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Organohalogenite-Catalyzed Spiroketalization: Enantioselective Synthesis of Bisbenzannulated Spiroketal Cores

Jijun Xue,[a,*] Hongrui Zhang,[a] Tian Tian,[a] Keshu Yin,[a] Dongxue Liu,[a] Xianxing Jiang,[b,*] Ying Li,[a,*] Xiaojie Jin,[a] and Xiaojun Yao[a]

[a] State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, 730000 Gansu, People's Republic of China
E-mail: xuejj@lzu.edu.cn or liying@lzu.edu.cn

[b] School of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510006, People's Republic of China
E-mail: jiangxx5@mail.sysu.edu.cn

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Abstract: A new core structure-motivated strategy for the intramolecular aromatic spiroketalization process was found and used for the enantioselective synthesis of bisbenzannulated spiroketals, the bioactive core of rubromycins, with high levels of enantioselectivity (up to 98% *ee*) *via* an organohalogenite-mediated asymmetric intramolecular aromatic spiroketalization. This is the first organocatalytic method for the construction of optically pure bisbenzannulated spiroketals.

Keywords: asymmetric synthesis; organocatalysis; organohalogen; spiroketalization

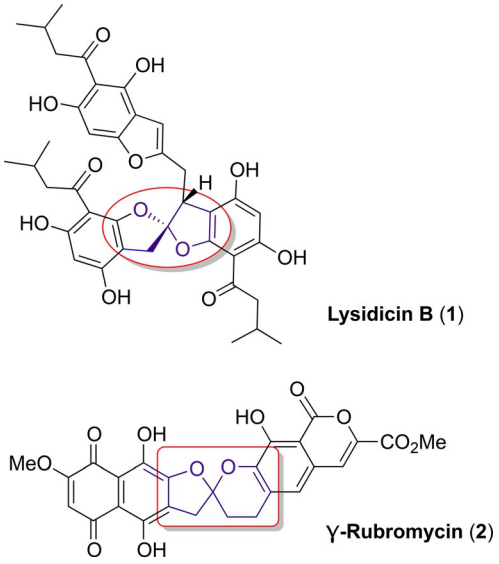
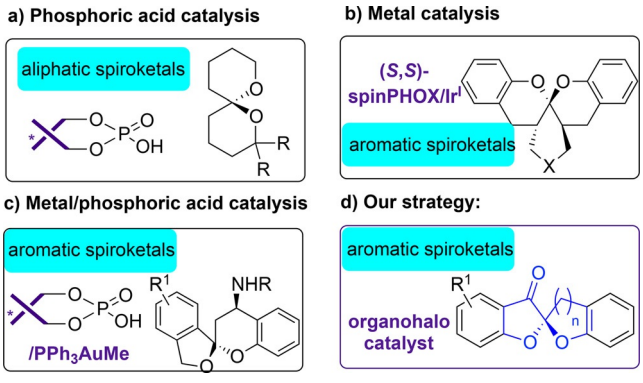


Figure 1. Important natural spiroketal products.



Scheme 1. Different catalytic strategies for spiroketalization.

Core-scaffold-lead synthesis through rapid construction of chiral molecular complexity around the biologically relevant framework using a highly efficient strategy is a key goal of organic and medicinal synthesis. Benzannulated spiroketals, as a privileged structural moiety found in a large series of bioactive naturally occurring alkaloids and pharmaceutically relevant assays, such as Lysidicin[1] and rubromycins[2] (Figure 1), exhibit a range of biological and pharmaceutical activities.[3] Although many strategies were designed to construct spiroketals[4] and related natural products,[5] the direct asymmetric catalytic approaches to access them are still scarce.

