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Organocatalytic Enantioselective Stereoablative Hydroxylation of 3-Halooxindoles: An Effective Method for the Construction of Enantioenriched 3-Substituted 3-Hydroxy-2-Oxindoles

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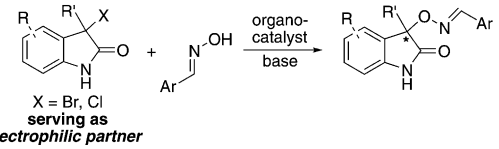
The highly efficient and stereoselective construction of enantioenriched heterocyclic compounds has attracted considerable attention in organic synthesis. In particular, the 3-substituted 3-hydroxy-2-oxindole framework has emerged as an attractive synthetic target, because of its prevalence in a large number of alkaloid natural products and pharmaceutically relevant compounds.[1] Additionally, it has been shown that both the defined substituent and the absolute configuration of the tetrasubstituted stereogenic center at C-3 of the 3-hydroxy-2-oxindoles greatly influence the biological activity.[1,2] Accordingly, the importance of the 3-substituted 3-hydroxy-2-oxindole scaffold in synthetic and medicinal chemistry continues to encourage the development of creative methods to access this relevant structural motif.[3] Recent asymmetric synthetic methods for 3-substituted 3-hydroxy-2-oxindoles mainly include the nucleophilic addition to isatins,[4] the hydroxylation of 3-monosubstituted oxindoles,[5] and other cyclization reactions.[6] However, the development of an alternative and efficient strategy for the construction of structurally diverse 3-substituted 3-hydroxy-2-oxindoles is of great importance and highly desirable. Herein, we report an unprecedented synthetic method for the construction of optically active 3-substituted 3-hydroxy-2-oxindoles in high yields and excellent enantioselectivities with broad substrate scope.

The stereoselective functionalization of the 3-substituted oxindole moiety, in which this unit serves as a nucleophile, has proven to be the most commonly used method for the preparation of oxindoles bearing a tetrasubstituted stereogenic center at C-3.[3,5,7] In sharp contrast, the process taking advantage of the oxindole moiety as electrophilic partner to build a tetrasubstituted stereocenter at C-3 of the oxindole skeleton remains highly underdeveloped.[8] Consequently, this prompted us to explore a more novel method by using the 3-substituted oxindole moiety as an electrophile for generating optically active 3,3-disubstituted oxindole derivatives. We envisioned that the realization of this concept would open new avenues to access the important oxindole framework containing a tetrasubstituted stereogenic center at C-3 of the oxindole. Therefore, on the basis of some successes in stereoablative reactions[8a,9] and as a continuation of our investigations aimed at developing new strategies for the synthesis of structurally diverse 3,3-disubstituted oxindole derivatives,[10] we developed a new strategy for the enantioselective synthesis of 3-substituted 3-hydroxy-2-oxindoles through stereoablative hydroxylation of 3-halooxindoles with environmentally benign organocatalysts and by using oximes[11] as oxygen nucleophiles (Scheme 1). To the best of our knowledge, this represents the first example employing 3-substituted oxindoles as electrophilic partners for the generation of enantioenriched 3-substituted 3-hydroxy-2-oxindole derivatives.



Scheme 1. Stereoablative hydroxylation of 3-halooxindoles.

Our initial studies focused on the reaction between racemic 3-benzyl-3-bromooxindole (**2a**) and (*E*)-benzaldehyde oxime (**3a**) by using a series of cinchona alkaloids **1a–i** as catalysts (Table 1). The reaction proceeded smoothly in THF at room temperature without any chiral catalyst and with only one equivalent of K_2CO_3 as base, giving product **4a** in 83% yield (Table 1, entry 1). When adding 20 mol% quinidine (**1a**) as chiral catalyst, **4a** was produced in 88% yield, but surprisingly as a racemic mixture (Table 1,

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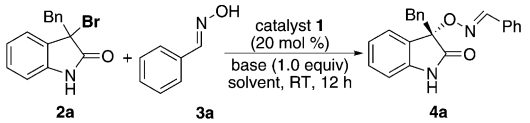
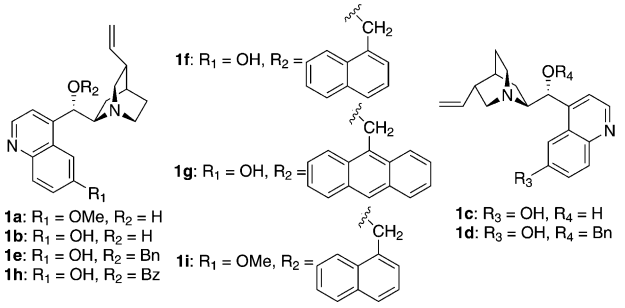
Table 1. Screening of various conditions for the reaction between 3-benzyl-3-bromooxindole (**2a**) and (*E*)-benzaldehyde oxime (**3a**).[a]





