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Organocatalyzed Asymmetric Synthesis of Dihydrodibenzofurans Based on a Dienamine Process

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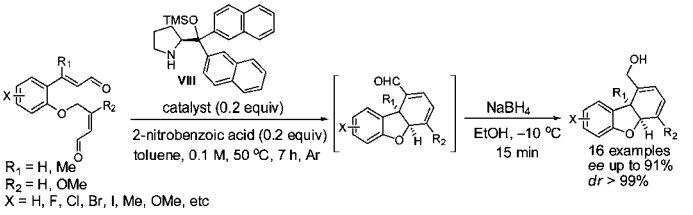
ABSTRACT



The first organocatalyzed asymmetric method for the synthesis of dihydrodibenzofurans based on a dienamine process has been developed. This two-step protocol works with a broad range of substrates and delivers only the *cis*-diastereomer in good yield with up to 91% ee. The enantioenriched products have been transformed to highly functionalized and partially hydrogenated dibenzofurans in excellent diastereoselectivities.

The partially hydrogenated dibenzofurans represent a very familiar substructure in many natural products and biologically important compounds (Figure 1).[1] Therefore, their synthesis has drawn considerable attention. They can be traditionally synthesized by two main strategies (Scheme 1). One of them involves formation of the aryl−alkyl carbon−carbon bond through Heck reaction, followed by metal-catalyzed oxidative cyclization[2] or hydroaryloxylation[3] (strategy I, Scheme 1). On the contrary, the other one employs a reverse sequence (strategy II, Scheme 1).[4] Although much progress has been made for both strategies in the past decades, efficient metal-free synthesis of partially hydrogenated dibenzofurans remains underdeveloped and is highly desirable for pharmaceutical and agrochemical synthesis.

In recent years, the organocatalytic approaches have been widely used in the synthesis of useful chiral building

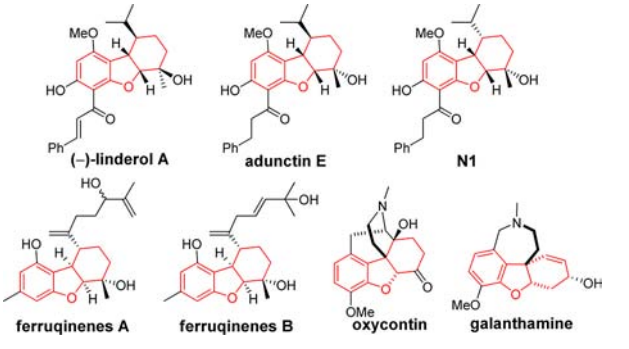


Figure 1. Compounds containing partially hydrogenated dibenzofuran.

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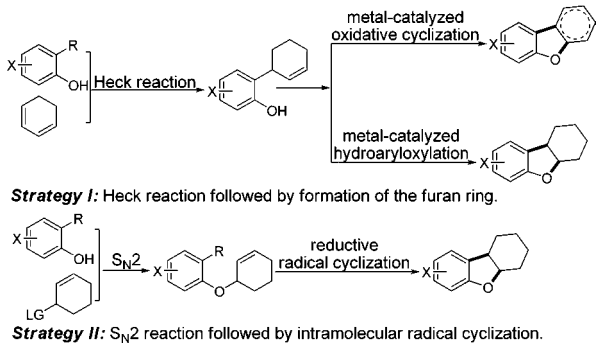
Scheme 1. Conventional Synthesis of Partially Hydrogenated Dibenzofurans



blocks. In 2006, Jørgensen and co-workers reported a dienamine catalysis by converting the inherent electrophilic α,β-unsaturated aldehydes into nucleophiles for direct asymmetric γ-amination with diethyl azodicarboxylate.[5] Since then, many efficient transformations have been developed on the basis of the dienamine catalysis concept.[6] For instance, Hong and co-workers developed an enantioselective [3 + 3]-cycloaddition of crotonaldehyde catalyzed by proline derivatives in 2006;[7] two years later, Christmann and co-workers published their work on the amine-catalyzed intramolecular cyclization of tethered α,β-unsaturated aldehydes through the dienamine activation;[8] and Chen and co-workers developed the first direct chemo-, regio-, and enantioselective Michael addition of γ,γ-disubstituted α,β-unsaturated aldehydes to α-nitroalkenes through dienamine catalysis.[9]

Dihydrodibenzofuran is a very useful building block. Compared with the dibenzofuran which contains two aromatic rings, partially hydrogenated dibenzofurans can be easily transformed to other useful targets through the functionalization of the double bond on the nonaromatic ring. However, to the best of our knowledge, enantioselective synthesis of dihydrodibenzofurans has not been well developed up to now. Herein we report the first organocatalyzed asymmetric synthesis of the dihydrodibenzofurans based on a dienamine process.

