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Chiral Amine Thiourea-Promoted Enantioselective Michael Addition Reactions of 3-Substituted Benzofuran-2(3*H*)-ones to Maleimides

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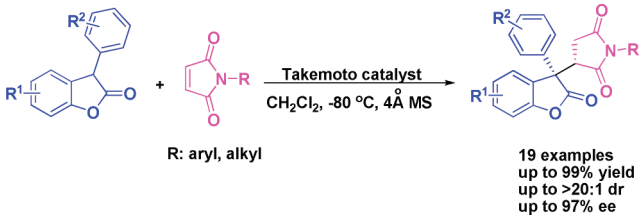
Received September 22, 2010



A highly diastereo- and enantioselective Michael addition reaction with respect to prochiral 3-substituted benzofuran-2(3*H*)-ones and maleimides by a chiral bifunctional thiourea−tertiary amine catalyst was investigated. The corresponding adducts, containing a quaternary center at the C3-position of the benzofuran-2(3*H*)-one as well as a vicinal tertiary center, were generally obtained in high yields (up to 99%) with very good diastereo- (up to >20:1 dr) and enantioselectivities (up to 97% ee).

Asymmetric conjugate addition reactions with carbon nucleophiles, which is one of the most powerful and versatile processes for the formation of C−C bonds in organic synthesis, have been successfully used in creating molecular complexity with high stereocontrol.[1] As a result, a wide variety of compounds that can serve as electrophiles and nucleophiles and, consequently, a diverse array of products can be generated with versatile structures by rational design. Despite many notable advances in this arena, an efficient and stereoselective conjugate addition reaction that generates adjacent quaternary−tertiary stereocenters is still one of the most difficult challenges in asymmetric catalysis,[2] in which the whole catalysis is a tandem conjugate addition−protonation process with simultaneous control of two stereocenters.

Over the past 10 years, significant efforts have been directed toward to the development of asymmetrically synthetic methodology for this challenging area.[3,4] In a particularly valuable context, conjugate addition of 3-substituted oxindoles to appropriate electrophiles promoted by organocatalysts provides a very straightforward approach to access oxindole-type derivatives bearing two adjacent quaternary−tertiary stereocenters,[4] whose structural motifs are ubiquitous in a wide range of biologically and pharmaceutically active natural alkaloids.[5] However, the 3-substituted benzofuran-2(3*H*)-ones, whose structures are very similar to the 3-substituted oxindoles, have been rarely considered as nuclephiles in asymmetric catalysis. It should be pointed out that the conjugate addition products by such a process use 3-substituted benzofuran-2(3*H*)-ones as nucleophiles, which have quarternary chiral centers at the C3-position of benzofuran-2(3*H*)-ones, would serve as key structural motifs that are ubiquitous in a number of biologically active heterocyclic compounds (Figure 1), such as radulifolin,[6] 3-hydroxycacalolide,[7] daphnodorins A−F,[8]

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DOI: 10.1021/jo101832e Published on Web 11/24/2010

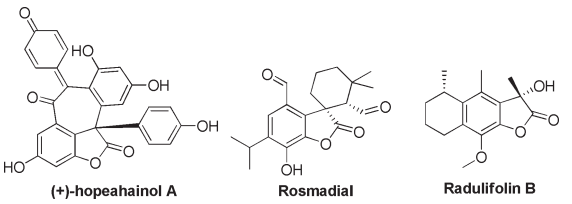


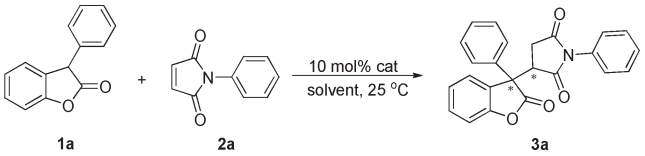
FIGURE 1. Benzofuran-2(3*H*)-one-type natural products with quarternary chiral centers at the C3-positions.

macrophyllols A and B,[9] licoagrodin,[10] erysenegalensein J,[11] and hopeahainol A.[12] In this context, organocatalysis for the synthesis of chiral 3,3-disubstituted benzofuran-2(3*H*)-ones has been scarcely studied.[13,14] Discovering electrophiles to react with prochiral 3-substituted benzofuran-2(3*H*)-ones for the synthesis of diversely structured 3,3-disubstituted benzofuran-2(3*H*)-ones should be a direct and valuable strategy and is strongly desired.

