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Asymmetric Michael-Aldol Tandem Reaction of 2-Substituted Benzofuran-3-ones and Enones: A Facile Synthesis of Griseofulvin Analogues

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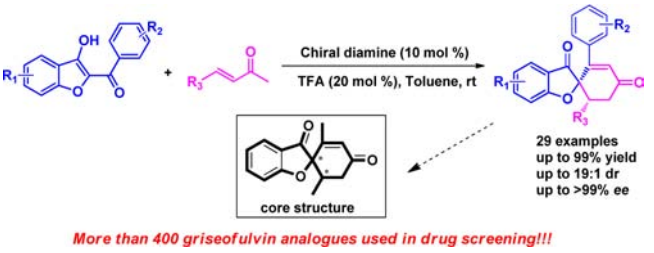
ABSTRACT



A highly enantioselective Michael–aldol tandem reaction with respect to prochiral 2-substituted benzofuran-3-ones and enones by a facile primary amine catalyst was investigated. The approach provides rapid access to the desired pharmaceutically active griseofulvin analogues.

Spirocyclic benzofuran-3-ones (Figure 1) have attracted extensive attention since the structural motif of this type of compound is a prominent feature in a number of biologically and pharmaceutically active natural products.[1] Specifically, griseofulvin, isolated from filamentous fungi in 1939 (Figure 1),[2] has been known as an antifungal agent for decades.[3] Furthermore, griseofulvin also exhibits good anticancer and antiviral properties.[4] Because of the pharmaceutical activity mentioned above, griseofulvin has been prepared by several routes.[5] However, most of the syntheses reported thus far yield the racemate. Only one study reported the synthesis of the enantiomer of natural griseofulvin with the key step of rhodium-catalyzed sigmatropic rearrangement of oxonium ylides.[6] On the other hand, more than 400 griseofulvin analogues, which were used to the drug screening, have been synthesized in the past 50 years.[7]

In general, these natural product analogues contain a unique 2-spirocyclohexanonic benzofuran-3-one core

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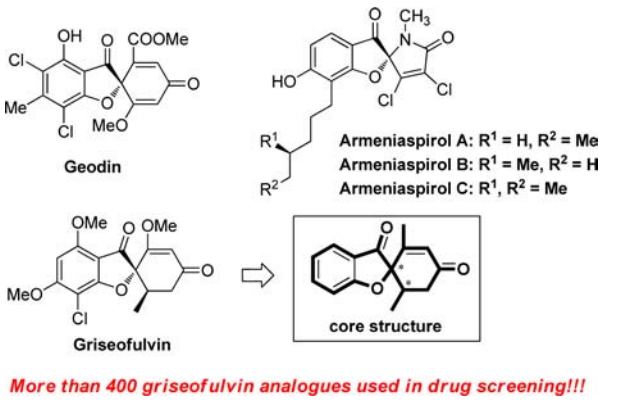


Figure 1. Spirocyclic benzofuran-3-one-type natural products.

structure (Figure 1). In the literature,[8] strategies to obtain these potential drug analogues are all derived from the modification of griseofulvin synthesis. To the best of our knowledge, direct and valuable strategies for the asymmetric synthesis of chiral 2-spirocyclic benzofuran-3-ones core structure have never been studied. Therefore, strategies using the catalytic asymmetric synthesis of chiral 2-spirocyclic benzofuran-3-ones type compounds are highly desired.