Recently, List[6] and Nagorny[7] developed the asymmetric catalytic construction of aliphatic spiroketals by chiral phosphoric acid-catalyzed spiroketalizations (**a**, Scheme 1), respectively. However, compared to the asymmetric formation of aliphatic spiroketals, the enantioselective construction of aromatic spiroketals represents a considerable challenge because the aromatic hydroxy groups have less nucleophilicity. Therefore, it is not surprising that the catalytic enantioselective synthesis of aromatic spiroketals has been rarely

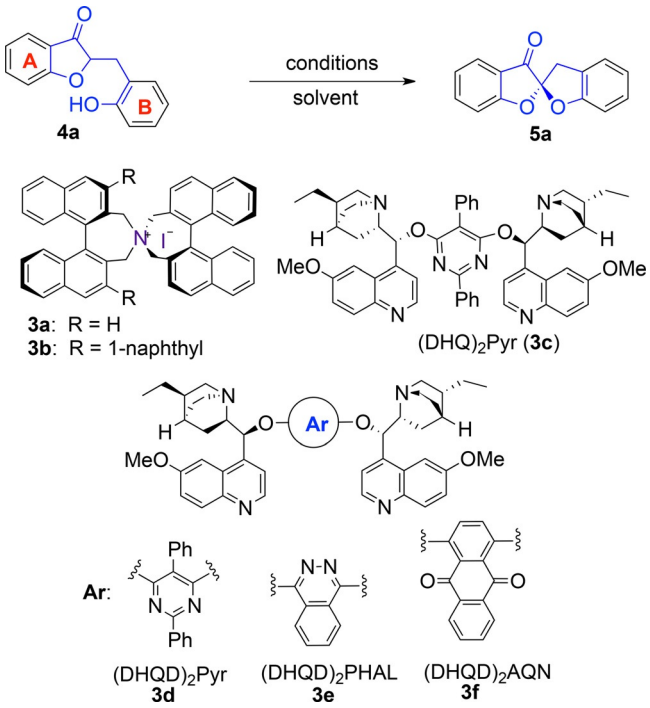
reported, and all of only two examples fall into the more complex transition metal- or metal/phosphoric acid combination-catalyzed strategies from Ding[8] and Gong[9] group (**b** and **c**, Scheme 1), respectively. The development of efficient methodologies that enable cheaper, simpler, and more concise approaches to access molecular complexity with exquisite levels of stereocontrol remains a preeminent goal in modern organic chemistry. Herein, we introduce an organohalogenite catalytic strategy as a new and convenient platform for the core-structure-motivated design of intramolecular aromatic spiroketalization processes. In this context, we document a highly enantioselective synthesis of bisbenzannulated spiroketal cores by developing the first organocatalytic aromatic spiroketalization (**d**, Scheme 1).

In the past two decades, organohalo compounds have been increasingly explored and proved to be very versatile intermediates as environmentally benign reagents[10] to replace expensive and toxic heavy metal materials in halogenation,[11] oxidation,[1c,12] and catalysis processes.[13] Amongst the most challenges and interests for synthetic chemists is the development of efficient organohalo catalysts that allow the rapid construction of stereo- and skeleton-chemically defined molecular complexity. There are a number of efforts devoted to tandem reactions involving organohalogen-mediated halogenation as a transition process,[14,15,16] especially for halolactonization[14] and related halocyclizations.[16] Notably, compared with enantioselective halogenations and halolactonizations, the catalytic asymmetric halocycloetherification has attracted less attention, although it may be more convenient and feasible for the enantioselective construction of spiroketals.

On the basis of the above considerations, our recent efforts are to develop halocycloetherification for the construction of spiroketals by using *in-situ* generated hypoiodite catalysis system.[17] Herein, we hope to expand our studies beyond the racemic compounds and develop an efficient protocol through organocatalytic intramolecular aromatic spiroketalization for accessing chiral bisbenzannulated spiroketals. In this text, we present our preliminary results on this topic.

