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Enantioselective decarboxylative aldol addition of β-ketoacids to isatins catalyzed by binaphthyl-modified organocatalyst

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ABSTRACT

The catalytic enantioselective decarboxylative aldol addition reaction of isatins with β-ketoacids promoted by chiral bifunctional organocatalysts have been developed, allowing facile synthesis of the corresponding chiral 3-hydroxy-3-phenacyloxindole derivatives with excellent enantioselectivity (up to 97% ee).

The 3-substituted-2-oxindoles, one class of compounds bearing the indole skeletal structure, exist in a number of biologically active alkaloids and pharmacological agents.[1] Intensive efforts have been devoted to the development of asymmetric transformations using isatin as an electrophile.[2] They provide powerful tools for the rapid and efficient construction of 3-hydroxy-2-oxindole containing chiral quaternary carbon center at its 3-position.[3] Among them, the aldol addition of appropriate ketones to isatins should be one of the most concise and straightforward approaches to this kind of compounds.[4] However, such direct aldol reactions of aromatic ketones were very slow, requiring four to seven days to complete.[5] In recent years, the enantioselective decarboxylative additions of malonic acid half thioesters as ester enolate equivalents have received much attention.[6] Although a number of reactions of malonic acid half-thioesters as carbon nucleophiles to various electrophiles have been reported,[7] the corresponding β-ketoacids have received relatively little attention as carbon nucleophiles. There have been a few reported examples of decarboxylative aldol, alkylation, Mannich, and Michael reactions of β-ketoacids as surrogates of ketones.[8] Very recently, Lu groups described organocatalytic enantioselective decarboxylative aldol-type reactions of β-ketoacids with isatins.[9] There are still some drawbacks to the previously reported procedure, such as the high catalyst loading and long reaction time required for good enantioselectivity.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[10] we recently reported enantioselective C–C bond formations of active methylenes and methines using chiral catalysts.[11] Herein, we wish to describe the direct enantioelective decarboxylative Michael addition of β-ketoacids to isatins catalyzed by bifunctional organocatalysts bearing both central and axial chirality.

To determine suitable reaction conditions for the catalytic enantioselective decarboxylative Michael addition reaction of β-ketoacids, we initially investigated the reaction system with isatins **1** and benzoylacetic acid (**2a**) in the presence of 10 mol % of catalysts (Fig. 1) in chloroform at room temperature. We first examined the influences of the structure of isatin derivatives **1a**–**1a**″ on the reactivity and selectivity (Table 1, entries 1–3). *N*-Boc isatin (**1a**) was selected as optimum substrate. We also examined the impact of the structure of catalysts **I**–**VI** (Fig. 1) on the enantioselectivities (79–92% ee, Table 1, entries 1 and 4–8). The best results were obtained with catalyst **IV** which is binaphthyl-modified squaramide bifunctional organocatalyst bearing central and axial chiral elements. In order to improve the selectivity, different solvents were then tested in the presence of 10 mol % of catalyst **IV** together with benzoylacetic acid (**2a**) and *N*-Boc isatin (**1a**). Aprotic solvents, such as dichloromethane, carbon tetrachloride, 1,2-dichloroethanes, 1,1,2-trichloroethane, diethyl ether, THF, toluene, and accetonitrile were tolerated well in this conjugate addition with slightly significant decrease in the enantioselectivities (31–89% ee, Table 1, entries 6 and 9–16). Protic polar solvent such as MeOH

