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Ru-Catalyzed Asymmetric Hydrogenation of γ-Heteroatom Substituted β-Keto Esters

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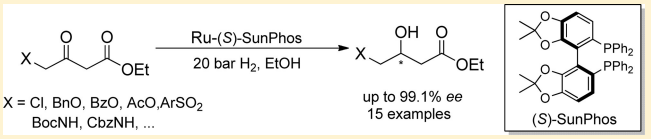
Supporting Information

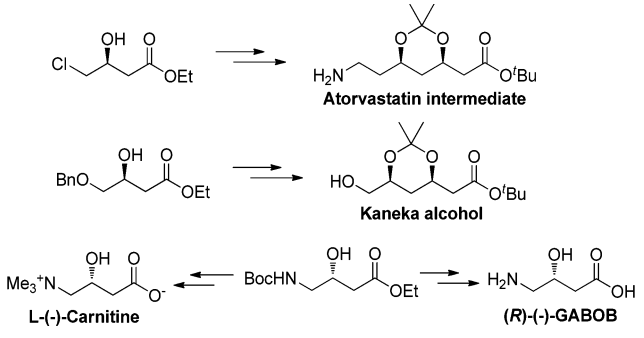
ABSTRACT: A series of enantiomerically pure γ-heteroatom substituted β-hydroxy esters were synthesized with high enantioselectivities (up to 99.1% ee) by hydrogenation of γ-heteroatom substituted β-keto esters in the presence of Ru-(*S*)-SunPhos catalyst. These asymmetric hydrogenations provide key building blocks for a variety of naturally occurring and biologically active compounds.



INTRODUCTION

Catalytic asymmetric hydrogenation, one of the most practical and efficient methods for the synthesis of chiral building blocks, has attracted much attention in both academia and industry.[1] Enantiomerically pure γ-heteroatom substituted β-hydroxy esters are useful building blocks for the synthesis of a variety of naturally occurring and biologically active compounds.[2] In particular, γ-heteroatom substituted β-hydroxy esters serve as key precursors of Atorvastatin chiral side-chain,[2a] Kaneka alcohol,[2b] L-(−)-carnitine, and (*R*)-(−)-GABOB[2c,d] ((*R*)-γ-amino-β-hydroxybutyric acid) (Scheme 1). Accordingly, the search for efficient, highly enantioselective and practical approaches to synthesize optically pure γ-heteroatom substituted β-hydroxy esters is of great significance.

Scheme 1. Selected Pharmaceutical Applications of Optically Pure γ-Heteroatom Substituted β-Hydroxy Esters



The asymmetric hydrogenation of β-keto esters catalyzed by ruthenium complexes with chiral phosphine ligands has been extensively studied.[3] Following the pioneering work of Noyori's use of BINAP (2,2′-bis(diphenylphosphosino)-1,1′-binaphthyl), many other effective chiral diphosphines have been developed for this important transformation.[4] In contrast, there are limited substrates being investigated, usually restricted to simple β-alkyl or aryl substituents. Until recently, several investigations involved substrates bearing adjacent heteroatoms, such as a benzyloxyl group,[5] an alkoxyl group,[6] halogen atoms,[7] or carbonylamino groups,[8] in the vicinity of the keto group. Up to now, γ-heteroatom substituted β-keto esters were still relatively intractable substrates as the competitive coordinations of multiple coordinating groups to the catalyst.[9a] Therefore, the asymmetric hydrogenation of β-keto esters bearing adjacent functional coordinating groups is still a challenging work.

Recently, we designed new biaryl phosphine ligands and explored their applications in ruthenium-catalyzed asymmetric hydrogenation of various functionalized ketones and their applications in organic synthesis.[9] In this paper, we disclose a general and highly enantioselective hydrogenation reaction of γ-heteroatom substituted β-keto esters.

RESULTS AND DISCUSSION

In order to systematically study the impact of the adjacent heteroatoms on asymmetric hydrogenation of γ-heteroatom substituted β-keto esters, four representative substrates were screened simultaneously to accelerate the optimization process: γ-benzyloxyl substituted β-keto ester (**1a**), the resulting product of which could be used to synthesize the chiral side-chain of Stains;[2b] γ-benzoate substituted β-keto ester (**1d**), the reduced product of which is the main precursor of optically pure 3-hydroxy γ-butyrolactone;[10] γ-phenylsulfonyl substituted β-keto ester (**1j**), the resulting product of which could be further transformed into chiral allylic alcohol by reacting with aldehyde/ketone via Julia reaction;[11] γ-*N*-carbobenzoxy substituted β-keto ester (**1m**), the hydrogenated product of which is a useful intermediate to prepare L-(−)-carnitine and (*R*)-(−)-GABOB.[2d]

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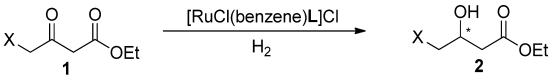
The catalyst (RuCl(benzene)(*S*)-SunPhos)Cl was readily prepared from $(RuCl_2(benzene))_2$ and (*S*)-SunPhos by refluxing them in degassed ethanol/dichloromethane for 1 h and then drying them under reduced pressure.[9] The asymmetric hydrogenation was carried out under 20 bar of H_2, 70 °C in EtOH for 16 h with 1 mol % of (RuCl(benzene)-(*S*)-SunPhos)Cl. We obtained full conversions and high enantioselectivities of the desired product **2a** (98.2% ee), **2d** (97.3% ee), **2j** (97.9% ee), and **2m** (97.1% ee) (Table 1, entry 1). Additionally, three commercially available chiral bidentate ligands, (*S*)-SegPhos, (*S*)-C3-TunePhos, and (*R*)-BINAP, were also tested under the same reaction conditions (Figure 1).

Table 1. Asymmetric Hydrogenation of γ-Heteroatom Substituted β-Keto Esters 1 with (RuCl(Benzene)L)Cl[a]



X = BnO, **1a**; BzO, **1d**; $PhSO_2$, **1j**; CbzNH, **1m**

entry[b]	ligands	1a	1d	1j	1m
1	(*S*)-SunPhos	98.2	97.3	97.9	97.1
2	(*S*)-SegPhos	98.6	97.6	97.3	97.3
3	(*S*)-C3-TunePhos	98.7	97.3	96.8	97.5
4	(*R*)-BINAP	95.4	92.0	91.0	94.6

[a]All reactions were carried out with a substrate (1.0 mmol) concentration of 0.4 M in EtOH under 20 bar of H_2 and at 70 °C for 16 h, substrate/$(RuCl_2(benzene))_2$/ligand =100/0.5/1.1. Conversion: 100%. [b]Values of ee were determined by HPLC on a Chiralpak IB-3 column.

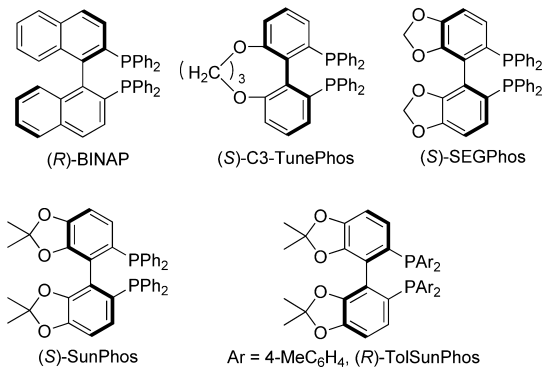
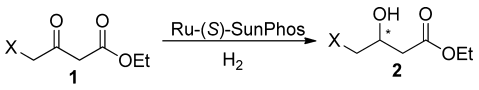


Figure 1. Structure of chiral bidentate ligands.

Similar results were obtained when (*S*)-SegPhos and (*S*)-C3-TunePhos were used as ligands (Table 1, entries 2, 3). However, enantioselectivities of all the products, **2a** (95.4% ee), **2d** (92.0% ee), **2j** (91.0% ee), and **2m** (94.6% ee), were lower when (*R*)-BINAP was employed (Table 1, entry 4).

