

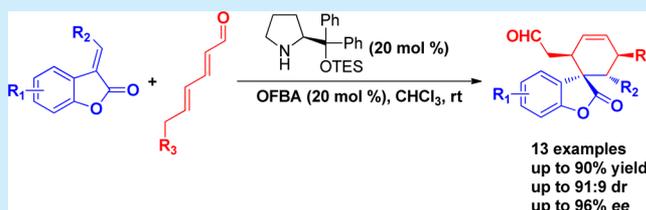
Asymmetric Diels–Alder Reaction of 3-Olefinic Benzofuran-2-ones and Polyenals: Construction of Chiral Spirocyclic Benzofuran-2-ones

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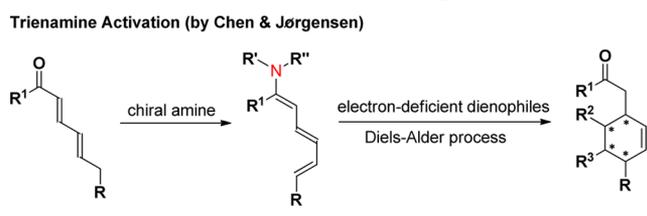
S Supporting Information

ABSTRACT: A highly enantioselective Diels–Alder reaction of 3-olefinic benzofuran-2-ones with polyenals catalyzed by diphenylprolinolsilyl ether through a trienamine activation strategy was developed.



Asymmetric aminocatalysis¹ has constituted a perfect scenario for activating carbonyl compounds, which facilitated a range of chiral transformations. The widely known enamine activation² and iminium ion activation³ modes have provided a reliable synthetic platform for generating stereogenic centers at the α and β positions of unmodified carbonyls. Recently, the interest of chemists has shifted toward the stereocontrolled generation of stereocenters of a carbonyl substrate requiring the propagation of the electronic effects inherent to enamine and iminium ion activations through the conjugated π -system of poly unsaturated carbonyls, which is called the “aminocatalytic remote functionalization strategy”.⁴ Complying with this trend, a new type of catalytic strategy, named “trienamine activation”, was jointly developed by Chen and Jørgensen (Scheme 1).^{5,6} Their

Scheme 1. Trienamine Activation Strategy

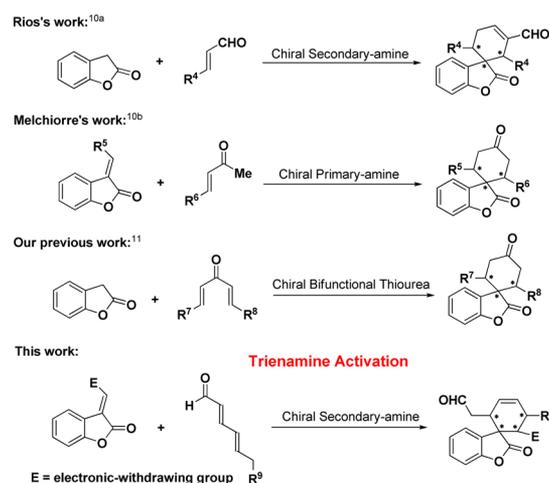


work found that trienamine intermediates were produced in situ through the propagated HOMO-raising electronic effect, in which Diels–Alder reaction were easily occur in the further process. Such a catalytic tool allows the rapid construction of stereochemically dense cyclohexenyl rings adorned with a broad spectrum of functional groups and with high stereo-control. A number of highly functionalized chiral cyclohexene derivatives,⁷ especially spirocycles,⁸ were synthesized with excellent stereoselectivities.

