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Highly Enantioselective [4 + 2] Cycloaddition of Allenoates and 2-Olefinic Benzofuran-3-ones

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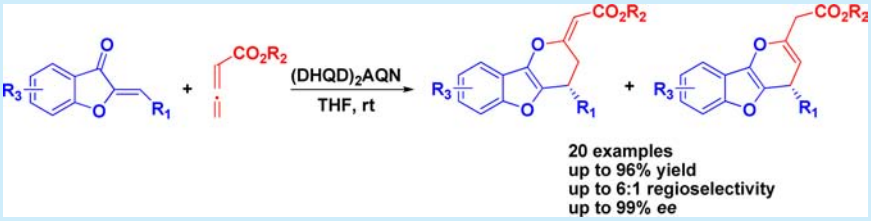
Supporting Information



ABSTRACT: A highly enantioselective [4 + 2] cycloaddition of allenoates with 2-olefinic benzofuran-3-ones catalyzed by $(DHQD)_2AQN$, which allowed the synthesis of optically active dihydropyran-fused benzofurans, was developed.

Benzofuro[3,2-*b*]pyrans and dihydropyran fused benzofurans (Figure 1) have attracted extensive attention because

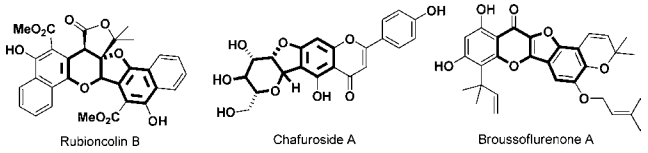


Figure 1. Natural products with benzofuro[3,2-*b*]pyran and dihydropyran fused benzofuran ring.

the structural motifs of these two types of compounds are a prominent feature in a number of biologically active natural products.[1] For example, Chafuroside A, which is isolated from Chinese oolong tea, has displayed potential inhibitory activity against DNFB (2,4-dinitrofluorobenzene) induced contact hypersensitivity in mice.[2] Due to the important biological activities of benzofuro[3,2-*b*]pyran and dihydropyran fused benzofuran derivatives, the synthesis of the corresponding structures attracted wide interest.[3] However, direct and valuable strategies for the asymmetric synthesis of the framework of benzofuro[3,2-*b*]pyrans and dihydropyran fused benzofurans, to the best of our knowledge, have never been reported. Therefore, the development of efficient methodologies to obtain chiral benzofuro[3,2-*b*]pyran and dihydropyran fused benzofuran derivatives is strongly desired.

The phosphine promoted cycloaddition reactions of allenoates with electron-deficient olefins or imines, which can be served as a highly useful synthetic method for preparing different kinds of carbocycles or heterocycles from readily available starting materials, have attracted considerable research interest.[4] After pioneering work by Lu in 1995,[5] corresponding synthetic strategies to a wide range of polarized C═X bonds (X = N, O, and C) have been progressed rapidly in the past few years. Although the development of phosphine-catalyzed cycloaddition reactions of allenoates was very fast paced, we noticed that only limited examples existed for allenoate cycloaddition catalyzed by tertiary amine. In 2011, Masson and Zhu developed cinchona alkaloid derivative catalyzed asymmetric [2 + 2] cycloadditions between allenoates and imines.[6a] Soon after, Tong and Borhan independently reported asymmetric [4 + 2] cycloadditions of allenoates with β,γ-unsaturated ketone in the presence of amine type organocatalysts.[6b,c] Lately, Shi and Wei developed asymmetric [4 + 2] cycloadditions of β,γ-unsaturated α-ketophosphonates and α-ketoesters with allenic esters by the amine type organocatalysts derived from cinchona alkaloids.[6d,e] Furthermore, using the analogous catalyst, the same group also realized highly enantioselective [2 + 2] annulations of allenoates with trifluoromethyl ketones.[6f] Recently, Sasai presented a chiral amine catalyzed [2 + 2] cycloaddition of ketimines with allenoates.[6g]

Prompted by the above-mentioned considerations, we envisaged that asymmetric [4 + 2] cycloaddition between 2-olefinic benzofuran-3-one and allenoate could be useful for the formation of the chiral dihydropyran fused benzofuran core structure (Scheme 1). In an effort to continue our studies of the synthesis of chiral benzofuran type compounds,[7] herein we disclose enantioselective [4 + 2] cycloadditions of 2-olefinic benzofuran-3-ones and allenoates using a chiral tertiary amine as the catalyst. It is valuable to note that the eletrophilicity of alkene on 2-olefinic benzofuran-3-ones **A**, coexisting with its resonance form **B** (Scheme 1), would become lower when attacked by the zwitterionic intermediate of allenoate, which enables the cyclization to bemuch more challenging.

