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Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of β-Substituted α-Oxobutyrolactones

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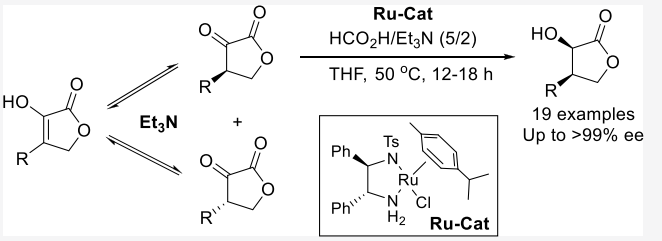
ABSTRACT: A concise and effective ruthenium-catalyzed asymmetric transfer hydrogenation of β-substituted α-oxobutyrolactones has been developed, delivering a series of *cis*-β-substituted α-hydroxybutyrolactone derivatives with excellent yields, enantioselectivities, and diastereoselectivities. Two consecutive stereogenic centers were constructed in one step through dynamic kinetic resolution under basic conditions. The reaction could be conducted on a gram scale without loss of activity and enantioselectivity. The reductive products could be easily transformed into useful building blocks.



Chiral α-hydroxy esters,[1] especially α-hydroxybutyrolactones, are commonly found in natural products, drugs, and biologically active molecules (Figure 1). For instance,

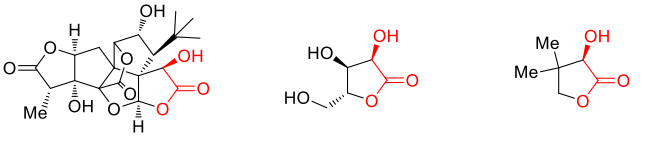


Figure 1. Bioactive compounds and intermediates containing α-hydroxybutyrolactone frameworks

Ginkgolide J,[2a] which was extracted from ginkgo biloba, has the effect of relieving and improving myocardial ischemia. D-(+)-Ribonic acid γ-lactone[2b,c] and D-(−)-pantolactone[2d,e] are key intermediates for the synthesis of 5-thio-D-ribose and pantothenic acid, respectively. Therefore, the construction of chiral α-hydroxybutyrolactone skeletons has aroused widespread attention over the past several decades. To date, the synthesis of chiral α-hydroxybutyrolactones was usually conducted through multiple steps.[3] Strategies to direct reduction of α-oxobutyrolactones access those compounds were relatively unknown except special substrates.[4] The early study on the asymmetric reduction of α-oxobutyrolactones was achieved by utilizing the biocatalysis,[4a,b] transition-metal Rh,[4c−g] and Ru[4h] catalyst, and the substrates were limited in ketopantoyl lactone and dihydrofuran-2,3-dione. Therefore, developing an effective method for the construction of various chiral α-hydroxybutyrolactones is highly desirable in organic synthetic chemistry.[5]

Asymmetric (transfer) hydrogenation reactions are of great interest to the chemistry community because of their atom efficiency and minimal environmental impact.[6] Due to the high efficiency in the hydrogenation of ketones, ruthenium-catalyzed asymmetric transfer hydrogenation has gained increasing attention.[7] Encouraged by our previous works[8] on asymmetric (transfer) hydrogenative desymmetrization of diketones and that β-substituted α-oxobutyrolactones are prone to enol-keto tautomerism in the presence of a base such as triethylamine, which promoted the rapid racemization of the substrates (Scheme 1), we wondered whether β-substituted α-oxobutyrolactones can be hydrogenated with the

Scheme 1. Synthesis of β-Substituted α-Hydroxybutyrolactones

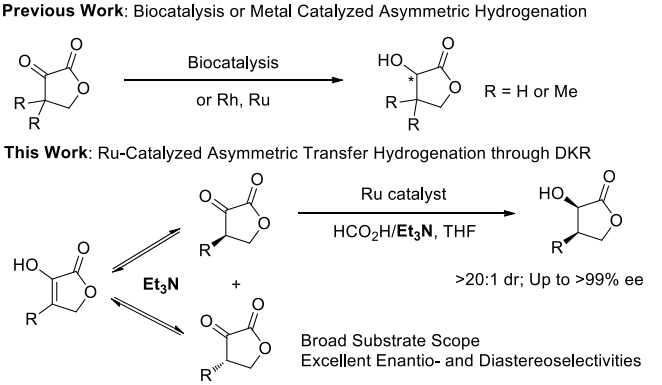


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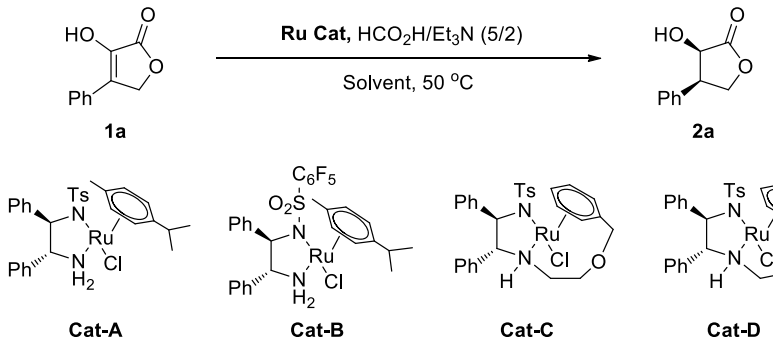
Table 1. Optimization of Ru-Catalyzed Asymmetric Transfer Hydrogenation Reaction



entry[a]	Ru cat.	solvent	HCO_2H/Et_3N (mL)	t (h)	yield (%)[b]	ee (%)[c]
1	**Cat-A**	EtOAc	1.00	24	>95	>99
2	**Cat-A**	THF	1.00	12	>95	>99
3	**Cat-A**	toluene	1.00	24	75	>99
4	**Cat-A**	DCE	1.00	24	89	>99
5	**Cat-A**	DMF	1.00	24	<5	
6	**Cat-A**	Neat	1.00	24	60	99
7	**Cat-A**	THF	0.50	12	>95	>99
8	**Cat-A**	THF	0.25	12	>95	>99
9	**Cat-A**	THF	0.125	12	>95	>99
10	**Cat-B**	THF	0.125	12	70	>99
11	**Cat-C**	THF	0.125	12	>95	>99
12	**Cat-D**	THF	0.125	12	49	>99
13[e]	**Cat-A**	THF	0.125	12	>95	>99
14[f]	**Cat-A**	THF	0.125	12	66	>99
15	**Cat-A**	THF	0.125	12	>95 (93)[d]	>99

[a]**1a** (0.25 mmol), Ru Cat (3 mol %), HCO_2H/Et_3N, solvent (2.0 mL), 50 °C. [b]Determined by ^1H NMR using dibromomethane as an internal standard. [c]Determined by HPLC. [d]Isolated yield. [e]**Cat-A** (2 mol %). [f]**Cat-A** (1 mol %). The diastereoselectivity of all reactions > 20:1.

ruthenium catalyst system under basic conditions through dynamic kinetic resolution, and two consecutive stereogenic centers could be constructed. Herein, we present an efficient ruthenium-catalyzed asymmetric transfer hydrogenation of β-substituted α-oxobutyrolactones for the preparation of chiral β-substituted α-hydroxybutyrolactones with two contiguous stereogenic centers through dynamic kinetic resolution.

