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Catalytic Enantioselective Synthesis of Spirooxindoles by Oxidative Rearrangement of Indoles

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Abstract: Oxidative rearrangement of indoles to access oxindoles has been widely used as a key step in complex molecule synthesis. Herein we report a catalytic enantioselective variant of this transformation by chiral phosphoric acid catalysis, providing rapid access to a range of enantioenriched spirooxindoles. The high enantioselectivity is controlled by dynamic kinetic resolution.

Spirooxindole is a ubiquitous substructure in natural products and bioactive molecules.[1] Specifically, the pyrrolidinyl-spirooxindole unit represents a privileged core of a plethora of alkaloids and therapeutic agents (Figure 1).[1a-b,2] Their appealing molecular architecture and versatility as intriguing pharmacophore have attracted enormous synthetic efforts.[1-5] Oxidative rearrangement of tetrahydro-β-carbolines is considered biomimetic and presents the most popular approach owing to its conciseness and ready substrate accessibility (Scheme 1a).[1,4,5] However, a catalytic enantioselective variant of this transformation still remains elusive.

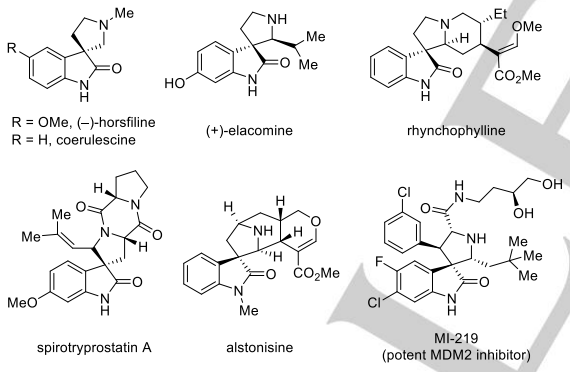
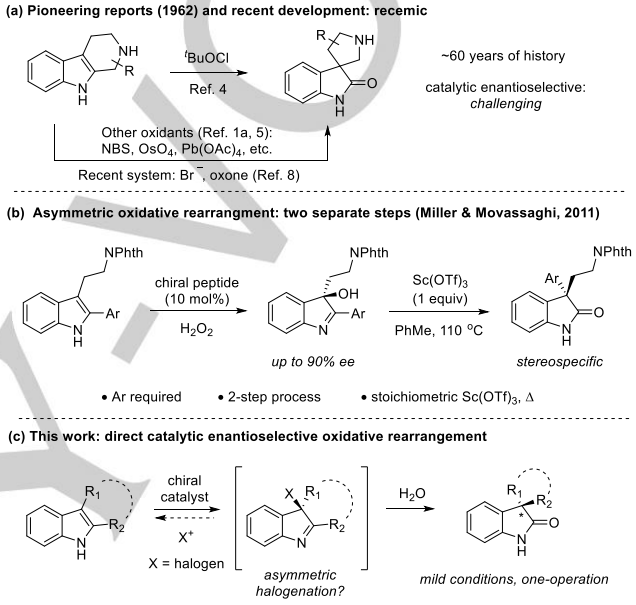


Figure 1. Useful molecules with a pyrrolidinyl-spirooxindole unit.

In 2011, Miller and Movassaghi reported an elegant peptide-catalyzed asymmetric oxidation of indoles to enantioenriched 3-hydroxy-indolenines, which underwent stereospecific rearrangement to enantioenriched oxindoles mediated by stoichiometric $Sc(OTf)_3$ at 110 °C (Scheme 1b).[6] However, this two-step process likely cannot be rendered truly catalytic in one operation due to the incompatible and relatively harsh conditions in the second step.[7] Furthermore, the required 2-aryl substituent in the indole substrate also prevented its application in the synthesis of pyrrolidinyl-spirooxindoles. Thus, a mild one-step catalytic enantioselective variant remains in high demand.



Scheme 1. Oxidative rearrangement of indoles

The forcing conditions in the rearrangement of 3-hydroxy-indolenine might be related to the weak leaving ability of the 3-hydroxyl group. On the other hand, electrophilic halogen sources have been well-established oxidants to achieve mild rearrangement.[1a,5] Recently, Tong and coworkers reported an elegant green protocol with in-situ generated Br^+ as oxidant (Scheme 1a).[8] We hypothesized that catalytic asymmetric halogenation in the indole 3-position might lead to an enantioenriched 3-halo-indolenine intermediate. The good leaving ability of halide should allow the subsequent stereospecific rearrangement to take place under mild conditions (Scheme 1c).

