C	2 h	95%	78:22
9	**III**	Toluene	-20 ^{o}C	36 h	93%	85:15
10[d]	**III**	**Toluene**	-20 ^{o}C	**36 h**	**96%**	**89:11**

[a] Unless noted, reactions were performed with **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (20 mol%), CsF (0.1 mmol), 18-Crown ether-6 (0.1 mmol) in the indicated solvent (1.0 mL, 0.1 M). [b] Isolated yield. [c] Determined by chiral HPLC. [d] 2 mL of toluene (0.05 M).

After establishing satisfactory reaction conditions,[16] we started to probe the scope of TBS-protected phenol components firstly. As shown in Table 2, various phenol substrates proceeded smoothly in this asymmetric formal [4+1] annulation reaction, affording the corresponding 2-benzoyl-2,3-dihydrobenzofurans in excellent yields and moderate enantiomeric ratio (80-98% yields, 79:21-89:11 e.r.). The electronic property of benzene ring did not affect the yield much and generally, good stereoselectivities were achieved (Table 2, entries 1-6). Furthermore, disubstituted phenol derivative **1g** could readily participate in this reaction, providing the corresponding benzofuran **3ga** with good results (Table 2, entry 7). While in the absence of 18-Crown ether-6, the reaction at -20 ^{o}C was too slow to consume the starting materials completely. And the enantioslectivity of **3ga** was decreased to 69:19 e.r.[16]

As summarised in Table 3, this asymmetric [4+1] annulation was also general with respect to sulfur ylides. For example, for most arylacyl-substituted sulfur ylides, regardless of their substitution pattern and electronic property system of benzene ring, reactions could perform well to give the corresponding products in generally high yields with moderate to good

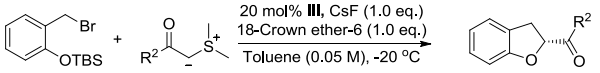
Table 2. Scope of TBS-protected phenol substrates **1**.[a]



Entry	**1,** R^1	**3**	Yield[b]	e.r.[c]
1	**1a**, H	**3aa**	96%	89:11
2	**1b**, 4-OMe	**3ba**	80%	85:15
3	**1c**, 4-Me	**3ca**	96%	89:11
4	**1d**, 4-F	**3da**	98%	78:22
5	**1e**, 4-Cl	**3ea**	96%	83:17
6	**1f**, 4-Br	**3fa**	98%	85:15
7	**1g**, 4,6-Br_2	**3ga**	98%	86:14

[a] Unless noted, reactions were performed with **1** (0.2 mmol), **2a** (0.24 mmol), catalyst **III** (20 mol%), CsF (0.2 mmol), 18-Crown ether-6 (0.2 mmol) in toluene (4.0 mL, 0.05 M). [b] Isolated yield. [c] Determined by chiral HPLC.

Table 3. Scope of sulfur ylide components.[a]



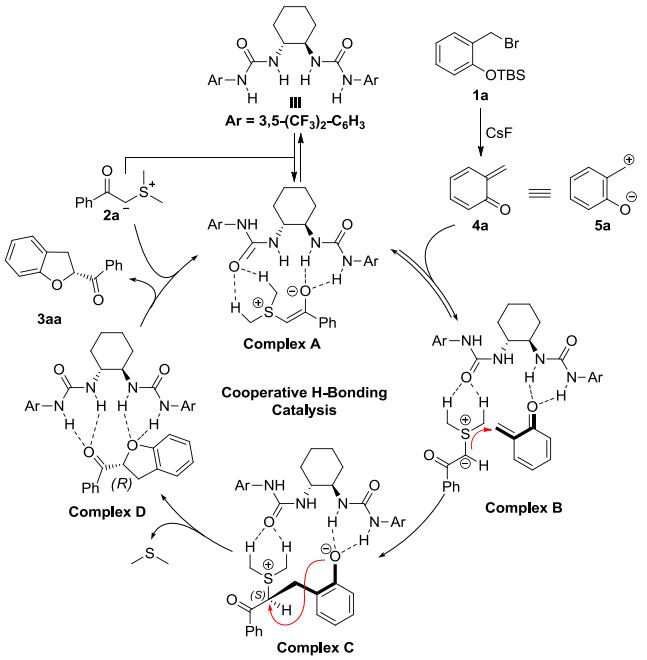
Entry	**2,** R^2	**3**	Yield[b]	e.r.[c]
1	**2b**, *p*-MeC_6H_4	**3ab**	95%	89:11
2	**2c**, *p*-$OMeC_6H_4$	**3ac**	93%	83:17
3	**2d**, *p*-FC_6H_4	**3ad**	96%	83:17
4	**2e**, *p*-ClC_6H_4	**3ae**	96%	77:23
5	**2f**, *m*-ClC_6H_4	**3af**	98%	84:16

