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Highly Enantioselective Michael Addition Reactions of 3-Substituted Benzofuran-2(3*H*)-ones to Chalcones Catalyzed by a Chiral Alkyl-Substituted Thiourea

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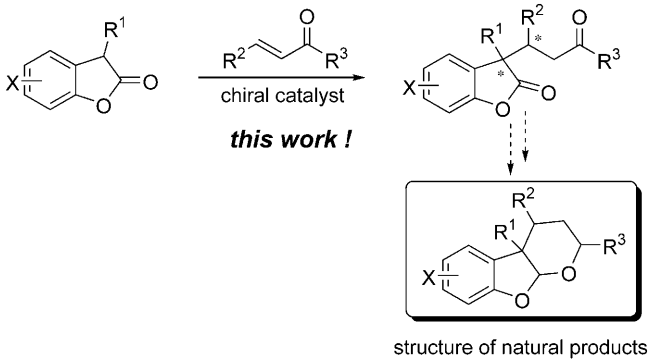
Abstract: A highly enantioselective Michael addition of 3-substituted benzofuran-2(3*H*)-ones to chalcones catalyzed by a chiral bifunctional thiourea was developed. Several chiral 3,3′-substituted benzofuran-2(3*H*)-ones derivatives, bearing adjacent quaternary-tertiary stereocenters, were efficiently synthesized with excellent enantioselectivities.

Keywords: benzofuran-2(3*H*)-ones; chiral thioureas; Michael addition; organocatalysis; quaternary-tertiary stereocenters

Asymmetric conjugate addition reactions with carbon nucleophiles, which represent one of the most versatile C–C bond transformations, have been very successful in creating molecular complexity with high stereocontrol.[1] Despite many notable advances in this area, an efficient and stereoselective conjugate addition reaction that generates adjacent quaternary-tertiary stereocenters still poses a formidable challenge in asymmetric catalysis.[2] One such synthetic challenge is to stereoselectively construct benzofuran-2(3*H*)-one-type lactones bearing a quaternary stereocenter at the 3-position. This type of structural motif is widely distributed in a number of bioactive compounds such as radulifolin,[3a] 3-hydroxycacalolide,[3b] daphnodorins A–F,[4] macrophyllols A and B,[5] licoagrodin[6] and erysenegalensein J.[7] Due to their biological and medicinal activities and unique structural features, these natural products have been of interests in total synthesis.[8] Retrosynthetically, asymmetric conjugate addition reactions of 3-substituted benzofuran-2-ones would serve as potentially key chiral transformations for the synthesis of these benzofuranone-containing structures with all-carbon quaternary centers at the 3-position (Scheme 1). Unfortunately, this type of reaction, to the best of our knowledge, has not been reported so far.



Scheme 1. Synthetic route to benzofuro[2,3-*b*]pyran derivatives.

Recently, we have developed a simple alkyl-substituted thiourea catalyst *via* electronic scanning and its potential has been successfully demonstrated in the synthesis of oxindole compounds with all-carbon quaternary centers.[9a,b] In our continuing efforts on the construction of potentially bioactive compounds by asymmetric catalysis,[9] we were delighted to find that this alkyl-substituted thiourea catalyst is also a very effective catalyst for the Michael addition reaction of 3-substituted benzofuran-2-ones to chalcones. Herein, we report the first asymmetric Michael addition reactions of 3-substituted benzofuran-2(3*H*)-ones.

