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Highly enantioselective hydrogenation of 2-oxo-4-arybutanoic acids to 2-hydroxy-4-arylbutanoic acids

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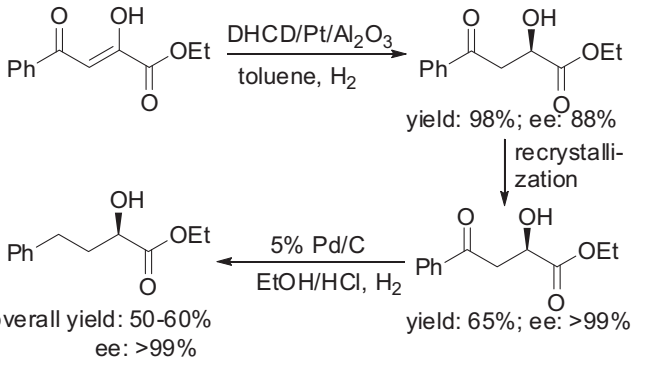
ABSTRACT

The Ru-catalyzed asymmetric hydrogenation of 2-oxo-4-arybutanoic acids to afford 2-hydroxy-4-arybutanoic acids was accomplished by employing SunPhos as chiral ligand and 1 M aq HBr as additive. The high enantioselectivities (88.4%–92.6% ee) and efficiency (TON=10,000, TOF=300 h^{-1}) make this method efficient for the synthesis of an important intermediate, (*R*)-2-hydroxy-4-phenylbutanoic acid, for ACE inhibitors.

1. Introduction

The optically pure α-hydroxy acids and their derivatives are important chiral structural units, which have been used as a convenient building block in organic synthesis of a wide variety of natural products and biologically active molecules.[1] For instance, ethyl (*R*)-2-hydroxy-4-phenylbutyrate is an intermediate of a variety of commercially angiotensin-converting enzyme (ACE) inhibitors, such as benazepril, cilazapril and delapril hydrochloride.[2] Some synthetic routes to ethyl (*R*)-2-hydroxy-4-phenylbutyrate have been developed, including classical kinetic resolution of chemical or enzyme,[3] catalytic enantioselective reduction of its prochiral precursor 2-oxo-4-phenylbutanoic acid or its ethyl ester by microbe and enzyme,[4] multistep asymmetric synthesis[5] and heterogeneous asymmetric hydrogenation.[6] Among these strategies, asymmetric hydrogenation of the corresponding α-keto acid and its derivatives to give enantiomerically pure ethyl (*R*)-2-hydroxy-4-phenylbutyrate is most practical and powerful.[1]

Recently, some significant progresses have been achieved in the synthesis of optically pure 2-hydroxy-4-phenylbutanoic acid and its ester by transition metal-catalyzed asymmetric hydrogenation. Hydrogenation of ethyl 2-hydroxy-4-oxo-4-phenyl-2-butenoate with heterogeneous platinum/Al_2O_3 catalyst modified with dihydrocinchonidine (DHCD) to give the product with up to 88% ee, on 100–200 g scale with 50–60% yield and >99% ee of the final product, but the repeatability and future hydrogenation of the carbonyl group to methylene group with Pd/C make the method less attractive (Scheme 1);[7] Rh complexes (AMPP,[8] BoPhoz[9]) and Ru complexes (MandyPhos,[10] TaniaPhos,[10] PQ-Phos,[11,12b] TunePhos[12] and etc.[13]) were applied as catalysts in the asymmetric hydrogenation of ethyl 2-oxo-4-phenylbutanoate, fair to excellent enantioselectivities were obtained, however, α-keto esters are unstable substrates for asymmetric hydrogenation, which makes it difficult to repeat even under delicately optimized reaction conditions.[7a,14]



Scheme 1. DHCD/Pt/Al_2O_3 catalyzed asymmetric hydrogenation of ethyl 2-hydroxy-4-oxo-4-phenyl-2-butenoate.[7]

