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Direct Catalytic Asymmetric Synthesis of Oxindole-Derived δ-Hydroxy-β-ketoesters by Aldol Reactions

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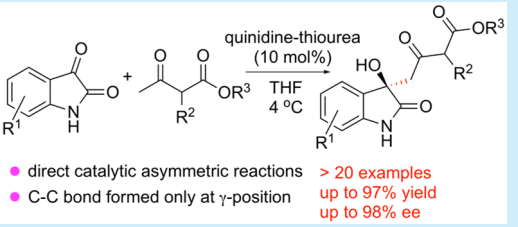
Supporting Information

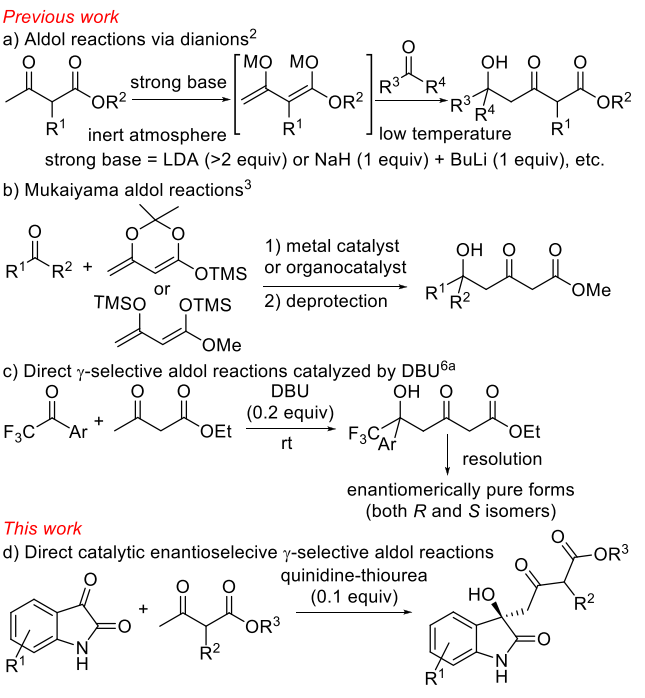
ABSTRACT: Direct asymmetric synthesis of δ-hydroxy-β-ketoesters was accomplished via regio- and enantioselective aldol reactions of β-ketoesters with isatins catalyzed by cinchona alkaloid thiourea derivatives. The C−C bond formation of the reactions occurred only at the γ-position of the β-ketoesters. Reaction progress monitoring and product stability analyses under the conditions that included the catalyst indicated that the γ-position reaction products were formed kinetically. Various δ-hydroxy-β-ketoesters bearing 3-alkyl-3-hydroxyoxindole cores relevant to the development of bioactive molecules were synthesized.



δ-Hydroxy-β-ketoesters are useful building blocks for the synthesis of biologically important natural products and pharmaceutical leads.[1−4] Common methods to access δ-hydroxy-β-ketoesters include reactions of dianions[2] generated from β-ketoesters by using two or more equivalents of strong base(s) or reactions of preformed silyl dienol ethers or alkyl dienol ether derivatives[3] with carbonyl compounds (Scheme 1a and b). These methods require either severe conditions or tedious protection and deprotection procedures. There are only a few reports of direct use of β-ketoesters[4] in aldol reactions as nucleophiles to synthesize δ-hydroxy-β-ketoesters under mild conditions.[5,6] For example, direct aldol reactions of β-ketoesters catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[6] or other bases[5] that form the C−C bond at the γ-position of the β-ketoesters to provide δ-hydroxy-β-ketoester derivatives have been reported (Scheme 1c).[6a] Although enantiomerically pure δ-hydroxy-β-ketoesters were obtained by resolutions of the aldol products using homochiral amines,[6a] catalytic asymmetric processes are desired.[4b] Here, we report the direct asymmetric synthesis of oxindole-derived δ-hydroxy-β-ketoesters via regio- and enantioselective aldol reactions of β-ketoesters with isatins catalyzed by cinchona derivatives[7,8] (Scheme 1d). Isatins were used as electrophiles in the aldol reactions because the products 3-alkyl-3-hydroxyoxindoles are found in biologically active natural products.[7a−c,9]