Optimal experiments were carried out with 3-hydroxy-4-phenylfuran-2(5*H*)-one **1a** as a model substrate. Ruthenium complex **Cat-A** was used as a catalyst, and an azeotrope of formic acid and triethylamine (5:2) was chosen as the hydrogen source in ethyl acetate under a nitrogen atmosphere. To our delight, full conversion was observed with >99% ee and >20:1 dr (Table 1, entry 1). Next, the commonly used solvents were examined (entries 2−5) and found that solvents had an obvious effect on reactivity. Compared with the initial result in ethyl acetate, tetrahydrofuran gave higher reactivity (entry 2). Moderate yields were obtained with toluene and 1,2-dichloroethane (entries 3 and 4). The strong polar solvent *N*,*N*-dimethylformamide gave poor reactivity (entry 5). When the reaction was conducted without a solvent, a moderate 60% conversion was observed, which might ascribe to the poor solubility of the substrate (entry 6). Then, the amount of the hydrogen source was decreased for enhancing the atom economy (entries 7−9). The reaction was not affected when decreasing the amount of the hydrogen source to 6 equiv (entry 9).

Subsequently, a variety of chiral ruthenium catalysts were evaluated, and low reactivity, albeit excellent enantioselectivity, was obtained with **Cat-B** and **Cat-D** (entries 10 and 12). **Cat-C** gave the same high reactivity and excellent enantioselectivity as **Cat-A** (entry 11). Considering the price and availability, **Cat-A** was chosen as the optimal catalyst. When the catalyst loading was further decreased to 1 mol %, a moderate 66% conversion was obtained (entry 14). Considering 2 mol % of the catalyst might be the boundary condition, we chose 3 mol % of Ru catalyst **Cat-A** for asymmetric transfer hydrogenation and determined entry 9 as the optimal conditions.

With the optimized conditions in hand, a series of β-substituted α-oxobutyrolactones were then explored to evaluate the substrate scope and functional group tolerance. To our delight, substrates **1** performed well under the optimized conditions (Scheme 2). First, the steric and electronic properties of the substituent on the aryl group were investigated. Me, Cl, or MeO introduced into the *ortho*-, *meta*-, or *para*-position on the phenyl ring could conduct smoothly with high yields and excellent stereoselectivities (**2b**−**2j**). The reaction was also well-tolerated in the presence of electron-withdrawing functional groups such as Br, F, or F_3C at *para*-position of the phenyl ring (**2k**−**2m**). As for the 1-naphthyl- and 2-naphthyl- substituted substrates, both excellent yields and enantioselectivities could also be obtained (**2n**, **2o**). When methoxy was introduced into the 3 and 4 positions of the phenyl ring (**1p**), hydrogenation could also work smoothly. It is worth noting that a low reactivity was observed for 2,6-dichlorophenyl-substituted substrate **1q**, which might attribute to steric hindrance. Fortunately, when substrates bearing different alkyl groups (**2r**−**2t**) were employed, asymmetric hydrogenation could also proceed,

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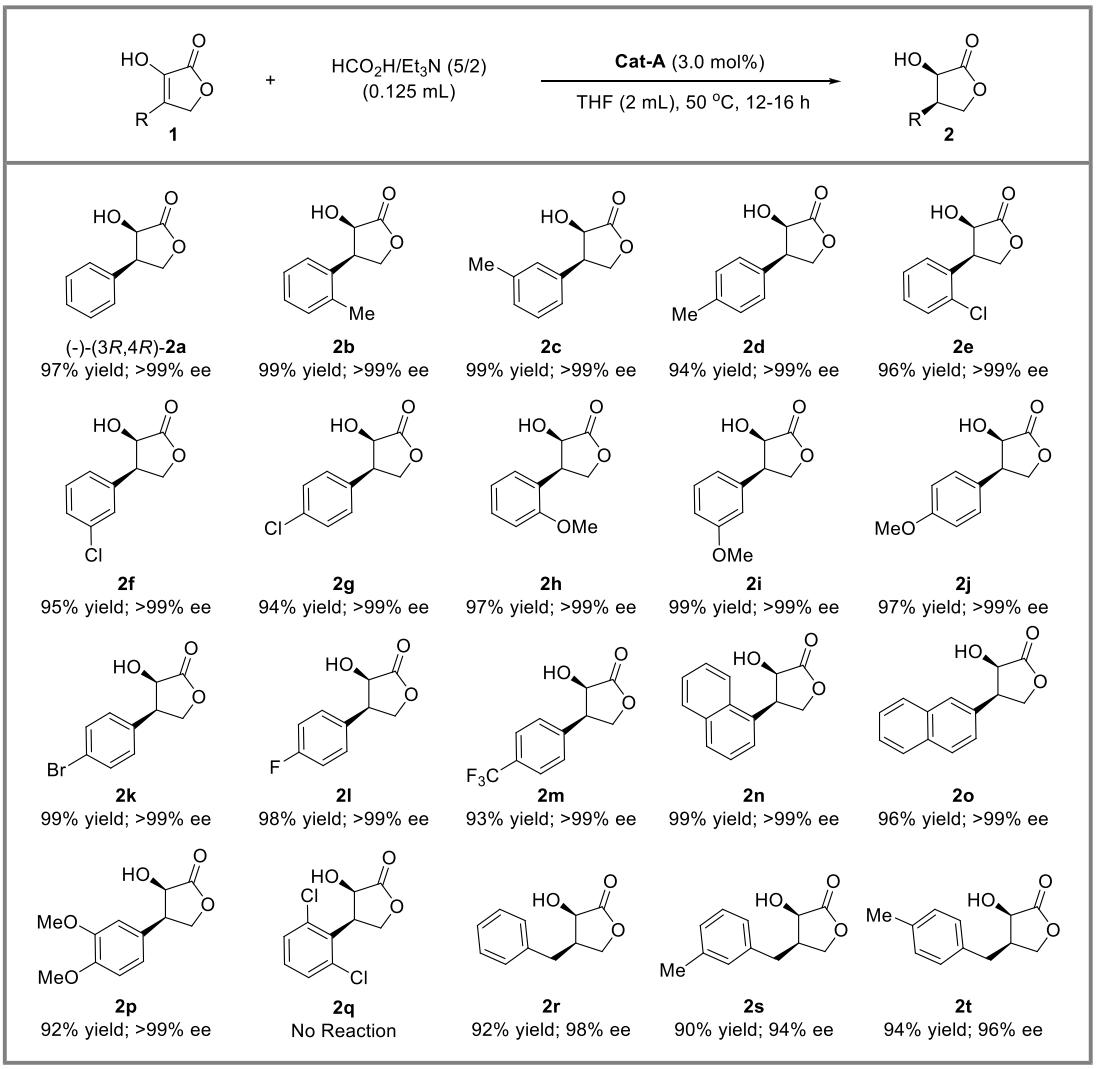
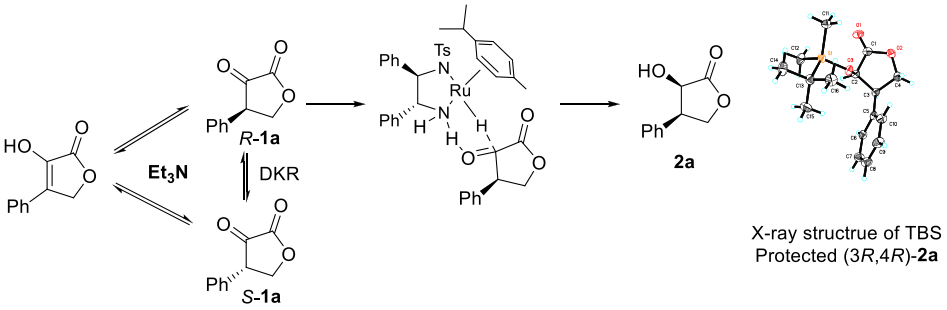
Scheme 2. Substrate Scope for the Synthesis of α-Hydroxybutyrolactones



