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Dearomatization of Indoles *via* a Phenol-Directed Vanadium-Catalyzed Asymmetric Epoxidation and Ring-Opening Cascade

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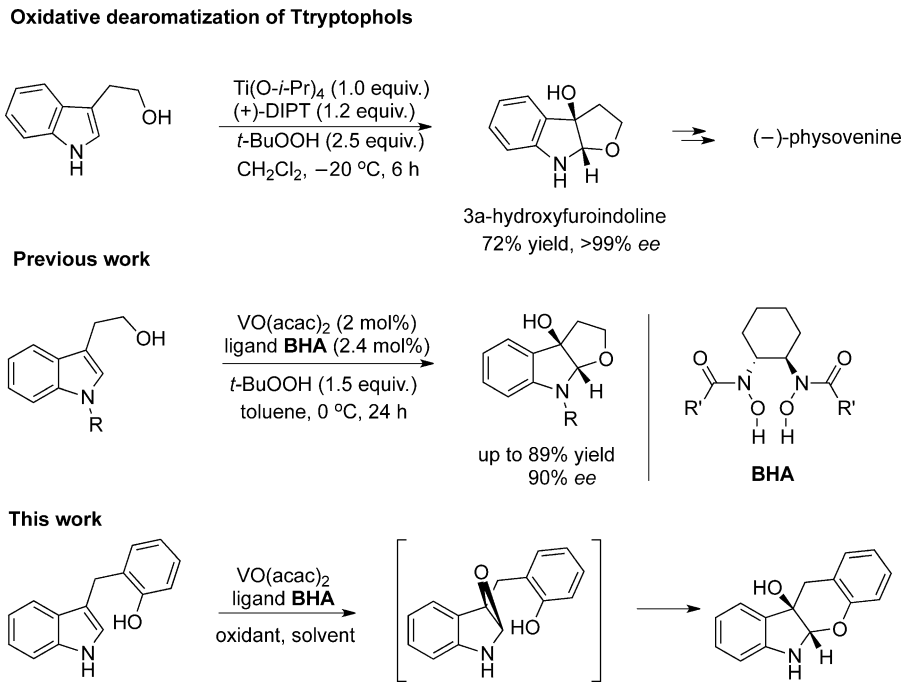
Abstract: An enantioselective dearomatization of indole derivatives was realized by the complexes derived from the vanadium complex $VO(acac)_2$ and C_2-symmetric bis-hydroxamic acid (BHA) ligands. The reaction proceeded *via* asymmetric epoxidation and ring-opening by the linked phenol cascade, affording 5a,6,10b,11-tetrahydrochromeno[2,3-*b*]-indol-10b-ol derivatives in up to 83% yield and 98% *ee* under mild reaction conditions.

Keywords: asymmetric catalysis; dearomatization; epoxidation; indoles; vanadium

Epoxides exist as key moieties in numerous natural products and biologically active molecules, and also serve as important synthetic intermediates associated with versatile sequential ring opening processes.[1] Since more than one stereogenic center could be launched in a single step, asymmetric epoxidation reactions have received broad research interest and witnessed dramatic growth during the past decades.[2] Enantiomerically enriched epoxides derived from unfunctionalized olefins,[3] electron-deficient olefins[4] and (homo)allylic alcohols[5] have been achieved by well-developed chiral catalytic systems including either transition metal catalysts or organocatalysts. Meanwhile, catalytic asymmetric dearomatization



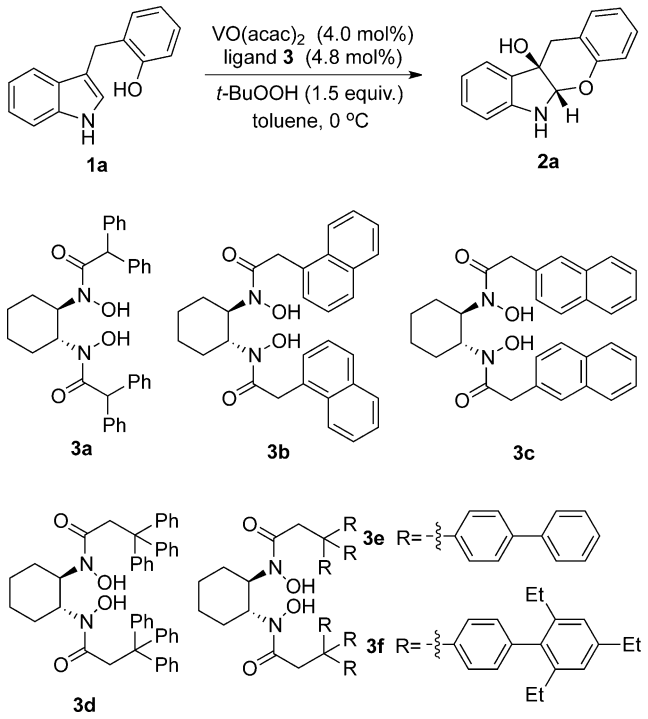
Scheme 1. Enantioselective epoxidative dearomatization reaction.