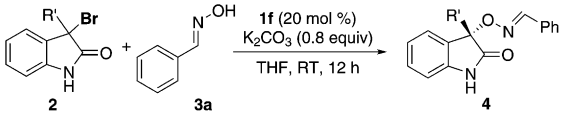
Entry	1	Solvent	Base	Yield [%][b]	*ee* [%][c]
1	–	THF	K_2CO_3	83	–
2	**1a**	THF	K_2CO_3	88	0
3	**1b**	THF	K_2CO_3	93	55
4	**1c**	THF	K_2CO_3	93	93[d]
5	**1d**	THF	K_2CO_3	88	96[d]
6	**1e**	THF	K_2CO_3	90	96
7	**1f**	THF	K_2CO_3	88	99
8	**1g**	THF	K_2CO_3	86	97
9	**1h**	THF	K_2CO_3	87	38
10	**1i**	THF	K_2CO_3	83	0
11	**1f**	DCM	K_2CO_3	90	97
12	**1f**	EtOAc	K_2CO_3	88	95
13	**1f**	toluene	K_2CO_3	89	86
14	**1f**	THF	Na_2CO_3	60	96
15	**1f**	THF	$KHCO_3$	83	99
16	**1f**	THF	Et_3N	64	96
17	**1f**	THF	DIPEA	69	92
18	**1f**	THF	K_2CO_3	89	99[e]

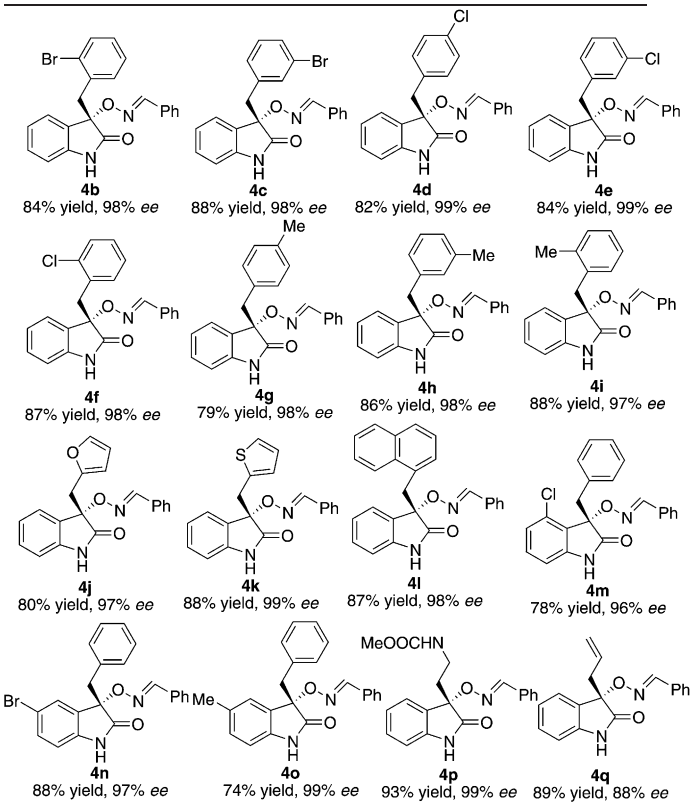
[a] Unless otherwise noted, reactions were carried out with **2a** (0.1 mmol), **3a** (0.12 mmol), base (0.1 mmol), and **1** (0.02 mmol) in the solvent (1.0 mL) at room temperature for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The opposite configuration of the product was observed. [e] 0.08 mmol K_2CO_3 were used. Bn = benzyl; Bz = benzoyl; DIPEA = *N*,*N*-diisopropylethylamine.

