JOC Article

Highly Enantioselective Sequential Hydrogenation of Ethyl 2-Oxo-4-arylbut-3-enoate to Ethyl 2-Hydroxy-4-arylbutyrate

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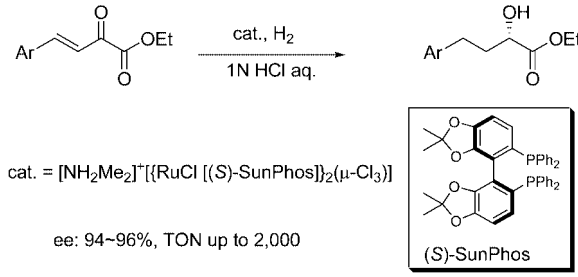

The hydrogenation of (*E*)-ethyl 2-oxo-4-arylbut-3-enoate with $[NH_2Me_2]^+[\{RuCl\ [(S)\text{-SunPhos}]\}_2(\mu\text{-}Cl_3)]$ gave ethyl 2-hydroxy-4-arylbutyrate with 94−96% ee. Further investigation has proved that the hydrogenation proceeded via a sequential hydrogenation of C═O and C═C bonds, which is sensitive to the reaction temperature. Hydrolysis of ethyl 2-hydroxy-4-phenylbutyrate (ee 93%) provided the 2-hydroxy-4-phenylbutyric acid with 81% yield at 99% ee after a single recrystallization from 1, 2-dichloroethylene.

Introduction

Asymmetric hydrogenation catalyzed by transition metal complexes containing optically active phosphine ligands has attracted significant interest in industry and academia for its synthetic utility.[1] A variety of commercially important angiotensin-converting enzyme (ACE) inhibitors containing an (*S*)-homophenylalanine moiety can be synthesized from various chiral building blocks.[2] Among them, enantiomerically pure ethyl (*R*)-2-hydroxy-4-phenylbutyrate is a useful intermediate to prepare such ACE inhabitors. A number of routes to (*R*)-2-hydroxy-4-phenylbutyrate have been developed, including classical resolution of the hydroxyl racemic acid;[3] catalytic enantioselective reduction of a prochiral ketone by chemical,[4] microbial, or enzymatic reduction;[5] and chiral pool synthesis.[6] Enantioselective hydrogenation of ethyl 2-oxo-4-phenylbutanoate is likely one of the most economic and efficient method; however, it suffers from instability of the α-ketoesters and sensitivity of enantioselective hydrogenation to substrate purity.[1i,4f] Therefore, the search for effective, highly enantioselective, and

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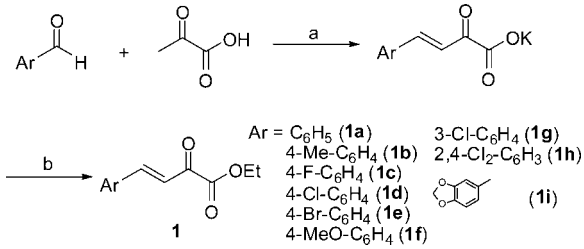
SCHEME 1. Synthesis of Ethyl 2-Oxo-4-arylbut-3-enoates[a]



[a] Reagents and conditions: (a) KOH, MeOH, 20−40 °C, 10−15 h; (b) AcCl, EtOH, 70 °C, 6−8 h.

practical approaches to (*R*)-2-hydroxy-4-phenylbutyrate is still of significance.

Recently we have been focusing on the design and application of new biaryl phosphine ligands.[7] Initial work in this area has resulted in the identification of a series of bidentate ligands highly effective in enantioselective hydrogenation of β-ketoesters,[7a,b] α-ketoesters,[7c,e] and β-keto sulfones.[7d] Asymmetric hydrogenation of monofunctionalized olefins or ketones has been investigated extensively in recent decades, and high enantioselectivities have usually been attained with substrates that have another functional group at a neighboring position; in contrast, bifunctionalized and even polyfunctionalized olefins or ketones have rarely attracted attention. In this paper, we report a highly enantioselective synthesis of ethyl 2-hydroxy-4-arylbutyrates by sequential hydrogenation of (*E*)-ethyl 2-oxo-4-arylbut-3-enoates, which can be prepared conveniently by two steps starting from the corresponding aryl aldehydes and pyruvic acid (Scheme 1).[8]

