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Dearomatization of tryptophols *via* a vanadium-catalyzed asymmetric epoxidation and ring-opening cascade†

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An enantioselective epoxidation of tryptophols followed by an intramolecular epoxide opening reaction was realized by chiral vanadium catalysts derived from C_2 symmetric bis-hydroxamic acid (BHA) ligands. 3a-Hydroxyfuroindoline derivatives with up to 89% yield and 90% ee were obtained under mild reaction conditions.

As very useful tools in the total synthesis of natural products, dearomatization reactions have recently undergone their renaissance with the intention of developing new dearomative protocols and efficient stereoselective control of the processes.[1] In this area, oxidative dearomatization approaches are undoubtedly of great potential since large amounts of aromatic rings are electron-rich chemical entities, which are reactive under oxidative conditions.[2] In fact, oxidative dearomatization reactions have a long history in the total synthesis of natural products, and recent studies have contributed many valuable methodologies in an enantioselective manner.[3] However, the current developments in asymmetric oxidative dearomatization reactions should be pointed out: (1) the substrates are focused on phenols, and the vast majority of other aromatic rings have been relatively less explored; (2) the existing strategies of enantioselective control mainly rely on chiral oxidants or stepped reactions combining the oxidative dearomatization and the subsequent asymmetric desymmetrization;[4] (3) many well-established enantioselective oxidative conditions have not been fully taken into consideration for application to asymmetric dearomatization reactions, and thus relative utilization in the total synthesis is rare.

3a-Hydroxyfuroindoline represents a preliminary structure in numerous natural products (Fig. 1).[5–7] In 2000, Ōmura and co-workers reported a pioneering study using the Sharpless asymmetric epoxidation reaction and a subsequent intramolecular cyclization to build this valuable scaffold (Scheme 1).[5–8] However, due to the inherent limitation of the Sharpless asymmetric epoxidation reaction, a stoichiometric amount of the chiral Ti complex was required, and the experimental operation was very strict in order to achieve the best result. In contrast, several asymmetric catalytic systems have been demonstrated to be efficient for the epoxidation of electron-rich olefins.[9] Among them, the chiral vanadium complexes derived from the C_2 symmetric bis-hydroxamic acid (BHA) ligands designed by Yamamoto and co-workers proved to be ideal catalysts for the enantioselective epoxidation of allylic as well as homoallylic alcohols.[10] Given our continuous research interest in asymmetric dearomatization reactions to construct polycyclic compounds with multiple chiral centers,[11] we envisaged that an enantioselective catalytic epoxidation of tryptophols followed by an epoxide opening could yield the **3a**-hydroxyfuroindoline derivatives conveniently. Herein, we report such a catalytically enantioselective cascade oxidative dearomatization reaction.

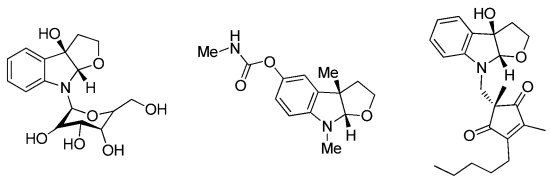
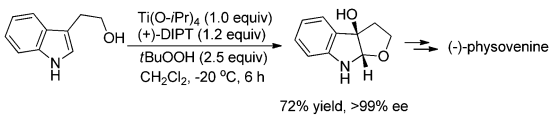


Fig. 1 Representative natural products with **3a**-hydroxyfuroindoline scaffold.



Scheme 1 Enantioselective synthesis of **3a**-hydroxyfuroindolines *via* the Sharpless asymmetric epoxidation reaction.

Firstly, tryptophol (**1a**) was selected as the model substrate to test the feasibility of our hypothesis. To our great delight, the initial testing with the catalyst derived from $VO(acac)_2$ and BHA

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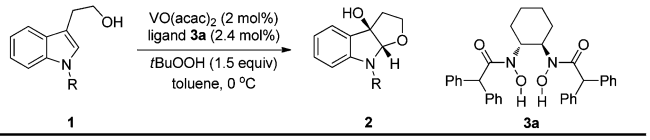
Table 1 Optimization of the reaction conditions – protecting groups[a]



1 2 3a

Entry	1, R	Time (h)	Yield of 2[b] (%)	ee[c] (%)
1	**1a**, H	14	**2a** 63	61
2	**1b**, Me	12	**2b** 66	43
3	**1c**, Bn	12	**2c** 62	82
4	**1d**, 1-naphthyl	18	**2d** 79	80
5	**1e**, 9-anthryl	18	**2e** 56	10
6	**1f**, Boc	18	**2f** trace	N.A.