We next performed the hydrogenation under different temperatures (50, 70, and 90 °C) at 20 bar of H_2 (Table 2, entries 1–3). All substrates were reduced with high ee values under selected temperatures, but very close ee values were observed. Values of ee at 70 °C were only slightly higher than those under other temperatures (except for **1a**, higher ee was observed at 90 than at 70 °C), which was then selected as the optimized temperature. The effect of different hydrogen pressure (10 and 50 bar H_2) was then investigated at 70 °C with (*S*)-SunPhos (Table 2, entries 4, 5 vs 2). The results of slightly lower ee values illustrated that lower or higher pressure

Table 2. Effects of Temperature and Hydrogen Pressure[a]



X = BnO, **1a**; BzO, **1d**; $PhSO_2$, **1j**; CbzNH, **1m**

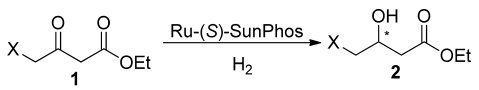
entry[b]	T (°C)/P (bar)	1a	1d	1j	1m
1	50/20	98.2	96.0	96.7	96.9
2	**70/20**	**98.2**	**97.3**	**97.9**	**97.1**
3	90/20	98.6	96.7	97.2	97.1
4	70/10	98.1	96.7	97.3	96.8
5	70/50	98.7	96.9	97.4	96.9

[a]All reactions were carried out with a substrate (1.0 mmol) concentration of 0.4 M in EtOH for 18 h, substrate/$(RuCl_2(benzene))_2$/(*S*)-SunPhos =100/0.5/1.1. Conversion: 100%. [b]Values of ee were determined by HPLC on a Chiralpak IB-3 column.

may have a slightly negative influence on the enantioselectivity (except for **1a**, higher ee was observed under 50 bar). In order to establish general reaction conditions for asymmetric hydrogenation of γ-heteroatom substituted β-keto esters, we chose the initial hydrogen pressure of 20 bar and reaction temperature of 70 °C throughout of this study.

A comparison study with other ruthenium sources was also carried out (Table 3). The hydrogenation results catalyzed by $(RuCl_2(benzene))_2$ were comparable to those obtained with $(RuCl_2(p\text{-cymene}))_2$. Although full conversions and high ee values were obtained with both ruthenium precatalysts, they showed different enantioselectivities to different substrates. For **1a**, **1d**, and **1j**, $(RuCl_2(benzene))_2$ gave lower ee than $(RuCl_2(p\text{-cymene}))_2$ did. But for **1m**, the trend was reversed: when the precatalyst $(RuCl_2(benzene))_2$ was replaced by $(RuCl_2(p\text{-cymene})_2$, ee dropped from 97.1 to 91.6%. Therefore, $(RuCl_2(p\text{-cymene}))_2$ is applied for the hydrogenation of substrates bearing alkyloxy groups, carboxylate groups, and arylsulfonyl groups in the vicinity of the keto group, whereas $(RuCl_2(benzene))_2$ for γ-carbamate substituted β-keto esters.

Table 3. Effects of Ruthenium Source[a]



X = BnO, **1a**; BzO, **1d**; $PhSO_2$, **1j**; CbzNH, **1m**

entry[b]	Ru source	1a	1d	1j	1m
1	$(RuCl_2(benzene))_2$	98.2	97.3	97.9	97.1
2	$(RuCl_2(p\text{-cymene}))_2$	99.1	97.7	98.2	91.6

[a]All reactions were carried out with a substrate (1.0 mmol) concentration of 0.4 M in EtOH under 20 bar of H_2 and at 70 °C for 18 h, substrate/Ru/(*S*)-SunPhos =100/0.5/1.1. Conversion: 100%. [b]Values of ee were determined by HPLC on a Chiralpak IB-3 column.

Preliminary studies have shown that complete conversions and high enantioselectivities could be obtained when the reaction was carried out at 70 °C in EtOH, under 20 bar of H_2 with an appropriate catalyst. Thus, using in situ prepared chiral Ru-catalysts under the above reaction conditions, a range of γ-heteroatom substituted β-keto esters were hydrogenated with complete conversions and high enantioselectivities, as listed in Table 4. When γ-benzyloxy and γ-*tert*-butoxy substituted β-keto esters were hydrogenated, excellent ee values of **2a** (99.1%) and **2b** (97.9%)[13] were obtained (Table 4, entries 1, 2). Substrate with γ-chloro substituted β-keto ester (**1c**) was hydrogenated

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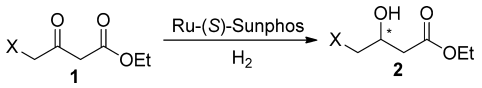
Table 4. Asymmetric Hydrogenation of γ-Heteroatom Substituted β-Keto Esters[a]



entry	X	ee/%[b]
1	BnO (**1a**)	99.1
2	^{t}BuO (**1b**)	97.9[c]
3	Cl (**1c**)	95.5[c]
4[d]	Cl (**1c**)	96.5[c]
5	$PhCO_2$ (**1d**)	97.7
6	AcO (**1e**)	99.0[c]
7	TBSO (**1f**)	98.6[c]
8	OH (**1g**)	88.6[c]
9	4-ClC_6H_4S (**1h**)	64.9
10	4-$ClC_6H_4SO_2$ (**1i**)	96.9
11	$PhSO_2$ (**1j**)	98.2
12	4-$MeC_6H_4SO_2$ (**1k**)	98.2
13	4-$BrC_6H_4SO_2$ (**1l**)	97.5[e]
14[f]	CbzNH (**1m**)	97.1
15[f]	FmocNH (**1n**)	97.2
16[f]	BocNH (**1o**)	98.0[c]

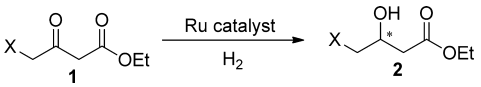
[a]All reactions were carried out with a substrate (1.0 mmol) concentration of 0.4 M in EtOH under 20 bar of H_2 at 70 °C for 18 h unless otherwise noted. Substrate/$(RuCl_2(p\text{-cymene}))_2$/(*S*)-SunPhos =100/0.5/1.1. Conversion=100%. [b]Values of ee were determined by HPLC. [c]Values of ee of their *p*-nitrobenzoates. [d]Reaction at 90 °C. [e]Debromination was observed. [f](RuCl(Benzene)-(*S*)-SunPhos)Cl as catalyst.

under optimized conditions to give **2c** with 95.5% ee (Table 4, entry 3). When the temperature was elevated to 90 °C, the ee value of **2a** was increased to 96.5% (Table 4, entry 4), which was in compliance with Noyori's report that higher temperatures could impair the competitive directing effects of chloride atom.[9b,12] Our ligand was also fruitful in the asymmetric hydrogenation of γ-benzonate and γ-acetate substituted β-keto esters (**1d** and **1e**), giving excellent ee values of **2d** (97.7%) and **2e** (99.0%), respectively. It was noteworthy that the TBS group in **1f** was removed during the asymmetric hydrogenation, which afforded the product ethyl 3,4-dihydroxybutyrate with 98.6% ee. To find out whether the TBS group was lost before or after the completion of the asymmetric hydrogenation of **1f**, a control test was performed. Hydrogenation of an unprotected form of **1f** (γ-hydroxy β-keto ester, **1g**) gave the corresponding product **2g** with only 88.6% ee, which showed that competitive coordination between the hydroxyl and carboxylic ester group greatly impaired the enantioselectivity. Thus, we inferred that the TBS group should be cleaved after the hydrogenation is completed.

