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

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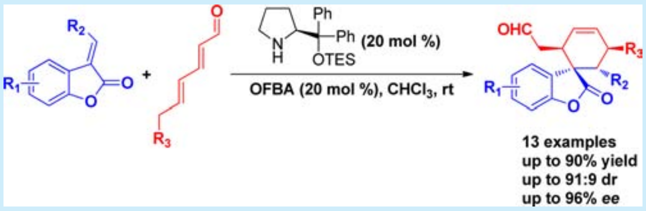
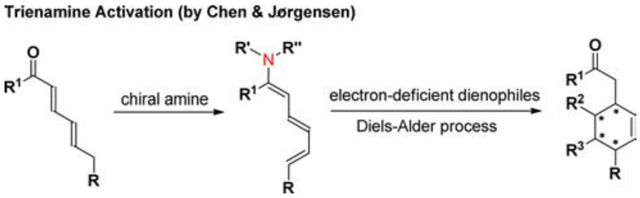
Supporting Information

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.



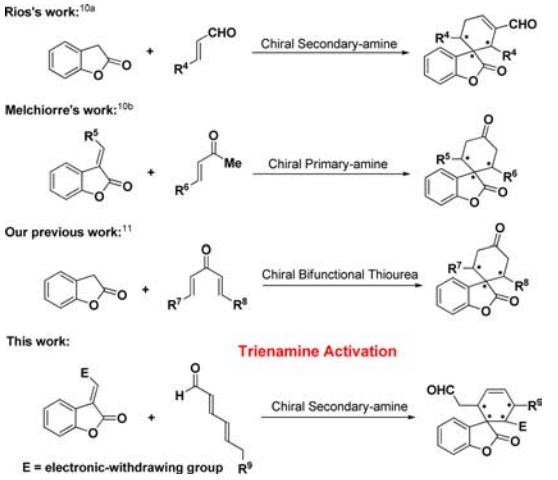
Asymmetric aminocatalysis[1] has constituted a perfect scenario for activating carbonyl compounds, which facilitated a range of chiral transformations. The widely known enamine activation[2] and iminium ion activation[3] modes have provided a reliable synthetic platform for generating stereogenic centers 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 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 stereocontrol. A number of highly functionalized chiral cyclohexene derivatives,[7] especially spirocycles,[8] were synthesized with excellent stereoselectivities.

Scheme 1. Trienamine Activation Strategy



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 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

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



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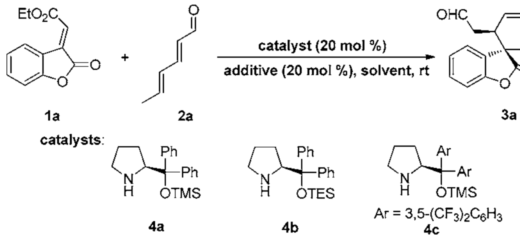
which functionalized chiral spirocyclic benzofuran-2-ones were obtained (Scheme 2).[11] In addition, there are only a few examples of the synthesis of chiral 3,3′-substituted benzofuran-2-ones by asymmetric catalysis.[12] Given that a different class of spirocycle ring system may show promise in medicinally 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 $CHCl_3$ at room temperature (Table 1). To our delight, **4a** exhibited high catalytic activity, 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*-NO_2 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 $CHCl_3$ 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 $CHCl_3$ 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 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

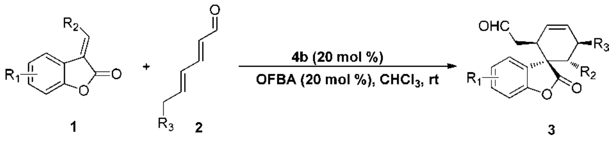
Table 1. Screening of Conditions.[a]



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_2Cl_2	18	86	89:11	93
8	**4b**	OFBA	$ClCH_2CH_2Cl$	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_2O	18	trace	76:24	nd[e]
13	**4b**	OFBA	1,4-dioxane	18	47	75:25	94

[a] The 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. [b] Yield of the isolated major diastereoisomer of product **3a** after chromatographic purification on silica gel. [c] Determined by ^{1}H NMR of crude product. [d] Measured by chiral HPLC analysis. [e] Not determined.

