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Synthesis of Enantiopure γ-Lactones via a RuPHOX-Ru Catalyzed Asymmetric Hydrogenation of γ-Keto Acids

Jing Li,[a] Yujie Ma,[a] Yufei Lu,[a] Yangang Liu,[a] Delong Liu,[a,*] and Wanbin Zhang[a,b,*]

[a] Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. China
[b] School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. China
Fax: (+)86-21-54743265; Phone: (+)86-21-34207176; E-mail: dlliu@sjtu.edu.cn; wanbin@sjtu.edu.cn

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Abstract. A RuPHOX-Ru catalyzed asymmetric hydrogenation of γ-keto acids has been developed, affording the corresponding enantiopure γ-lactones in high yields and with up to 97% ee. The reaction could be performed on a gram scale with a relatively low catalyst loading (up to 10000 S/C) under the indicated reaction conditions and the resulting products can be transformed to several enantiopure building blocks, biologically active compounds and enantiopure drugs.

Keywords: Enantiopure γ-lactone; RuPHOX-Ru; Asymmetric hydrogenation; γ-Keto acid

Introduction

The enantiopure γ-lactone skeleton is present in numerous natural products, biologically active compounds and drugs,[1] such as insect pheromones,[2] (+)-harzialactone A[3] and plakolide A,[4] etc. (Figure 1, up). The enantiopure γ-lactone motif is also found in important precursors for the synthesis of many enantiopure drugs. For example, it can be transferred to several norepinephrine reuptakes inhibiting antidepressants which treat psychiatric disorders (Figure1, down).[5]

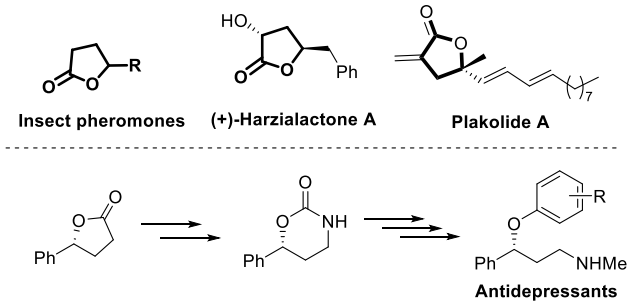
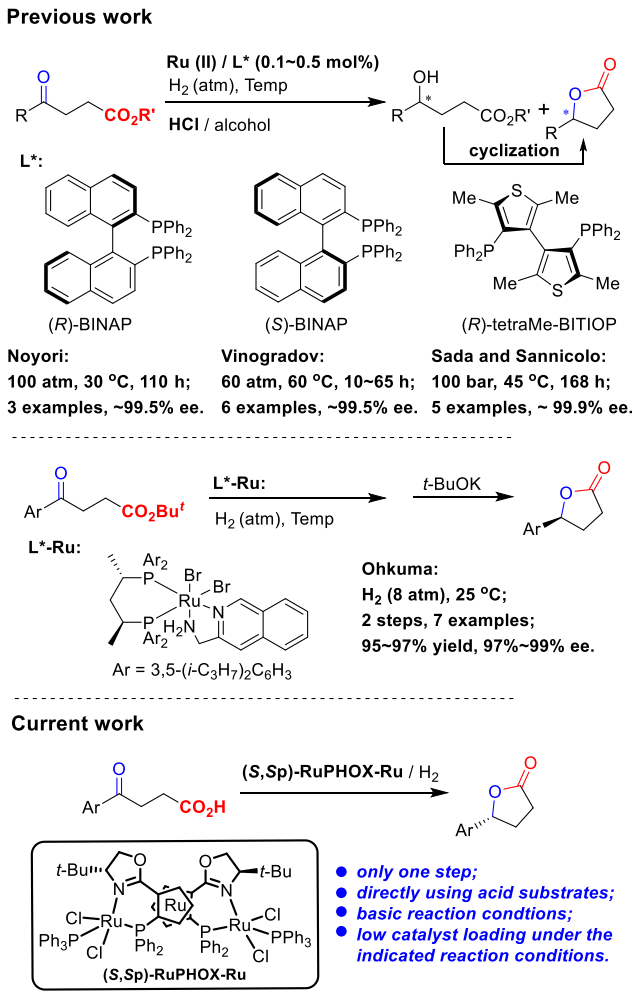


