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Chiral Silver Alkoxide Catalyzed Asymmetric Aldol Reaction of Alkenyl Esters with Isatins

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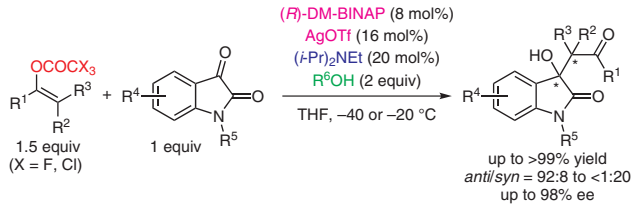

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Abstract A catalytic enantioselective aldol reaction of alkenyl esters with isatins was achieved using a DM-BINAP·AgOTf complex as the chiral precatalyst and *N*,*N*-diisopropylethylamine as the base precatalyst in the presence of methanol or 2,2,2-trifluoroethanol. Optically active 3-alkylated 3-hydroxy-2-oxindoles having up to 98% ee were diastereoselectively obtained in moderate to high yields not only from cyclic alkenyl esters but also from acyclic ones through the in situ generated chiral silver enolates.

Key words aldol reaction, alkenyl ester, asymmetric catalysis, isatin, silver

Isatin and its derivatives are versatile synthetic precursors for diverse biologically active molecules.[1] For instance, convolutamydine A (Figure 1) displays potent inhibitory activity towards the differentiation of HL-60 human promyelocytic leukemia cells.[2]

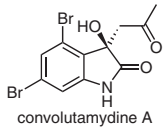
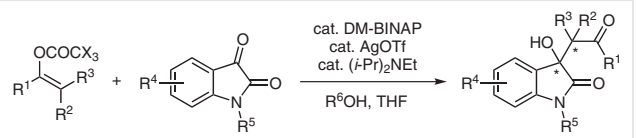


Figure 1

One of the efficient routes to obtain such an optically active 3-alkylated 3-hydroxy-2-oxindole moiety is the catalytic asymmetric aldol reaction of isatins. Although numerous chiral organocatalysts[3] have been developed for the enantioselective transformation, as far as we know, there are few examples of the catalytic reaction that employs chiral Lewis acid catalysts.[4] We report herein an asymmetric synthesis of enantiomerically enriched 3-alkylated 3-hydroxy-2-oxindoles from isatins through an enantioselective aldol reaction with alkenyl esters using a DM-BINAP·AgOTf complex as the chiral precatalyst and *N*,*N*-diisopropylethylamine as the base precatalyst (Scheme 1).



Scheme 1 Chiral silver alkoxide catalyzed asymmetric aldol reaction of alkenyl esters with isatins

We have previously reported that an asymmetric aldol reaction of aldehydes with alkenyl trihaloacetates takes place smoothly in the presence of a catalytic amount of a chiral silver methoxide.[5] The alkenyl esters are effectively converted into chiral silver enolates in situ and the chiral silver catalyst is regenerated from the aldol products under the influence of methanol. The reaction provides the corresponding optically active β-hydroxy carbonyl compounds with high enantioselectivities. We envisioned that if an isatin or its derivative could show similar reactivity to an aldehyde, the carbonyl compound would also undergo the aforementioned chiral silver-catalyzed asymmetric aldol reaction to afford nonracemic β-hydroxyketones having a 3-hydroxy-2-oxindole structure. Thus, we attempted to carry out the reaction of 1-tetralone-derived alkenyl trifluoroacetate **1a**[6] with *N*-benzyl isatin (**2d**) using a chiral phosphine, silver triflate, and *N*,*N*-diisopropylethylamine as precatalysts with MeOH, and as a result, anticipated aldol adduct **3ad** was produced in high yield with notable asymmetric induction. For example, when a mixture of **1a** (1.5 equiv) and **2d** (1 equiv) was treated with (*R*)-BINAP (8 mol%), AgOTf (16 mol%),[7] and (*i*-Pr)$_2$NEt (40 mol%) in the presence of MeOH (5 equiv) in THF at –40 °C for 22 h, **3ad** was obtained in 92% yield with the *anti*/*syn* ratio of 45:55 (Table 1, entry 1). The *anti* isomer of **3ad** had 67% ee. Then, we investigated the asymmetric induction ability of chiral