First, we searched for catalysts and conditions suitable for the aldol reaction of isatin (**1a**) with methyl acetoacetate (**2a**) to afford aldol product δ-hydroxy-β-ketoester **3a** (Table 1). After a screening using various organocatalysts,[8] we found that cinchona alkaloid quinidine (**I**) catalyzed the aldol reaction to give **3a** with some enantioselectivity (Figure 1 and Table 1, entry 2). Thus, we focused on the screening of cinchona

Scheme 1. Synthesis of δ-Hydroxy-β-ketoesters



alkaloid-based organocatalysts to give **3a** in high yield with high enantioselectivity. When a quinidine derivative bearing a primary amine (**II**) was used as catalyst, the reaction did not

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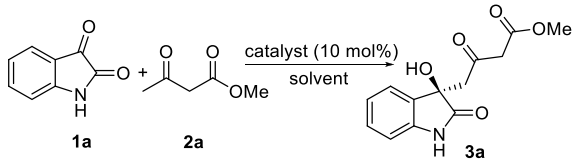
Table 1. Optimization of the Aldol Reaction of 1a and 2a To Afford 3a[a]



entry	catalyst	solvent	time [h]	yield [%][b]	ee [%][cd]
1	DBU	THF	8	99	--
2	**I**	THF	48	32	21 (*R*)
3	**II**	THF	48	--	--
4	**III**	THF	48	--	--
5	**IV**	THF	24	98	71 (*R*)
6	**V**	THF	24	88	59 (*R*)
7	**VI**	THF	24	93	64 (*S*)
8	**VII**	THF	24	91	60 (*S*)
9	**IV**	CH_2Cl_2	24	42	63 (*R*)
10	**IV**	CH_3CN	24	65	58 (*R*)
11	**IV**	MeOH	24	72	36 (*R*)
12	**IV**	$PhCH_3$	24	33	65 (*R*)
13[e]	**IV**	THF	96	95	94 (*R*)
14[ef]	**IV**	THF	96	65	94 (*R*)
15[eg]	**IV**	THF	96	46	90 (*R*)

[a]Conditions: **1a** (0.2 mmol), **2a** (1.0 mmol), and catalyst (0.02 mmol) in solvent (1.0 mL) at room temperature (25 °C), except where noted. Catalysts are shown in Figure 1. [b]Isolated yield of **3a**. [c]Determined by HPLC analysis using a chiral-phase column. [d]The major enantiomer configuration is shown in parentheses. [e]The reaction was carried out at 4 °C. [f]Catalyst (0.01 mmol) was used. [g]**2a** (0.5 mmol) was used.

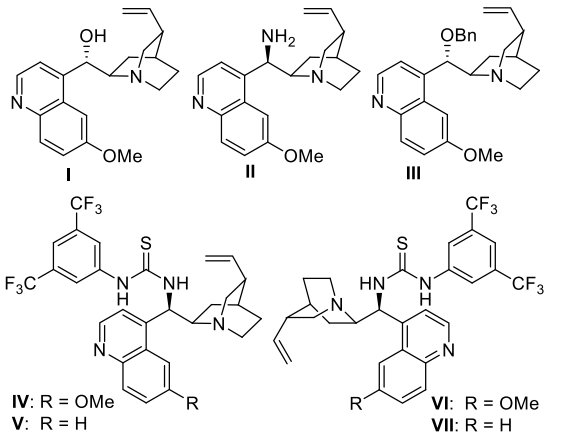


Figure 1. Catalysts tested for the reaction of **1a** and **2a** to afford **3a**; see Table 1.

proceed at all (Table 1, entry 3). Catalyst **III**, in which the hydroxy group of quinidine was protected with a benzyl group, was also unable to catalyze the aldol reaction to give **3a** (Table 1, entry 4). These results indicate that the hydroxy group of quinidine is important for catalysis of the aldol reaction of **1a** and **2a**. The hydroxy group of catalyst **I** may act as an acid for the catalysis. Because it has been reported that thiourea groups can function as acids to form hydrogen bonds with oxygen and other atoms that have lone pairs[8] and because thiourea-derived cinchona derivatives have been used as catalysts for aldol reactions,[7] including those that use isatin derivatives as electrophiles,[7a−c] cinchona derivatives bearing a thiourea group (**IV**−**VII**) were evaluated in the aldol reaction to form **3a** (Table 1, entries 5−8).