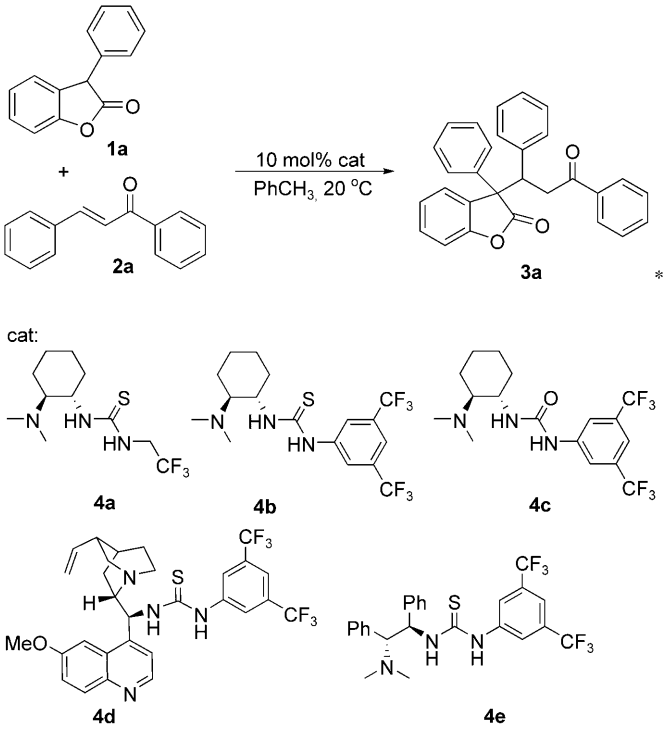
The Michael addition reaction of 3-phenylbenzofuran-2(3*H*)-one **1a** to chalcone **2a** was selected as our initial test reaction. Five widely used bifunctional tertiary-amine thioureas/urea **4a**–**4e** with different chiral scaffolds[10,11] were screened in the model reaction at 20 °C in toluene. To our delight, all of the catalysts exhibited high catalytic activities and the Michael addition products were isolated with very good yields (Table 1, entries 1–5). Although the diastereoselectivities are generally low (1.3:1–1.1:1), the enantioselectivities are acceptable with 56–92% *ee* for the major diastereomers and 38–87% *ee* for the minor diastereomers. Among the thiourea catalysts examined, the alkyl-substituted thiourea **4a** was found to give the best enantioselectivity (93% yield, 1.2:1 *dr* and 92/87% *ee*, Table 1, entry 1).

The reaction was next optimized by screening solvent, temperature and additive in the presence of 10 mol% of **4a**. It was found that the reaction in the initially selected solvent toluene gave the best results (Table 1, entries 1 and 6–11). The addition of 4 Å molecular sieves to the reaction mixture slightly increased both the yield and stereoselectivity (Table 1, entry 12). Further improvement could be achieved by lowering the reaction temperature (Table 1, entry 13). Collectively, the best results with respect to yield and enantioselectivity were obtained by performing the reaction at −20 °C in toluene in the presence of 4 Å molecular sieves, affording **3a** in 95% yield, 3:2 *dr* and 97/94% *ee* (Table 1, entry 14). Although the diastereoselectivity is rather poor under the conditions and efforts for further improvements were in vain, it is worthy of note that the diastereoisomers are easily separated with excellent enantioselectivity, thus providing readily two structurally complex and valuable chiral benzofuran-2(3*H*)-one-type products.

Under the optimized conditions, the substrate scope was next explored (Table 2). The reactions were shown to work well with a range of chalcones bearing either electron-withdrawing or electron-donating substituents (Table 2, entries 4–17). In all these cases, the corresponding products were obtained in high yields (80–99%), with moderate diastereoselectivities (1:1–3:1) and excellent enantioselectivities (78–98% *ee* for major diastereomers and 81–95% *ee* for minor diastereomers). Two differently substituted 3-arylbenzofuran-2(3*H*)-ones were also investigated. Similarly, the desired Michael products were obtained with good yields and high enantioselectivities for both diastereomers in spite of low diastereoselectivities (Table 2, entries 2 and 3).