Figure 1. Enantiopure γ-lactones and their transformation

Many methodologies have been reported for the synthesis of enantiopure γ-lactones, including asymmetric oxidation,[6] hydroboration,[7] hydrosilylation,[8] transfer hydrogenation,[9] and enzyme catalysis,[10] etc. Generally, asymmetric hydrogenation is undoubtedly an efficient pathway for the construction of enantiopure γ-lactones because of its high efficiency, environmental friendliness, and low economic cost (Scheme 1).[11-14] In 1990, Noyori and co-workers developed an asymmetric hydrogenation of γ-keto esters by using the BINAP-Ru catalyst, providing high enantioselectivity for substrates bearing alkyl groups (Scheme 1, up).[12] However, harsh reaction conditions (100 atm) and a long reaction time (110 h) were needed to ensure the completion of the reaction. Adopting a similar catalytic system to that mentioned above (except using $RuCl_3$ as a metal salt), the Vinogradov group were able to promote the reaction using a somewhat lower H_2 pressure (60 atm) but high reaction temperature (60 °C).[13a] Although excellent enantioselectivities were obtained, a long reaction time was still needed. Sada and Sannicolo carried out this reaction by using a diphosphine ligand with an atropisomeric biheteroaromatic backbone.[13b] Nevertheless, harsh reaction conditions (100 bar) and a long reaction time (168 h) were also required. In addition, a solution of HCl in alcohol has been used in all of the above reactions in order to improve reaction activities, resulting in corrosion of the stainless-steel autoclave. Furthermore, the above reactions often give a mixture of products containing cyclic γ-lactones and acyclic γ-hydroxy esters, and an additional cyclization is needed to obtain the uniform cyclic γ-lactones. Just recently, Ohkuma and co-workers disclosed a P,N-Ru-complex catalyzed asymmetric hydrogenation of γ-keto esters, with the corresponding γ-hydroxy esters as the main products (including γ-lactones) being obtained in high yields and excellent enantioselectivities (Scheme 1, middle).[14] The mixed products were then subjected to a further lactonization with *t*-BuOK as a base to

deliver terminal enantiopure γ-lactones. By using γ-keto esters as substrates, harsh reaction conditions and/or an additional cyclization is generally needed for the synthesis of enantiopure γ-lactones. Therefore, the development of a reaction system to deliver enantiopure γ-lactones directly via the use of alternative substrates, e.g. γ-keto acids, under basic reaction conditions, is essential.

Our group has previously developed a planar enantiopure ruthenocenyl phosphino-oxazoline-ruthenium complex (RuPHOX-Ru), which has shown promising catalytic activity in several asymmetric reactions.[15-16] Specifically, RuPHOX-Ru has been employed as an efficient enantiopure catalyst in several asymmetric hydrogenations with excellent asymmetric catalytic behavior.[16] Herein, we report an efficient RuPHOX-Ru catalyzed asymmetric hydrogenation of γ-keto acids for the synthesis of enantiopure γ-lactones (Scheme 1, down).

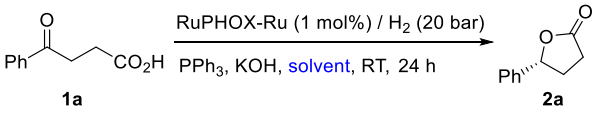


Scheme 1. Asymmetric hydrogenation of γ-aryl keto acids/esters.

Results and Discussion

Our initial experiments began with the asymmetric hydrogenation of 4-oxo-4-phenylbutanoic acid (γ-keto acid **1a**) using RuPHOX-Ru as a catalyst. As shown in Table 1, MeOH was first used as a solvent and the desired product (*R*)-5-phenyldihydrofuran-2(*3H*)-one (enantiopure γ-lactone **2a**) was obtained in poor conversion but with 94% ee (entry 1). The use of EtOH increased the conversion and provided a higher enantioselectivity than that of MeOH (entry 2). When *n*-PrOH was used as a solvent, the corresponding product **2a** was obtained with 96% conversion and 94% ee (entry 3). The substrate was fully transformed to the desired product with 94% ee when the reaction was carried out in *i*-PrOH (entry 4). For comparison, low conversion and enantioselectivity were observed when *n*-BuOH was employed in the above reaction (entry 5).

Table 1. Screening of solvent.[a]

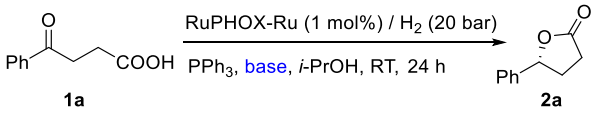


Entry	Solvent	Yield (%)[b]	Ee (%)[c,d]
1	MeOH	13	94
2	EtOH	90	96
3	*n*-PrOH	96	94
4	*i*-PrOH	>99	94
5	*n*-BuOH	89	92

[a] Conditions: **1a** (0.3 mmol), RuPHOX-Ru (1 mol%), KOH (2.0 equiv), and solvent (3 mL) under 20 bar hydrogen pressure at RT for 24 h.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC analysis using the Chiralcel AS-H column.
[d] The absolute configuration of **2a** was determined as *R*-configuration by comparing the specific rotation with reported data.[9b]

The effect of different bases on the reaction was then investigated (Table 2). Several strong inorganic bases were examined (entries 1-4). It was shown that

Table 2. Screening of base.[a]



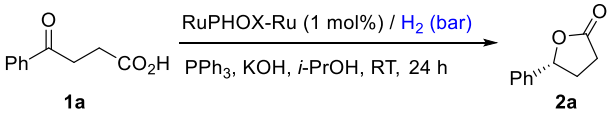
Entry	Base	Conv (%)[b]	Ee (%)[c,d]
1	LiOH•H$_2$O	50	90
2	NaOH	96	91
3	KOH	>99	94
4	*t*-BuOK	>99	92
5[e]	KOH	43	92
6[f]	KOH	>99	92
7	Et$_3$N	NR[g]	-

[a] Using the optimal reaction conditions shown in Table 1 with *i*-PrOH as a solvent.
[b-d] As mentioned in Table 1.
[e] Using 1.0 equiv of base.
[f] Using 3.0 equiv of base.
[g] "NR" means no reaction occurred.

reaction with KOH as the base provided the best result (entry 3). When the amount of KOH was reduced, a sharp decrease in reaction activity was observed (entry 5). Additionally, increasing the amount of KOH did not influence the reaction outcome (entry 6). To our surprise, no reaction occurred when an organic base such as Et_3N was used instead of inorganic bases (entry 7). Therefore, KOH was found to be the most suitable base and was used in subsequent screening.