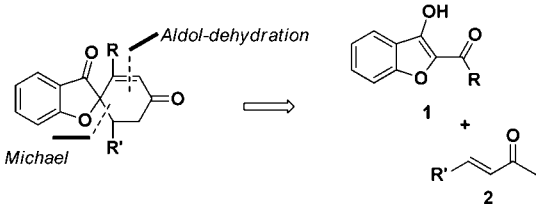
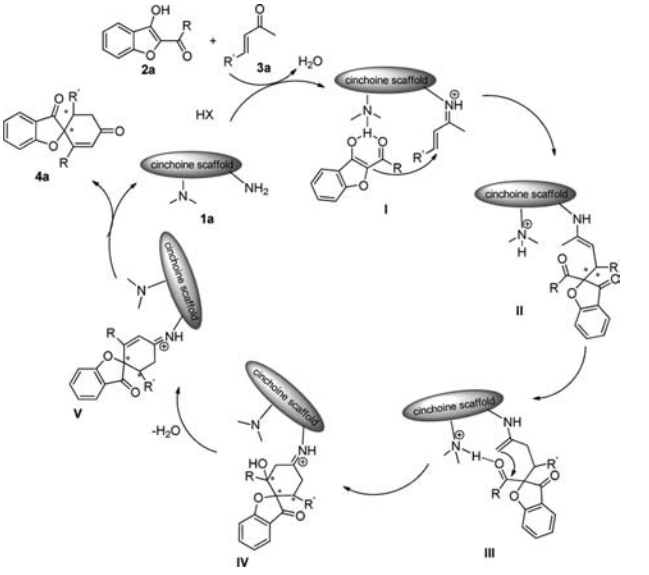


Figure 2. Retrosynthetic analysis.

Cascade reactions are powerful tools for rapidly achieving molecular complexity.[9] We envisaged that a tandem organocatalytic Michael–aldol dehydration of 2-substituted benzofuran-3-ones (**1**) and enones (**2**) could be useful for the formation of the chiral 2- spirocyclohexanonic benzofuran-3-one core structure (Figure 2). Prompted by the above-mentioned considerations, and in an effort to continue our studies of organocatalytic annulations for the synthesis of chiral benzofuranones type compounds,[10] herein we disclose a tandem reaction of 2-substituted benzofuran-3-ones and enones using chiral primary amine as catalyst. This study provides a very simple and convenient method for the synthesis of pharmaceutically active griseofulvin analogues.

Scheme 1. Strategy for Catalytic Process



To identify the validation of our hypothesis, the reaction of 2-benzoylbenzofuran-3-one (**1a**) to 4-phenyl-3-buten-2-one (**2a**) served as the model reaction. Six widely used primary–tertiary vicinal diamine catalysts **3**–**6**[11] (Figure 3) were screened. To our delight, all of the catalysts exhibited high catalytic activities, and the tandem Michael–aldol products were isolated with very good yields and good to excellent stereoselectivities (Table 1). The success of this strategy is due to the chiral amine catalyst, which has an active role in both tandem steps, initially forming the activated iminium ion species and later the electron-rich enamine intermediate (Scheme 1). Among the six catalysts examined, **4a** was found to give the optimal stereoselectivity (Table 1, entry 3, 96% yield, 3:1 dr and 99% ee). After further optimization of the reaction, the best result was obtained by performing the reaction at room temperature in toluene with 10 mol % of **4a** and 20 mol % of TFA (see Table S1, Supporting Information).

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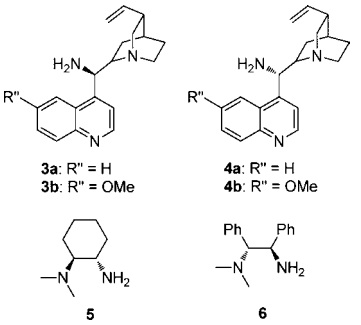
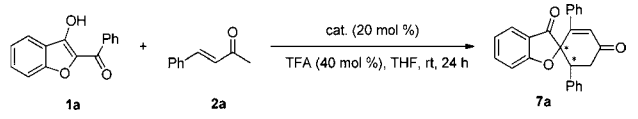


Figure 3. Catalysts screened in this study.

Table 1. Catalyst Screening[a]



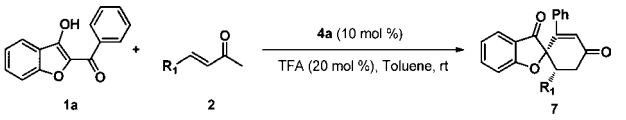
entry	cat.	yield[b] (%)	dr[c]	ee[d] (%)
1	**3a**	99	4:1	88/89
2	**3b**	89	6:1	84/78
3	**4a**	96	3:1	99/96
4	**4b**	92	1:1	97/84
5	**5**	72	3:1	99/64
6	**6**	89	2:1	97/94

[a] Unless otherwise noted, reactions were conducted with 0.1 mmol of **1a**, 0.2 mmol of **2a**, 20 mol % of catalyst, and TFA as cocatalyst in 0.5 mL of THF at room temperature for 24 h. [b] Isolated yields. [c] Determined by ^{1}H NMR of crude product. [d] Measured by chiral HPLC analysis.

