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Catalytic Asymmetric Synthesis of α-Alkylidene-β-hydroxy Esters via Dynamic Kinetic Asymmetric Transformation Involving Ba-Catalyzed Direct Aldol Reaction

Akitake Yamaguchi, Shigeki Matsunaga,* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received June 5, 2009; E-mail: smatsuna@mol.f.u-tokyo.ac.jp; mshibasa@mol.f.u-tokyo.ac.jp

The direct catalytic asymmetric aldol reaction is a powerful and atom-economical method for synthesizing chiral β-hydroxycarbonyl compounds.[1] To date, many metal and organocatalysts for reactions of ketone and aldehyde donors have been developed.[1,2] These catalysts kinetically control aldol reactions via a simple proton-transfer process, avoiding undesirable retro-aldol reactions that would cause racemization of the products. In contrast, direct catalytic asymmetric aldol reactions with ester donors are limited to reactions with α-isocyanoacetate,[3a] α-cyanoacetate,[3b] α-diazoacetate,[4] and glycinate Schiff base donors.[5] Although the utility of several α-alkyl-substituted ester-equivalent donors in direct aldol reactions has been nicely demonstrated,[6,7] esters without α-heteroatoms and/or electron-withdrawing substituents have not been utilized, possibly because of the low acidity of α-protons in esters and/or undesirable retro-aldol reactions that occur under basic reaction conditions. Herein, we report the use of ester donors in dynamic kinetic asymmetric transformation (DYKAT)[8] for catalytic asymmetric synthesis of β-hydroxy esters. DYKAT involving Ba(O-*i*Pr)$_2$/**1a**-catalyzed direct aldol/retro-aldol reactions of β,γ-unsaturated esters **2** (Figure 1) afforded α-alkylidene-β-hydroxy esters in up to 99% ee.

A retro-aldol reaction is generally considered an undesirable pathway in kinetically controlled direct asymmetric aldol reactions. We planned to utilize the direct aldol/retro-aldol process in DYKAT to obtain chiral α-alkylidene-β-hydroxy esters. Our working hypothesis is summarized in Scheme 1. Dienolates generated in situ from β,γ-unsaturated ester **2** by a chiral catalyst would react with aldehyde **3** at the α- and/or γ-position. If the chiral catalyst promotes rapid retro-aldol reaction of the α-adduct **4**, isomerization of **4** to the more thermodynamically stable α-alkylidene-β-hydroxy ester **5** can be a DYKAT.

On the basis of this hypothesis, we screened chiral catalysts for the reaction of ester **2a** and aldehyde **3a**, and 1:1 Ba(O-*i*Pr)$_2$/**1a** mixture gave promising results (Table 1).[9,10] The desired aldol reaction/isomerization sequence was promoted by 10 mol % (*S*)-Ba-**1a** in THF at 0 °C, giving **5aa** in 41% yield and 91% ee (entry 1). To improve the α/γ selectivity, we optimized the reaction conditions (entries 2−7). Performing the reaction in THF/DME drastically improved the α/γ selectivity to 11:1 (entry 4). Other metal sources, such as alkali metal (entry 5, Li-**1a**) and rare-earth metal (entry 6, La-**1a**), resulted in poor reactivity and selectivity. The best result was obtained in DME alone with Ba-**1a**, giving predominantly the *E* adduct **5aa** with α/γ > 20:1 in 85% yield and 99% ee after 24 h at 0 °C (entry 7). Ethyl ester **2b** also gave the desired product in 99% ee, but both the α/γ selectivity and yield of the desired product decreased (entry 8). With sterically hindered *t*-butyl ester **2c**, the reactivity was poor (entry 9).

The substrate scope of the reaction is summarized in Table 2. The reactions of some aldehydes in Table 2 gave a better yield using (*S*)-Ba-**1b** rather than (*S*)-Ba-**1a**. Thus, we examined both

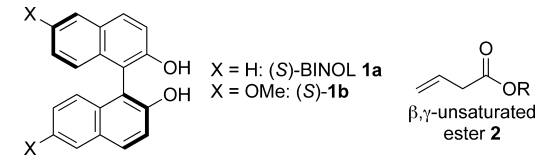


Figure 1. Structures of (*S*)-BINOL (**1a**), (*S*)-6,6′-(MeO)$_2$-BINOL (**1b**), and β,γ-unsaturated ester **2**.

