

Enantioselective Morita–Baylis–Hillman Reaction of Isatins with Acrylates: Facile Creation of 3-Hydroxy-2-oxindoles

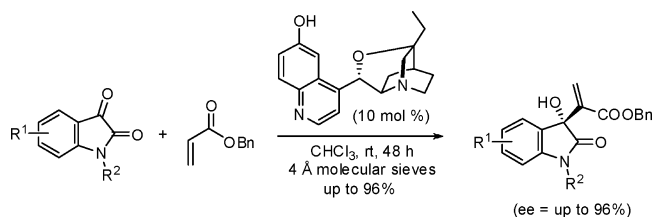
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ABSTRACT



The first tertiary amine catalyzed enantioselective Morita–Baylis–Hillman (MBH) reaction of isatins with acrylates has been demonstrated, allowing asymmetric synthesis of biologically significant 3-substituted-3-hydroxy-2-oxindoles in good yields and with excellent enantioselectivities. The C6'–OH group of β -isocupreidine (β -ICD) is believed to facilitate the key proton transfer step in the MBH reaction, via an intramolecular proton relay process.

3-Substituted-3-hydroxy-2-oxindoles are important structural motifs found in many natural products and therapeutically useful agents.¹ Given their biological significance, and the fact that different 3-hydroxy stereoisomers induce different biological activities, asymmetric synthesis of 3-hydroxy-2-oxindoles has become an intensively investigated research area. Over the years, many excellent synthetic approaches based on transition metal catalysis have been developed to tackle this synthetic challenge. Construction of 3-hydroxy-oxindoles was realized by metal-mediated arylation² or alkylation³ reactions employing isatins as electrophiles. Shibata and Toru reported catalytic enantioselective hy-

droxylation reactions of both 3-aryl- and 3-alkyl-2-oxindoles using a DBFOX–Zn(II) complex.⁴ Parallel to the explosive growth of organocatalysis, many elegant asymmetric organocatalytic synthetic methods have been reported in recent years. One widely used approach is the addition of carbonyl substrates to isatins via enamine activation, creating chiral quaternary 3-hydroxy-2-oxindoles.⁵ Direct hydroxylation of oxindole substrates represents an alternative strategy. Itoh et al. achieved asymmetric hydroxylation of oxindoles by molecular oxygen using a phase-transfer catalyst.⁶ Very recently, Barbas and co-workers reported a dimeric quinidine-

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catalyzed enantioselective aminooxygenation of oxindoles to access 3-hydroxyoxindole derivatives.⁷

The Morita–Baylis–Hillman (MBH) reaction is one of the most synthetically valuable reactions for the construction of densely functionalized products in a highly atom economic manner.⁸ The asymmetric version of this reaction has been extensively studied by employing either chiral amines⁹ or phosphines¹⁰ as the catalyst. The electrophiles in the MBH reactions are mostly aldehydes and imines, and the use of ketones as electrophiles is very limited.¹¹ Owing to their high electrophilicity, isatin derivatives have emerged as new electrophilic components for the MBH reaction.¹² As part of our ongoing research program toward enantioselective creation of quaternary stereogenic centers,¹³ we were interested in developing asymmetric MBH reactions employing isatins as electrophiles, since such processes would yield tremendously useful 3-substituted-3-hydroxy-2-oxindoles.¹ At the outset of our research, the enantioselective MBH reaction of isatins was unknown. During the preparation of this manuscript, Zhou and co-workers disclosed an elegant asymmetric organocatalytic MBH reaction of isatins and

acrolein.¹⁴ Herein, we document our independent studies on a highly enantioselective MBH reaction of isatins with acrylates. Our process delivers the MBH adducts in high yields and with excellent enantiomeric purity at ambient reaction temperature.

