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Asymmetric Aldol Reaction of 3-Acetyl-2*H*-chromen-2-ones and Isatins Catalyzed by a Bifunctional Quinidine Urea Catalyst

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Abstract

The asymmetric aldol reaction of 3-acetyl-2*H*-chromen-2-ones and isatins has been realized by using a bifunctional quinidine-derived urea as the catalyst. The corresponding 3-hydroxyoxindole derivatives containing a 2*H*-chromen-2-one moiety were obtained in good yields and high enantioselectivities. When (*Z*)-ethyl 2-benzylideneacetoacetate was used as the substrate, a mixture of two diastereomers (both *Z* and *E*) was obtained due to the isomerization of the double bond under the reaction conditions.

Keywords

aldol reaction; asymmetric catalysis; isatin; 3-acetyl-2*H*-chromen-2-one; enolate; bifunctional catalyst

3-Substituted-3-hydroxy-2-oxindole, a moiety that may be found in many biologically active natural products,^[1] has become an emerging scaffold for drug discovery with potential anti-cancer and other biological activities in recent years.^[2] Because of the biological relevance of the 3-substituted 3-hydroxyoxindole derivatives, lately a lot of attentions have been paid to develop novel synthetic methodologies to access these compounds in high stereoselectivities.^[3] Among those reported approaches,^[4] organocatalytic cross aldol reactions of ketones or aldehydes and isatins provide a green method for an easy access to these interesting molecules.^[5,6] Most of these reported methods entail a primary or a secondary amine derivative as the catalyst that catalyzes the reaction through an enamine intermediate,^[5] and high stereoselectivities have been achieved with some of these reported catalysts. Nonetheless, since the formation of an enamine requires a very electrophilic carbonyl group, this approach cannot be applied to ketone derivatives that are less electrophilic due to electronic and/or steric effects.

Our group recently reported a new way to conduct the organocatalyzed aldol and Mannich reactions of unfunctionalized ketones via a complete noncovalent catalysis that involves an enolate intermediate.^[6] Since the formation of an enolate does not depend on the

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electrophilicity of the carbonyl group, we and others have demonstrated that poor electrophilic ketone substrates can still be applied to the aldol reaction with isatins for the synthesis of 3-hydroxyoxindole derivatives.^[6a,b,7] Continuing on this theme, we envisioned that 3-acetyl-2*H*-chromen-2-ones could be used as the substrates in the base-catalyzed aldol reaction with isatins via the enolate mechanism. 3-Acetyl-2*H*-chromen-2-ones are poor substrates for the enamine-mediated aldol reaction because the α,β -unsaturated system and the large 2*H*-chromen-2-one moiety are detrimental to the electrophilicity of the ketone group. However, these two moieties are helpful for increasing the α -proton acidity.^[6,7] Herein we wish to report an organocatalyzed enantioselective aldol reaction of 3-acetyl-2*H*-chromen-2-ones and isatins for the asymmetric synthesis of 3-substituted 3-hydroxy-2-oxindole derivatives containing a 2*H*-chromen-2-one moiety using a quinidine urea catalyst.

On the basis of our previous findings,^[6] we initially screened several bifunctional Brønsted bases, most of which are cinchona alkaloid derivatives (Figure 1), as the catalyst for the desired aldol reaction, using isatin (**1a**) and 3-acetyl-2*H*-chromen-2-one (**2a**) as the model substrates. The results are summarized in Table 1.