Scheme 3. Proposed Possible Catalytic Mechanism



affording the desired reductive products with excellent reactivity, diastereoselectivities, and enantioselectivities.

Based on the experimental results, a plausible mechanism was proposed as shown in Scheme 3. First, enol substrate **1a** tautomerized to *R*-**1a** or *S*-**1a** under the basic conditions through a dynamic kinetic resolution process. The asymmetric transfer hydrogenation happened with *R*-**1a**, which avoided the disfavored steric interaction between the phenyl ring of the ligand and the substrate. As a result, the desired *cis*-product **2a** was obtained.

To demonstrate the potential synthetic utility of our protocol, gram-scale transfer hydrogenation was carried out, furnishing the desirable product (−)-**2a** in 94% yield and with >99% ee without any loss of activity, diastereoselectivity, and enantioselectivity (Scheme 4). Synthetic transformation of (−)-**2a** was conducted. First, chiral silyl ether (+)-**3** was prepared according to the known synthetic procedure[9] with *tert*-butyldimethylsilyl chloride (Scheme 4), and the absolute configuration of (+)-**3** could be assigned as (3*R*,4*R*) by X-ray diffraction analysis (Scheme 3). Thus, the absolute config-

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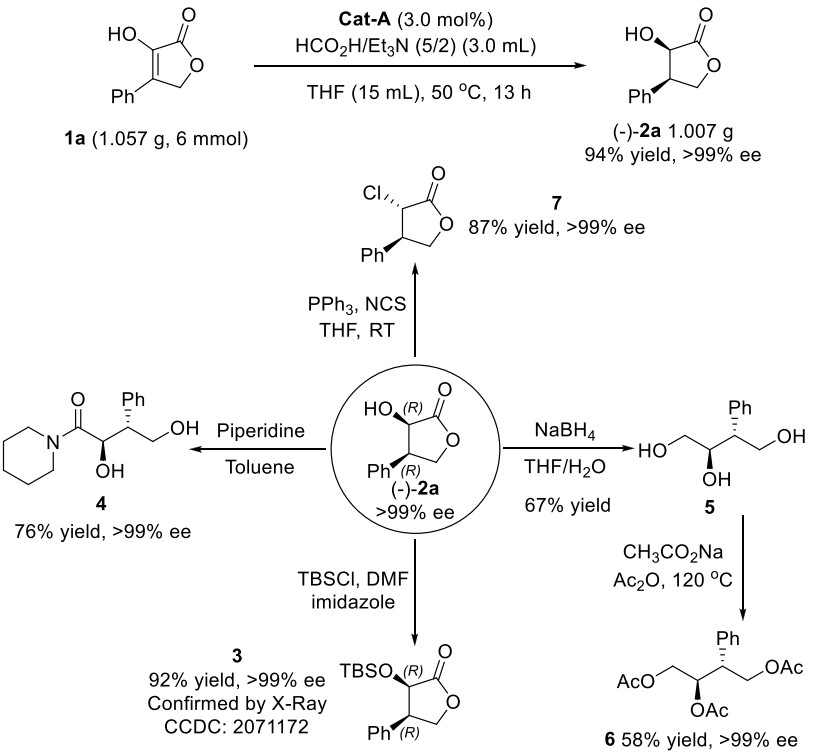
Scheme 4. Scale-up Experiment and Product Elaboration



uration of (−)-**2a** was unambiguously assigned as (3*R*,4*R*). Second, amide **4** was obtained in 76% yield when (−)-**2a** was exposed to piperidine at elevated temperatures (Scheme 4).[10] The reduction of (−)-**2a** with sodium borohydride could afford triol **5**,[11a] which was further derivatized by acetic anhydride.[11b] S_N2 substitution of hydroxy with PPh_3/NCS[12] afforded the *trans*-α-chlorobutyrolactone **7** in 87% yield without any loss of enantiopurity (Scheme 4).

In conclusion, we have developed a ruthenium-catalyzed asymmetric transfer hydrogenation of β-substituted α-oxobutyrolactones for facile synthesis of a variety of optically active β-substituted α-hydroxybutyrolactones, and two consecutive stereogenic centers were constructed in one step through dynamic kinetic resolution. The reaction can also proceed smoothly at the gram scale without any loss of reactivity and enantioselectivity. The transformations of reductive products provided a solution to a diversity of synthetically or pharmaceutically useful chiral skeletons. Further asymmetric transfer hydrogenation of other substrates is ongoing in our laboratory.

EXPERIMENTAL SECTION

All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques, unless otherwise noted. Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded at room temperature in $CDCl_3$ or DMSO-d_6 on a 400 MHz instrument with tetramethylsilane as an internal standard. The following abbreviations were used to symbolize the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, brs = broad singlet. Enantiomeric excess was determined by HPLC analysis, using a chiral column described below in detail. Optical rotations were measured by a polarimeter. Flash column chromatography was performed on silica gel (200−300 mesh). All reactions were monitored by TLC analysis. High-resolution mass spectrometry (HRMS (ESI-TOF) *m*/*z*) was measured on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry. The heat source for all heating reactions was the oil bath.

