# Asymmetric Vinylogous Mukaiyama Aldol Reaction of Isatins under Bifunctional Organocatalysis: Enantioselective Synthesis of Substituted 3-Hydroxy-2-Oxindoles

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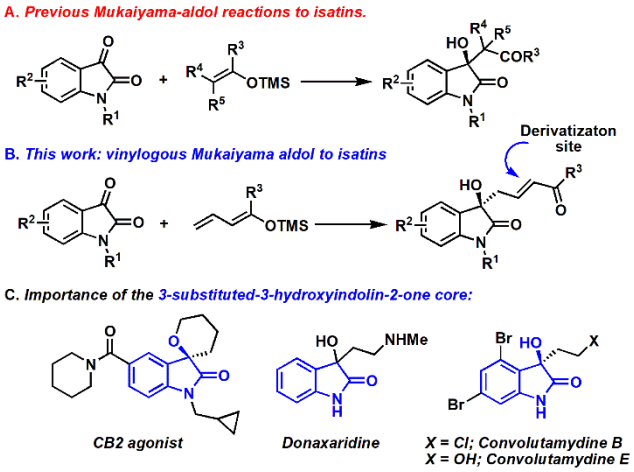
**A highly enantioselective organocatalytic vinylogous Mukaiyama aldol reaction of silyloxy dienes and isatins under bifunctional organocatalysis is presented. Substituted 3-hydroxy-2-oxindoles are synthesised in good yields and enantioselectivities. These synthetic intermediates are used for the construction of more complex molecules with biological properties such as the formal synthesis of a CB2 agonist presented.**

The development of efficient and practical strategies for the stereoselective construction of privileged structures is an ongoing objective and still holds a preferred position in organic chemistry research.[1] Among these privileged structures, 3-substituted-3-hydroxyindolin-2-ones have attracted much attention from organic and medicinal chemists. These heterocyclic motifs constitute the core structure of a family of diverse natural and non-natural products[2] with biological and pharmaceutical activities.[3] Therefore, the asymmetric synthesis of 3-hydroxy-2-oxindole derivatives such as Donaxaridine[4] or Convolutamyde[5] has been widely pursued (C, Scheme 1). The substitution at the C3 position as well as the configuration of the quaternary center are known to be crucial for the activity of this family of compounds.[2c] Consequently, the functionalisation of the isatin (C3) at that position is of great interest to the research community and is currently an open area in asymmetric catalysis. In order to face this challenge, the direct addition of different nucleophiles to isatins under catalytic conditions has been the method of choice for different research groups,[6] including enantioselective direct aldol reactions.[7] The




**Scheme 1.** Previous works (A), present work (B) and importance of the isatin core in biologically active molecules and commercial drugs (C).

construction of these challenging quaternary centers has also been attempted *via* the Mukaiyama-aldol reaction under either metal or organo-catalytic conditions (A, Scheme 1).[8] In recent years, the organocatalysed asymmetric vinylogous aldol reaction[9] has appeared as a powerful tool for the generation of multifunctional chiral alcohols with easily derivatizable unsaturated carbon chains that allow the construction of more complex structures (B, Scheme 1).[10] The organocatalysed vinylogous Mukaiyama-aldol (VMA) reaction has been widely developed and has become the preferred method for the stereoselective synthesis of aldol type products.[11] This approach is the favoured protocol to furnish vinylogous aldol adducts, overcoming regioselectivity issues and multistep synthesis. Despite the importance of these aldolic products (C, Scheme 1), no catalytic enantioselective version of the VMA reaction to isatins has been described. To the best of our knowledge, only Kobayashi *et al.*[5a] have described the enantioselective synthesis of Covolutamydes B and E, using silyloxy diene derivatives bearing a chiral inductor. Therefore, we believe that the development of an efficient asymmetric

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organocatalytic VMA reaction to isatins would be highly desirable. The adducts obtained which can bear larger unsaturated alkyl chains will facilitate easy functionalisations, making this approach a very attractive method. Therefore, this approach would have the potential to efficiently reach interesting platforms for the synthesis of more complex molecules with proven properties.