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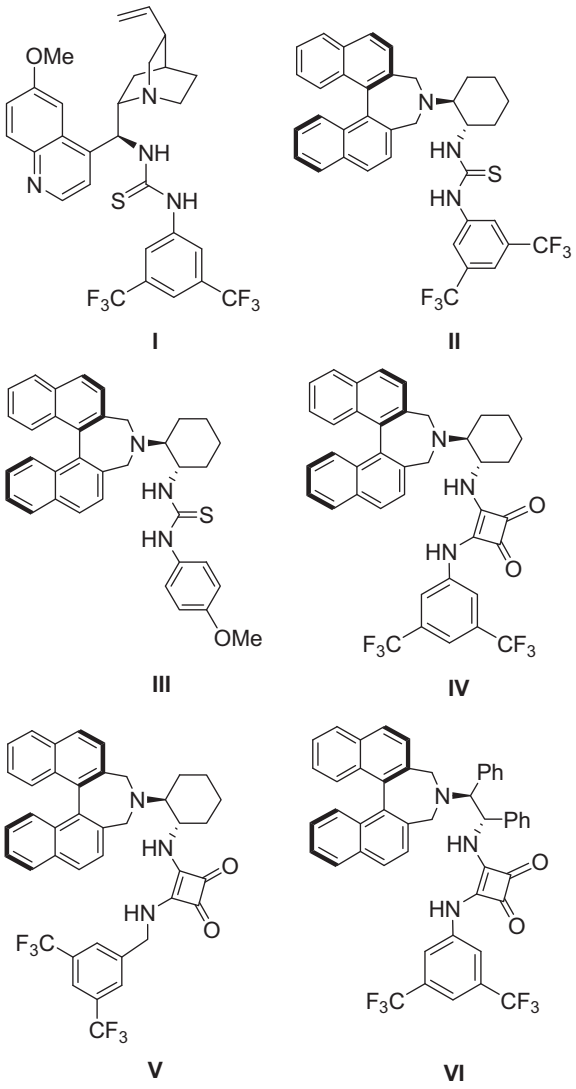
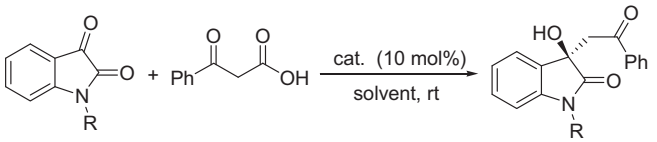


Figure 1. Structures of chiral organocatalysts.

Table 1
Optimization of reaction conditions [a]



1a : R = Boc
1a' : R = H
1a'' : R = Ts

2a

3

Entry	Cat.	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**I**	$CHCl_3$	4	87	85
2[d]	**I**	$CHCl_3$	4	82	17
3[e]	**I**	$CHCl_3$	4	71	5
4	**II**	$CHCl_3$	3	90	85
5	**III**	$CHCl_3$	3	91	79
6	**IV**	$CHCl_3$	3	92	92
7	**V**	$CHCl_3$	2	85	91
8	**VI**	$CHCl_3$	2	86	86
9	**IV**	CH_2Cl_2	2	85	85
10	**IV**	CCl_4	1	70	79
11	**IV**	$ClCH_2CH_2Cl$	1	80	87
12	**IV**	Cl_2CHCH_2Cl	1	76	89
13	**IV**	Et_2O	1	80	47
14	**IV**	THF	1	77	31
15	**IV**	toluene	1	78	81
16	**IV**	MeCN	1	80	61
17	**IV**	MeOH	2	82	83
18[f]	**IV**	$CHCl_3$	3	91	90
19[g]	**IV**	$CHCl_3$	3	90	92
20[h]	**IV**	$CHCl_3$	3	91	88
21[i]	**IV**	$CHCl_3$	3	61	74
22[h,j]	**IV**	$CHCl_3$	3	90	97

[a] Reaction conditions: isatin (**1a**, 0.30 mmol), benzoylacetic acid (**2a**, 0.45 mmol), catalyst (0.03 mmol), $CHCl_3$ (3 mL) at room temperature.
[b] Isolated yield.
[c] Enantiopurity was determined by HPLC analysis using a Chiralpak ID column.
[d] Isatin (**1a**′) was used as substrate.
[e] *N*-Tosyl isatin (**1a**′′) was used as substrate.
[f] 5 mol % of catalyst loading.
[g] 2.5 mol % of catalyst loading.
[h] 1 mol % of catalyst loading.
[i] 0.1 mol % of catalyst loading.
[j] This reaction was conducted at 0 °C.