Procedures for Synthesis of β-Substituted α-Oxobutyrolactones 1. The aryl-substituted α-oxobutyrolactones **1a**−**1q** could be synthesized from readily available dehydroamino acids[13a] according to Method A with a slight modification.[13b] Among them, **1a**, **1b**, **1d**, **1f**−**1n**, and **1q** are the known compounds.[13b] The alkyl-substituted α-oxobutyrolactones **1r**−**1t** could be synthesized from the known 4-aroyl-3-hydroxy-2(5*H*)-furanones according to Method B with slight modification.[14a] Among them, **1r** and **1s** are the known compounds.[14]

Method A. To a 150 mL sealed bottle containing dehydroamino acids (6.0 mmol) were added nickel acetate tetrahydrate (30 mg, 2 mol %), lithium acetate (1.188 g, 18.0 mmol), 4 Å molecular sieve dust (1.320 g), dibromomethane (15 mL), *N*,*N*-dimethylformamide (3.0 mL), and water (0.12 mL) in an open atmosphere, and the mixture was heated to keep the reaction temperature at 150 °C (oil bath temperature). After completion of the reaction (16−24 h, monitored by TLC), ethyl acetate was added into the reaction mixture and filtered through a short pad of Celite. Then, the volatiles were evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexanes/ethyl acetate (4:1) as an eluent to give the desired aryl-substituted α-oxobutyrolactones **1**.

Method B. In a Parr autoclave, 4-aroyl-3-hydroxy-2(5*H*)-furanones (2.0 mmol), Pd/C (10% wt.) (40.0 mg), and methanol (4.0 mL) were added. The mixture was hydrogenated under hydrogen (50 psi) for 3 h. The catalyst was filtered off, and the volatiles were evaporated under the reduced pressure. The residue was purified by flash column chromatography on silica gel using hexanes/ethyl acetate (5:1) as an eluent to give alkyl-substituted α-oxobutyrolactones **1r**−**1t**.

*3-Hydroxy-4-(m-tolyl)furan-2(5H)-one (**1c**):* 0.707 g, 62% yield, yellow solid, mp = 198−199 °C, new compound, R_f = 0.60 (hexanes/ethyl acetate 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57−7.39 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.71 (brs, 1H), 5.14 (s, 2H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.4, 138.7, 136.2, 130.4, 129.8, 128.9, 127.3, 126.6, 123.8, 68.4,

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21.5. HRMS (ESI-TOF): m/z calcd for $C_{11}H_{11}O_3$ $[M + H]^+$, 191.0703; found, 191.0704.

*4-(2-Chlorophenyl)-3-hydroxyfuran-2(5H)-one (**1e**):* 0.344 g, 43% yield, yellow solid, mp = 178−179 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, J = 7.5, 1.9 Hz, 1H), 7.45 (dd, J = 7.7, 1.6 Hz, 1H), 7.39−7.30 (m, 2H), 6.44 (brs, 1H), 5.31 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.4, 137.9, 132.1, 131.3, 130.7, 130.4, 128.8, 127.2, 125.5, 69.9. HRMS (ESI-TOF): m/z calcd for $C_{10}H_8ClO_3$ $[M + H]^+$, 211.0156 (^{35}Cl) and 213.0130 (^{37}Cl); found, 211.0154 (^{35}Cl) and 213.0122 (^{37}Cl).

*3-Hydroxy-4-(naphthalen-2-yl)furan-2(5H)-one (**1o**):* 0.606 g, 45% yield, brown solid, mp = 248−249 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 3:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 8.17 (s, 1H), 8.01−7.91 (m, 4H), 7.55 (dd, J = 6.2, 3.2 Hz, 2H), 5.31 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 170.6, 138.3, 133.2, 133.1, 128.9, 128.74, 128.68, 128.1, 127.3, 127.2, 126.4, 125.7, 124.5, 68.2. HRMS (ESI-TOF): m/z calcd for $C_{14}H_{11}O_3$ $[M + H]^+$, 227.0703; found, 227.0705.

*4-(3,4-Dimethoxyphenyl)-3-hydroxyfuran-2(5H)-one (**1p**):* 0.594 g, 42% yield, yellow solid, mp = 234−235 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 1.7 Hz, 1H), 7.07 (dd, J = 8.4, 1.9 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.29 (s, 1H), 5.11 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.4, 150.2, 149.3, 135.0, 126.9, 122.9, 119.2, 111.1, 110.2, 68.3, 55.98, 55.96. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{12}O_5$ $[M + H]^+$, 237.0757; found, 237.0758.

*4-Benzyl-3-hydroxyfuran-2(5H)-one (**1r**):* 0.144 g, 38% yield, white solid, mp = 60−61 °C, known compound,[14a] R_f = 0.40 (hexanes/ethyl acetate 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.26 (m, 3H), 7.20 (d, J = 7.1 Hz, 2H), 5.78 (brs, 1H), 4.58 (s, 2H), 3.73 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.3, 137.2, 136.8, 131.0, 129.0, 128.6, 127.1, 69.5, 31.0. HRMS (ESI-TOF): m/z calcd for $C_{11}H_{11}O_3$ $[M + H]^+$, 191.0703; found, 191.0701.

*3-Hydroxy-4-(3-methylbenzyl)furan-2(5H)-one (**1s**):* 0.171 g, 54% yield, white solid, mp = 79−80 °C, known compound,[14b] R_f = 0.40 (hexanes/ethyl acetate 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.02−6.94 (m, 2H), 6.08 (brs, 1H), 4.57 (s, 2H), 3.68 (s, 2H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.3, 138.7, 137.1, 136.7, 131.2, 129.3, 128.8, 127.8, 125.6, 69.5, 30.9, 21.4. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{15}O_3$ $[M + H]^+$, 205.0859; found, 205.0860.

*3-Hydroxy-4-(4-methylbenzyl)furan-2(5H)-one (**1t**):* 0.206 g, 63% yield, white solid, mp = 101−102 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04−7.16 (m, 4H), 5.76 (brs, 1H), 4.57 (s, 2H), 3.68 (s, 2H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.5, 137.1, 136.7, 133.7, 131.6, 129.6, 128.5, 69.5, 30.6, 21.0. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{13}O_3$ $[M + H]^+$, 205.0859; found, 205.0860.

General Procedure for Ru-Catalyzed ATH of β-Substituted α-Oxobutyrolactones. Substrates **1** (0.50 mmol), RuCl[(*R*,*R*)-Tsdpen](*p*-cymene) (9.6 mg, 0.015 mmol, 3 mol %), tetrahydrofuran (4.0 mL), and formic acid-triethylamine azeotrope (0.25 mL, 6.0 equiv) were placed in a dried Schlenk tube under nitrogen gas. The mixture was stirred at 50 °C (oil bath temperature) for 12−18 h. After completion of the reaction, the volatiles were removed under reduced pressure. A saturated ammonium chloride aqueous solution (15 mL) was added, and the water layer was extracted three times with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexanes/ethyl acetate (3:1) as an eluent to give desirable reductive products **2**. The racemates could be synthesized through the above transfer hydrogenation procedure with racemic complex RuCl[(±)-Tsdpen](*p*-cymene) as a catalyst.