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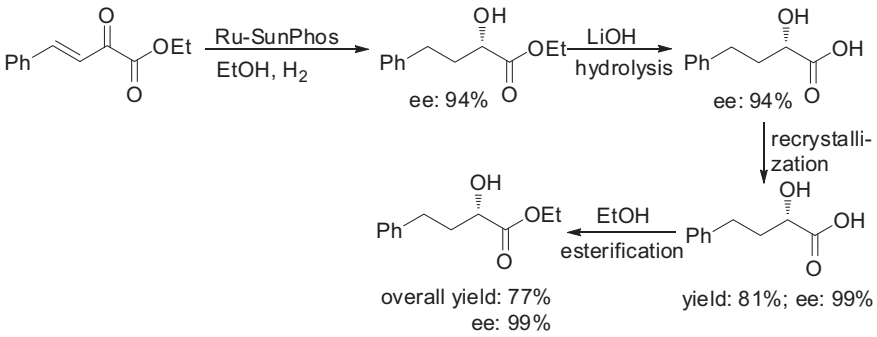
To solve this problem, we chose (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate as the hydrogenation substrate and Ru-SunPhos complex as catalyst, an excellent enantioselectivity (up to 94% ee, TON up to 2000) was obtained. Both catalytic efficiency and repeatability were improved, however, hydrolysis and recrystallization of the resulting acid were still needed to upgrade the enantiomeric purity of the product (Scheme 2).[15]



Scheme 2. Asymmetric hydrogenation of ethyl 2-oxo-4-phenylbut-3-enoate with Ru-SunPhos catalyst.[15]

Therefore, we have designed a direct conversion of (*E*)-2-oxo-4-phenylbut-3-enoic acid to corresponding optically pure saturated hydroxyl acid by asymmetric hydrogenation. Although α-keto acids and α-hydroxy acids usually serve as ligands, which compete with the counter anion of the catalyst and affect the enantioselectivity and/or reactivity of catalyst,[16] with the help of a Brønsted acid as additive, we succeeded in hydrogenating two unsaturations in the substrates and obtained hydroxy acids with good enantioselectivities.[17] Further investigation indicated that the hydrogenation did not proceed via a sequential hydrogenation of C=O and C=C double bonds, and the reduction of α-keto acids proceeded even faster. Therefore, an extensive investigation of asymmetric hydrogenation of 2-oxo-4-arylbutanoic acids was conducted.

2. Results and discussion

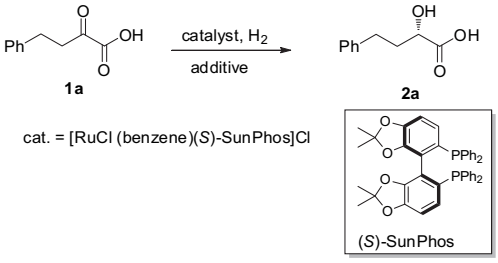
We first chose 2-oxo-4-phenylbutanoic acid **1a** as the substrate, employ [RuCl(benzene)(*S*)-SunPhos]Cl as catalyst, THF as solvent to examine the effects of the reaction temperature and H_2 pressure. The representative results are summarized in Table 1 (entries 1–5). The influence of temperature is dramatic, when the reaction was run at temperature lower than 50 °C, no reaction was observed; when the reaction was conducted at a temperature higher than 70 °C, the reaction rate was improved at a cost of scarifying enantioselectivity. H_2 pressure also impact a slight effect on the enantioselectivity (Table 1, entries 1 vs 4, 5), finally, the reaction condition was set at a H_2 pressure of 400 psi and reaction temperature of 70 °C.

In the hydrogenation of 2-oxo-4-aryl-3-butenoic acids, we employed aqueous solutions of Brønsted acids and Lewis acids as additives and found that not only enantioselectivities but also catalytic efficiency were improved,[17] we screened a number of commonly-used aqueous solutions of Brønsted as additives accordingly in the asymmetric hydrogenation of 2-oxo-4-phenylbutanoic acid, the results were also summarized in Table 1 (entries 6–17).