Scheme 1. Working Hypothesis of DYKAT Involving Direct Aldol/Retro-Aldol Reaction for Catalytic Asymmetric Synthesis of α-Alkylidene-β-hydroxy Esters

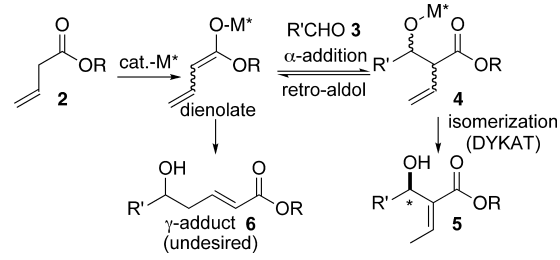
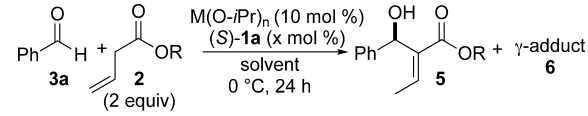


Table 1. Optimization of Reaction Conditions



2a: R = Bn; **2b**: R = Et; **2c**: R = *t*Bu

entry	M	*x*	**2**	solvent	**5**/**6**[a]	% yield of **5**	% ee of **5**
1	Ba(O-*i*Pr)$_2$	10	**2a**	THF	1.8:1	41	91
2	Ba(O-*i*Pr)$_2$	10	**2a**	1:9 THF/toluene	−	trace	−
3	Ba(O-*i*Pr)$_2$	10	**2a**	1:9 THF/EtOAc	0.8:1	4	69
4	Ba(O-*i*Pr)$_2$	10	**2a**	1:9 THF/DME	11:1	79	98
5	Li(O-*i*Pr)	5	**2a**	1:9 THF/DME	1.6:1	8	9[b]
6	La(O-*i*Pr)$_3$	15	**2a**	1:9 THF/DME	−	0	−
7	Ba(O-*i*Pr)$_2$	10	**2a**	DME	>20:1	85	99
8	Ba(O-*i*Pr)$_2$	10	**2b**	DME	5.6:1	69	99
9	Ba(O-*i*Pr)$_2$	10	**2c**	DME	−	trace	−

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] *ent*-**5** was obtained as the major isomer.

(*S*)-Ba-**1a** and (*S*)-Ba-**1b** for each aldehyde, and the best results are shown in Table 2.[11] (*S*)-Ba-**1** catalysts were applicable to a broad range of aldehydes, giving predominantly *E* adducts **5** in all entries. Aryl aldehydes **3b**−**d** with either an electron-donating group (entries 2 and 3) or an electron-withdrawing group (entry 4) gave the desired products **5ba**−**5da** in 99−96% ee. High enantioselectivity was also achieved with heteroaryl and alkenyl aldehydes **3e**−**h** (entries 5−8, 99−97% ee). Readily enolizable alkyl aldehydes, including linear aldehyde **3j**, were applicable as well, although the enantioselectivity was slightly lower than for other aldehydes

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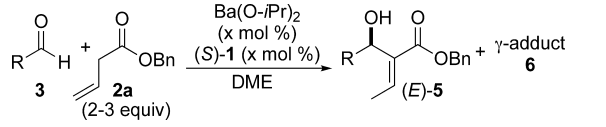
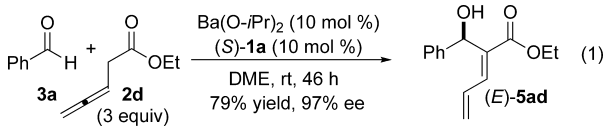
Table 2. Ba-Catalyzed Asymmetric Synthesis of α-Alkylidene-β-hydroxy Esters via DYKAT[a]



