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Chitosan Aerogel Catalyzed Asymmetric Aldol Reaction in Water: Highly Enantioselective Construction of 3-Substituted-3-hydroxy-2-oxindoles

Hui Dong [1,2], Jie Liu [2], Lifang Ma [1,*] and Liang Ouyang [2,*]

[1] School of Chemical Engineering, Sichuan University, Chengdu 610065, China; donghui0553@163.com
[2] State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, and Collaborative Innovation Center for Biotherapy, Chengdu 610041, China; liujie2011@scu.edu.cn
* Correspondence: mlfang11@scu.edu.cn (L.M.); ouyangliang@scu.edu.cn (L.O.); Tel.: +86-28-8540-5221 (L.M.); +86-28-8550-3817 (L.O.)

Academic Editor: Luca Gonsalvi
Received: 3 October 2016; Accepted: 21 November 2016; Published: 28 November 2016

Abstract: A chitosan aerogel catalyzed asymmetric aldol reaction of ketones with isatins in the presence of water is described. This protocol was found to be environmentally benign, because it proceeds smoothly in water and the corresponding aldol products were obtained in excellent yields with good enantioselectivities.

Keywords: chitosan aerogel; aldol reaction; water; isatin

1. Introduction

The 3-substituted-3-hydroxy-2-oxindoles have a stereogenic quaternary center at the C-3 position and a core unit that appears in many natural products and biologically active compounds [1–8]. Representative examples are: TMC-95A [9,10], Dioxibrassinine [11,12], SM-130686 [13], 3′- Hydroxygluoisatisin [14], and Convolutamydines (Figure 1) [15]. Consequently, the 3-substituted-3-hydroxy-2-oxindole framework has been an intensively investigatedsynthetic target. To construct 3-substituted-3-hydroxy-2-oxindoles, asymmetric aldol reaction has been considered one of the most powerful and efficient measures for the formation of carbon–carbon bond at C-3 position [16–21]. In this context, the asymmetric aldol reaction between isatin and carbonyl compounds has attracted much attention. As a pioneering work in this field, Tomasini and coworkers demonstrated the enantioselective aldol reaction of isatin with acetone catalyzed by a dipeptide-based organocatalyst [22]. Along these lines, Toru et al. employed sulfonamides as catalysts for the enantioselective aldol reaction of acetaldehyde with isatin, and successfully achieved the first highly enantioselective crossed-aldol reaction of acetaldehydes with ketones [23]. Later on, Zhao et al. described the utilization of quinidine thiourea for the highly enantioselective synthesis of 3-alkyl-3-hydroxyindolin-2-ones [24]. Lin et al. disclosed the enzymatic enantioselective aldol reaction of isatin derivatives with cyclic ketones, which produced products in high yields with moderately good stereoselectivity [25]. Very recently, natural amino acid salts were successfully developed to catalyze direct aldol reactions of isatin with ketones [26]. Despite this reported success, it is still important and desirable to develop new catalysts with operational simplicity and high catalytic efficiency for asymmetric aldol reactions.

