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Asymmetric Construction of Spirocyclopentenebenzofuranone Core Structures via Highly Selective Phosphine-Catalyzed [3 + 2] Cycloaddition Reactions

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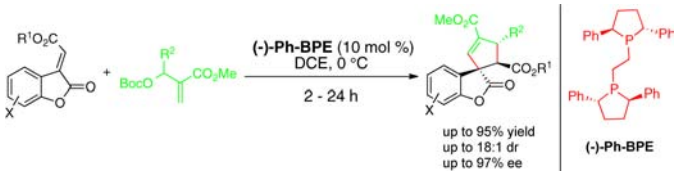
ABSTRACT



An efficient organocatalytic asymmetric [3 + 2] cycloaddition reaction between 3-substituted methylenebenzofuranone derivatives and diverse Morita–Baylis–Hillman carbonates to provide complex polysubstituted spirocyclopentenebenzofuranone scaffolds in a single step is reported. C2-symmetric phospholanes were efficient nucleophilic catalysts of this transformation under mild conditions, providing reaction products comprised of three consecutive stereocenters, including one all-carbon center, with excellent enantioselectivity.

Even though tremendous progress has been made in the construction of complex chemical structures, the rapid and selective assembly of complex asymmetric molecules from simple precursors remains a challenge in asymmetric synthesis. The spirocyclobenzofuranone motif (Figure 1) is prevalent in many natural products that have wide-ranging biological activities. For example, abiesinol E is a member of the spiro-biflavonoid family with antitumor-initiating effects,[1] while bis-diterpene ferrubietolide, isolated from *Dysoxylum lenticellare*, a member of the mahogany family, is a pesticide.[2] The high density of substituents on the spirocyclic ring, often including all-carbon quaternary chiral centers, makes the asymmetric assembly of these molecules a challenging task. There are but a few examples, typically single compound examples, concerning the catalytic asymmetric construction of spirocyclobenzofuranone scaffolds.[3] To the best of our knowledge, methods for highly selective catalytic asymmetric assembly of diverse spirocyclopentanebenzofuranone core structures have not been disclosed.

Recently, organocatalytic cascade or domino reactions have been used for the rapid construction of numerous pharmaceuticals, natural products, and synthetically valuable

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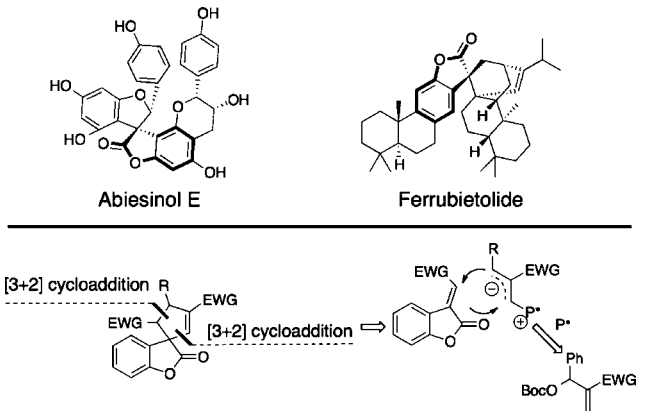

Figure 1. Natural products with spirocyclopentanone core structure and strategy for the assembly of this scaffold.

chiral building blocks.[4] A number of transformations have been disclosed involving chiral phosphine catalysts,[5] and a few examples of asymmetric construction of complex structures, such as spirocyclic scaffolds equipped with several chiral centers, have been reported.[6] Recently, our laboratory became interested in the asymmetric construction of elaborate spirocyclic oxindole skeletons,[7] and we disclosed a phosphine-catalyzed [3 + 2] cycloaddition reaction to construct spirocyclopenteneoxindoles through a modified allylic phosphonium ylide strategy.[6c]

We hypothesized that the spirocyclobenzofuranone scaffold could be constructed from 3-substituted methylenebenzofuranones and a phosphonium ylide, derived from Morita–Baylis–Hillman carbonates (MBHC)[8,6b–e] under chiral phosphine catalysis (Figure 1). Herein we report a highly stereoselective phosphine-catalyzed [3 + 2] cycloaddition reaction that enabled us to construct a wide range of spirocyclopentenebenzofuranone core structures in a single step from easily accessible starting materials in high yield and selectivity.