Substrate with γ-sulfide substituted β-keto ester (**1h**) was first introduced into asymmetric hydrogenation, which afforded the corresponding product **2h** with a moderate 64.9% ee (Table 4, entry 9). The moderate enantioselectivity of **2h** may be caused by the competitive coordination of the sulfur atom, which made the coordination of catalyst with ester carbonyl not so dominant. This was verified by replacing sulfide with a sulfone group, a weaker coordination group compared to that of the sulfide: the asymmetric hydrogenation of sulfone **1i** delivered the reduced product **2i** with ee up to 96.9% (Table 4, entry 10). Likewise, substrates with γ-phenlysulfonyl and γ-(4-methylphenl)sulfonyl substituted β-keto esters were hydrogenated to give the reduced products with equally excellent ee (98.2%) (Table 4, entries 11 and 12).[14] However, the asymmetric hydrogenation of γ-(4-bromophenyl)sulfonyl substituted β-keto ester (**1l**) afforded the debromination product ethyl 4-phenylsulfonyl-3-hydroxybutyrate (**2l**) in >99% yield with 97.5% ee (Table 4, entry 13). Noyori et al. had reported that using electron-withdrawing amino-protecting groups may reduce the competitive directing effects of the amino group versus the ester group within one molecule.[8,9f,12] Therefore, we employed electron-withdrawing rather than electron-donating amino groups in our study. The γ-carbamate substituted β-keto esters, such as *N*-Cbz-γ-amino substituted β-keto ester (**1m**), and *N*-Fomc-γ-amino substituted β-keto ester (**1n**) and *N*-Boc-γ-amino substituted β-keto ester (**1o**), were also hydrogenated with excellent ee values ranging from 97.1 to 98.0%, in contrast to the enantioselective hydrogenation of **1o** with $RuBr_2$[(*S*)-BINAP] in ethanol at 29 °C, in which **2o** of 87% ee was obtained.[8]

To test the applicability to larger scale preparation of enantiomerically pure ethyl 4-benzyloxy-3-hydroxybutyrate (**2a**) and ethyl 4-phenylsulfonyl-3-hydroxybutyrate (**2j**), higher substrate to catalyst ratio hydrogenation reactions were conducted (Table 5). As shown in Table 5, when the substrate

Table 5. Preparative and Scale-Up Experiments[a]



entry	X	S/C[b]	ee/%[c]
1	BnO (**1a**)	2000	98.8
2[d]	BnO (**1a**)	3000	98.4
3	$PhSO_2$ (**1j**)	2000	98.1
4	$PhSO_2$ (**1j**)	5000	97.3

[a]The reactions were carried out with a substrate (20 mmol) concentration of 0.5 M in EtOH under 20 bar of H_2 for 18 h and at 70 °C except where indicated. Conversion: 100%. [b]Molar ratio of substrate/(RuCl(*p*-cymene)(*S*)-SunPhos)Cl. [c]Values of ee were determined by HPLC on a Chiralpak IB-3 column. [d]Fifty grams of substrate was used, and (RuCl(benzene)(*S*)-TolSunPhos)Cl was used as a catalyst.

to catalyst ratio increased to 2000 with a substrate concentration of 0.5 M, the hydrogenation of ethyl 4-benzyloxy-3-hydroxybutyrate (**1a**) gave **2a** with complete conversion and excellent enantiomeric excess of 98.8% ee (Table 5, entry 1). When our ligand (*R*)-TolSunPhos was assayed in combination with $(RuCl_2(p\text{-cymene}))_2$ in the asymmetric hydrogenation of **1a** with a substrate to catalyst ratio of 3000, complete conversion and excellent enantioselectivity (98.4% ee) were achieved for product **2a** (Table 5, entry 2). Additionally, the asymmetric hydrogenation of ethyl 4-phenylsulfonyl-3-oxobutyrate (**1j**) with a substrate to catalyst ratio of 2000 under the same reaction conditions afforded **2j** with complete conversion and excellent enantioselectivity of 98.1% ee (Table 5, entry 3). When we raised the ratio to 5000, the high ee almost remained. The asymmetric hydrogenation of **1j** was realized to afford **2j** with complete conversion and high enantioselectivity up to 97.3% ee (Table 5, entry 4).

To illustrate the utility of hydrogenated product, Kaneka alcohol was produced starting from compound **2a** (Scheme 2). Claisen condensation was employed, and β-keto esters **3a** were obtained in 75% yield, which were subjected to diastereose-

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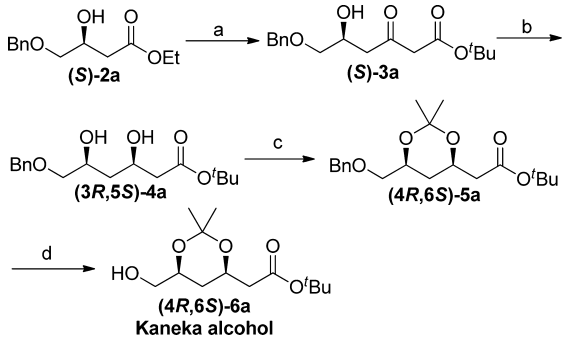
Scheme 2. Synthesis of Kaneka Alcohol 6a[a]



[a]Reagents: (a) AcO^{t}Bu, LDA, THF, −40 °C, 2 h, 75% yield; (b) (1) Et_2BOMe, $NaBH_4$, MeOH/THF, −60 °C, 5 h, (2) H_2O_2, THF/H_2O, 10 °C, 1 h, 86% yield; (c) 2,2-dimethoxypropane, cat. *p*-TsOH, 96% yield; (d) (1) 10 bar H_2, 10% Pd/C, AcOEt, rt, 5 h, (2) AcCl, pyridine, DCM, r.t, (3) recrystallization, (4) K_2CO_3, MeOH, rt, 89% yield.

lective reduction via the Evans−Prasad 1,3-syn diol synthesis to furnish **4a** in 86% yield and 97.2% de.[2b] Compound **4a** was further protected with 2,2-dimethoxylpropane and followed by hydrogenolysis of the benzyl protecting group to give Kaneka alcohol **6a**. In order to upgrade the enantiomeric and diastereomeric purities of **6a**, purification was carried out by acylation of **6a**, followed by crystallization of the ester from hepatane and hydrolysis of the acyl group with potassium carbonate; upgraded **6a** was delivered with >99.5% ee and >99.5% de in 89% yield.

■ CONCLUSION

In conclusion, we have developed a convenient and general protocol for highly enantioselective synthesis of γ-heteroatom substituted β-hydroxy esters by asymmetric hydrogenation. Among all the reduced products, optically pure ethyl 4-arylsulfonyl-3-hydroxybutyrate was achieved for the first time through asymmetric hydrogenation. Catalyzed by (RuCl(*p*-cymene)(*S*)-SunPhos)Cl with up to 5000 TON (turnover number), enantioselectivity of this reduced product remained. This asymmetric hydrogenation protocol provides a useful method for constructing important intermediates with multiple chiral centers; for illustration, Kaneka alcohol (**6a**) was synthesized from the hydrogenated product, which could be used as an important intermediate of statin drugs.

■ EXPERIMENTAL SECTION

General Procedures. Commercially available reagents were used throughout without further purification other than those detailed below. Methylene chloride was distilled over calcium hydride. Ethanol was distilled over magnesium under nitrogen. All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques or in a nitrogen-filled glovebox, unless otherwise noted. ^{1}H NMR spectra were recorded at 400 MHz with TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz and referenced to the central peak of 77.00 ppm for $CDCl_3$. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplications. Mass spectroscopy data were collected on an HRMS-EI instrument. Flash column chromatography was performed on silica gel (300−400 mesh). $[\alpha]_D$ values are given in deg cm^2 g^{-1} and were recorded at the D-line of sodium (589 nm) at 20 °C.