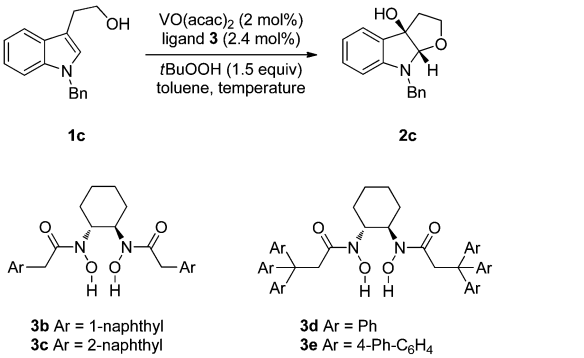
[a] Reaction conditions: 0.5 mmol **1**, 2.0 mol% $VO(acac)_2$, 2.4 mol% ligand **3a** and 0.75 mmol *t*BuOOH (70 wt% aqueous solution) in toluene (1.0 mL) at 0 °C. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H).

ligand **3a** provided the desired epoxide opening product **2a** in 63% yield and 61% ee (entry 1, Table 1). By comparing the sign of the optical rotation with that of the known compound reported in the literature, the absolute configuration of **2a** was assigned as (3a*R*,8a*S*).[6b,12] Several commonly used solvents were tested for this transformation, and toluene was found to be the optimal one.[12] Considering the possibility that the free N–H of indoles brings negative effects to the epoxidation transformation, various protecting groups were investigated.[12] As shown in Table 1, electron-donating and bulky groups (Bn and 1-naphthyl) on the indole *N* led to improved enantioselectivity (entries 3 and 4, Table 1). However, when the 9-anthryl group was introduced, the enantioselectivity dropped significantly, which might be due to the fact that this extremely bulky group was not suitable for the chiral environment provided by the vanadium complex during the epoxidation step (entry 5, Table 1). The Boc group was also tested, and the sluggish transformation revealed that electron-deficient substrates were not suitable for this reaction (entry 6, Table 1). Finally, Bn was selected as the protecting group.

Several BHA ligands with diverse chiral environments have been examined in the cascade reaction of **1c**, and ligand **3a** remained to be the optimal one in terms of the enantioselective control (entries 1–5, Table 2). Next, with 2.0 mol% of $VO(acac)_2$ and 2.4 mol% of ligand **3a**, the effect of the reaction temperature was further investigated. Lowering the reaction temperature to −10 °C led to a prolonged reaction time but an improved enantioselectivity (87% ee, entry 6, Table 2). However, further decreasing the reaction temperature to −30 °C could not improve the enantioselectivity any more (entry 7, Table 2).

With the optimal reaction conditions in hand, the scope of the reaction was then explored. The results are summarized in Scheme 2. For the *N*-Bn substrates with various substituents on the phenyl moiety of indoles, a good and parallel level of enantioselectivity could be provided, irrespective of the positions or the electronic natures of these substituents (83% to 90% ee, **2g** to **2n**, Scheme 2). Due to the moderate activity of all substrates during this transformation, prolonging the reaction time was anticipated to deliver their corresponding products in good yields. However, all the **3a**-hydroxyfuroindoline derivatives

Table 2 Optimization of the reaction conditions – chiral ligands and temperature[a]

