Catalytic Enantioselective Synthesis of Chiral Isatin Derivatives by an Aldol Approach

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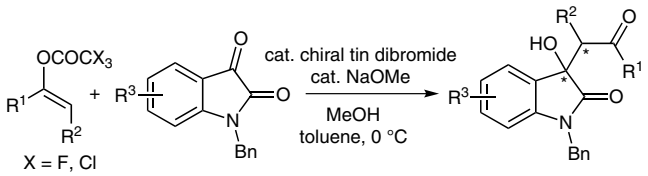
Received: 16.04.2012; Accepted after revision: 23.05.2012

Abstract: A catalytic enantioselective aldol reaction of alkenyl esters with isatins was achieved using an (*S*)-BINOL-derived chiral tin dibromide possessing a 4-*tert*-butylphenyl group at 3- and 3′-positions as the chiral pre-catalyst in the presence of sodium methoxide and methanol. Optically active 3-alkylated 3-hydroxy-2-oxindoles having up to 98% ee were diastereoselectively obtained in high yields not only from cyclic alkenyl esters but also from acyclic ones under the influence of the in situ generated chiral tin bromide methoxide.

Key words: aldol reaction, alkenyl ester, asymmetric catalysis, isatin, tin

Isatin and its derivatives are key synthetic intermediates for numerous biologically active compounds.[1] For example, convolutamydine A shows potent activity in the differentiation of HL-60 human promyelocytic leukemia cells.[2] One of the convenient methods for the construction of such a nonracemic 3-alkylated 3-hydroxy-2-oxindole structure is the catalytic enantioselective aldol reaction of isatins. Various chiral organocatalysts[3] have been developed for the asymmetric transformation; however, as far as we know, there are very few examples of the catalytic reaction that uses chiral Lewis acid catalysts.[4] We report here a novel example of the catalytic asymmetric synthesis of enantiomerically enriched 3-alkylated 3-hydroxy-2-oxindoles from isatins via an enantioselective aldol reaction with alkenyl esters catalyzed by an in situ generated chiral tin bromide methoxide (Scheme 1).



Scheme 1 The asymmetric aldol reaction of alkenyl esters with isatins catalyzed by an in situ generated chiral tin bromide methoxide

We have already shown that an asymmetric aldol reaction of aldehydes with alkenyl trichloroacetates proceeds smoothly in the presence of a catalytic amount of a chiral tin alkoxide.[5] The alkenyl esters are efficiently transformed into chiral tin enolates in situ, and the chiral tin catalyst is regenerated from the aldol products under the influence of an alcohol. The reaction affords the corresponding optically active β-hydroxy carbonyl compounds with high enantioselectivities. We considered that if an isatin or its derivative could exhibit reactivity comparable to that of an aldehyde, the electrophile would also undergo the above-mentioned chiral tin-catalyzed asymmetric aldol reaction to provide enantiomerically enriched β-hydroxy ketones possessing a 3-hydroxy-2-oxindole moiety. Thus, we tried to react 6-methoxy-1-tetralone-derived alkenyl trichloroacetate **1a** with *N*-benzyl isatin (**2a**) using chiral tin dibromide **4a** and sodium methoxide as precatalysts, and, as a consequence, expected aldol adduct **3aa** was formed in high yield with remarkable asymmetric induction. For instance, when a mixture of **1a** (2 equiv) and **2a** (1 equiv) was treated with chiral tin dibromide **4a** (10 mol%) and NaOMe (10 mol%) in the presence of MeOH (10 equiv) in toluene at room temperature for 20 minutes, a 66:34 diastereomeric mixture of **3aa** was obtained in almost quantitative yield (Table 1, entry 1). The major diastereomer of **3aa** had 79% ee. Then, we tested sodium ethoxide and ethanol instead of sodium methoxide and methanol, and found that the latter combination gave a better result in terms of enantioselectivity (Table 1, entry 2). In order to obtain product **3aa** with a higher enantiomeric ratio, we investigated the reaction conditions. Lowering the reaction temperature to –20 °C raised the enantioselectivity up to 85% ee (Table 1, entry 5). In the screening for solvent, toluene was found to provide the highest yield and enantiomeric excess (Table 1, entries 6–9). We further examined the catalytic activity of chiral tin precatalysts **4b**–**e**, but **4a** was found to be superior to **4b**–**e** with respect to enantiomeric excess (Table 1, entry 4 vs. entries 10–13).