As the data in Table 1 show, when Takemoto thiourea (**4**, 10 mol %) was used as the catalyst, the desired aldol product **3a** was obtained in a good yield of 83% after reacting in THF for 2.5 h at rt. The ee value of this product was determined to be 64% (Table 1, entry 1). It should be pointed out that 2*H*-chromen-2-one is also an important pharmacophore.^[8] The incorporation of these two biologically active moieties into a single molecule may result in some interesting biological activities of the new product. Under similar conditions, quinidine (**5**) led to a poorer product yield and much lower product ee value (16% ee, entry 2), and cupreidine (**6**) showed almost no catalytic activity even after extended reaction time (entry 3). In contrast, quinine thiourea (**7**) and quinidine thiourea (**8**), the enantiomeric products of **3a** were obtained in an excellent 96% yield and high ee values of 90% and 92% ee, respectively (entries 4 and 5). These data indicated that a thiourea moiety is both important for the reactivity and the enantioselectivity of this aldol reaction, which is in agreement with our previous observations.^[6a,b] *N*-Substituted isatins were then evaluated with the quinidine thiourea catalyst **8**. *N*-Benzylisatin (**1b**) was found to be as good as isatin itself (entry 6), whereas *N*-tritylisatin (**1c**) is a much worse substrate than isatin (**1a**) and *N*-benzylisatin (**1b**) in terms of both the product yield and the ee value (entry 7). Since *N*-substituted isatins show no advantage over unsubstituted isatin, isatin (**1a**) was used for further screenings. Slightly lower yields and ee values were obtained when *N*-phenyl-substituted quinidine thiourea (**9**) and urea (**10**) were adopted as the catalyst (entries 8 and 9). When *N*-[3,5-bis(trifluoromethyl)phenyl]-substituted quinidine urea (**11**) was applied, a slightly higher ee value of 94% was obtained for **3a**, with a high yield of 98% (entry 10). Very good results were also obtained for the *N*-(4-nitrophenyl)-substituted urea catalyst **12** (entry 11). Thus, this screen identified urea **11** as the best catalyst for this reaction, whereas thioureas **7** and **8** and urea **12** are also very good catalysts for this reaction. Next the solvent effects on this reaction were evaluated by using **11** as the catalyst. A high yield and a slightly lower ee value of 92% was obtained in 1,4-dioxane (entry 12). The same ee value of 92% was also obtained in dimethoxyethane, albeit with a much lower product yield (67%, entry 13). Much poorer ee values of **3a** were obtained in diethyl ether and MTBE (entries 14

and 15). The product yields also dropped dramatically in these solvents. Poor results were also obtained in toluene (entry 16). The low yields obtained in these three solvents were most likely due to the poor solubility of isatin in these solvents. High yields were obtained in more polar dichloromethane and acetonitrile (entries 17 and 18). However, for an unknown reason, DMF led to a lower product yield (entry 19). The ee value of **3a** obtained from these three solvents was 88%, which is lower than that obtained from THF. The temperature effects on the enantioselectivity of this reaction were then evaluated using the best solvent THF. When the reaction was carried out at 5 °C, the ee value of the product was slightly improved to 96% at the expense of the reactivity (22 h vs. 2.5 h at rt, entry 20). Further dropping of the reaction temperature to -5 °C showed no improvement in the product ee value (entry 21).

Once the reaction conditions were optimized, the scope of this reaction was studied. The results are summarized in Table 2. As the data in Table 2 show, besides isatin (**1a**, Table 2, entry 1), substituted isatins with an electron-withdrawing group at position 5 of the isatin ring (**1d-h**) produce the desired aldol reaction products (**3b-f**) in high yields and excellent enantioselectivities (94% ee) with 3-acetyl-2*H*-chromen-2-one (**2a**) (Table 2, entries 2-6). An electron-donating group at this position leads to slower reaction (**1i** and **1j**, entries 7-8). While 5-methylisatin (**1i**) yields a slightly lower ee value (88% ee) for the aldol product **3g** (entry 7), the aldol product (**3h**) of 5-methoxyisatin (**1j**) has a high ee value of 96% (entry 8). On the other hand, 4-bromoisatin (**1k**, entry 9), 5-bromoisatin (**1f**, entry 4), 6-bromoisatin (**1l**, entry 10), and 7-bromoisatin (**1m**, entry 11) all give the expected aldol products with **2a** in similarly high yields and ee values (**3d**, **3i-k**, 92-96% ee). These results indicate that the position of the substituent on the isatin ring has only minimum influence on the reactivity and the enantioselectivity of this reaction. As expected, a high yield (99%) and a high ee value (90% ee) was obtained for the aldol product (**3l**) of 5,7-dibromoisatin (**1n**) (entry 12). The substituent effects were then further evaluated by using substituted 3-acetyl-2*H*-chromen-2-ones (**2b-e**) as the substrates. As the data in Table 2 show, the substituents at position 6 of 3-acetyl-2*H*-chromen-2-one has a major influence on the reactivity and the enantioselectivity of this reaction (entries 13-16). When there is an electron-withdrawing group at position 6 (**2b-d**), the reactions became so sluggish that a higher catalyst loading (20 mol %) was necessary. Even with more catalyst loading, much lower yields (76-80%) of the desired aldol products (**3m-o**, entries 13-15) were obtained, and the product ee values were unsatisfactory (58-70%). In contrast, with an electron-donating methoxy group at position 6 (**2e**, entry 16), the reactivity and high enantioselectivity (94% ee, **3p**) of this aldol reaction was restored. The exact reason for the observed influence of these remote groups on the enantioselectivities of this aldol reaction is not clear at this moment, but most likely this was due to some subtle electronic effects.