Subsequently, we carried out the reaction under a low hydrogen pressure with the aim of using milder reaction conditions (Table 3). Similar results were obtained when the reaction was conducted at a high hydrogen pressure (entry 1). We thus focused our attention on screening the reaction conditions using a low hydrogen pressure. It was found that lowering the hydrogen pressure had no influence on the asymmetric behavior of the hydrogenation (entries 2-4) To our delight, almost the same catalytic behavior was observed when the hydrogenation was carried out under 6 bar hydrogen pressure (entry 4). Further decreasing the hydrogen pressure to 2 bar resulted in only 45% conversion and 60% ee (entry 5).

Table 3. Screening of hydrogen pressure.[a]

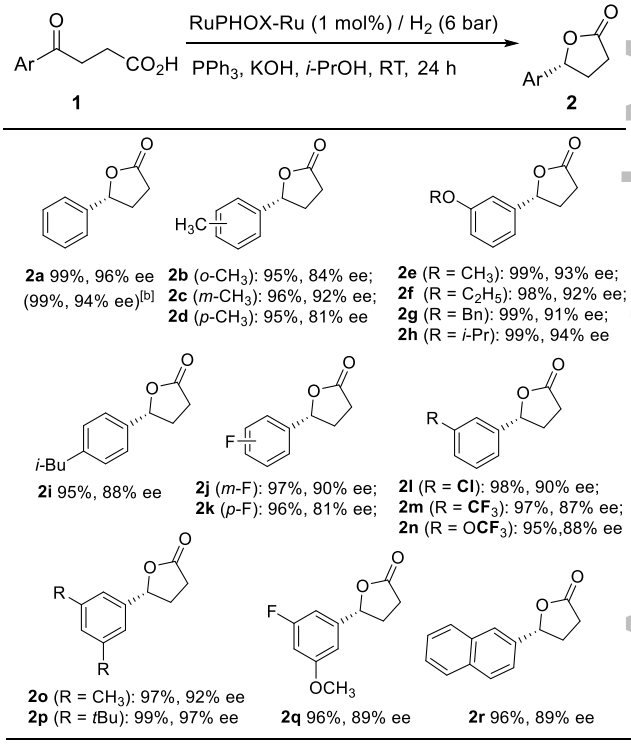


Entry	H_2 (bar)	Conv (%)[b]	Ee (%)[c,d]
1	50	>99	93
2	20	>99	94
3	10	>99	95
4	6	>99	96
5	2	45	60

[a] Using the optimal reaction conditions shown in Table 1 with *i*-PrOH as a solvent. [b-d] As mentioned in Table 1.

With the optimized reaction conditions in hand, the scope of hydrogenation substrates was investigated (Table 4). Firstly, the asymmetric hydrogenation of the potassium salt of **1a** was carried out under the optimal reaction conditions in the presence of 1 equiv of KOH. The desired product **2a** was obtained in quantitative yield and 94% ee. Then, **1** bearing different electron-donating substituents at the phenyl ring, was examined. Substrates with a Me group located at the *o*, *m* or *p*-positions of the phenyl ring were reduced, with the desired products being obtained in excellent yields and with ees of approximately 90% (**2b**–**2d**). Substrates possessing a *m*-Me substituent provided the corresponding products with higher ee (**2c**) compared with their *o*- and *p*-substituted counterparts (**2b** and **2d**). We, therefore, synthesized different substrates with electron-donating groups at the *m*-position of the phenyl ring. To our delight, the desired products were obtained in quantitative yields and ees higher than 90% were obtained for all of the reactions (**2e**–**2h**). The asymmetric hydrogenation of a substrate with an *i*-Bu group at the *p*-position of the phenyl ring also provided 95% yield and 88% ee (**2i**). Next, **1** bearing different electron-withdrawing substituents at the phenyl ring, was examined. Substrates bearing a F atom located at the *m* or *p*-positions of the phenyl ring were first examined. A similar trend was observed for the asymmetric hydrogenation of **1** bearing electron-withdrawing groups and substrates possessing *m*-substituents (**2j**) provided higher *ee* values than that of substrates possessing *p*-substituents (**2k**). Subsequently, substrates bearing electron-withdrawing groups on the *m*-position of the phenyl ring were examined, with the desired products being obtained in excellent yields and approximately 90% ee (**2l**–**2n**). When the reactions of substrates bearing two electron-donating groups on the phenyl ring were carried out, the products were obtained in high yields and excellent enantioselectivities (**2o** and **2p**). **2p** with two *t*-Bu groups on the phenyl ring was obtained in quantitative yield and 97% ee. The reaction of a substrate bearing two electronically different groups on the phenyl ring was also carried out, with the hydrogenated products being obtained in excellent yield and good enantioselectivity (**2q**). Finally, a naphthalene substrate also provided its corresponding product in high yield and enantioselectivity (**2r**, up to 96% yield and 89% ee).