Scheme 2. Proposed Dienamine Pathway for the Synthesis of Chiral Dihydrodibenzofuran Derivatives

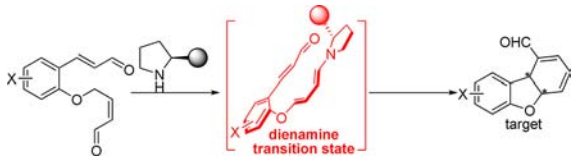
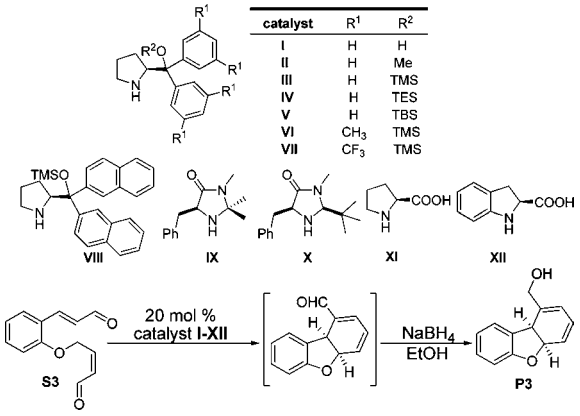


Table 1. Catalyst Screening[a]



entry	cat.	additive	time (h)	yield[b] (%)	conversion (%)	ee (%)
1	**I**	PhCOOH	4	36	54	ND[e]
2	**II**	PhCOOH	4	81	100	24
3	**III**	PhCOOH	4	66	100	46
4	**IV**	PhCOOH	4	34	100	20
5	**V**	PhCOOH	4	37	100	46
6	**VI**	PhCOOH	3	47	100	32
7	**VII**	PhCOOH	27	47	100	−62
8	**VIII**	PhCOOH	4	57	100	53
9	**IX**	HCl	4	<5	100	ND[e]
10	**X**	TFA	4	<5	100	ND[e]
11[d]	**XI**		36	<5	89	ND[e]
12[d]	**XII**		70	<5	62	ND[e]

[a] Unless otherwise noted, the reaction was performed with **S3** (0.3 mmol), catalyst (20 mol %), and additive (20 mol %) in 3 mL of toluene at 80 °C followed by filtration and reduction by $NaBH_4$ (1.0 equivalent) in 1.0 mL ethanol at −10 °C. [b] Isolated yield based on conversion. [c] Not determined. [d] 1,2-Dichloroethane was used as the solvent at room temperature.

Based on the chemistry of organocatalytic dienamine catalysis,[5−9] we envisaged that the bisenal substrate could be transformed to the dihydrodibenzofuran with two chiral centers through a dienamine transition state with a chiral secondary amine as the catalyst (Scheme 2). We initially investigated the cascade intramolecular cyclization of **S3** with the (*S*)-diphenylprolinol methyl ether **II** (20 mol %) as the catalyst and benzoic acid (20 mol %) as the additive in toluene at room temperature. Disappointingly,

(5) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

(6) For the reviews about dienamine catalysis, see: (a) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248. (b) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632. (c) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865. (d) Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Org. Lett.* **2012**, *14*, 3740. (e) Cassani, C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 5590.

