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Highly enantioselective synthesis of 3-cycloalkanone-3-hydroxy-2-oxindoles, potential anticonvulsants

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ABSTRACT

Highly enantioselective catalytic synthesis of 3-cycloalkanone-3-hydroxy-2-oxindoles was achieved by using primary-tertiary diamine-Brønsted acid catalyst in both organic medium and aqueous medium. The products, thus obtained act as potential anticonvulsants.

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Oxindoles, having a quaternary stereogenic center at C-3 position, are of immense interest in organic synthesis as these structural moieties exist in large number of natural products[1,2] and pharmaceutically active compounds.[3] Among them, 3-cycloalkanone-3-hydroxy-2-oxindoles are quite promising in the field of medicinal chemistry.[4] It has been reported that these compounds possess an anticonvulsant activity. For example, compounds **A** and **B** antagonize the maximal electroshock seizures (anti-MES) and **C** antagonizes the pentylenetetrazol-induced convulsions (anti-PTZ) in mice (Fig. 1).[4]

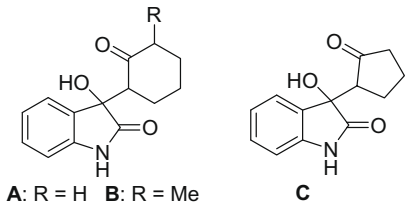
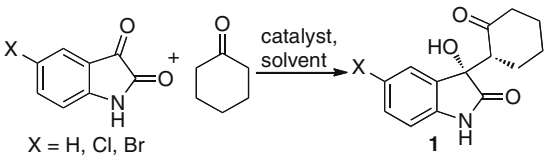


Figure 1. Bioactive 3-cycloalkanone-3-hydroxy-2-oxindoles.

Since biological activities are sensitive to the absolute configuration of stereogenic center, an efficient catalytic enantioselective synthesis of these oxindoles is highly desirable. The most obvious approach to these chiral compounds is via asymmetric direct aldol reaction of cycloalkanones with isatin and its derivatives. From a green chemistry perspective, asymmetric organocatalytic aldol reaction would be the method of choice for synthesizing these compounds. To the best of our knowledge, enantioselective synthesis of these compounds is not known by any of the methods. Herein, we report the first asymmetric organocatalytic approach to 3-cyclohexanone-3-hydroxy-2-oxindoles **1** with excellent diastereoselectivities and enantioselectivities under mild reaction conditions (Scheme 1).



Scheme 1. Asymmetric direct aldol reaction for the synthesis of 3-cyclohexanone-3-hydroxy-2-oxindoles.

At the outset, we carried out the reaction of cyclohexanone with isatin in the presence of a secondary amine catalyst **2** which was developed in our laboratory and well known for carrying out asymmetric aldol reactions[5] (Fig. 2). Unfortunately, the reaction did not proceed even after 4 days. Given the success to primary-tertiary diamine-based catalysts for aldol reaction pioneered by Cheng and co-workers[6] we designed another series of primary-tertiary diamines **3a–c**,[7] bearing aromatic groups (Fig. 2). The idea behind this is that aromatic groups will form a hydrophobic cavity with

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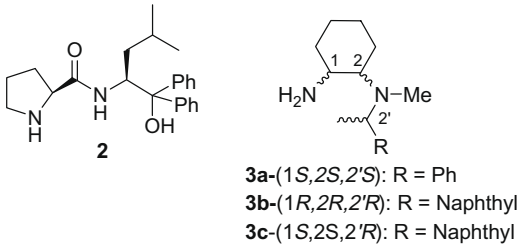
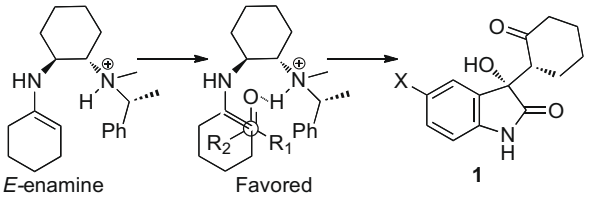
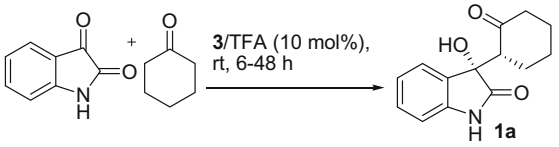


Figure 2. Series of organocatalysts.



Scheme 2. General mechanism of the reaction catalyzed by organocatalysts **3a–c**.

Table 1
Optimization of the reaction conditions



Entry	Catalyst	Solvent	Ketone (equiv)	Yield[a] (%)	*syn:anti*[b]	ee[c] (%)
1	**3a**	Water	4	90	97:3	97
2	**3a**	Water	2	90	96:4	98
3[d]	**3a**	Water	2	85	96:4	92
4	**3a**	Brine	2	84	95:5	90
5	**3a**	DMF	4	93	98:2	>99
6	**3a**	DMF	2	92	99:1	>99
7[e]	**3b**	DMF	2	91	97:3	98
8	**3c**	DMF	2	92	98:2	99

[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC using chiral column.
[d] **3a**/TFA (5 mol %).
[e] Opposite enantiomer.

reactants in an aqueous medium. High reactivity and enantioselectivity would be expected from such systems as shown in Scheme 2. With a great hope, cyclohexanone was allowed to react with isatin in the presence of primary-tertiary diamine-Brønsted acid catalyst **3a**/TFA (10 mol %) using water as a medium. Gratifyingly, the aldol product **1a** was obtained in high diastereoselectivity (97:3) and enantioselectivity (Table 1, entry 1, 97% ee). On reducing the ketone equivalents from four to two with respect to aldehyde, diastereoselectivity and enantioselectivity of the reaction remained almost constant (Table 1, entry 2, 96:4 de, 98% ee). When the reaction was carried out at a lower catalyst loading of 5 mol %, enantioselectivity of the reaction decreased to 92% (Table 1, entry 3). Surprisingly, the use of brine as a reaction medium decreased the enantioselectivity of the product (Table 1, entry 4, 90% ee).