Spirocyclic benzofuran-2-one units are privileged structural motifs found in natural and unnatural compounds with diverse and important biological activities.⁹ Consequently, the search

for efficient methods for the construction of these compounds is therefore interesting in organic synthesis. Stereoselective construction of spiro[cyclohexanone-benzofuran-2-one] derivatives from benzofuran-2(3H)-ones and enals was accomplished by the group of Rios by using a chiral secondary amine (Scheme 2).^{10a} An asymmetric cascade reactions leading to

Scheme 2. General Strategy for the Construction of Chiral Spirocyclic Hexanones of Benzofuran-2-ones



enantiomerically pure spiro[cyclohexone-benzofuran-2-one] derivatives with 3-olefinic benzofuran-2-ones and enones was reported by Melchiorre and co-workers by using chiral primary-amine catalyst (Scheme 2).^{10b} We realized the highly enantioselective double Michael addition reaction of substituted benzofuran-2-ones to divinyl ketones by a simple Cinchona alkaloid type tertiary amine thiourea catalyst, in

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which functionalized chiral spirocyclic benzofuran-2-ones were obtained (Scheme 2).¹¹ In addition, there are only a few examples of the synthesis of chiral 3,3'-substituted benzofuran-2-ones by asymmetric catalysis.¹² Given that a different class of spirocyclic ring system may show promise in medicinally relevant compounds in drug development and biological phenomena studies, continued development of more creative methods for the synthesis of structurally diverse spirocyclic benzofuran-2-ones in an enantiopure form is significantly desired. We report herein a transformation of benzo-lactone type activated olefin by trienamine activation.¹³ An asymmetric Diels–Alder reaction of 3-olefinic benzofuran-2-ones with polyenals was achieved, thus generating enantiomeric enriched spirocyclic benzofuran-2-ones derivatives with chiral all-carbon quaternary centers (Scheme 2).

We initiated our investigations using 3-olefinic benzofuran-2-one (**1a**) and 2,4-hexadienal (**2a**) in the presence of 20 mol % of chiral secondary amine α,α -diphenylprolinolsilyl ether **4a** and *o*-F benzoic acid (OFBA) in CHCl₃ at room temperature (Table 1). To our delight, **4a** exhibited high catalytic activity,

Table 1. Screening of Conditions.^a

Reaction scheme showing the Diels–Alder reaction of 3-olefinic benzofuran-2-one (**1**) with 2,4-hexadienal (**2**) to form spirocyclic benzofuran-2-one (**3**). The reaction is catalyzed by 20 mol % of catalyst and 20 mol % of additive in solvent at room temperature (rt).

Catalysts: **4a** (OTMS), **4b** (OTES), **4c** (Ar = 3,5-(CF₃)₂C₆H₃).

entry	cat	acid	solvent	time (h)	yield ^b (%)	dr ^c	ee ^d (%)
1	4a	OFBA	CHCl ₃	18	86	88:12	86
2	4b	OFBA	CHCl ₃	18	90	91:9	95
3	4c	OFBA	CHCl ₃	18	trace	nd ^e	nd ^e
4	4b	BA	CHCl ₃	18	81	88:12	95
5	4b	PNBA	CHCl ₃	18	87	89:11	93
6	4b	TFA	CHCl ₃	18	15	nd ^e	nd ^e
7	4b	OFBA	CH ₂ Cl ₂	18	86	89:11	93
8	4b	OFBA	ClCH ₂ CH ₂ Cl	18	88	89:11	93
9	4b	OFBA	CCl ₄	18	29	71:29	94
10	4b	OFBA	Toluene	18	32	80:20	93
11	4b	OFBA	THF	18	47	87:13	94
12	4b	OFBA	Et ₂ O	18	trace	76:24	nd ^e
13	4b	OFBA	1,4-dioxane	18	47	75:25	94

^aThe reactions were conducted with 0.1 mmol of **1a**, 0.15 mmol of **2a**, 20 mol % of catalyst, and acids (20 mol %) as co-catalyst in 1 mL solvent at room temperature. ^bYield of the isolated major diastereoisomer of product **3a** after chromatographic purification on silica gel. ^cDetermined by ¹H NMR of crude product. ^dMeasured by chiral HPLC analysis. ^eNot determined.