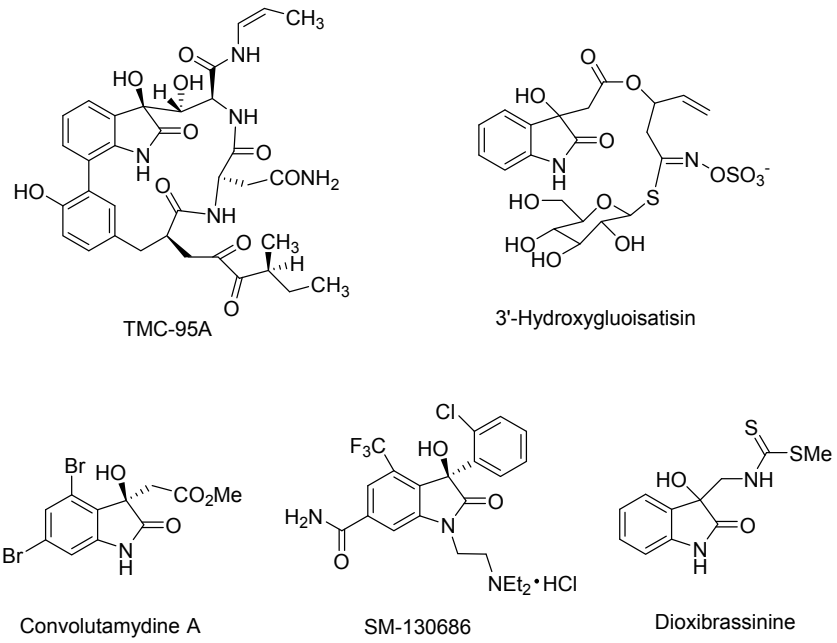


Figure 1. Representative examples of 3-substituted-3-hydroxy-2-oxindoles.

Recently, considerable focus has been placed on environmentally-friendly and sustainable resources and processes. In this regard, natural materials have been used directly as supports for catalytic applications, which has made this approach a very attractive strategy. In particular, biopolymers are a diverse and versatile class of materials that are inexpensive and abundant in nature [27]. Chitosan is a very abundant biopolymer obtained from the alkaline deacetylation of chitin, which is ubiquitous in the exoskeletons of crustaceans, the cuticles of insects and the cell walls of most fungi [28]. Chitosan functionalization is based on the presence of amino groups, which easily react with electrophilic reagents such as aldehydes, acid chlorides, acid anhydrides and epoxides [29–32]. Chitosan is a chiral polyamine and exhibits good flexibility, insolubility in many solvents and an inherent chirality and affinity for metal ions [33–36]. On the other hand, chitosan is an excellent candidate for building heterogeneous catalysts, since it can act as a support for chiral organic frameworks [37,38]. In addition, there are various advantages to using chitosan to catalyze reactions in water, which is a universally environmentally-friendly solvent.

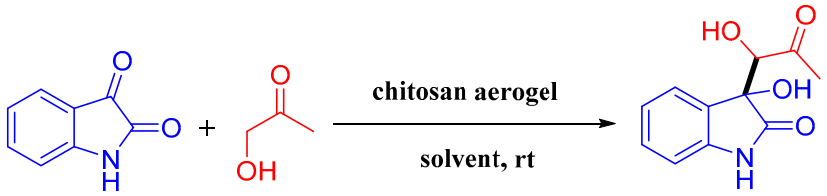
Although chitosan possesses these properties, the direct use of chitosan in base catalysis has been very poorly investigated. In 2006, Kantam et al. reported the use of chitosan hydrogels as a green and recyclable catalyst for the aldol and Knoevenagel reactions [39]. Since then, as an ideal alternative to organocatalysts, chitosan aerogels were utilized to catalyze the asymmetric aldol reaction in water, giving the desired products in high yields with good stereoselectivity and recyclability [40]. Not long ago, chitosan-supported cinchonine was developed as an organocatalyst for the direct asymmetric aldol reaction in water and this catalyst could be easily recovered and reused several times without a significant loss in activity [41]. In continuation of our previous efforts on asymmetric direct aldol reaction of isatins with ketones [26], herein, we report on the synthesis of 3-substituted-3-hydroxy-2-oxindoles catalyzed by chitosan aerogel in the presence of water.

2. Results and Discussion

The direct asymmetric aldol reaction of isatin and hydroxyacetone was selected as a template reaction to optimize the conditions for the reaction catalyzed using the chitosan aerogel. Using the optimized conditions, the desired product was obtained in high yield with excellent stereoselectvity and relative configurations assigned by comparison with previously reports [42,43].

Initially, the aldol reaction with hydroxyacetone **2a** was examined as the donor substrate and isatin **1a** as the acceptor using 10 mol % catalyst at room temperature and the results of this reaction are shown in Table 1.

Table 1. Screening of the solvents for the enantioselective aldol reaction of isatin and hydroxyacetone catalyzed by chitosan aerogel [a].



