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Direct Asymmetric Hydrogenation of 2-Oxo-4-arylbut-3-enoic Acids

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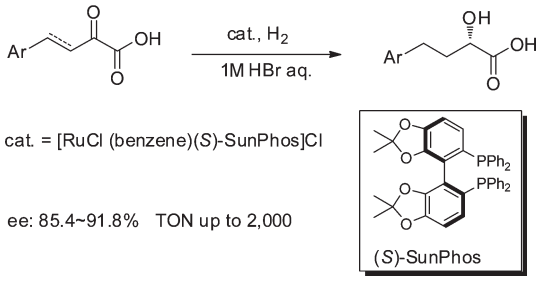

A challenging direct asymmetric hydrogenation of (*E*)-2-oxo-4-arylbut-3-enoic acids to give 2-hydroxy-4-arylbutanoic acids (85.4−91.8% ee) was achieved with a Ru catalyst based on SunPhos as the chiral ligand. Further investigation of the reaction revealed that partial isomerization of 2-hydroxy-4-arylbutenoic acids was involved in the hydrogenation process. Employing the reaction conditions to the hydrogenation of 2-oxo-4-phenylbutanoic acid resulted in better enantioselectivity (91.8% ee) and efficiency (TON = 2000, TOF = 200 h^{-1}), which offers a useful method for the synthesis of a common intermediate for ACE inhibitors.

Catalytic asymmetric hydrogenation has been established as one of the most efficient strategies for the synthesis of optically active molecules.[1] Metal-catalyzed asymmetric hydrogenation of functionalized olefins or ketones has been investigated extensively.[2] However, asymmetric hydrogenation of α-keto acids has rarely attracted attention,[3] and metal-catalyzed asymmetric hydrogenation of unsaturated α-keto acids is not reported.[4] To realize such a transformation, some issues should be taken into consideration: (i) the competitive coordination of the substrate with the counteranion of the catalyst, which might cause deactivation of the catalyst, thus leading to low enantioselectivity and/or reactivity; (ii) the liberation of the product, the hydroxy acid, which usually serves as a ligand, from the catalyst. Recently, we have developed a convenient protocol for highly enantioselective preparation of ethyl 2-hydroxy-4-arylbutyrates,[5] which can be employed in the synthesis of angiotensin-converting enzyme (ACE) inhibitors[6] by hydrogenation of (*E*)-ethyl 2-oxo-4-arylbut-3-enoates. The hydrogenation products, ethyl 2-hydroxy-4-arylbutyrate, are usually liquids, and the enantiomeric purities can only be upgraded by hydrolysis, acidification, and recrystallization. Furthermore, we have to prepare the hydrogenation substrates from their corresponding acids by esterification. Therefore, it is desirable to develop a direct method for the hydrogenation

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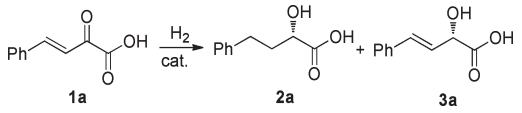
TABLE 1. Effects of Solvents, Pressure, and Temperature[a]



entry	solvent	$P/T/t$ (psi/°C/h)	product	ee (%)[b]
1	EtOH	400/90/20	**5a**[c]	64.2
2	*t*-BuOH	400/90/20	**2a**	58.2
3	*i*-Pr_2O	400/90/20	**2a**	69.4
4	dioxane	400/90/20	**2a**	82.6
5	THF	400/90/20	**2a**	87.1
6	THF	400/70/20	**2a** (30)/**3a**(70) [d]	90.5/74.6
7	THF	400/90/10	**2a** (97)/**3a**(3) [d]	89.1/47.2
8	THF	400/110/20	**2a**	64.4
9	THF	200/90/20	**2a**	86.6
10	THF	800/90/20	**2a**	85.8
11	THF	400/90/20	**2a**	65.0 [e]