After the reaction conditions were optimized, the substrate scope was explored. Overall, the reaction proceeded smoothly to give the desired products in high yields with perfect enantioselectivity. Different enones **2** were tested under the optimized reaction conditions (Table 2). These modifications of the substrates **2** were well tolerated, and the corresponding products **7a**–**k** were obtained with good diastereoselectivities and excellent enantioselectivities irrespective of the electronic nature or position of the substituents on the phenyl ring (up to 99% yields, 15:1 dr and > 99% ee, entries 1–11). Moreover, a larger aromatic ring could be accommodated in the reaction, giving high yield and excellent enantioselectivity (entry 12 in Table 2). Remarkably, the chemistry can be successfully extended to an aliphatic substituent in **2**, thus maintaining an excellent enantioselectivity but partially affecting the relative stereocontrol (entries 13–15 in Table 2).

In order to further extend the substrate scope, different substituted 2-benzoylbenzofuran-3-ones were also examined. As revealed in Table 3, the reactions were shown to work well with a range of 2-benzoylbenzofuran-3-ones bearing either electron-withdrawing or electron-donating groups to give the desired products with very good yields (91–99%), moderate to very good diastereoselectivities

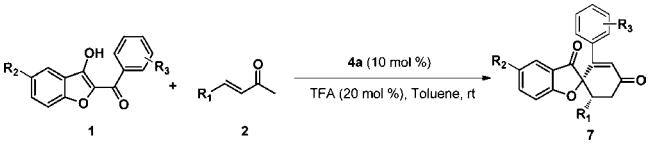
Table 2. Enone Scope[a]



entry	R_1	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	Ph-	24	**7a**/98	9:1	99
2	4-CH_3Ph-	18	**7b**/96	13:1	99
3	4-FPh-	18	**7c**/90	6:1	>99
4	4-CH_3OPh-	18	**7d**/94	13:1	97
5	4-BrPh-	18	**7e**/99	7:1	99
6	4-ClPh-	18	**7f**/94	4:1	97
7	4-CF_3Ph-	18	**7g**/87	7:1	>99
8	3-CH_3OPh-	18	**7h**/99	10:1	>99
9	3-CH_3Ph-	18	**7i**/99	15:1	>99
10	2-CH_3OPh-	18	**7j**/97	13:1	>99
11	3,5-diCH_3OPh-	18	**7k**/99	13:1	99
12	naphthyl	18	**7l**/95	11:1	96
13	CH_3	16	**7m**/87	3:1	99/99
14	*n*-propyl	20	**7n**/93	3:1	>99/>99
15	*n*-pentyl	20	**7o**/97	4:1	>99/>99

[a] Reactions were performed with 0.1 mmol of **1**, 0.1 mmol of **2**, 10 mol % of **4a**, and 20 mol % of TFA in 0.5 mL of toluene at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude products. [d] Measured by chiral HPLC analysis.

Table 3. Substrates Scope of 2-Substituted Benzofuran-3-ones[a]



entry	R_1	R_2	R_3	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	Ph-	H	4-Cl	18	**7p**/97	3:2	99/93
2	Ph-	H	4-Br	24	**7q**/99	3:1	>99
3	Ph-	H	4-Ph	18	**7r**/95	5:1	98
4	Ph-	H	4-CH_3O	20	**7s**/99	>19:1	>99
5	Ph-	H	3,4-diCl	24	**7t**/91	5:1	98
6	Ph-	I	H	18	**7u**/94	4:1	98
7	4-FPh-	H	4-CH_3O	16	**7v**/99	4:1	>99
8	4-CF_3Ph-	H	4-CH_3O	16	**7w**/91	13:1	97
9	3-ClPh-	H	4-CH_3O	18	**7x**/94	15:1	98
10	3-CH_3OPh-	H	4-CH_3O	14	**7y**/99	>19:1	95
11	3-CH_3Ph-	H	4-CH_3O	18	**7z**/90	16:1	99

[a] Reactions were performed with 0.1 mmol of **1**, 0.1 mmol of **2**, 10 mol % of **4a**, and 20 mol % of TFA in 0.5 mL of toluene at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude products. [d] Measured by chiral HPLC analysis.