Results and Discussion

Based on the initial success of asymmetric hydrogenation for functionalized ketones, the catalyst [RuCl(benzene)**L**]Cl was readily prepared from $[Ru(benzene)Cl_2]_2$ and a diphosphine ligand by refluxing them in degassed ethanol/dichloromethane for 1 h.[7] The chiral bidentate ligands **L1**−**L4** were tested for the asymmetric hydrogenation of ethyl 2-oxo-4-phenylbut-3-enoate (**1a**). The reaction was conducted with 1 mol % of [RuCl(benzene)**L**]Cl as catalyst at 70 °C in EtOH for 12 h. Under 14 bar of H_2, β,γ-unsaturated α-ketoester **1a** was successfully reduced to (*S*)-ethyl 2-hydroxy-4-phenylbutyrate with complete conversion and good ee. Enantioselectivity of the reaction was greatly dependent on ligands employed: with (*S*)-Binap as ligand, 67% ee was obtained; with (*S*)-DifluorPhos, (*S*)-SegPhos, and (*S*)-SunPhos as ligands, the corresponding ee values 75%, 85%, and 86% were achieved (Scheme 2).

It has been reported that additives play a crucial role in improving the reactivity and enantioselectivity of many asymmetric reactions.[7,9] Accordingly, we evaluated a number of additives for asymmetric hydrogenation of **1a** by using 1 mol % of [RuCl(benzene)(*S*)-SunPhos]Cl (**4**) as catalyst and 6 mol % of the additive in an attempt to promote the enantioselectivity. As shown in Table 1, among the tested aqueous solutions of Brønsted acids, the proper counteranion was essential for achieving better enantioselectivity (Table 1, entries 1−5), and the addition of catalytic amounts of 1 N HCl aqueous solution improved the enantiomeric excess up to 93% (Table 1, entry 4). In the presence of $CeCl_3 \cdot 7H_2O$, an effective additive in Ru-catalyzed enantioselective hydrogenation of aromatic α-ketoesters,[7c,e] the hydrogenation of **1a** afforded a mixture of ethyl 2-hydroxy-4-phenylbutanoate (**2a**) and (*E*)-ethyl 2-hydroxy-4-phenylbut-3-enoate (**3**) with decreased ee values (Table 1, entry 6, molar ratio of **2a/3** = 95/5). Different ruthenium complexes of the same ligand also influenced the ee values: up to 94% ee

SCHEME 2. Asymmetric Hydrogenation of 1a with L1−L4

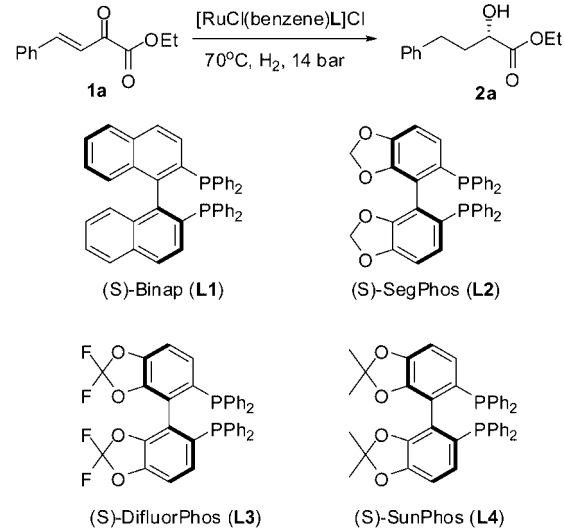
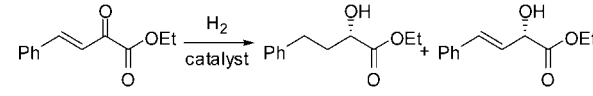


TABLE 1. Optimization Studies of Catalytic Asymmetric Hydrogenation of 1a[a]



entry	catalyst	additive	temp (°C)	product	ee (%)[b]
1	**4**	1 N H_2SO_4 aq	70	**2a**	80
2	**4**	1 N CSA aq	70	**2a**	90
3	**4**	1 N HBF_4 aq	70	**2a**	84
4	**4**	1 N HCl aq	70	**2a**	93
5	**4**	1 N H_3BO_3 aq	70	**2a**	88
6	**4**	$CeCl_3 \cdot 7H_2O$	70	**2a/3**, 95/5[c]	75/45[d]
7	**5**	none	70	**2a**	78
8	**5**	1 N HCl aq	70	**2a**	91
9	**6**	none	70	**2a**	90
10	**6**	1 N HCl aq	70	**2a**	94
11[e]	**6**	1 N HCl aq	70	**2a**	82
12[f]	**6**	1 N HCl aq	70	**2a**	49
13	**6**	1 N HCl aq	30	**2a/3**, 70/30	96/96[d]
14	**6**	1 N HCl aq	50	**2a/3**, 76/24	95/95[d]
15[g]	**6**	1 N HCl aq	50	**2a/3**, 79/21	94/94[d]