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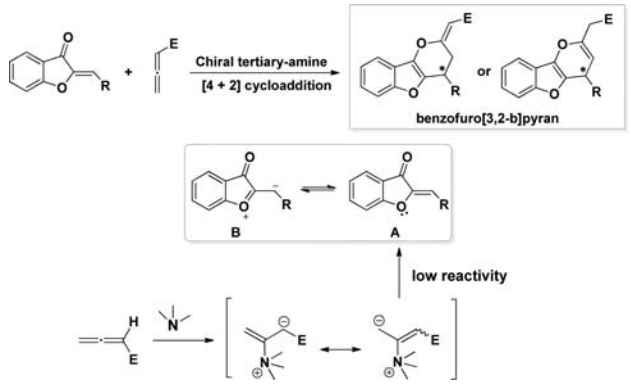
Scheme 1. General Strategy and Challenge for the Current Cyclization

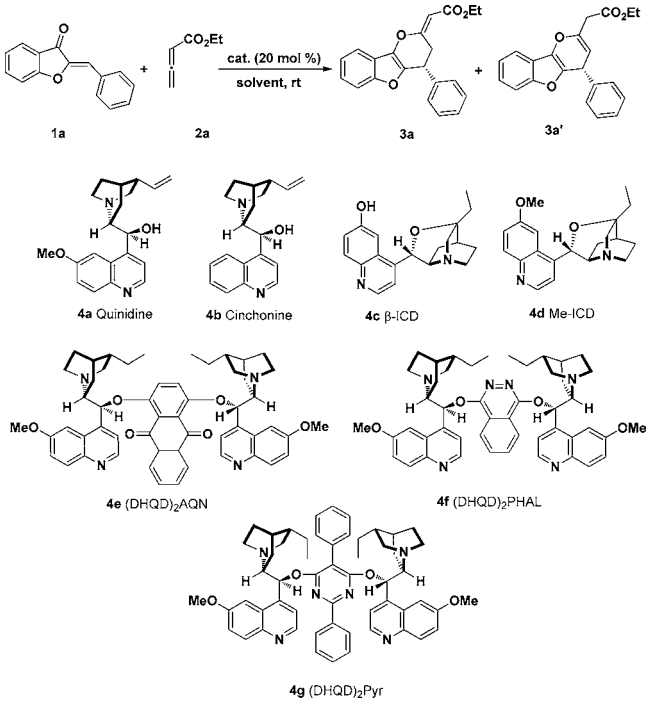


We initiated our investigations using (*Z*)-2-benzylidenebenzofuran-3-one (**1a**) and ethyl 2,3-butadienoate (**2a**) in the presence of quinidine **4a** in THF at rt. Although the cyclization product **3a** can be obtained with excellent enantioselectivity, the yield is poor (entry 1, Table 1). The catalytic activity of **4a** is obviously far from satisfactory. Then a number of widely used chiral tertiary-amine catalysts **4b**−**4g** were examined in this [4 + 2] cycloaddition. Generally, all the reactions proceeded for more than 4 days, which proved that the 2-olefinic benzofuran-3-one was less reactive. Under the catalysis of **4c**, the yield of the cyclization product **3a** was good; however, the enantioselectivity was moderate (entry 3, Table 1). Under identical conditions, **4d** was also active for this cyclization strategy, in which moderate enantioselectivity for the other regioisomer **3a**′ was obtained (entry 4, Table 1). A sharp increase in enantioselectivity was observed for catalyst **4e**, in which good yield and moderate regioselectivity were obtained. Albeit with the same excellent enantioselectivities, **4g** and **4f** gave poor yields. In comparison, $(DHQD)_2AQN$ (**4e**) was identified as optimal for both the catalytic reactivity and enantioselectivity, in which **3a** and **3a**′ were obtained in good combined yield (83%) with moderate regioselectivity and excellent enantioselectivities (99% *ee* for **3a** and 94% *ee* for **3a**′).

