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Dibutyltin dimethoxide and BINAP · silver(I) complex-catalyzed asymmetric aldol reaction of alkenyl trichloroacetates with aldehydes

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Abstract

A catalytic asymmetric aldol reaction of alkenyl trichloroacetates with aldehydes was achieved using dibutyltin dimethoxide and BINAP · silver(I) complex as catalysts in a mixed solvent consisting of THF and MeOH. Various optically active β-hydroxy ketones were diastereoselectively obtained not only from aromatic and α,β-unsaturated aldehydes but also from an aliphatic aldehyde with good enantioselectivity up to 92% ee.

Keywords: Asymmetric catalysis; Aldol reaction; Tin alkoxide; BINAP; Silver; Alkenyl esters; Aldehydes

1. Introduction

The β-hydroxy carbonyl group is an important synthon for natural products and biologically active organic molecules. In order to construct the functionality, various transformations have been developed and among them, aldol reaction is recognized as the most efficient and convenient method [1]. Numerous asymmetric catalytic aldol processes have so far been reported; however, most of these are the chiral Lewis acid- or chiral Lewis base-catalyzed Mukaiyama type-aldol reactions using silyl enolates as nucleophiles [2–4] and there have been no examples using alkenyl esters as masked enolates. We have previously found that alkenyl trichloroacetates react with trialkyltin methoxide to afford the corresponding trialkyltin enolates, which have sufficient reactivity toward aldehydes. In addition, in the presence of a catalytic amount of trialkyltin methoxide and a stoichiometric amount of methanol, the aldol reaction takes place smoothly to give the desired products in high yield [5]. An asymmetric version of the catalytic aldol process has been also achieved by addition of a BINAP · Ag(I) catalyst. Although various aldehydes are applicable to the asymmetric reaction, aliphatic aldehydes are less reactive under the standard reaction conditions [5]. To solve the problem on the reactivity, we further studied the catalytic activity of several tin alkoxides and found that dibutyltin dimethoxide is more reactive than tributyltin methoxide, and aliphatic aldehydes show high reactivity under the influence of the former tin catalyst [6]. We report here the asymmetric process of the $Bu_2Sn(OMe)_2$-catalyzed aldol reaction of alkenyl trichloroacetates with aldehydes using the BINAP · AgOTf complex as a chiral catalyst (Scheme 1).

2. Results and discussion

First, we studied the amounts of (*R*)-BINAP and AgOTf in the reaction of 1-trichloroacetoxy cyclohexene [7] with benzaldehyde. As we have reported before, a chiral silver(I) catalyst prepared from BINAP and an excess amount of silver(I) salt shows reactivity higher than that of the corre-

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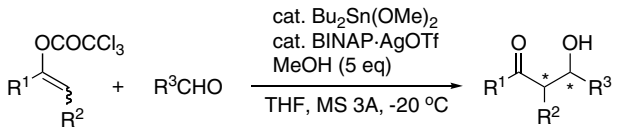
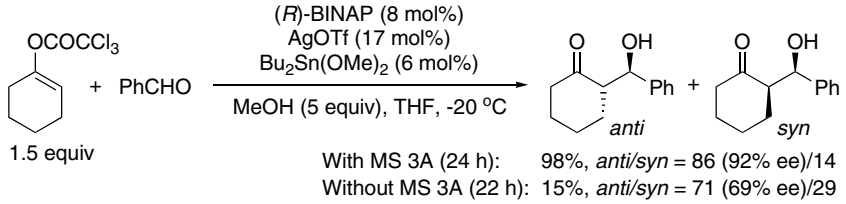


Scheme 1.

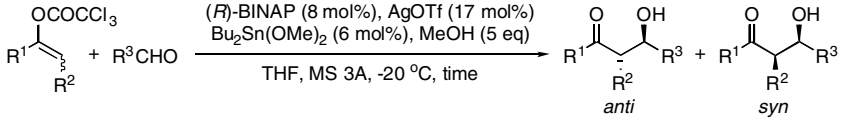
sponding 1:1 mixture, because a significant amount of a less reactive 2:1 complex of BINAP and Ag(I) salt is formed in addition to the desired 1:1 complex from the 1:1 mixture [8]. So we tested various ratios of (*R*)-BINAP and AgOTf in the present reaction and found that the chiral silver(I) complex prepared by mixing 8 mol% of (*R*)-BINAP and 17 mol% of AgOTf was the most effective in obtaining high yield and high enantioselectivity in combination with 6 mol% of $Bu_2Sn(OMe)_2$. For example, the reaction using these catalysts in the presence of 5 equiv. of MeOH at −20 °C for 24 h provided the aldol adduct in 98% yield with an *anti*/*syn* ratio of 86/14. The *anti*-isomer showed 92% ee (Scheme 2). In the reaction, molecular sieves 3A (MS 3A) was indispensable and the isolated yield was drastically decreased unless the additive was present.