Table 4. Scope of substrates **1**.[a]



[a] Using the optimal reaction conditions shown in Table 1; Ees were determined by chiral HPLC analysis of **2** using AS-H and IC-3 column; Absolute configuration of **2** was determined as *R*-configuration by comparing the specific rotation with **2a**.

[b] The reaction was carried out using the potassium salt of **1a** under the optimal reaction conditions in the presence of 1 equiv of KOH.

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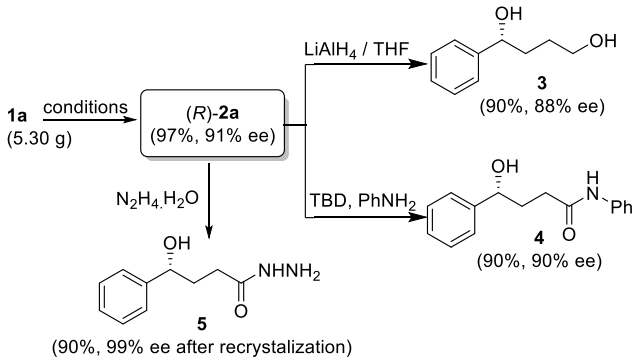
Unfortunately, no reaction occurred when several alkyl substituted keto esters, such as those bearing methyl, *tert*-butyl or cyclohexyl groups, were used.

To examine the efficiency of the catalyst system, the reaction was carried out on a gram scale with a low catalyst loading (Scheme 3). Thus, **1a** (5.30 g) was subjected to the optimal reaction conditions using a 0.01 mol% catalyst dosage (S/C = 10000) under 50 bar hydrogen pressure. The reaction went to completion within 72 h at RT, providing the desired product **2a** in 97% yield with somewhat loss of enantioselectivity (91% ee).

2a can be transformed into several different enantiopure building blocks, biologically active compounds, and drugs. For example, **2a** could be reduced to diol **3** in 90% yield and 88% ee, which is an important building block in organic synthesis.[17] After aminolysis with aniline, the ring-opening product **4** of **2a**, a valuable *N*-aryl amide scaffold, was obtained in good yield and ee.[18] Fluoxetine hydrochloride, a selective serotonin reuptake inhibitor developed by Eli Lilly, was approved by FDA in 1987.[19] The pivotal step to construct fluoxetine involves the preparation of the key intermediate **5** (Scheme 2). Thus, (*R*)-**2a** was dissolved in EtOH, followed by the addition of hydrazine hydrate in one portion, yielding the key intermediate **5** in 90% yield and with 99% ee.



Scheme 2. Transformations of (*R*)-**2a**

Conclusion

In conclusion, we have developed an efficient RuPHOX-Ru catalyzed asymmetric hydrogenation of γ-aryl ketone acids, with the corresponding enantiopure γ-lactones being obtained in 95~99% yield and with 81~97% ee. The reaction could be easily performed on a gram scale with a relatively low catalyst loading (up to 10000 S/C) under the indicated reaction conditions. The resulting products can be transformed into several enantiopure building blocks, biologically active compounds and enantiopure drugs. The current catalytic system employing the RuPHOX-Ru complex as an enantiopure catalyst provides an efficient pathway for the synthesis of enantiopure γ-lactones and their derivatives.

Experimental Section

General: All hydrogenation reactions were performed in an autoclave under an atmosphere of hydrogen, and the workup was carried out in air. Solvents were degassed using standard procedures. Commercially available reagents were used without further purification. Column chromatography was performed using 100-200 mesh silica gel. Melting points were measured with SGW X-4 micro melting point apparatus and the thermometer was uncorrected. NMR spectra were recorded on a Varian MERCURY plus-400 spectrometer with TMS as an internal standard. Enantioselectivity was measured by a high-performance liquid chromatography (HPLC) using Daicel Chiralcel AS-H or IC-3 column with *n*-hexane/*i*-PrOH as eluent.

General procedure for the asymmetric hydrogenation

In a nitrogen-filled glovebox, a hydrogenation tube was charged with a stirring bar, **1** (0.3 mmol), RuPHOX-Ru (5.2 mg, 1 mol%), KOH (33.7 mg, 2.0 equiv), PPh_3 (1.0 mg, 1 mol%), and MeOH (3 mL) were then injected into the hydrogenation tube using a syringe. The hydrogenation tube was then put into an autoclave. The system was evacuated and filled with hydrogen 3 times. The autoclave was then charged with hydrogen to 6 bar hydrogen pressure, and the reaction mixture was stirred at RT for 24 h. After releasing the hydrogen, the reaction mixture was acidified with 3 M HCl solution and extracted with EtOAc (3 × 5 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The conversion of the substrate was determined by ^{1}H NMR analysis and the ee value was determined by HPLC using the Chiralcel AS-H or IC-3 column.