We found that quinidine-derived thiourea **IV** catalyzed the aldol reaction efficiently; product **3a** was obtained in 98% yield with 71% ee (Table 1, entry 5). Catalysts **V**, **VI**, and **VII** also catalyzed the reaction to form **3a** with some enantioselectivity (Table 1, entries 6−8). Reactions using quinine-derived thiourea **VI** and cinchonidine-derived thiourea **VII** as catalysts afforded the enantiomer of **3a** that was the opposite to that obtained in the reactions catalyzed by **IV** and **V** (Table 1, entries 7 and 8 versus entries 5 and 6). After screening of some commonly used solvents in the presence of **IV**, we found that THF was optimal among those tested for catalyzing the aldol reaction to form **3a** with respect to both yield and enantioselectivity (Table 1, entries 5 and 9−12). The ee value of **3a** was 94% when the reaction was carried out at 4 °C rather than rt (25 °C), although the reaction took 96 h at 4 °C to afford **3a** in 95% (Table 1, entry 13). Reducing the loading of catalyst **IV** or *β*-ketoester **2a** slowed the reaction (Table 1, entries 14 and 15). Thus, the reaction conditions using **2a** (5 equiv) in the presence of **IV** (0.1 equiv) in THF at 4 °C (Table 1, entry 13) were the best among those tested.

Next, with the optimized conditions, the substrate scope of the aldol reaction in the presence of catalyst **IV** was studied (Scheme 2). In general, the reactions of **1** and **2** catalyzed by **IV** afforded a series of *δ*-hydroxy-*β*-ketoesters bearing the 3-alkyl-3-hydroxyoxindole motif in high yields with high enantioselectivities. *β*-Ketoesters with different ester groups, i.e., methy, ethyl, and isopropyl ester groups, were all accepted in the **IV**-catalyzed reactions to afford corresponding products **3a**−**c**. The reactions of isatins bearing either electron-donating or electron-withdrawing substituents at the 5-position of the indole ring also afforded desired products **3d**−**j** in high yields with excellent enantioselectivities (92−98% ee). Isatins with substituents at the 4- or 6-position of the indole also reacted with *β*-ketoesters in the presence of **IV** to give products **3k**−**m** in high yields but with slightly lower enantioselectivities (79−87% ee). The reactions of isatins with substituent at the 7-position gave products **3n**−**p** in high yields with good to high enantioselectivities (79−96% ee). Reactions of isatins with two substituents, such as 5,6-difluoro, 5,7-dimethyl, and 4-bromo-5-methyl groups on the indole ring, also afforded products **3q**−**s** in high yields with high enantioselectivities (85−95% ee). The reaction of ethyl 2-methylacetoacetate with isatin in the presence of **IV** also gave **3t** in 93% yield with 80% ee.

Whereas reactions of **1a** with **2a** in the presence of **IV** afforded product (*R*)-**3a**, the opposite enantiomer (*S*)-**3a** (*ent*-**3a**) was obtained from the reaction in the presence of catalyst **VI** (Table 1). Various *ent*-**3** were synthesized in high yields with good enantioselectivities using catalyst **VI** (Scheme 3).

To demonstrate the utility of the aldol reactions and to determine the product configuration, product **3a** was subjected to reactions providing **4**−**6** (Scheme 4). Reduction of the ketone group of **3a** to form **4** was performed without affecting to the enantiopurity depending on conditions (see the Supporting Information). An acid treatment of **3a** led the formation of known compound (*R*)-**5**;[7a,10] with this transformation, the absolute configuration of **3a** obtained from the **IV**-catalyzed reaction was determined to be *R*. With benzylamine, **3a** was transformed to stable enamine **6**.[6a,11]

Products **3** were stable as solids stored at room temperature (25 °C) or at 4 °C for at least 2 months. *β*-Aryl-substituted *β*-hydroxyketones are often isomerized and/or decomposed