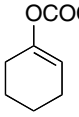
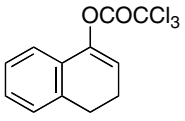
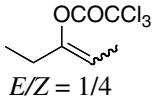
Under the optimized reaction conditions we performed the asymmetric aldol reaction of various combinations of alkenyl trichloroacetates and aldehydes. Selected examples are shown in Table 1. In the reaction of cyclohexanone-derived alkenyl trichloroacetate, aromatic and α,β-



Scheme 2.

Table 1
Enantioselective aldol reaction of alkenyl trichloroacetates with aldehydes catalyzed by $Bu_2Sn(OMe)_2$ and (*R*)-BINAP · AgOTf[a]



Entry	Alkenyl trichloroacetate	Aldehyde	Time/h	Yield/%[b]	*anti*/*syn*[c]	ee/%[d]
1		PhCHO	24	98	86/14	92
2		4-$MeOC_6H_4CHO$	25	92	86/14	91
3		1-$C_{10}H_7CHO$	24	90	94/6	90
4		(*E*)-PhCH=CHCHO	24	90	77/23	82
5[e]		$Ph(CH_2)_2CHO$	48	52	67/33	55
6		PhCHO	24	84	93/7	84
7		4-$MeOC_6H_4CHO$	24	58	92/8	84
8		(*E*)-PhCH=CHCHO	24	71	79/21	72[f]
9		$Ph(CH_2)_2CHO$	96	27	82/18	64
10		PhCHO	44	62	22/78	58
11		4-$MeOC_6H_4CHO$	53	77	17/83	70
12		$Ph(CH_2)_2CHO$	72	60	14/86	26

E/*Z* = 1/4

[a] Unless otherwise noted, the reaction was carried out using (*R*)-BINAP (8 mol%), AgOTf (17 mol%), dibutyltin dimethoxide (6 mol%), alkenyl trichloroacetate (1.5 equiv.), and aldehyde (1 equiv.) in THF containing MeOH (5 equiv.) at −20 °C for 24–96 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, OJ-H, or Chiralpak AD-H, AS-H).

[e] (*R*)-BINAP (9 mol%), AgOTf (19 mol%), and dibutyltin dimethoxide (7 mol%) were used.

[f] Determined by HPLC analysis (Daicel Chiralpak AD-H) of the corresponding saturated β-hydroxy ketone derived from the aldol adduct by hydrogenation (H_2, Pd–C, EtOAc, −20 °C).

unsaturated aldehydes gave the aldol adducts in high yield with *anti*-selectivity. The *anti*-isomers indicated high enantioselectivity up to 92% ee (entries 1–4). As for the α,β-unsaturated aldehyde, exclusive 1,2-selectivity was observed (entry 4). Aliphatic aldehydes also showed moderate reactivity and for example, hydrocinnamaldehyde afforded the desired product in 52% yield but with lower diastereo- and enantioselectivities (entry 5). Use of 1-tetralone-derived alkenyl trichloroacetate as a reaction partner resulted in a better *anti*/*syn* selectivity and enantioselectivity (entry 9). Not only cyclic alkenyl trichloroacetates but acyclic ones such as a 3-pentanone derivative also underwent the asymmetric aldol reaction. Noteworthy was the fact that the opposite *syn*-selectivity was observed for the reaction of the acyclic substrate (entries 10–12).

A plausible catalytic mechanism of the asymmetric aldol reaction is shown in Fig. 1. First, an alkenyl trichloroacetate **1** reacts with $Bu_2Sn(OMe)_2$ generating the dibutylmethoxytin enolate **2** and methyl trichloroacetate. Then, addition of the tin enolate **2** to an aldehyde occurs enantioselectively under the influence of the (*R*)-BINAP · AgOTf catalyst to produce the nonracemic aldol adduct **3**. Protonation of **3** by MeOH affords the final product **4** and regenerates the tin dimethoxide.

In summary, we have demonstrated a novel example of asymmetric aldol reaction of alkenyl trichloroacetates with aldehydes catalyzed by dibutyltin dimethoxide and BINAP · AgOTf. The procedure is operationally simple employing readily available chemicals and can produce various optically active β-hydroxy ketones with enantioselectivity up to 92% ee not only from aromatic and α,β-unsaturated aldehydes but also from an aliphatic aldehyde. This process is environmentally benign because the amount of the toxic organotin compound is a catalytic amount. Further work is now in progress on the asymmetric reaction.