The corresponding racemic product **2** was obtained using $NaBH_4$ as a reductant in MeOH at RT.

(*R*)-5-Phenyldihydrofuran-2(3*H*)-one (2a)[20]: Colorless oil (48.2 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.30 (m, 5H), 5.48 (t, J = 6.8 Hz, 1H), 2.68–2.58 (m, 3H), 2.23–2.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 139.3, 128.7, 128.4, 125.2, 81.2, 30.9, 28.9; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 75 : 25, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 12.98 min (major) and t_{R2} = 15.07 min (minor); ee = 96%; $[\alpha]_D^{27}$ = +16.42 (*c* 0.55, $CHCl_3$).

(*R*)-5-(*o*-Tolyl)dihydrofuran-2(3*H*)-one (2b)[14]: Colorless oil (50.2 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.16 (m, 4H), 5.71–5.66 (m, 1H), 2.69–2.60 (m, 3H), 2.31 (s, 3H), 2.15–2.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 137.5, 134.2, 130.7, 128.1, 126.4, 124.1, 78.8, 29.5, 28.6, 18.9;

HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 95 : 5, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 16.63 min (major) and t_{R2} = 18.90 min (minor); ee = 84%; $[\alpha]_D^{27}$ = +51.85 (*c* 0.50, $CHCl_3$).

(*R*)-5-(*m*-Tolyl)dihydrofuran-2(3*H*)-one (2c) [20]: Colorless oil (50.7 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.24 (m, 1H), 7.13–7.09 (m, 3H), 5.47–5.44 (m, 1H), 2.68–2.57 (m, 3H), 2.35 (s, 3H), 2.23–2.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 139.3, 138.5, 129.1, 128.6, 125.8, 122.2, 81.2, 30.9, 28.9, 21.3; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 80 : 20, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 14.87 min (major) and t_{R2} = 19.24 min (minor); ee = 92%; $[\alpha]_D^{27}$ = +18.69 (*c* 0.25, $CHCl_3$).

(*R*)-5-(*p*-Tolyl)dihydrofuran-2(3*H*)-one (2d) [20]: Colorless oil (50.2 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.11 (m, 4H), 5.48–5.40 (m, 1H), 2.66–2.54 (m, 3H), 2.33 (s, 3H), 2.21–2.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 138.3, 136.3, 129.4, 125.3, 81.3, 30.9, 29.0, 21.1; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 75 : 25, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 11.97 min (major) and t_{R2} = 14.45 min (minor); ee = 81%; $[\alpha]_D^{27}$ = +13.85 (*c* 0.30, $CHCl_3$).

(*R*)-5-(3-Methoxyphenyl)dihydrofuran-2(3*H*)-one (2e) [20]: Colorless oil (57.1 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.24 (m, 1H), 6.88–6.85 (m, 3H), 5.48–5.45 (m, 1H), 3.79 (s, 3H), 2.68–2.58 (m, 3H), 2.23–2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 159.8, 141.1, 129.8, 117.3, 113.8, 110.7, 80.9, 55.2, 30.9, 28.8; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 75 : 25, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 16.63 min (major) and t_{R2} = 19.85 min (minor); ee = 93%; $[\alpha]_D^{27}$ = 19.54 (*c* +0.65, $CHCl_3$).

(*R*)-5-(3-Ethoxyphenyl)dihydrofuran-2(3*H*)-one (2f): Colorless oil (60.6 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.27 (m, 1H), 6.87–6.84 (m, 3H), 5.49–5.44 (m, 1H), 4.02 (q, *J* = 6.8, 12.8 Hz, 2H), 2.66–2.58 (m, 3H), 2.22–2.10 (m, 1H), 1.39 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 159.2, 140.9, 129.8, 117.2, 114.2, 111.3, 81.0, 63.4, 30.9, 28.8, 14.7; IR (KBr) cm^{-1}: 2972, 2926, 2867, 1779, 1462, 1380, 1373, 879, 715; HR-MS (ESI): m/z=207.1025, calcd. for $C_{12}H_{14}O_3$ $[M+H]^+$: 207.1021; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 75 : 25, UV = 210 nm, flow rate = 0.8 mL/min), t_{R1} = 16.46 min (major) and t_{R2} = 19.65 min (minor), ee = 92%; $[\alpha]_D^{27}$ = +15.50 (*c* 0.75, $CHCl_3$).

(*R*)-5-(3-(Benzyloxy)phenyl)dihydrofuran-2(3*H*)-one (2g): White solid (79.7 mg, 99%). Mp 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.35 (m, 4H), 7.33–7.24 (m, 2H), 6.93–6.88 (m, 3H), 5.49–5.44 (m, 1H), 5.05 (s, 2H), 2.67–2.59 (m, 3H), 2.22–2.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 159.0, 141.0, 136.6, 129.9, 128.5, 128.0, 127.4, 117.6, 114.6, 111.7, 80.9, 70.0, 30.8, 28.8; IR (KBr) cm^{-1}: 2359, 2341, 1778, 1766, 1462, 1261, 1022, 798; HR-MS (ESI): m/z=291.0997, calcd. for $C_{17}H_{16}O_3$ $[M+Na]^+$: 291.0990; HPLC (Chiralcel IC-3, *n*-hexane/*i*-PrOH = 90 : 10, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 52.80 min (major) and t_{R2} = 57.05 min (minor); ee = 91%; $[\alpha]_D^{27}$ = +10.47 (*c* 0.50, $CHCl_3$).