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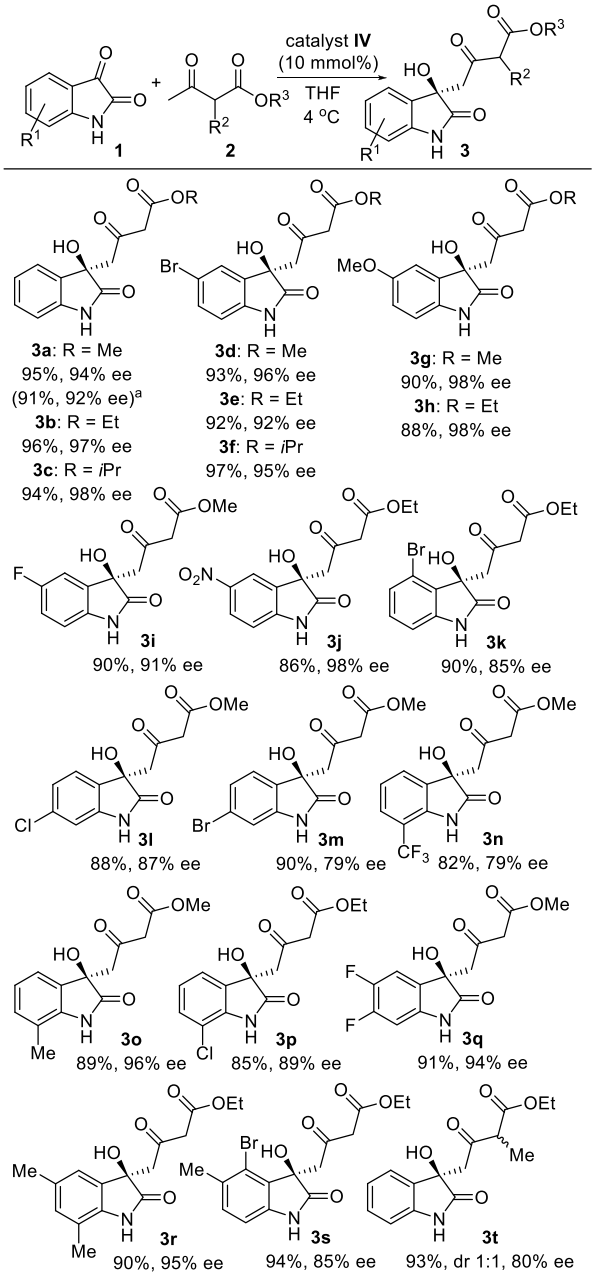
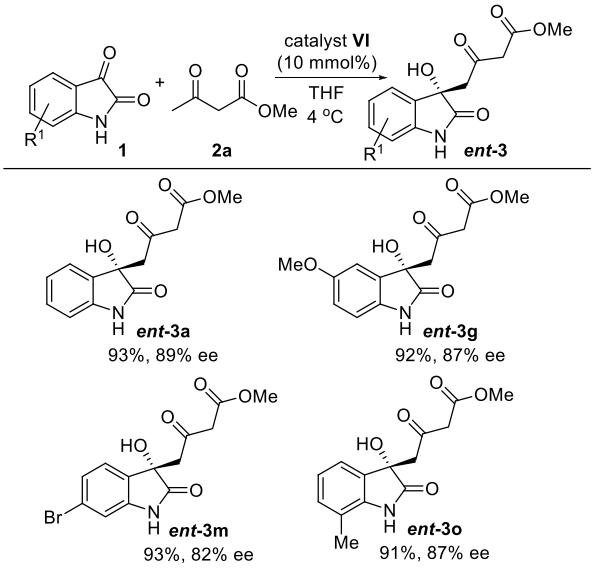
Scheme 2. Direct Catalytic Asymmetric Synthesis of 3 Catalyzed by IV



[a]Results from a 5 mmol scale reaction of **1a**.