We obtained the X-ray crystal structures of products **3j** and **3p′** (Figure 1),[12] which proved the absolution configurations for **3** and **3′** as depicted in Figure 1. The absolute configurations of other products can therefore be determined by analogy. A bifunctional catalytic mode in accodance with previous studies was proposed to account for the observed stereoselectivities.[10,11] Accordingly, the formaiton of diastereoisomers **3** and **3′** can be rationalized by considering ternary transition states **TS-I** and **TS-II**, respectively. The less face-differentiation of enolate in **TS-I**

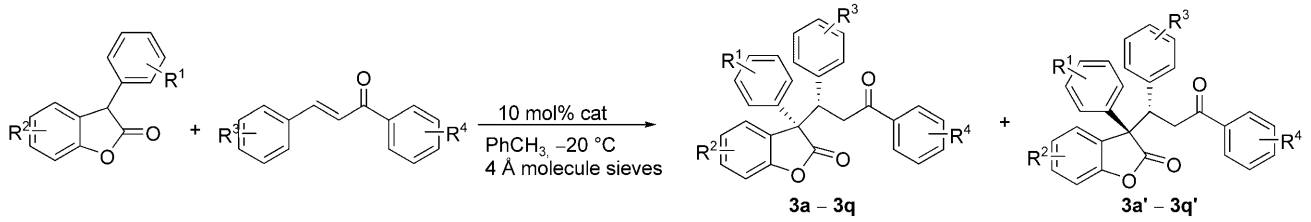
Table 1. Screening of different thiourea catalysts.[a]



Entry	cat	Solvent	Time [h]	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	**4a**	toluene	4	93	1.2:1	92/87
2	**4b**	toluene	4	94	1.2:1	83/74
3	**4c**	toluene	4	90	1.2:1	56/38
4	**4d**	toluene	4	95	1.1:1	77/81
5	**4e**	toluene	4	86	1.3:1	78/71
6	**4a**	CH_2Cl_2	4	92	1.6:1	85/86
7	**4a**	$CHCl_3$	4	82	1.2:1	89/81
8	**4a**	DCE	4	81	1.3:1	83/89
9	**4a**	benzene	4	93	1.2:1	90/85
10	**4a**	xylene	4	94	1.2:1	90/86
11	**4a**	THF	4	65	1:1	85/89
12	**4a**[e]	toluene	4	96	1.3:1	93/88
13	**4a**[f]	toluene	36	94	3:2	95/93
14	**4a**[g]	toluene	48	95	3:2	97/94

[a] The reaction was carried out on a 0.1 mmol scale in 400 μL solvent at 20 °C, and the molar ratio of **1a**/**2a** was 1/2.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.
[e] Reaction at 20 °C.
[f] Reaction at −10 °C.
[g] Reaction at −20 °C.

Table 2. Substrate scope.[a]



Entry	R^1	R^2	R^3	R^4	Reaction time [h]	Yield[b] [%]	*dr*[c] (**3**:**3′**)	*ee*[d] [%] (**3**/**3′**)
1	H	H	H	H	48	**3a** (**3a′**): 95	3:2	97/94
2	H	4-CH_3	H	H	36	**3b** (**3b′**): 92	2:1	97/90
3	4-Cl	H	H	H	36	**3c** (**3c′**): 91	3:2	98/96
4	H	H	4-CH_3O	H	84	**3d** (**3d′**): 80	1:1	97/93
5	H	H	4-CH_3	H	72	**3e** (**3e′**): 89	3:2	94/92
6	H	H	4-Ph	H	72	**3f** (**3f′**): 85	3:2	97/95
7	H	H	4-Cl	H	48	**3g** (**3g′**): 93	1:1	98/92
8	H	H	3-Cl	H	60	**3h** (**3h′**): 98	3:2	98/91
9	H	H	2-Cl	H	60	**3i** (**3i′**): 92	1:1	89/84
10	H	H	2-Br	H	60	**3j** (**3j′**): 91	1:1	78/83
11	H	H	H	4-F	54	**3k** (**3k′**): 91	2:1	96/92
12	H	H	H	4-Cl	48	**3l** (**3l′**): 94	2:1	96/81
13	H	H	H	3-Cl	48	**3m** (**3m′**): 99	2:1	97/94
14	H	H	H	4-Br	48	**3n** (**3n′**): 91	3:2	97/86
15	H	H	H	4-CF_3	72	**3o** (**3o′**): 80	2:1	97/94
16	H	H	3-Cl	4-Br	48	**3p** (**3p′**): 95	3:1	97/94
17	H	H	3-Cl	3-Cl	48	**3q** (**3q′**): 96	2:1	98/91

