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Asymmetric Aldol Reaction of Ketones with Alkenyl Trichloroacetates Catalyzed by Dibutyltin Dimethoxide and BINAP·Silver(I) Complex: Construction of a Chiral Tertiary Carbon Center

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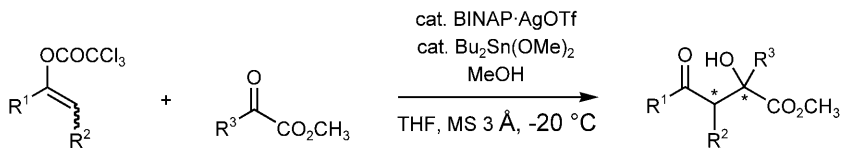
Abstract: A novel aldol reaction of alkenyl trichloroacetates with α-keto esters was realized by using dibutyltin dimethoxide as a catalyst, which was regenerated by the addition of methanol. The reaction was found to be remarkably accelerated by the addition of a catalytic amount of a bidentate phosphine·silver(I) complex. Use of the BINAP·silver triflate (AgOTf) complex as the chiral co-catalyst resulted in the formation of optically active aldol products possessing a chiral tertiary carbon with up to 93% *ee*. This catalytic method was further applied to the asymmetric reaction of diketene with methyl benzoylformate.

Keywords: aldol reaction; alkenyl esters; asymmetric catalysis; ketones; silver; tin

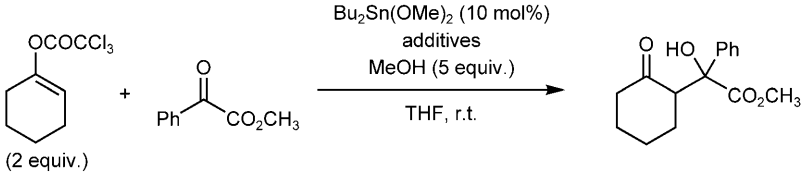
The enantioselective aldol reaction provides a beneficial route to non-racemic β-hydroxy carbonyl compounds that are often utilized as synthetic intermediates of natural products or biologically active compounds.[1] In order to obtain aldol products in high yield and satisfactory optical purity, various methods using chiral catalysts have been developed.[2–4] In particular, the application of ketones as electrophiles to the asymmetric transformation has recently attracted the attention of synthetic organic chemists, because products possessing a chiral tertiary alcohol moiety are synthetically useful. However, there are still only few examples of the catalytic asymmetric aldol reaction of ketones due to their low reactivity toward enolates as well as to the facile retro-aldol reaction of the aldol adducts. Here we describe a novel asymmetric aldol reaction of α-keto esters with alkenyl trichloroacetates catalyzed by dibutyltin dimethoxide and BINAP·silver triflate in the presence of methanol (Scheme 1).

We have previously found that dibutyltin dimethoxide acts as a catalyst in the aldol reaction of alkenyl trichloroacetates with aldehydes.[5] The tin compound is efficiently regenerated from the aldol adduct in the presence of MeOH and thus the reaction takes place catalytically. This protocol has been improved in terms of environmental friendliness because the amount of toxic organotin(IV) compound[6] is reduced to a catalytic amount. In addition, as dibutyltin dimethoxide is more reactive than tributyltin methoxide, the former tin catalyst has solved the problem that aliphatic aldehydes show almost no reactivity in the presence of the latter tin catalyst.[5] We expected that $Bu_2Sn(OMe)_2$ could also catalyze the addition of alkenyl trichloroacetates to ketones which are recognized to be less reactive electrophiles than aldehydes



Scheme 1. The asymmetric aldol reaction of α-keto esters with alkenyl trichloroacetates catalyzed by $Bu_2Sn(OMe)_2$ and BINAP·AgOTf.