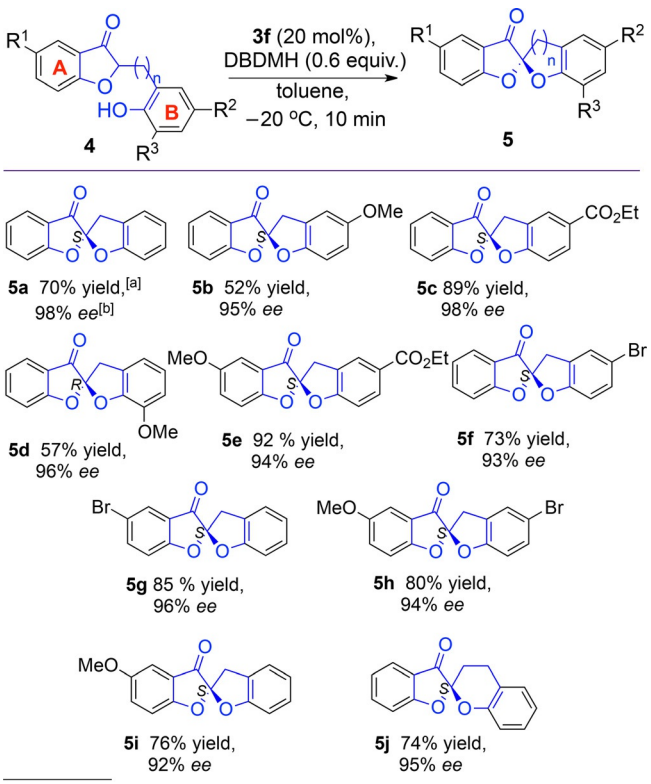
To explore the possibility of the proposed intramolecular bisbenzannulated spiroketalization process, our investigation began with a screening of several organocatalysts to evaluate their catalytic activities under the different reaction conditions. The model reaction of substrate **4a** was performed in the presence of a 20 mol% loading of ligand (Table 1). Besides the chiral catalysts **3a** and **3b** with diversely structured scaffolds, organocatalysts **3c**, **3d**, **3e** and **3f** were also tested. While the desired product **5a** could be obtained in the presence of **3a** or **3b** with an amount of *m*-chloroperoxybenzoic acid, only low yields and *ee* values were observed in the reactions (entries 1 and 2). In order to improve the yield and enantioselectivity, organocatalysts **3c–3f** and *N*-iodosuccimide (NIS)

Table 1. Studies and optimization of the reaction parameters.[a]



Entry	Cat.	Solvent	X^+ source	Yield[b]	*ee*[c]
1	**3a**[d]	toluene		21%	6%
2	**3b**[d]	toluene		18%	3%
3	**3c**	toluene	NIS	14%	7%
4	**3d**	toluene	NIS	20%	25%
5	**3e**	toluene	NIS	7%	0
6	**3f**	toluene	NIS	60%	35%
7	**3f**	THF	NIS	10%	0%
8	**3f**	$CHCl_3$	NIS	0%	0%
9	**3f**	CH_3CN	NIS	10%	5%
10	**3f**[e]	toluene	NIS	55%	81%
11	**3f**[f]	toluene	NIS	54%	84%
12	**3f**[g]	toluene	NIS	45%	83%
13	**3f**[f]	toluene	NBS	61%	98%
14	**3f**[f,h]	toluene	DBDMH	70%	98%

[a] Unless otherwise noted, the reaction was conducted with **4a** (0.2 mmol) using 20.0 mol% catalysts and X^+ source (0.22 mmol) for 10.0 min at 25 °C. DHQD: dihydroquinidine, and DHQ: dihydroquinine.
[b] Isolated yield.
[c] The *ee* values were determined by HPLC, and the configuration was assigned by comparison of CD spectra and X-ray crystal data of derivatives.
[d] Using *m*-chloroperoxybenzoic acid (0.2 mmol).
[e] At 0 °C.
[f] At −20 °C.
[g] At −40 °C.
[h] Using 0.12 mmol DBDMH.



[a] Isolated yield.

[b] The *ee* values were determined by HPLC, and the configuration was assigned by comparison of CD spectra and X-ray crystal data of derivatives.

Scheme 2. Investigations on the substrate scope. Unless noted otherwise, the reaction was conducted with **4a** (0.2 mmol) using 20.0 mol% catalysts and X^+ source (0.12 mmol) for 10.0 min at −20 °C.

as a halogen source were investigated. Further screening of **3c–3f** indicated that $(DHQD)_2AQN$ (**3f**) is the best catalyst, furnishing the products in 60% yield and 35% *ee* (entry 6). Subsequently, a survey of other solvents was carried out with catalyst **3f** (entries 6–9). These results indicated that a substantial change of the solvent has a significant effect on the reaction. Among the solvents tested, toluene appeared to be the most suitable reaction media in terms of chemical yield and enantioselectivity. To our delight, the best result was observed when the reaction was performed in toluene at −20 °C by a further optimization of the reaction temperature (54% yield and 84% *ee*, entry 11). In addition, other halogen sources were also attempted, such as *N*-bromosuccimide (NBS), 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (entries 13 and 14). As expected, the *N*-bromo reagent gave much better results in terms of yield and stereochemical outcome than the *N*-iodo reagent, and DBDMH proved to be the most efficient halogen source for catalytic intramolecular spiroketalization, leading to excellent enantioselectivity and good yield (98% *ee* and 70%, entry 14).