1a **2a** **3a**

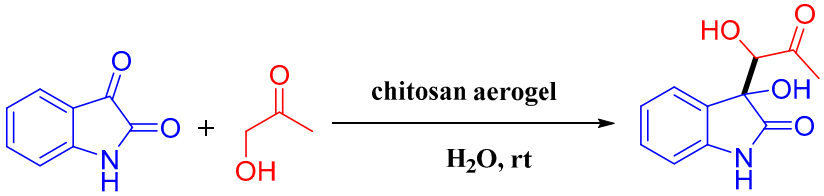
Entry	Solvent	Time (h)	Yield (%) [b]	syn:anti [c]	ee (%) [d]
1	EtOAc	3	92	71:29	11 (16)
2	MeCN	2	90	72:28	21 (20)
3	Et_2O	3	94	52:48	7 (4)
4	$CHCl_3$	2	92	65:35	31 (30)
5	PhMe	3	95	52:48	35 (22)
6	DCM	2	97	65:35	34 (10)
7	Hexane	1.5	93	65:35	40 (20)
8	H_2O	2	90	73:27	37 (57)
9	EtOH	2	80	70:30	17 (20)
10	MeOH	2	88	67:33	29 (20)
11	Dioxane	7	70	61:39	20 (13)
12	*i*-PrOH	6	70	57:43	18 (5)

[a] Unless otherwise indicated, all reactions were carried out with isatin **1a** (0.5 mmol), hydroxyacetone **2a** (2.5 mmol), and 0.05 mmol chitosan aerogel (10 mol %) at room temperature for the specified time; [b] Isolated yields after purification by flash column; [c] Determined by chiral HPLC analysis or ^{1}H NMR analysis of the crude mixture; [d] Determined by chiral HPLC analysis (results in parentheses refer to the minor diastereoisomer).

The data in Table 1 showed that the catalytic activity and stereoselectivity of the reaction were influenced by the reaction media. The solvents employed included EtOAc, MeCN and Et_2O which produced the product **3a** with 90%–94% yields, but with poor enantiomeric excess (ee) (Table 1, entries 1–3). Other solvents that were also tested produced **3a** in excellent yields (90%–97%) and with good ee (31%–40%) (Table 1, entries 4–8), but also produced high diastereoselectivity (syn:ant = 73:27) with water as the solvent (Table 1, entry 8). Although physical properties between hexane and water are greatly different, the product **3a** in yield and enantioselectivity in hexane were similar to that in water, this might be because the chitosan aerogel exhibited higher catalytic activity in water and hexane. In addition, compared to water, the solvents MeOH and EtOH exhibited lower yields (88% and 80%) and enantioselectivity (29% ee and 17% ee) (Table 1, entries 9–10). In addition, when dioxane and *i*-PrOH were used as the solvents, the results were unsatisfactory. Therefore, water was chosen as the solvent due to its good performance in this reaction.

After screening the solvents, the effect of the donor (hydroxyacetone) on the model aldol reaction was investigated. As summarized in Table 2, increasing the amount of hydroxyacetone from 5 to 20 equivalents led to a significant increase in the yields (88% up to 99%) and enantioselectivity (33% ee up to 44%) (Table 2, entries 1–3). A further increase in the hydroxyacetone dosage to over 20 equivalents resulted in a decrease in the enantioselectivity, albeit with excellent yields (99%) (Table 2, entry 4). This suggested that the donor dosage within a certain range can improve the chemoselectivity. Accordingly, 20 equivalents of hydroxyacetone was used as the optimum dosage.

Table 2. Effect of the amount of isatin for the enantioselective aldol reaction in the presence of water [a].