We employed Boc-protected tetrahydro-β-carboline **1a** as substrate and NBS as oxidant (Table 1). Chiral phosphoric acids (CPAs) were chosen as catalysts in view of their proven performance in asymmetric halogenation.[9,10] THF was used as solvent to allow some solubility of water, the oxygen source. The reaction of **1a** proceeded at 0 °C to form the desired product **2a** in essentially quantitative yield within 30 min. However, very low enantioselectivity was observed with **A1** as catalyst (18% ee, entry 1). Subsequent screening identified **B3** as the best catalyst (entry 6). Further optimization of other parameters (details in the SI) indicated that water loading was important.[11] By reducing the ratio of H_2O/THF from 5:7 to 1:7, the enantioselectivity was improved to 44% ee (entry 7). Further decreasing the ratio was not beneficial. The use of selectfluor and NCS as oxidant resulted in racemic product (entries 8-9). However, NIS led to dramatic increase in enantioselectivity (91% ee, entry 10). Other I^+-based oxidants did

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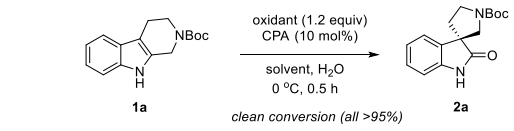
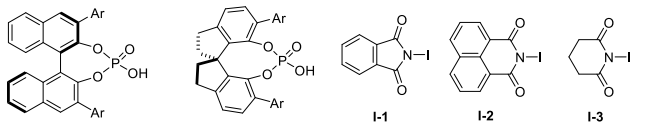
not further improve the good selectivity (entries 11-13). Other solvents were inferior (entries 14-15). Finally, decreasing the reaction temperature to –45 °C enhanced the enantioselectivity to 95% ee. The water loading was also decreased to avoid freezing (entry 16).

Table 1. Optimization of conditions.[a]



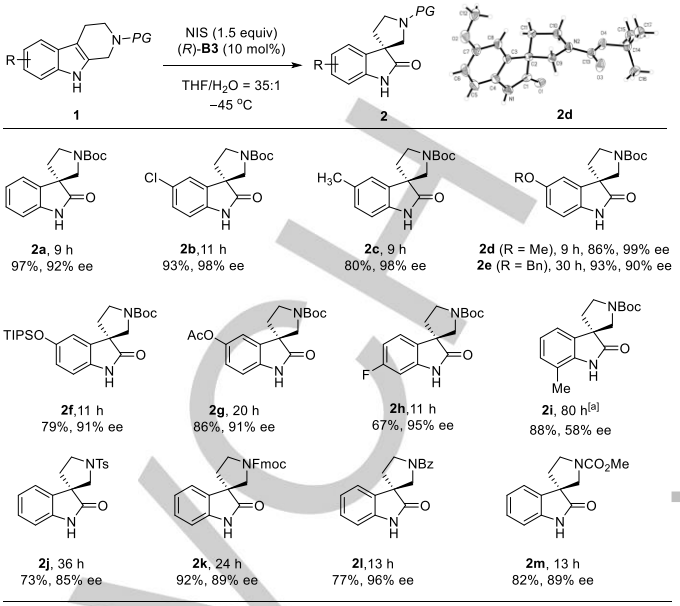


A1: Ar = 2,4,6-$Cy_3C_6H_2$ **B1**: Ar = 9-phenanthryl
A2: Ar = 9-phenanthryl **B2**: Ar = 9-anthracenyl
A3: Ar = 9-anthracenyl **B3**: Ar = 1-pyrenyl