(CADA) reactions have recently witnessed rapid development due to their advantage in constructing complex molecules from relatively simple starting materials.[6] Particularly, oxidative dearomatization reactions of various electron-rich aromatic rings have a great potential in the total synthesis of natural products.[7,8] However, the enantioselective oxidative dearomatization reactions are far from being fully explored, and the dearomatization reactions *via* asymmetric epoxidation approaches are rare. In 2000, Ōmura, Smith and their co-workers reported the enantioselective synthesis of 3a-hydroxyfuroindolines from tryptophols using Sharpless asymmetric epoxidation conditions.[9] Recently, we realized the catalytic asymmetric epoxidation of tryptophol derivatives with the chiral vanadium complexes derived from the C_2 symmetric bis-hydroxamic acid (BHA) ligands introduced by Yamamoto and co-workers.[5,10,11] Interestingly, our recent studies led to successful asymmetric epoxidation of alkenylphenol substrates, which has not been documented before.[12] Herein, we report the CADA reaction of indole derivatives *via* vanadium-catalyzed asymmetric epoxidation and subsequent phenol ring-opening reaction sequence (Scheme 1).

Firstly, variation of the BHA ligand structure was performed on model substrate **1a**. Ligand **3a** with biphenyl moieties was utilized in the asymmetric epoxidative dearomatization reaction, and the desired product **2a** was afforded in 33% yield and 49% *ee* (entry 1, Table 1). Slight elevation of the enantioselectivity was achieved with ligands **3b** and **3c** embedded with relatively more flexible moieties than biphenyl groups (60% *ee* and 66% *ee*, respectively; entries 2 and 3). To our great delight, excellent enantioselective control was realized when ligand **3d** was utilized (91% *ee*, entry 4). However, ligands **3e** and **3f**, designed based on **3d** with modified trityl groups, could not provide **2a** with better results (81% *ee* and 78% *ee*, respectively; entries 5 and 6).

With the optimal ligand in hand, the reaction parameters were then further optimized. As shown in Table 2, several oxidants were tested with toluene as the solvent, and *t*-BuOOH was chosen as the best one (entries 1–4, Table 2). Cumene hydroperoxide (CHP), slightly bulkier than *t*-BuOOH, provided similar results (entries 1 and 2). Further examination of the sol-

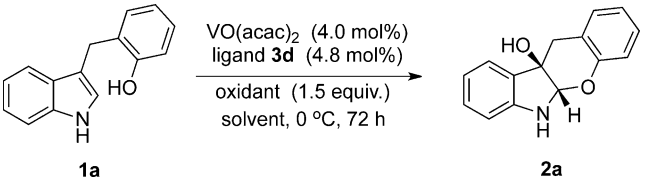
Table 1. Vanadium-catalyzed asymmetric epoxidation and ring-opening – ligand screening.[a]



Entry	Ligand	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	**3a**	72	33	49
2	**3b**	72	34	60
3	**3c**	72	34	66
4	**3d**	72	46	91
5	**3e**	72	40	81
6	**3f**	72	53	78

[a] *Reaction conditions:* 0.25 mmol **1a**, 4.0 mol% $VO(acac)_2$, 4.8 mol% ligand **3** and 0.375 mmol *t*-BuOOH (70% wt aqueous solution) in toluene (1.0 mL) at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis.

Table 2. Vanadium-catalyzed asymmetric epoxidation and ring-opening – reaction parameters.[a]



Entry	Oxidant	Solvent	Yield[b] [%]	ee[c] [%]
1	*t*-BuOOH	toluene	46	91
2	CHP[d]	toluene	49	89
3	*m*-CPBA	toluene	low conversion	–
4	30% H_2O_2	toluene	low conversion	–
5	*t*-BuOOH	CH_2Cl_2	58	95
6	*t*-BuOOH	THF	low conversion	–
7	*t*-BuOOH	MeOH	low conversion	–
8	*t*-BuOOH	*o*-xylene	46	92
9	*t*-BuOOH	$CHCl_3$	42	91
10[e]	*t*-BuOOH	CH_2Cl_2	46	94