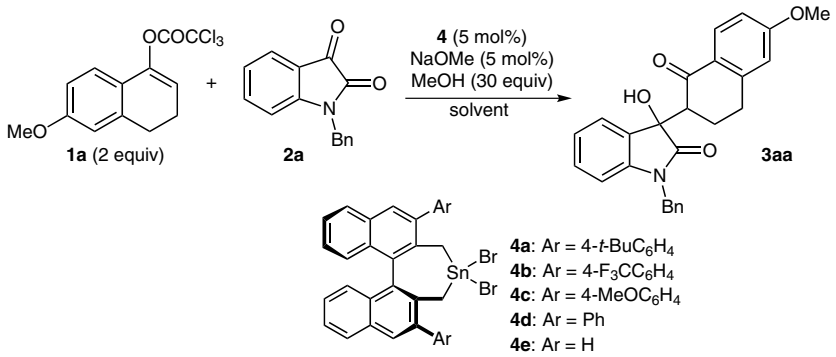
The protecting group on the nitrogen atom of an isatin derivative is considered to have an effect on the electronic and/or steric properties. Thus, we examined the potential use of N-protected isatins **2a**–**aE** in the asymmetric aldol reaction with alkenyl trichloroacetate **1a** at 0 °C in toluene (Table 2). *N*-Benzyl isatin (**2a**) exhibited the highest reactivity and enantioselectivity among the N-protected isatins examined (Table 2, compare entry 1 with entries 2–6). On the other hand, although N-tosylated derivative **2aE** afforded the highest diastereoselectivity, its reactivity and enantioselectivity were unsatisfactory (Table 2, entry 6). Use of sterically bulky trityl group was also effective in improving the diastereoselectivity (Table 2, compare en-

SYNLETT 2012, 23, 1783–1788
Advanced online publication: 29.06.2012
DOI: 10.1055/s-0032-1316551; Art ID: ST-2012-U0328-L

try 5 with entry 1). In order to improve enantioselectivity, we examined an electronic effect of the *p*-substituted benzyl group; however, better results were not obtained (Table 2, compare entries 2 and 3 with entry 1). Based on these results, we concluded that the benzyl group is the most appropriate N-protective group for isatins.

With the optimal reaction conditions in hand, we examined the catalytic asymmetric aldol reaction of **1a** with isatins **2a**–**h** (Table 3). High reactivities and enantioselectivities of up to 91% ee as well as good diastereoselectivities were observed for the reactions of isatins **2b**–**e**, all of which have an electron-withdrawing group at their 5-position (Table 3, entries 2–5). In contrast, the electron-donating-group-substituted isatin **2f** gave a product with relatively low enantiomeric excess (Table 3, entry 6). Then, we tested the suitability of alkenyl trifluoroacetates for the generation of chiral tin enolates. The alkenyl esters have been reported to be effective substrates for asymmetric protonation.[6] Thus, the asymmetric aldol reaction of 6-methoxy-1-tetralone-derived alkenyl trifluoroacetate **1a′** with isatins **2a**–**h** was carried out and as a result, targeted aldol products **3aa**–**ah** were obtained almost quantitatively in the presence of only 2 mol% of a chiral tin catalyst (Table 3, entries 1–8). In some cases, the reaction was completed in a shorter time than that using **1a** (Table 3, entries 2–6 and 8). Regarding stereoselectivity of the reaction, although the enantiomeric excesses of two products increased (Table 3, entries 3 and 6) and two other products decreased to some extent (Table 3, entries 2 and 7), the reason for the difference is unclear at present.