entry	CPA	solvent	oxidant	ee (%)[b]
1	(*S*)- **A1**	THF	NBS	18
2	(*S*)- **A2**	THF	NBS	28
3	(*R*)- **A3**	THF	NBS	−27
4	(*S*)- **B1**	THF	NBS	−23
5	(*S*)- **B2**	THF	NBS	−33
6	(*R*)- **B3**	THF	NBS	34
7[c]	(*R*)- **B3**	THF	NBS	44
	Evaluation of other oxidants			
8[c]	(*R*)- **B3**	THF	Selectfluor	0
9[c]	(*R*)- **B3**	THF	NCS	0
10[c]	(*R*)- **B3**	THF	NIS	91
11[c]	(*R*)- **B3**	THF	**I-1** (1 h)	91
12[c]	(*R*)- **B3**	THF	**I-2** (1 h)	86
13[c]	(*R*)- **B3**	THF	**I-3** (1 h)	91
14[c]	(*R*)- **B3**	CH_3CN	NIS	54
15[c]	(*R*)- **B3**	acetone	NIS	66
16[c][d]	(*R*)- **B3**	THF	NIS (4 h)	95

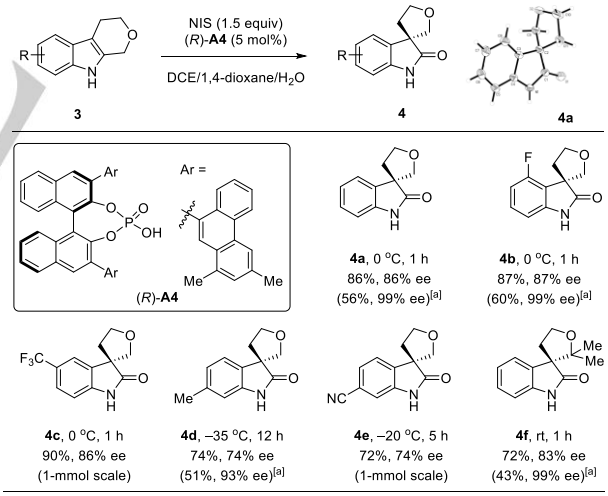
[a] **1a** (0.05 mmol), catalyst (10 mol%), oxidant (0.075 mmol), solvent (0.7 mL), H_2O (0.5 mL). [b] Ee value was determined by HPLC with a chiral stationary phase. [c] H_2O (0.1 mL). [d] H_2O (20 μL), –45 °C. Boc = *tert*-butyloxycarbonyl, NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide.

At a relatively larger scale, the NIS loading was increased to 1.5 equivalents to shorten the reaction time (Scheme 2). Thus, a range of tetrahydro-β-carbolines reacted to form the pyrrolidinyl-spirooxindoles with good to excellent efficiency and enantioselectivity. Various substituents on the indole ring did not affect the excellent outcome, except for **2i**. The low reactivity and enantioselectivity for **2i** was likely due to interference of the adjacent methyl substituent with hydrogen-bond interaction in the N-1 position. The mild conditions tolerated diverse functional groups, including aryl halide, ether, silyl-protected alcohol, and ester. Different *N*-protective groups were also suitable.



Scheme 2. Reaction scope. **1** (0.5 mmol), (*R*)-**B3** (10 mol%), NIS (1.5 equiv), THF/H_2O (v/v = 35:1, 7 mL), −45 °C. [a] Run with 15 mol% of (*R*)-**B3**. Ts = *p*-toluenesulfonyl, Fmoc = fluorenylmethoxycarbonyl, Bz = benzoyl.[16]

This process can also provide access to enantioenriched tetrahydrofuranyl-sprooxindoles (Scheme 3), another important core found in diverse natural and bioactive molecules.[12] Further condition optimization indicated that catalyst **A4** was able to induce good enantioselectivity for this type of molecules (see the SI for details). Notably, all these products are crystalline and their enantiopurity could be easily enhanced to an excellent level by crystallization.



Scheme 3. Synthesis of tetrahydrofuranyl-sprooxindoles. **3** (2.0 mmol), (*R*)-**A4** (5 mol%), NIS (1.5 equiv), H_2O (4 mL), DCE/1,4-dioxane (v/v = 1:1, 28 mL). Isolated yield. [a] Data in parentheses are after crystallization.[16]

We also examined other types of substrates (Scheme 4). For example, with catalyst **B2**, indole **1o**, without ring fusion in the 2,3-positions, reacted to afford the highly enantioenriched 3,3-disubstituted oxindole **2o**. Furthermore, indoles **5a–b** resulted in products **6** with ring fusion at the 2-position. The structure of **6b** was confirmed by X-ray crystallography.[16] While this inverted rearrangement has been known before,[13] the distinct selectivity control by such a minor difference in substituents is intriguing. It is believed that the heteromethyl substituent has a higher propensity to migrate.[14] Unfortunately, indole **1n** fused with a seven-membered nitrogen ring did not undergo rearrangement (see the SI for details).