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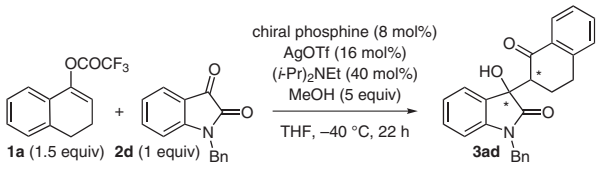
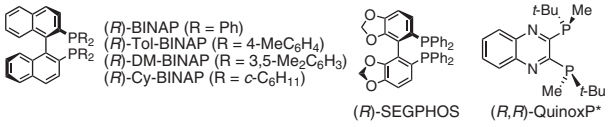
phosphines other than BINAP and found that (*R*)-DM-BINAP gave the best result in terms of diastereoselectivity and enantioselectivity (entry 3). (*R*)-Tol-BINAP was also a promising chiral phosphine ligand (entry 2); however, the use of (*R*)-Cy-BINAP, (*R*)-SEGPHOS, and (*R*,*R*)-QuinoxP* led to unsatisfactory results (entries 4–6).

Table 1 Optimization of Reaction Conditions: Chiral Phosphines[a]



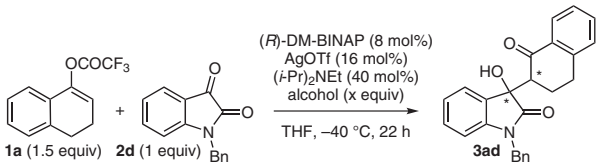
Entry	Chiral phosphine	Yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	(*R*)-BINAP	92	45:55	67/9
2	(*R*)-Tol-BINAP	52	52:48	68/24
3	(*R*)-DM-BINAP	19	63:37	73/9
4[e]	(*R*)-Cy-BINAP	49	16:84	–25/23
5	(*R*)-SEGPHOS	<1	–	–
6	(*R*,*R*)-QuinoxP*	21	43:57	7/6



[a] Unless otherwise specified, the reaction was carried out using chiral phosphine (8 mol%), silver triflate (16 mol%), *N*,*N*-diisopropylethylamine (40 mol%), alkenyl trifluoroacetate **1a** (1.5 equiv), isatin derivative **2d** (1 equiv), and MeOH (5 equiv) in THF at –40 °C for 22 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by HPLC analysis.
[e] MeOH (2 equiv) was used.

In order to obtain product **3ad** having improved enantiomeric ratio, we examined the effect of the amount of MeOH in the aldol reaction by employing (*R*)-DM-BINAP as the chiral ligand (Table 2, entries 1–4) and found that 3 equivalents of MeOH dramatically raised the isolated yield of **3ad** to >99% as well as the enantioselectivity of its *anti* isomer to 81% ee (entry 2). Further decrease in the amount of MeOH led to improvement of enantioselectivity and as a consequence, more than 94% ee of the *anti* isomer of **3ad** was obtained in the case of 1 or 2 equivalents of MeOH (entries 3 and 4). On the other hand, unsatisfactory yield and stereoselectivities were observed in the absence of MeOH (entry 5). Employment of EtOH also afforded promising results whereas CF_3CH_2OH reduced the yield of **3ad** due to competing protonation of alkenyl trifluoroacetate **1a** with the more acidic alcohol (entries 6 and 7). The optical purity of the *anti* isomer reached 98% ee when the reaction was carried out by using 20 mol% of (*i*-Pr)$_2$NEt for 0.5 h (entry 8).