We commenced our investigation by probing several C_2-symmetric phosphine catalysts (**I**–**VII**) and phosphine-containing ligands (Figure 2) in a model reaction of 3-substituted benzofuranone **1a** and MBHC **2a** in dichloromethane (DCM) at room temperature (Table 1). Phospholane derivatives **I**–**VI** provided the desired cycloaddition product **3a** in excellent yield and moderate to good selectivity (Table 1, entries 1–4). Bis-2,5-dimethyl-substituted 1,2-ethandiylphospholane **I**[9] provided **3a** in 68% enantiomeric excess (ee) after 4 h. In reactions of the sterically more hindered 2,5-bis-ethyl- and 2,5-bis-isopropyl-containing derivatives (**II** and **III**),[9] the enantioselectivities were 77% (for **II**, Table 1, entry 2) and 86% (for **III**, Table 1, entry 3), respectively. Bis-2,5-diphenyl-substituted 1,2-ethandiylphospholane **IV**[10] provided the cycloaddition product **3a** in a diastereomeric ratio (dr) of 8:1 and in 94% ee after 4 h at room temperature.

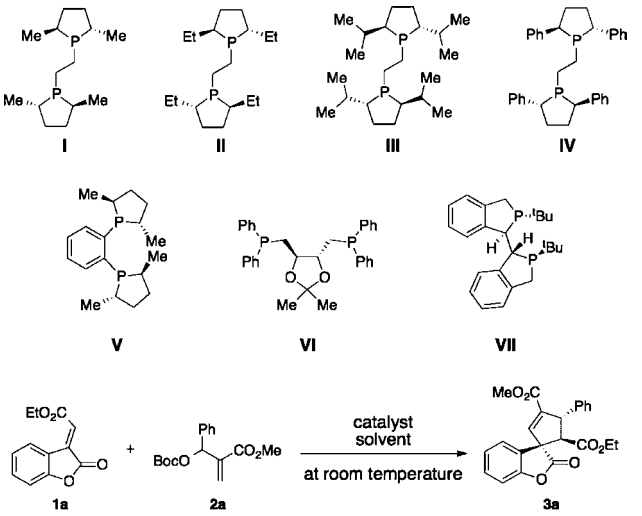

Figure 2. Chiral phosphine catalysts probed in the [3 + 2] cycloaddition reaction between **1a** and **2a**.

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Table 1. Catalyst Screen and Optimization Studies[a]

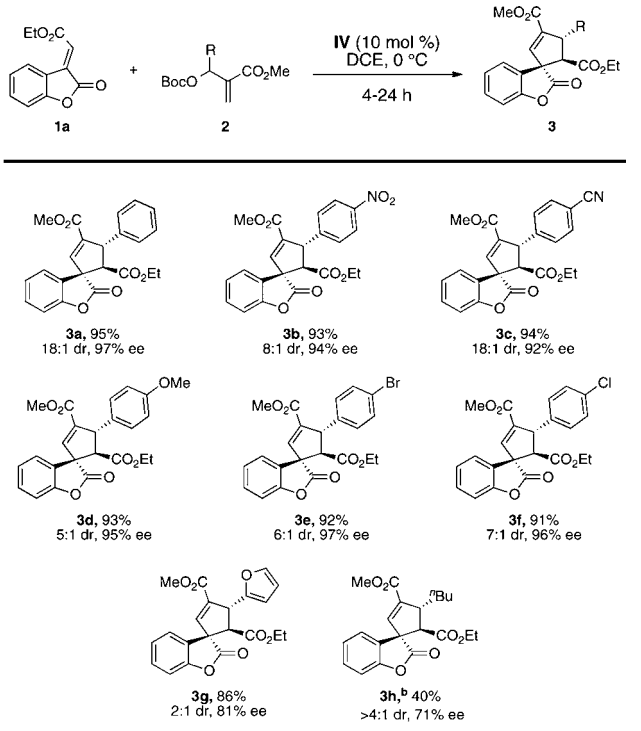
entry	catalyst mol (%)	catalyst loading (mol %)	solvent	time (h)	yield[b] (%)	dr[c] (%)	ee[d] (%)
1	**I**	20	DCM	4	99	n.d.	68
2	**II**	20	DCM	4	99	n.d.	77
3	**III**	20	DCM	4	99	n.d.	86
4	**IV**	20	DCM	4	99	8:1	94
5	**V**	20	DCM	24	20	n.d.	−50
6	**VI**	20	DCM	24	25	n.d.	0
7	**VII**	20	DCM	24	<5	n.d.	31
8	**IV**	20	DCE	4	99	9:1	94
9[e]	**IV**	20	DCE	4	99	9:1	98
10[e]	**IV**	10	DCE	4	99	18:1	97
11[e]	**IV**	5	DCE	24	60	16:1	96
12[e,f]	**IV**	10	DCE	24	99	12:1	96
13[e,g]	**IV**	10	DCE	2.5	99	8:1	98
14[e,h]	**IV**	10	DCE	24	80	18:1	96