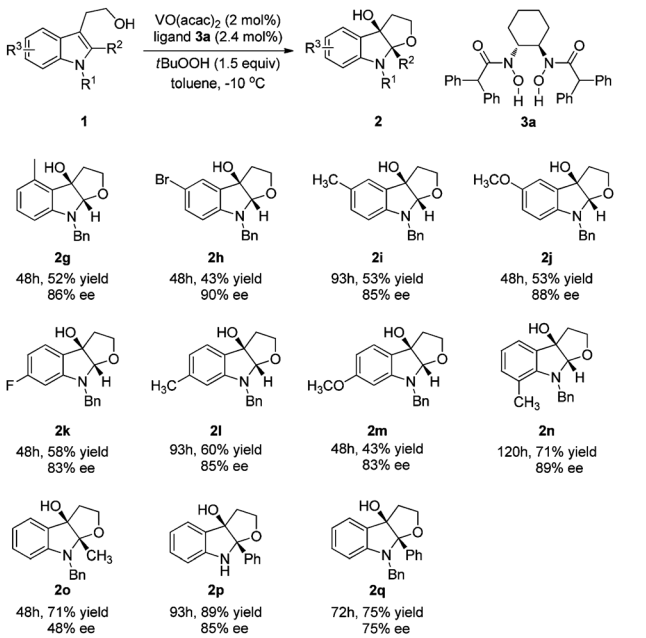


1c 2c

3b Ar = 1-naphthyl
3c Ar = 2-naphthyl
3d Ar = Ph
3e Ar = 4-Ph-C_6H_4

Entry	Ligand	*T* (°C)	Time (h)	Yield of 2c[b] (%)	ee[c] (%)
1	**3a**	0	12	62	82
2	**3b**	0	24	22	62
3	**3c**	0	24	26	66
4	**3d**	0	24	50	60
5	**3e**	0	24	43	67
6	**3a**	−10	24	70	87
7	**3a**	−30	36	49	87

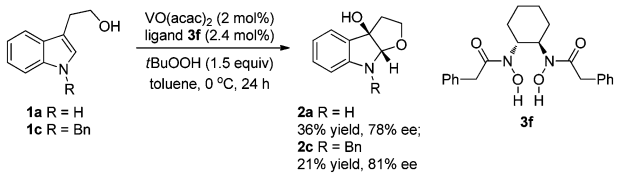
[a] Reaction conditions: 0.5 mmol **1c**, 2.0 mol% $VO(acac)_2$, 2.4 mol% ligand **3** and 0.75 mmol *t*BuOOH (70 wt% aqueous solution) in toluene (1.0 mL) at *T* °C. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H).



1 2 3a

Scheme 2 Substrate scope.[12]

decomposed to some extent during the reaction, and only reasonable yields could be obtained (43% to 70%, **2g** to **2n**, Scheme 2). Substrates with substituents at the 2-position of indoles were also explored. The substrate with the 2-methyl group provided the corresponding product with only moderate enantioselectivity (71% yield, 47% ee, **2o**, Scheme 2). However, the substrates with the 2-phenyl group were transformed to their corresponding products with relatively better results



Scheme 3 Epoxidation of **1a** and **1c** with ligand **3f**.[12]

(85% ee for **2p**, 75% ee for **2q**, Scheme 2). In contrast to the results from those substrates without 2-substituents, the *N*-protecting group was not necessary for this type of substrates to obtain good enantioselectivity. A gram-scale reaction was carried out for **1c**, and the desired product could be obtained in 66% yield and 87% ee, which were comparable with those of the 0.5 mmol scale reaction (entry 6, Table 2).[12]

Inspired by the results obtained for **2p** and **2q**, we envisaged that the substrates without the *N*-protecting group might provide good levels of enantioselectivity with an optimal chiral ligand. To our delight, the preliminary results indicated that a very simple BHA ligand **3f** could provide similar reasonable results for substrates **1a** and **1c** (Scheme 3). These results indicated that with a suitable chiral ligand, the tryptophol derivatives with or without the substituted group on indole *N* could all be suitable substrates for this cascade reaction to deliver the **3a**-hydroxyfuroindoline derivatives with good enantioselectivity. It should also be mentioned that due to the inherent stability of the chiral vanadium catalyst to moisture and air, the reaction could be operated in air with a readily available aqueous oxidant (70 wt% aqueous solution of *t*BuOOH for the present reaction).

In summary, we have developed an enantioselective epoxidative dearomatization of tryptophols followed by an intramolecular epoxide opening reaction to construct the framework of enantio-enriched **3a**-hydroxyfuroindoline derivatives in moderate yields and good levels of enantioselectivity. Further extension of the reaction scope and the synthetic application of this methodology are currently underway in our laboratory.

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