Ethyl 4-(Benzyloxy)-3-oxobutanoate (1a).[2b] Benzyl alcohol (34.5 g, 319 mmol) was added dropwise to a stirred suspension of 60% sodium hydride (26.7 g, 668 mmol) in THF (200 mL); occasional cooling was required with an ice bath to maintain ambient temperature. After hydrogen evolution ceased, the thick slurry was allowed to stir for 2 h. Ethyl 4-chloroacetoacetate (50.0 g, 304 mmol) was then added dropwise within 3 h, and the reaction mixture was stirred for 16 h. The reaction mixture was carefully added into 5% HCl solution (200 mL) at 5 °C and extracted with EtOAc (100 mL × 3). The organic layers were washed with saturated $NaHCO_3$ (60 mL x 2) and then saturated NaCl (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexanes/ethyl acetate = 8:1) to give **1a** (65.3 g, 91%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.30 (m, 5H), 4.59 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.14 (s, 2H), 3.54 (s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 166.9, 136.8, 128.4, 128.0, 127.7, 74.6, 73.3, 61.3, 45.9, 13.9.

Ethyl 4-(*tert*-Butoxy)-3-oxobutanoate (1b).[15] Ethyl 4-chloroacetoacetate (10.0 g, 60.8 mmol) was added dropwise to a stirred suspension of 60% sodium hydride (3.7 g, 91.0 mmol) and potassium *tert*-butoxide (7.5 g, 60.8 mmol) in THF (80 mL) over 30 min. The reaction was stirred at rt until TLC analysis indicated consumption of the starting material (~12 h). The reaction mixture was carefully added into 5% HCl solution (80 mL) at 5 °C and extracted with EtOAc (60 mL × 3), and the combined organic layers were washed with $NaHCO_3$ (50 mL × 2) and then saturated NaCl (50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexanes/ethyl acetate = 8:1) to give **1b** (10.6 g, 86%) as a pale yellow oil. Mixture of keto and enol forms: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 0.05H), 5.34 (s, 0.06H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.01 (s, 2H), 3.97 (s, 0.17H), 3.55 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.23 (s, 0.85H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 167.2, 88.1, 74.2, 67.9, 61.1, 59.9, 46.1, 27.2, 27.1, 14.1, 14.0.

4-Ethoxy-2,4-dioxobutyl Benzoate (1d).[16] Sodium benzoate (17.5 g, 121.5 mmol) was added to a solution of ethyl 4-chloroacetoacetate (10.0 g, 60.8 mmol) in acetic acid (80 mL); the resulting mixture was heated at 90 °C for 18 h, then cooled to rt The mixture was diluted with H_2O (150 mL) and extracted with EtOAc (80 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the crude product that was purified by silica gel chromatography (hexanes/ethyl acetate = 8:1) to provide **1d** (6.4 g, 42%) as a pale yellow oil. Mixture of keto and enol forms: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.11 (s, 0.09H), 8.09−8.07 (m, 2H), 7.62−7.56 (m, 2H), 7.49−7.45 (m, 2H), 5.28 (s, 0.10H), 5.01 (s, 2H), 4.89 (s, 0.31H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.58 (s, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 166.3, 165.5, 133.4, 129.7, 129.6, 128.8, 128.4, 89.1, 68.1, 62.3, 61.6, 60.3, 46.0, 14.0, 13.9. HRMS: Calculated for $C_{13}H_{14}O_5$ $(M + H)^+$: 251.0919. Found: 251.0927.

Ethyl 4-Acetoxy-3-oxobutanoate (1e).[16] Prepared by treating ethyl 4-chloroacetoacetate with potassium acetate using the same procedure for the preparation of **1d** to afford **1e** (6.1 g, 53%) as a pale yellow oil. Mixture of keto and enol forms: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.04 (s, 0.06H), 5.20 (s, 0.07H), 4.79 (s, 2H), 4.65 (s, 0.37H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.50 (s, 2H), 2.17 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 169.9, 166.2, 89.3, 68.2, 67.7, 62.0, 61.6, 46.0, 25.9, 20.2, 14.0, 13.9.

Ethyl 4-[(*tert*-Butyldimethylsilyl)oxy]-3-oxobutanoate (1f). To a solution of ethyl 4-hydroxy-3-oxobutanoate (1.0 g, 6.8 mmol) in 20 mL of DCM were added imidazole (699 mg, 10.3 mmol) and DMAP (42 mg); the resulting solution was cooled to 0 °C. TBSCl (1.1 g, 7.5 mmol) in 5 mL of DCM was added portion-wise to the solution. The reaction was allowed to warm to rt and stirred for an additional 12 h. The mixture was diluted with DCM (50 mL) and washed with 1 M HCl (20 mL × 2), saturated $NaHCO_3$ (20 mL × 2), and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography (hexanes/ethyl acetate = 8:1) to provide **1f** (1.5 g, 84%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.56 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 167.2, 68.8, 61.2, 45.5, 25.6, 18.1, 14.0,

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−5.7. HRMS: Calculated for $C_{12}H_{24}O_4Si$ $(M + H)^+$: 261.1522. Found: 261.1539.

Ethyl 4-Hydroxy-3-oxobutanoate (1g).[17] Pd/C (10%, 0.5 g) was added to a solution of **1b** (5.0 g, 21.2 mmol) in EtOAc (50 mL), which was placed in a 300 mL autoclave. The autoclave was purged and then filled with H_2 (10 bar). The mixture was stirred at rt for 5 h. The catalyst was filtrated with a clarifying pad, and the filtrate was condensed in vacuo to give the product **1g** (2.8 g, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (d, J = 3.6 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.50 (s, 2H), 3.00 (s, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 166.6, 68.3, 61.5, 45.1, 13.8.

Ethyl 4-[(4-Chlorophenyl)thio]-3-oxobutanoate (1h).[18] The 4-chlorobenzenethiol (10.8 g, 74.8 mmol) was added into a solution of potassium hydroxide (4.6 g, 82.0 mmol) in methanol (100 mL) at rt and stirred for 0.5 h. Then ethyl 4-chloroacetoacetate (11.2 g, 68.0 mmol) was added, and the mixture was stirred at rt for 6 h. The mixture was filtered, and the filtrate was evaporated in vacuo. The residue was diluted with DCM (100 mL), washed with 1 M HCl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product by flash chromatography (EtOAc/hexanes = 1:30) afforded **1h** (15.1 g, 81%). Mixture of keto and enol forms: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.12 (s, 0.17H), 7.33−7.24 (m, 4H), 5.10 (s, 0.16H), 4.18 (q, J = 7.1 Hz, 0.15H), 4.17 (q, J = 7.2 Hz, 2H), 3.80 (s, 2H), 3.62 (s, 2H), 3.54 (s, 0.22H), 1.27 (t, J = 7.1, 0.23), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 166.8, 133.2, 132.4, 131.7, 131.1, 129.2, 129.0, 90.8, 61.4, 60.3, 46.4, 46.3, 43.9, 37.7, 14.0, 13.9.

Ethyl 4-[(4-Chlorophenyl)sulfonyl]-3-oxobutanoate (1i). Compound **1h** (2.9 g, 10.6 mmol) was dissolved in EtOH (30 mL) and cooled to 0 °C. In a separate flask, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (2.6 g, 2.1 mmol) was dissolved in 30% H_2O_2 (10 mL) at 0 °C to give a yellow solution. The oxidant solution was added to the sulfide. After 2 h, the reaction mixture was condensed in vacuo. The mixture was further diluted with H_2O (30 mL) and extracted with DCM (30 mL × 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to afford the crude product that was purified by silica-gel column chromatography (PE/EA = 5:1) to provide **1i** (2.6 g, 80%). Mixture of keto and enol forms: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.86 (s, 0.40H), 7.88−7.82 (m, 2H), 7.58−7.53 (m, 2H), 5.20 (s, 0.40H), 4.39 (s, 1.11H), 4.21 (q, J = 7.1 Hz, 2H), 3.93 (s, 0.91H), 3.75 (s, 1.11H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 171.6, 166.3, 163.6, 141.3, 141.0, 136.9, 136.7, 130.0, 129.8, 129.7, 129.5, 95.7, 66.5, 61.84, 61.78, 60.8, 49.5, 14.1, 14.0. HRMS: Calculated for $C_{12}H_{13}ClO_5S$ $(M + Na)^+$: 327.0070. Found: 327.0085.