Table 2 Optimization of Reaction Conditions: Alcohols[a]



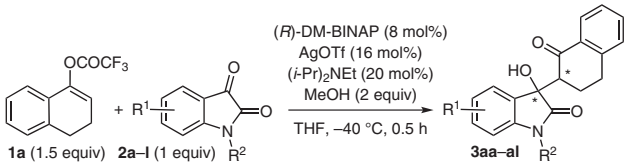
Entry	Alcohol	x (equiv)	Yield (%)[b]	*anti*/*syn*[c]	ee[d] (%)
1	MeOH	5	19	63:37	73/9
2	MeOH	3	>99	55:45	81/14
3	MeOH	2	82	40:60	95/25
4	MeOH	1	>99	46:54	94/18
5	–	–	22	36:64	19/26
6	EtOH	2	>99	55:45	82/19
7	CF_3CH_2OH	2	58	28:72	49/20
8[e]	MeOH	2	>99	75:25	98/6

[a] Unless otherwise specified, the reaction was carried out using (*R*)-DM-BINAP (8 mol%), silver triflate (16 mol%), *N*,*N*-diisopropylethylamine (40 mol%), alkenyl trifluoroacetate **1a** (1.5 equiv), isatin derivative **2d** (1 equiv), and alcohol (x equiv) in THF at –40 °C for 22 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by HPLC analysis.
[e] The reaction was performed by using *N*,*N*-diisopropylethylamine (20 mol%) for 0.5 h.

With the optimum reaction conditions in hand, we examined the catalytic asymmetric aldol reaction of alkenyl trifluoroacetate **1a** with isatins **2a–f** (Table 3). The protecting group on the nitrogen atom of an isatin derivative is expected to have an effect on the electronic and/or steric nature. First, isatin (**2a**) without an *N*-protective group was tested in the asymmetric aldol reaction and target product **3aa** was obtained with the *anti*/*syn* ratio of 40:60 in 43% combined yield. The minor *anti* isomer showed 77% ee (entry 1). Use of *N*-methyl isatin (**2b**) resulted in raising the isolated yield of product **3ab** to >99% and *anti* selectivity (entry 2). In contrast, the opposite *syn* selectivity as well as a lower reactivity was observed for the reaction of isatin derivative **2c**, which has a Boc group as the *N*-protective group (entry 3). *N*-Benzyl isatin (**2d**) displayed the highest *anti*/*syn* selectivity and enantioselectivity among the *N*-protected isatins **2b–f** examined (compare entry 4 with entries 2, 3, 5, and 6). Although *N*-*p*-methoxybenzylated derivative **2e** and *N*-tritylated derivative **2f** also afforded encouraging results with respect to yield and/or *anti*/*syn* selectivity, their enantioselectivities were somewhat unsatisfactory (entries 5 and 6). Based on these results, we came to the conclusion that the benzyl group is the most suitable *N*-protective group for isatins. Subsequently, we studied the catalytic asymmetric aldol reaction of alkenyl trifluoroacetate **1a** with isatin derivatives **2g–l** derived from diversely monosubstituted isatins (Table 3). High reactivity and enantioselectivity were seen in the reaction of

isatin derivative **2j**, which has an electron-withdrawing group at 6-position (entry 10). Isatins **2h** and **2i**, which have a substituent at 5-position, furnished products **3ah** and **3ai** in satisfactory isolated yields, respectively, and the *anti* isomers exhibited good enantioselectivities (entries 8 and 9). However, isatins **2g** and **2k** gave unexpected results: the bromo group at 4-position brought about an inverse *syn* selectivity probably because of its steric effect, producing *syn* isomer with 81% ee (entry 7), whereas 7-F substituted isatin **2k** significantly reduced the enantiomeric excess of product **3ak** (entry 11), although the reason for the low enantioselectivity is unclear at present. There were, however, remarkable improvements in reactivity and enantioselectivity when *N*-tritylated isatin derivative **2l** was employed instead of **2k** (entry 12).

Table 3 Enantioselective Aldol Reaction of Alkenyl Trifluoroacetate **1a** with Isatin (**2a**) and Isatin Derivatives **2b–l** Catalyzed by (*R*)-DM-BINAP·AgOTf[a]