1a **2a** **3a**

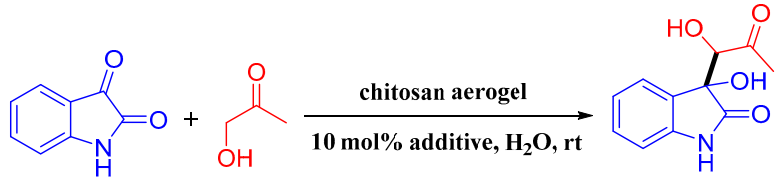
Entry	Hydroxyacetone (Equivalents)	Time (h)	Yield (%) [b]	syn:anti [c]	ee (%) [d]
1	5	2.5	88	71:29	33 (43)
2	10	2	96	72:28	40 (51)
3	20	2	99	57:43	44 (59)
4	40	1.5	99	53:47	31 (30)

[a] Unless otherwise indicated, all reactions were carried out with isatin **1a** (0.5 mmol), hydroxyacetone **2a** and 0.05 mmol chitosan aerogel (10 mol %) in water (0.5 mL) stirred at room temperature for the specified time; [b] Isolated yields after purification by flash column; [c] Determined by chiral HPLC analysis or ^{1}H NMR analysis of the crude mixture; [d] Determined by chiral HPLC analysis (results in parentheses refer to the minor diastereoisomer).

To further enhance the yield and enantioselectivity of **3a**, the effect of different types of additives was investigated (Table 3). The results showed that 2,5-dihydroxybenzoic acid was the most effective additive, producing product **3a** in a 96% yield with 66% ee (Table 3, entry 16). By contrast, compared to 2,5-dihydroxybenzoic acid, some additives such as sulfamic acid, formic acid and 1,1′-bi-2-naphthol exhibited higher yields but lower enantioselectivity (Table 3, entries 1, 2 and 15). It is also conceivable that the 2,5-dihydroxybenzoic acid that exhibited higher enantioselectivity might also provide an additional asset for chitosan, favoring the recognition of this reagent by the catalyst. Other additives were also tested using the template reaction, which produced product **3a** in good yields along with lower enantioselectivity (Table 3, entries 3–14). Moreover, considering that the reaction temperature is related to the enantioselectivity, the reaction was conducted at 0 °C. Fortunately, it was found that the enantioselectivity of the product was significantly increased by maintaining the reaction temperature at 0 °C (Table 3, entry 17). Hence, the optimum conditions for this reaction were found to be the use of 2,5-dihydroxybenzoic acid as an additive and maintaining the reaction at 0 °C.

Using these optimized conditions, the scope of this reaction was studied and the results are summarized in Table 4.The results showed that the isatin and hydroxyacetone gave the corresponding aldol product **3a** in high yield and good ee (Table 4, **3a**). Isatin containing weaker electron-withdrawing groups such as halogens, also gave excellent yields, but lower enantioselectivity (Table 4, **3b** and **3e**). Unfortunately, although the product **3c** was obtained inexcellent yield, the ee could not be determined. Interestingly, isatin containing strong electron-withdrawing substituents, such as 5-nitroisatin, reacted easily with hydroxyacetone to give **3d** in high yield (92%) and good enantioselectivity (92% ee), along with excellent diastereoselectivity (Table 4, **3d**). Subsequently, *N*-benzylisatins with various substitution patterns were studied, and the corresponding products **3f**–**3i** were obtained in better yields (93%–97%) and good enantioselectivity (72%–94% ee) (Table 4, **3f**–**3i**). However, the product **3j** showed lower enantioselectivity (Table 4, **3j**). *N*-methylisatin was also employed to produce product **3k** in higher yield and ee (Table 4, **3k**). When *N*-boc and *N*-acethylisatins were used, the corresponding products **3l** and **3m** exhibiting an enantiomeric excess could not be clearly identified. Finally, using methoxyacetone as the donor substrate, the resulting products **3n**–**3p** were obtained in excellent yields and enantioselectivity (Table 4, **3n**–**3p**).

Table 3. Effects of additives for the enantioselective aldol reaction in the presence of water [a].