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_2Et	**2a**: H	18	**3a**: 90	91:9	95
2	**1b**: H	CO_2tBu	**2a**: H	24	**3b**: 90	91:9	96
3	**1c**: H	CO_2Bn	**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-*t*-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_2Et	**2b**: *n*-C_3H_7	48	**3j**: 72	80:20	93
11	**1a**: H	CO_2Et	**2c**: *n*-C_4H_9	48	**3k**:75	82:18	91
12	**1a**: H	CO_2Et	**2d**: *n*-C_5H_{11}	48	**3l**:79	81:19	91
13	**1a**: H	CO_2Et	**2e**: *n*-C_6H_{13}	48	**3m**:74	80:20	91

[a] The 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 $CHCl_3$ at room temperature. [b] Yield of the isolated major diastereoisomer of product **3** after chromatographic purification on silica gel. [c] Determined by ^{1}H NMR of crude products. [d] Measured by chiral HPLC analysis.

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 products were tentatively assigned by referring to that of **3a**. A catalytic mode in accordance with previous studies[5] was proposed to account for the observed stereoselectivities (Scheme 3).

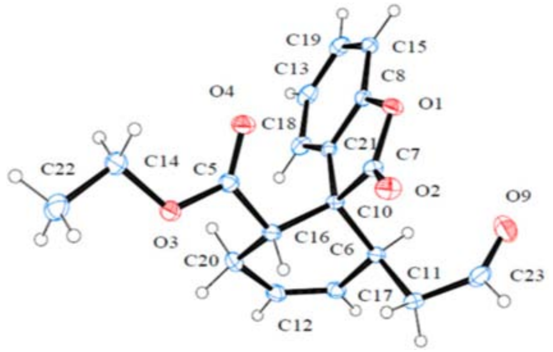
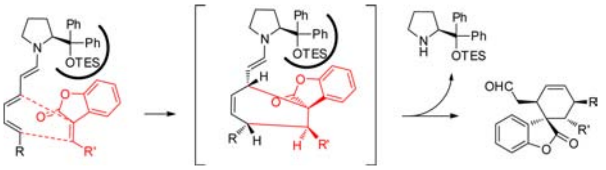
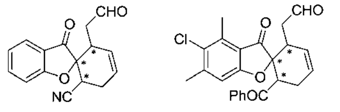


Figure 1. X-ray crystal structure of **3a**.

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 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.

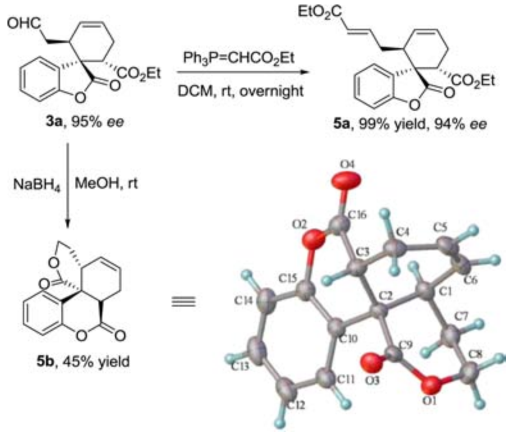


3n: 168 h, 90% yield overall 63:37 dr, 93/91% *ee* **3o**: 24 h, 98% yield overall 77:23 dr, 91/92% *ee*

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

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 $Ph_3P{=}CHCO_2Et$ 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**.

Scheme 4. Transformations of the Products



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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(14) CCDC 968601 and 965954 contain the supplementary crystallographic data for compounds **3a** and **5b**. This 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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