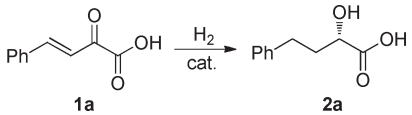
[a]Unless otherwisely noted, all reactions were carried out with a substrate (1 mmol) concentration of 0.20 M in a solvent for 20 h, 1 M aq HCl as the additive, substrate/catalyst/additive = 100/1/6, conversion = 100%. [b]Determined by HPLC on a Chiralpak OD-H column after transferring acids to esters. [c]The acid transferred to its corresponding ester during the hydrogenation process. [d]The numbers in parentheses refer to a molar ratio of **2a/3a**, which was determined by ^{1}H NMR. [e]No additive.

of α-keto acids. In this paper, we report an enantioselective synthesis of 2-hydroxy-4-arylbutanoic acids by direct asymmetric hydrogenation of their corresponding (*E*)-2-oxo-4-arylbut-3-enoic acids, which are prepared conveniently by reaction of corresponding arylaldehydes and pyruvic acid.[7]

On the basis of our success in asymmetric hydrogenation of ethyl 2-oxo-4-arylbut-3-enoates, we arbitrarily employ [RuCl(benzene)(*S*)-SunPhos]Cl and catalytic amounts of aqueous 1 M HCl as catalyst to test the hydrogenation of 2-oxo-4-phenylbutanoic acid across a range of solvents, reaction temperatures, and hydrogen pressures (Table 1, entries 1−10).

The purpose of the addition of HCl is to protonate the product formed to achieve a quick leaving of the product from the catalytic center and to use Cl^- as the ligand to expel the product from the catalyst. In fact, THF is the best solvent investigated (Table 1, entry 5). At lower temperature or shorter reaction time (Table 1, entries 6 and 7), **1a** was also hydrogenated with complete conversion to give a mixture of **2a** and **3a**, which revealed that rates of the hydrogenation of the C=O bond and C=C bond are different, and the hydrogenation of the C=O bond is much faster because we did not detect any 2-oxo-4-phenylbutanoic acid during the hydrogenation process. The fact that the enantiomeric excesses of **2a** and **3a** are not equal also implies that the hydrogenation process is not a simple sequential hydrogenation of the C=O double bond followed by hydrogenation of the C=C double bond. Increasing the temperature improved the rate of hydrogenation of the C=C bond (Table 1, entry 5 vs 6) but decreased the enantioselectivities (Table 1, entry 5 vs 8). The hydrogenation reaction is not sensitive to hydrogen pressure (Table 1, entries 5, 9, and 10).

TABLE 2. Effects of Additives and Catalysts[a]



entry	additive	ee (%)[b]
1	1 M HCl aq[c]	86.8
2	1 M HCl aq	87.1
3	1 M HCl aq[d]	85.9
4	1 M HBF_4 aq	78.4
5	1 M H_3BO_3 aq	82.2
6	1 M H_2SO_4 aq	84.4
7	1 M CSA aq	87.4
8	1 M HBr aq	89.2
9	1 M HI aq	86.6
10	$CeCl_3 \cdot 6H_2O$	73.8
11	I_2	66.8
12	none	65.0
13	H_2O[e]	85.0
14	1 M $CeCl_3$ aq	82.3
15[f]	1 M HBr aq	86.0
16[g]	1 M HBr aq	88.5
17[h]	1 M HBr aq	48.0
18[i]	1 M HBr aq	84.0
19[j]	1 M HBr aq	84.8
20	HBr (gas)	68.7

[a]Unless otherwisely noted, all reactions were carried out under 400 psi of hydrogen with a substrate (1 mmol) concentration of 0.20 M in THF for 20 h, substrate/catalyst/additive = 100/1/6, conversion = 100%. [b]Determined by HPLC on a Chiralpak OD-H column after transferring acids to esters. [c]3% 1 M HCl aq. [d]12% 1 M HCl aq. [e]0.06 mL of H_2O. [f]Catalyst is [Ru(cymene)Cl(*S*)-Sunphos]Cl. [g]Catalyst is [Ru(benzene)-Br(*S*)-Sunphos]Br. [h]Catalyst is [Ru(benzene)Cl(*S*)-Binap]Cl. [i]Catalyst is [Ru(benzene)Cl(*S*)-C_3-Tunephos]Cl. [j]Catalyst is [Ru(benzene)Cl(*S*)-Segphos]Cl.