The reaction was then optimized by screening the solvent, concentration, and additive in the presence of **4e** (entries 8−14, Table 1). As shown in Table 1 (entries 6 and 8−12), initially used THF gave the best result among a range of screened solvents. Increasing the reaction concentration slightly shortened the reaction time (entry 13, Table 1). Addition of 4 Å molecular sieves to the reaction mixture significantly increased the regioselectivity; however, the enantioselectivity of **3a** decreased significantly (entry 14, Table 1). Collectively, the best result with respect to yield and *ee* values was obtained by conducting the [4 + 2] cycloaddition at rt in THF with 20 mol % of **4e** in a concentration of 0.4 M. Under the optimized conditions, the cyclization product was obtained with a 90% yield and 99% *ee* for **3a** (95% *ee* for **3a**′) (entry 13, Table 1).

With the optimized reaction conditions in hand, we then surveyed the scope of the reaction by varying the structure of 2-olefinic benzofuran-3-ones. As exhibited in Table 2, the reactions worked well with a range of 2-subsituted aryl vinyl benzofuran-3-ones bearing either electron-withdrawing or -donating substituents (entries 1−10, Table 2). In most cases, the corresponding cyclization products were obtained in high yields (71−96%) and excellent enantioselectivities for both regioisomers **3** (98−99% *ee*) and **3**′ (93−98% *ee*). A lower yield

Table 1. Screening for the [4 + 2] Cycloaddition[a]



entry	cat.	solvent	time (d)	yield (%)[b]	3/3′[c]	*ee* (3,%)[d]	*ee* (3′,%)[d]
1	**4a**	THF	5	18	>20:1	98	–
2	**4b**	THF	5	15	>20:1	74	–
3	**4c**	THF	5	76	2:1	56	64
4	**4d**	THF	4	96	1:3	1	49
5	**4e**	THF	6	83	2:1	99	94
6	**4f**	THF	5	21	>20:1	98	–
7	**4g**	THF	5	27	>20:1	99	–
8	**4e**	CH_2Cl_2	6	84	1:1	98	88
9	**4e**	$CHCl_3$	6	72	>20:1	84	–
10	**4e**	ether	6	91	5:2	98	89
11	**4e**	toluene	6	45	>20:1	95	–
12	**4e**	dioxane	6	51	>20:1	93	–
13[e]	**4e**	THF	5	90	10:7	99	95
14[f]	**4e**	THF	6	87	15:1	92	–

[a]The reactions were conducted with 0.1 mmol of **1a**, 0.15 mmol of **2a**, and 20 mol % catalyst in 0.5 mL of solvent at rt. [b]Isolated yields. No *Z*-isomer of cycloadduct was detected. [c]Determined by ^{1}H NMR of crude product. [d]Determined by chiral HPLC analysis. [e]The reaction was conducted with 0.1 mmol of **1a**, 0.15 mmol of **2a**, and 20 mol % **4e** in 0.25 mL of THF at rt. [f]The reaction was conducted with 0.1 mmol of **1a**, 0.15 mmol of **2a**, and 20 mol % **4e** in 0.5 mL of THF with 50 mg of 4 Å M.S at rt.

and enantioselectivity were obtained, when *o*-substituted aryl vinyl benzofuran-3-one with an electron-donating substituent was selected as the substrate (entry 11, Table 2). A larger aromatic ring could also be accommodated in the reaction, giving a good yield and excellent enantioselectivity (entry 13, Table 2). Furthermore, when the substrate was heterocyclic ring substituted vinyl benzofuran-3-one (**1n**), the [4 + 2] cycloaddition could still proceed smoothly with moderate yield and excellent enantioselectivity (entry 14, Table 2).