*(−)-(3R,4R)-3-Hydroxy-4-phenyldihydrofuran-2(3H)-one (**2a**):* 86 mg, 97% yield, >20:1 dr, yellow solid, mp = 139−140 °C, new compound, R_f = 0.25 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −10.40 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.30 (m, 3H), 7.25−7.19 (m, 2H), 4.75−4.69 (m, 1H), 4.68−4.60 (m, 2H), 3.88−3.80 (m, 1H), 2.31 (d, J = 6.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.3, 134.9, 129.2, 128.22, 128.18, 70.6, 70.1, 46.0. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 15.8 min (major). HRMS (ESI-TOF): m/z calcd for $C_{10}H_{11}O_3$ $[M + H]^+$ 179.0703; found, 179.0704.

*(+)-3-Hydroxy-4-(o-tolyl)dihydrofuran-2(3H)-one (**2b**):* 95 mg, 99% yield, >20:1 dr, yellow solid, mp = 175−176 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ +41.68 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.19 (m, 4H), 4.81−4.75 (m, 1H), 4.69−4.62 (m, 2H), 4.15−4.09 (m, 1H), 2.37 (s, 3H), 2.17 (d, J = 6.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.4, 137.7, 133.3, 130.8, 128.1, 127.1, 125.9, 70.4, 70.2, 41.5, 20.1. HPLC: Chiralpak ID column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 80:20, flow = 0.7 mL/min, retention time 17.4 min (major). HRMS (ESI-TOF): m/z calcd for $C_{11}H_{13}O_3$ $[M + H]^+$ 193.0859; found, 193.0856.

*(−)-3-Hydroxy-4-(m-tolyl)dihydrofuran-2(3H)-one (**2c**):* 95 mg, 99% yield, >20:1 dr, purple solid, mp = 93−94 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −19.00 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.26 (m, 1H), 7.20−7.11 (m, 1H), 7.10−6.91 (m, 2H), 4.75−4.67 (m, 1H), 4.66−4.59 (m, 2H), 3.85−3.77 (m, 1H), 2.35 (s, 3H), 2.19 (brs, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.6, 139.0, 134.7, 129.11, 129.07, 128.8, 125.2, 70.6, 70.1, 45.9, 21.5. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 14.4 min (major). HRMS (ESI-TOF): m/z calcd for $C_{11}H_{13}O_3$ $[M + H]^+$ 193.0859; found, 193.0856.

*(−)-3-Hydroxy-4-(p-tolyl)dihydrofuran-2(3H)-one (**2d**):* 90 mg, 94% yield, >20:1 dr, purple solid, mp = 143−144 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −12.00 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22−7.14 (m, 2H), 7.15−7.07 (m, 2H), 4.68 (dd, J = 7.3, 4.9 Hz, 1H), 4.65−4.57 (m, 2H), 3.84−3.76 (m, 1H), 2.34 (s, 3H), 2.26 (d, J = 5.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.4, 138.1, 131.7, 129.9, 128.0, 70.7, 70.1, 45.6, 21.1. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 15.9 min (major). HRMS (ESI-TOF): m/z calcd for $C_{11}H_{13}O_3$ $[M + H]^+$ 193.0859; found, 193.0855.

*(+)-4-(2-Chlorophenyl)-3-hydroxydihydrofuran-2(3H)-one (**2e**):* 102 mg, 96% yield, >20:1 dr, white solid, mp = 157−158 °C, new compound, R_f = 0.70 (hexanes/ethyl acetate 4:1), >99% ee, $[\alpha]_D^{20}$ +62.47 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−7.37 (m, 1H), 7.34−7.26 (m, 3H), 4.82 (dd, J = 7.8, 4.5 Hz, 1H), 4.67−4.57 (m, 2H), 4.49−4.40 (m, 1H), 2.62 (brs, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.2, 134.9, 133.1, 129.9, 129.2, 128.0, 127.6, 70.1, 69.5, 42.2. HPLC: Chiralpak IC column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 39.0 min (major). HRMS (ESI-TOF): m/z calcd for $C_{10}H_{10}ClO_3$ $[M + H]^+$ 213.0313 (^{35}Cl) and 215.0286 (^{37}Cl); found, 213.0318 (^{35}Cl) and 215.0615 (^{37}Cl).

*(−)-4-(3-Chlorophenyl)-3-hydroxydihydrofuran-2(3H)-one (**2f**):* 101 mg, 95% yield, >20:1 dr, yellow solid, mp = 92−93 °C, new compound, R_f = 0.15 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −3.20 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.26 (m, 2H), 7.22 (s, 1H), 7.14−7.07 (m, 1H), 4.71 (dd, J = 7.6, 5.2 Hz, 1H), 4.65−4.54 (m, 2H), 3.83−3.76 (m, 1H), 2.87 (d, J = 5.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.4, 137.2, 134.8, 130.3, 128.5, 128.3, 126.3, 70.4, 69.8, 45.7. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 16.9 min (major). HRMS (ESI-TOF): m/z calcd for $C_{10}H_{10}ClO_3$ $[M + H]^+$ 213.0313 (^{35}Cl) and 215.0286 (^{37}Cl); found, 213.0312 (^{35}Cl) and 215.0283 (^{37}Cl).

*(−)-4-(4-Chlorophenyl)-3-hydroxydihydrofuran-2(3H)-one (**2g**):* 100 mg, 94% yield, >20:1 dr, pink solid, mp = 153−154 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −15.10 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.30 (m, 2H), 7.21−7.14 (m, 2H), 4.71 (dd, J = 7.8, 5.2 Hz, 1H), 4.66−4.55 (m, 2H), 3.86−3.79 (m, 1H), 2.36 (d, J = 5.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.1, 134.2, 133.4, 129.6, 129.2, 70.4,

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69.9, 45.5. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 20.4 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{10}H_{10}ClO_3$ $[M + H]^+$ 213.0315 (^{35}Cl) and 215.0286 (^{37}Cl); found, 213.0318 (^{35}Cl) and 215.0272 (^{37}Cl).

(−)-3-Hydroxy-4-(2-methoxyphenyl)dihydrofuran-2(3H)-one ***(2h):*** 101 mg, 97% yield, >20:1 dr, pink solid, mp = 131−132 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −32.50 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.28 (m, 1H), 7.16 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.00−6.90 (m, 2H), 4.69 (dd, *J* = 8.8, 6.2 Hz, 1H), 4.65−4.59 (m, 1H), 4.46−4.40 (m, 1H), 4.16−4.08 (m, 1H), 3.82 (s, 3H), 2.50 (d, *J* = 6.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.7, 157.3, 129.6, 129.4, 124.4, 121.3, 111.0, 70.5, 69.2, 55.3, 41.4. HPLC: Chiralpak ID column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 80:20, flow = 0.7 mL/min, retention time 23.7 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{13}O_4$ $[M + H]^+$ 209.0808; found, 209.0811.