entry 2). However, the reaction with catalyst **1b** bearing a C6′−OH group gave **4a** in 93% yield with 55% *ee* (Table 1, entry 3). Encouraged by this promising lead, we next examined the other catalysts under the same reaction conditions (Table 1, entries 4–10). Catalyst **1f** was found to be the most effective in comparison with catalysts **1a–e** and **1g–i**, giving **4a** in 88% yield with 99% *ee* (Table 1, entry 7). Notably, the pronounced effect of the C6′−OH (**1b–h**) or C6′−OMe (**1a** and **1i**) groups on the asymmetric induction demonstrates that the C6′−OH group is of vital importance for the enantioselectivity (Table 1, entries 3–9 vs. 2 and 10). Afterwards, the screening of different solvents revealed THF to be the most suitable solvent in terms of enantioselectivity (Table 1, entry 7 vs. entries 11–13). Additionally, the investigation of bases showed that the use of 0.8 equivalents of K_2CO_3 was an optimum parameter for the reaction (Table 1, entry 18 vs. entries 7 and 14–17).

With the optimized conditions in hand, we turned our focus on the substrate scope and generality of the reaction. At first, a wide range of 3-substituted 3-bromooxindoles **2** were prepared[12] and reacted with (*E*)-benzaldehyde oxime (**3a**) under the optimized conditions (Table 2). We were

Table 2. Substrate scope for the **1f**-catalyzed reaction of (*E*)-benzaldehyde oxime (**3a**) with various 3-substituted-3-bromooxindoles **2**.[a]





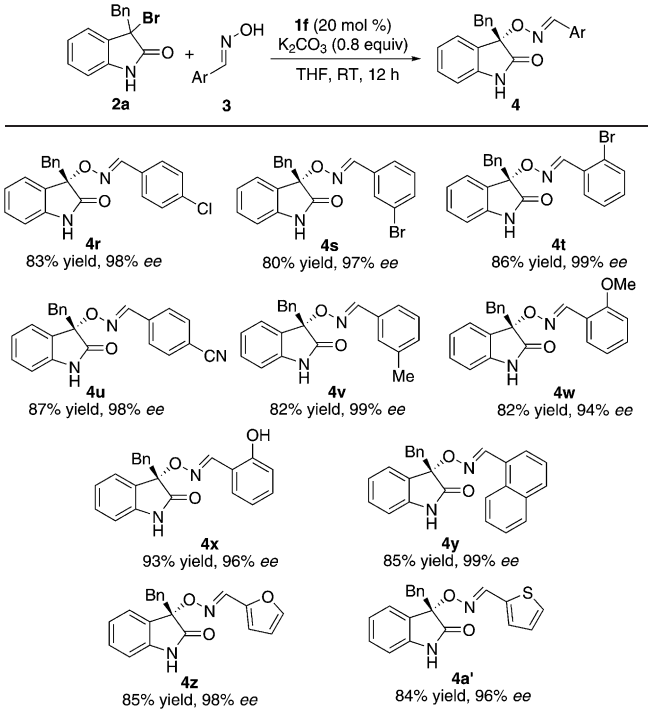
[a] All reactions were performed by using **2** (0.1 mmol), **3a** (0.12 mmol), K_2CO_3 (0.08 mmol), and **1f** (0.02 mmol) in THF (1.0 mL) at room temperature for 12 h. All yields refer to isolated yields of products. The *ee* values were determined by chiral HPLC.

pleased to find that the introduction of electron-withdrawing or -donating groups on both the oxindole core and the benzene ring of the R′ group smoothly provided the corresponding products in good yields (74–88%) with excellent enantioselectivities (96–99% *ee*) (Table 2, **4b–i** and **4m–o**). Nevertheless, oxindoles **2** bearing a heteroaromatic ring on the R′ group were also viable substrates for the **1f**-catalyzed enantioselective stereoablative hydroxylation reaction (Table 2, **4j–k**). Meanwhile, we also found that the bulkier 3-naphthalen-1-ylmethyl-3-bromooxindole could be readily transformed into the desired product **4l** in 87% yield with 98% *ee*. Notably, a functional group, such as methoxycarbonylamide, incorporated into the substituent at C-3 of the oxindole core, was very well tolerated under the mild reaction

conditions (Table 2, **4p**). Even with a substrate bearing an allyl substituent at C-3 of the oxindole core, a good yield and enantioselectivity (89% yield, 88% *ee*) were obtained (Table 2, **4q**).