Addition of anhydrous hydrohalogenic acid (anhydrous HI was generated in situ with I_2 and hydrogen) resulted decrease of enantioselectivity (entries 6, 7); aqueous hydrohalogenic acid improved the enantioselectivity, and the ee was increased to 92.2% with catalytic amount of 1 M aq HBr. It implies that water plays an important role in affecting the enantioselectivity and activity of catalyst, however, addition of pure water gave even poorer ee (entry 11 vs entry 1). Addition of other aqueous Brønsted acid showed negligible effect on enantioselectivity (entries 12–17).

To examine the ligand effects, (*S*)-SunPhos, (*R*)-**L5**, (*R*)-**L6** and three commercially available chiral bidentate phosphines, (*S*)-Binap, (*S*)-C_3-TunePhos and (*S*)-SegPhos (Fig. 1) were screened under the same reaction conditions (Table 2). The catalyst was prepared similarly from $[Ru(benzene)Cl_2]_2$ and a diphosphine ligand by refluxing them in degassed EtOH/DCM, the results were summarized in Table 2. Unfortunately, of the ligands investigated, none gave better enantioselectivity. When structurally similar ligands were employed, such as (*S*)-C_3-TunePhos, (*S*)-SegPhos, (*R*)-**L5** and (*R*)-**L6**, similar ees have been observed (Table 2, entries 1–4); when Binap was applied as ligand, the enantioselectivity dropped as low as 45.6% (Table 2, entry 5).

Table 1
The effects of pressure, temperature and additive[a]



Entry	Additive	Press (psi)	Temp (°C)	Time (h)	ee[b] (%)
1	None	400	70	12	87.8
2	None	400	90	12	81.4
3	None	400	110	12	73.8
4	None	200	70	12	83.0
5	None	600	70	12	83.8
6	I_2	400	70	12	81.6
7	HBr (gas)	400	70	12	76.5[c]
8	1 M HCl aq	400	70	12	89.4
9	1 M HI aq	400	70	12	89.6
10	1 M HBr aq	400	70	12	92.2
11	H_2O	400	70	12	84.5[d]
12	1 M CF_3CO_2H aq	400	70	12	85.8
13	1 M CF_3SO_3H aq	400	70	12	89.2
14	1 M H_3BO_3 aq	400	70	12	86.2
15	1 M H_2SO_4 aq	400	70	12	86.2
16	1 M CSA aq	400	70	12	88.2
17	1 M HBF_4 aq	400	70	12	88.9

[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, substrate/catalyst/additive=200/1/12, conversion: >99%.
[b] ee values were determined by HPLC on a Chiralpak OD-H column after transferring acid **2a** to ester **3a**.
[c] HBr (6 mol %) gas in solvent.
[d] H_2O (60 μL).

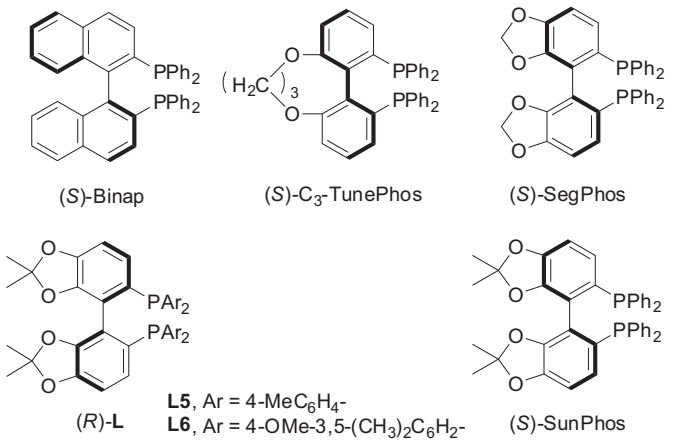


Fig. 1. Struture of chiral bidentate ligands.