and the Diels–Alder product was isolated with good yield and very good stereoselectivity (88:12 dr and 86% ee) (entry 1 in Table 1). Improvements could be achieved by employing the more sterically demanding *O*-triethylsilyl (*O*-TES) ether analogue **4b** (entry 2 in Table 1). When electron-withdrawing substituted secondary amine **4c** was used as the catalyst, only a trace of the desired product was isolated (entry 3 in Table 1). Furthermore, acid additives proved to have decisive effects on the reactivity. The weaker acid benzoic acid (BA) decreased the reaction rate and resulted in lower isolated yield with the

retentive enantioselectivity (entry 4 in Table 1). A less favorable result was obtained when more acidic *p*-NO₂ benzoic acid (PNBA) was selected as additive (entry 5 in Table 1), while a further increase in the acidity of the additive led to a significant drop in reactivity (entry 6 in Table 1). With the optimal combination of **4b** and OFBA, we then screened solvents. As illustrated in Table 1, initial used CHCl₃ gave the best result among a range of screened solvents (entries 2 and 7–13 in Table 1). Collectively, the best result with respect to yield and stereoselectivity was obtained by performing the reaction at room temperature in CHCl₃ with 20 mol % of **4b** and 20 mol % of OFBA. Under these conditions, the reaction provided the desired product with 90% yield in 91:9 dr and 95% ee (entry 2 in Table 1).

After the reaction conditions were optimized, scope was explored. As shown in Table 2, the reaction proceeded

Table 2. Scope of the Diels–Alder Reaction^a

entry	R ₁	R ₂	R ₃	time (h)	yield ^b (%)	dr ^c	ee ^d (%)
1	1a : H	CO ₂ Et	2a : H	18	3a : 90	91:9	95
2	1b : H	CO ₂ <i>t</i> Bu	2a : H	24	3b : 90	91:9	96
3	1c : H	CO ₂ Bn	2a : H	24	3c : 86	90:10	95
4	1d : H	COMe	2a : H	7	3d : 80	86:14	92
5	1e : H	COPh	2a : H	5	3e : 81	85:15	93
6	1f : H	CO(4-Br)Ph	2a : H	5	3f : 81	86:14	94
7	1g : H	CO(4-MeO)Ph	2a : H	4	3g : 85	89:11	93
8	1h : 5,7- <i>t</i> -Bu	COPh	2a : H	5	3h : 70	80:20	83
9	1i : H	CN	2a : H	24	3i : 78	82:18	89
10	1a : H	CO ₂ Et	2b : <i>n</i> -C ₃ H ₇	48	3j : 72	80:20	93
11	1a : H	CO ₂ Et	2c : <i>n</i> -C ₄ H ₉	48	3k : 75	82:18	91
12	1a : H	CO ₂ Et	2d : <i>n</i> -C ₅ H ₁₁	48	3l : 79	81:19	91
13	1a : H	CO ₂ Et	2e : <i>n</i> -C ₆ H ₁₃	48	3m : 74	80:20	91

^aThe reactions were conducted with 0.1 mmol of **1**, 0.15 mmol of **2**, 20 mol % of **4b**, and 20 mol % of OFBA as cocatalyst in 1 mL of CHCl₃ at room temperature. ^bYield of the isolated major diastereoisomer of product **3** after chromatographic purification on silica gel. ^cDetermined by ¹H NMR of crude products. ^dMeasured by chiral HPLC analysis.

smoothly to give the desired products in high yields with very good enantioselectivity for different ester substituted dienophiles (**1a–c**, entries 1–3, in Table 2). Moreover, the reactions were shown to work well with a range of acyl-group substituted benzofuran-2-one alkenes bearing either electron-withdrawing or electron-donating groups (**1d–h**, entries 4–8, in Table 2) to give the desired products **3d–h** with very good yields (up to 85%), moderate diastereoselectivities (up to 89:11 dr), and good enantioselectivities (83–94% ee). A more accurate analysis of these results showed that the enantioselectivity of the reaction is sensitive to the steric effect of benzofuranone. Lower ee value was obtained when **1h** was applied as the dienophile. Remarkably, the chemistry can be

successfully extended to a cyanogroup substituent in **1**, thus maintaining good enantioselectivity (entry 9 in Table 2).