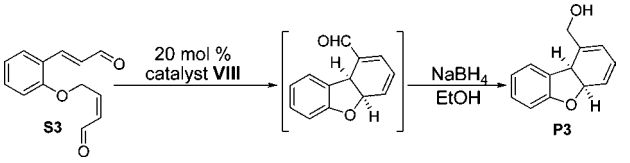
(7) (a) Hong, B. C.; Wu, M. F.; Tseng, H. C.; Liao, J. H. *Org. Lett.* **2006**, *8*, 2217. (b) Hong, B. C.; Wu, M. F.; Tseng, H. C.; Huang, G. F.; Su, C. F.; Liao, J. H. *J. Org. Chem.* **2007**, *72*, 8459. (c) Hong, B. C.; Tseng, H. C.; Chen, S. H. *Tetrahedron* **2007**, *63*, 2840. Similar work by Watanabe: Bench, B. J.; Liu, C.; Evett, C. R.; Watanabe, C. M. H. *J. Org. Chem.* **2006**, *71*, 9458.

(8) Figueiredo, R. M.; Fröhlich, R.; Christmann, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1450.

(9) (a) Han, B.; Xiao, Y. C.; He, Z. Q.; Chen, Y. C. *Org. Lett.* **2009**, *11*, 4660. For Chen's other related paper, see: (b) Han, B.; He, Z. Q.; Li, J. L.; Li, R.; Jiang, K.; Liu, T. Y.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5474. (c) Li, J. L.; Kang, T. R.; Zhou, S. L.; Li, R.; Wu, L.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6418. (d) Jia, Z. J.; Zhou, Q.; Zhou, Q. Q.; Chen, P. Q.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 8638. (e) Han, B.; Xiao, Y. C.; Yao, Y.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 10189. (f) Li, J. L.; Zhou, S. L.; Han, B.; Wu, L.; Chen, Y. C. *Chem. Commun.* **2010**, *46*, 2665.

only a trace amount of the desired product (yield < 5%) was obtained. We ascribed the poor yield to the more rigid conformation of the aromatic ring containing substrate, which may increase the activation energy of the reaction. Therefore, the reaction was performed at a higher temperature (80 °C). Indeed, the desired *cis*-dihydrodibenzofuran **P3** was isolated in 81% yield as the only diastereomer,[10a] albeit with low enantioselectivity (ee 24%: Table 1, entry 2). Then, the catalyst screening was extended to other (*S*)-diarylprolinol ethers **III**–**VIII**, MacMillan's imidazolidinone type catalysts **IX** and **X**, and bifunctional catalysts **I**, **XI**, and **XII** (Table 1); catalyst **VIII** turned out to be the best in terms of enantioselectivity (Table 1, entry 8). It was interesting to note that the fluorine-containing catalyst **VII** showed inverse enantioselectivity and low reactivity (Table 1, entry 7).

Table 2. Optimization of Reaction Conditions[a]