Table 2
Catalytic asymmetric hydrogenation of **1a** with [RuCl(benzene)L]Cl[a]

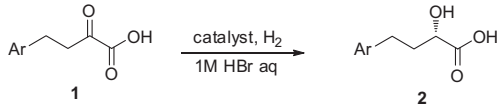
Entry	Ligand	ee[b] (%)	Config[c]
1	(*S*)-C$_3$-TunePhos	84.2	(*S*)
2	(*S*)-SegPhos	85.8	(*S*)
3	(*R*)-L5	86.7	(*R*)
4	(*R*)-L6	89.0	(*R*)
5	(*S*)-Binap	45.6	(*S*)
6	(*S*)-SunPhos	92.2	(*S*)

[a] Unless otherwisely noted, all reactions were carried out with a substrate (1 mmol) concentration of 0.20 M in a solvent for 12 h, 1 M HBr aq as the additive, substrate/catalyst/additive=200/1/12, conversion: >99%.
[b] ee values were determined by HPLC on a Chiralpak OD-H column after transferring acid **2a** to ester **3a**.
[c] The configuration was determined to be *S* or *R* by comparing the specific rotation with reported data.

Based on the results, the optimized reaction conditions were therefore set as the following: 1.0 mmol **1** as substrate, 0.5 mol % of [RuCl(benzene)(*S*)-SunPhos]Cl as the catalyst, 6 mol % of 1 M aq HBr as the additive, THF as the solvent with a substrate concentration of 0.2 M under 400 psi of H_2 at 70 °C.

Under the optimized reaction conditions, a variety of 2-oxo-4-arylbutanoic acids were examined for the hydrogenation reaction with [RuCl(benzene)(*S*)-SunPhos]Cl as the catalyst (Table 3).

Table 3
Asymmetric hydrogenation of **1** with [RuCl(benzene)(*S*)-SunPhos]Cl[a]



1 2

Entry	Substrate	ee[b] (%)	Config[c]
1	C_6H_5 (**1a**)	92.2	(*S*)
2	2-F–C_6H_4 (**1b**)	88.4	(*S*)
3	3-F–C_6H_4 (**1c**)	89.2	(*S*)
4	4-F–C_6H_4 (**1d**)	89.9	(*S*)
5	4-Cl–C_6H_4 (**1e**)	92.6	(*S*)
6	4-Br–C_6H_4 (**1f**)	90.8	(*S*)
7	2,4-Cl_2–C_6H_3 (**1g**)	92.6	(*S*)
8	4-Me–C_6H_4 (**1h**)	91.9	(*S*)
9	4-MeOC_6H_4 (**1i**)	92.0	(*S*)
10	Benzo[*d*][1,3]dioxol-5-yl (**1j**)	92.4	(*S*)
11	C_6H_5 (**1a**)	91.6[d]	(*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 70 °C for 20 h. Substrate/catalyst/1 M HBr aq=200/1/12, conversion: >99%.
[b] ee values of corresponding esters **3**.
[c] The configuration was determined to be *S* by comparing the specific rotation with reported data.
[d] The reaction was run at substrate/catalyst=10,000, substrate: 20 mmol, conversion: >99%.

Although the substitution pattern of the aryl did not impact a remarkable influence (88.4–92.6% ee), the substrates with electron-donating substituents generally gave a little better enantioselectivities (Table 3, entries 5–10 vs entries 2–4). It is worth noting that when the substrate to catalyst ratio was increased to 10,000, the asymmetric hydrogenation complete in 30 h with neglectable enantioselectivity decrease (Table 3, entry 11).

As was reported in our previous publications,[15,17] the resulted acids can be easily upgraded to >99.0% ee by simple recrystallization, and this method provides a most direct and efficient way up to now in asymmetric hydrogenation reactions to make optically pure ethyl 2-hydroxy-4-phenylbutanoate.