[a] Unless otherwise noted, all reactions were carried out with a substrate (1 mmol) concentration of 0.20 M in EtOH under 14 bar of H_2 for 12 h, substrate/catalyst/additive = 100/1/6, conversion 100%. [b] ee values were determined by HPLC on a Chiralpak OD-H column. [c] Molar ratio of **2a/3** was determined by ^1H NMR. [d] ee values of **2a/3**. [e] $ClCH_2CH_2Cl$ as the solvent. [f] Toluene as the solvent. [g] P (H_2) = 41 bar.

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was achieved with $[NH_2Me_2]^+[\{RuCl[(S)\text{-SunPhos}]\}_2(\mu\text{-}Cl_3)]$ (**6**)[10] as the catalyst in the presence of 1 N HCl (Table 1, entry 10), but with $RuCl_2[(S)\text{-SunPhos}](DMF)_m$ (**5**)[11] as the catalyst, only 78% ee was obtained (Table 1, entry 7). On the basis of these findings, the catalyst system $[NH_2Me_2]^+[\{RuCl[(S)\text{-SunPhos}]\}_2(\mu\text{-}Cl_3)]$ (**6**) and catalytic amounts of 1 N HCl was tested across a range of solvents, reaction temperature, and hydrogen pressure (Table 1, entries 11−15). As a matter of fact, aprotic solvents (toluene or 1, 2-dichloroethane) gave lower enantioselectivity than ethanol (Table 1, entries 11 and 12 vs entry 10). At lower temperature, **1a** was also hydrogenated with complete conversion and gave a mixture of **2a** and **3** with slightly higher ee values. Increasing the hydrogen pressure improved the rate of hydrogenation of the C=C bond while decreasing the enantioselectivities (Table 1, entry 14 vs entry 15). The results indicated that the reactivity of the C=O bond toward hydrogenation is better than that of the C=C bond; however, all attempts to achieve selective hydrogenation of the C=O bond proved in vain. The optimized reaction conditions were therefore set as the following: 1 mol % of $[NH_2Me_2]^+[\{RuCl[(S)\text{-SunPhos}]\}_2(\mu\text{-}Cl_3)]$ (**6**) as the catalyst, 6 mol % of 1 N HCl as the additive, and ethanol as the solvent, with the substrate concentration of 0.2 M, and 14 bar of H_2 at 70 °C.

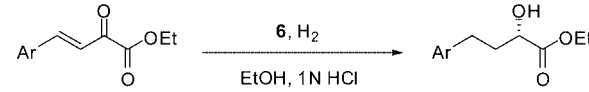
Under the optimized reaction conditions, a series of (*E*)-ethyl 2-oxo-4-arylbut-3-enoates were hydrogenated using $[NH_2Me_2]^+[\{RuCl[(S)\text{-SunPhos}]\}_2(\mu\text{-}Cl_3)]$ (**6**) as catalyst (Table 2). High enantioselectivities have been achieved with all tested substrates. The results show that the electron density and steric factors of the aromatic ring of the substrate have little effect on the enantioselectivities (ee 94−96%, entries 1−9).

When the substrate/catalyst ratio increased from 100 to 2000, the hydrogenation of **1a** still proceeded smoothly, keeping the enantioselectivity almost unchanged (ee 94%, entry 1 vs ee 93%, entry 10). Hydrolysis of (*S*)-ethyl 2-hydroxy-4-phenylbutyrate (ee 93%) provided the (*S*)-2-hydroxy-4-phenylbutyric acid (**7**) with 81% yield at 99% ee after a single recrystallization from 1,2-dichloroethylene (Scheme 3). Compared with ethyl 2-oxo-4-phenylbutanoate (**8**), the β,γ-unsaturated α-ketoesters **1** are more stable, easier to make, and more suitable for asymmetric hydrogenation. This is a promising procedure for the preparation of enantiomerically pure 2-hydroxy-4-phenylbutyric acid at large scale.