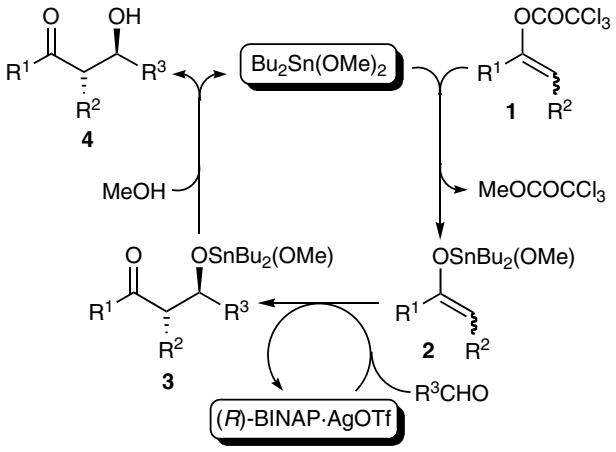


Fig. 1. A suggested catalytic cycle for the asymmetric aldol reaction catalyzed by $Bu_2Sn(OMe)_2$ and (R)-BINAP · AgOTf.

3. Experimental

3.1. General

Analytical TLC was done on precoated (0.25 mm) silica gel plates. Column chromatography was conducted with 70–230 mesh silica gel. Infrared (IR) spectra were recorded on an FTIR spectrometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometers. Chemical shifts of ^{1}H NMR spectra were reported relative to tetramethylsilane (δ 0). Splitting patterns are indicated as s, singlet; d, doublet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on 100 MHz spectrometers. Chemical shifts of ^{13}C NMR spectra were reported relative to $CDCl_3$ (δ 77.0). Analytical high-performance liquid chromatography (HPLC) was done using a chiral column (4.6 mm × 25 cm, Daicel Chiralcel OD-H, OJ-H, or Chiralpak AD-H, AS-H). All experiments were carried out under an atmosphere of standard grade argon gas (oxygen <10 ppm). Alkenyl trichloroacetates were prepared by treatment of the corresponding ketones with trichloroacetic anhydride in the presence of a catalytic amount of *p*-toluenesulfonic acid and purified by distillation before use [7]. Other chemicals were used as purchased.

3.2. A typical procedure for the asymmetric aldol reaction of benzaldehyde with 1-trichloroacetoxy cyclohexene catalyzed by (R)-BINAP · AgOTf complex and dibutyltin dimethoxide: synthesis of (2S,1′R)-2-(hydroxyphenylmethyl)cyclohexanone (anti-isomer, Scheme 2 and entry 1 in Table 1) [9]

A mixture of AgOTf (43.2 mg, 0.167 mmol), (*R*)-BINAP (49.8 mg, 0.080 mmol), and MS 3 A (0.8 g) was dissolved in dry THF (5 mL) under argon atmosphere and with direct light excluded, and stirred at 20 °C for 10 min. To the resulting solution were added dropwise benzaldehyde (102 μL, 1.00 mmol), 1-trichloroacetoxy cyclohexene (365.3 mg, 1.50 mmol), dibutyltin dimethoxide (13.8 μL, 0.060 mmol), and MeOH (202 μL, 5.00 mmol) successively at −20 °C. After being stirred for 24 h at this temperature, the mixture was treated with MeOH (2 mL). The mixture was then treated with brine (2 mL) and solid KF (ca. 1 g) at ambient temperature 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 *in vacuo* after filtration. The residual crude product was purified by column chromatography on silica gel to afford a mixture of the aldol adducts (200.7 mg, 98% yield) as a colorless oil. The *anti*/*syn* ratio was determined to be 86/14 by ^{1}H NMR analysis. The enantioselectivity of the *anti* isomers was determined to be 92% ee by HPLC analysis using a chiral column (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min): $t_{syn\text{-minor}}$ = 13.3 min (2*S*,1′*S*), $t_{syn\text{-major}}$ = 14.5 min (2*R*,1′*R*), $t_{anti\text{-major}}$ = 15.8 min (2*S*,1′*R*), $t_{anti-\text{minor}}$ = 22.1 min (2*R*,1′*S*). The absolute configurations of all stereoisomers were unambiguously

established by Denmark and co-workers [9d]. Spectral data of the *anti*-isomer (oil, 92% ee): TLC R_f 0.24 (1:4 ethyl acetate/hexane); IR (neat) 3590–3350, 2937, 2862, 1693, 1572, 1495, 1449, 1402, 1311, 1227, 1202, 1128, 1039, 746, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24–1.35 (m, 1H, one proton of CH_2), 1.48–1.82 (m, 4H, $2CH_2$), 2.05–2.13 (m, 1H, one proton of CH_2), 2.32–2.41 (m, 1H, one proton of CH_2), 2.45–2.52 (m, 1H, one proton of CH_2), 2.58–2.66 (m, 1H, CH), 3.70 (br s, 1H, OH), 4.79 (d, 1H, $J = 8.9$ Hz, C*H*(OH)), 7.27–7.37 (m, 5H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 27.8, 30.8, 42.6, 57.4, 74.7, 127.0 (2C), 127.9, 128.3 (2C), 140.8, 215.6; $[\alpha]_D^{18} + 20.2^\circ$ (*c* 1.0, $CHCl_3$). Spectral data (TLC, IR, ^1H NMR, and ^{13}C NMR) of the *anti* and *syn*-isomers indicated good agreement with reported data [5,8a,8b–10].

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