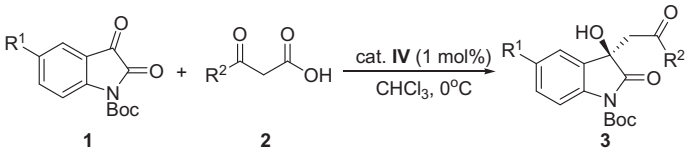
also afforded product with high yield and high selectivity (Table 1, entry 17). Among the solvents probed, the best results (92% yield and 92% ee) were achieved when the reaction was conducted in chloroform (Table 1, entry 6). The present catalytic system tolerates catalyst loading down to 5.0, 2.5, or 1.0 mol % without compromising the yield or the enantioselectivity (Table 1, entries 18–21). Finally, we conducted the aldol addition at low temperature in order to improve the enantioselectivity. The enantioselectivity was elevated up to 97% ee at 0 °C in the presence of 1.0 mol % of catalyst **IV** (entry 22).

To examine the generality of the catalytic enantioselective decarboxylative aldol addition reaction of the β-ketoacid derivatives **2** by using chiral bifunctional organocatalyst **IV**, we studied the aldol addition of various β-ketoacids **2** with *N*-Boc isatin derivatives **1** in the presence of 1.0 mol % of catalyst **IV** in chloroform at 0 °C (Table 2).[12] A range of electron-donating and electron-withdrawing substitutions on the β-aryl ring of the β-ketoacids **2** provided the reaction products in high yields (76–90%) and with excellent enantioselectivities (87–97%, Table 2, entries 1–6). The naphthyl- and heteroaryl-substituted β-ketoacids **2** provided the products with high selectivity (Table 2, entries 7–8). However, the β-alkyl-substituted β-ketoacid, 3-oxobutanoic acid, was also an acceptable starting material and provided the corresponding aldol product in moderate yield with high enantioeselectivity (Table 2, entries 9–16). We then explored the possibility of using a wide range of isatins **1** with benzoylacetic acid (**2a**) in the presence of 1.0 mol % of catalyst **IV** in chloform at 0 °C (Table 2). A range of electron-donating and electron-withdrawing substitutions on the aromatic ring of isatins **1** provided the reaction products in high yields (83–98%) and with excellent enantioselectivities (93–95% ee, Table 2, entries 17–19) The absolute configuration of the adducts **3** was determined for some derivatives by comparison of their optical and HPLC properties with literature values.[9]

The present method is operationally simple and efficient and, thus, may be valuable for practical chemical synthesis. As shown in Scheme 1, when 3-oxo-*p*-tolylpropanoic acid (**2b**) was treated with *N*-Boc isatin (**1a**) under the optimal reaction conditions, the reaction proceeded smoothly to afford the desired product **3b** at the gram scale with 92% yield and 95% ee (Scheme 1).

In conclusion, we have developed a highly efficient catalytic enantioselective decarboxylative aldol addition reaction of β-ketoacids to isatins using 1.0 mol % of a binaphthyl-derived bifunctional organocatalyst. The desired aldol products were obtained in good to high yields, and excellent enantioselectivities (up to 97% ee) were observed for all the substrates examined in this work. We believe that this method provides a practical entry for the

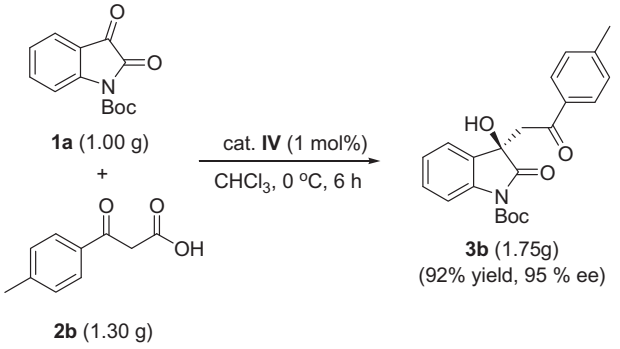
Table 2
Substrate Scope[a]