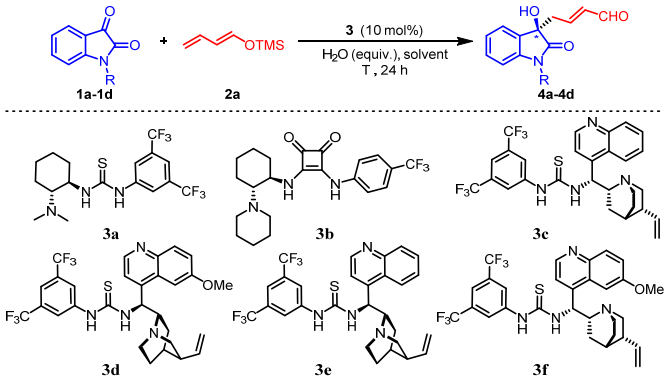
In this paper we describe the enantioselective addition of silyl dienol ethers to isatins under bifunctional organocatalytic conditions (B, Scheme 1). This VMA reaction provides direct and rapid access to δ-hydroxylated α,β-unsaturated carbonyls, which are themselves prevalent arrays in biologically relevant natural molecules, or are privileged platforms for their construction.

Based on our experience in bifunctional catalysis,[12] we began our investigations by studying the reaction of isatins (**1a-1d**) with a trimethyl silyl enolate derivative **2a** and different thiourea and squaramide bifunctional organocatalysts, in presence of $H_2O$ (Table 1).[13] Firstly, we examined the reaction of the *N*-unprotected isatin **1a** in dichloromethane, and observed moderate stereocontrol but full regioselectivity. Only 1,5 product **4a** was observed in the crude mixture without detection of the corresponding 1,3 product.

We then decided to investigate the impact of the *N*-substitution of the isatin. Therefore, we carried out the reaction of methyl and benzyl *N*-protected isatin derivatives (entries 2 and 3). In both cases, methyl (**1b**) and benzyl (**1c**), showed an increase in enantioselectivity. The benzyl-protected isatin showed the best enantiomeric ratio, even when the catalyst loading was decreased by up to 10 mol % (entry 4). We then examined different bifunctional organocatalysts (entries 4-9). The squaramide-based catalyst (Rawal´s catalyst, **3b**) showed low stereocontrol, while the thiourea-catalysts (**3a**, **3c**-**f**) presented better enantiomeric ratios. Among them, the cinchone organocatalysts led to the highest *e.r.* (entries 6-9). Different solvents were then studied (entries 10-12 and see ESI). THF was found to be the optimum solvent (entry 12) with a 91:9 enantiomeric ratio. The role of water is crucial for this reaction.[12] In the absence of water almost no conversion occurred, whereas the presence of 1 equiv. led to **4c** with a 57 % conversion (entries 13 and 14). However, an excess of water (6 equiv.) produced the hydrolysis of **2a** and provoked a decrease in the final conversion of **4c** (entry 15). A lower temperature (–30 °C) slightly enhanced the *e.r.* (entry 13-16). Interestingly, the bulkier *N*-*p*$^t$Bu-benzyl group yielded the desired product **4d**, with complete enantiocontrol (entry 17), while a lower catalyst loading (5 mol%) strongly decreased the final conversion (entry 18).

Once the reaction conditions had been optimised (entry 17, Table 1), we then studied the scope of the reaction considering different substitutions in the aromatic ring of the isatin (Table 2). Electron-donating groups, such as the 5-OMe, 5-Me and 6-OMe substituents in the aromatic ring of the isatin, gave **4e**, **4f** and **4g**, with good yields and enantiomeric ratios. The reaction proceeded smoothly with isatins bearing electron-withdrawing groups (5-F, 6-$CF_3$ and 5-$NO_2$), and the desired products: **4h**, **4m** and **4r** were obtained in good yields and with high stereocontrol. The protocol enabled access to the corresponding 3-hydroxyindoles bearing more synthetically useful halogens such as bromo groups (**4h** and **4j**) in the aromatic ring. The presence of any substituent at position 7 of the phenyl ring could have been affecting the efficient coordination of the substrate to the catalyst, leading to a slightly lower enantiocontrol (**4k**, **4n** and **4p**). Therefore, we envisioned that a smaller protecting group at the nitrogen atom of the isatin could potentially prevent the plausible steric interaction with the very bulky *N*-protecting group. To our delight, the *N*-benzyl protected derivatives allowed access to the desired 7-substituted adducts with higher enantiomeric ratios (**4l**, **4o** and **4q**). Other silyl nucleophiles were also tested in order to gain a better understanding of the process and to expand the scope of the reaction. The reaction with the silyl-enolate **2b** led to the ketones **4s** and **4t** in good yields but with

