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# Enantioselective synthesis of 3-hydroxy oxindoles by ytterbium-catalysed decarboxylative addition of β-ketoacids to isatins†

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**A ytterbium(III)-indapybox catalysed enantioselective decarboxylative addition reaction of β-ketoacids to isatins is described. The biologically important 3-hydroxy oxindoles were obtained in high yields and excellent enantioselectivities.**

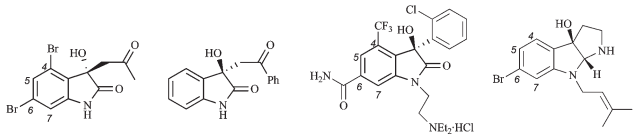


**Fig. 1** Bioactive 3-hydroxy-3-substituted oxindoles.

## Introduction

Oxindole motifs bearing C3-quaternary structures are widely distributed in many natural products and pharmaceutical molecules.[1] Recent interest has focused on the study of 3-hydroxy oxindoles possessing different substituents at the 3-position due to their significant biological activities.[2] For example, the convolutamydines can inhibit human promyelocytic leukemia cells, and flustraminol B is a potential antagonist of cholecystokinin (Fig. 1).[3] The biological activities of these compounds are greatly affected by the configuration of the hydroxyl group and the substituents at the C3 position of the oxindole.[4] Thus far, several efficient and facile methods have been developed for the preparation of functionalised 3-hydroxy oxindoles. Carbonyls,[5–7] arenes,[8] alkenes,[9] nitroalkanes[10] and oxindoles[11] were successfully installed on the oxindole framework with good enantioselective control. However, the development of other highly functionalised 3-hydroxyoxindoles is still desirable.

In recent years, the enantioselective decarboxylative additions of β-ketoacids as surrogates of ketones have received much attention.[12] Our interest in ytterbium-catalysed reactions led to the discovery that β-ketoacids can undergo a decarboxylative aldol sequence, which involves the generation of the nucleophile *in situ* using an $Yb(OTf)_3$–pybox catalytic system. Recently, Lu and co-workers[13] reported a tertiary amine–thiourea catalysed aldol reaction between β-ketoacids and isatins. 3-Hydroxy oxindoles with different substituents at C5 and C7 were afforded with good enantioselectivities. However, oxindoles with substituents at C4 and C6, which are the precursors of bioactive convolutamydines and flustraminols, were not recorded,[13,14] probably due to the steric and electronic resistance of the organocatalyst with the corresponding isatin substrate. Herein, we document our successful development of a new ytterbium-catalysed enantioselective decarboxylative addition of β-ketoacids to isatin, generating biologically important 3-hydroxy-3-substituted oxindoles in excellent yields and enantioselectivities, especially with different substituents at C4 and C6.

## Results and discussion

We started our investigation by examining the decarboxylative aldol reaction between β-ketoacid **1a** and *N*-benzyl isatin **2a** in the presence of ytterbium(III)-pybox catalysts in toluene. A number of pybox ligands were evaluated. They all furnished the desired decarboxylative products in high yields (Table 1, entries 1–4). Pybox ligands **L1**, **L2** and **L3** showed remarkable catalytic effects, and excellent enantioselectivities were achieved. **L3** (indapybox) was chosen as it gave the best results (Table 1, entry 3). **L4** led to low ee's (Table 1, entry 4). The addition of 4 Å molecular sieves was able to accelerate the reaction without compromising the enantioselectivity (Table 1,

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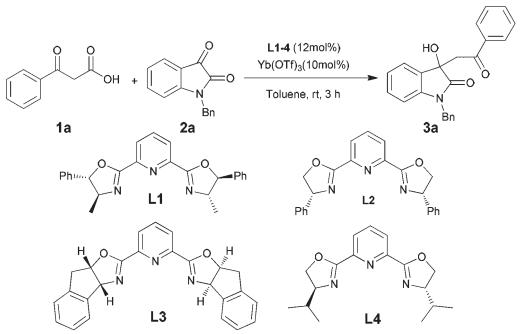
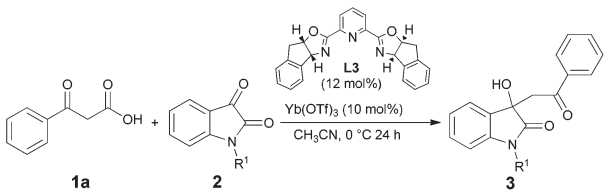
**Table 1** Reaction optimisation[a]




| Entry | Ligand | Additive | Solvent | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | **L1** | No | Toluene | 91 | 88 |
| 2 | **L2** | No | Toluene | 93 | −87 |
| 3 | **L3** | No | Toluene | 90 | 91 |
| 4 | **L4** | No | Toluene | 91 | 32 |
| 5 | **L3** | 4 Å MS | Toluene | 91 | 91 |
| 6 | **L3** | 4 Å MS | $CH_2Cl_2$ | 95 | 97 |
| 7 | **L3** | 4 Å MS | $CH_3Cl$ | 93 | 95 |
| 8 | **L3** | 4 Å MS | $CH_3CN$ | 98 | 99 |
| 9 | **L3** | 4 Å MS | THF | — | — |
| 10 | **L3** | 4 Å MS | $CH_3CN$ | 94 | 98[d] |
| 11 | **L3** | 4 Å MS | $CH_3CN$ | 95 | 97[e] |

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), $Yb(OTf)_3$ (10 mol%), and ligand (12 mol%). [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis using Chiralcel IA column. [d] $Yb(OTf)_3$ (5 mol%), ligand (6 mol%). [e] $Yb(OTf)_3$ (2 mol%), ligand (2.4 mol%).