Table 1. Additive effects on aldol reaction of methyl benzoylformate with an alkenyl trichloroacetate of cyclohexanone catalyzed by $Bu_2Sn(OMe)_2$.[a]



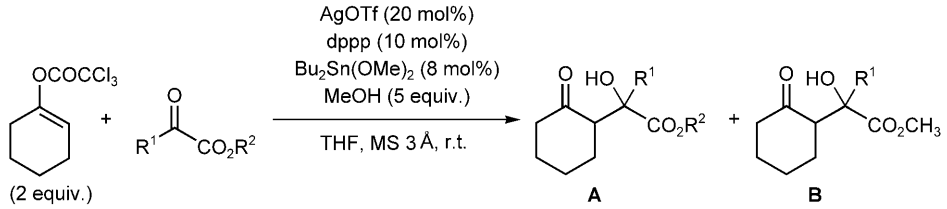
Entry	Additive	*t* [h]	Yield[b] [%]	*dr*[c]
1	none	2	27	71:29
2	dppp (10 mol%), AgOTf (20 mol%), MS 3 Å	3	88	57:43
3	dppf (10 mol%), AgOTf (20 mol%), MS 3 Å	2	60	22:78

[a] Unless otherwise noted, the reaction was performed using $Bu_2Sn(OMe)_2$ (10 mol%), 1-trichloroacetoxycyclohexene (2 equiv.), and methyl benzoylformate (1 equiv.) in dry THF containing MeOH (5 equiv.) at room temperature (22–24 °C) for 2–3 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.

in the conventional Lewis acid-promoted Mukaiyama-type aldol reaction of silyl enolates or ketene silyl acetals.[7,8] First, we tested the catalytic activity of $Bu_2Sn(OMe)_2$ in the reaction of 1-trichloroacetoxycyclohexene (2 equiv.) with methyl benzoylformate (1 equiv.), and found that the targeted β-hydroxy ketone was obtained in 27% yield with a diastereomeric ratio of 71:29 in the presence of 10 mol% of the catalyst and 5 equiv. of MeOH in THF at room temperature (22–24 °C) for 2 h (entry 1, Table 1). We then examined the utility of a bidentate phosphine·silver(I) complex as an additive in an effort to increase the yield of the product. As a result, we found that the yield of the product improved to 88% in the presence of 10 mol% of dppp and 20 mol% of AgOTf with MS 3 Å (entry 2). Employment of dppf in place of dppp also resulted in a significant acceleration of the aldol reaction, but the opposite diastereoselectivity was obtained probably due to the ligand bite angle effects,[9] which might affect the transition state structure (entry 3).

We next performed the aldol reaction of 1-trichloroacetoxycyclohexene with various α-keto esters using $Bu_2Sn(OMe)_2$ and dppp·AgOTf as catalysts (Table 2). From ethyl benzoylformate, the desired aldol product was furnished in 43% yield; however, the corresponding methyl ester was also formed in 14% yield probably due to transesterification pro-

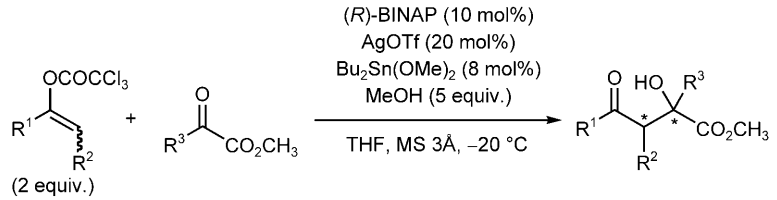
Table 2. Aldol reaction of α-keto esters with an alkenyl trichloroacetate of cyclohexanone catalyzed by $Bu_2Sn(OMe)_2$ and dppp·AgOTf.[a]

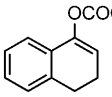
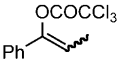


Entry	R^1	R^2	*t* [h]	Yield [%][b]	
				A	**B**
1	Ph	Et	4	43	14
2	Ph	Bn	4	40	23
3	CH_3	Bn	18	80	6
4[c]	CH_3	Bn	13	36	2

[a] Unless otherwise noted, the reaction was performed using dppp (10 mol%), AgOTf (20 mol%), $Bu_2Sn(OMe)_2$ (8 mol%), 1-trichloroacetoxycyclohexene (2 equiv.), and α-keto ester (1 equiv.) in dry THF containing MeOH (20 equiv.) at room temperature (22–24 °C) for 4–18 h.
[b] Determined by ^{1}H NMR analysis.
[c] Without MS 3 Å.