3. Conclusion

In conclusion, we have presented an effective strategy for the conversion of inexpensive 2-oxo-4-arylbutanoic acids directly into optically active 2-hydroxy-4-arylbutanoic acids by asymmetric hydrogenation. And up to 92.6% ee has been achieved with [RuCl(benzene)(*S*)-SunPhos]Cl as the catalyst and 1 M aq HBr as the additive. The ee of 2-hydroxy-4-phenylbutanoic acid was easily upgraded to 99% after a single recrystallization. The application of this procedure for the large scale preparation of ethyl 2-hydroxy-4-phenylbutanoate is in progress.

4. Experimental section

4.1. General procedure for the preparation of 2-oxo-4-arylbutanoic acids 1

2-Oxo-4-arylbutanoic acids were synthesized according to the literatures.[18]

*4.1.1. Compound **1a**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.18 (m, 5H), 3.23 (t, *J*=7.6 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 161.8, 140.2, 128.9, 128.6, 126.6, 40.4, 29.0.

*4.1.2. Compound **1b**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.18 (m, 2H), 7.08–6.99 (m, 2H), 3.27 (t, *J*=7.2 Hz, 2H), 3.00 (t, *J*=7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5, 161.4 (d, *J*=209.2 Hz), 160.0, 130.8 (d, *J*=4.5 Hz), 128.6 (d, *J*=7.7 Hz), 126.6 (d, *J*=15.8 Hz), 124.3 (d, *J*=5.2 Hz), 115.5 (d, *J*=21.9 Hz), 38.2, 22.9 (d, *J*=3.5 Hz).

*4.1.3. Compound **1c**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.24 (m, 1H), 6.99–6.90 (m, 3H), 3.30 (t, *J*=7.5 Hz, 2H), 2.99 (t, *J*=7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 163.0 (d, *J*=244.1 Hz), 160.2, 142.2 (d, *J*=7.2 Hz), 130.2 (d, *J*=8.3 Hz), 124.1 (d, *J*=7.5 Hz), 115.5 (d, *J*=21.1 Hz), 113.7 (d, *J*=24.3 Hz), 39.1, 28.7 (d, *J*=1.7 Hz).

*4.1.4. Compound **1d**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.15 (m, 2H), 7.00–6.96 (m, 2H), 3.27 (t, *J*=7.4 Hz, 2H), 2.96 (t, *J*=7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 161.8 (d, *J*=208.4 Hz), 160.4, 135.3 (d, *J*=4.0 Hz), 129.9 (d, *J*=8.8 Hz), 115.5 (d, *J*=10.7 Hz), 39.7, 28.2. HRMS: calculated for $C_{10}H_9FO_3$ $(M-H)^+$: 195.0457, found: 195.0471.

*4.1.5. Compound **1e**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2H), 7.15–7.13 (m, 2H), 3.28 (t, *J*=7.3 Hz, 2H), 2.96 (t, *J*=7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 160.3, 138.1, 132.4, 129.8, 128.9, 39.3, 28.3.

*4.1.6. Compound **1f**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.41 (m, 2H), 7.16–6.82 (m, 2H), 3.29 (t, *J*=7.4 Hz, 2H), 2.97 (t, *J*=7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 160.9, 138.8, 131.8, 130.2, 120.4, 39.6,

28.4. HRMS: calculated for $C_{10}H_9BrO_3$ $(M-H)^+$: 254.9657, found: 254.9661.

4.1.7. Compound ***1g***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 3H), 3.30 (t, J=7.4 Hz, 2H), 3.06 (t, J=7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 159.9, 135.8, 134.7, 133.3, 131.6, 129.6, 127.45, 37.5, 26.6. HRMS: calculated for $C_{10}H_8Cl_2O_3$ $(M-H)^+$: 244.9772, found: 244.9767.

4.1.8. Compound ***1h***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (m, 4H), 3.25 (t, J=7.4 Hz, 2H), 2.94 (t, J=7.4 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 161.4, 136.9, 136.0, 129.3, 128.26, 40.2, 28.6, 21.0.