It has been reported that catalytic amounts of additives play a crucial role in improving the reactivity and enantioselectivities in many asymmetric reactions,[8] and it has also been proven that HCl is a good additive in our preliminary work; we then evaluated a number of other additives for the asymmetric hydrogenation of **1a**. As shown in Table 2, among the tested aqueous solutions of Brønsted acids, it seems that the proper counteranion was essential for achieving high enantioselectivities (Table 2, entries 1−9), the addition of catalytic amounts of 1 M aq HBr solution improved the enantiomeric excess to 89.2%, which is better than that with 1 M aq HCl solution (Table 2, entry 2 vs 8) and much better than that with 1 M aq HBF_4 as additive (Table 2, entry 4 vs 8). To eliminate the possibility that mixed counterions may have a complex effect on the enantioselectivity, [RuBr(benzene)(*S*)-SunPhos]Br was synthesized and applied as catalyst, and essentially no enantiomeric excess improvement was observed (Table 2, entry 8 vs 16), while [RuCl-(cymene)(*S*)-SunPhos]Cl gave decreased ee (Table 2, entry 15).

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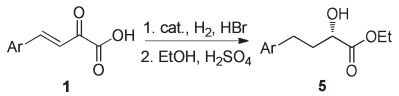
TABLE 3. Asymmetric Hydrogenation of 1 with [RuCl(benzene)(*S*)-SunPhos]Cl[a]



entry	substrate	ee (%)[b]	configuration[c]
1	C_6H_5 (**1a**)	89.2	(*S*)
2	4-Me-C_6H_4 (**1b**)	89.2	(*S*)
3	4−F-C_6H_4 (**1c**)	85.4	(*S*)
4	4−Cl-C_6H_4 (**1d**)	87.6	(*S*)
5	4−Br-C_6H_4 (**1e**)	87.6	(*S*)
6	4-$MeOC_6H_4$ (**1f**)	89.4	(*S*)
7	3−Cl-C_6H_4 (**1g**)	87.3	(*S*)
8	2,4-Cl_2−C_6H_3 (**1h**)	88.2	(*S*)
9	benzo[*d*][1,3]dioxol-5-yl (**1i**)	89.5	(*S*)

[a]All reactions were carried out under 400 psi of hydrogen with a substrate (1 mmol) concentration of 0.20 M in THF at 90 °C for 20 h; substrate/catalyst/1 M HBr aq = 100/1/6, conversion = 100%. [b]Values of corresponding esters **5**. [c]The configuration was determined to be *S* by comparing the specific rotation with reported data.[5]

Trace of pure water also plays an important role in promoting the enantioselectivity (Table 2, entry 12 vs 13); it gives a comparable result to that when 1 M aq HBr is used as additive. To make it clear whether the acidic condition or the aqueous condition is more important in achieving better enantioselectivity,[9] anhydrous HBr was employed as additive. To our surprise, the reaction gave much lower ee than when water was used as additive (Table 2, entry 20). The addition of water also improved hydrogenation rate, but the combination of Brønsted acid and water is superior to either of them in terms of reaction rate and enantioselectivity.

When Binap was used as ligand, the enantiomeric excess dropped as low as 48.0% (Table 2, entry 17); C_3-tunephos and structurally related SegPhos gave similar results as Sunphos, and products with 84.0 and 84.8% ee, respectively, were obtained (Table 2, entries 18 and 19).

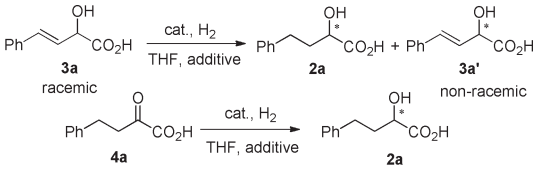
On the basis of these results, the optimized reaction conditions were therefore set as follows: 1 mol % of [RuCl-(benzene)(*S*)-SunPhos]Cl as the catalyst, 6 mol % of 1 M aqueous HBr as the additive, THF as the solvent with a substrate concentration of 0.2 M under 400 psi of H_2 at 90 °C.