Ethyl 3-Oxo-4-(phenylsulfonyl)butanoate (1j).[19] To a stirred suspension of sodium benzenesulfinate (100 g, 608 mmol) and potassium iodide (10 g, 61 mmol) in EtOH (500 mL) was added portion-wise ethyl 4-chloroacetoacetate (11.2 g, 68.0 mmol) over 1 h, and then the mixture was stirred at rt for an additional 30 min. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was crystallized from 500 mL of Et_2O/hexanes (1:3) to give the product **1j** (122 g, 74%) as a white solid. Mixture of keto and enol forms: ^{1}H NMR (400 MHz, CD_3Cl) δ 11.83 (s, 0.75H), 7.91−7.89 (m, 2H), 7.68−7.64 (m, 1H), 7.57−7.53 (m, 2H), 5.15 (s, 0.74H), 4.37 (s, 0.35H), 4.17 (q, J = 7.2 Hz, 2H), 3.92 (s, 1.80H), 3.74 (s, 0.33H), 1.25 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 171.5, 166.2, 163.8, 138.34, 138.29, 134.3, 134.1, 129.3, 129.1, 128.3, 128.1, 95.4, 66.4, 61.6, 60.6, 49.4, 13.9, 13.8. HRMS: Calculated for $C_{12}H_{14}O_5S$ $(M + Na)^+$: 293.0460. Found: 293.0468.

Ethyl 3-Oxo-4-tosylbutanoate (1k).[19] Prepared from sodium *p*-toluenesulfinate and ethyl 4-chloroacetoacetate using the same procedure for preparation of **1j** to afford **1k** (10.1 g, 81%) as a white solid. Mixture of keto and enol forms: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (s, 0.82H), 7.80−7.75 (m, 2H), 7.37−7.35 (m, 2H), 5.19 (s, 0.83H), 4.35 (s, 0.13H), 4.20 (q, J = 7.1 Hz, 2H), 3.91 (s, 2H), 3.77 (s, 0.14H), 2.46 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 171.5, 166.1, 164.0, 145.3, 145.0, 135.4, 135.3, 129.7, 129.5, 128.2, 128.0, 95.1, 66.5, 61.43, 61.36, 60.4, 49.2, 21.4, 13.8, 13.7. HRMS: Calculated for $C_{13}H_{16}O_5S$ $(M + Na)^+$: 307.0616. Found: 307.0633.

Ethyl 4-[(4-Bromophenyl)sulfonyl]-3-oxobutanoate (1l).[18] Compound 4-bromobenzenethiol (7.8 g, 41.0 mmol) was added into a solution of potassium hydroxide (2.5, 45.0 mmol) in MeOH (100 mL) at rt and stirred for 0.5 h. Then ethyl 4-chloroacetoacetate (6.2 g, 38.0 mmol) was added, and the mixture was stirred at rt for 6 h. In a separate flask, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (4.7 g, 3.8 mmol) was dissolved in H_2O_2 (30%, 20 mL) at 0 °C to give a yellow solution. The oxidant solution was added to the sulfide at 0 °C and stirred for an additional 2 h. The reaction mixture was condensed in vacuo, further diluted with H_2O (30 mL), and then extracted with DCM (30 mL × 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo to afford the crude product that was purified by silica-gel column chromatography (PE/EA = 5:1) to provide **1l** (9.3 g, 71%). Mixture of keto and enol forms: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.86 (s, 0.44H), 7.79−7.70 (m, 4H), 5.20 (s, 0.41H), 4.38 (s, 1.30H), 4.21 (q, J = 7.2 Hz, 2H), 3.93 (s, 0.99H), 3.79−3.69 (m, 1.33H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 171.5, 166.1, 163.5, 137.4, 137.2, 132.5, 132.4, 129.9, 129.8, 129.5, 95.5, 66.2, 61.6, 61.5, 60.7, 49.4, 13.93, 13.86. HRMS: Calculated for $C_{12}H_{13}BrO_5S$ $(M + Na)^+$: 370.9565. Found: 370.9579.

Ethyl 4-{[(Benzyloxy)carbonyl]amino}-3-oxobutanoate (1m).[20] To a solution of *N*-Cbz-glycine (15.0 g, 72 mmol) in THF was added *N*,*N*′-carbonyldiimidazole (12.8 g, 79 mmol), and the resulting solution was stirred at rt for 4 h. Treatment of potassium monoethyl malonate (16.5 g, 86 mmol) with magnesium chloride (9.6 g, 100 mmol) and triethyl amine (15.0 mL, 108 mmol) at rt for 4 h generated the dianion as its magnesium chelate. To this solution was added the imidazolide solution, and a gummy precipitate began to form immediately. After the resulting mixture was stirred at rt for 16 h, the reaction was poured into ice-cold 1 M HCl. Extraction with EtOAc (100 mL × 2) followed by washing the combined organics with saturated $NaHCO_3$ (50 mL × 2) and brine (50 mL) and drying over $MgSO_4$. Evaporation of the solvent gave the crude product, which was further purified by silica-gel column chromatography (PE/EA = 4:1) to give the desired product **1m** (16.7 g, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 5.53 (s, 1H), 5.11 (s, 2H), 4.43−3.94 (m, 4H), 3.48 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 166.4, 156.0, 135.9, 128.0, 127.6, 127.5, 66.4, 61.1, 50.2, 45.8.

Ethyl 4-({[(9H-Fluoren-9-yl)methoxy]carbonyl}amino)-3-oxobutanoate (1n).[20] Prepared from *N*-Fmoc-glycine and potassium monoethyl malonate using the same procedure for preparation of **1m**; **1n** (2.9 g, 89%) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.29 (m, 1H), 5.50 (s, 1H), 4.41−4.18 (m, 1H), 3.49 (s, 1H), 1.28 (t, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 166.5, 156.1, 143.6, 141.1, 127.5, 127.2, 126.9, 124.9, 119.8, 66.9, 61.5, 50.6, 46.9, 46.2, 13.8. HRMS: Calculated for $C_{21}H_{21}NO_5$ $(M + Na)^+$: 390.1317. Found: 390.1320.

Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-3-oxobutanoate (1o).[20] Prepared from *N*-Boc-glycine and potassium monoethyl malonate using the same procedure for synthesis of **1m**; **1o** (3.1 g, 86%) was obtained as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (s, 1H), 4.21 (q, J = 7.2 Hz, 2H), 4.14 (d, J = 5.4 Hz, 2H), 3.49 (s, 2H), 1.45 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 166.6, 155.5, 79.8, 61.5, 50.4, 46.4, 28.1, 13.9.

Typical Procedure for the Asymmetric Hydrogenation. To a 20 mL Schlenk tube were added $(RuCl_2(benzene))_2$ (10 mg, 0.020 mmol) or $(RuCl_2(p\text{-cymene}))_2$ (12 mg, 0.020 mmol) and (*S*)-SunPhos (30 mg, 0.044 mmol). The tube was vacuumed and purged with nitrogen three times before the addition of freshly distilled and degassed EtOH/DCM (3 mL/3 mL). The resulting mixture was heated at 50 °C for 1 h and then cooled to rt. The solvent was removed under vacuum to give the catalyst. This catalyst was dissolved in degassed ethanol (10 mL) and distributed equally to four vials. The β-keto esters (1.0 mmol) were added to these vials, separately, and were transferred to an autoclave. The autoclave was purged with H_2 three times, and the pressure of H_2 was set to 20 bar. Then the

autoclave was stirred under specific reaction conditions. After 18 h, the autoclave was then cooled to room temperature and the H_2 was carefully released. The autoclave was opened, and the ethanol was evaporated. The enantiomeric excess was determined by HPLC after passing the residue through a short pad of silica gel column with petroleum ether and ethyl acetate.