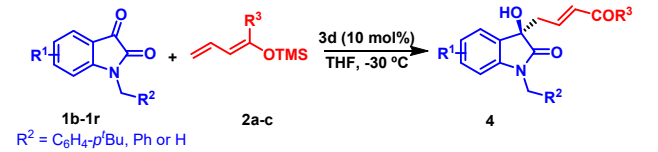
**Table 1.** Screening reaction conditions for the addition of **2a** to **1a-d** in the presence of different catalysts **3**.[a]

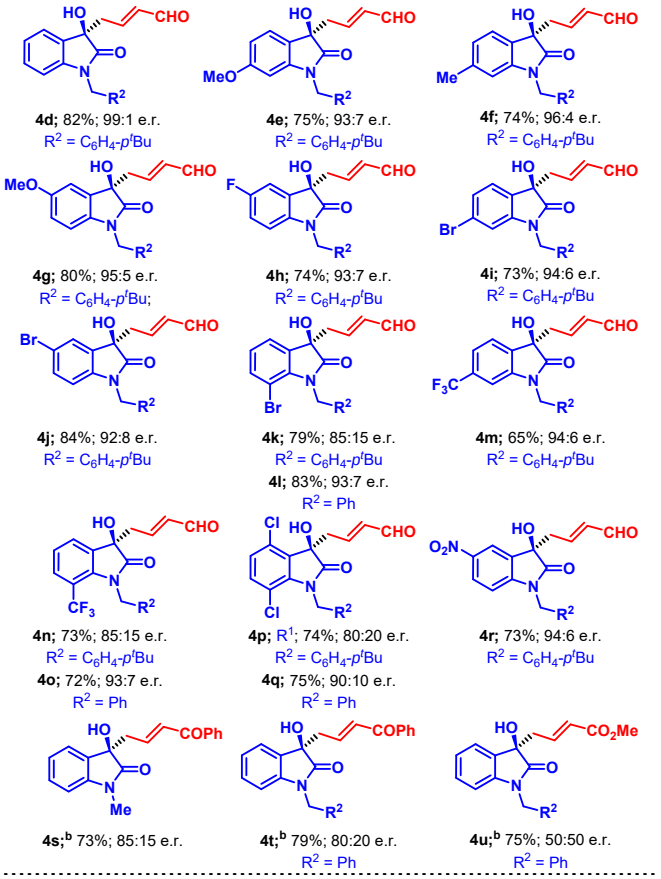



| Ent | R | 3 | $H_2O$ (equiv) | Solvent | T (°C) | Conv. (%)[b] | *e.r.* (%)[c] |
|---|---|---|---|---|---|---|---|
| *1*[d] | H | **3a** | 3 | DCM | rt | 100 | 30:70 |
| *2*[d] | Me | **3a** | 3 | DCM | rt | 100 | 19:81 |
| *3*[d] | Bn | **3a** | 3 | DCM | rt | 100 | 13:87 |
| *4* | Bn | **3a** | 3 | DCM | rt | 100 | 13:87 |
| *5* | Bn | **3b** | 3 | DCM | rt | 100 | 33:67 |
| *6* | Bn | **3c** | 3 | DCM | rt | 100 | 87:13 |
| *7* | Bn | **3d** | 3 | DCM | rt | 100 | 89:11 |
| *8* | Bn | **3e** | 3 | DCM | rt | 100 | 12:88 |
| *9* | Bn | **3f** | 3 | DCM | rt | 100 | 12:88 |
| *10* | Bn | **3d** | 3 | Dioxane | rt | 100 | 88:12 |
| *11* | Bn | **3d** | 3 | Tol | rt | 100 | 85:15 |
| *12* | Bn | **3d** | 3 | THF | rt | 100 | 91:9 |
| *13* | Bn | **3d** | 0 | THF | -30 | 5 | - |
| *14* | Bn | **3d** | 1 | THF | -30 | 57 | 92:8 |
| *15* | Bn | **3d** | 6 | THF | -30 | 56 | 92:8 |
| *16* | Bn | **3d** | 3 | THF | -30 | 100 | 93:7 |
| ***17*** | **-$CH_2C_6H_4$-*p*$^t$Bu** | **3d** | **3** | **THF** | **-30** | **100** | **99:1** |
| *18*[e] | -$CH_2C_6H_4$-*p*$^t$Bu | 3d | 3 | THF | -30 | 45 | 99:1 |