Very recently, we reported the first asymmetric Michael addition reaction of 3-substituted benzofuran-2(3*H*)-ones, in which a chiral bifunctional thiourea-catalyzed addition of 3-substituted benzofuran-2(3*H*)-ones with chalcones was conducted.[13] Owing to the synthetic importance of chiral 3,3-disubstituted benzofuran-2(3*H*)-ones derivatives, and based on our continuing interest in the construction of potentially bioactive compounds by asymmetric catalysis,[15] herein we disclose an asymmetric conjugate addition of 3-substituted benzofuran-2(3*H*)-ones and maleimides[16] promoted by a bifunctional tertiary-amine thiourea catalyst to give a new range of 3,3′-disubstituted benzofuran-2(3*H*)-one derivatives bearing vicinal quaternary−tertiary carbon centers in high yields and with very good diastereo- and enantioselectivities.

We initiated our study by investigating the Michael addition reaction of benzofuran-2(3*H*)-one **1a** to maleimide **2a**

TABLE 1. Optimization of Reaction Conditions[a]



entry	cat.	solvent	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**4a**	toluene	24	nr[e]	nd[f]	nd[f]
2	**4b**	toluene	2	75	1.5:1	0
3	**4c**	toluene	2	90	3:1	71
4	**4d**	toluene	2	99	7:1	81
5	**4e**	toluene	2	92	5:1	78
6	**4f**	toluene	2	99	5:1	66
7	**4g**	toluene	2	85	5:1	−67
8	**4d**	CH_2Cl_2	2	99	9:1	83
9	**4d**	$CHCl_3$	2	98	4:1	72
10	**4d**	DCE	2	95	6:1	80
11	**4d**	benzene	2	96	7:1	78
12	**4d**	xylene	2	95	8:1	82
13	**4d**	THF	2	90	4:1	64
14	**4d**[g]	CH_2Cl_2	8	97	15:1	87
15	**4d**[h]	CH_2Cl_2	24	96	19:1	90
16	**4d**[i]	CH_2Cl_2	48	93	>20:1	94
17	**4d**[j]	CH_2Cl_2	48	98	>20:1	96

[a]The reaction was carried out on a 0.1 mmol scale in 400 μL of solvent at 25 °C, and the molar ratio of **1a**/**2a** is 1/2. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC. [e]No reaction. [f]Not determined. [g]The reaction was carried out under the general conditions at −20 °C. [h]The reaction was carried out under the general conditions at −40 °C. [i]The reaction was carried out under the general conditions at −80 °C. [j]The reaction was carried out under the general conditions with 4 Å molecular sieves at −80 °C.

(Table 1). A brief survey of the single hydrogen-bonding catalyst failed, providing none of the desired addition product when used with a catalytic amount of thiourea **4a**[17] (Table 1, entry 1). We postulated that bifunctional tertiary-amine hydrogen-bonding compounds would serve as mild catalysts for the activation of both the benzofuran-2(3*H*)-one and maleimide, thereby promoting the reaction. Indeed, the use of **4b**[18] provided the desired addition product **3a** in 75% yield in toluene after 2 h reaction time (Table 1, entry 2).