We chose the MBH reaction between *N*-benzyl isatin **5a** and methyl acrylate **6a** as a model reaction to start our investigation, and the catalytic effects of different amine catalysts **1**–**4** (Figure 1) were examined. While quinidine

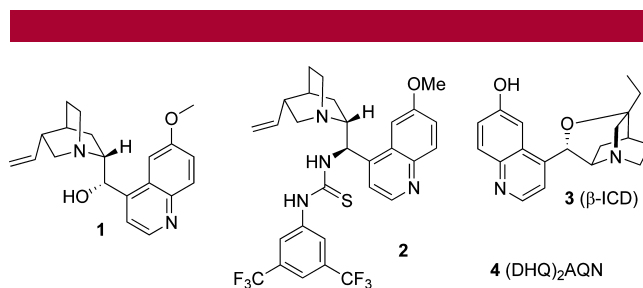


Figure 1. Structures of the organocatalysts screened.

1, quinidine-based thiourea **2**, and bisinchona alkaloid **4** were found to be completely ineffective (Table 1, entries 1, 2, and 4), β -isocupreidine (β -ICD) **3**^{9a,15} displayed remarkable catalytic effects, affording the desired adduct in 94% yield and with 85% ee (entry 3). Different acrylates were next explored. Employment of ethyl acrylate **6b** slightly improved the enantioselectivity; however, the chemical yield dropped dramatically (entry 5). *tert*-Butyl acrylate **6c** was virtually unreactive (entry 6). When hexafluoroisopropyl acrylate (HFIPA) **6d** or 2-naphthyl acrylate **6e** was utilized, the reaction proceeded rapidly, but the enantioselectivity was disappointing (entries 7–8). Utilization of benzyl acrylate **6f** slightly increased the ee of the adduct (entry 9), and **6f** was thus chosen for further studies. A solvent screening¹⁶ revealed that CHCl₃ was the solvent of choice, delivering the product in a moderate yield and with 96% ee (entry 10). Further experimental conditions were investigated in order to improve the yield of the reaction, without sacrificing the enantioselectivity. We were pleased to find that the addition of 4 Å molecular sieves to the reaction mixture was beneficial. Under the optimized conditions, the MBH product could be obtained in 83% yield and with 96% ee (entry 13). The benzyl protection on the nitrogen atom of isatin proved to be crucial, as the isatin with a free amino group or with acetyl protection gave very poor results (entries 14–15). When the reaction was performed in wet CHCl₃, a decrease in enantioselectivity was observed (entry 16).

With the optimized reaction conditions in hand, the substrate scope was next studied (Table 2). Various *N*-alkylated isatins could be used, and excellent enantioselectivity

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(16) See Supporting Information for the details.

Table 1. Exploration of the MBH Reaction of Isatins with Acrylates^a

5a: R¹ = Bn 6a: R = Me; 6b: R = Et
 5b: R¹ = H 6c: R = *t*Bu; 6d: R = CH(CF₃)₂
 5c: R¹ = Ac 6e: R = 2-naphthyl; 6f: R = Bn

entry	cat.	5/6	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	1	5a/6a	THF	48	—	—
2	2	5a/6a	THF	48	—	—
3	3	5a/6a	THF	40	94	85
4	4	5a/6a	THF	48	—	—
5	3	5a/6b	THF	40	77	88
6	3	5a/6c	THF	48	<20	—
7	3	5a/6d	THF	1	93	26
8	3	5a/6e	THF	24	92	71
9	3	5a/6f	THF	48	89	90
10	3	5a/6f	CHCl ₃	48	53	96
11 ^d	3	5a/6f	CHCl ₃	48	69	94
12 ^d	3	5a/6f	CHCl ₃	72	81	94
13 ^{d,e}	3	5a/6f	CHCl ₃	72	83	96
14 ^{d,e}	3	5b/6f	CHCl ₃	48	26	33
15 ^{d,e}	3	5c/6f	CHCl ₃	48	17	30
16 ^f	3	5a/6f	CHCl ₃	48	85	88

^a Reactions were performed with **5** (0.05 mmol), **6** (0.1 mmol), and the catalyst (0.005 mmol) in anhydrous solvent (250 μ L) under argon. ^b Isolated yield. ^c The ee values were determined by HPLC analysis on a chiral stationary phase. ^d Reaction was performed in CHCl₃ (100 μ L). ^e Molecular sieve (4 Å, 20 mg) was added. ^f Wet CHCl₃ (100 μ L) was used as the solvent.