(*R*)-5-(3-Propoxyphenyl)dihydrofuran-2(3*H*)-one (2h): White solid (65.4 mg, 99%). Mp 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.23 (m, 1H), 6.85–6.81 (m, 3H), 5.46–5.43 (m, 1H), 4.58–4.49 (m, 1H), 2.67–2.56 (m, 3H), 2.21–2.09 (m, 1H), 1.31 (d, *J* = 5.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 158.1, 140.9, 129.8, 117.1, 115.4, 112.7, 81.0, 69.8, 30.9, 28.8, 21.9; IR (KBr) cm^{-1}: 2977, 2933, 1781, 1603, 1584, 1489, 1449, 1384, 1373, 788, 699; HR-MS (ESI): m/z=221.1179, calcd. for $C_{13}H_{16}O_3$ $[M+H]^+$: 221.1178; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 75 : 25, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 13.00 min (major) and t_{R2} = 15.03 min (minor); ee = 94%; $[\alpha]_D^{27}$ = +13.58 (*c* 0.60, $CHCl_3$).

(*R*)-5-(4-Isobutylphenyl)dihydrofuran-2(3*H*)-one (2i): Colorless oil (62.2 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 5.47–5.44 (m, 1H), 2.64–2.58 (m, 3H), 2.45 (d, *J* = 6.8 Hz, 2H), 2.23–2.12 (m, 1H), 1.88–1.78 (m, 1H), 0.87 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 142.1, 136.4, 129.4, 125.1, 81.3, 45.0, 30.8, 30.1, 29.0, 22.3; IR (KBr) cm^{-1}: 2980, 2931, 1770, 1604, 1585, 1455, 1393, 1361, 786, 699; HR-MS (ESI): m/z=219.1385, calcd. for $C_{14}H_{18}O_2$ $[M+H]^+$: 219.1385; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 75 : 25, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 9.06 min (major) and t_{R2} = 10.69 min (minor); ee = 88%; $[\alpha]_D^{27}$ = +13.74 (*c* 0.50, $CHCl_3$).

(*R*)-5-(3-Fluorophenyl)dihydrofuran-2(3*H*)-one (2j): Colorless oil (52.4 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.30 (m, 1H), 7.08–6.97 (m, 3H), 5.50–5.45 (m, 1H), 2.69–2.60 (m, 3H), 2.20–2.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 162.9 (d, *J* = 245.6 Hz), 141.9 (d, *J* = 7.3 Hz), 130.4 (d, *J* = 8.1 Hz), 120.7 (d, *J* = 2.9 Hz), 115.2 (d, *J* = 20.9 Hz), 112.2(d, *J* = 22.6 Hz), 80.2, 30.8, 28.6; IR (KBr) cm^{-1}: 2970, 1720, 1592, 1490, 1451, 1269, 1140, 1024, 911, 789, 694; HR-MS (ESI): m/z=181.0665, calcd. for $C_{10}H_9FO_2$ $[M+H]^+$: 181.0659; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 95 : 5, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 14.40 min (major) and t_{R2} = 17.50 min (minor); ee = 90%; $[\alpha]_D^{27}$ = +27.10 (*c* 0.60, $CHCl_3$).

(*R*)-5-(4-Fluorophenyl)dihydrofuran-2(3*H*)-one

(2k)[20]: Colorless oil (51.9 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, J = 6.0 Hz, 2H), 7.04 (t, J = 8.4 Hz, 2H), 5.46–5.43 (m, 1H), 2.68–2.56 (m, 3H), 2.19–2.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 162.6 (d, J = 245.8 Hz), 135.0 (d, J = 3.1 Hz), 127.2 (d, J = 8.3 Hz), 115.7 (d, J = 21.6 Hz), 80.6, 31.0, 29.0; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 98 : 2, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 16.82 min (major) and t_{R2} = 19.60 min (minor); ee = 81%.

(*R*)-5-(3-Chlorophenyl)dihydrofuran-2(3*H*)-one (2l)[9a]: Colorless oil (57.8 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.29 (m, 3H), 7.23–7.19 (m, 1H), 5.49–5.44 (m, 1H), 2.70–2.61 (m, 3H), 2.20–2.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 141.4, 134.7, 130.1, 128.5, 125.4, 123.2, 80.1, 30.8, 28.7; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90 : 10, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 83.77 min (major) and t_{R2} = 114.60 min (minor); ee = 90%; $[\alpha]_D^{27}$ = +19.57 (c 0.50, $CHCl_3$).