Ethyl 4-(Benzyloxy)-3-hydroxybutanoate (2a).[2b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 4.57 (s, 2H), 4.28−4.21 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.54−3.46 (m, 2H), 2.97 (d, J = 4.0 Hz, 1H), 2.54 (d, J = 6.4 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 137.8, 128.4, 127.8, 127.7, 73.3, 73.1, 67.1, 60.7, 38.2, 14.1; HPLC (Chiralcel IB-3 column, *n*-hexane/*i*-PrOH = 85:15, 0.5 mL/min, 215 nm) t_1 = 17.6 min, t_2 = 18.9 min.

Ethyl 4-(*tert*-Butoxy)-3-hydroxybutanoate (2b).[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (q, J = 7.2 Hz, 1H), 4.15−4.10 (m, 1H), 3.41−3.32 (m, 2H), 2.93 (d, J = 4.5 Hz, 1H), 2.54−2.52 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 73.2, 67.5, 64.8, 60.5, 38.4, 27.4, 14.1.

Ethyl 4-Chloro-3-hydroxybutanoate (2c).[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30−4.17 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.65−3.58 (m, 2H), 3.16 (d, J = 5.0 Hz, 1H), 2.69−2.58 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.5, 150.6, 134.8, 130.8, 123.5, 70.6, 61.0, 44.9, 36.2, 14.0.

4-Ethoxy-2-hydroxy-4-oxobutyl Benzoate (2d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.05 (m, 2H), 7.60−7.56 (m, 1H), 7.56−7.43 (m, 2H), 4.44−4.35 (m, 3H), 4.19 (q, J = 7.2 Hz, 2H), 3.24 (s, 1H), 2.69−2.58 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 166.3, 133.0, 129.5(2C), 128.2, 67.5, 66.2, 60.8, 38.1, 13.9; HPLC (Chiralcel IB-3 column, *n*-hexane/*i*-PrOH = 92:8, 0.5 mL/min, 215 nm) t_1 = 19.0 min, t_2 = 21.4 min. HRMS: Calculated for $C_{13}H_{16}O_5$ (M + H)$^+$: 275.0895. Found: 275.0904.

Ethyl 4-Acetoxy-3-hydroxybutanoate (2e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30−4.25 (m, 1H), 4.22−4.07 (m, 4H), 3.17−3.15 (m, 1H), 2.55−2.53 (m, 2H), 2.10 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 170.8, 66.9, 65.9, 60.6, 37.9, 20.5, 13.8. HRMS: Calculated for $C_8H_{14}O_5$ (M + Na)$^+$: 213.0739. Found: 213.0747.

Ethyl 3,4-Dihydroxybutanoate (2g).[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, J = 7.1 Hz, 2H), 4.17−4.11 (m, 1H), 3.71−3.66 (m, 1H), 3.56−3.50 (m, 1H), 3.42 (d, J = 3.6 Hz, 1H), 2.59−2.43 (m, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 68.6, 65.6, 60.8, 37.9, 14.0.

Ethyl 4-[(4-Chlorophenyl)thio]-3-hydroxybutanoate (2h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 4H), 4.16 (q, J = 7.2 Hz, 2H), 4.14−4.08 (m, 1H), 3.22 (d, J = 3.9 Hz, 1H), 3.10−3.00 (m, 2H), 2.67−2.53 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 133.8, 132.4, 130.8, 129.1, 66.5, 60.8, 40.2, 39.8, 14.0; HPLC (Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 0.6 mL/min, 254 nm) t_1 = 20.2 min, t_2 = 23.0 min. HRMS: Calculated for $C_{12}H_{15}ClO_3S$ (M + Na)$^+$: 297.0328. Found: 292.0330.

Ethyl 4-[(4-Chlorophenyl)sulfonyl]-3-hydroxybutanoate (2i). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.77 (m, 2H), 7.65−7.39 (m, 2H), 4.65−4.40 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.52 (d, J = 3.7 Hz, 1H), 3.42−3.30 (m, 2H), 2.61 (d, J = 6.2 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 140.8, 137.8, 129.6, 129.5, 63.1, 61.3, 61.0, 40.3, 14.0; HPLC (Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 75:25, 0.5 mL/min, 220 nm) t_1 = 22.1 min, t_2 = 24.1 min. HRMS: Calculated for $C_{12}H_{15}ClO_5S$ (M + H)$^+$: 307.0407. Found: 307.0410.

Ethyl 3-Hydroxy-4-(phenylsulfonyl)butanoate (2j).[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.94 (m, 2H), 7.71−7.67 (m, 1H), 7.62−7.58 (m, 2H), 4.56−4.49 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.61 (d, J = 3.5 Hz, 1H), 3.43−3.31 (m, 2H), 2.62 (d, J = 6.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 139.2, 134.0, 129.3, 127.9, 63.0, 61.1, 60.9, 40.4, 14.0; HPLC (Chiralcel IB-3 column, *n*-hexane/*i*-PrOH = 85:15, 0.5 mL/min, 215 nm) t_1 = 29.7 min, t_2 = 31.8 min. HRMS: Calculated for $C_{12}H_{16}O_5S$ (M + H)$^+$: 273.0797. Found: 273.0814.

Ethyl 3-Hydroxy-4-tosylbutanoate (2k). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.81 (m, 2H), 7.39−7.37 (m, 2H), 4.51−4.48 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.63 (d, J = 3.4 Hz, 1H), 3.40−3.32 (m, 2H), 2.61 (d, J = 6.2 Hz, 2H), 2.46 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 145.0, 136.1, 129.9, 127.9, 63.0, 61.1, 60.8, 40.4, 21.5, 13.9; HPLC (Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 80:20, 0.5 mL/min, 225 nm) t_1 = 21.0 min, t_2 = 26.3 min. HRMS: Calculated for $C_{13}H_{18}O_5S$ (M + Na)$^+$: 309.0773. Found: 309.0802.

Ethyl 4-{[(Benzyloxy)carbonyl]amino}-3-hydroxybutanoate (2m).[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.30 (m, 5H), 5.25 (s, 1H), 5.11 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 4.14−4.11 (m, 1H), 3.45−3.38 (m, 2H), 3.22−3.15 (m, 1H), 2.58−2.39 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 156.8, 136.3, 128.4, 128.01, 127.96, 67.3, 66.7, 60.8, 45.8, 38.6, 14.0; HPLC (Chiralcel IB-3 column, *n*-hexane/*i*-PrOH = 85:15, 0.5 mL/min, 215 nm) t_1 = 18.9 min, t_2 = 22.7 min.

Ethyl 4-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-3-hydroxybutanoate (2n). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.30 (m, 8H), 5.24 (s, 1H), 4.42 (d, J = 6.9 Hz, 2H), 4.23−4.12 (m, 4H), 3.44−3.39 (m, 2H), 3.31−3.06 (m, 1H), 2.53−2.42 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 156.9, 143.8, 141.2, 127.6, 127.0, 125.0, 119.9, 67.3, 66.7, 60.9, 47.2, 45.8, 38.4, 14.1; HPLC (Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 0.5 mL/min, 220 nm) t_1 = 18.0 min, t_2 = 20.7 min. HRMS: Calculated for $C_{21}H_{23}NO_5$ (M + H)$^+$: 370.1654. Found: 370.1663.

Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-3-hydroxybutanoate (2o).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (s, 1H), 4.17 (q, J = 7.1 Hz, 1H), 4.13−4.09 (m, 1H), 3.52 (d, J = 3.3 Hz, 1H), 3.36−3.22 (m, 1H), 3.15−3.09 (m, 1H), 2.54−2.43 (m, 2H), 1.45 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 156.4, 79.4, 67.5, 60.6, 45.4, 38.7, 28.2, 14.0.

Typical Procedure for the Preparation of 3. A 25 mL round flask was charged with **2b** (1 mmol), pyridine (0.4 mL, 5 mmol), 4-nitrobenzoyl chloride (278 mg, 1.5 mmol), DMAP (6 mg), and CH_2Cl_2 (10 mL). The mixture was stirred at 25−30 °C for 6 h, saturated aqueous $NaHCO_3$ solution (5 mL) was added, and the organic layer was separated. The organic layer was washed with 1 M aqueous hydrochloric acid, saturated aqueous $NaHCO_3$ solution, and brine. The washed organic solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to obtain the crude product, which was purified by column chromatography (PE/EA = 3:1) to give the title compound (268 mg, 85%).

Likewise, **3c** and **3o** were prepared from the corresponding alcohols and 4-nitrobenzoyl chloride.

1-(*tert*-Butoxy)-4-ethoxy-4-oxobutan-2-yl 4-Nitrobenzoate (3b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.18 (m, 4H), 5.58−5.52 (m, 1H), 4.15−4.10 (m, 2H), 3.66−3.55 (m, 2H), 2.88−2.77 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 163.7, 150.3, 135.4, 130.6, 123.3, 73.3, 71.5, 62.0, 60.5, 36.1, 27.2, 14.0; HPLC (Chiralcel AS-H column, *n*-hexane/*i*-PrOH = 85:15, 0.5 mL/min, 254 nm) t_1 = 13.5 min, t_2 = 14.7 min. HRMS: Calculated for $C_{17}H_{23}NO_7$ (M + Na)$^+$: 376.1372. Found: 376.1390.

1-Chloro-4-ethoxy-4-oxobutan-2-yl 4-Nitrobenzoate (3c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32−8.20 (m, 4H), 5.72−5.67 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.93−3.84 (m, 2H), 2.94−2.92 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.5, 150.6, 134.8, 130.8, 123.5, 70.6, 61.0, 44.9, 36.2, 14.0; HPLC (Chiralcel AS-H column, *n*-hexane/*i*-PrOH = 85:15, 0.5 mL/min, 254 nm) t_1 = 29.3 min, t_2 = 31.6 min. HRMS: Calculated for $C_{13}H_{14}ClNO_6$ (M + H)$^+$: 316.0588. Found: 316.0596.

5-Oxotetrahydrofuran-3-yl 4-Nitrobenzoate (3e−g). The hydrogenated products of **1e**, **1f**, and **1g** were treated with 1 M HCl at rt for 8 h to give the same product 4-hydroxydihydrofuran-2(3H)-one, which was further derived to its *p*-nitrobenzoate derivative **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33−8.20 (m, 4H), 5.76−5.74 (m, 1H), 4.66 (dd, J = 11.3, 4.7 Hz, 1H), 4.58−4.55 (m, 1H), 3.03 (dd, J = 18.6, 6.6 Hz, 1H), 2.84−2.79 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 178.7, 167.2, 153.8, 138.1, 134.3, 127.3, 76.1, 75.6, 37.7; HPLC (Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 60:40, 0.5 mL/min, 210

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nm) t_1 = 22.3 min, t_2 = 27.3 min. HRMS: Calculated for $C_{11}H_9NO_6$ $(M + H)^+$: 252.0508. Found: 252.0522.

1-[(*tert*-Butoxycarbonyl)amino]-4-ethoxy-4-oxobutan-2-yl 4-Nitrobenzoate (3o). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.19 (m, 4H), 5.57−5.51 (m, 1H), 4.82 (t, J = 5.9 Hz, 1H), 4.17−4.10 (m, 2H), 3.55 (t, J = 5.8 Hz, 2H), 2.84−2.72 (m, 2H), 1.40 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 163.8, 155.8, 150.3, 135.1, 130.7, 123.3, 79.4, 71.4, 60.7, 42.8, 36.4, 28.0, 13.9; HPLC (Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 85:15, 0.5 mL/min, 254 nm) t_1 = 31.5 min, t_2 = 33.6 min. HRMS: Calculated for $C_{18}H_{24}N_2O_8$ $(M + Na)^+$: 419.1430. Found: 419.1425.

Ethyl (*S*)-4-(Benzyloxy)-3-hydroxybutanoate (2a).[2b] To a 25 mL Schlenk tube were added $(Ru(p\text{-Cymene})Cl_2)_2$ (12 mg, 20 μmol) and (*R*)-TolSunPhos (32 mg, 44 μmol). The tube was vacuumed and purged with nitrogen three times before the addition of freshly distilled and degassed EtOH/CH_2Cl_2 (3 mL/3 mL). The resulting mixture was heated at 50 °C for 1 h and then cooled to rt. The solvent was removed under vacuum to give the catalyst. The catalyst was dissolved in degassed ethanol (10 mL). In the meantime, a 300 mL autoclave was charged with absolute EtOH (90 mL) and **1a** (47.3 g, 200.0 mmol). The catalyst solution (via syringe) was introduced into the autoclave, and the autoclave was closed under N_2. H_2 (20 bar) was introduced three times and released each time through a valve into a ventilated hood. The autoclave was then filled with H_2 (20 bar) and heated to 70 °C (inner temperature), and the contents were stirred for 18 h. The autoclave was cooled to room temperature. TLC analysis indicated consumption of the starting material. The reaction solution was concentrated in a rotary evaporator, and the residue was distilled under reduced pressure to give **2a** (43.1 g, 90%) as a colorless oil. $[\alpha]^{20}_D$ = −10.0 (c = 1.18, EtOH), which was in agreement with the literature data $[\alpha]^{20}_D$ = −9.0 (c = 1.18, EtOH).[2b] HPLC (ChiralPak OD-H column, flow 0.5 mL/min, IPA/*n*-Hex = 5:95, 215 nm, (*S*)-**2a** t_1 = 30.4 min, (*R*)-**2a** t_2 = 35.2 min): 98.4% ee of the (*S*)-configuration.

***tert*-Butyl (*S*)-6-(Benzyloxy)-5-hydroxy-3-oxohexanoate (3a).**[2b] A 2.5 M solution of *n*-BuLi (237 mL, 590 mmol) was added at −10 °C within 45 min to a solution of *i*-Pr_2NH (86 mL, 609 mmol) in THF (200 mL). The resulting mixture was stirred 30 min at 0 °C. *tert*-Butyl acetate (66.0 g, 570 mmol) was added dropwise within 60 min at −40 °C. A solution of **2a** (34.0 g, 143 mmol) in THF (200 mL) was added dropwise within 30 min at −40 °C, and the mixture was stirred for 1 h at −40 °C. After completion of the reaction, H_2O (200 mL) was added to the reaction mixture (without cooling) within 30 min, leading to an inner temperature of 0 °C. The mixture was concentrated via rotary evaporation and diluted with EtOAc (150 mL); the layers were separated, the aqueous layer was extracted with EtOAc (100 mL × 2), and the combined organic layers were washed with saturated NaCl (80 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography with hexanes and ethyl acetate (7:1) as eluent to afford **3a** (33.0 g, 75%) as a pale yellow oil. $[\alpha]^{20}_D$ = +14.0 (c = 1.12, $CHCl_3$), which was in agreement with the literature data $[\alpha]^{20}_D$ = +11.2 (c = 0.84, $CHCl_3$):[21a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.52 (s, 2H), 4.30−4.23 (m, 1H), 3.48−3.40 (m, 2H), 3.37 (s, 2H), 3.26 (s, 1H), 2.71 (d, J = 6.4 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 166.2, 137.8, 128.5, 127.8, 127.7, 73.4, 73.1, 66.7, 51.2, 46.2, 28.0.