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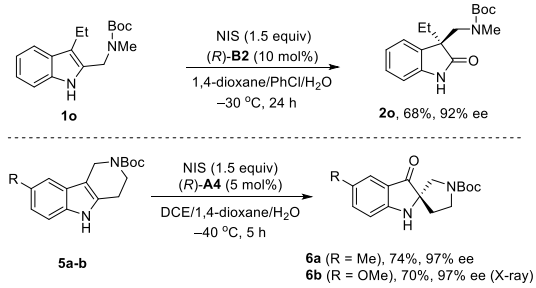
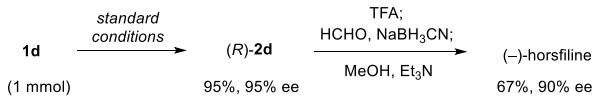


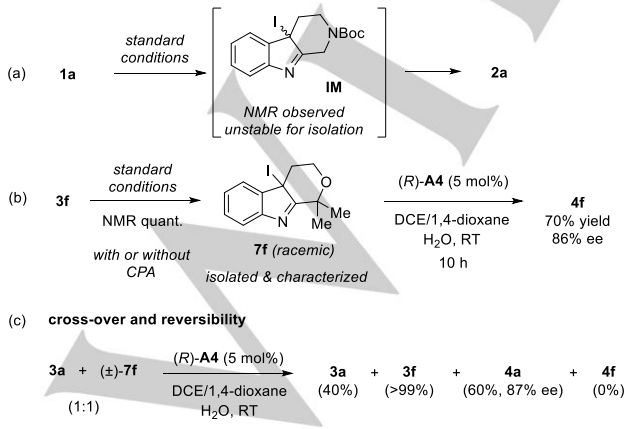
Scheme 4. Other substrates.

A 1-mmol reaction of **1d** successfully produced (*R*)-**2d** (Scheme 5). Subsequent simple steps led to the synthesis of natural product (–)-horsfiline (Figure 1). Compared with its previous synthesis,[5b] our protocol is more efficient and does not require a chiral auxiliary.



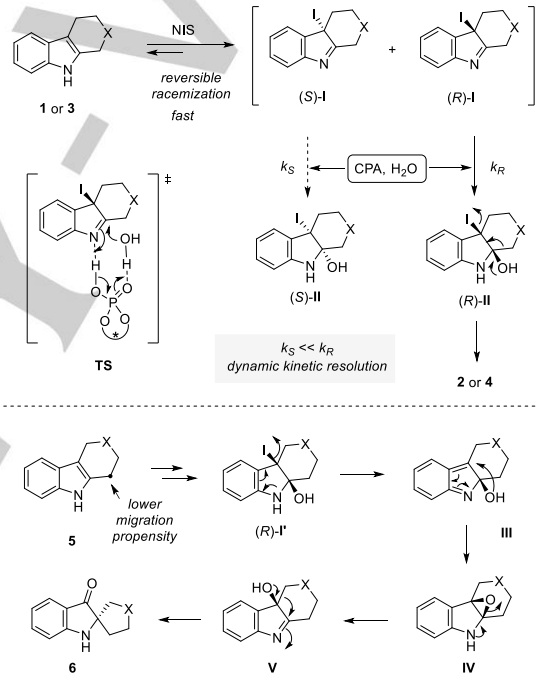
Scheme 5. Synthesis of (−)-horsfiline. TFA = trifluoroacetic acid.