(−)-3-Hydroxy-4-(3-methoxyphenyl)dihydrofuran-2(3H)-one ***(2i):*** 103 mg, 99% yield, >20:1 dr, pink solid, mp = 99−100 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −21.50 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.28−7.25 (m, 1H), 6.88−6.75 (m, 3H), 4.69 (d, *J* = 7.9 Hz, 1H), 4.64−4.56 (m, 2H), 3.83−3.76 (m, 4H), 2.52 (brs, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.4, 160.1, 136.5, 130.2, 120.2, 114.2, 113.3, 70.6, 70.0, 55.3, 46.0. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 90:10, flow = 0.7 mL/min, retention time 33.5 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{13}O_4$ $[M + H]^+$ 209.0808; found, 209.0810.

(−)-3-Hydroxy-4-(4-methoxyphenyl)dihydrofuran-2(3H)-one ***(2j):*** 101 mg, 97% yield, >20:1 dr, pink solid, mp = 128−129 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −10.20 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.69−4.64 (m, 1H), 4.64−4.54 (m, 2H), 3.81−3.75 (m, 4H), 2.37 (d, *J* = 6.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.4, 159.4, 129.3, 126.6, 114.6, 70.8, 70.1, 55.3, 45.3. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 23.0 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{13}O_4$ $[M + H]^+$ 209.0808; found, 209.0809.

(−)-4-(4-Bromophenyl)-3-hydroxydihydrofuran-2(3H)-one ***(2k):*** 128 mg, 99% yield, >20:1 dr, pink solid, mp = 155−156 °C, new compound, R_f = 0.28 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −10.30 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 4.70 (d, *J* = 7.4 Hz, 1H), 4.66−4.53 (m, 2H), 3.85−3.76 (m, 1H), 2.59 (brs, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.2, 134.0, 132.2, 129.9, 122.2, 70.4, 69.8, 45.5. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 21.8 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{10}H_{10}BrO_3$ $[M + H]^+$ 256.9808 (^{79}Br) and 258.9788 (^{81}Br); found, 256.9809 (^{79}Br) and 258.9795 (^{81}Br).

(−)-4-(4-Fluorophenyl)-3-hydroxydihydrofuran-2(3H)-one ***(2l):*** 115 mg, 98% yield, >20:1 dr, pink solid, mp = 131−132 °C, new compound, R_f = 0.10 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −6.20 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.25−7.14 (m, 2H), 7.12−6.99 (m, 2H), 4.70 (dd, *J* = 7.6, 5.3 Hz, 1H), 4.66−4.54 (m, 2H), 3.86−3.79 (m, 1H), 2.68 (d, *J* = 4.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.4, 162.5 (d, $^1J_{F-C}$= 245.0 Hz), 130.7 (d, $^4J_{F-C}$= 3.0 Hz), 130.0 (d, $^3J_{F-C}$= 9.0 Hz), 116.0 (d, $^2J_{F-C}$= 21.0 Hz), 70.7, 69.9, 45.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −113.99. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 17.6 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{10}H_{10}FO_3$ $[M + H]^+$ 197.0608; found, 197.0609.

(−)-3-Hydroxy-4-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one ***(2m):*** 114 mg, 93% yield, >20:1 dr, pink solid, mp = 132−133 °C, new compound, R_f = 0.10 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ −5.30 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 4.76 (dd, *J* = 7.8, 4.3 Hz, 1H), 4.69−4.58 (m, 2H), 3.94−3.88 (m, 1H), 2.72 (d, *J* = 4.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.2, 139.2, 130.4 (q, $^2J_{F-C}$ = 33.0 Hz), 128.7, 125.9 (q, $^4J_{F-C}$ = 3.8 Hz), 123.9 (q, $^1J_{F-C}$ = 272.7 Hz), 70.3, 69.8, 45.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.72. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 18.2 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{10}F_3O_3$ $[M + H]^+$, 247.0577; found, 247.0576.

(+)-3-Hydroxy-4-(naphthalen-1-yl)dihydrofuran-2(3H)-one ***(2n):*** 113 mg, 99% yield, >20:1 dr, pink solid, mp = 140−141 °C, new compound, R_f = 0.55 (hexanes/ethyl acetate 3:1), >99% ee, $[\alpha]_D^{20}$ +131.19 (*c* 1.00, THF). ^1H NMR (400 MHz, $CDCl_3$) δ7.96 (d, *J* = 7.8 Hz, 1H), 7.87−7.42 (m, 2H), 7.54−7.45 (m, 2H), 7.44−7.36 (m, 2H), 4.88−4.81 (m, 1H), 4.71 (dd, *J* = 9.5, 2.5 Hz, 1H), 4.67−4.56 (m, 2H), 2.49 (d, *J* = 5.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.5, 133.8, 132.4, 131.1, 129.0, 128.7, 126.6, 126.1, 125.6, 124.2, 123.2, 70.6, 70.4, 41.0. HPLC: Chiralpak ID column, 230 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 29.6 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{14}H_{13}O_3$ $[M + H]^+$, 229.0859; found, 229.0864.

(−)-3-Hydroxy-4-(naphthalen-2-yl)dihydrofuran-2(3H)-one ***(2o):*** 110 mg, 96% yield, >20:1 dr, yellow solid, mp = 188−189 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate 2:1), >99% ee, $[\alpha]_D^{20}$ −261.08 (*c* 1.00, THF). ^1H NMR (400 MHz, DMSO-d_6): δ 7.99−7.86 (m, 3H), 7.72 (s, 1H), 7.51−7.48 (m, 2H), 7.37−7.35 (m, 1H), 6.07 (d, *J* = 5.9 Hz, 1H), 4.75−4.72 (m, 1H), 4.70−4.66 (m, 1H), 4.59−4.55 (m, 1H), 3.97−3.93 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 177.1, 135.2, 133.3, 132.6, 128.1, 128.0, 127.9, 127.7, 127.2, 126.6, 126.2, 70.5, 69.4, 46.2. HPLC: Chiralpak ID column, 254 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 32.1 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{14}H_{13}O_3$ $[M + H]^+$, 229.0859; found, 229.0856.

(−)-4-(3,4-Dimethoxyphenyl)-3-hydroxydihydrofuran-2(3H)-one ***(2p):*** 110 mg, 92% yield, >20:1 dr, yellow solid, mp = 167−168 °C, new compound, R_f = 0.15 (hexanes/ethyl acetate 2:1), >99% ee, $[\alpha]_D^{20}$ −42.60 (*c* 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, *J* = 8.2 Hz, 1H), 6.80 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H), 4.71−4.66 (m, 1H), 4.66−4.57 (m, 2H), 3.87 (s, 6H), 3.82−3.77 (m, 1H), 3.73 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.2, 149.4, 149.0, 127.0, 120.1, 111.7, 111.3, 70.7, 70.1, 55.9, 45.7. HPLC: Chiralpak AD-H column, 230 nm, 30 °C, *n*-hexane/*i*-PrOH = 80:20, flow = 0.7 mL/min, retention time 19.3 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{15}O_5$ $[M + H]^+$, 239.0912; found, 239.0914.