[a] The reaction was carried out on a 0.1 mmol scale with 40 mg 4 Å molecular sieves in 400 μL toluene at −20 °C, and the molar ratio of 3-arylbenzofuran-2(3*H*)-ones/chalcones was 1/2.
[b] Isolated yield.
[c] Determined by ^{1}H NMR or based on isolated yields.
[d] Determined by chiral HPLC.

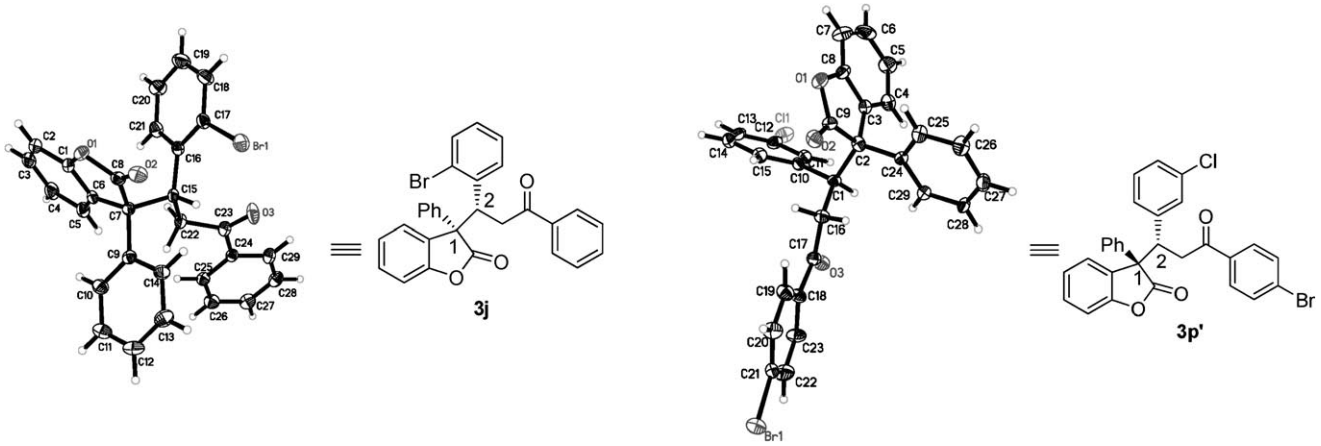
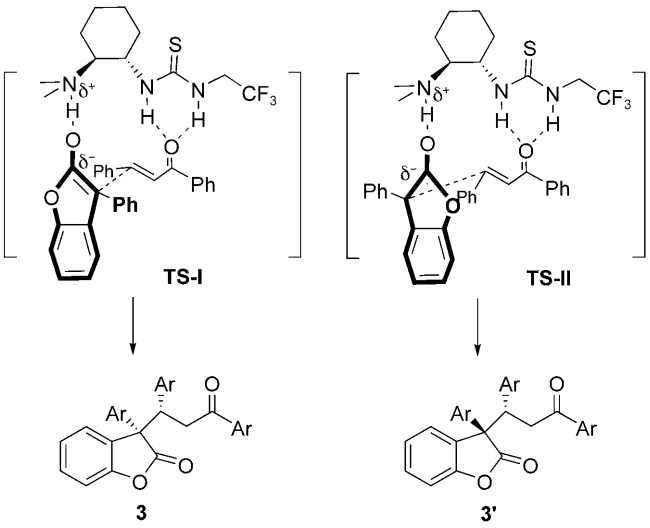


Figure 1. X-ray crystal structures of **3j** and **3p′**.

and **TS-II** might be a reason for the low diastereoselectivity (Scheme 2).