In order to further extend the substrate scope, other trienamine precursors **2b–e** were also examined. As revealed in Table 2 (entries 10–13), the reactions were shown to work well with a range of polyconjugated enals bearing different alkyl substituted groups to give the desired products with good yields (up to 79%), moderate diastereoselectivities (up to >82:18 dr) and good enantioselectivities (91–93% ee).

The absolute configuration of product **3a** was determined by X-ray analysis (Figure 1).¹⁴ And the configurations of other

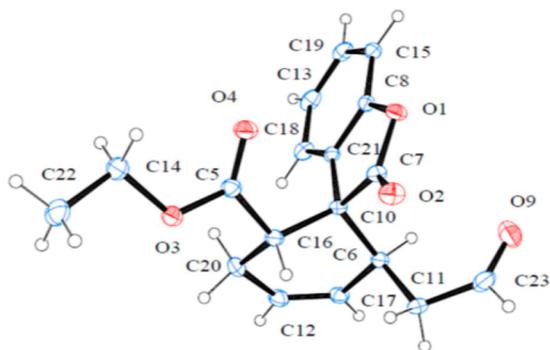
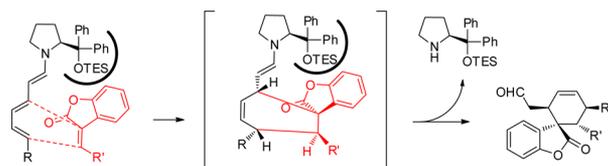


Figure 1. X-ray crystal structure of **3a**.

products were tentatively assigned by referring to that of **3a**. A catalytic mode in accordance with previous studies⁵ was proposed to account for the observed stereoselectivities (Scheme 3).

Scheme 3. Rationalization for Generating the Consecutive Chiral Centers



Finally, application of this methodology to the synthesis of chiral 2-spirocyclohexane benzofuran-3-ones has been envisioned due to the widespread 2-spirocyclic benzofuran-3-one framework in natural products and biologically active derivatives.¹⁵ From the results in Figure 2, we can see that

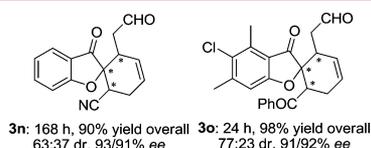
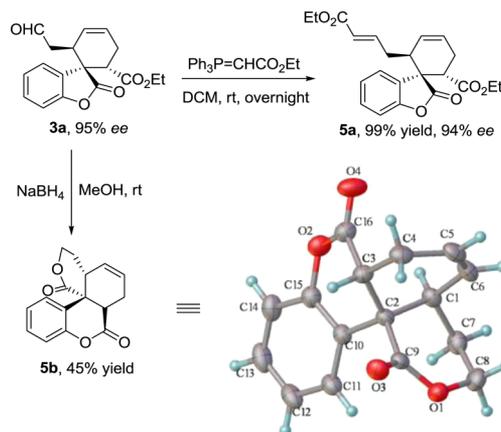


Figure 2. Application of benzofuran-3-one-type active alkenes.

the methodology was also worked well with benzofuran-3-one type electron-deficient alkenes. As a result, the corresponding Diels–Alder reaction products 2-spirocyclohexane benzofuran-3-ones **3n** and **3o** were obtained in very good yields with moderate diastereoselectivities and good enantioselectivities.

To further expand the utility of our work, conversions of the studied Diels–Alder adduct were examined. As shown in Scheme 4, treated **3a** with Wittig reagent $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$

Scheme 4. Transformations of the Products



gave product **5a** with almost retentive enantioselectivity. Reduction of **3a** by NaBH_4 led to the formation of a novel ester ring-opening rearrangement product **5b**.

In summary, we have presented the chiral secondary amine promoted highly enantioselective Diels–Alder reaction with 3-olefinic benzofuran-2-ones and polyenals by a triamine-activation strategy. The reaction scope is substantial, and a number of substituted benzofuran-2-ones and polyenals could be successfully applied to give multifunctional chiral benzofuran-2-one derivatives bearing spirocyclic hexanes at the 3-position with moderate diastereoselectivities and good enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, analytic data for all new compounds, and X-ray crystallographic data of **3a** and **5b** (CIF). 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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