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Catalytic Asymmetric Chlorocyclization of 2-Vinylphenylcarbamates for Synthesis of 1,4-Dihydro-2*H*-3,1-benzoxazin-2-one Derivatives

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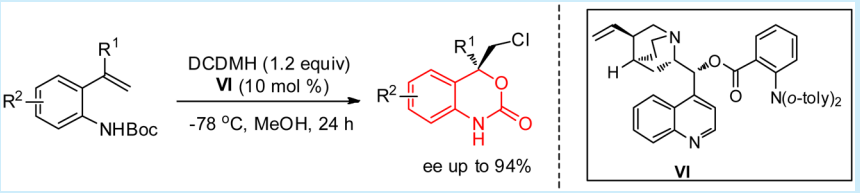
Supporting Information



ABSTRACT: A facile synthetic approach to a series of chiral 4-chloromethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives has been described. This transformation is achieved through the catalytic asymmetric chlorocyclization of 2-vinylphenylcarbamates using a newly developed organocatalyst. Furthermore, the resulting products can be easily converted into diverse bioactive agents.

Compounds owning the skeleton of 1,4-dihydro-2*H*-3,1-benzoxazin-2-one (Figure 1) have received much attention for their potential biological applications such as progesterone receptor antagonist, HIV-1 reverse transcriptase inhibitor.[1] For instance, Efavirenz, as a potent nonnucleoside reverse transcriptase inhibitor, is still one of the first-line drugs in the clinical treatment of AIDS (Figure 1).[2]

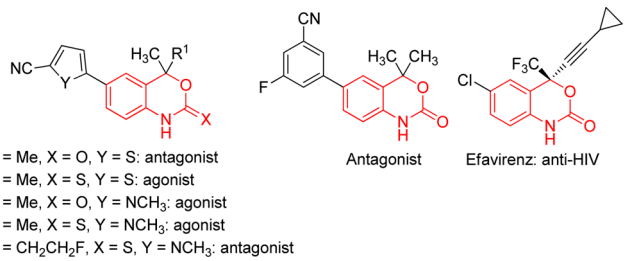


Figure 1. Representative bioactive 1,4-dihydro-2*H*-3,1-benzoxazin-2-one and its derivatives.

Although a series of strategies for the construction of the 1,4-dihydro-2*H*-3,1-benzoxazin-2-one skeleton have been reported, there are few reports on the asymmetric synthesis of these compounds.[3] To facilitate the biological evaluation of optically active 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives, the development of a catalytic system for the enantioselective synthesis of these chiral derivatives are highly desirable.

The past few years have witnessed much work in the area of catalytic asymmetric halocyclization reactions,[4] for example, halolactonizations,[5] haloetherifications,[6] haloaminocyclizations,[7] and related reactions.[8] Particularly inspired by the success of chlorocyclization reaction,[9] we wish to communicate here our success in achieving the practical and novel synthesis of the chiral 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives via the halocyclization of carbamates catalyzed by organocatalysts.

We commenced our studies by using *t*-butyl *N*-[2-(1-phenylethenyl)phenyl]carbamate **1a**, which was easily synthesized from corresponding 2-alkenylanilines as the model substrate to search for the optimal reaction conditions.[10] Reactions for screening the catalysts were carried out in *n*-PrOH at −40 °C for 24 h with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as the chlorenium source. $(DHQD)_2PHAL$ gave the desired product **2a** in a slightly low yield with poor enantioselectivity (Table 1, entry 1). Although the Cinchonidine-based thiourea catalyst **II** was able to impart excellent yield, the enantioselectivity was unacceptable (Table 1, entry 2). Eventually, we are pleased to find that by using the chiral ester **III** as catalyst, which was assembled by Cinchonidine and 2-(diphenylphosphino)benzoic acid, the ee value could be increased to 45% (Table 1, entry 3). Replacing the phosphorus atom of **III** with nitrogen atom made no difference on the enantioselectivity surprisingly (Table 1, entry 4). *p*-Tolyl substitution on the nitrogen led to the same ee (Table 1, entry 5). These results promoted us to believe that increasing the steric bulk of the substituents on the nitrogen could increase the enantioselectivity. Then the catalyst with bulk substituent has been synthesized and applied in this reaction. To our delight, this was indeed the case. The *o*-tolyl-substituted catalyst **VI** brought a tremendous improvement to the enantioselectivity (Table 1,