Some control experiments were designed to understand the mechanism (Scheme 6). During the standard reaction of **1a**, we were able to observe an intermediate (likely **IM**) that was initially formed and then consumed. However, it was unstable for characterization (Scheme 6a). Gratifyingly, with substrate **3f**, the corresponding intermediate **7f** was stable enough for chromatography and full characterization. Unfortunately, **7f** was found to be racemic. However, when it was subjected to the rearrangement conditions with **A4**, oxindole **4f** was obtained in 86% ee. This observation excluded the possibility of asymmetric halogenation as the enantiodetermining step. Further attempt to obtain an enantioenriched sample of **7f** proved fruitless. Indeed, a solution of **7f** gradually turned purple (likely due to iodine formation), together with formation of substrate **3f**. This observation suggested that the halogenation step is reversible. We then carried out a cross-over experiment. In the absence of NIS, a 1:1 mixture of **3a** and **7f** was treated with catalyst **A4** (Scheme 6c). The cross-over product **4a** was formed in 60% yield and 87% ee, and **7f** was completely converted back to **3f**. The slow rearrangement of **7f** to **4f** failed in this competition due to steric issue. These results further confirmed that the halogenation step is reversible and the following step determines enantioselectivity.



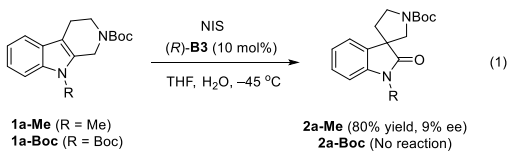
Scheme 6. Mechanistic studies.

Based on the above results, we proposed a possible mechanism (Scheme 7). The reaction begins with rapid and reversible halogenation in the indole 3-position, leading to racemic intermediate **I**. Then, water addition to the imine motif generates hemiaminal **II**. As depicted in the transition state (**TS**), the CPA serves as a bifunctional catalyst to activate both imine **I** and water. Thus, the two enantiomers of **I** react in different rates due to chiral recognition by the catalyst, with (*R*)-**I** being much faster that (*S*)-**I**. The slow (*S*)-**I** then racemizes via reversible halogenation, thereby representing a dynamic kinetic resolution scenario. Finally, the predominant (*R*)-**II** isomer undergoes 1,2-migration to form the enantioenriched oxindole product. To further account for the inverted rearrangement of substrate **5** where the 3-substituent has a higher migration propensity, we believe that the first few steps follow the same pathway to hemiaminal (*R*)-**I'**. Due to the low migration ability of the 2-substituent, it cyclizes to form epoxide **IV**, presumably via aza-quinone methide **III**.[14] Subsequent epoxide ring-opening assisted by the amine lone pair forms 3-hydroxylindolimine **V**. Finally, a semi-pinacol type rearrangement furnishes the product **6**.



Scheme 7. Proposed mechanism.

Next, we examined the reactions of the *N*-protected substrates **1a-Me** and **1a-Boc** (eq 1). The former was reactive toward oxindole product **2a-Me**, but with almost no enantioselectivity, suggesting the crucial role of hydrogen bonding for enantiocontrol. The latter one did not show any reactivity, presumably due to the reduced electron density of the indole ring because of the Boc group.



In conclusion, we have developed a catalytic enantioselective oxidative rearrangement of indoles to oxindoles. This process is particularly well-suited for the rapid assembly of spirooxindoles. With NIS as the superior oxidant and a suitable CPA as the catalyst, high

efficiency and excellent enantioselectivity have been achieved under mild conditions. This protocol has also been applied in a concise synthesis of (–)-horsfiline. Mechanistically, this process involves rapid and reversible halogenation followed by water addition and rearrangement. Dynamic kinetic resolution of the racemic halide intermediate is responsible for the observed high enantioselectivity, in which CPA serves as a bifunctional catalyst.

Acknowledgements

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Keywords: asymmetric catalysis • organocatalysis • hydrogen bonds • heterocycles • rearrangement

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[16] The X-ray data have been deposited at the Cambridge Crystallographic Data Center (CCDC 2024347 for **2d**, CCDC 2024348 for **4a**, and CCDC 2024354 for **6b**).

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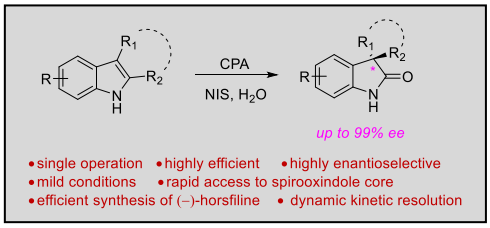

A catalytic asymmetric oxidative rearrangement of indoles to oxindoles with high efficiency and enantioselectivity is achieved. This process is particularly powerful for the assembly of spirooxindoles, a privileged core structure of natural products.