(*R*)-5-(3-(Trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one (2m): Colorless oil (67.0 mg, 97%). (400 MHz, $CDCl_3$): δ 7.61–7.57 (m, 2H), 7.51–7.48 (m, 2H), 5.54–5.51 (m, 1H), 2.75–2.64 (m, 3H), 2.21–2.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 140.4, 131.3, 131.0, 129.3, 128.4, 125.2 (q, J = 3.8, 7.6 Hz), 122.0 (q, J = 3.9, 7.6 Hz), 80.1, 30.9, 28.7; IR (KBr) cm^{-1}: 2954, 1718, 1695, 1610, 1427, 1408, 1328, 1256, 1164, 940, 803, 697; HR-MS (ESI): m/z = 231.0636, calcd. for $C_{11}H_9F_3O_2$ $[M+H]^+$: 231.0633; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 75 : 25, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 9.30 min (major) and t_{R2} = 11.20 min (minor); ee = 87%; $[\alpha]_D^{27}$ = +14.38 (*c* 0.25, $CHCl_3$).

(*R*)-5-(3-(Trifluoromethoxy)phenyl)dihydrofuran-2(3*H*)-one (2n): Colorless oil (70.2 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.19–7.17 (m, 2H), 5.49–5.47 (m, 1H), 2.72–2.62 (m, 3H), 2.19–2.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 149.5, 141.7, 130.2, 123.4, 120.7, 120.3 (q, J = 255.2 Hz), 117.8, 80.0, 30.8, 28.6; IR (KBr) cm^{-1}: 2922, 1782, 1492, 1451, 1259, 1216, 1169, 929, 799, 702; HR-MS (ESI): m/z = 247.0583, calcd. for $C_{11}H_9F_3O_3$ $[M+H]^+$: 247.0582; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 75 : 25, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 9.62 min (major) and t_{R2} = 11.70 min (minor); ee = 88%; $[\alpha]_D^{27}$ = +7.98 (*c* 0.65, $CHCl_3$).

(*R*)-5-(3,5-Dimethylphenyl)dihydrofuran-2(3*H*)-one (2o): Colorless oil (55.4 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (s, 1H), 6.91 (s, 2H), 5.43–5.40 (m, 1H), 2.63–2.56 (m, 3H), 2.29 (s, 6H), 2.20–2.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 139.3, 138.3, 129.9, 122.9, 81.3, 30.9, 28.9, 21.2; IR (KBr) cm^{-1}: 2918, 2359, 2341, 1714, 1608, 1462, 1217, 1138, 848, 807, 703; HR-MS (ESI): m/z=191.1069, calcd. for $C_{12}H_{14}O_2$ $[M+H]^+$: 191.1072; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 75 : 25, UV =210 nm, flow rate = 0.8 mL/min) t_{R1} = 10.23 min (major) and t_{R2} = 13.17 min (minor); ee = 92%; $[\alpha]_D^{27}$ = +6.92 (*c* 0.15, $CHCl_3$).

(*R*)-5-(3,5-Di-tert-butylphenyl)dihydrofuran-2(3*H*)-one (2p): White solid (81.5 mg, 99%). Mp 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 1H), 7.13 (s, 2H), 5.50–5.46 (m, 1H), 2.67–2.62 (m, 3H), 2.26–2.14 (m, 1H), 1.30 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 151.3, 138.3, 122.5, 119.4, 82.1, 34.9, 31.4, 31.0, 29.2; IR (KBr) cm^{-1}: 2962, 2918, 2848, 1781, 1595, 1458, 1437, 1363, 1260, 843, 799, 686; HR-MS (ESI): m/z = 275.2006, calcd. for $C_{18}H_{26}O_2$ $[M+H]^+$: 275.2011; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90 : 10, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 7.35 min (major) and t_{R2} = 8.13 min (minor), ee = 97%; $[\alpha]_D^{27}$ = +9.91 (*c* 0.52, $CHCl_3$).

(*R*)-5-(3-Fluoro-5-methoxyphenyl)dihydrofuran-2(3*H*)-one (2q): Colorless oil (60.5 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.64–6.54 (m, 3H), 5.45–5.41 (m, 1H), 3.78 (s, 3H), 2.67–2.60 (m, 3H), 2.19–2.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 163.7 (d, J = 244.8 Hz), 161.2 (d, J = 10.7 Hz), 142.5 (d, J = 9.4 Hz), 106.6 (d, J = 2.6 Hz), 104.2 (d, J = 23.1 Hz), 101.3 (d, J = 24.9 Hz), 80.2 (d, J = 2.2 Hz), 55.6, 30.7, 28.6; IR (KBr) cm^{-1}: 2972, 1781, 1462, 1379, 1134, 1023, 910, 799, 686; HR-MS (ESI): m/z = 211.0772, calcd. for $C_{11}H_{11}FO_3$ $[M+H]^+$: 211.0770; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 75 : 25, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 18.33 min (major) and t_{R2} = 22.15 min (minor); ee = 89%; $[\alpha]_D^{27}$ = +20.00 (*c* 0.45, $CHCl_3$).

(*R*)-5-(Naphthalen-2-yl)dihydrofuran-2(3*H*)-one (2r)[9a]: White solid (61.1 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87–7.79 (m, 4H), 7.49–7.48 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H), 5.70–5.65 (m, 1H), 2.76–2.66 (m, 3H), 2.31–2.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 136.6, 133.1, 133.0, 128.8, 128.0, 127.7, 126.5, 126.4, 124.2, 122.8, 81.2, 30.8, 28.8; HPLC (Chiralcel AS-H, *n*-hexane/*i*-PrOH = 90 : 10, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 15.01 min (major) and t_{R2} = 19.73 min (minor); ee = 89%; $[\alpha]_D^{27}$ = +8.31 (*c* 0.25, $CHCl_3$).