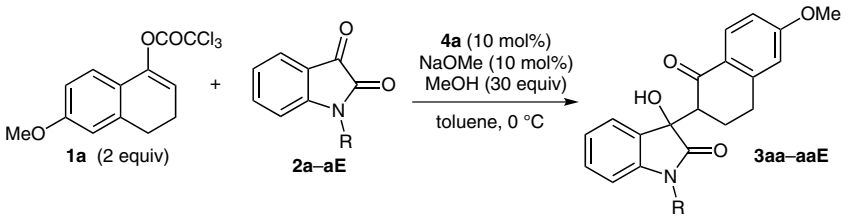
Table 1 Optimization of Catalytic Asymmetric Aldol Reaction of Alkenyl Trichloroacetate **1a** with Isatin Derivative **2a**[a]



Entry	4	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1[e–g]	**4a**	toluene	r.t.	0.33	>99	66:34	79
2[e,h]	**4a**	toluene	r.t.	0.33	>99	74:26	68
3[e–g]	**4a**	toluene	0	2	>99	60:40	80
4	**4a**	toluene	0	0.5	>99	60:40	82
5[e,f]	**4a**	toluene	–20	24	88	60:40	85
6	**4a**	toluene	–20	30	>99	57:43	84
7	**4a**	CH_2Cl_2	–20	48	97	60:40	72
8	**4a**	THF	–20	48	78	52:48	45
9	**4a**	Et_2O	–20	48	32	51:49	49
10	**4b**	toluene	0	0.5	>99	53:47	62
11	**4c**	toluene	0	0.5	>99	63:37	80
12	**4d**	toluene	0	0.5	>99	59:41	79
13	**4e**	toluene	0	0.5	>99	58:42	18

[a] Unless otherwise specified, the reaction was carried out using chiral tin dibromides **4a**–**e** (5 mol%), NaOMe (5 mol%), alkenyl trichloroacetate **1a** (2 equiv), isatin derivative **2a** (1 equiv), and MeOH (30 equiv) in the specified solvent.
[b] Isolated yield of **3aa**.
[c] Determined by ^{1}H NMR analysis.
[d] The value corresponds to the major diastereomer of **3aa**. Determined by HPLC analysis.
[e] Tin dibromide **4a** (10 mol%) was used.
[f] NaOMe (10 mol%) was used.
[g] MeOH (10 equiv) was used.
[h] NaOEt (10 mol%) and EtOH (10 equiv) were used in place of NaOMe and MeOH.

Table 2 Catalytic Asymmetric Aldol Reaction of Alkenyl Trichloroacetate **1a** with Various N-Protected Isatins **2a–aE**[a]

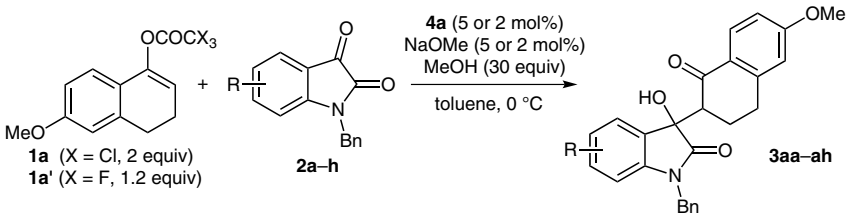


Entry	Isatin	R	Time (h)	Product	Yield (%)[b]	dr[c]	ee (%)[d]
1	**2a**	Bn	0.5	**3aa**	>99	60:40	82
2	**2aA**	4-$MeOC_6H_4CH_2$	20	**3aaA**	>99	50:50	76
3	**2aB**	4-$BrC_6H_4CH_2$	1	**3aaB**	>99	60:40	77
4	**2aC**	Ph_2CH	20	**3aaC**	>99	58:42	62
5	**2aD**	Tr	20	**3aaD**	>99	78:22	80
6	**2aE**	Ts	5	**3aaE**	81	89:11	63

[a] Unless otherwise specified, the reaction was carried out using chiral tin dibromide **4a** (10 mol%), NaOMe (10 mol%), alkenyl trichloroacetate **1a** (2 equiv), isatin derivatives **2a**–**aE** (1 equiv), and MeOH (30 equiv) in toluene at 0 °C.
[b] Isolated yields of **3aa**–**aaE**.
[c] Determined by ^{1}H NMR analysis.
[d] The value corresponds to the major diastereomer of **3aa**–**aaE**. Determined by HPLC analysis.