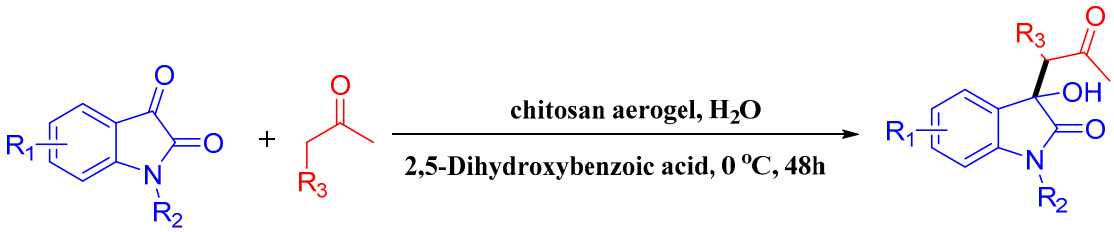


1a **2a** **3a**

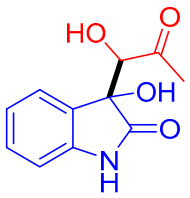
Entry	Additive	Time (h)	Yield (%) [b]	syn:anti [c]	ee (%) [d]
1	sulfamic acid	2.5	98	56:44	2 (1)
2	formic acid	4	97	68:32	38 (47)
3	*p*-toluenesulfonic acid	2.5	93	60:40	11 (20)
4	4 Å molecular sieves(10 mg) [e]	2.5	90	54:46	11 (26)
5	4 Å molecular sieves(20 mg) [e]	2.5	93	61:39	10 (12)
6	4 Å molecular sieves(30 mg) [e]	4.5	96	72:28	31 (56)
7	acetic acid glacial	2.5	94	59:41	17 (22)
8	L-proline	2.5	95	64:36	24 (29)
9	benzoic acid	2.5	97	57:43	16 (18)
10	stearic acid	5	94	51:49	11 (4)
11	3-nitrobenzoic acid	4	92	61:39	29 (25)
12	2,4-dinitrophenol	4	94	69:31	47 (60)
13	polyethylene glycol	6	87	65:35	34 (41)
14	oxalic acid	2.5	82	58:42	46 (50)
15	1,1′-bi-2-naphthol	3	98	68:32	63 (62)
16	2,5-dihydroxybenzoic acid	2.5	96	69:31	66 (72)
17 [f]	2,5-dihydroxybenzoic acid	48	90	53:47	75 (80)

[a] Unless otherwise indicated, all reactions were carried out with isatin **1a** (0.5 mmol), hydroxyacetone **2a** (10 mmol), 0.05 mmol chitosan aerogel (10 mol %) and 0.05 mmol additive (10 mol %) in water (0.5 mL) stirred at room temperature for the specified time; [b] Isolated yields after purification by flash column; [c] Determined by chiral HPLC analysis or ^{1}H NMR analysis of the crude mixture; [d] Determined by chiral HPLC analysis(results in parentheses refer to the minor diastereoisomer); [e] Pulverized without activation; [f] The reaction was conducted at 0 °C.

Table 4. Asymmetric aldol reaction between various isatins and ketones catalyzed by chitosan aerogel under optimized conditions [a,b,c,d].