To extend the substrate scope, different substituted allenoates were examined. As shown in Table 2, the reactions worked well with the evaluated allenoates, in which the desired products were obtained with moderate to good yields (50−80%), different

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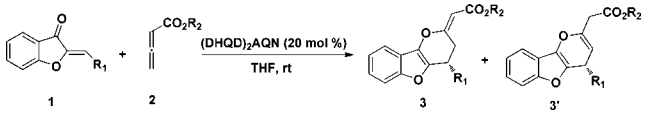
Table 2. Substrate Scope[a]



1 2 3 3'

entry	R_1	R_2	time (d)	yield (%)[b]	3/3'[c]	*ee* (3,%)[d]	*ee* (3',%)[d]
1	**1a**: Ph	**2a**: Et	5	90	10:7	**3a**: 99	**3a'**: 95
2	**1b**: 4-CH_3OPh	**2a**: Et	10	71	1:1	**3b**: 98	**3b'**: 93
3	**1c**: 4-CH_3Ph	**2a**: Et	7	83	5:2	**3c**: 98	**3c'**: 93
4	**1d**: 4-FPh	**2a**: Et	9	81	3:2	**3d**: 98	**3d'**: 96
5	**1e**: 4-ClPh	**2a**: Et	4	93	3:1	**3e**: 99	**3e'**: 97
6	**1f**: 4-BrPh	**2a**: Et	4	91	5:2	**3f**: 98	**3f'**: 97
7	**1g**: 4-CNPh	**2a**: Et	2	88	3:2	**3g**: 98	**3g'**: 98
8	**1h**: 3-ClPh	**2a**: Et	2	87	4:1	**3h**: 99	**3h'**: 97
9	**1i**: 3-BrPh	**2a**: Et	2	78	3:1	**3i**: 99	**3i'**: 98
10	**1j**: 3,4-diClPh	**2a**: Et	2	96	5:2	**3j**: 99	**3j'**: 98
11	**1k**: 2-OMePh	**2a**: Et	10	63	5:2	**3k**: 87	**3k'**: 95
12	**1l**: 2-ClPh	**2a**: Et	2	85	5:2	**3l**: 94	**3l'**: 87
13	**1m**: 2-Naphthyl	**2a**: Et	6	73	1:1	**3m**: 98	**3m'**: 96
14	**1n**: 2-Thienyl	**2a**: Et	13	52	2:3	**3n**: 99	**3n'**: 87
15	**1a**: Ph	**2b**: Me	8	50	1:1	**3o**: 99	**3o'**: 92
16	**1a**: Ph	**2c**: ^{i}Pr	6	80	6:1	**3p**: 99	**3p'**: 93
17	**1a**: Ph	**2d**: Bn	8	77	3:10	**3q**: 99	**3q'**: 91

[a]The reactions were conducted with 0.1 mmol of **1**, 0.15 mmol of **2**, and 20 mol % $(DHQD)_2AQN$ in 0.25 mL of THF at rt. [b]Isolated yields. No *Z*-isomer of cycloadduct was detected. [c]Determined by ^1H NMR of crude product. [d]Determined by chiral HPLC analysis.

levels of regioselectivities (up to 6:1), and excellent enantioselectivities (99% *ee* for **3o**−**3q** and 91−93% *ee* for **3o**′−**3q**′, entries 15−17 in Table 2). Moreover, we found that the methodology can work with more electron-deficient benzofuran-3-one alkenes. However, the *ee* values decreased dramatically (Figure 2).

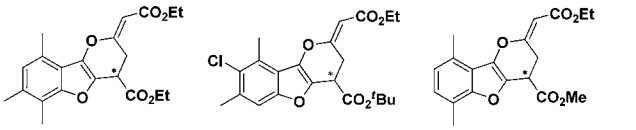


Figure 2. Result for more electron-deficient benzofuran-3-one alkenes.

In fact, the efficiency of the studied [4 + 2] cycloaddition is not satisfactory. In order to overcome this shortcoming, we also attempted to reduce to the catalyst loading with increasing temperature. As shown in Figure 3, the cyclization can be finished within 4 days; however, the inversion of the regioselectivity was observed. Furthermore, the enantioselectivity of the major product **3a**′ was decreased.