The results of experiments under the optimized conditions that probed the scope of the reaction are summarized in Scheme 2. The catalytic intramolecular bisbenzannulated spiroketalization in the presence of 20 mol% **3f** with DBDMH was performed in toluene at −20 °C. A variety of substrates **4** including those bearing electron-withdrawing and electron-donating substituents on the aryl ring were examined. Gratifyingly, all of the reactions could provide the excellent enantioselectivities (93–98% *ee*). It is noteworthy that the substituents on ring A or B can significantly influence yield of the reaction. In general, the results showed that all reactions with aromatic substrates proceeded quickly affording the desired products in yields ranging from 52 to 92%.

The configurations of products were confirmed in two ways. The first way is the CD spectrum (Figure 2). The electronic circular dichroisms (ECDs)

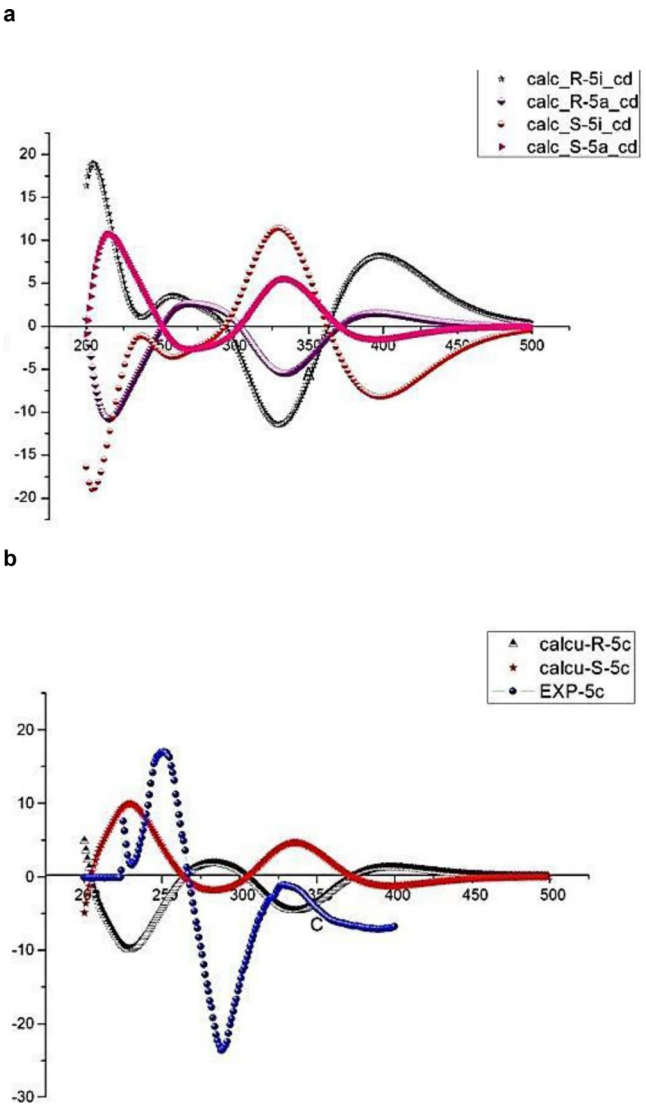
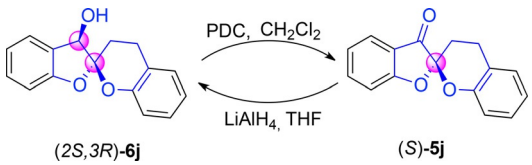


Figure 2. (**a**) The calculated CDs of **5a** and **5i**. (**b**) The calculated CD of **5c** and experimental CD of **5c**.