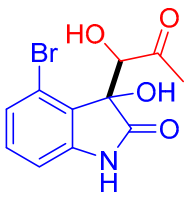


1a-m **2a-b** **3a-p**



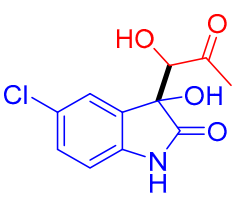
3a

90%, 53:47, 75%ee



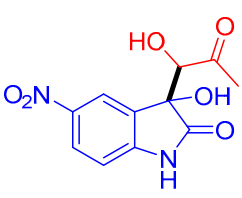
3b

90%, 83:17, 36%ee



3c

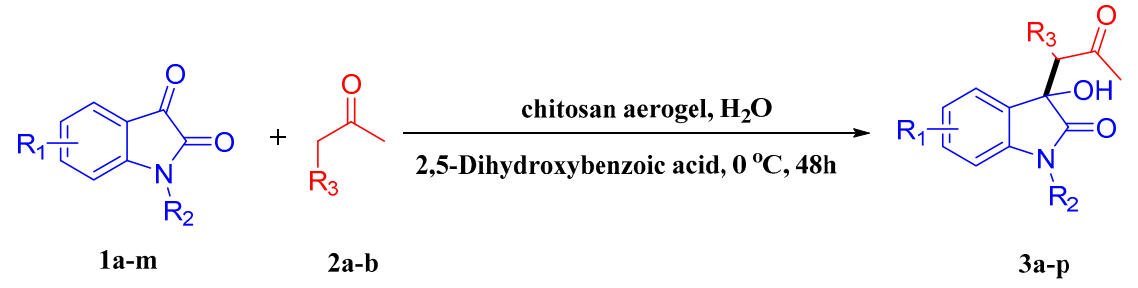
93%, 71:29

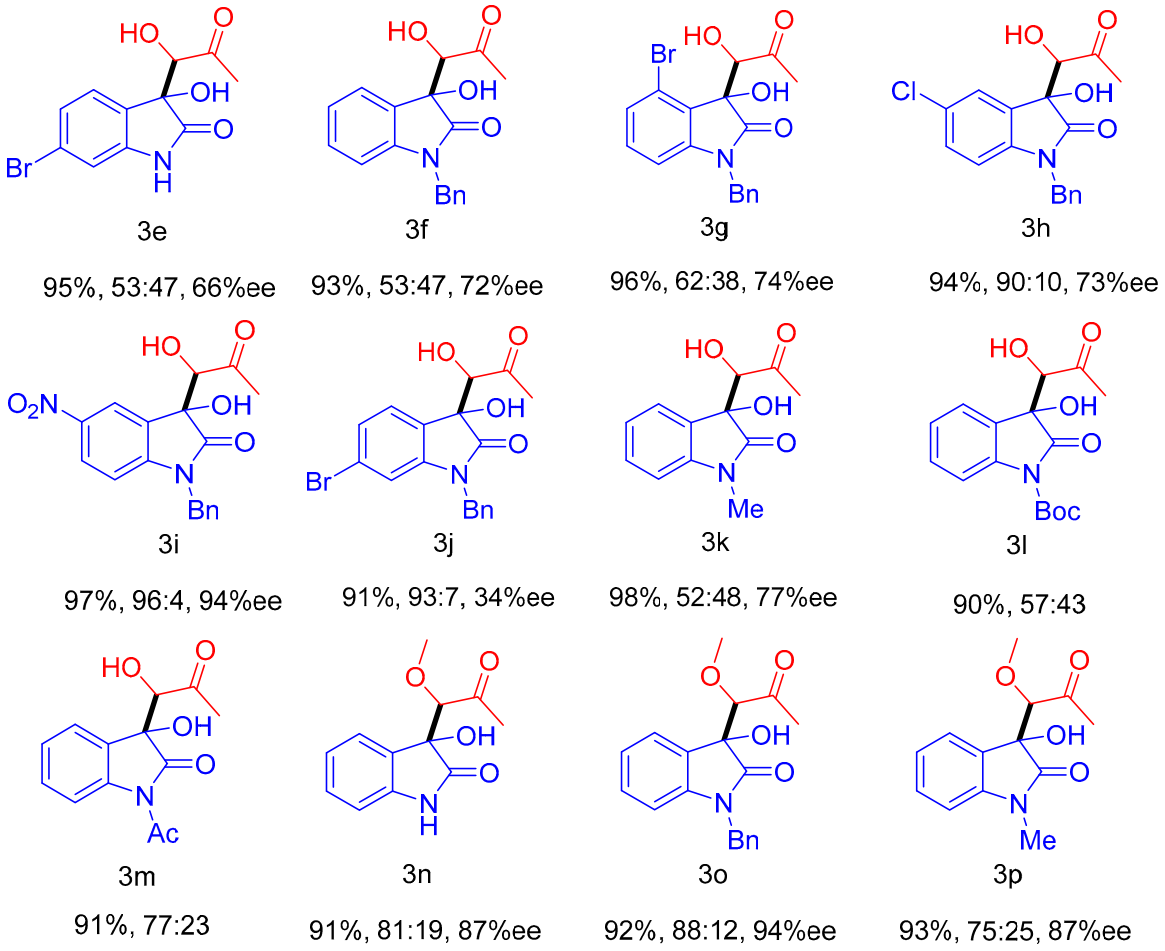


3d

92%, >99:1, 92%ee

Table 4. *Cont.*





[a] All reactions were carried out with isatin **1a** (0.5 mmol), hydroxyacetone **2a** (10 mmol), 0.05 mmol chitosan aerogel (10 mol %) and 0.05 mmol 2,5-dihydroxybenzoic acid (10 mol %) in water (0.5 mL) stirred at 0 °C for 48 h; [b] Isolated yields after purification by flash column; [c] Determined by chiral HPLC analysis or ^{1}H NMR analysis of the crude mixture; [d] Determined by chiral HPLC analysis.

3. Materials and Methods

3.1. General Methods

All solvents and reagents in this work were acquired from different commercial sources and used without further purification. Chitosan aerogel microspheres were prepared as in previous literature [32]. Thin layer chromatography (TLC) was conducted on GF254 silica gel plates, which were visualized by UV at 254 nm. Column chromatography separations were performed using silica gel 300–400 mesh. Chiral High-performance liquid chromatography (HPLC) analysis was conducted with a Waters Alliance 2695 instrument (Waters corporation, Milford, MA, USA), using a UV–visible

light (Vis) Waters PDA 2998 detector (Waters corporation), and working at 254 nm. ^{1}H NMR spectra were recorded on a Bruker AM400 NMR spectrometer (Bruker corporation, Karlsruhe, Germany), and NMR spectra were obtained as $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.26 ppm) or dimethyl sulfoxide-d_6 (DMSO-d_6) (2.50 ppm). High-resolution mass spectrometry (HRMS) data were recorded using a Waters Q-Tof premier mass spectrometer (Waters corporation).

3.2. General Procedure for the Asymmetric Aldol Reaction of Isatins with Ketones