The aforementioned results emboldened us to study the utility of numerous alkenyl trichloroacetates or alkenyl trifluoroacetates in the catalytic asymmetric aldol reaction with isatins. The results are shown in Table 4. Not only cyclic alkenyl esters **1b** and **1c** but also acyclic ones **1e**–**i** could be employed as the precursors of chiral tin enolates

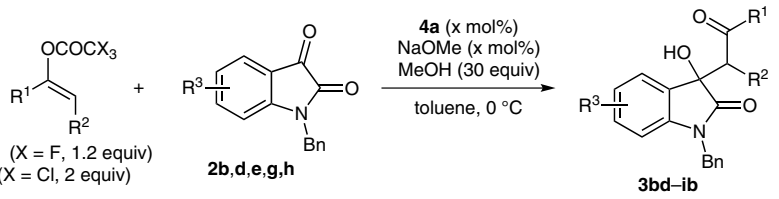
Table 3 Catalytic Asymmetric Aldol Reaction of Alkenyl Trichloroacetate **1a** or Alkenyl Trifluoroacetate **1a′** with Various Isatins **2a–h**[a]

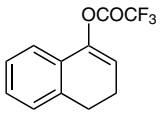
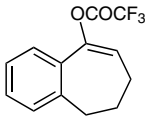
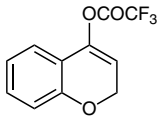
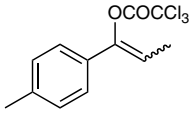
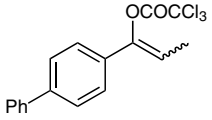
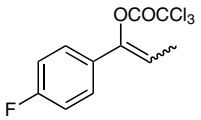
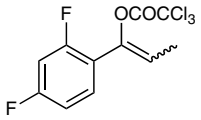
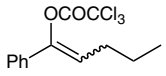


Entry	Isatin	R	Time (h)[b]	Product	Yield (%)[b,c]	dr[b,d]	ee (%)[b,e]
1	**2a**	H	0.5 (1)	**3aa**	>99 (>99)	60:40 (60:40)	82 (80)
2	**2b**	5-F	3 (1)	**3ab**	>99 (>99)	74:26 (74:26)	85 (76)
3	**2c**	5-Cl	3 (1.5)	**3ac**	>99 (>99)	78:22 (85:15)	78 (86)
4	**2d**	5-Br	1.5 (1)	**3ad**	>99 (>99)	82:18 (86:14)	91 (91)
5	**2e**	5-I	3 (2)	**3ae**	>99 (>99)	84:16 (84:16)	84 (85)
6	**2f**	5-MeO	3 (2)	**3af**	>99 (>99)	75:25 (83:17)	50 (77)
7	**2g**	6-Br	3 (3)	**3ag**	>99 (>99)	69:31 (72:28)	84 (75)
8	**2h**	7-F	3 (1)	**3ah**	>99 (>99)	64:36 (64:36)	75 (76)

[a] Unless otherwise specified, the reaction was carried out using chiral tin dibromide **4a** (5 mol% for **1a**, 2 mol% for **1a′**), NaOMe (5 mol% for **1a**, 2 mol% for **1a′**), alkenyl trichloroacetate **1a** (2 equiv) or alkenyl trifluoroacetate **1a′** (1.2 equiv), isatin derivatives **2a**–**h** (1 equiv), and MeOH (30 equiv) in toluene at 0 °C.
[b] The data for the reaction using **1a′** are shown in parentheses.
[c] Isolated yields of **3aa**–**ah**.
[d] Determined by ^{1}H NMR analysis.
[e] The value corresponds to the major diastereomer of **3aa**–**ah**. Determined by HPLC analysis.