6	**2g**, *m*-BrC_6H_4	**3ag**	98%	86:14
7	**2h**, 2,4-F_2-C_6H_3	**3ah**	96%	52:48
8	**2i**, 2-thienyl	**3ai**	97%	73:27
9	**2j**, 2-furyl	**3aj**	70%	72:28
10[d]	**2k**, *t*Bu	**3ak**	98%	75:25
11[d]	**2l**, CH_2=CH_2Ph	**3al**	70%	70:30
12[d]	**2m**, NEt_2	**3am**	90%	75:25

[a] Unless noted, reactions were performed with **1a** (0.2 mmol), **2** (0.24 mmol), catalyst **III** (20 mol%), CsF (0.2 mmol), 18-Crown ether-6 (0.2 mmol) in toluene (4.0 mL, 0.05 M). [b] Isolated yield. [c] Determined by chiral HPLC. [d] **2** (0.4 mmol, 2,0 equiv.) was used.

enantioselectivity (Table 3, entries 1-7). While, sulfur ylide **2h** with difluoro-substituents gave a poor enantiomeric ratio probably due to the electronic effect of sulfur ylide (Table 3, entry 7). Note that the heteroaromatic groups, such as furyl and thienyl, were also well tolerated (Table 3, entries 8-9). Moreover, the scope of sulfur ylides could be significantly extended to alkyl-, alkenyl- and amino-substituted acyl sulfur ylides, providing the corresponding products in 70-98% yields and 70:30 to 75:25 e.r. (Table 3, entries 10-12). Additionally, TBS-protected phenol substrates with substituents at the benzylic position were also used in the reactions. Unfortunately, racemic 2,3-disubstituted dihydrobenzofurans were obtained during the transformations probably due to the steric effect.

To better understand this reaction, a possible catalytic cycle involving Michael addition-S_N2 displacement cascade was depicted in Scheme 2. We presumed that the exposure of sulfur ylide **2a** to multiple H-bonding catalyst **III** would afford complex **A**.[10a,c] Then, the formed complex **A** incorporated with *o*-QMs **5a**, which was generated *in situ* from TBS-protected phenol substrate **1a** in the presence of CsF,[12c] to give complex **B**. Possibly, in this complex the catalyst **III** governed the orientation of both substrates by the H-bonding interaction and an asymmetric Michael addition occurred to provide complex **C**. Finally, the intramolecular S_N2 displacement of the complex **C** delivered the chiral cycloadduct **3aa** with the release of catalyst **III** for the next catalytic cycle.



Scheme 2. Proposed reaction mechanism.

Conclusions

In conclusion, we have developed a catalytic asymmetric [4+1] annulation reaction of sulfur ylides and TBS-protected phenol derivatives by using a multiple H-bonding urea catalyst. This protocol provided a straightforward route to enantio-enriched 2,3-dihydrobenzofurans with good yields and moderate enantiomeric ratios. Further exploitation of annulation reactions with sulfur ylides are currently on going in our laboratory.

Experimental Section

General procedure: To a 10 mL schlenk tube equipped with a magnetic stir bar were added sulfur ylide **2a** (0.22 mmol), catalyst **III** (0.04 mmol), 18-crown ether-6 (0.2 mmol), CsF (0.2 mmol) and dry toluene (3.0 mL). Then the reaction mixture was stirred under -20 ^oC for half an hour. Later, the solution of TBS-protected phenol substrate **1a** (0.2 mmol) in toluene (1.0 mL) was added dropwise to the above reaction mixture. Upon consumption of the starting materials monitored by TLC, the reaction mixture was purified by flash chromatography on silica gel (ethyl acetate : petroleum ether = 1:10) to give the desired product **3aa** as a white solid in 96% yield, 89:11 e.r..

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Keywords: asymmetric catalysis • H-bonding catalysis • dihydrobenzofuran • sulfur ylides • [4+1] annulation

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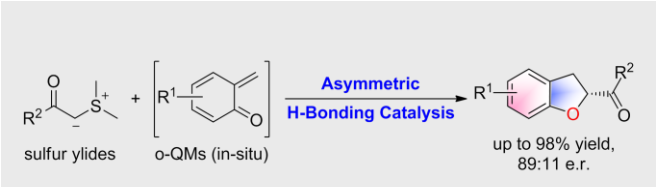
[16] See more details in the supporting information.

SHORT COMMUNICATION



The title H-bonding catalytic asymmetric [4+1] annulations of sulfur ylides with in situ-generated *ortho*-quinone methides enable for the enantioselective synthesis of chiral 2,3-dihydrobenzofurans in good results.

Organocatalysis

Qing-Qing Yang and Wen-Jing Xiao*

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Catalytic Asymmetric Synthesis of Chiral Dihydrobenzofurans via A Formal [4+1] Annulation Reaction of Sulfur Ylides and In Situ-Generated *ortho*-Quinone Methides