**Table 2** Effect of protecting groups on the isatins[a]

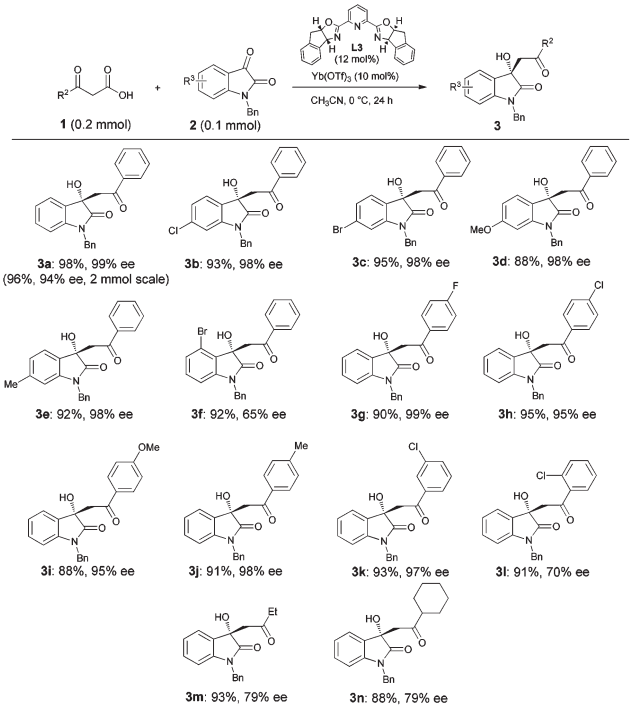



| Entry | $R^1$ | Product | Time | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | Bn | **3a** | 12 | 98 | 99 |
| 2 | H | **3o** | 24 | 90 | 27 |
| 3 | Me | **3p** | 24 | 91 | 93 |
| 4 | Boc | **3q** | 24 | 99 | 0 |
| 5 | $CPh_3$ | **3r** | 24 | 93 | 33 |

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), $Yb(OTf)_3$ (10 mol%), and ligand (12 mol%). [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis using chiralcel column.

entry 5). Subsequent solvent screening showed that $CH_3CN$ was the more suitable solvent (Table 1, entry 8). The reaction efficiency was maintained when the catalyst loading was as low as 2 mol% (Table 1, entry 11).

To test the scope of the optimised reaction conditions, a variety of isatin derivatives with different substituents were examined (Table 2). The protecting group on the nitrogen




**Scheme 1** Substrate scope of enantioselective decarboxylative addition of β-ketoacids to isatins.

showed a crucial influence on the reactivity of the electrophiles (Table 2, entries 1–5). Without any protecting group, isatin could provide the desired product in a similar yield but much lower enantioselectivity compared with the benzyl substituted isatin (Table 2, entries 1 and 2). 93% ee was obtained with a methyl group (Table 2, entry 3). More sterically hindered protecting groups such as triphenylmethyl and *tert*-butylcarbonyl (Boc) also led to low enantioselectivities (Table 2, entries 4–5).

Based on these results, isatins with different substituents on the aromatic ring were also investigated (Scheme 1). Substitution at the 6-position with electron-donating and electron-withdrawing groups afforded consistently high yields and excellent enantioselectivities. When 4-bromo isatin was employed, the ee dropped to 65%, suggesting that the nucleophilic addition was inhibited by steric interference between the substituent at C4 and the metal–ligand complex. Furthermore, the scope of β-ketoacid substrates for nucleophilic addition to isatins was investigated, and the substituents on the phenyl rings with electron-donating and electron-withdrawing groups afforded high yields and excellent enantioselectivities. When a 2-chloro β-ketoacid was used, the ee dropped slightly (**3l**). Notably, the reaction proceeded smoothly with aliphatic β-ketoacids, affording the hydroxy oxindoles in excellent yields and good enantiomeric excesses (**3n**). The absolute configurations of the products were assigned by comparing the optical rotation with the value reported in the literature and confirmed by crystallography.

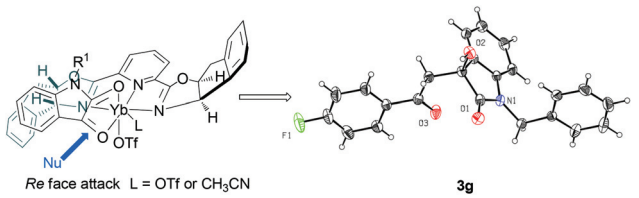



**Fig. 2** Stereochemical model for the mechanistic study.

The stereoinduction for this reaction can be rationalised by an octahedral model similar to the previous report[8d] (Fig. 2). The nucleophile approaches from the *Re* face, consistent with the absolute configuration of the observed products.

## Conclusions

In conclusion, we have successfully developed the highly enantioselective catalytic decarboxylative addition of β-keto-acids to isatins catalysed by ytterbium(III)-indapybox. A series of biologically valuable 3-hydroxy oxindoles were obtained in up to 98% yield and up to 99% ee. Further investigation of other decarboxylative addition reactions of β-ketoacids is in progress.

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