Some other electrophiles, such as activated terminal alkenes and nitrostyrene, were also attempted in this study (Scheme 3). The addition reactions of 3-phenylbenzofuran-2(3*H*)-one to vinyl ketones including methyl vinyl ketone, ethyl vinyl ketone and phenyl vinyl ketone worked well to give the desired products in high yields with unfortunately low enantioselectivity (**5**: 95% yield and 27% *ee*; **6**: 82% yield and 7% *ee*; **7**: 78% yield and 0% *ee*).[13] In the reaction of 3-phenylbenzofuran-2(3*H*)-one to phenyl vinyl sulfone,



Scheme 2. Proposed transition states.

Michael product **8** was obtained after 7 days with 80% yield and 35% *ee* at 0 °C in toluene. 2-Chloroacrylonitrile could also be applied to give Michael adduct **9** bearing 1,3-non-adjacent stereocenters with 60% *ee*. In the case of nitrostyrene, although the reaction was very fast, no stereoselectivity was observed (Scheme 3, product **10**).

In conclusion, we have developed a highly enantioselective Michael addition reaction of 3-arylbenzofuran-2(3*H*)-ones to chalcones by a simple alkyl-substituted bifunctional thiourea catalyst. The reactions work with a broad range of chalcones, giving chiral 3,3′-substituted benzofuran-2(3*H*)-one-type compounds with adjacent quaternary-tertiary stereocenters in high yields (up to 99%), moderate *dr* (up to 3:1) and excellent *ee* (up to 98%). Further studies on the exploration and application of the current reaction in asymmetric catalysis and synthesis are ongoing in our laboratory.

Experimental Section

General Experimental Procedure for the Michael Reaction

To a stirred solution of 3-arylbenzofuran-2(3*H*)-one (0.1 mmol) and chalcone (2.0 equiv.) with 40 mg 4 Å molecular sieves in dry toluene (400 μL) was added the thiourea catalyst (0.1 equiv.) at −20 °C. After the reaction was complete, the reaction solution was concentrated under vacuum and the crude material was purified by flash chromatography to afford the desired product.

Acknowledgements

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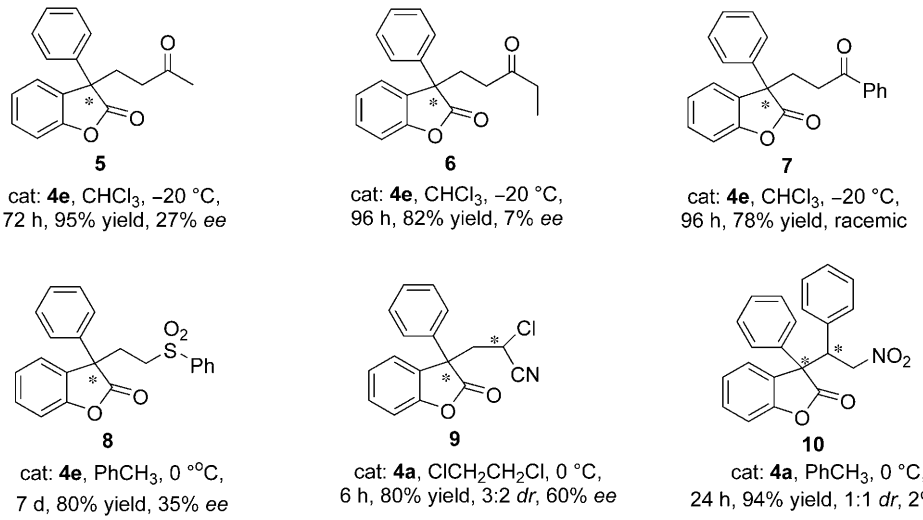

Scheme 3. Experimental results with other Michael acceptors.

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[12] CCDC 763977 and CCDC 763976 contain the supplementary crystallographic data for compounds **3j** and **3p′**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details of the crystallographic data of **3j** and **3p′** see also Tables S1 and S2 in the Supporting Information.

[13] For details of optimization of the reaction conditions see Table S3 in the Supporting Information.