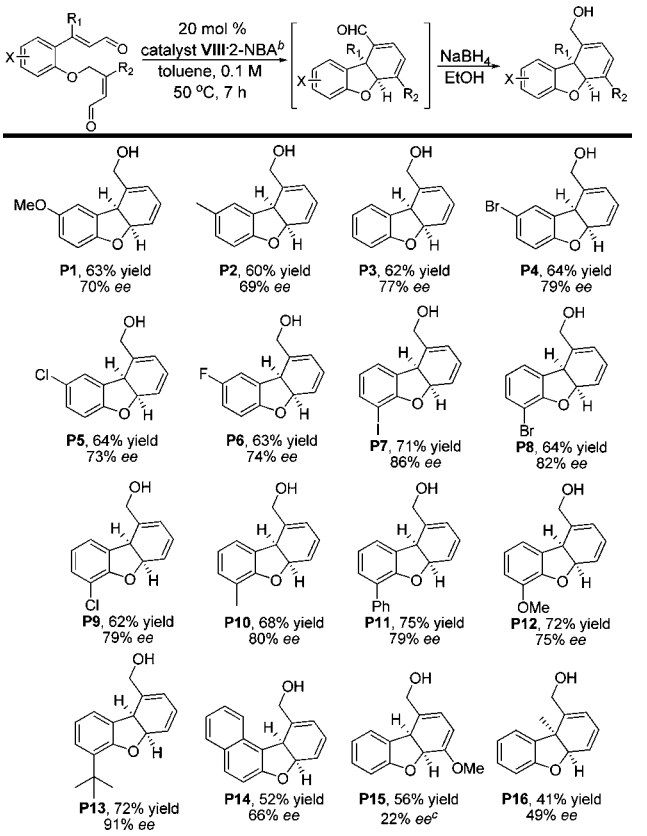


entry	solvent	additive	temp (°C)	time (h)	yield[b] (%)	ee (%)
1	DCM	PhCOOH	reflux	5	61	40
2	$CHCl_3$	PhCOOH	reflux	6	69	37
3	DCE	PhCOOH	80	6	67	46
4	Et_2O	PhCOOH	reflux	9	23	−15
5	dioxane[c]	PhCOOH	80	5	30	−40
6	DMF	PhCOOH	80	7	34	−42
7	toluene	PhCOOH	80	4	57	53
8	PhCl	PhCOOH	80	8	62	50
9	xylene	PhCOOH	80	4	38	32
10	DCE	2-NBA[d]	rt	39	39	66
11	toluene	2-NBA[d]	80	4	60	70
12	toluene	2-NBA[d]	60	4	60	76
13	toluene	2-NBA[d]	50	7	62	77
14	toluene	2-NBA[d]	rt	42	44	65

[a] Unless otherwise noted, the reaction was performed with **S3** (0.3 mmol), **VIII** (20 mol %), and additive (20 mol %) in 3 mL of solvent at the indicated temperature, followed by filtration and reduction with $NaBH_4$ (1.0 equiv) in 1.0 mL of ethanol at −10 °C. [b] Isolated yield. [c] 1,4-Dioxane. [d] 2-Nitrobenzoic acid.

With the optimal catalyst **VIII** in hand, several other factors were investigated subsequently. The survey of solvents indicated that toluene was the best reaction medium (Table 2, entry 7). 2-Nitrobenzoic acid was identified as the optimal proton source after systematic additive screening (Table 2, entry 11). A higher ee (77%) was obtained at low temperature (50 °C Table 2, entry 13). Further optimization on the concentration, catalyst loading and additive did not make any improvement in the enantioselectivity.[10b] Under the optimized conditions (Table 2, entry 13), the substrate scope of this reaction was

Scheme 3. Substrate Scope[a,b,c]



[a] Unless otherwise noted, the reaction was performed with bisenal (0.3 mmol), **VIII** (20 mol %), and 2-NBA (20 mol %) in 3 mL of solvent at 50 °C for 7 h, followed by filtration and reduction by $NaBH_4$ (1.0 equivalent) in 1.0 mL ethanol at −10 °C. [b] 2-Nitrobenzoic acid. [c] Reaction condition: 80 °C for 6 h, isolated yield based on 68% conversion.

evaluated. As shown in Scheme 3, a broad range of bisenals were good substrates for this transformation. Substrates with substituents of different electronic natures on the 4-position of the phenyl ring could be transformed to the desired *cis*-dihydrodibenzofurans[11] in good yields (60–64%) and good enantioselectivities (69–79% ee) (**P1**–**P6**). Substrates with different substituents on the 6-position of the phenyl ring were also compatible (**P7**–**P13**). It is worthy to mention that substrates with bulky substituents on the 6-position of the phenyl ring usually give products with higher ee (Scheme 3, 86% ee for **P7** and 91% ee for **P13**). The substrate originated from 2-hydroxy-1-naphthaldehyde (**P14**) could be transformed to the desired product with a slightly lower ee (66%). Moreover, the substrate with an electron-rich OMe group in one of the side chains (**P15**) was inert under the optimal condition. In this case, an elevated temperature (80 °C) could offer a good conversion (68%) with a lower ee (22%). The angular methyl group of **P16** has detrimental effects on both yield (41%) and enantioselectivity (49% ee). In addition, the stereochemical outcome of this method was confirmed based

(10) (a) The trans-product has much higher ring strain; see: Gordon, H. L.; Freeman, S.; Hudlicky, T. *Synlett* **2005**, 2911. (b) The details of condition screening are shown in the Supporting Information.

(11) The structure was confirmed by X-ray crystallography and 2D NMR analysis.

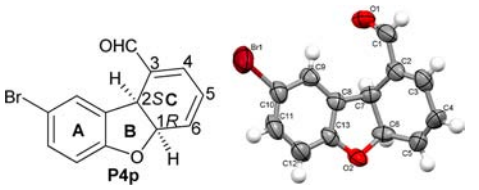


Figure 2. X-ray crystal structure of **P4p**.