Under the optimized reaction conditions, a series of (*E*)-2-oxo-4-arylbut-3-enoic acids were hydrogenated using [RuCl-(benzene)(*S*)-SunPhos]Cl as catalyst (Table 3). Judging from the results, although the influence is not remarkable, substrates with electron-donating substituents gave better enantioselectivities than substrates with electron-withdrawing substituents; steric factor of the aromatic ring seems to be not important on the enantioselectivities.

To investigate whether the C=C double bond in **3a** could be isomerized into its corresponding saturated α-keto acid, 2-oxo-4-phenylbutanoic acid, before hydrogenation, some control hydrogenation reactions were conducted under different reaction conditions, which provided further insight into the reaction pathways. The results are summarized in Table 4.

Hydrogenation of racemic **3a** was conducted with [RuCl(benzene)(*S*)-SunPhos]Cl as catalyst in the presence

TABLE 4. Asymmetric Hydrogenation of 3a and 4a[a]



entry	substrate	additive	time (h)	ee (%)[b] (configuration[c])
1	**3a**	1 M HCl aq	20	13.0 (*R*)
2	**3a**	1 M HBr aq	20	21.2 (*R*)
3	**3a**	1 M HI aq	20	23.0 (*R*)
4	**4a**	1 M HCl aq	5	89.3 (*S*)
5	**4a**	1 M HBr aq	5	91.8 (*S*)
6	**4a**	1 M HI aq	5	91.4 (*S*)
7	**4a**	1 M HBr aq	10	90.1[d]/99.0[e] (*S*)

[a]Unless otherwisely noted, all reactions were carried out under 400 psi of hydrogen with a substrate (1 mmol) concentration of 0.20 M in THF, substrate/catalyst/additive = 100/1/6. [b]Determined by HPLC on a Chiralpak OD-H column after transferring acids to esters. [c]The configuration was determined by comparing the specific rotation with reported data. [d]Substrate/catalyst = 2000/1 at 20 mmol scale. [e]Enantiomeric excess value after upgrading.

of hydrochloric acid. The reaction time was intentionally set short to detect the isomerized product and to analyze the enantiomeric excess of the product and the unreacted starting material. Both the starting material and the product are nonracemic; unfortunately, we did not detect any isomerized product, 2-oxo-4-phenylbutanoic acid.[10] From the data (Table 4, entries 1−3) obtained, the reaction is apparently not a kinetic resolution reaction; otherwise, the enantiomeric excess of the product will be 0 with complete conversion of the starting material. These results imply that the hydrogenation of **3a** is not a purely direct hydrogenation reaction of the C=C bond; isomerization of **3a** to **4a** is probably one of the pathways, which is not rare in ruthenium-catalyzed reactions.[11] The results in Table 4 (entries 4−6) showed that the reduction of **4a** is much faster than those of **1a** and **3a**; therefore, it is reasonable that we have not detected any **4a** in the hydrogenation of racemic **3a**.

On the basis of the observed results, we proposed the reaction pathways from **1a** to **2a** as follows (Scheme 1): reduction of **1a** to give **3a** is a fast step, while the reduction of **3a** to **2a** is relatively slow but faster than the isomerization of **3a** to **4a**. Although we could not rule out the possibility of the hydrogenation of the C=C bond prior to the hydrogenation of the C=O bond in **2a**,[12] we believe that the reduction, if there is any, should be very slow.

In conclusion, we have presented an effective strategy for the conversion of inexpensive (*E*)-2-oxo-4-arylbut-3-enoic

(9) After reviewing our manuscript, one reviewer kindly suggested we do more experiments to make it clear whether the counterion or the aqueous reaction condition plays a more important role in achieving high enantioselectivity.