entry	R	3	1 (x)	temp (°C)	time (h)	5	5/6[b]	% yield of 5[c]	% ee
1	Ph	**3a**	**1a** (10)	0	24	**5aa**	>20:1	85	99
2	4-MeC_6H_4	**3b**	**1a** (10)	0	42	**5ba**	17:1	77	98
3	3-MeOC_6H_4	**3c**	**1b** (10)	−20	24	**5ca**	15:1	81	99
4	3-BrC_6H_4	**3d**	**1a** (10)	0	42	**5da**	>20:1	78	96
5	2-thienyl	**3e**	**1a** (10)	0	34	**5ea**	>20:1	80	98
6	3-thienyl	**3f**	**1b** (10)	−20	40	**5fa**	>20:1	85	97
7	3-furyl	**3g**	**1a** (10)	0	34	**5ga**	>20:1	82	98
8	(*E*)-PhCH=CH	**3h**	**1b** (10)	−20	28	**5ha**	>20:1	63	99
9	*i*Bu	**3i**	**1b** (10)	0	42	**5ia**	>20:1	76	91
10	*n*Pr	**3j**	**1a** (10)	0	48	**5ja**	>20:1	53	87
11	Ph	**3a**	**1a** (5)	0	55	**5aa**	>20:1	84	99

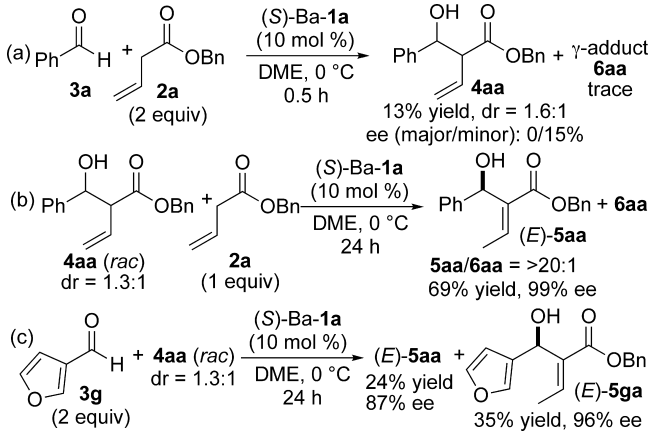
[a] In entries 1 and 11, 2 equiv of **2a** were used; in entries 2−10, 3 equiv of **2a** were used. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Isolated yield after purification by column chromatography.

(entries 9 and 10, 91−87% ee). The catalyst loading was successfully reduced to 5 mol % without decreasing the yield or enantioselectivity, but a longer reaction time was required (entry 11, 55 h). (*S*)-Ba-**1a** also promoted the aldol/isomerization sequence of ester **2d** with an allenyl moiety at room temperature, giving (*E*)-**5ad** in 79% yield and 97% ee (eq 1).



To gain preliminary insight into the enantiodiscriminating step in the present reaction, several experiments were performed (Scheme 2). When the reaction of aldehyde **3a** with ester **2a** catalyzed by (*S*)-Ba-**1a** was analyzed at the initial stage (0.5 h), only trace amounts of **5aa** and **6aa** were observed. Instead, α-adduct **4aa** was obtained in 13% yield, but with poor dr and ee (Scheme 2a, dr = 1.6:1, major/minor = 0/15% ee). The poor ee for **4aa** indicated that the isomerization step from **4** to **5** was highly enantioselective. In fact, when diastereomixtures of racemic **4aa** were treated with (*S*)-Ba-**1a** in the presence of 1 equiv of **2a**, (*E*)-**5aa** was obtained in 69% yield and 99% ee after 24 h (Scheme 2b). The yield and ee of **5aa** in Scheme 2b suggested the

Scheme 2. Mechanistic Studies of Ba-Catalyzed DYKAT



presence of a retro-aldol reaction under the reaction conditions, and this was further confirmed by the crossover experiment shown in Scheme 2c. Treatment of aldehyde **3g** and racemic **4aa** with (*S*)-Ba-**1a** in DME gave both **5aa** (24% yield, 87% ee) and **5ga** (35% yield, 96% ee) after 24 h. These results confirmed that the present system is a Ba-**1**-catalyzed DYKAT involving a direct aldol/retro-aldol process.

In summary, we have developed a Ba-catalyzed DYKAT involving a direct aldol/retro-aldol reaction of β,γ-unsaturated ester donors. α-Alkylidene-β-hydroxy esters were obtained from aryl, heteroaryl, alkenyl, and alkyl aldehydes under simple proton-transfer conditions in 99−87% ee and >20:1 to 15:1 α/γ selectivity. Further studies to improve the reaction rate and catalyst loading are ongoing.

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Supporting Information Available: Experimental procedures, spectral data for new compounds, and determination of stereochemistry. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Detailed results comparing (*S*)-Ba-**1a** with (*S*)-Ba-**1b** are shown in the Supporting Information.

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