There are three possible reaction pathways from **1a** to **2a** (Figure 1): (A) the C=C bond of **1a** is first hydrogenated to generate saturated ethyl 2-oxo-4-phenylbutanoate (**8**), and then the C=O bond of **8** is reduced;[12] (B) the C=O bond of **1a** is first hydrogenated to give allylic alcohol **3**, whose C=C double bond is then reduced; or (C) allylic alcohol **3** isomerizes to **8**,[13] followed by hydrogenation of **8** directly in the presence of ruthenium catalyst.

Our results have proved that the C=O bond of **1a** is easier to be hydrogenated to generate allylic alcohol **3** (Table 1, entries 13−15). However, we cannot determine whether the double bond can be isomerized prior to the reduction of the C=O double bond. To gain further insight into the reaction pathway, three experiments were conducted (Scheme 4). Hydrogenation of **8** gave **2a** with 91% ee, somewhat lower than 94% (Table 1, entry 10); hydrogenation of **1a** and racemic **3** at 1:1 ratio in one pot afforded **2a** with only 36% ee; hydrogenation of racemic

TABLE 2. Asymmetric Hydrogenation of 1 with $[NH_2Me_2]^+[\{RuCl[(S)\text{-SunPhos}]\}_2(\mu\text{-}Cl_3)]$ (6)[a]



1 2

entry	Ar	ee (%)[b]	config.[c]
1	C_6H_5(**1a**)	94	(+)
2	4-Me-C_6H_4(**1b**)	95	(+)
3	4-F-C_6H_4(**1c**)	95	(+)
4	4-Cl-C_6H_4(**1d**)	95	(+)
5	4-Br-C_6H_4(**1e**)	96	(+)
6	4-$MeOC_6H_4$(**1f**)	95	(+)
7	3-Cl-C_6H_4(**1g**)	95	(+)
8	2,4-Cl_2-C_6H_5(**1h**)	95	(+)
9	 (**1i**)	95	(+)
10[d]	C_6H_5(**1a**)	93 (99[e])	(+)

[a] All reactions were carried out under 14 bar of hydrogen with a substrate (1 mmol) concentration of 0.20 M in EtOH under 14 bar of H_2 at 70 °C for 12 h. substrate/**6**/1 N HCl = 100/1/6, conversion 100%. [b] ee values were determined by HPLC analysis. [c] Configuration was determined to be *S* by comparing the specific rotation with reported data or by analogy. [d] **1a** (30 mmol), S/C = 2000, 24 h, conversion was 100%. [e] ee value after purification.

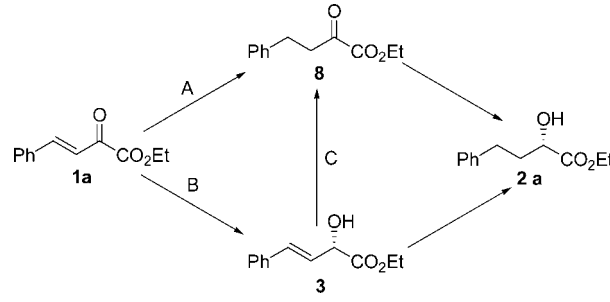
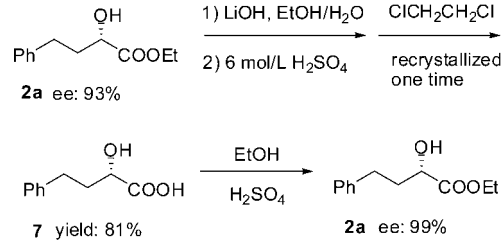


FIGURE 1. Three possible reaction pathways from **1a** to**2a**.