(−)-4-Benzyl-3-hydroxydihydrofuran-2(3H)-one ***(2r):*** 88 mg, 92% yield, gray solid, mp = 71−72 °C, known compound,[5b] R_f = 0.40 (hexanes/ethyl acetate 3:1), 98% ee, $[\alpha]_D^{20}$ −15.67 (*c* 0.66, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.3 Hz, 2H), 7.22 (dd, *J* = 13.8, 7.4 Hz, 3H), 4.57 (d, *J* = 7.1 Hz, 1H), 4.16 (d, *J* = 3.9 Hz, 2H), 3.16 (dd, *J* = 14.1, 4.8 Hz, 1H), 2.99−2.79 (m, 2H), 2.42 (dd, *J* = 14.1, 11.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 177.4, 138.5, 129.1, 128.8, 126.7, 69.7, 68.8, 42.2, 31.1. HPLC: Chiracel AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 95:5, flow = 0.7 mL/min, retention time 30.9 and 36.5 min (major). HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{13}O_3$ $[M + H]^+$, 193.0859; found, 193.0860.

(−)-3-Hydroxy-4-(3-methylbenzyl)dihydrofuran-2(3H)-one ***(2s):*** 93 mg, 90% yield, white solid, mp = 102−103 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate 3:1), 94% ee, $[\alpha]_D^{20}$ −4.94 (*c* 1.02, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (t, *J* = 7.5 Hz, 1H), 7.03 (dd, *J* = 23.0, 9.3 Hz, 3H), 4.57 (dd, *J* = 7.1, 1.6 Hz, 1H), 4.15 (d, *J* = 3.8 Hz, 2H), 3.12 (dd, *J* = 14.1, 4.7 Hz, 1H), 2.94−2.83 (m, 2H), 2.41−2.35 (m, 1H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 177.4, 138.5, 138.4, 129.9, 128.7, 127.4, 126.1, 69.8, 68.7, 42.1, 31.0, 21.4. HPLC: Chiracel IC column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 90:10, flow = 0.7 mL/min, retention time 30.5 min (major) and 38.0. HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{15}O_3$ $[M + H]^+$, 207.1016; found, 207.1017.

(−)-3-Hydroxy-4-(4-methylbenzyl)dihydrofuran-2(3H)-one ***(2t):*** 97 mg, 94% yield, white solid, mp = 113−114 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate 3:1), 96% ee, $[\alpha]_D^{20}$ −16.94 (*c* 0.85, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.17−7.05 (m, 4H), 4.56

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(d, J = 7.0 Hz, 1H), 4.15 (d, J = 3.8 Hz, 2H), 3.11 (dd, J = 14.1, 4.6 Hz, 1H), 2.93−2.77 (m, 2H), 2.43−2.35 (m, 1H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 177.3, 136.3, 135.3, 129.5, 129.0, 69.7, 68.7, 42.2, 30.7, 21.0. HPLC: Chiracel AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 90:10, flow = 0.7 mL/min, retention time 13.3 and 16.1 min (major). HRMS (ESI-TOF): m/z calcd for $C_{12}H_{15}O_3$ $[M + H]^+$ 207.1016; found, 207.1015.

*Synthesis of (+)-(3R,4R)-3-(tert-Butyldimethylsilyloxy)-4-phenyldihydrofuran-2(3H)-one (**3**).* To a dried Schlenk tube under a nitrogen atmosphere were added (−)-**2a** (45 mg, 0.25 mmol, >99% ee), imidazole (26 mg, 0.38 mmol), and dry *N*,*N*-dimethylformamide (3.0 mL). The solution was cooled to 0 °C, and *tert*-butyldimethylsilyl chloride (57 mg, 0.38 mmol) was then added. The mixture was stirred at 0 °C for 5 min and then warmed to room temperature. After completion of the reaction (monitored by TLC), water (10 mL) was added, and the water layer was extracted with diethyl ether three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under the reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexanes/ethyl acetate (20:1) as an eluent to give the product (+)-**3**: 67 mg, 92% yield, >20:1 dr, white solid, mp = 92−93 °C, new compound, R_f = 0.45 (hexanes/ethyl acetate 20:1), >99% ee, $[\alpha]_D^{20}$ +12.61 (*c* 0.80, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.26 (m, 3H), 7.25−7.20 (m, 2H), 4.63−4.53 (m, 2H), 4.43 (d, J = 6.6 Hz, 1H), 3.68−3.59 (m, 1H), 0.73 (s, 9H), 0.00 (s, 3H), −0.13 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.2, 134.8, 129.0, 128.4, 127.7, 70.7, 70.5, 47.6, 25.5, 18.1, −5.0, −5.4. HPLC: Chiralpak IB column, 220 nm, 30 °C, *n*-Hexane/ *i*-PrOH = 95:5, flow = 0.7 mL/min, retention time 11.2 min (major). HRMS (ESI-TOF): m/z calcd for $C_{16}H_{25}O_3Si$ $[M + H]^+$, 293.1567; found, 293.1567.

*Synthesis of (−)-(2R,3R)-2,4-Dihydroxy-3-phenyl-1-(piperidin-1-yl)butan-1-one (**4**).* To a dried Schlenk tube under a nitrogen atmosphere were added (−)-**2a** (90 mg, 0.50 mmol, >99% ee), toluene (4.0 mL), and piperidine (0.24 mL, 2.50 mmol). Then the solution was heated to reflux. After the completion of the reaction, the volatiles were removed under the reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexanes/ethyl acetate (2:1) as an eluent to give the amide product (−)-**4**: 93 mg, 76% yield, >20:1 dr, yellow solid, mp = 112−113 °C, new compound, R_f = 0.15 (hexanes/ethyl acetate 1:1), >99% ee, $[\alpha]_D^{20}$ −63.85 (*c* 0.70, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.27 (m, 5H), 4.71−4.64 (m, 1H), 4.24−4.16 (m, 1H), 4.11 (d, J = 7.2 Hz, 1H), 3.89−3.81 (m, 1H), 3.70−3.61 (m, 1H), 3.49−3.41 (m, 1H), 3.24−3.16 (m, 1H), 3.06−2.94 (m, 2H), 2.60 (s, 1H), 1.61−1.25 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.4, 139.8, 128.8, 128.4, 127.4, 70.6, 63.7, 51.8, 46.1, 43.8, 25.8, 25.3, 24.2. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 85:15, flow = 0.7 mL/min, retention time 18.9 min (major). HRMS (ESI-TOF): m/z calcd for $C_{15}H_{22}NO_3$ $[M + H]^+$, 264.1598; found, 264.1594.