At this point, it was thought that polar aprotic solvent such as DMF might give better results as it would make the reaction mixture homogeneous. It was indeed the case. The reaction of cyclohexanone and isatin in the presence of 10 mol % of the catalyst **3a** and TFA in DMF was completed in 6 h, providing a product **1a** with very high chemical yield, excellent diastereoselectivity and enantioselectivity (Table 1, entries 5 and 6, 98:2 de, >99% ee and 99:1 de, >99% ee, respectively). Under the optimized conditions (10 mol % catalyst, 2 equiv of ketone, TFA as a Brønsted acid and DMF as a solvent), different catalysts **3b–c** were screened for this reaction. The catalyst **3b** gave product with 97:3 de and 98% ee (Table 1, entry 7). The catalyst **3c** gave similar results (Table 1, entry 8, 98:2 de, 99% ee). As expected, the catalyst **3b** gave product with opposite configuration (Table 1, entries 1–6 and 8 vs entry 7). Thus, we were able to synthesize both the enantiomeric forms of the compound **1a**.

The absolute configuration of the product with two newly formed stereogenic centers was determined by single-X-ray diffraction analysis of the crystal **1a**, obtained by slow evaporation of ethyl acetate solution. The X-ray analysis of crystal **1a** showed that the absolute configuration of the stereocenters was (*S*) and (*R*) (Fig. 3).

Among these organocatalysts, the **3a** was chosen for further screening of the reaction with regard to both cycloalkanones[8] and substituted isatins. We focused our attention on the reaction of cyclohexanone with substituted isatins under identical conditions as mentioned above. It was found that 5-bromo isatin in DMF gave product **1b** with high diastereoselectivity of 97:3 and enantioselectivity of 99% (Table 2, entry 1). Furthermore, a similar reaction with 5-chloro isatin in DMF gave product **1c** with 93:7 de and 87% ee (Table 2, entry 4). The reaction of 5-bromo isatin and 5-chloro isatin with cyclohexanone in the presence of water or brine gave products with moderate to good diastereoselectivities and enantioselectivities (Table 2, entries 2–3 and 5–6).

It is to be emphasized that the product derived from isatin and cyclohexanone was active in the maximal electroshock seizure test (MES) whereas, the products derived from substituted isatins and cyclohexanone were inactive. In contrast, the product derived from 5-bromo isatin was active in the pentylenetetrazol seizure threshold test (PTZ), thus acts as a potential anticonvulsant.[4]

In summary, we have developed the first direct catalytic asymmetric approach to 3-cyclohexanone-3-hydroxy-2-oxindoles in

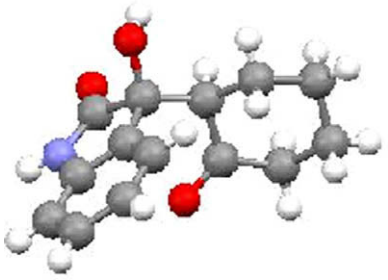
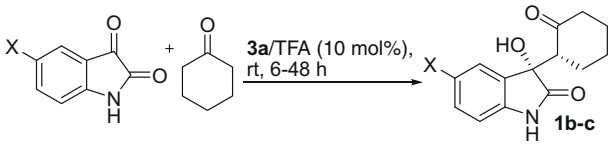


Figure 3. X-ray structure of crystal **1a**.

Table 2
Scope of the reaction



Entry	X	Solvent	Yield[a] (%)	*syn:anti*[b]	ee[c] (%)
1	Br	DMF	**1b**/92	97:3	99
2	Br	Water	**1b**/87	99:1	65
3	Br	Brine	**1b**/83	92:8	60
4	Cl	DMF	**1c**/90	93:7	87
5	Cl	Water	**1c**/85	98:2	85
6	Cl	Brine	**1c**/84	95:5	80

[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC using chiral columns.

high yields, excellent diastereoselectivities and enantioselectivities by carrying out aldol reaction of cyclohexanone with isatin and its derivatives in the presence of new organocatalysts. The products can be synthesized in both the enantiomeric forms. The reaction is operationally simple and environmentally benign in that an organocatalyst is employed and water is used as the reaction medium. The products obtained are active in maximal electroshock seizure test (MES) and pentylenetetrazol seizure threshold test (PTZ) thus, act as potential anticonvulsants.[4]

Acknowledgments

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Supplementary data

Supplementary data (CCDC 715937 and 715938 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) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.082.

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8. The reaction with cyclopentanone and isatin using **3a**/TFA (20 mol %) in DMF gave product with low yield (55%), diastereoselectivity (73:27) and enantioselectivity (30%). For details see Supplementary data.