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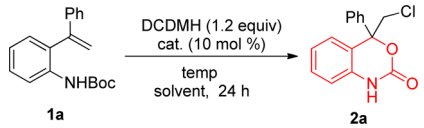
Table 1. Studies on Reaction Condition[a]



entry	cat.	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	**I**	*n*-PrOH	−40	35	13
2	**II**	*n*-PrOH	−40	78	0
3	**III**	*n*-PrOH	−40	71	45
4	**IV**	*n*-PrOH	−40	64	45
5	**V**	*n*-PrOH	−40	76	45
6	**VI**	*n*-PrOH	−40	72	77
7	**VI**	MeOH	−40	87	80
8	**VI**	EtOH	−40	74	80
9	**VI**	*n*-BuOH	−40	69	75
10	**VI**	CH_2Cl_2	−40	12	35
11	**VI**	$CHCl_3$	−40	N.D.[d]	
12	**VI**	$CHCl_3$/hexane[e]	−40	<5	31
13	**VI**	MeOH	−60	78	86
14	**VI**	MeOH	−78	86	90

[a]The reaction was carried out with **1a** (0.10 mmol), DCDMH (0.12 mmol), and chiral catalyst (0.01 mmol) in solvent (2.0 mL) unless otherwise stated; DCMDH = 1,3-dichloro-5,5-dimethylhydantoin. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Not detected. [e]$CHCl_3$/hexane = 1/1.

entry 6), and the X-ray crystallography of VI further confirmed the steric hindrance on the nitrogen (Figure 2).[11] To determine

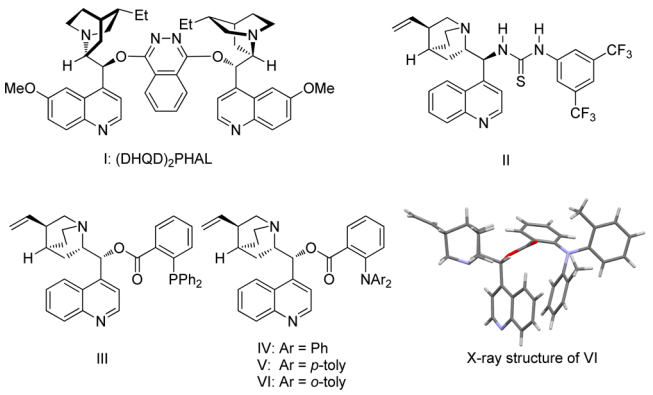
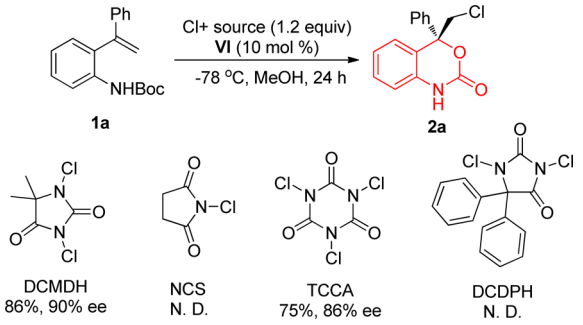


Figure 2. Selected examples of chiral catalysts examined.