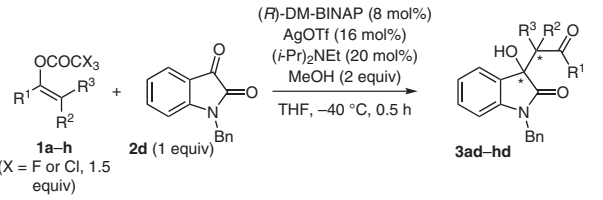


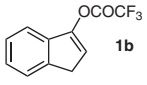
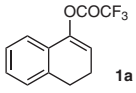
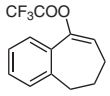
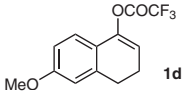
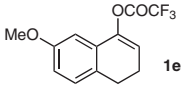
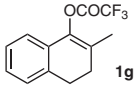
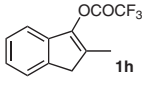
Entry	Isatins **2a–l**		Product	Yield (%)[b]	*anti*/*syn*[c]	ee[d] (%)
	R^1	R^2				
1	H	H (**2a**)	**3aa**	43	40:60	77/10
2	H	Me (**2b**)	**3ab**	>99	67:33	70/17
3	H	Boc (**2c**)	**3ac**	45	31:69	71/5
4	H	Bn (**2d**)	**3ad**	>99	75:25	98/6
5	H	PMB (**2e**)	**3ae**	>99	75:25	91/4
6	H	Tr (**2f**)	**3af**	78	69:31	87/88
7	4-Br	Bn (**2g**)	**3ag**	87	30:70	44/81
8	5-Me	Bn (**2h**)	**3ah**	97	65:35	70/21
9	5-F	Bn (**2i**)	**3ai**	82	44:56	86/<1
10	6-Cl	Bn (**2j**)	**3aj**	93	55:45	97/3
11	7-F	Bn (**2k**)	**3ak**	78	59:41	<1/12
12	7-F	Tr (**2l**)	**3al**	>99	50:50	75/12

[a] Unless otherwise specified, the reaction was carried out using (*R*)-DM-BINAP (8 mol%), silver triflate (16 mol%), *N*,*N*-diisopropylethylamine (20 mol%), alkenyl trifluoroacetate **1a** (1.5 equiv), isatin derivative (**2a–l**, 1 equiv), and MeOH (2 equiv) in THF at –40 °C for 0.5 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by HPLC analysis.

The above-mentioned results encouraged us to study the utility of diverse alkenyl trifluoroacetates in the catalytic asymmetric aldol reaction of isatins. First, we focused on cyclic alkenyl trifluoroacetates and summarize our results in Table 4.[8] 1-Benzosuberone derivative **1c** gave the corresponding product **3cd** in an almost quantitative yield with enantioselectivity of 91% ee (entry 3). The reaction of 1-indanone derivative **1b** also furnished aldol product **3bd** in high yield, but the *anti*/*syn* ratio and the optical purity were low (entry 1). Similar high reactivity was observed in the cases of 6-methoxy-1-tetralone derivative **1d** and 7-me-

Table 4 Enantioselective Aldol Reaction of Cyclic Alkenyl Esters **1a–h** with Isatin **2d** Catalyzed by (*R*)-DM-BINAP·AgOTf[a]

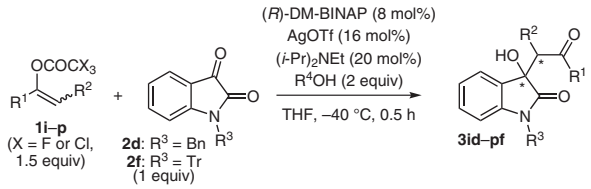


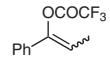
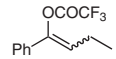
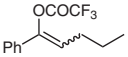
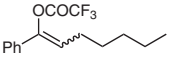
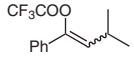
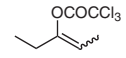
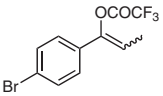
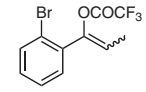
Entry	Alkenyl ester	Product	Yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1		**3bd**	92	47:53	2/3
2		**3ad**	>99	75:25	98/6
3		**3cd**	>99	92:8	91/21
4		**3dd**	>99	69:31	69/20
5		**3ed**	>99	70:30	81/7
6		**3fd**	75	65:35	51/11
7e		**3gd**	16	11:89	52/36
8f		**3hd**	96	12:88	18/1