tivities were obtained in all the examples examined (entries 1–7), although a slight increase in catalyst loading or longer reaction time may be required in some cases. The reaction was applicable to isatins with different aromatic moieties. Halogenated isatins at the C5 and C7 positions displayed high reactivity, and the desired adducts were obtained in nearly quantitative yields and with very high enantioselectivities (entries 8–12). Isatins with electron-rich aryl rings were found to be less reactive; an increased catalyst loading could effectively improve the chemical yields of the reactions (entries 14–16). The presence of the nitro group on the isatin slightly reduced the enantioselectivity of the MBH adduct, which may be correlated to the hydrogen bonding capability of the nitro group (entry 13). The absolute configurations of the MBH products were determined based on the X-ray crystal structure of **7h** (see the Supporting Information for details).

Despite intensive research over the years, the mechanism of the MBH reactions is not entirely clear. Recent elegant mechanistic studies supported that the intramolecular proton transfer from the α -carbon atom to the anion at the adjacent carbon is the rate-determining step (RDS) for the MBH reaction.¹⁷ To gain insights into our reaction mechanism, a few further experiments were performed and the results are summarized in Table 3. We were interested in the potential roles that the C6'–OH of β -ICD might have played in the

Table 2. Enantioselective MBH Reaction of Different Isatins with Acrylate **6f**^a

entry	R ¹ /R ² (product)	yield (%) ^b	ee (%) ^c
1 ^d	H/Bn (7a)	83	96
2 ^d	H/ <i>p</i> -OMe-Bn (7b)	62	95
3 ^d	H/CHPh ₂ (7c)	63	93
4 ^e	H/CPh ₃ (7d)	88	92
5	H/Ph (7e)	61	90
6	H/ <i>p</i> -OMe-Ph (7f)	95	92
7 ^d	H/Me (7g)	67	95
8	7-Cl/Bn (7h)	96	96
9	7-F/Bn (7i)	96	92
10	5-F/Bn (7j)	95	92
11	5-Cl/Bn (7k)	95	91
12	5-Br/Bn (7l)	92	94
13	5-NO ₂ /Bn (7m)	94	85
14	5-Me/Bn (7n)	66	92
15 ^e	5-OMe/Bn (7o)	88	91
16 ^e	5,7-Me/Bn (7p)	76	95

^a Reactions were performed with **5** (0.05 mmol), **6f** (0.1 mmol), **3** (0.005 mmol), and 4 Å molecular sieve (20 mg) in anhydrous CHCl₃ (100 μ L) under argon. ^b Isolated yield. ^c The ee values were determined by HPLC analysis on a chiral stationary phase. ^d Reaction was run for 72 h. ^e The catalyst loading was 20 mol %.

Table 3. Investigation of the Effects of Various Additives^a

entry	cat.	additive	yield (%) ^b	ee (%) ^c
1	3	—	69	96
2	8	—	<10	71
3	8	100 mol % <i>i</i> -PrOH	<10	70
4	8	10 mol % PhOH	11	32
5	8	10 mol % PhCOOH	35	10
6	3	100 mol % <i>i</i> -PrOH	65	96
7	3	10 mol % PhOH	62	88
8	3	10 mol % PhCOOH	64	35
9	3	100 mol % PhCOOH	15	3

^a A mixture of **5a** (0.05 mmol), **6f** (0.1 mmol), the catalyst (0.005 mmol), 4 Å molecular sieve (20 mg), and the additive in CHCl₃ (100 μ L) was stirred at room temperature. ^b Isolated yield. ^c Determined by HPLC analysis on a chiral stationary phase.

enantioselective MBH reaction. Thus, β -isocinchonine **8** without the free phenolic hydroxy group was prepared and applied in the reaction. The desired MBH adduct was obtained in very low yield, but with 71% ee (entry 2). This result indicated that the monofunctional cinchona alkaloid could provide a certain degree of stereochemical control; however, the C6'–OH group is indispensable in inducing