Encouraged by these preliminary results, we explored the use of available chiral bifunctional hydrogen-bonding catalysts. Five widely used bifunctional tertiary-amine thioureas or urea catalysts **4c**−**g**[19,20] (Figure 2) with different scaffolds were screened in the model reaction at 25 °C. To our delight, most of the catalysts exhibited high catalytic activities, and the Michael products were isolated with good to excellent

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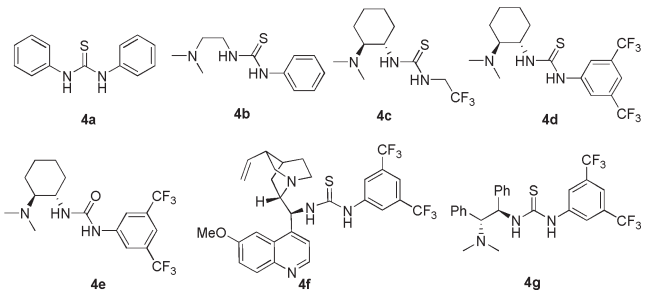
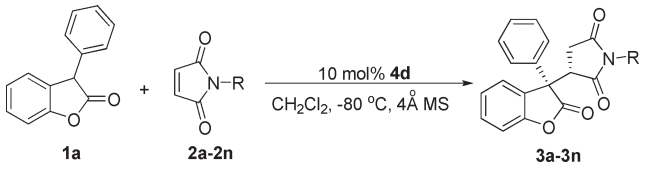


FIGURE 2. Bifunctional tertiary amine thioureas and urea catalysts.

TABLE 2. Substrate Scope[a]



entry	substrate: R =	time (h)	yield[b] (%)	dr[c]	ee[d](%)
1	**2a**: Ph	24	**3a**: 98	>20:1	96
2	**2b**: 4-MeOPh	48	**3b**: 91	16:1	93
3	**2c**: 4-MePh	48	**3c**: 95	>20:1	95
4	**2d**: 4-*t*-BuPh	48	**3d**: 96	>20:1	92
5	**2e**: 4-FPh	48	**3e**: 93	>20:1	93
6	**2f**: 4-ClPh	24	**3f**: 98	>20:1	94
7	**2g**: 3-ClPh	24	**3g**: 99	>20:1	94
8	**2h**: 4-BrPh	24	**3h**: 99	>20:1	92
9	**2i**: 3-BrPh	24	**3i**: 98	>20:1	95
10	**2j**: 3-Cl(4-Me)Ph	24	**3j**: 94	15:1	91
11[e]	**2k**: 2,4,6-triMePh	48	**3k**: 88	6:1	74
12[e]	**2l**: Bn	48	**3l**: 92	7:1	91
13[e]	**2m**: cyclohexyl	48	**3m**: 97	15:1	97
14[e]	**2n**: octanyl	48	**3n**: 95	16:1	95

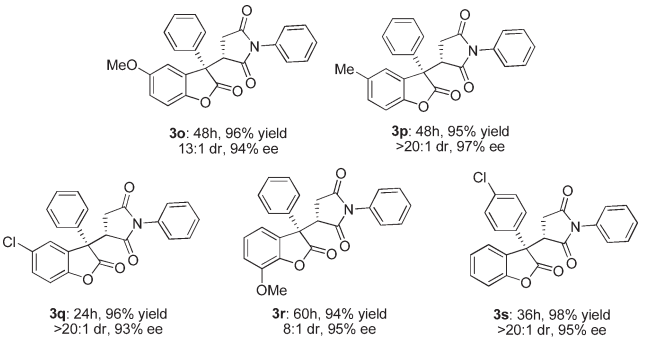
[a]The reaction was carried out on a 0.1 mmol scale in 400 μL of CH_2Cl_2 with 4 Å molecular sieves at −80 °C, and the molar ratio of **1a**/**2** is 1/2. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC. [e]The reaction was carried out on the optimized conditions at −40 °C.

yields (85−99%) and moderate stereoselectivities (3:1−7:1 dr and 66−81% ee, Table 1, entries 2−6). Among the five bifunctional hydrogen-bonding catalysts examined, Takemoto catalyst **4d** was found to give the optimal stereoselectivity (Table 1, entry 4, 99% yield, 7:1 dr and 81% ee).