Gram-scale synthesis of 2a

The gram scale synthesis of **2a** was carried out based on the optimal reaction conditions: **1a** (5.30 g, 29.7 mmol), RuPHOX-Ru (1.7 mg, 0.01 mol%), KOH (3.34 g, 59.5 mmol) in MeOH (20 mL) under 50 bar hydrogenation pressure at RT for 72 hours. After releasing the hydrogen, the reaction mixture was acidified with 3 M HCl solution and extracted with EtOAc (3 × 50 mL). The extract was dried over Na_2SO_4 and concentrated on a rotary evaporator. The

crude product was purified by flash column chromatography (PE/EtOAc = 4/1) to afford **2a** as colorless oil (4.67 g, 97%, 91% ee).

The synthesis of (*R*)-1-Phenylbutane-1,4-diol (3)[17]

To a solution of **2a** (162.2 mg, 1.0 mmol) in THF was added $LiAlH_4$ in portions. The reaction was monitored by TLC for the disapperance of starting material and was quenched by water. The mixture was then extracted with EtOAc (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator to afford **3** as a colorless oil (149.6 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, J = 4.4 Hz, 4H), 7.29–7.23 (m, 1H), 4.73–4.69 (m, 1H), 3.70–3.60 (m, 2H), 2.92 (s, 1H), 2.46 (s, 1H), 1.88–1.82 (m, 2H), 1.72–1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 128.3, 127.3, 125.8, 74.2, 62.6, 36.3, 29.1; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 95 : 5, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 31.48 min (major) and t_{R2} = 35.63 min (minor); ee = 88%; $[\alpha]_D^{27}$ = +41.22 (*c* 0.50, $CHCl_3$).

The synthesis of (*R*)-4-hydroxy-N,4-diphenylbutanamide (4)[18]

A screw-capped vial was charged with **2a** (65.0 mg, 0.4 mmol), aniline (43 μL,0.48 mmol) and TBD (17.0 mg, 30 mol%). The reaction mixture was stirred at 40 °C for 24 h. Then the mixture was purified by flash chromatography (PE : EtOAc = 1 : 1), affording the corresponding product as a white solid (90.9 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (brs, 1H), 7.49–7.47 (m, 2H), 7.35–7.25 (m, 7H), 7.10 (t, J = 7.2 Hz, 1H), 4.80–4.78 (m, 1H), 3.41 (brs, 1H), 2.55–2.43 (m, 2H), 2.20–2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 144.1, 137.7, 128.9, 128.4, 127.5, 125.7, 124.3, 120.0, 73.5,34.1, 33.9; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH = 70 : 30, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 7.69 min (minor) and t_{R2} = 8.73 min (major); ee = 90%; $[\alpha]_D^{27}$ = +15.50 (*c* 0.50, $CHCl_3$).

The synthesis of (*R*)-4-Hydroxy-4-phenylbutyric Acid Hydrazide (5)[19]

A 25 mL round-bottom flask equipped with a magnetic stirring bar was charged with **2a** (324.4 mg, 2.0 mmol) and 4 mL EtOH. After all the solids had dissolved, hydrazine hydrate (126 μL, 2.6 mmol) was added in one portion, and the mixture was heated at reflux for 5 h. After cooling to RT, the mixture was filtered to give the product as a white microcrystalline powder (350 mg, 90%, no further purification was necessary). ^{1}H NMR (400 MHz, d_6–DMSO): δ 8.92 (s, 1H), 7.34–7.19 (m, 5H), 5.26 (d, J = 4.4 Hz, 1H), 4.53–4.48 (m, 1H), 4.13 (s, 2H), 2.10–2.02 (m, 2H), 1.81–1.76 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 172.0, 146.3, 128.4, 127.1, 126.1, 72.1, 35.5, 30.3; HPLC (Chiralcel AD-H, *n*-hexane/*i*-PrOH = 90 : 10, UV = 210 nm, flow rate = 0.8 mL/min) t_{R1} = 28.30 min (minor) and t_{R2} = 37.01 min (major); ee = 99%; $[\alpha]_D^{27}$ = +58.00 (*c* 0.5, $CHCl_3$).

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UPDATE

Synthesis of Enantiopure γ-Lactones via a RuPHOX-Ru Catalyzed Asymmetric Hydrogenation of γ-Keto Acids

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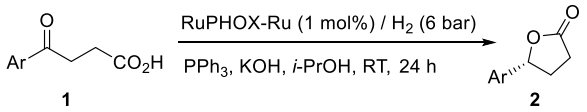
J. Li, Y. Ma, Y. Lu, Y. Liu, D. Liu,* W. Zhang*



18 examples, up to 10,000/1 S/C, 95~99% yield and 81~97% ee

- *only one step;*
- *directly using acid substrates;*
- *basic reaction condtions;*
- *low catalyst loading under the indicated reaction conditions.*