[a] Unless otherwise specified, the reaction was carried out using (*R*)-DM-BINAP (8 mol%), silver triflate (16 mol%), *N*,*N*-diisopropylethylamine (20 mol%), cyclic alkenyl ester **1a–h** (1.5 equiv), isatin derivative **2d** (1 equiv), and MeOH (2 equiv) in THF at –40 °C for 0.5 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by HPLC analysis.
[e] The reaction was performed for 22 h.
[f] The reaction was performed for 24 h.

thoxy-1-tetralone derivative **1e**, but with moderate diastereo- and enantioselectivities (entries 4 and 5). Use of cyclohexanone-derived cyclic alkenyl ester **1f**[9] resulted in a decrease in both the yield and the enantiomeric excess of product **3fd**[10] (entry 6). Noteworthy is the fact that 2-methyl-1-tetralone derivative **1g** afforded the desired product **3gd** in an unsatisfactory yield (entry 7), but 2-methyl-1-indanone derivative **1h** had high reactivity toward isatin **2d**, regardless of the steric bulkiness at 2-position (entry 8).

Table 5 Enantioselective Aldol Reaction of Acyclic Alkenyl Esters **1i–p** with Isatins **2d** and **2f** Catalyzed by (*R*)-DM-BINAP·AgOTf[a]



Entry	Alkenyl ester	R^3	R^4	Product	Yield (%)[b]	*anti*/*syn*[c]	ee[d] (%)
1	 **1i** (*E*/*Z* < 1/20)	Bn	Me	**3id**	>99	32:68	51/16
2	**1i** (*E*/*Z* < 1:20)	Tr	Me	**3if**	90	42:58	4/65
3	**1i** (*E*/*Z* < 1:20)	Tr	CF_3CH_2	**3if**	69	38:62	22/75
4	 **1j** (*E*/*Z* < 1/20)	Tr	CF_3CH_2	**3jf**	68	32:68	52/82
5	 **1k** (*E*/*Z* = 1/8)	Tr	CF_3CH_2	**3kf**	59	44:56	50/80
6	 **1l** (*E*/*Z* = 1/10)	Tr	CF_3CH_2	**3lf**	86	39:61	28/83
7	 **1m** (*E*/*Z* < 1/20)	Tr	CF_3CH_2	**3mf**	78	<1:20	–/96
8	 **1n** (*E*/*Z* = 1/4)	Tr	CF_3CH_2	**3nf**	88	47:53	66/71
9	 **1o** (*E*/*Z* < 1/20)	Tr	CF_3CH_2	**3of**	75	40:60	43/71
10	 **1p** (*E*/*Z* = 1/2)	Tr	CF_3CH_2	**3pf**	55	<1:20	–/87

[a] Unless otherwise specified, the reaction was carried out using (*R*)-DM-BINAP (8 mol%), silver triflate (16 mol%), *N*,*N*-diisopropylethylamine (20 mol%), alkenyl ester **1i–p** (1.5 equiv), isatin derivative **2d** or **2f** (1 equiv), and MeOH or CF_3CH_2OH (2 equiv) in THF at –40 °C for 0.5 h.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] Determined by HPLC analysis.
[e] The reaction was performed at –20 °C.