Besides 3-acetyl-2*H*-chromen-2-ones, an open-chain Knoevenagel product (*Z*)-ethyl 2-benzylidenacetoacetate (**13**) may also be applied in this reaction (eq 1). With catalyst **11** (20 mol % loading), the desired aldol product **3q** was obtained in a total yield of 96% as an inseparable 1:1 diastereomeric mixture due to the isomerization of the double bond under the reaction conditions. Each of these two diastereomers was obtained in 90% ee. When (*E*)-**13** was applied in this reaction, a similar result was obtained.

(1)

The absolute configuration of the major enantiomer obtained in this reaction was assigned on the basis of the X-ray crystallography analysis of the aldol product **3d**, which indicates that the newly generated stereogenic center has an *R*-configuration (Figure 2).^[9]

On the basis of the product absolute configuration and our previously reported enolate aldol reaction mechanism,^[6a,b] a plausible transition state is proposed to explain the stereochemical outcome of this reaction (Scheme 1). As shown in Scheme 1, 3-acetyl-2*H*-chromen-2-one is deprotonated by the tertiary amine in the quinidine urea catalyst backbone. After deprotonation, the enolate associates closely with the catalyst due to ionic interactions and potential hydrogen bonding between the ammonium and the carbonyl oxygen of 3-acetyl-2*H*-chromen-2-one.

Simultaneously, two hydrogen bonds are formed between the isatin carbonyl groups and the urea moiety of the quinidine urea catalyst. Besides activating the ketone group for the enolate attack, these hydrogen bonds also direct the approach of isatin. As in the previous cases,^[6a,b] the *re* face orientation of isatin is favored. The attack of the enolate from the back onto the *si* face of the isatin ketone group leads to the formation of the observed major *R* enantiomer.

Since the aldol products obtained in this study have functional groups in right distance for an intra-molecular oxa-Michael reaction, which should lead to potentially bioactive spirooxindole tetrahydropyranones,^[10] the intramolecular oxa-Michael reaction was attempted as a potential application of the reaction products. Unfortunately, the treatment of **3a** with bases such as DBU, NaH, DABCO, TMG, and K₂CO₃ does not yield the desired spirooxindole tetrahydropyranone product. Likewise, the reaction with camphor sulfonic acid and Lewis acids copper triflate and boron trifluoride does not produce the desired product, either. All these reagents promoted the retro-aldol reaction that lead to the formation of the starting isatin and 3-acetyl-2*H*-chromen-2-one. Nonetheless, **3a** may be reduced with hydrogen under the catalysis of Pd/C to give compound **4** as a 1:1 diastereomeric mixture (eq. 2).

(2)

In summary, we have developed the first enantioselective aldol reaction of 3-acetyl-2*H*-chromen-2-ones and isatins via the enolate mechanism. The reaction provides an easy access of 3-hydroxy-2-oxindoles with a 2*H*-chromen-2-one moiety in the side chain of the 3-substituent: A unique structure feature that incorporates these two pharmacophores in the same molecule. Under the catalysis of a quinidine-derived urea catalyst **11**, the corresponding aldol products may be obtained in excellent yields and high enantioselectivities. The reaction may also be applied to a Knoevenagel type compound 2-benzylidenacetoacetate and the corresponding aldol product may be obtained in high yield and ee value, although the reaction conditions cause the isomerization of the double bond.

