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Enantioselective Chlorocyclization of Indole Derived Benzamides for the Synthesis of Spiro-indolines

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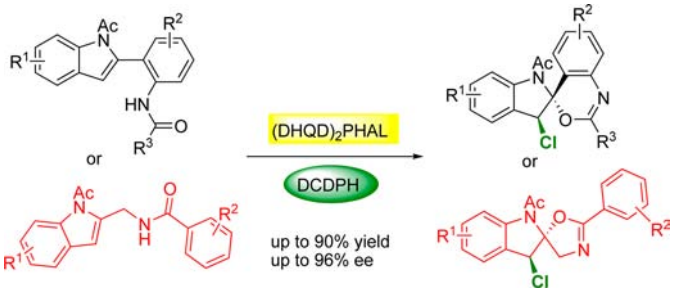
ABSTRACT



$(DHQD)_2PHAL$ catalyzed enantioselective chlorocyclization of indole derived benzamides was realized. Spiro-indolines containing a continuous quaternary carbon center and tertiary carbon center were obtained in good yields with excellent enantioselectivity (up to 90% yield and 96% ee).

Chiral halogenated compounds are ubiquitous in natural products and among the most versatile building motifs in the construction of molecular complexity.[1] Stereoselective incorporation of halogen atoms, therefore, has received tremendous interests. Enantioselective electrophilic halogenation of alkene, a straightforward strategy to obtain functionalized halogenated compounds, has thus far eluded organic chemists until recently.[2] An efficient Co-salen catalyzed enantioselective iodoetherification reaction has been developed by Kang and co-workers in 2003.[3] Later, Gao and co-workers reported the first organocatalytic enantioselective iodolactonization reaction with quaternary ammonium salts derived from cinchonidine.[4] In 2010, Tang and co-workers reported an elegant enantioselective bomolactonization of enynes by a cinchona alkaloid derived urea.[5] Since then, notable advances have been achieved in enantioselective iodocyclization[6] and bromocyclization reactions.[7−9] However, efficient enantioselective chlorocyclizations remain rare due to the highly reactive nature of chloronium ions. Recently, with $(DHQD)_2PHAL$ as the catalyst, Borhan and co-workers have realized asymmetric chlorocyclization reactions of 4-substituted 4-pentenoic acids and unsaturated amides to construct chiral lactones or oxazolines and dihydrooxazines, respectively.[10−12] Meanwhile, catalytic asymmetric dearomatization reactions have recently emerged as efficient methods converting aromatics to enantiopure spirocyclic compounds.[13] Asymmetric dearomatization of indoles represents an intriguing protocol to synthesize

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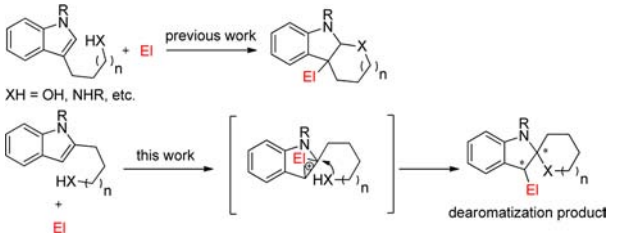
chiral indolines and related alkaloids. In this regard, indole substrates with preinstalled nucleophiles at the C3-position are generally utilized. Gouverneur and co-workers have developed an enantioselective fluorocyclization of indoles bearing an embedded heteronucleophile tethered at the C3 or N1 position.[14] As a continuation of our interest in the catalytic asymmetric dearomatization reaction,[15] we envisaged that enantioselective electrophilic chlorocyclization of indoles bearing a nucleophile at the C2 position could lead to a spiro-indoline containing a continuous spiro quaternary carbon center and tertiary carbon center (Scheme 1). Herein, we report the results from this study.

Scheme 1. Chlorocyclization of Indoles Bearing an Embedded Nucleophile



We began our studies by testing the reactions of indole-derived benzamide **1a** with different halogen sources. Fortunately, the reactions could all proceed smoothly *via* a 6-*exo*-trig cyclization to generate spiro benzoxazines (Table 1). To our delight, with 1,3-dichloro-5,5-diphenylhydantoin (DCDPH) as the halogen source and $(DHQD)_2PHAL$ as the catalyst, the chlorocyclization of **1a** led to **2a** in excellent yields with moderate enantioselectivity at −30 °C using DCM or CH_3CN as the solvent respectively (85−94% yields, 75−77% ee, entries 1 and 2, Table 1). Product **2a** could be obtained in 89% yield and 90% ee when mixed solvents (DCM/CH_3CN: 2/1) were employed (entry 3, Table 1). Reactions with several other halogen sources gave much lower activity or enantioselectivity. For example, only 10% conversion was obtained when NCS was used (entry 4, Table 1). 1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) gave the desired product with a full conversion and 85% ee (entry 5, Table 1). Further screening of solvents revealed $CHCl_3$ is the optimal one, affording the desired product in 82% yield with 95% ee (entries 6−10, Table 1). Elevating the reaction temperature to −10 °C led to a slightly decreased yield and enantioselectivity (entry 11, Table 1). The absolute configuration of the product was determined by a single crystal X-ray analysis of enantiopure **2a** (see the Supporting Information).