*Synthesis of (−)-(2R,3R)-3-Phenylbutane-1,2,4-triol (**5**).* To a dried Schlenk tube under a nitrogen atmosphere were added (−)-**2a** (53 mg, 0.30 mmol, >99% ee) and tetrahydrofuran/water (1.8 mL/0.2 mL). The solution was cooled to 0 °C, and sodium borohydride (45 mg, 1.20 mmol) was then added. The reaction was stirred at 0 °C for 5 min. Then, the reaction was allowed to warm to room temperature. After completion of the reaction (monitored by TLC), brine (10 mL) was added, and the water layer was extracted with diethyl ether three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under the reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexanes/ethyl acetate (1:2) as an eluent to give the reductive product (−)-**5**: (note that the ee of this product was determined by the analysis of product derived by acetic anhydride) 37 mg, 67% yield, white solid, mp = 71−72 °C, new compound, R_f = 0.15 (hexanes/ethyl acetate 1:2), $[\alpha]_D^{20}$ −11.20 (*c* 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.26 (m, 3H), 7.21−7.15 (m, 2H), 4.18−4.09 (m, 2H), 3.96−3.88 (m, 1H), 3.62−3.39 (m, 2H), 3.39−3.30 (m, 1H), 3.02−2.94 (m, 1H), 2.81 (s, 1H), 2.19 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.3, 129.2, 128.3, 127.6, 76.3, 67.0, 65.3, 50.2. HRMS (ESI-TOF): m/z calcd for $C_{10}H_{15}O_3$ $[M + H]^+$, 183.1017; found, 183.1016.

*Synthesis of (−)-(2R,3R)-3-Phenylbutane-1,2,4-triyl Triacetate (**6**).* In a dried Schlenk tube under nitrogen atmosphere, sodium acetate (15 mg, 0.18 mmol) and acetic anhydride (2.0 mL) were stirred at 120 °C for 30 min. Then (−)-**5** (18 mg, 0.10 mmol) was added. The reaction was stirred at this temperature for another 3 h. After completion of the reaction (monitored by TLC), the mixture was poured into ice water, and saturated sodium bicarbonate solution was added until the pH reached 7. Dichloromethane (10 mL) was added, and the water layer was extracted three times with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under the reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexanes/ethyl acetate (20:1) as an eluent to give the acetyl protected product (−)-**6**: 18 mg, 58% yield, >20:1 dr, viscous solid, new compound, R_f = 0.60 (hexanes/ethyl acetate 5:1), >99% ee, $[\alpha]_D^{20}$ −4.60 (*c* 0.68, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.27 (m, 3H), 7.26−7.21 (m, 2H), 5.50−5.43 (m, 1H), 4.43 (dd, J = 11.1, 6.6 Hz, 1H), 4.26 (dd, J = 11.1, 4.4 Hz, 1H), 4.19 (dd, J = 12.2, 2.7 Hz, 1H), 3.77 (dd, J = 12.2, 5.8 Hz, 1H), 3.32−3.24 (m, 1H), 2.11 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.8, 170.6, 170.4, 137.7, 129.0, 128.4, 127.8, 71.5, 64.7, 63.7, 45.6, 21.0, 20.9, 20.7. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 93:7, flow = 0.7 mL/min, retention time 13.7 min (major). HRMS (ESI-TOF): m/z calcd for $C_{16}H_{20}O_6$ $[M + NH_4]^+$, 326.1598; found, 326.1601.

*Synthesis of (−)-(3S,4R)-3-Chloro-4-phenyldihydrofuran-2(3H)-one (**7**).* In a dried Schlenk tube under a nitrogen atmosphere, (−)-**2a** (36 mg, 0.20 mmol, >99% ee) was dissolved in dry tetrahydrofuran (2.0 mL), and then triphenylphosphine (79 mg, 0.30 mmol) and *N*-chlorosuccinimide (53 mg, 0.40 mmol) were added. The mixture was stirred at room temperature. After the completion of the reaction, the solvent was removed under the reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexanes/ethyl acetate (20:1) as an eluent to give the desired product (−)-**7**: 34 mg, 87% yield, >20:1 dr, colorless liquid, the known compound,[15] R_f = 0.60 (hexanes/ethyl acetate 5:1), >99% ee, $[\alpha]_D^{20}$ −74.66 (*c* 0.60, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.35 (m, 3H), 7.32−7.27 (m, 2H), 4.75 (dd, J = 9.2, 7.9 Hz, 1H), 4.53 (d, J = 9.2 Hz, 1H), 4.37 (t, J = 9.0 Hz, 1H), 3.84 (q, J = 8.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.5, 135.3, 129.5, 128.7, 127.0, 71.0, 56.7, 51.1. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-hexane/*i*-PrOH = 90:10, flow = 0.7 mL/min, retention time 18.6 min (major). HRMS (ESI-TOF): m/z calcd for $C_{10}H_{10}ClO_2$ $[M + H]^+$, 197.0362 (^{35}Cl) and 199.0328 (^{37}Cl); found, 197.0364 (^{35}Cl) and 199.0342 (^{37}Cl).

Scale-up Experiment. 3-Hydroxy-4-(phenyl)furan-2(5*H*)-one **1a** (6.0 mmol, 1.057 g), RuCl[(*R*,*R*)-Tsdpen]-(*p*-cymene) (0.115 g, 0.18 mmol, 3 mol %), tetrahydrofuran (25 mL), and formic acid-triethylamine azeotrope (3.0 mL, 36.0 mmol) were placed in a dried Schlenk tube under a nitrogen atmosphere. The mixture was stirred at 50 °C (oil bath temperature) for 13 h. After the completion of the reduction, the volatiles were removed under the reduced pressure. A saturated ammonium chloride aqueous solution (25 mL) was added, and the water layer was extracted with dichloromethane three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexanes/ethyl acetate as an eluent to give the desirable product (−)-**2a**: 1.007 g, 94% yield, 99% ee.

Determination of the Absolute Configuration of Compound (+)-3. To determine the absolute configuration of (*tert*-butyldimethylsilyl)-oxy)-4-phenyldihydrofuran-2(3*H*)-one (+)-**3**, (+)-**3** (20 mg, >99% ee) was dissolved in dichloromethane (0.5 mL), and *n*-hexane (2.0 mL) was added slowly at room temperature. The solvent diffused slowly, and the single crystal was obtained after 3 days. The structure in Figure S1 showed that the absolute configuration of (+)-**3** is (3*R*,4*R*). The CCDC number is 2071172. Thus, the absolute configuration of the reductive product (−)-**2a** was

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unambiguously assigned as (3*R*,4*R*). These details can be obtained free of charge via www.ccdc.com.ac.uk/data_request/cif from the Cambridge Crystallographic Data Centre.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02156.

Copies of ^{1}H, $^{13}C\{^{1}H\}$,and $^{19}F\{^{1}H\}$ spectra of all new compounds and X-ray crystallography data (PDF)

Accession Codes

CCDC 2071172 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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