Table 3. The asymmetric aldol reaction of α-keto esters with alkenyl trichloroacetates catalyzed by $Bu_2Sn(OMe)_2$ and (*R*)-BINAP·AgOTf.[a]

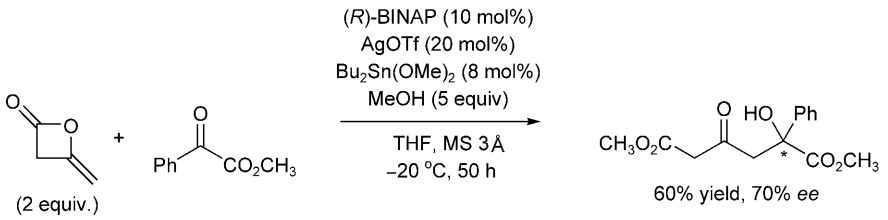


Entry	Alkenyl trichloroacetate	R^3	*t* [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1		Ph	4	99	66:34	74[e]
2		4-BrC_6H_4	4	99	53:47	61[f]
3		4-$MeOC_6H_4$	5	86	83:17	90[g]
4		Ph	24	58	97:3	89
5		Ph	24	38	>99:1	93
6	*E*:*Z* = 1:4	CH_3	24	40	52:48	60[h]

[a] Unless otherwise noted, the reaction was performed using (*R*)-BINAP (10 mol%), AgOTf (20 mol%), $Bu_2Sn(OMe)_2$ (8 mol%), alkenyl trichloroacetate (2 equiv.), and α-keto ester (1 equiv.) in dry THF containing MeOH (5 equiv.) at −20 °C for 4–24 h.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] The value corresponds to the major diastereomer. Determined by HPLC analysis (Daicel Chiralcel OD-H, Chiralpak AD-H, or AS-H).
[e] The minor isomer: 67% *ee*.
[f] The minor isomer: 57% *ee*.
[g] The minor isomer: 79% *ee*.
[h] The minor isomer: 60% *ee*.

moted by the tin methoxide (entry 1).[10] With benzyl benzoylformate, the transesterification could not be suppressed either (entry 2). In contrast, use of benzyl pyruvate led to a satisfactory result in terms of selectivity although a longer reaction time was required to gain a higher yield (entry 3). It is noteworthy that MS 3 Å plays an important role in the present aldol reaction; in fact, the chemical yield of the targeted aldol adduct was decreased to 36% in the absence of MS 3 Å (entry 4).

The above-mentioned results further prompted us to use the BINAP·silver(I) complex as a chiral catalyst for the dibutyltin dimethoxide-catalyzed aldol reaction. We have shown before that the BINAP·AgOTf complex is a good chiral catalyst for the asymmetric aldol reaction of aldehydes with alkenyl trichloroacetates in the presence of a catalytic amount of $Bu_2Sn(OMe)_2$.[11] Treatment of methyl benzoylformate with 1-trichloroacetoxycyclohexene in the presence of (*R*)-BINAP (10 mol%), AgOTf (20 mol%), dibutyltin dimethoxide (8 mol%), and MeOH (5 equiv.) in dry THF at −20 °C for 4 h gave a 66:34 diastereomeric mixture of optically active aldol adduct in 99% combined yield (Table 3, entry 1). The major diastereomer had 74% *ee*. The substituent at the *para*-position of methyl benzoylformate influenced to some extent the diastereomeric ratio and the enantiomeric excess of the product (entries 2 and 3). For the *p*-methoxy derivative, in particular, the enantioselectivity of the reaction reached 90% *ee* (entry 3). The electron-donating group might enhance the Lewis basicity of the carbonyl oxygen, which is anticipated to more strongly coordinate with the silver Lewis acid leading to a more favorable transition state structure for asymmetric induction. The utility of the present $Bu_2Sn(OMe)_2$- and (*R*)-BINAP·AgOTf-catalyzed asymmetric aldol reaction was then demonstrated by using alkenyl trichloroacetates prepared from diverse ketones (entries 4–6). In addition to cyclic substrates, an acyclic substrate was also allowed to react with α-keto esters enantioselectively, although long reaction times were necessary to produce satisfactory yields (entries 5 and 6). Worthy of note is that the reaction with methyl benzoylformate showed nearly exclusive diastereoselectivity and the highest enantioselectivity (93% *ee*, entry 5). In contrast, the reaction with methyl pyruvate proceeded with almost no diastereoselectivity