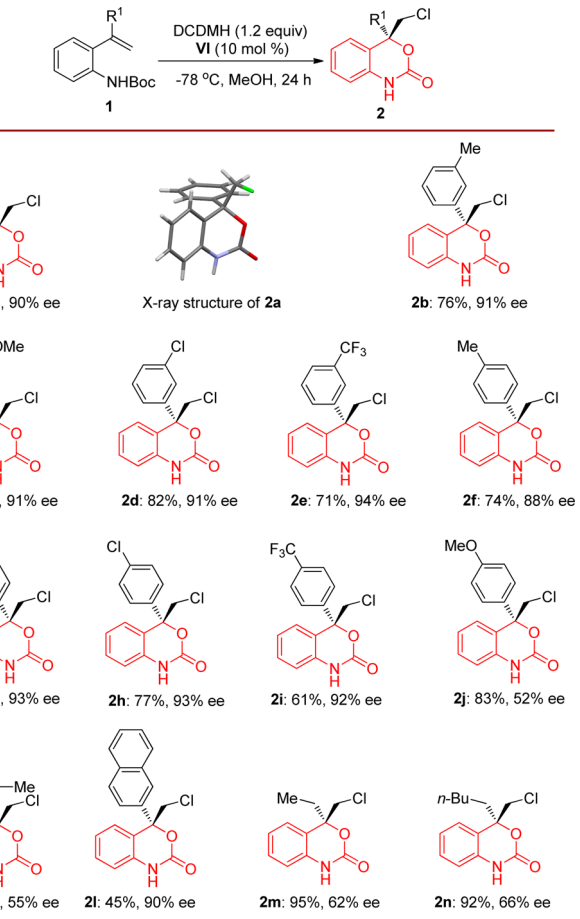
the optimal reaction conditions with catalyst **VI**, the solvents were first screened (Table 1, entries 7−12). The results indicated that alcoholic solvents showed obvious advantage, and the solvent effect is consistent with the reported literature.[9] Among the tested alcohols, methanol provided the best result in terms of the enantioselectivity and the yield. Decreasing the reaction temperature resulted in a further increase of enantioselectivity. The best enantioselectivity and yield were achieved at −78 °C. The effect of other chlorenium source such as trichloroisocyanuric acid (TCCA), *N*-chlorosuccinimide (NCS), and 1,3-dichloro-5,5-diphenylimidazolidine-2,4-dione (DCDPH) was also explored (Scheme 1). However, none of them could provide favorable results.

With the optimized conditions in hand, the scope of the reaction with other substrates has been investigated. First, the *t*-butyl 2-vinylphenylcarbamates bearing various substituents was studied (Scheme 2). All the substrates bearing *meta*-substituted

Scheme 1. Effect of Chlorenium Source



Scheme 2. Scope of Substrates[a]



[a]Reaction conditions: **1** (0.10 mmol), DCDMH (0.12 mmol), and catalyst **VI** (0.01 mmol) in MeOH (2.0 mL) at −78 °C, isolated yields.

phenyl groups afforded the corresponding products in good yields with more than 90% ee (Scheme 2, **2b**−**2e**). Substrates with *para*-methyl, *para*-F, *para*-Cl, and *para*-CF_3 on the phenyl ring also gave high enantioselectivities (Scheme 2, **2f**−**2i**). In contrast, there is a sharp loss of ee value when it is methoxyl group (Scheme 2, **2j**), which could be ascribed to the enhanced background reaction. The yield and ee of the *o*-Me substituted substrate were only 65% and 55% (Scheme 2, **2k**) probably due to the steric effect. Using 2-naphthyl substituted *t*-butyl 2-vinylphenylcarbamate as the substrate, product **2l** could be obtained in moderate yield and good ee. For aliphatic substrates, chlorocyclizations were both achieved in excellent yields, but lower enantioselectivities (Scheme 2, **2m** and **2n**). The absolute