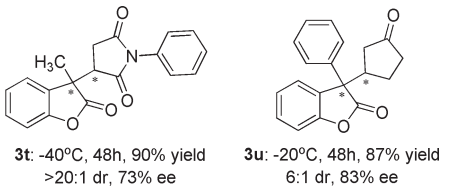
The reaction was then optimized by screening solvent, temperature, and additive in the presence of 10 mol % of **4d**. As illustrated in Table 1, dichloromethane (CH_2Cl_2) gave the best result among a range of screened solvents (Table 1, entries 4 and 8−13). Further improvement could be achieved by lowering the reaction temperature (Table 1, entries 14−16). Addition of 4 Å molecular sieves to the reaction mixture slightly increased both the diastereoselectivity and enantioselectivity (Table 1, entry 17). Collectively, the best results with respect to yield and stereoselectivity were obtained by performing the reaction at −80 °C in CH_2Cl_2 in the presence of 4 Å molecular sieves. Under these conditions, the reaction provided the desired product with 98% yield in >20:1 dr and 96% ee (Table 1, entry 17).

With these conditions decided, we then turned our attention toward the scope of the reaction as summarized in Table 2. The reactions were shown to work well with a number of *N*-aryl-substituted maleimides bearing either electron-withdrawing or electron-donating substituents (Table 2, entries 1−11). In most cases, the corresponding products were obtained in high yields (91−99%), with moderate to very good diastereoselectivities (15:1 → 20:1dr) and very good enantioselectivities (91−96% ee). However, the yield and stereoselectivity of the reaction are sensitive to the substitution position of the aryl group. Lower reactivity and selectivity were obtained when *N*-2,4,6-triMePh-substituted maleimide **2k** was selected as the Michael acceptor (Table 2, entry 11). As a result, the corresponding conjugate addition product **3k** was obtained in 88% yield with 6:1 dr and 74% ee.

SCHEME 1. Results of Michael Addition Reactions of Five Different Substituted Benzofuran-2(3*H*)-ones and Maleimide 2a



SCHEME 2. Results of Michael Addition Reactions of 3-Methyl-Substituted Benzofuran-2(3*H*)-one with 2a and 1a with 2-Cyclopenten-1-one



Furthermore, three *N*-alkyl-substituted maleimides were also examined as electrophiles in the current Michael addition strategy (Table 2, entries 12−14). We found that the *N*-alkyl-substituted maleimides **2l**−**n** proved to be less reactive and required a higher reaction temperature. After further optimization, −40 °C was used to desired the reaction rate. However, the stereoselectivities were still satisfied, in which the desired conjugate products **3l**−**n** were obtained with 92−97% yield, 7:1−16:1 dr, and 91−97% ee (Table 2, entries 12−14).

We also explored the influence of Michael donor. A number of benzofuran-2(3*H*)-ones, which have different substitution patterns and positions, were reacted with maleimide **2a** under the optimized conditions, and the results are shown in Scheme 1. To our delight, the desired Michael products **3o**−**s** were similarly obtained with high yields (94−98%), moderate to very good diastereoselectivities (8:1→20:1 dr), and very good enantioselectivities (93−97% ee).

To further expand the substrate scope, reactions of 3-methyl benzofuran-2(3*H*)-one as nuclephile to react with **2a** and 2-cyclopenten-1-one as electrophile to react with **1a** were also attempted in this study (Scheme 2). To our delight, both reactions proceeded smoothly and provided the desired products in good yields with good selectivities (90% yield, >20:1 dr and 73% ee for **3t**; 87% yield, 6:1 dr and 83% ee for **3u**).