Scheme 2. The asymmetric aldol reaction of diketene with methyl benzoylformate catalyzed by $Bu_2Sn(OMe)_2$ and (*R*)-BINAP·AgOTf.

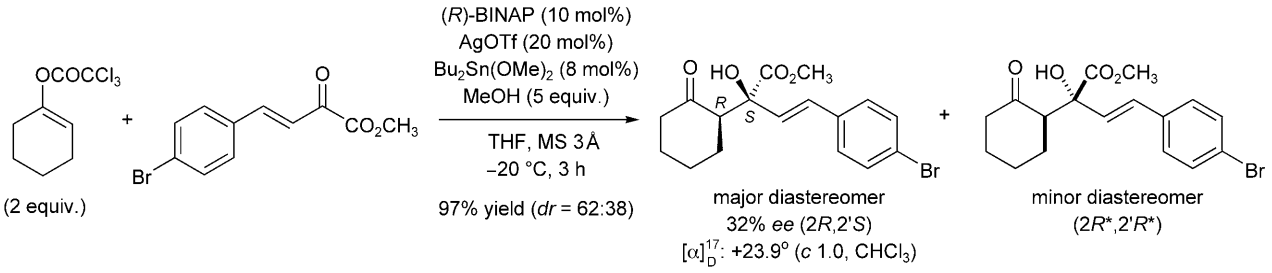
(entry 6). Furthermore, we investigated the reactivity of classical ketones such as acetophenone and cyclohexanone under the standard reaction conditions (−20 °C, 4–20 h); however, these simple ketones did not afford the desired product in the reaction with the alkenyl trichloroacetates of cyclohexanone and α-tetralone, respectively.

We further applied the present asymmetric catalytic process to the reaction of diketene with an α-keto ester in which a tin enolate generated from $Bu_2Sn(OMe)_2$ and diketene might be recycled in the presence of MeOH.[12] Under conventional reaction conditions for alkenyl trichloroacetates, good enantioselectivity (70% *ee*) was obtained along with good chemical yield when a mixture of diketene (2 equiv.) and methyl benzoylformate (1 equiv.) was treated with 10 mol% of (*R*)-BINAP, 20 mol% of AgOTf, and 8 mol% of $Bu_2Sn(OMe)_2$ in THF containing MeOH (5 equiv.) at −20 °C for 50 h (Scheme 2).