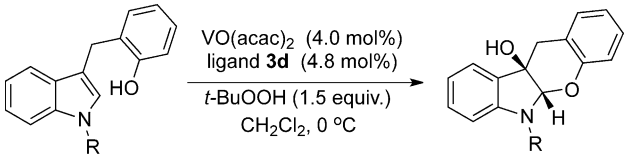
[a] *Reaction conditions:* 0.25 mmol **1a**, 4.0 mol% $VO(acac)_2$, 4.8 mol% ligand **3** and 0.375 mmol oxidant in solvent (1.0 mL) at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] CHP = cumene hydroperoxide.
[e] Room temperature, 4 h.

vent disclosed that reaction in CH_2Cl_2 delivered the best results (58% yield, 95% *ee*, entries 5–9). Further increasing the catalyst loading to 10 mol% led to slightly higher yield (62%) without affecting the *ee*. Finally, the reaction temperature was increased to facilitate the reaction rate. Unfortunately, a lower yield resulted due to the decomposition of the product at room temperature (46% yield, 94% *ee*, entry 10).

Prolonged reaction time (120 h) led to a slightly lower yield (50%) due to the decomposition of **2a** (entry 1, Table 3). Therefore, several N-protecting groups were investigated to offset the instability of the products caused by the free N–H of indoles. With a methyl group installed, the reaction occurred in a higher yield albeit with lower enantiomeric excess (62% yield, 86% *ee*, entry 2). When a Bn group was introduced, a significant improvement of yield was observed although the enantioselective control declined slightly (89% yield, 90% *ee*, entry 3). Other electron-donating groups such as *p*-MeO-C_6H_4 and 1-naphthyl led to similar results with higher yields but lower *ee* values (entries 4 and 5, Table 3). Finally, no desired product was detected when the Boc group was tested indicating that an electron-rich indole is needed for the current reaction (entry 6, Table 3).

Various N–H and N–Bn indole derivatives were then examined under the optimized reaction conditions (entry 5, Table 2). The results are depicted in Scheme 2. Excellent enantioselectivities and moderate yields were obtained for most N–H substrates with varied substituents (5-Cl, 6-Cl, 6-F, 6-Br, 5-Br, 4-Br, 7-Br and 7-CH_3) on the phenyl moiety of indoles (**2g**–**2n**, Scheme 2). Two N–Bn indole substrates were also investigated. As shown in Scheme 2, the dearomatized

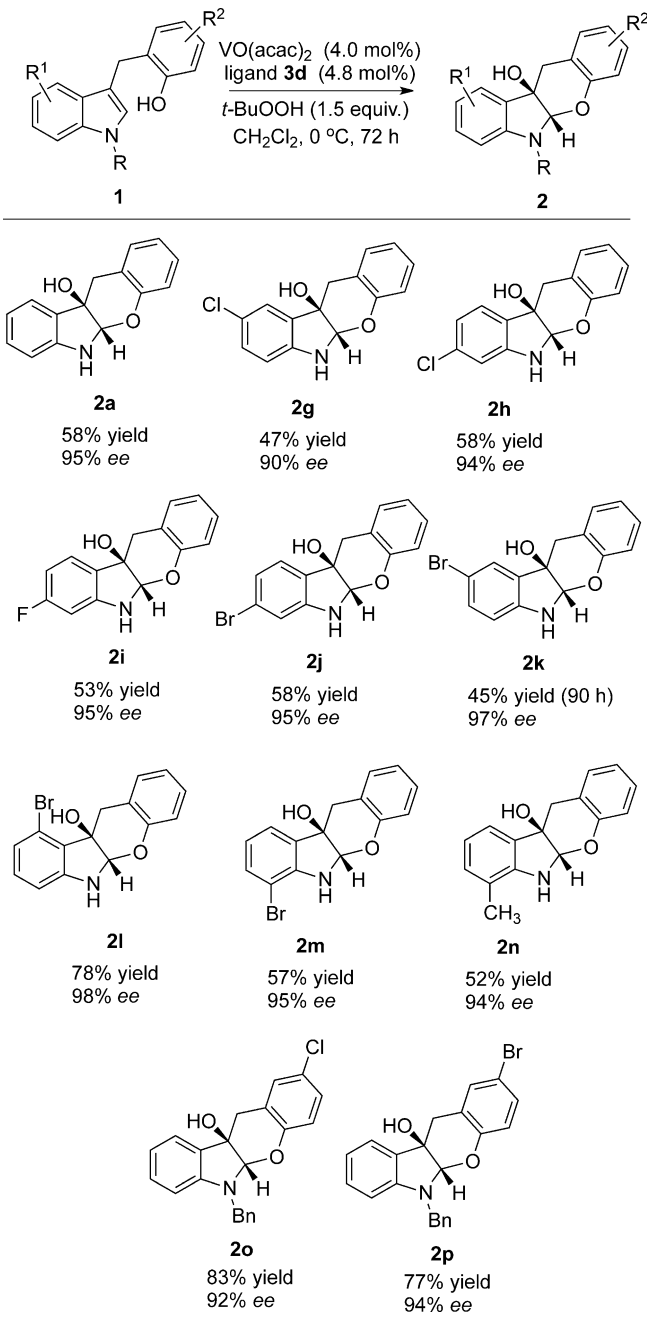
Table 3. Vanadium-catalyzed asymmetric epoxidation and ring-opening – N-protecting groups.[a]