The absolute configuration of the products was assigned based on the crystallographic analysis. Taking advantage of the crystallinity of **3i** we obtained its crystallographic structure (Figure 4).[8] The absolute configurations of all the other products

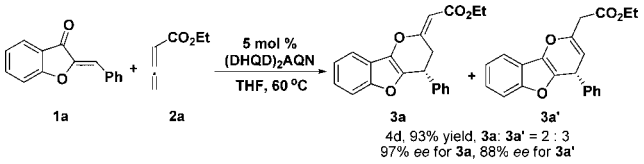


Figure 3. Result for the model reaction with 5 mol % catalyst at 60 °C.

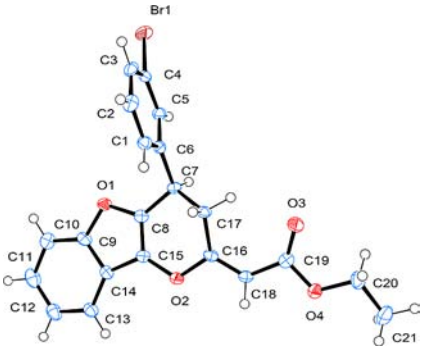


Figure 4. ORTEP diagram showing of compound **3i**.

were tentatively assigned by referring to that of **3i**. In light of this result, a plausible transition state is outlined in Figure 5. With the

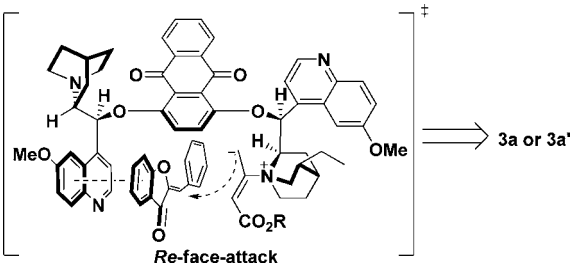


Figure 5. Plausible transition state.

catalyst in the open conformation, the 2-olefinic benzofuran-3-one, which was stabilized by the $\pi-\pi$ stacking between the phenyl ring of benzofuranone and the quinoline moiety, was attacked by the zwitterion intermediate resulting from the combination of allenoate and the nitrogen atom of the quinuclidine, from the *Re*-face to obtain the highly enantioselective products. Nevertheless, further study should be required to elucidate the mechanism.

The utility of the [4 + 2] cycloaddition reaction was further demonstrated by transformations of the cyclization products. As outlined in Figure 6, **3i** can be easily reduced to **5** by DIBAL-H in moderate yield and retentive enantioselectivity. Subsequent esterification between **5** and 4-nitrobenzoyl chloride afforded **6** in good yield with continuous high enantioselectivity. Moreover, under the conditions of Pd/C and H_2, **3a** can also be reduced to **7**.

In conclusion, we have developed an asymmetric [4 + 2] cycloaddition reaction of allenoates with 2-olefinic benzofuran-3-ones via tertiary-amine type Lewis base catalysis. The cyclization strategy was quite successful, which enabled the construction of an all carbon tertiary chiral center in dihydropyran-fused benzofuran. As a result, a series of chiral dihydropyran fused benzofuran derivatives were obtained in moderate regioselectivities and excellent enantioselectivities.

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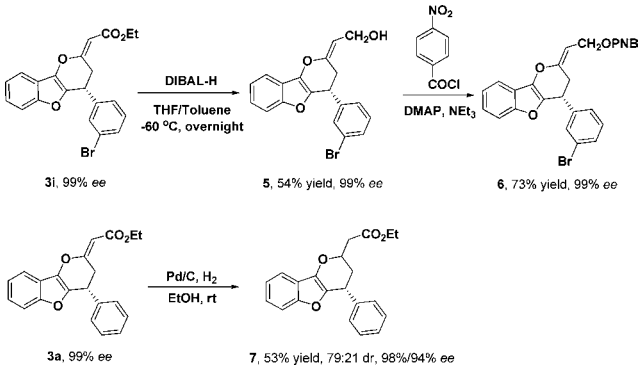

Figure 6. Tansformations of the products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^{1}H NMR, ^{13}C NMR, and HRMS spectra for new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) CCDC 1035258 contains the supplementary crystallographic data for compound **3i**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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