Finally, we attempted to determine the absolute stereochemistry of the asymmetric aldol reaction of α-keto esters with alkenyl trichloroacetates catalyzed by $Bu_2Sn(OMe)_2$ and BINAP·AgOTf. For that purpose, we chose (*E*)-methyl 4-(4-bromophenyl)-2-hydroxy-2-(2-oxocyclohexyl)but-3-enoate as a suitable product, because the absolute configuration of one stereoisomer has been unambiguously established by Zhao and co-workers.[8h] When (*E*)-methyl 4-(4-bromophenyl)-2-oxobut-3-enoate was reacted with 1-trichloroacetoxycyclohexene under the influence of (*R*)-BINAP (10 mol%), AgOTf (20 mol%), dibutyltin dimethoxide (8 mol%), and MeOH (5 equiv.) in dry THF at −20 °C for 3 h it furnished a 62:38 diastereomeric mixture of the target product in 97% combined yield (Scheme 3). The absolute configuration of the major diastereomer was assigned to be 2*R*,2′*S* by comparison of its ^{1}H NMR, ^{13}C NMR, chiral HPLC retention time, and optical rotation with reported data.[8h] Although its optical purity was not sufficiently high (32% *ee*), a similar stereochemistry seems to be applicable to the products shown in Table 3.

A plausible catalytic cycle for the asymmetric aldol reaction of alkenyl trichloroacetates with α-keto esters is illustrated in Figure 1. First of all, $Bu_2Sn(OMe)_2$ reacts with alkenyl trichloroacetate **1** to yield tin enolate **2** accompanied by methyl trichloroacetate. Enolate **2** is then allowed to add to an α-keto ester enantioselectively in the presence of the (*R*)-BINAP·AgOTf complex, affording the tin alkoxide of aldol adduct **3**. Finally, protonation of tin alkoxide **3** with MeOH results in the formation of the optically active aldol product **4** and the regeneration of dibutyltin dimethoxide. The rapid methanolysis of alkoxide **3** promotes the catalytic cycle.

In summary, we have presented an example of an aldol reaction of alkenyl trichloroacetates with α-keto esters catalyzed by $Bu_2Sn(OMe)_2$ and a bidentate phosphine·AgOTf complex in the presence of MeOH, and its asymmetric version using the BINAP·AgOTf complex as a chiral co-catalyst. The main features of the present method are as follows: (1) the procedure is operationally simple, employs readily available chemicals and can provide optically active β-hydroxy ketones possessing a chiral tertiary carbon center with



Scheme 3. Determination of absolute stereochemistry of the asymmetric aldol reaction of an α-keto ester with an alkenyl trichloroacetate catalyzed by $Bu_2Sn(OMe)_2$ and (*R*)-BINAP·AgOTf.

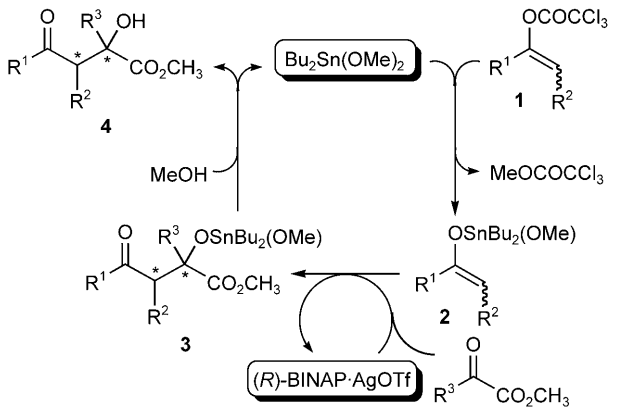


Figure 1. A plausible catalytic mechanism for the asymmetric aldol reaction of α-keto esters catalyzed by $Bu_2Sn(OMe)_2$ and (*R*)-BINAP·AgOTf.

high enantioselectivity of up to 93% ee; (2) diketene can be converted into a non-racemic dimethyl 2-hydroxy-4-oxohexanedioate derivative by applying this method; (3) the *in situ* generated tin enolate reacts much faster with an α-keto ester than with MeOH and the resulting tin alkoxide of the aldol adduct is readily protonated by MeOH to regenerate $Bu_2Sn(OMe)_2$; and (4) this method is environmentally benign as the amount of toxic organotin(IV) compound is reduced to a catalytic amount. To the best of our knowledge, this is the first example of an asymmetric aldol reaction of ketones using alkenyl esters as masked enolates. Current efforts in our laboratory are directed towards the application of the present catalytic system to other asymmetric reactions.