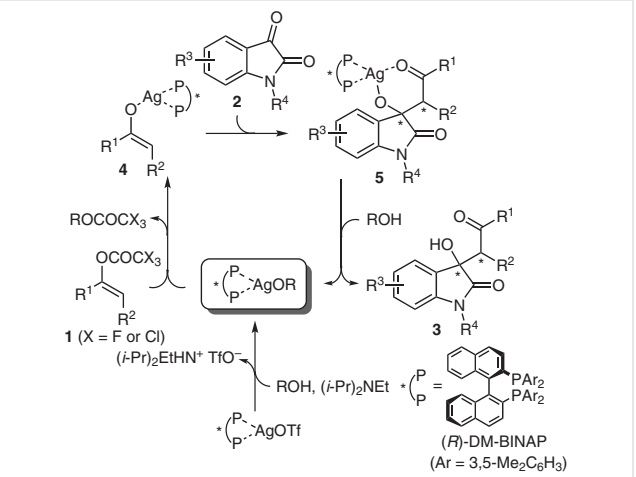
In contrast to the cyclic alkenyl esters, acyclic alkenyl esters **1i–p** furnished the opposite *syn* selectivity, as shown in Table 5. When propiophenone derivative **1i** (*E*/*Z* <1/20) was employed as the substrate in the catalytic asymmetric aldol reaction under the standard reaction conditions, a 32:68 *anti*/*syn* mixture of targeted aldol adduct **3id** was obtained in a nearly quantitative yield but the optical purity of the *syn* isomer was low (entry 1). Changing the R^3 protective group into the Tr group was effective in acquiring a higher enantiomeric excess (entry 2). Further improvement in the enantiomeric excess of the product was attained when CF_3CH_2OH was adopted as the alcohol in place of MeOH (entry 3). Under the modified reaction conditions, we examined various acyclic ketone-derived alkenyl trifluoroacetates **1j–p** as the precursors of chiral silver enolates in the asymmetric aldol reaction and found that *syn* adducts were formed selectively in every case (entries 4–10). The employment of an acyclic aromatic ketone derivative possessing a long or a bulky alkyl substituent was effective in increasing the extent of the asymmetric induction. In fact, the highest enantioselectivity (96% ee) was seen in the reaction of acyclic alkenyl trifluoroacetate **1m** with **2f** (entry 7). 1-(2-Bromophenyl)propan-1-one derivative **1p** was also a favorable acyclic substrate for realizing a high enantioselectivity (entry 10).

A proposed reaction mechanism is illustrated in Scheme 2. First, (*R*)-DM-BINAP·AgOTf reacts with an alcohol in the presence of *N*,*N*-diisopropylethylamine to give the corresponding (*R*)-DM-BINAP·AgOR, which is the true catalyst in the present asymmetric aldol reaction. Subsequently, the thus-formed chiral silver alkoxide attacks alkenyl trihaloacetate **1** to give chiral silver enolate **4**. The following aldol reaction of chiral silver enolate **4** with isatin derivative **2** yields chiral silver alkoxide of aldol adduct **5**. Lastly, chiral silver alkoxide of aldol adduct **5** undergoes protonation with an alcohol to provide optically active β-hydroxy ketone **3** with regeneration of the chiral silver alkoxide. The rate of alcoholysis of silver alkoxide **5** plays a crucial role in the catalytic cycle.[11]

In summary, we have achieved a novel method for the catalytic asymmetric synthesis of chiral isatin derivatives through the enantioselective aldol reaction of alkenyl trihaloacetates with isatins. The use of in situ generated chiral silver alkoxide[12] as the chiral catalyst has permitted the synthesis of various optically active 3-alkylated 3-hydroxy-2-oxyindoles in a diastereoselective manner, and high enantioselectivities of up to 98% ee have been attained not only from cyclic alkenyl esters but also from acyclic ones. Further studies of related reactions catalyzed by a chiral silver alkoxide are under way.

Conflict of Interest

The authors declare no conflict of interest.



Scheme 2 Plausible catalytic cycle for the asymmetric aldol reaction

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1479-4694.

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(8) **Typical Experimental Procedure for the Asymmetric Aldol Reaction Catalyzed by (*R*)-DM-BINAP·AgOTf and (*i*-Pr)$_2$NEt: Synthesis of 1-Benzyl-3-hydroxy-3-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)indolin-2-one (3ad, Entry 8 in Table 2, Entry 4 in Table 3, and Entry 2 in Table 4)**