(10) If the hydrogenation was terminated after 5 h, the conversion is 25%. The product **2a** (*S*) was 35.4% ee, and the unreacted starting material **3a′** (*R*) was 19.0% ee.

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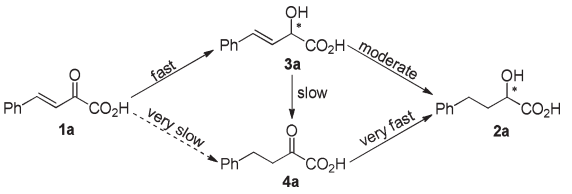
SCHEME 1. Reaction Pathways from 1a to 2a



acids directly into optically active 2-hydroxy-4-arylbutanoic acids employing a homogeneous Ru-Sunphos catalyst. Further investigation has proven that the hydrogenation proceeds via three possible reaction pathways. The enantiomeric excesses of 2-hydroxy-4-phenylbutanoic acids were easily upgraded to 99% after a single recrystallization. This reaction has indicated a potential procedure for the preparation of the useful intermediates for ACE inhibitors.

Experimental Section

General Procedure for the Preparation of (*E*)-2-Oxo-4-arylbut-3-enoic acid 1: To a stirred solution of benzaldehyde (21.2 g, 0.20 mol) in methanol (15 mL) was added pyruvic acid (17.2 g, 0.20 mmol) at 0 °C under nitrogen. A solution of KOH (16.8 g, 0.30 mmol) in methanol (60 mL) was added dropwise to keep the reaction temperature below 15 °C; after the addition of 2/3 of the alkali, the rest of the alkali was added in one portion before precipitation of potassium pyruvate could occur. Then the ice bath was removed, and the temperature of the reaction mixture increased from 20 to 35−40 °C. The reaction mixture was stirred at this temperature for 3 h and then cooled to 10 °C and maintained at this temperature for 10 h. The solid precipitated out was filtered on a Buchner funnel under suction and washed with chilled methanol (75 mL) followed by diethyl ether (75 mL) to afford potassium 2-oxo-4-phenylbut-3-enoate as a yellow solid (38.3 g, 89%).

A saturated solution of the salt at 40 °C was poured into a rapidly stirred solution of hydrochloric acid (2 M), and the resulting benzylidenepyruvic acid precipitated from water as a hydrate. The hydrated product was dissolved in benzene after azotropic removal of water with benzene, and product (**1a**) was obtained (26.5 g, 84%) by cooling the benzene solution to room temperature.

Typical Procedure for the Asymmetric Hydrogenation of 1: [RuCl(benzene)(*S*)-SunPhos]Cl (40 mg, 0.04 mmol) was dissolved in degassed THF (20 mL) containing 1 M aq HBr (240 μL), and then the solution was put into four vials equally. To these vials were introduced (*E*)-2-oxo-4-arylbut-3-enoic acids (1 mmol), and then the vials were taken into an autoclave. The autoclave was purged three times with H_2, and the pressure of H_2 was set to 400 psi. The autoclave was stirred under specified reaction conditions. After being cooled to ambient temperature and release of hydrogen, the autoclave was opened and the solvent was evaporated. The residue was refluxed in EtOH with a drop of concentrated sulfuric acid for 5 h, and the ester was passed through a short pad of silica gel with petroleum ether and ethyl acetate before the ee was determined by HPLC.

Procedure for the Improvement of Enantiomeric Purity. Hydrogenation reaction of **1a** was run at 20 mmol scale. The reaction solvent was evaporated under reduced pressure at 40 °C, and then the residue was dissolved in ethyl acetate (20 mL) and washed with brine (5 mL × 3). After the organic layer was separated and dried over $MgSO_4$, the solvent was evaporated to give the crude product which was recrystallized from 1,2-dichloroethylene (20 mL) to give **2a** (3.0 g, 85%) with an enantiomeric purity of 99%.

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Supporting Information Available: NMR and HPLC data of compounds **1**, **2a**, **3a**, **4a**, **5**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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