[a] Reaction conditions unless otherwise noted: **1a** (0.05 mmol, 1 equiv), **2a** (0.075 mmol, 1.5 equiv), solvent (400 μL, 0.125 M); direct silica gel column, no workup. [b] Percent conversion of **1a**. [c] Determined by ^{1}H NMR of crude product. [d] Determined by HPLC analysis of purified product. [e] Reaction performed at 0 °C. [f] Reaction of 0.05 mmol (1 equiv) of **2a**. [g] Solvent: 200 μL, 0.25 M. [h] Solvent: 800 μL, 0.0635 M. DCM = dichloromethane, DCE = dichloroethane.

In an effort to increase the selectivity of the transformation, we investigated catalysts **V**−**VII**. Reactions with these catalysts provided **3a** in lower selectivity and poorer yield than those carried out with catalyst **IV**. For example, the reaction catalyzed by bis-2,5-dimethyl-substituted phospholane derivative **V**[9] afforded the target compound in 20% yield and 50% ee (Table 1, entry 5). Catalyst **VI**[11] provided the reaction product with 25% conversion in racemic form (Table 1, entry 6), whereas catalyst **VII**[12] afforded **3a** in low conversion and 31% ee (Table 1, entry 7).

Based on these results, phospholane derivative **IV** was selected as catalyst for a series of reactions to investigate the influence of the reaction medium and temperature on the selectivity of the transformation. The best results were obtained when the reaction was performed in nonpolar aprotic solvents.[13] Dichloroethane (DCE) was the most suitable of solvents evaluated, yielding **3a** in 9:1 dr and 94% ee after 4 h (Table 1, entry 8). Lowering the reaction temperature to 0 °C afforded **3a** in of 98% ee and 9:1 dr (Table 1, entry 9). In an effort to probe the efficiency of the process, the catalyst loading was decreased incrementally from 20 mol % to 5 mol %. The dr was 9:1 at 20 mol % catalyst loading and was increased to 18:1 at 10 mol % (Table 1, entries 9 and 10). Further reduction of the catalyst loading to 5 mol % led to a slightly decreased selectivity compared to 10 mol %, and a reaction time of 24 h was needed to obtain 60% conversion (Table 1, entry 11). The ee was essentially independent of catalyst loading.

Scheme 1. Reaction of Various Morita−Baylis−Hillman Carbonates with 3-Substituted Benzofuranone **1a**[a]



[a] Reaction conditions unless otherwise noted: **1a** (0.1 mmol, 1 equiv); **2** (0.15 mmol, 1.5 equiv); solvent (800 μL, 0.125 M); direct silica gel column, no workup; isolated yield shown; dr determined by ^{1}H NMR of crude product; ee determined by HPLC analysis. DCE = dichloroethane. [b] 0.02 mmol of **IV**.

When Baylis−Hillman carbonate **2a** was used at 1 equiv relative to **1a**, product **3a** was obtained in 12:1 dr and 96% ee after 24 h (Table 1, entry 12). Increasing the concentrations of reactants resulted in lower selectivity (Table 1, entry 12). Lowering the reaction concentration had no influence on selectivity; however, a reaction time of more than 24 h was required to achieve 80% conversion under these conditions (Table 1, entry 14).

We then evaluated the reaction between 3-substituted benzofuranone derivative **1a** and various MBHCs (**2a**−**h**) catalyzed by 10 mol % **IV** in DCE at 0 °C (Scheme 1). Significantly, a wide range of MBHCs with aromatic as well as aliphatic substituents were well tolerated in the cycloaddition reaction, providing reaction products in excellent yield and selectivity. Electron-neutral phenyl-substituted Baylis−Hillman carbonate **2a** provided the target compound **3a** in 18:1 dr, 97% ee and 95% yield in 2.5 h. MBHCs containing electron-deficient substituents such as *p*-NO_2-phenyl (**2b**) and *p*-CN-phenyl (**2c**) provided products **3b** (8:1 dr, 94% ee) and **3c** (18:1 dr, 92% ee), respectively, in only 2 h in excellent yield and selectivity. Reaction with the electron-rich aryl substituent *p*-OMe-phenyl afforded **3d** in 5:1 dr and 95% ee and 93% yield;