Table 4 Catalytic Asymmetric Aldol Reaction of Various Alkenyl Esters **1b–i** with Isatins **2b**,**d**,**e**,**g**,**h**[a]

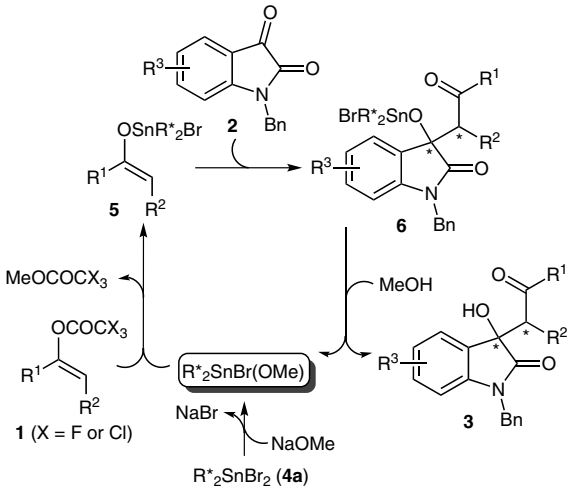


Entry	Alkenyl ester	**2** (R^3)	x	Time (h)	Product	Yield (%)[b]	dr[c]	ee (%)[d]
1	 **1b**	**2d** (5-Br)	2	2	**3bd**	>99	79:21	89
2	 **1c**	**2d** (5-Br)	2	1	**3cd**	>99	64:36	90
3	 **1d**	**2d** (5-Br)	2	24	**3dd**	63	76:24	90
4	 **1e** (*E*/*Z* = 1:4)	**2d** (5-Br)	2	24	**3ed**	>99	72:28	83
5	 **1f** (*E*/*Z* = 1:99)	**2g** (6-Br)	5	6	**3fg**	>99	70:30	87
6	 **1g** (*E*/*Z* = 1:4)	**2h** (7-F)	2	1	**3gh**	98	82:18	82
7	 **1h** (*E*/*Z* = 1:9)	**2e** (5-I)	5	5	**3he**	99	77:23	80
8	 **1i** (*E*/*Z* = 1:4)	**2b** (5-F)	2	24	**3ib**	>99	41:59	98[e]

[a] Unless otherwise specified, the reaction was carried out using chiral tin dibromide **4a** (2 or 5 mol%), NaOMe (2 or 5 mol%), alkenyl trifluoroacetates **1b–d** (1.2 equiv) or alkenyl trichloroacetates **1e–i** (2 equiv), isatin derivative **2b**, **2d**, **2e**, **2g**, or **2h** (1 equiv), and MeOH (30 equiv) in toluene at 0 °C.
[b] Isolated yields of **3bd–ib**.
[c] Determined by ^{1}H NMR analysis.
[d] The value corresponds to the major diastereomer of **3bd–he**. Determined by HPLC analysis.
[e] The value corresponds to the minor diastereomer of **3ib**. Determined by HPLC analysis.

without lowering the chemical yields of products **3bd**,**cd**,**ed**–**3ib** (Table 4, entries 1, 2, and 4–8). On the other hand, a remarkable decrease in reactivity was seen in the case of 4-chromanone derivative **1d** (Table 4, entry 3). The use of an acyclic aromatic ketone derivative having a long alkyl substituent as the substrate was effective in increasing the extent of asymmetric induction. In fact, the highest enantioselectivity (98% ee) was observed in the reaction of acyclic alkenyl trichloroacetate **1i** with **2b**, even if that value was for the minor diastereomer of product **3ib** (Table 4, entry 8). The origin of the high stereocontrol is not elucidated yet and studies on effect of *E*/*Z* ratio of acyclic alkenyl esters on the stereoselectivity would be necessary for the elucidation.

A catalytic cycle is postulated for the asymmetric aldol reaction (Scheme 2). First, chiral tin dibromide **4a** reacts with an equimolar amount of sodium methoxide to give the corresponding chiral tin bromide methoxide, which is the true catalyst in the present transformation. Subsequently, the generated chiral tin bromide methoxide attacks alkenyl ester **1** to form chiral tin enolate **5** and methyl trihaloacetate. The following aldol reaction between chiral tin enolate **5** and isatin derivative **2** affords tin alkoxide of β-hydroxy ketone **6**. Lastly, tin alkoxide **6** undergoes protonation with methanol to give optically active β-hydroxy ketone **3** with regeneration of the chiral tin bromide methoxide. The rate of methanolysis of tin alkoxide **6** plays a crucial role in the catalytic cycle.