1 2

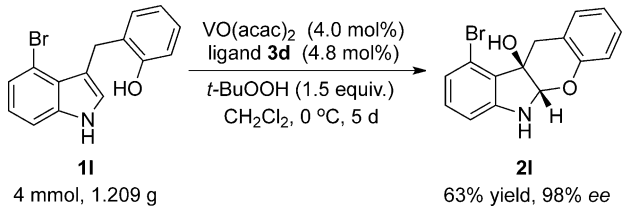
Entry	**1**, R	Time [h]	**2**, Yield[b] [%]	*ee*[c] [%]
1	**1a**, H	72/120	**2a**, 58/50	95/95
2	**1b**, Me	72	**2b**, 62	86
3	**1c**, Bn	48	**2c**, 89	90
4	**1d**, *p*-$MeOC_6H_4$	48	**2d**, 64	88
5	**1e**, 1-naphthyl	48	**2e**, 71	92
6	**1f**, Boc	24	**2f**, N.R.	–

[a] *Reaction conditions:* 0.25 mmol **1**, 4.0 mol% $VO(acac)_2$, 4.8 mol% ligand **3d** and 0.375 mmol *t*-BuOOH (70% wt aqueous solution) in CH_2Cl_2 (1.0 mL) at 0 °C.
[b] Isolated yield.
[c] The *ee* of **2** was determined by HPLC analysis.



Scheme 2. Vanadium-catalyzed asymmetric epoxidation and ring-opening – substrate scope.

products **2o** and **2p** were obtained in 83% and 77% yields, respectively, and the enantioselective control for these products was also satisfactory (**2o** and **2p**, Scheme 2).[13] Finally, a gram-scale reaction of **1l** was performed to evaluate the practicality of this asymmetric dearomatization reaction, and the corresponding product **2l** was obtained in 63% yield and 98% *ee* (Scheme 3). The absolute configuration was assigned as (5a*S*,10b*R*) by a single crystal X-ray analysis of enantiopure **2m**.[14]



Scheme 3. The gram-scale reaction.

In summary, we have developed an asymmetric dearomatization of indole derivatives *via* a vanadium-catalyzed asymmetric epoxidation followed with an intramolecular phenol-directed epoxide opening reaction. This process features excellent enantioselective control and operational simplicity. Studies to further extend the asymmetric epoxidative dearomatization reactions are currently ongoing in our laboratory.

Experimental Section

General Procedure for the Asymmetric Dearomatization Reaction of Indoles

To a solution of $VO(acac)_2$ (0.02 mmol, 5.2 mg) in DCM (2 mL) was added ligand **3** (0.024 mmol, 17.2 mg), and the mixture was stirred for 1 h at room temperature. The above mixture was stirred at 0 °C for 10 min, *tert*-butyl hydroperoxide (0.75 mmol, 104 μL, 70% aqueous solution) and substrate **1** (0.5 mmol) were then added. After the reaction was complete as monitored by TLC, aqueous saturated Na_2SO_3 (2 mL) was added. The organic layer was separated and the aqueous layer was extracted with DCM (3×2 mL). The combined organic layers were washed with brine (4 mL), separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (DCM/EtOAc = 40/1, v/v) to afford the desired product **2**.

Acknowledgements

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[13] All our attempts to deprotect *N*-benzyl groups have failed so far. These include Pd/C mediated hydrogenation (no reaction), Na/liquid NH_3 and Li/liquid NH_3 conditions (product decomposed), BBr_3 conditions (a messy mixture), and acylative conditions (no reaction). This is mainly due to the sensitive nature of the dearomatized products **2**. Thus, the N-H free substrates need to be used directly if the N-protecting groups are not needed.

[14] CCDC 1404683 (**2m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