(up to > 19:1 dr), and excellent enantioselectivities (95– > 99% ee). Furthermore, other functionalized enones were also well tolerated by this synthetic methodology (Figure 4).

The utility of the Michael–aldol tandem reaction was further demonstrated by transformations of the product **7m** (Figure 5). Reduction and phenylhydrazonation of **7m**

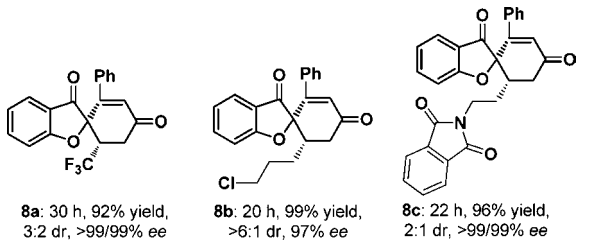


Figure 4. Products obtained from functionalized enones.

gave substituted cyclohexenespirobenzofuran-3-one derivatives **9a** and **9b**, respectively.

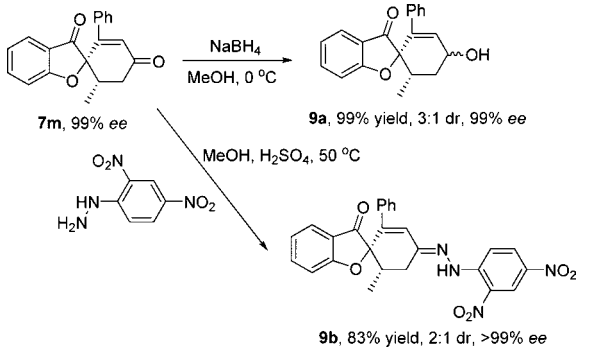


Figure 5. Transformations of the products.

The absolute configuration of product **9c** was determined by X-ray analysis (Figure 6).[12] The configurations of other products were tentatively assigned by referring to that of **9c**.

In conclusion, we have developed an all carbon-based asymmetric tandem Michael–aldol reaction of 2-substituted benzofuran-3-ones with enones via imine–enamine catalysis. The domino strategy was quite successful, which enabled the construction of two adjacent quaternary-tertiary chiral centers in the 2-spirocyclic benzofuran-3-one structure. As a result, a series of highly functioned 2-spirocyclic benzofuran-3- ones were obtained in excellent diastereo- and enantioselectivities. Such enantioenriched natural product mimics may have potential in medicinal chemistry or chemical biology studies.

(12) CCDC 948125 contains the supplementary crystallographic data for compound **9c**. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.

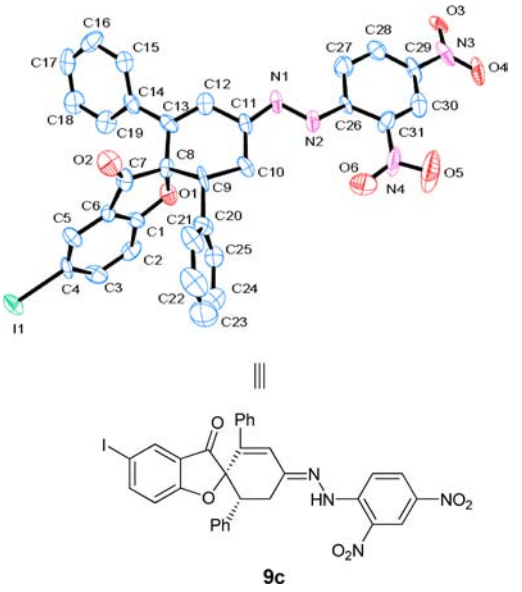


Figure 6. X-ray crystal structure of **9c**.

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Supporting Information Available. Experimental details, analytical data for all new compounds, and X-ray crystallographic data of **9c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.