4.1.9. Compound ***1i***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.11 (m, 2H), 6.85–6.82 (m, 2H), 3.79 (s, 3H), 3.25 (t, J=7.4 Hz, 2H), 2.93 (t, J=7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 160.8, 158.0, 132.0, 129.4, 114.1, 55.4, 39.9, 28.1.

4.1.10. Compound ***1j***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74–6.65 (m, 3H), 5.93 (s, 2H), 3.24 (dd, J=9.1, 5.7 Hz, 2H), 2.91 (t, J=7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 160.2, 147.8, 146.2, 133.5, 121.3, 108.9, 108.5, 101.0, 39.7, 28.8. HRMS: calculated for $C_{11}H_{10}O_5$ $(M-H)^+$: 221.0450, found: 221.0444.

4.2. Typical procedure for the asymmetric hydrogenation of 1

The catalyst [RuCl(benzene)(*S*)-SunPhos]Cl (40 mg, 0.04 mmol) was dissolved in degassed THF (40 mL) containing 1 M of aq HBr (480 μL), and then the solution was put into eight vials equally. To these vials 2-oxo-4-arylbutanoic acids **1** (1 mmol) were introduced, 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 **2** were refluxed in EtOH with a drop of concentrated sulfuric acid for 5 h, and the corresponding esters were passed through a short pad of silica gel with petroleum ether and ethyl acetate before the ees were determined by HPLC.

4.2.1. Compound ***2a***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.18 (m, 5H), 4.27 (dd, J=4.0, 8.0 Hz, 1H), 2.80 (t, J=8.0 Hz, 2H), 2.23–2.14 (m, 1H), 2.05–1.97 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 140.9, 128.8, 128.7, 126.4, 69.7, 35.9, 31.2.

4.2.2. Compound ***2b***. ^{1}H NMR (400 MHz, DMSO) δ 7.26–7.16 (m, 2H), 7.07–6.99 (m, 2H), 4.27 (dd, J=4.0, 8.0 Hz, 1H), 2.84 (t, J=8.0 Hz, 2H), 2.20–2.16 (m, 1H), 2.05–1.98 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 160.7 (d, J=241.4 Hz), 130.9 (d, J=5.2 Hz), 128.2 (d, J=16.2 Hz), 128.1 (d, J=4.1H), 124.5 (d, J=3.6 Hz), 115.2 (d, J=20.9 Hz), 69.2, 35.5, 24.4 (d, J=3.1 Hz). HRMS: calculated for $C_{10}H_{11}FO_3$ $(M-H)^+$: 197.0603, found: 197.0606.

4.2.3. Compound ***2c***. ^{1}H NMR (400 MHz, DMSO) δ 7.35–7.30 (m, 1H), 7.05–6.98 (m, 3H), 3.91 (dd, J=8.4, 4.1 Hz, 1H), 2.69 (t, J=7.9 Hz, 2H), 1.95–1.89 (m, 1H), 1.85–1.77 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 162.3 (d, J=242.5 Hz), 144.6 (d, J=7.2 Hz), 130.2 (d, J=8.3 Hz), 124.5 (d, J=1.9H), 115.1 (d, J=20.7 Hz), 112.7 (d, J=20.8 Hz), 68.9, 35.5, 30.4 (d, J=62.9 Hz). HRMS: calculated for $C_{10}H_{11}FO_3$ $(M-H)^+$: 197.0603, found: 197.0601.

4.2.4. Compound ***2d***. ^{1}H NMR (400 MHz, DMSO) δ 7.26–7.21 (m, J=8.0, 6.4 Hz, 2H), 7.13–7.08 (m, 2H), 3.91 (dd, J=8.4, 4.1 Hz, 1H), 2.65 (t, J=7.9 Hz, 2H), 1.94–1.86 (m, 1H), 1.83–1.76 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 175.9, 160.8 (d, J=239.7 Hz), 137.7 (d, J=2.8 Hz), 130.2 (d, J=7.2 Hz), 115.1 (d, J=21.0 Hz), 69.0, 35.9, 30.2.