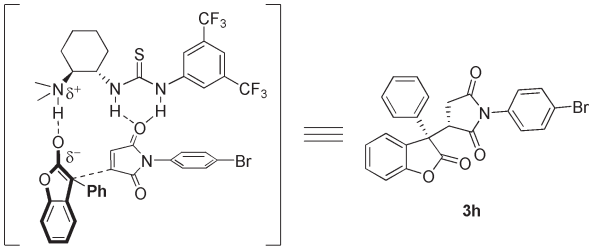
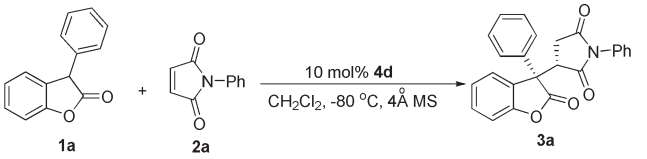


FIGURE 3. Proposed transition state.

SCHEME 3. Reaction Carried out on a Large Scale



We obtained the X-ray crystal structure of product **3h** (Figure S1, Supporting Information),[21] which proved the absolute configuration for **3h**. The absolute configurations of other products can therefore be determined by analogy.

A bifunctional catalytic mode in accordance with previous studies was proposed to account for the observed stereoselectivities (Figure 3).

To investigate the synthetic potential of current Michael strategy, 3-phenylbenzofuran-2(3*H*)-one **1a** (5 mmol, 1.05 g) and maleimide **2a** (10 mmol, 1.73 g) were reacted under the optimal conditions, and the corresponding product was obtained without any loss of yield (1.89 g, 99% yield) or selectivity (> 20:1 dr and 96% ee, Scheme 3).

In summary, we have presented a highly diastereoselective and enantioselective Michael addition reaction of 3-substituted benzofuran-2(3*H*)-ones to maleimides by simple bifunctional tertiary-amine thiourea organocatalyst. The reaction scope is substantial, and a number of aryl- or alkylmaleimides and 3-substituted benzofuran-2(3*H*)-ones could be successfully applied to give multifunctional chiral benzofuran-2(3*H*)-ones compounds bearing an adjacent all carbon-substituted quaternary stereocenter and a tertiary stereocenter with very good enantioselectivities. Our current work is actively underway to utilize versatile benzofuran-2(3*H*)-ones as nucleophiles with chiral organocatalysts for asymmetric catalysis.

(21) CCDC 787619 contains the supplementary crystallographic data for compound **3h**. This 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 **3h**, see Table S1 in the Supporting Information.

Experimental Section

General Experimental Michael Reaction Procedure. To a stirred solution of 3-phenylbenzofuran-2(3*H*)-one (0.1 mmol) and maleimide (2.0 equiv) with 40 mg of 4 Å molecular sieves in 400 μL of dry CH_2Cl_2 was added amine thiourea catalyst (0.1 equiv) at −80 °C After the reaction was completed, the reaction solution was concentrated in vacuo and the crude was purified by flash chromatography to afford the product.

Compound 3a. The Michael product was synthesized according to the general procedure as a white solid in 98% overall yield: $[\alpha]^{25}_D$ −103.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.16 (14H, m), 4.32−4.27 (1H, m), 3.06−2.97 (1H, m), 2.50−2.42 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.8, 174.1, 173.3, 153.5, 135.8, 131.4, 130.6, 129.2, 129.1, 128.8, 128.5, 127.0, 126.3, 125.4, 125.1, 111.7, 56.2, 46.3, 32.2 ppm; IR (KBr) ν 1716, 1620, 1597, 1499, 1186, 696 cm^{-1}; HRMS (EI$^+$) calcd for $C_{24}H_{17}NO_4$ 383.1158, found 383.1161. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol/hexane = 3:7), 1.0 mL/min; t_R = 15.2 min (major), 22.8 min (minor).

Acknowledgment. This work was supported by the Natural Science Foundation (Grant Nos. 20721062, 20702052, and 20902091) and MOST (2009ZX09501-018 and 2010CB833301). X.L. thanks the China Postdoctoral Science Foundation for support and the reviewers for helpful suggestions on this work.

Supporting Information Available: Experimental details, analytical data for all new compounds, and X-ray crystallography of **3h**. This material is available free of charge via the Internet at http://pubs.acs.org.