Scheme 2 Plausible catalytic cycle for the asymmetric aldol reaction

In conclusion, we have developed a novel method for the catalytic asymmetric synthesis of chiral isatin derivatives via the enantioselective aldol reaction of alkenyl trihaloacetates with achiral isatins. The employment of in situ generated chiral tin bromide methoxide as the chiral catalyst has enabled the synthesis of various nonracemic 3-alkylated 3-hydroxy-2-oxindoles in a diastereoselective manner, and high enantioselectivities of up to 98% ee have been realized even from acyclic ketone-derived alkenyl esters. Further studies of the application of the catalytic asymmetric aldol reaction to other substrates and the biological activities of the products are under way.

Typical Experimental Procedure for the Asymmetric Aldol Reaction: Synthesis of 1-Benzyl-3-hydroxy-3-(6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)indolin-2-one (3aa, Entry 4 in Table 1, Entry 1 in Table 2, and Entry 1 in Table 3)

To a suspension of chiral tin dibromide **4a**[5] (20.6 mg, 0.025 mmol) in dry toluene (3 mL) was added NaOMe in MeOH (25 μL, 0.025 mmol) and MeOH (0.58 mL) at r.t. The resulting mixture was stirred for 30 min. Then, isatin derivative **2a** (118.0 mg, 0.5 mmol) and alkenyl trichloroacetate **1a** (321.5 mg, 1.0 mmol) were added to the mixture at 0 °C. After being stirred for 30 min at 0 °C, the reaction mixture was treated with MeOH (1 mL), brine (1 mL), and solid KF (0.5 g) at ambient temperature for 10 min. The resulting precipitate was filtered off, the filtrate was dried over Na_2SO_4, and then concentrated in vacuo. The residual crude product was purified by column chromatography on silica gel to give aldol product **3aa** (206.2 mg, >99% yield). The diastereomeric ratio was determined to be 60:40 by ^{1}H NMR analysis. The enantioselectivity of the major diastereomer was determined to be 82% ee by HPLC analysis using a chiral column [Daicel Chiralpak AD-H, hexane–*i*-PrOH (9:1), flow rate = 1.0 mL/min] t_{R1} = 69.6 min (major), t_{R2} = 95.2 min (minor).

Spectral Data of the Product

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, 1 H, *J* = 8.9 Hz, ArH), 7.25–7.34 (m, 6 H, ArH), 7.14 (t, 1 H, *J* = 7.7 Hz, ArH), 6.93 (t, 1 H, *J* = 7.6 Hz, ArH), 6.86 (dd, 1 H, *J* = 2.3, 8.9 Hz, ArH), 6.71 (d, 1 H, *J* = 8.0 Hz, ArH), 6.61 (m, 1 H, ArH), 6.58 (s, 1 H, OH), 5.00 (d, 1 H, *J* = 15.8 Hz, CH), 4.84 (d, 1 H, *J* = 15.5 Hz, CH), 3.83 (s, 3 H, OCH), 3.39 (dd, 1 H, *J* = 4.6, 13.8 Hz, CH), 3.00 (m, 1 H, CH), 2.68–2.75 (m, 1 H, CH), 1.76–1.88 (m, 1 H, CH), 1.29–1.38 (m, 1 H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 29.0, 44.1, 51.3, 55.7, 79.0, 109.6, 112.5, 113.8, 123.5, 124.9, 125.9, 127.5 (2 C), 127.9, 128.9 (2 C), 129.7, 129.8, 130.2, 135.6, 143.1, 147.2, 164.7, 175.0, 200.6. IR (neat): 3343, 3062, 2939, 2840, 1724, 1669, 1597, 1495, 1466, 1360, 1252, 1178, 1109, 910, 731 cm^{-1}. HRMS (ESI^+): *m/z* (%) calcd for $C_{26}H_{23}NO_4Na$ $[M + Na]^+$: 436.1519; found: 436.1508; $[\alpha]_D^{22.9}$ –33.2 (*c* 0.95, $CHCl_3$, 82% ee).

Acknowledgment

We gratefully acknowledge the financial support from the Iodine Research Project in Chiba University led by Professor Hideo Togo and the COE Start-up Program in Chiba University led by Professor Takayoshi Arai.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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