4.2.5. Compound ***2e***. ^{1}H NMR (400 MHz, DMSO) δ 7.35–7.32 (m, 2H), 7.25–7.21 (m, 2H), 3.90 (dd, J=8.4, 4.2 Hz, 1H), 2.66 (t, J=7.9 Hz, 2H), 1.95–1.79 (m, 1H), 1.78–1.74 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 140.6, 130.5, 130.3, 120.3, 68.9, 35.6, 30.3.

4.2.6. Compound ***2f***. ^{1}H NMR (400 MHz, DMSO) δ 7.48–7.45 (m, 2H), 7.19–7.17 (m, 2H), 3.90 (dd, J=8.4, 4.1 Hz, 1H), 2.64 (t, J=7.9 Hz, 2H), 1.95–1.86 (m, 1H), 1.83–1.74 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 176.4, 141.6, 131.8, 131.3, 119.5, 69.5, 36.2, 30.9. HRMS: calculated for $C_{10}H_{11}BrO_3$ $(M-H)^+$: 256.9813, found: 256.9819.

4.2.7. Compound ***2g***. ^{1}H NMR (400 MHz, DMSO) δ 7.56 (d, J=1.0 Hz, 1H), 7.37 (t, J=4.9 Hz, 2H), 3.96 (dd, J=8.2, 4.2 Hz, 1H), 2.77 (t, J=8.0 Hz, 2H), 1.95–1.88 (m, 1H), 1.83–1.74 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 175.6, 138.1, 133.9, 131.9, 131.5, 128.7, 127.4, 69.0, 33.7, 28.4. HRMS: calculated for $C_{10}H_{10}Cl_2O_3$ $(M-H)^+$: 246.9929, found: 246.9920.

4.2.8. Compound ***2h***. ^{1}H NMR (400 MHz, DMSO) δ 7.08–7.00 (m, 4H), 3.88 (dd, J=8.4, 4.1 Hz, 1H), 2.60 (t, J=7.9 Hz, 2H), 2.24 (s, 3H), 1.91–1.82 (m, 1H), 1.79–1.70 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 175.9, 138.5, 134.7, 1289.0, 128.3, 69.0, 36.0, 30.6, 20.7.

4.2.9. Compound ***2i***. ^{1}H NMR (400 MHz, DMSO) δ 7.12 (d, J=8.6 Hz, 2H), 6.84 (dd, J=9.1, 2.5 Hz, 2H), 3.90 (dd, J=8.3, 4.1 Hz, 1H), 3.72 (s, 3H), 2.60 (t, J=7.8 Hz, 2H), 1.91–1.83 (m, 1H), 1.89–1.71 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 176.0, 147.3, 145.4, 135.4, 121.2, 108.9, 108.2, 100.7, 69.0, 36.1, 30.7.

4.2.10. Compound ***2j***. ^{1}H NMR (400 MHz, DMSO) δ 6.77 (dd, J=14.3, 4.6 Hz, 2H), 6.65 (dd, J=7.9, 1.6 Hz, 1H), 5.96 (s, 2H), 3.94–3.83 (m, 1H), 2.66–2.53 (m, 2H), 1.94–1.81 (m, 1H), 1.82–1.66 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 176.0, 147.3, 145.4, 135.4, 121.2, 108.9, 108.2, 100.7, 69.0, 36.1, 30.7. HRMS: calculated for $C_{11}H_{12}O_5$ $(M-H)^+$: 223.0606, found: 223.0606.

4.3. 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 (50 mL) and washed with brine (20 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, 83%) with enantiomeric purity of 99%.

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Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR spectra of all substrates and hydrogenation products, and copies of HPLC data of the corresponding chiral esters.

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.06.071.

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