Experimental Section

General Remarks

Column chromatography was conducted with 70–230 mesh silica gel. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts of the ^{1}H NMR spectra were reported relative to tetramethylsilane (δ 0). Splitting patterns are indicated as s, singlet; d, doublet; or m, multiplet. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer. Chemical shifts of the ^{13}C NMR spectra were reported relative to $CDCl_3$ ($\delta = 77.0$). Analytical high-performance liquid chromatography (HPLC) was done using a chiral column (4.6 mm × 25 cm, Daicel Chiralcel OD-H). Optical rotation was measured on a JASCO P-1020 polarimeter. All experiments were carried out under an atmosphere of standard grade argon gas (oxygen < 10 ppm). Alkenyl trichloroacetates were prepared by treating the corresponding ketone with trichloroacetic anhydride in the presence of a catalytic amount of *p*-toluenesulfonic acid and purified by distillation before use.[13] Methyl *p*-bromophenylglyoxylate and methyl *p*-methoxyphenylglyoxylate were prepared according to reported procedures.[14] Other chemicals were used as purchased.

Typical Experimental Procedure for Asymmetric Aldol Reaction of α-Keto Esters: Synthesis of Methyl 2-Hydroxy-2-(2′-oxocyclohexyl)-2-phenylacetate (entry 1 in Table 3)[8a]

A mixture of AgOTf (25.7 mg, 0.10 mmol), (*R*)-BINAP (31.1 mg, 0.050 mmol), and MS 3 Å (0.3 g) was dissolved in dry THF (2.5 mL) under an argon atmosphere and with direct light excluded, and stirred at 20 °C for 10 min. To the resulting solution were added dropwise methyl benzoylformate (70.8 μL, 0.50 mmol), dibutyltin dimethoxide (9.2 μL, 0.040 mmol), MeOH (100 μL, 2.48 mmol), and 1-trichloroacetoxycyclohexene (243.5 mg, 1.00 mmol) successively at −20 °C. After stirring for 4 h at this temperature, the mixture was treated with MeOH (2 mL). The mixture was then treated with solid KF (*ca.* 1 g) and brine (2 mL) at −20 °C for 30 min. The resulting precipitate was filtered off with a glass filter funnel filled with Celite® and silica gel. The filtrate was dried over Na_2SO_4 and concentrated under vacuum after filtration. The residual crude product was purified by column chromatography on silica gel to afford a mixture of the aldol adducts; yield: 130.1 mg (99%). The diastereomeric ratio was determined to be 66:34 by ^{1}H NMR analysis. The enantioselectivity of the major isomer was determined to be 74% *ee* by HPLC analysis using a chiral column (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL min^{-1}): $t_{major} = 33.1$ min, $t_{minor} = 48.7$ min. Spectral data of the product: ^{1}H NMR (400 MHz, $CDCl_3$, a 66:34 mixture of the diastereomers): $\delta = 1.51$–2.12 (m, 6H, 3 CH_2), 2.30–2.47 (m, 2H, CH_2), 3.21 (dd, 0.66H, $J = 5.8$, 12.8 Hz, CH), 3.43 (dd, 0.34H, $J = 6.0$, 11.8 Hz, CH), 3.73 (s, 1.02H, CH_3), 3.79 (s, 1.98H, CH_3), 3.90 (s, 0.34H, OH), 4.20 (s, 0.66H, OH), 7.26–7.38 (m, 3H, aromatic), 7.48–7.51 (m, 1.32H, aromatic), 7.56–7.60 (m, 0.68H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer): $\delta = 25.3$, 27.8, 30.5, 43.0, 52.8, 59.5, 79.3, 125.4, 127.9, 128.3, 140.2, 173.3, 212.8; $[\alpha]_D^{21}$: −19.7° (*c* 1.0, $CHCl_3$, major isomer). The above-mentioned spectral data exhibited good agreement with reported data.[8a]

Acknowledgements

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