A mixture of AgOTf (20.6 mg, 0.08 mmol) and (*R*)-DM-BINAP (29.4 mg, 0.04 mmol) was dissolved in dry THF (6 mL) under an argon atmosphere with direct light excluded and stirred at room temperature for 20 min. To the resulting solution were added MeOH (40.6 μL, 1.0 mmol) and (*i*-Pr)$_2$NEt (17 μL, 0.10 mmol) successively at –40 °C. The mixture was stirred at that temperature for 5 min. Then, alkenyl trifluoroacetate **1a** (181.6 mg, 0.75 mmol) and isatin derivative **2d** (118.6 mg, 0.5 mmol) were successively added drop by drop to the resulting solution at –40 °C. After stirring for 30 min at that temperature, the mixture was treated with MeOH (3 mL). Then, the mixture was filtered with a glass filter funnel filled with Celite® and washed with EtOAc, and the combined filtrate and washes were concentrated *in vacuo*. The residual crude product was purified by column chromatography on silica gel to give corresponding β-hydroxy ketone **3ad** (191.7 mg, >99% yield). The *anti*/*syn* ratio was determined to be 75:25 by ^{1}H NMR analysis. The enantiomeric ratio of the *anti* isomer was determined to be 98% ee by HPLC analysis using a chiral column [Daicel Chiralpak AD-3, hexane–*i*-PrOH (4:1), flow rate = 1.0 mL/min]: t_1 = 36.0 min (major), t_2 = 47.1 min (minor). The enantiomeric ratio of the *syn* isomer was determined to be 6% ee by HPLC analysis using a chiral column [Daicel Chiralpak AD-3, hexane–*i*-PrOH (4:1), flow rate = 1.0 mL/min]: t_1 = 23.1 min (minor), t_2 = 28.7 min (major).

Spectral Data of the Product

***anti* Isomer**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.41 (dd, *J* = 7.3, 0.8 Hz, 1 H), 7.18–7.35 (m, 8 H), 7.06 (td, *J* = 7.5, 0.8 Hz, 1 H), 6.71 (d, *J* = 7.9 Hz, 1 H), 6.23 (s, 1 H), 4.87 (dd, *J* = 29.8, 15.7 Hz, 2 H), 3.21 (dd, *J* = 13.2, 4.7 Hz, 1 H), 2.83–2.98 (m, 2 H), 1.80–1.97 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8, 176.8, 143.9, 143.6, 135.5, 134.1, 132.5, 130.0, 128.7 (2 C), 128.6, 128.4, 127.9, 127.6, 127.3 (2 C), 127.0, 123.9, 123.2, 109.5, 78.3, 51.6, 43.8, 28.9, 24.2. IR (neat): 3300, 2959, 1681, 1614, 1496, 1467, 1433, 1389, 1358, 1321, 1264, 1221, 1183, 1156, 1073, 1015, 998, 932 cm^{-1}. MS (ESI): *m*/*z* calcd for $[C_{25}H_{21}O_3NNa]^+$ ([M + Na]$^+$): 406.1414; found: 406.1409; $[\alpha]_D^{23.8}$ –51.0 (*c* 1.0, $CHCl_3$, 98% ee); mp 178–180 °C.

***syn* Isomer**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.9, 1.1 Hz, 1 H), 7.50 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.27–7.37 (m, 7 H), 7.14–7.20 (m, 2 H), 6.93 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.73 (d, *J* = 7.9 Hz, 1 H), 6.23 (s, 1 H), 5.00 (d, *J* = 15.5 Hz, 1 H), 4.86 (d, *J* = 15.7 Hz, 1 H), 3.45 (dd, *J* = 13.8, 4.4 Hz, 1 H), 3.01–3.10 (m, 1 H), 2.79 (dt, *J* = 16.7, 3.4 Hz, 1 H), 1.83–1.89 (m, 1 H), 1.40 (qd, *J* = 13.2, 4.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 174.7, 144.3, 143.0, 135.4, 134.6, 132.2, 129.6, 129.5, 128.8 (2 C), 128.7, 127.7, 127.4, 127.3 (2 C), 126.9, 124.6, 123.3, 109.5, 78.6, 51.9, 43.9, 28.5, 24.7. IR (neat): 3399, 1685, 1615, 1492, 1456, 1371, 1226, 1172, 1073, 940 cm^{-1}. MS (ESI): *m*/*z* calcd for $[C_{25}H_{21}O_3NNa]^+$ ([M + Na]$^+$): 406.1414; found: 406.1407; $[\alpha]_D^{23.9}$ +6.3 (*c* 0.99, $CHCl_3$, 6% ee); mp 147–148 °C.

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(11) Use of small amount of ROH decreases the rate of alcoholysis of silver alkoxide **5** resulting in low yield of the desired product **3**, while excess amount of ROH accelerate the protonation of chiral silver enolate **4** and reduces the yield of **3**.

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