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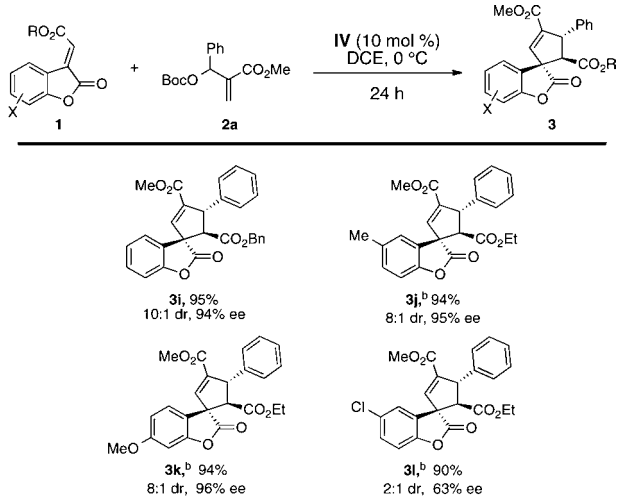
(13) See the Supporting Information.

however, a reaction time of 24 h was necessary to obtain the product in satisfactory yield. Various halide-substituted MBHCs were also suitable reactants. *p*-Br-phenyl- and *p*-Cl-phenyl-substituted starting material afforded **3e** and **3f** in excellent yields and drs of up to 7:1 and ees of up to 97% in 5 h (Scheme 1). Heterocyclic-aryl substituents were also well tolerated (**3g**); however, a reduced dr of 2:1 and 81% ee was observed. With alkyl-substituted **2h**, product **3h** was obtained in >4:1 dr, 71% ee and 40% yield.

Scheme 2. Reaction of Various 3-Substituted Benzofuranone Derivatives with Morita–Baylis–Hillman Carbonate **2a**[a]



[a] Reaction conditions unless otherwise noted: **1a** (0.1 mmol, 1 equiv); **2** (0.15 mmol, 1.5 equiv); solvent (800 μL, 0.125 M); direct silica gel column, no work up; isolated yield shown; dr determined by ^{1}H NMR of crude product; ee determined by HPLC analysis. DCE = dichloroethane. [b] 0.02 mmol of **IV**.

We then focused on benzofuranone diversification with with MBHC **2a** catalyzed by 10 mol % of **IV** in DCE at 0 °C (Scheme 2). When ethyl ester-containing methylenebenzofuranone **1a** was replaced with benzyl ester-modified derivative **1b,** cycloaddition product **3i** was obtained in 95% yield, 10:1 dr, and 94% ee. Various benzofuranones equipped with electron-donating substituents were also well tolerated in the phosphene-catalyzed [3 + 2] cycloaddition reaction. However, slightly longer reaction times of 24 h were required. In the reaction of 5-Me-substituted **1c**, **3j** was obtained in 8:1 dr, 95% ee, and 96% yield. 7-MeO-substituted **1d** provided **3k** in 94% yield, without loss of selectivity. We were able to further extend the scope of the reaction to halide-substituted reaction products such as **3l**, which was obtained in 90% yield, 2:1 dr, and 63% ee.

In accord with our previously reported phosphine-catalyzed cycloaddition reactions, we suggest that the reaction proceeds in a stepwise fashion with a phosphonium-ylide first generated by reaction of a Morita–Baylis–Hillman carbonate and a chiral phospholane. The phosphonium ylide subsequently attacks the methylenebenzofuranone, followed by ring closure through an intramolecular conjugate addition (Figure 1).[6c] The absolute configurations of the products afforded by the [3 + 2] cycloaddition reactions were assigned based on the X-ray crystal structure of compound **3j.**[13]

In summary, we have demonstrated for the first time that a wide range of complex polysubstituted spirocyclopentenebenzofuranone scaffolds can be efficiently assembled in high stereoselectivity in a single step from readily available starting materials. The transformation proceeds smoothly at 0 °C, providing reaction products comprised of three consecutive stereocenters, including one all-carbon center, in high yield and selectivity. We believe this methodology may enable the discovery of novel spirocyclopentenebenzofuranones with interesting biological activities.

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Supporting Information Available. Experimental procedures and compound characterization (^{1}H NMR, ^{13}C NMR, HPLC) including X-ray data.This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.