excellent enantioselectivity. The influence of adding various external proton donors was next investigated. With **8** employed as the catalyst, adding *i*-PrOH (100 mol %) had little influence on the enantioselectivity (entry 3). On the other hand, the addition of more acidic phenol (10 mol %) or benzoic acid (10 mol %) increased the reaction rate and led to very poor enantioselectivity (entries 4–5). For the MBH reaction catalyzed by **3**, the addition of a large excess of *i*-PrOH had little effect; both yield and ee were maintained (entry 6). The presence of molar equivalence of phenol, which mimics the phenolic OH group in β -ICD, led to a small decrease in both chemical yield and enantioselectivity (entry 7). With the addition of a stronger proton donor, benzoic acid at 10 mol %, the enantioselectivity of the reaction dropped dramatically (entry 8). Moreover, a large excess of benzoic acid deterred the reaction, yielding virtually racemic products in extremely poor yield, which may due to the overstabilization or protonation of the enolate intermediate induced by the benzoic acid (entry 9).

On the basis of the above experimental findings, we propose the mechanism of β -ICD-promoted MBH reaction as shown in Figure 2. The enolate **A** is generated upon nucleophilic addition of β -ICD **3** to the acrylate, which is stabilized by the C6'–OH group of **3** via an intramolecular hydrogen bonding interaction. The subsequent aldol reaction of **A** with isatin **5a** leads to the formation of zwitterionic intermediate **B**. The following proton transfer is the key step, which has been suggested by the recent studies to be the RDS for the MBH reaction. We believe the acidic proton of the C6'–OH group serves as a “proton shuttle” to facilitate the intramolecular proton transfer from the α -carbon to the neighboring oxygen anion. This proton transfer step also likely differentiates the four diastereomers of **B** (pathway generating the major stereoisomer shown), leading to the creation of the desired isomer **C**. Finally, intermediate **C** undergoes β -elimination to afford the MBH adduct **7a** and regenerates **3** at the same time. Our study on the additive effects agrees well with this proposal. Being less acidic than the phenolic OH, even excess *i*-PrOH could not interrupt the intramolecular proton relay process (Table 3, entry 6). More acidic phenol could assist the proton transfer process in a nonstereoselective manner, resulting in a decreased ee (entry 7). When more acidic benzoic acid was introduced, it competed favorably as the external hydrogen bond donor with the C6'–OH group in the proton transfer process, leading to a dramatically decreased enantioselectivity (entry 8). Therefore, it is clear that C6'–OH of **3** plays a critical

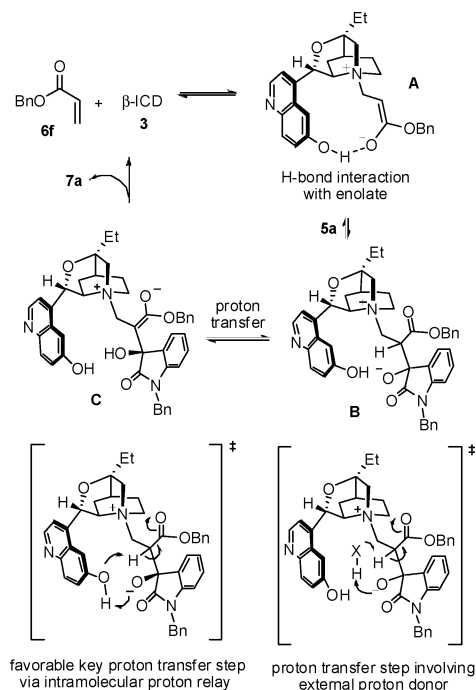


Figure 2. Plausible mechanism.

role in the proton transfer process and contributes significantly to the overall rate of the reaction and the observed enantioselectivity.

In summary, we have successfully demonstrated the first asymmetric MBH reaction of isatins with acrylates. The reactions proceeded efficiently at room temperature, yielding the desired adducts in high yields and with excellent enantioselectivities. The method reported represents a novel approach to access structurally challenging and biologically important chiral 3-hydroxy-2-oxindoles. Additive studies performed suggested that the C6'–OH group of β -ICD facilitates the proton transfer step via its participation in an intramolecular proton relay process. We anticipate the methodology described here will find wide applications in the synthesis of novel 3-hydroxy-2-oxindoles and mechanistic insights gained in this study may facilitate the rational design of novel catalytic systems for the asymmetric MBH reactions.

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Supporting Information Available: Representative experimental procedures, HPLC chromatogram, X-ray structure and cif file of **7h**, and NMR spectra of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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