To further explore the substrate scope of the developed methodology, we attempted to change the structure of oximes **3**. We prepared a library of aromatic aldehyde oximes **3** and employed them in the reaction with 3-benzyl-3-bromooxindole (**2a**) under the optimized reaction conditions (Table 3). Gratifyingly, high yields and excellent enantioselectivities were obtained in all cases. Nevertheless, studies also showed that various functional groups incorporated into the phenyl group of the oximes were well-tolerated under the mild reaction conditions (Table 3, **4r–w**), and even an unprotected hydroxyl group could be used without any difficulty (Table 3, **4x**). Furthermore, a bulkier oxime, such as (*E*)-1-naphthaldehyde oxime, gave the corresponding product **4y** with 99% *ee*. Heteroaromatic aldehyde oximes could also be employed in this reaction to give the expected products with excellent enantioselectivities (Table 3, **4z** and **4a′**).

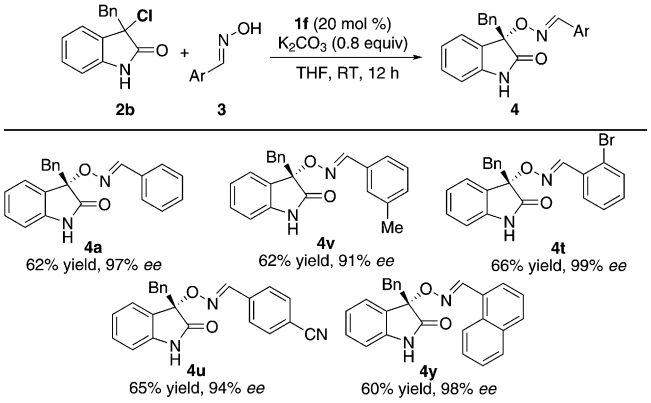
Table 3. Substrate scope for the **1f**-catalyzed reaction of 3-benzyl-3-bromooxindole (**2a**) with various oximes **3**.[a]



[a] For details, see the footnote of Table 2.

Furthermore, we also applied the newly developed enantioselective stereoablative hydroxylation protocol to 3-benzyl-3-chlorooxindole (**2b**). To our delight, the reactions between **2b** and some oximes **3** proceeded well to give the desired products in good yields (60–66%) with high to excellent enantiomeric excesses ranging from 91 to 99% *ee* under the standard reaction conditions (Table 4). Moreover,

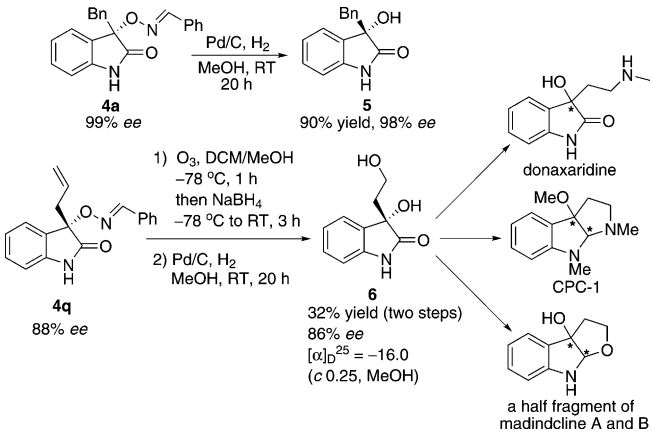
Table 4. Substrate scope for the **1f**-catalyzed reaction of 3-benzyl-3-chlorooxindole (**2b**) with various oximes **3**.[a]



[a] For details, see the footnote of Table 2.

these reactions also revealed that the variation of the electronic and steric properties of the functional groups at the benzene ring of oximes **3** had no drastic effect on the reactivity and enantioselectivity.

With product **4a** as starting material, the 3-benzyl-3-hydroxy-2-oxindole **5** could be readily accessed by hydrogenation with $Pd/C/H_2$ in MeOH at room temperature for 20 h without loss in enantiopurity (Scheme 2).[13] The product **4q** is a potentially valuable building block for asymmetric synthesis, as it is functionalized with an allyl group at C-3. As shown in Scheme 2, **4q** could be readily converted to a synthetically important chiral 1,3-diol oxindole **6** in two steps.[13] It is worth noting that 1,3-diol oxindole **6** is the precursor for the asymmetric synthesis of chiral donaxaridine,[2d] CPC-1, and a half fragment of madindcline A and B (Scheme 2).[14] By comparison of the optical rotation of **6** with that reported in the literature, we assigned the absolute configuration as *S*.[14] As no reaction occurred at the stereogenic center in **4q** during the transformations into **6**, **4q** was thus assigned as *S* configured. The absolute configurations



Scheme 2. Transformations of the products and the potential synthetic application.

of the remaining products shown in Tables 2–4 were tentatively proposed by analogy.