1 2 3

Entry	R^1, R^2	Time (h)	Yield[b] (%)	ee[c] (%)
1	H, Ph	3	**3a**, 90	97
2	H, 4-MeC_6H_4	2	**3b**, 84	94
3	H, 4-MeOC_6H_4	2	**3c**, 85	87
4	H, 4-FC_6H_4	2	**3d**, 86	94
5	H, 4-ClC_6H_4	3	**3e**, 76	97
6	H, 3-ClC_6H_4	3	**3f**, 81	91
7	H, 2-Naphthyl	1	**3g**, 86	91
8	H, 2-Thienyl	3	**3h**, 85	93
9	H, Me	2	**3i**, 68	89
10	H, Et	23	**3j**, 95	93
11	H, *n*-Pr	23	**3k**, 75	96
12	H, *i*-Pr	25	**3l**, 92	93
13	H, *t*-Bu	16	**3m**, 76	91
14	H, Cyclohexyl	26	**3n**, 88	96
15	H, Bn	18	**3o**, 75	91
16	H, $PhCH_2CH_2$	16	**3p**, 94	94
17	Me, Ph	5	**3q**, 98	95
18	Cl, Ph	3	**3r**, 94	93
19	Br, Ph	2	**3s**, 83	95

[a] Reaction conditions: isatin (**1**, 0.30 mmol), β-ketoacid (**2**, 0.45 mmol), catalyst (3.0 μmol), $CHCl_3$ (3 mL) at 0 °C.
[b] Isolated yield.
[c] Enantiopurity was determined by HPLC analysis using Chiralpak ID (for **3a**–**3j**



Scheme 1. Gram scale aldol addition of 3-oxo-*p*-tolylpropanoic acid (**2b**) with *N*-Boc isatin (**1a**).

preparation of biologically important chiral 3-hydroxy-3-phenacyloxindole derivatives. Further study of this catalytic enantioselective decarboxylative addition reaction of β-ketoacids with various carbon electrophiles is in progress.

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12. *Typical procedure for the aldol addition reaction of benzoylacetic acid (**2a**) with N-Boc isatin (**1a**):* To a stirred solution of *N*-Boc isatin (**1a**, 65.2 mg, 0.30 mmol) and catalyst **IV** (2.1 mg, 3.0 μmol) in chloroform (3 mL) was added benzoylacetic acid (**2a**, 73.9 g, 0.45 mmol) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. After completion of the reaction, the resulting solution was concentrated in vacuo and the obtained residue was purified by flash chromatography (EtOAc/hexane, 1:2) to afford the 99.2 mg (90%) of the aldol adduct **3a**.
(R)-tert-Butyl 3-hydroxy-2-oxo-3-(2-oxo-2-phenylethyl)indoline-1-carboxylate

(***3a***): $[\alpha]_D^{26}$ +80.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.84 (m, 2H), 7.55 (t, *J* = 8.5 Hz, 1H), 7.33–7.43 (m, 4H), 7.12 (m, 1H), 4.30 (br s, 1H), 3.88 (d, *J* = 17.2 Hz, 1H), 3.68 (dd, *J* = 1.4 Hz, 17.2 Hz, 1H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 175.1, 149.1, 140.0, 135.9, 133.7, 130.1, 128.7, 128.6, 128.1, 124.7, 123.5, 115.4, 84.5, 74.0, 45.6, 28.0; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{21}NNaO_5$ $[M+Na]^+$ 390.1317, found 390.1313; HPLC (80:20, *n*-hexane/*i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak ID, t_R = 10.3 min (minor), t_R = 11.7 min (major), 97% ee.