Experimental Section

Typical Experimental Procedure for the Enantioselective Reaction

A mixture of 3-acetyl-2*H*-chromen-2-one (**2a**, 94.0 mg, 0.50 mmol) and catalyst **11** (5.8 mg, 0.010 mmol, 10 mol %) in dry THF (0.2 mL) was cooled to 5 °C and stirred for 20 min at this temperature. Then isatin (**1a**, 14.7 mg, 0.1 mmol) was added in one portion. The reaction mixture was further stirred at this temperature for 22 h (monitored by TLC). After the reaction was completed, the mixture was directly transferred to a silica gel column. The product was purified by flash column chromatography (hexane/AcOEt = 85:15 to 40:60) to give (*R*)-3-hydroxy-3-[2-oxo-2-(2-oxo-2*H*-chromen-3-yl)ethyl]indolin-2-one (**3a**, 33.2 mg, 99% yield).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Catalyst Screened for the direct aldol reaction [Ar = 3,5-(CF₃)₂C₆H₃-]

Figure 2. ORTEP drawing of compound 3d

Scheme 1. Proposed transition state to account for the formation of the major *R*-enantiomer

Table 1
Screening of the Catalysts and Optimization of the Reaction Conditions^[a]

Entry	Catalyst	Solvent	Yield (%) ^[b]	ee (%) ^[c]
1	4	THF	83	64
2	5	THF	60	16
3 ^[d]	6	THF	<5	nd ^[e]
4	7	THF	96	90 ^[f]
5	8	THF	96	92
6 ^[g]	8	THF	95	92
7 ^[h]	8	THF	32	70
8	9	THF	72	84
9	10	THF	80	88
10	11	THF	98	94
11	12	THF	95	92
12	11	1,4-dioxane	97	92
13	11	DME ^[i]	69	92
14	11	Et ₂ O	10	82
15	11	MTBE	13	70
16	11	toluene	9	66
17	11	DCM	96	88
18	11	CH ₃ CN	98	88
19	11	DMF	60	88
20 ^[j]	11	THF	99	96
21 ^[k]	11	THF	96	96

^[a] Unless otherwise specified, all reactions were carried out at rt with isatin (**1a**, 0.10 mmol), 3-acetyl-2H-chromen-2-one (**2a**, 0.50 mmol), and the catalyst (0.010 mmol, 10 mol %) in the indicated solvent (0.2 mL) for 2.5 h.

^[b] Yield of the isolated product after column chromatography.

^[c] Values of ee were determined by chiral HPLC analyses on a ChiralPak IB column.

^[d] The reaction was carried for 24 h.

^[e] Not determined.

^[f] The opposite (*S*)-enantiomer was obtained as the major product in this case.

[g] *N*-Benzylisatin (**1b**) was used as the substrate in this case.

[h] *N*-Tritylisatin (**1c**) was used as the substrate in this case.

[i] Dimethoxyethane.

[j] The reaction was conducted at 5 °C for 22 h.

[k] The reaction was conducted at -5 °C for 24 h.

Table 2

Substrate Scope of Direct Aldol Reaction^[a]

Entry	R ¹	R ²	1/2/3	Time (h)	Yield (%) ^[b]	ee (%) ^[c]
1	H	H	a/a/a	22	99	96
2	5-F	H	d/a/b	24	98	94
3	5-Cl	H	e/a/c	24	96	95
4	5-Br	H	f/a/d	24	97	96
5	5-I	H	g/a/e	24	95	94
6	5-NO ₂	H	h/a/f	24	92	96
7	5-Me	H	i/a/g	48	90	88
8	5-OMe	H	j/a/h	48	75	96
9	4-Br	H	k/a/i	30	93	96
10	6-Br	H	l/a/j	24	94	92
11	7-Br	H	m/a/k	24	99	94
12	5,7-Br ₂	H	n/a/l	24	99	90
13 ^[d]	H	Cl	a/b/m	24	76	62
14 ^[d]	H	Br	a/c/n	24	77	58
15 ^[d]	H	NO ₂	a/d/o	24	80	70
16	H	OMe	a/e/p	24	85	94

^[a]Unless otherwise specified, all reactions were carried out at 5 °C with isatin (**1**, 0.10 mmol), 3-acetyl-2H-chromen-2-one (**2**, 0.50 mmol), and catalyst **11** (0.010 mmol, 10 mol %) in THF (0.2 mL).

^[b]Yield of the isolated product after column chromatography.

^[c]Values of ee were determined by chiral HPLC analysis on a ChiralPak IB, a ChiralCel AD-H, or a ChiralPak ID column.

^[d]The reactions were carried out with 20 mol % of catalyst **11** in THF (2 mL) at room temperature.