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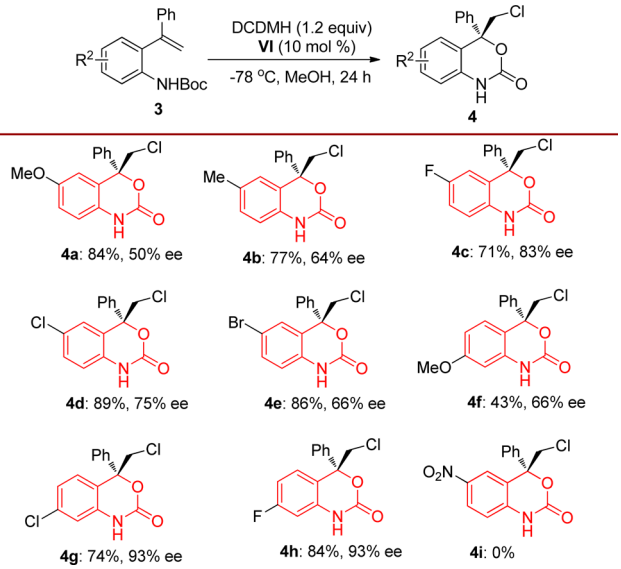
configuration of **2** was confirmed by an X-ray study on the product **2a**.[11]

Subsequently, the effects of substituents residing on the aromatic moiety of *t*-butyl 2-vinylphenylcarbamates have been further investigated (Scheme 3). The electronic nature of

Scheme 3. Scope of Substrates[a]

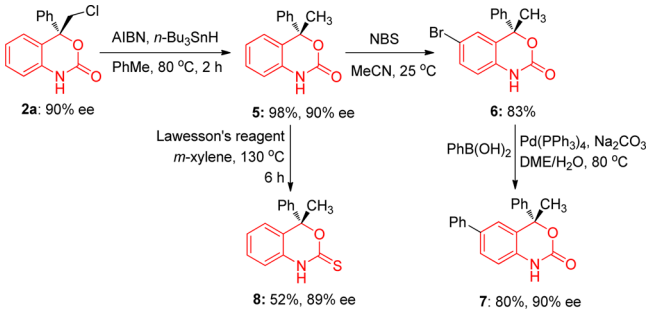


[a]Reaction conditions: **1** (0.10 mmol), DCDMH (0.12 mmol), and chiral catalyst (0.01 mmol) in MeOH (2.0 mL) at −78 °C, isolated yields.

substituent *para* to the aromatic ring of amino moiety exerted obvious impact on the enantioselectivity (Scheme 3, **4a**−**4e**). Electron-withdrawing groups F and Cl provided higher ee value than electron-donating groups (Scheme 3, **4c** and **4d**). Unfortunately, substrate with the strong electron-withdrawing group NO_2 at the para position appeared to have completely retarded the reaction (Scheme 3, **4i**). For substrates bearing halogen group para to the alkene moiety, good yields and high ees were generally obtained (Scheme 3, **4g** and **4h**). For the substrates bearing *para*- and *meta*-methoxyl group (Scheme 3, **4a** and **4f**), however, relatively low ees were observed, which were consistent with the previous observations.

The synthetic utility of this methodology is demonstrated in Scheme 4. As a novel class of potent, selective, and orally active progesterone receptor antagonists, the 6-aryl-1,4-dihydrobenzoxazin-2-ones **7** could be obtained in 65% total yield without any loss of ee through a three-step sequence of reduction with *n*-Bu_3SnH, bromination using NBS, and a standard Suzuki

Scheme 4. Demonstration of Synthetic Utility



coupling. Furthermore, the conversion of the carbamate group to the thiocarbamate was also achieved with good stereochemical integrity by heating with Lawesson's reagent in *m*-xylene at 130 °C for 6 h.

In conclusion, we have described an efficient catalytic asymmetric synthesis of 1,4-dihydro-2*H*-3,1-benzoxazin-2-ones using a newly developed organocatalyst. Notably, the versatile transformations of the product warrant the synthetic utility of this methodology in the areas of organic and medicinal chemistry. The investigations on the biological evaluation of these optically active 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives and further application of the new catalyst in asymmetric catalysis are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00272.

Detailed experimental procedures and spectral data (PDF)

X-ray crystallographic data of compounds **VI** (CIF)

X-ray crystallographic data of compound **2a** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1525739 and CCDC 1524861 contain the supplementary crystallographic data for compounds **VI** and **2a**, respectively.

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