SCHEME 3. Purification of (*S*)-Ethyl 2-Hydroxy-4-phenylbutyrate



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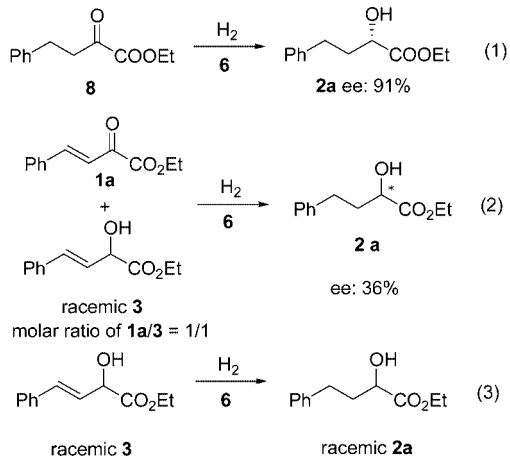
SCHEME 4. Asymmetric Hydrogenation of 8, 1a, and/or Racemic 3



3 yielded racemic **2a**. On the basis of the experimental results observed, the isomerization of allylic alcohol **3** to saturated ketone **8** could be ruled out. Because we have not isolated or detected compound **8** during and after the reaction, we assume that hydrogenation of the C═O bond occurred prior to the hydrogenation of the C═C bond in **1a**; with the accumulation of the primary hydrogenation product, hydrogenation of the C═C bond in **3** occurred directly to give the completely hydrogenated product **2a**.

In conclusion, we have developed a convenient protocol for highly enantioselective preparation of ethyl 2-hydroxy-4-arylbutyrate by hydrogenation of (*E*)-ethyl 2-oxo-4-arylbut-3-enoate. Further investigation has proved that the hydrogenation proceeds via a sequential hydrogenation of the C═O and C═C bonds. The enantiomeric excess of ethyl 2-hydroxy-4-phenylbutyrate can be easily upgraded from 93% to >99% after simple recrystallization. This reaction has provided a useful procedure for the preparation of the key intermediates for ACE inhibitors.

Experimental Section

Typical Procedure for the Asymmetric Hydrogenations. The catalyst $[NH_2Me_2]^+[\{RuCl\ [(S)\text{-SunPhos}]\}_2(\mu\text{-}Cl_3)]$ (**6**) was dissolved in degassed ethanol (20 mL) containing 1 N HCl aqueous solution (240 μL), and then the solution was put into four vials equally. To these vials were introduced the β,γ-unsaturated α-ketoesters (1 mmol), and then the four vials were taken into one autoclave. The autoclave was purged three times with H_2, and the pressure of H_2 was set to 14 bar. The vials in the autoclave were stirred under the specified reaction conditions. After cooling to ambient temperature and release of the hydrogen, the autoclave was opened and the solvent was evaporated. The enantiomeric excess was determined by HPLC after passing the samples through a short pad of silica gel with hexanes and ethyl acetate.

Procedure for the Purification of the Hydrogenation Product. (*S*)-Ethyl 2-Hydroxy-4-phenylbutyrate (6.13 g, 30 mmol) was dissolved in EtOH/H_2O (40/40 mL). $LiOH\cdot H_2O$ (1.39 g, 33 mmol) was then added, and the mixture was stirred at 40 °C for 2 h. The solvent was evaporated under reduced pressure at 40 °C, and the residue was acidified by 6 mol/L H_2SO_4 aqueous solution and extracted with ethyl acetate (30 mL × 3). After the organic layer was separated and dried over $MgSO_4$, the solvent was evaporated, and the crude product was recrystallized from 1, 2-dichloroethylene to give **7** (4.38 g, 81%). After transfer of **7** to **2a** in refluxing EtOH with a drop of concentrated sulfuric acid, the ee value of **7** was determined to be 99%. **Data for 7:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97−2.06 (m, 1H), 2.14−2.23 (m, 1H), 2.80 (t, J = 8.0 Hz, 2 H), 4.27 (dd, J = 4.0, 8.0 Hz, 1 H), 7.18−7.31 (m, 5H).^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 35.6, 69.5, 126.3, 128.48, 128.54, 147.0, 179.8. **Data for 2a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3 H), 1.90−1.99 (m, 1H), 2.10−2.16 (m, 1H), 2.70−2.79 (m, 2H), 2.81 (br, 1H), 4.17−4.20 (m, 1H), 4.21 (q, J = 7.2 Hz, 2 H), 7.20−7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 30.9, 35.8, 61.5, 69.6, 125.8, 128.2, 128.4, 141.0, 175.1. HPLC (Chiralcel OD-H column, hexane/^{i}PrOH 95/5, 0.8 mL min^{-1}, 220 nm): t_R (major) = 10.3 min, t_R (minor) = 15.6 min.

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Supporting Information Available: NMR and/or HPLC data of compounds **1**, **2**, **3**, **7** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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