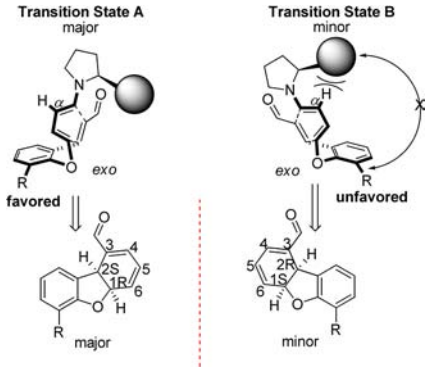
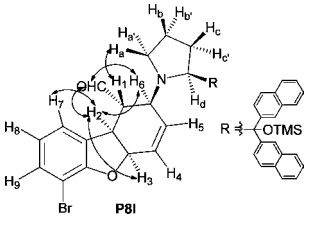


Figure 3. Proposed transition states for the cycloaddition.

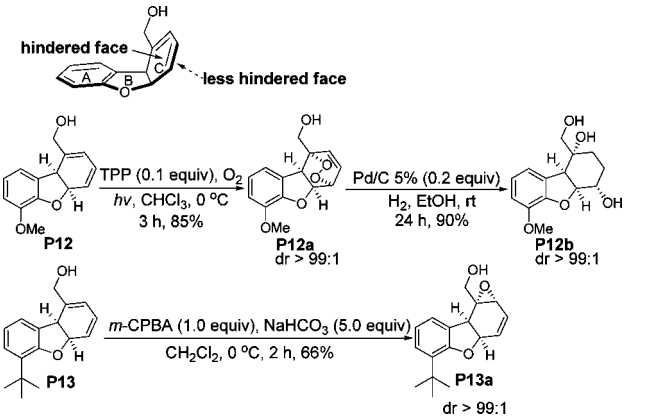
on a single crystal of aldehyde **P4p**, the precursor of **P4**. As shown in Figure 2, the absolute configurations of the two newly generated stereocenters of **P4p** are 1*R*, 2*S* and the newly formed **B**/**C** ring adopts a *cis*-configuration.

On the basis of the stereochemistry of the dihydrodibenzofuran product and an isolated intermediate **P8I**,[12] we propose that the cyclization might proceed through a concerted process via an *exo*-transition state. As shown in Figure 3, two transition states for the concerted *exo* cyclization of the in situ generated dienamine are possible. **Transition state B** is not favored due to the steric interaction between the α-proton and the bulky auxiliary of the secondary amine catalyst. The substrates with the bulky 6-R group favor **transition state A** because the 6-R group of the substrates in **transition state A** is further away from the bulky auxiliary of the secondary amine catalyst than in **transition state B**.

(12) We successfully isolated compound **P8I** using 1.0 equiv of secondary amine catalyst and substrate **S8** at rt and determined the relative stereochemistry of **P8I** based on the 2-D NMR analysis. Observed NOE correlations of **P8I** are shown below:



Scheme 4. Further Functionalization of Dihydrodibenzofurans



As shown in Scheme 4, the upper face of C ring of the newly formed *cis*-dihydrodibenzofuran product was blocked by the A and B rings. This unique structure allows highly stereoselective functionalization of the C ring. The conversion of **P12** to **P12a** using singlet oxygen showed excellent diastereoselectivity (dr > 99:1). Compound **P12a** could be readily converted to triol **P12b** through a two-step, one-pot hydrogenation. Upon treatment of **P13** with *m*-CPBA under basic conditions, the OH-directed highly regioselective epoxidation delivered the desired product **P13a** in 66% yield with excellent diastereoselectivity (Scheme 4).

In summary, we have developed the first organocatalyzed asymmetric method for the synthesis of the dihydrodibenzofurans based on a dienamine process. This two-step protocol works with a broad range of substrates and delivers only the *cis*-diastereoisomer in good yields with moderate to good enantioselectivities. A concerted *exo*-transition state has been proposed on the basis of the stereoselectivity of the reaction. Further functionalization of the *cis*-dihydrodibenzofuran products' C ring has been realized in excellent diastereoselectivity (dr > 99:1).

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Supporting Information Available. Experimental details and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.