***tert*-Butyl (3*R*,5*S*)-6-(Benzyloxy)-3,5-dihydroxyhexanoate (4a).**[2b] To a solution of **3a** (30.0 g, 97.3 mmol) in THF (150 mL) and MeOH (30 mL) was added Et_2BOMe (21.4 g, 107.0 mmol, 50% in THF), and the solution was stirred for 30 min at rt before being cooled to −78 °C. $NaBH_4$ (4.1 g, 107.0 mmol) was added portionwise over 10 min (moderate gas evolution observed). After the solution was stirred for 4.5 h at −78 °C, 120 mL of 30% aqueous H_2O_2 was slowly added to the cold solution via addition funnel. The mixture was allowed to warm to rt and then stirred for 2 h at rt. The mixture was concentrated and extracted with EtOAc (100 mL × 3). The combined layers were washed successively with saturated $NaHCO_3$ (50 mL × 2), then water (80 mL), saturated $Na_2S_2O_3$ (80 mL), and saturated NaCl (80 mL) before being dried over Na_2SO_4 and concentrated in vacuo to give a viscous pale yellow oil. Flash chromatography with 40% EtOAc/hexanes as eluent provided the desired product (25.9 g, 86%) as a colorless oil. $[\alpha]^{20}_D$ = −12.9 (c = 0.83, $CHCl_3$), which was in agreement with the literature data $[\alpha]^{20}_D$ = −9.0 (c = 1.10, $CHCl_3$):[23a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 4.56 (s, 2H), 4.27−4.20 (m, 1H), 4.10−4.05 (m, 1H), 3.77 (d, J = 2.4 Hz, 1H), 3.47−3.41 (m, 2H), 3.27 (d, J = 1.6 Hz, 1H), 2.43−2.41 (m, 2H), 1.68−1.61 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 137.9, 128.4, 127.7 (2C), 81.3, 74.1, 73.3, 70.4, 68.2, 42.5, 38.8, 28.0; HPLC analysis indicated >98.4% ee and >97.2% de (Chiralcel IB-3 column analysis, flow 0.2 mL/min, *i*-PrOH/*n*-hexane = 25:75, 215 nm) (3*R*,5*S*) t_R = 43.5 min (desired), (3*S*,5*R*) t_R = 35.0 min, retention times for the two undetermined isomers are 25.6 and 31.5 min.

***tert*-Butyl 2-{(4*R*,6*S*)-6-[(Benzyloxy)methyl]-2,2-dimethyl-1,3-dioxan-4-yl}acetate (5a).**[2b] To a solution of **4a** (20.0 g, 64.4 mmol) in acetone (30 mL) were added 2,2-dimethoxypropane (13.4 g, 128.9 mmol) and *p*-toluenesulfonic acid monohydrate (613 mg, 5 mol %); the resulting mixture was stirred at rt until TLC analysis indicated consumption of the starting material (~4 h). Saturated $NaHCO_3$ (20 mL) was added into the reaction mixture, and the mixture was stirred for 30 min (pH 6−7). The mixture was concentrated and diluted with EtOAc (100 mL). The layers were separated, the aqueous layer was extracted with EtOAc (50 mL × 2), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography with 10% EtOAc/hexanes as eluent to afford **5a** (21.6 g, 96%) as a colorless oil: $[\alpha]^{20}_D$ = −5.8 (c = 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H), 4.57 (q, J = 12 Hz, 2H), 4.32−4.25 (m, 1H), 4.15−4.08 (m, 1H), 3.50 (dd, J = 6.0, 9.6 Hz, 1H), 3.38 (dd, J = 4.6, 9.8 Hz, 1H), 2.43 (dd, J = 7.2, 15.2 Hz, 1H), 2.31 (dd, J = 5.8, 15.0 Hz, 1H), 1.60 (dt, J = 2.4, 13.2 Hz, 1H), 1.47 (s, 3H), 1.44 (s, 9H), 1.40 (s, 3H), 1.25 (q, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.2, 128.3, 127.7, 127.6, 98.8, 80.6, 73.4, 73.3, 68.4, 65.9, 42.7, 33.2, 30.0, 28.1, 19.6.

***tert*-Butyl 2-[(4*R*,6*S*)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (6a).**[2b] Pd/C (10%, 1.0 g) was added to a solution of **5a** (20 g, 57.0 mmol) in EtOAc (50 mL) in a 300 mL autoclave. The autoclave was purged with H_2 and then filled with H_2 (10 bar). The mixture was stirred at constant H_2 pressure with cooling at 25−30 °C inner temperature for 5 h. The catalyst was filtrated with a clarifying pad, and the filtrate was evaporated in vacuo. The residue was dissolved in DCM (100 mL), and pyridine (18 mL, 165 mmol) was added. To the resulting solution, AcCl (5.2 g, 65.9 mmol) was added dropwise, and then the mixture stirred at rt for 30 min. After completion of the reaction, the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (30 mL × 2) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was crystallized from 50 mL heptane to afford 15.9 g *tert*-butyl 2-[(4*R*,6*S*)-6-(acetoxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate: $[\alpha]^{20}_D$ = 13.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32−4.26 (m, 1H), 4.15−3.99 (m, 3H), 2.45 (dd, J = 15.2, 7.0 Hz, 1H), 2.32 (dd, J = 15.2, 6.1 Hz, 1H), 2.08 (s, 3H), 1.57 (dt, J = 12.8, 2.4 Hz, 1H), 1.47 (s, 3H), 1.45 (s, 9H), 1.39 (s, 3H), 1.37−1.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.9, 98.7, 80.5, 67.0, 66.8, 65.6, 42.4, 32.3, 29.7, 27.9, 20.7, 19.4.

To a solution of *tert*-butyl 2-[(4*R*,6*S*)-6-(acetoxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (15.9 g, 52.6 mmol) in MeOH (50 mL) was added K_2CO_3 (3.6 g, 26.3 mmol); the resulting mixture was stirred at rt until TLC analysis indicated consumption of the starting material (~30 min). The reaction mixture was filtrated, and the filtrate was concentrated in vacuo. The residue was diluted with EtOAc (50 mL) and extracted. The organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and subjected to the column chromatography (15% EtOAc in hexanes) to give the Kaneka alcohol **6a** (13.2 g, 89%) as a colorless oil. $[\alpha]^{20}_D$ = +12.0 (c = 0.94, $CHCl_3$), which was in agreement with the literature data $[\alpha]^{20}_D$ = +9.9 (c = 2.0, $CHCl_3$), −6.8 (c = 1.5, MeOH):[23b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32−4.27 (m, 1H), 4.04−3.99 (m, 1H), 3.65−3.59 (m, 1H), 3.53−3.47 (m, 1H),

2.45 (dd, J = 15.2, 7.1 Hz, 1H), 2.32 (dd, J = 15.2, 6.1 Hz, 1H), 2.09−2.06 (m, 1H), 1.52−1.48 (m, 1H), 1.48 (s, 3H), 1.45 (s, 9H), 1.39 (s, 3H), 1.37−1.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 98.8, 80.6, 69.5, 65.8, 65.7, 42.5, 31.7, 29.8, 28.0, 19.9. Compound **6a** was converted to *tert*-Butyl (3*R*,5*S*)-6-(benzyloxy)-3,5-dihydroxyhexanoate **4a** for chiral purity analysis by chiral HPLC. HPLC analysis (Chiralcel IB-3 column analysis, flow 0.2 mL/min, IPA/*n*-Hex = 25:75, 215 nm) indicated >99.5% ee and >99.5% de.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The NMR and/or HPLC data of compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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