A reaction mixture of isatin (0.5 mmol), ketone (10 mmol), chitosan aerogel beads (10 mol %) and 2,5-dihydroxybenzoic acid (10 mol %) in water (0.5 mL) was stirred at 0 °C until the complete conversion of the starting material. Then the solvent was removed in vacuo to give the crude product and purified by column chromatography on silica gel (petroleum ether/ethyl acetate) or crystallization from petroleum ether/ethyl acetate to afford the desired compounds.

4. Conclusions

In conclusion, an environmentally-friendly enantioselective aldol reaction to construct the 3-substituted-3-hydroxy-2-oxindoles is established by using isatins and ketones as starting materials. In this reaction, chitosan aerogel is successfully employed as a green organocatalyst and works smoothly in the presence of water. The reaction has a large substrate scope and the corresponding products are all produced in high yields and with high chemoselectivity. Moreover, 2,5-dihydroxybenzoic acid was found to be an effective additive to modulate the asymmetric aldol reactions. Further studies of this system can broaden the scope of this reaction to other ketone donors.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/6/12/186/s1, Figures S1–S16: ^{1}H NMR and ^{13}C NMR analysis of compound **3a**–**3p**, Figures S17–S29: Chiral High-performance liquid chromatography (HPLC) analysis of compound **3a**–**3p**.

Acknowledgments: This work was supported by the National Natural Science Foundation of China (81473091, 81673290) and the Fundamental Research Funds for the Central Universities and Distinguished Young Scholars of Sichuan University (2015SCU04A41).

Author Contributions: Lifang Ma and Liang Ouyang conceived and designed the experiments; Hui Dong performed the experiments; Jie Liu analyzed the data; Liang Ouyang and Jie Liu contributed reagents/materials/analysis tools; Hui Dong and Liang Ouyang wrote the paper. All authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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