Under the optimized reaction conditions, various substituted indole-derived benzamides were tested to probe the generality of the reaction. The results are summarized in Scheme 2. Either an electron-donating group (**2b**−**2d**, 80−87% yields, 91−95% ee) or an electron-withdrawing group (**2e**, 70% yield, 95% ee) at the *meta* or *para* position of the benzamide (R^3) were well tolerated. In addition, **1f** containing heteroarylamide was also a suitable substrate (**2f**, 86% yield, 94% ee). A decreased ee, however, was obtained when the benzamide was replaced with an pivalamide (**2g**, 76% yield, 80% ee). The substrates bearing an electron-donating group (**2h**, 90% yield, 96% ee) or an electron-withdrawing group (**2i**, 82% yield, 90% ee) on the indole core were well tolerated.

Substrates varying the substituents on aniline were also carried out to further examine the reaction scope. In all

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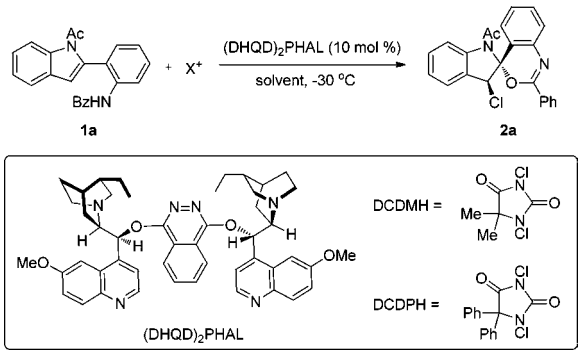
Table 1. Optimization of the Reaction Conditions



entry[a]	solvent	X^+, product	time (h)	yield (%)[b]	*ee* (%)[c]
1	DCM	DCDPH, **2a**	16	85	75
2	CH_3CN	DCDPH, **2a**	2	94	77
3	DCM/CH_3CN (2/1)	DCDPH, **2a**	12	89	90
4	DCM/CH_3CN (2/1)	NCS, **2a**	24	<10	86
5	DCM/CH_3CN (2/1)	DCDMH, **2a**	12	92	85
6	DCE	DCDPH, **2a**	12	93	53
7	CCl_4	DCDPH, **2a**	12	88	58
8	toluene	DCDPH, **2a**	12	55	54
9	CF_3CH_2OH	DCDPH, **2a**	3	88	78
10	$CHCl_3$	DCDPH, **2a**	30	82	95
11[d]	$CHCl_3$	DCDPH, **2a**	30	67	91

[a] Reactions were performed with **1a** (0.1 mmol), X^+ (0.15 mmol), and 10 mol % of $(DHQD)_2PHAL$ at −30 °C. [b] Isolated yield. [c] Determined by HPLC. [d] Reaction was performed at −10 °C.

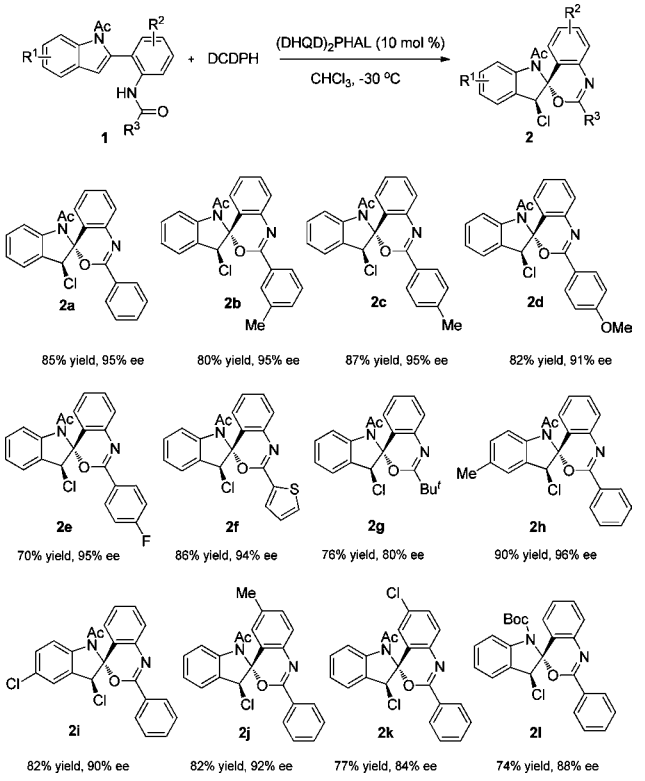
cases, good yields and enantioselectivity were achieved (**2j**–**2k**, 77–82% yields, 84–92% ee). When the protecting group of the indole N1 position was changed from Ac to Boc, the corresponding chlorocyclization product **2l** was obtained in 74% yield with 88% ee.