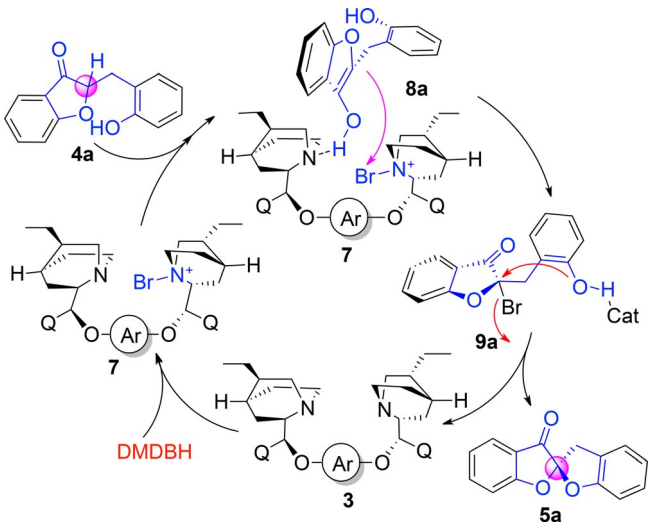
Scheme 3. Characterization of **5j** with its derivatives.

of two possible candidate stereoisomers of **5a**, **5c** and **5i** were calculated (see the Supplorting Information). The results indicated that the *R*-**5a**, **5c**, and **5i** have similar ECDs by comparison with *R*-**5a** CD spectrum (a, Figure 2, the *S*-configuration products have the opposite curves). From the comparison of positive CEs at 270 nm and 330 nm (b, Figure 2), the results also showed that the experimental spectrum of prepared **5c** could match the calculated ECD curve of ***S*-5c**. Therefore, **5c** prepared by our method herein, is more likely to have the *S*-configuration (Figure 2).

All the attempts to obtain the X-ray structures of compounds **5** failed, so (2*S*,3*R*)-**6j** was prepared according to the procedure reported by our group previously.[18a] The X-ray structure of (2*S*,3*R*)-**6j** was then obtained.[18b] The oxidation of (2*S*,3*R*)-**6j** gave (*S*)-**5j** (Scheme 3), which was then compared with **5j** prepared from our method. The same specific optical rotations were observed, which indicated that **5j** herein should have the *S*-configuration.

In fact, reducing our product **5j** with $LiAlH_4$ in THF can give (2*S*,3*R*)-**6j**, which was characterized by X-ray crystallography. This also proved that our product is (*S*)-**5j**. Similarly, **5a** has the *S*-configuration, too.

On the basis of the experimental results described above and recent studies,[6,14c,15] a possible mechanism is shown in Scheme 4. The 1,3-dibromo-5,5-dimethylhydantoin reacts with organocatalyst $(DHQD)_2AQN$ to form the chiral *N*-bromo quaternary ammonium salt intermediate **7**, which will play dual roles in the following transformation. The *N*-bromo quaternary ammonium salt **7** not only could promote the enolization of substrate **4a** through the catalyst bearing tertiary amine moiety, but also could serve as an electrophile to react with the *in situ* formed enol **8a**, thus triggering an electrophilic bromo-addition process to afford bromobenzofuranone **9a**. The subsequent intramolecular nucleophilic substitution of bromo intermediate **9a** provides for the release of catalyst **3** to generate the final product **5a**.



Scheme 4. The proposed mechanism.

In summary, we have disclosed a new core-structure-motivated design of an intramolecular aromatic spiroketalization process to synthesize bisbenzannulated spiroketals with high levels of enantioselectivity (up to 98% *ee*) *via* an organohalogenite catalytic intramolecular aromatic spiroketalization. This representative synthetic example demonstrates the inherent synthetic potential of this kind of organohalogenite catalytic strategy for bioactive natural products like rubromycins and lysidicins, and the total synthesis of these compounds using this protocol are underway.

Experimental Section

General Procedure for Compound 5

To a solution of compound **4** (0.2 mmol) and catalyst **3f** (0.04 mmol) in toluene (4.0 mL) was added the halogen source (0.12 mmol), the resulting solution was then stirred at an appropriate temperature. After the starting material was completely consumed as monitored by TLC, the mixture was filtered to remove the catalyst and the filtrate was concentrated under vacuum. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc = 16:1, v/v) to give **5**.

Acknowledgements

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