Although a detailed mechanism has yet to be elucidated, a plausible transition state model, based on the experimental results and previous studies,[8a,9] is proposed in Figure 1.

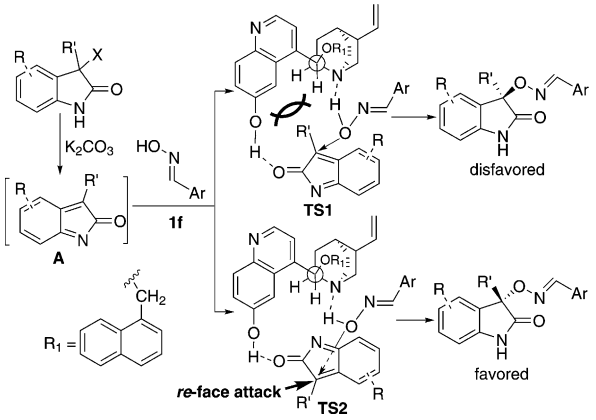


Figure 1. Proposed transition state for the enantioselective stereoablative hydroxylation of 3-halooxindoles.

In the present catalytic system, a putative *o*-azaxylylene intermediate **A** is readily generated in situ from 3-halooxindoles and K_2CO_3.[8a,9b] The synergistic cooperative activation of the intermediate **A** and oxime by the hydroxyl and tertiary amine group of **1f** is likely to be essential for the observed high enantioselective discrimination. The *S* configuration is predominately formed when the oxime attacks the *re*-face of the *o*-azaxylylene intermediate **A**. However, the transition state **TS1** should be disfavored, likely owing to the severely steric repulsion between the catalyst and the R′ group of intermediate **A**.

In conclusion, we have developed an unprecedented method for the construction of enantioenriched 3,3-disubstituted oxindoles through a stereoablative hydroxylation of 3-halooxindoles with a cinchona alkaloid derivative as catalyst and by using aromatic oximes as hydroxylating agents. The protocol is amenable to a wide variety of substrates, affording structurally diverse hydroxylated 3-substituted oxindoles in high yields (up to 93%) and excellent enantioselectivities (up to 99% *ee*) under mild conditions. Notably, the current process that uses 3-substituted oxindoles as electrophilic partners not only differs from the convention of commonly using 3-substituted oxindoles as nucleophiles, but also provides a viable entry to optically active 3-substituted 3-hydroxy-2-oxindole derivatives. Further efforts will be devoted to understanding the reaction mechanism, as well as developing more catalytic asymmetric systems to expand the application of 3-halooxindoles as electrophiles.

Experimental Section

General experimental procedure for the enantioselective stereoablative hydroxylation of 3-halooxindoles: A solution of 3-alkyl halooxindole **2** (0.1 mmol), aromatic oxime **3** (0.12 mmol), catalyst **1f** (0.02 mmol) and K_2CO_3 (0.08 mmol) in THF (1 mL) was stirred at room temperature for 12 h. Then, the reaction mixture was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give the corresponding product **4**.

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Keywords: alkaloids · asymmetric catalysis · organocatalysis · oximes · oxindoles

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Asymmetric Synthesis

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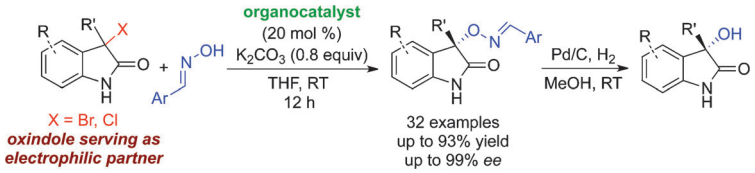
Organocatalytic Enantioselective Stereoablative Hydroxylation of 3-Halooxindoles: An Effective Method for the Construction of Enantioenriched 3-Substituted 3-Hydroxy-2-Oxindoles



3-Substituted oxindoles as electrophilic partners: An unprecedented method for the construction of hydroxylated 3-substituted oxindoles in high yields and excellent enantioselectivities through stereoablative hydroxylation of 3-halooxindoles with an organocatalyst has been developed. This process not only differs from the common convention of using 3-substituted oxindoles as nucleophiles, but also provides a viable entry to optically active 3-substituted 3-hydroxy-2-oxindoles (see scheme).