To further broaden the structural diversity of the products, indol-2-yl benzamide substrates were also tested to afford the corresponding oxazolines (Scheme 3).

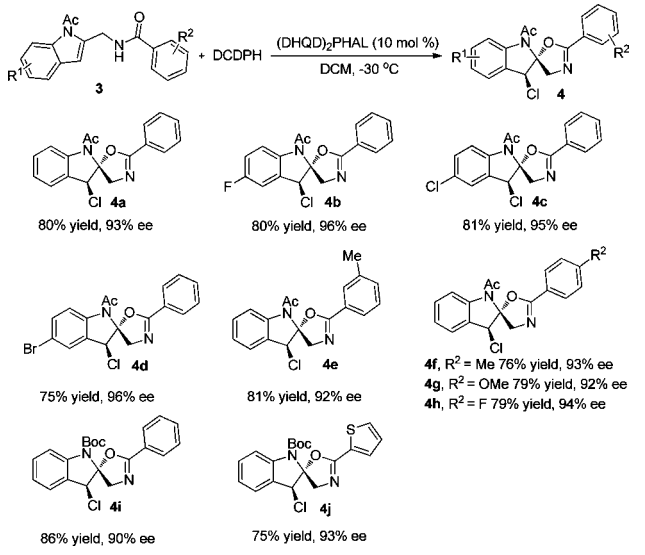
Under slightly revised reaction conditions, substrates with an electron-withdrawing group on the indole core could be well tolerated in good yields with excellent enantiocontrol (**4a**–**4d**, 75–81% yields, 93–96% *ee*). Benzamides containing various substituents on the benzene ring were also suitable substrates to give the corresponding chlorocyclization products with excellent enantioselectivity (**4e**–**4h**, 76–81% yields, 92–94% *ee*). In addition, *N*-Boc indole and 2-thienyl derived substrates could both be well tolerated (**4i**–**4j**, 75–86% yields, 90–93% *ee*).

The products obtained here containing a chiral C–Cl bond provide an opportunity for diverse transformations (Scheme 4). For instance, when **2a** (92% ee) was treated with silver nitrate in aqueous phase, nitrate **5a** was obtained with good stereochemical integrity (74% yield, 93% ee). The alcohol **6a** could be obtained in good yield after

Scheme 2. Substrate Scope for Chlorocyclization of **1**

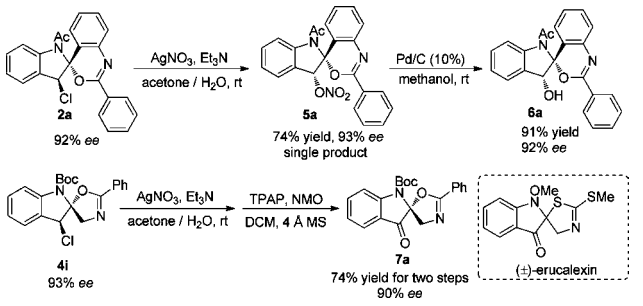


Scheme 3. Substrate Scope for Chlorocyclization of **3**



subjecting nitrate **5a** to Pd/C hydrogenation conditions (91% yield, 92% ee). The relative stereochemistry of product **6a** was established by NOESY NMR analysis (see the Supporting Information). Furthermore, product **4i** (93% ee) could be converted to enantioenriched indoline-3-one **7a** *via* a hydrolysis and Ley oxidation reaction sequence. Notably, **7a** has a skeleton similar to that of

Scheme 4. Transformations of Products



natural product erucalexin, which shows antifungal activity against *S. sclerotiorum* and *R. solani*.[16]

As for the working model of this reaction, we speculate that, on the one hand, the phthalazine nitrogen in the catalyst forms a hydrogen bond with the benzamide NH in the substrate to increase the nucleophilic property of the amide group; on the other hand, the tertiary amine nitrogen in the catalyst acts as a Lewis base to activate the chloronium species to provide a chiral environment to induce high enantioselectivity (a). It seems that, in our system, the dichlorohydantoin was not activated by the hydrogen-bond interaction with the protonated amino-group (b), as a racemic product was obtained when BzOH (1 equiv) was added as an additive (Figure 1).[10a]

In summary, we have developed an efficient method for the construction of chiral indoline skeletons with a continuous spiro quaternary carbon center and tertiary carbon center by enantioselective chlorocyclization of indole derived benzamides. With $(DHQD)_2PHAL$ as the catalyst, dearomatization products were obtained in good yields and excellent enantioselectivity under mild reaction conditions with operationally simple procedures.

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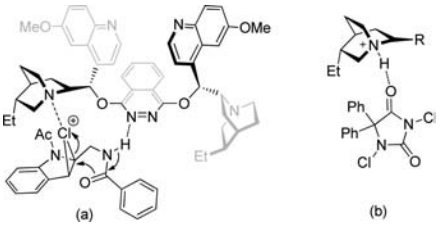

Figure 1. Proposed working model.

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Supporting Information Available. Detailed experimental procedures and spectroscopic data for all new compounds and X-ray crystal data of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.