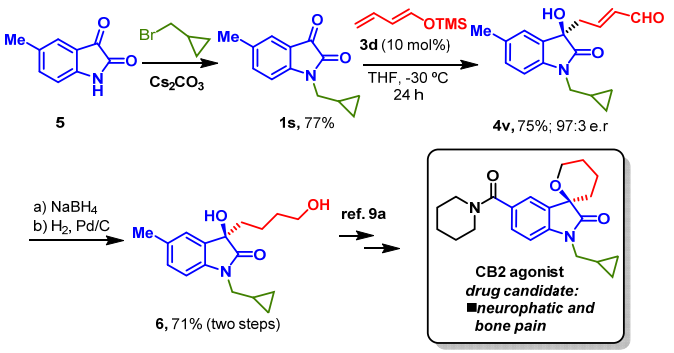
[a] All the reactions were performed in 0.1 mmol scale in presence of $H_2O$ (X equiv.) in 0.3 mL of solvent. [b] Determined by $^1$H NMR analysis of the crude. [c] Determined by SFC chromatography. [d] Experiment carried out with 20 mol % of **3a**. [e] Experiment carried out with 5 mol % of **3a.**

**Table 2.** Scope reaction for the addition of **2** to **1** in the presence of **3d**.[a]




[a] All the reactions were performed in 0.1 mmol scale in presence of 3 equiv. of $H_2O$ in 0.3 mL of THF. Enantiomeric ratio was determined by SFC chromatography. [b] Reaction carried out at room temperature.




**Scheme 2.** Vinylogous Mukaiyama for medicinal chemistry scaffold construction.

lower enantioselectivity. Unfortunately, the result obtained using the silyl enolate formed from the analogous ester, gave **4u** in very low enantiomeric excess. The absolute configuration of 3-hydroxyindole products **4** was assigned by correlation with a known compound in the literature (**4s**) and was determined as 3*R,* assuming the same stereochemical outcome for the rest of compounds **4** (*see* ESI).

This vinylogous Mukaiyama protocol enables access to versatile building blocks using commercially available materials, which can be used for the synthesis of natural and bioactive products. A simple alkylation of the readily available and cheap isatin **5** (8 euros/gram) with the bromocyclopropyl derivative led to the *N*- alkylated isatin (**1s**) in a good yield. Then, the VMA reaction gave the aldehyde **4v** with good yield and high enantioselectivity. The subsequent $NaBH_4$ reduction of the aldehyde to the alcohol and the Pd(C) catalysed hydrogenation of the double bond led to the aliphatic primary alcohol **6** in an excellent yield without any loss of enantioselectivity. This alcohol **6** is the key intermediate in the synthesis of a potential drug candidate (CB2 agonist)[3g,9a] for reducing neuropathic and bone pain.

In summary, we have described the vinylogous Mukaiyama aldol reaction of silyl dienolates to isatins under bifunctional organocatalysis, which is able to direct both coupling partners. The reaction proceeded with good yields and high enantioselectivities with a reasonably high range of differently substituted isatins. The methodology described offers an easy and straightforward method for the synthesis of enantioenriched biologically relevant 3-substituted-2-oxindole derivatives. Moreover, the products obtained have demonstrated that they can be easily transformed to biologically valuable compounds.

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13 $H_2O$ plays an important role to trigger the aldol reaction and in the interaction with the catalysts. See ESI and ref. 12d.

**GRAPHICAL ABSTRACT:**