Scheme 3. Direct Catalytic Asymmetric Synthesis of *ent*-3 Catalyzed by VI



Scheme 4. Transformation of 3a

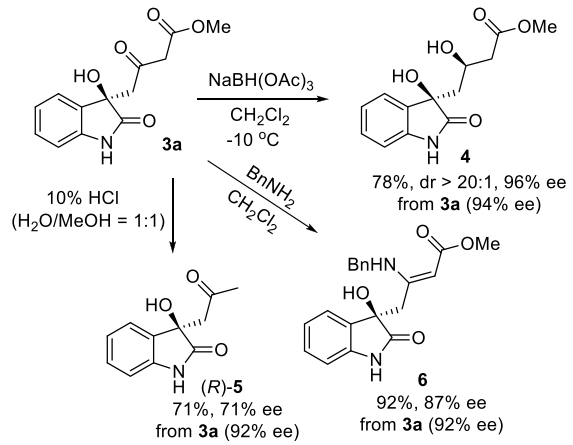
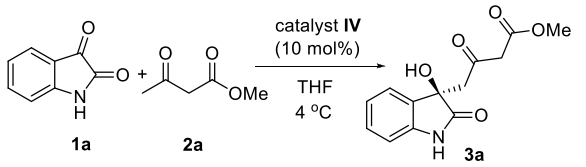


Table 2. Analysis of the Time Course of the IV-Catalyzed Reaction



reaction time (h)	12	24	48	72	96
conversion (%)[a]	23	39	65	85	96
ee of **3a** (% ee)[b]	94	93	94	94	93

[a]Determined by ^{1}H NMR analysis based on the ratio of **3a** relative to **1a**. [b]Determined by HPLC analysis. The major enantiomer was (*R*)-**3a**.

under basic or acidic conditions.[12,13] For the transformations of **3**, selections of conditions were also important to retain the enantiopurity in the products.

To understand the mechanism of the reaction catalyzed by catalyst **IV** for the formation of **3a**, the reaction of **1a** and **2a** in the presence of **IV** was analyzed at various time points (Table 2). Only the formation of the γ-selective aldol product **3a** was observed by ^{1}H NMR analysis. Even at the initial stages of the reaction (such as at 1, 2, 4, 8, and 12 h), no product with the bond formation at the α-position of the β-ketoester was detected. The ee values of **3a** isolated from the reaction at reaction times from 12 to 96 h (conversion 23−96%) were essentially the same (93−94% ee). Thus, product **3a** appears to be kinetically and directly formed in the **IV**-catalyzed reaction of **1a** with **2a**.

Although detailed mechanisms are under investigation, a plausible transition state (TS) for the formation of **3a** from **1a** in the presence of catalyst **IV** is shown in Scheme 5. The results described above suggest that the C−C bond formation occurs directly on the γ-position of **2a** to afford **3a**. Once the

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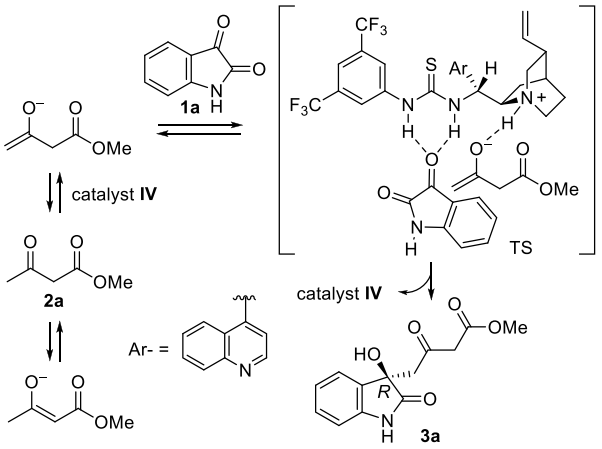
Scheme 5. Plausible Pathway and Transition State



enolate formation at γ-position of **1a** occurs, the enolate is more reactive than the enolate of the α-position of **1a**.[6b]

In summary, we have accomplished the direct asymmetric synthesis of δ-hydroxy-β-ketoesters through regio- and enantioselective aldol reactions of isatins with β-ketoesters catalyzed by quinidine-derived thiourea catalyst. In these reactions, the C−C bond formed selectively at the γ-position of β-ketoesters. A series of 3-alkyl-3-hydroxyoxindoles containing a δ-hydroxy-β-ketoester motif were synthesized in excellent yields with high enantioselectivity. Both enantiomers of the products were obtained by the use of pseudoenantiomers of the cinchona-derived catalysts. The aldol method that affords δ-hydroxy-β-ketoesters described here will be useful for the development of biologically active compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03527.

Detailed experimental procedures; analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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