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Palladium-Catalyzed Asymmetric Hydrogenation of 4-Substituted 3-Alkoxycarbonylfuran-2(5*H*)-ones

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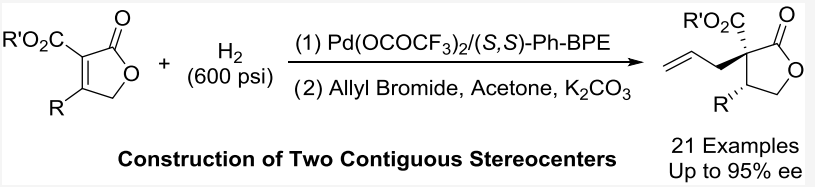

ABSTRACT: Palladium-catalyzed asymmetric hydrogenation of tetrasubstituted olefin 4-substituted 3-alkoxycar-bonylfuran-2(5*H*)-ones was developed for the construction of 1,2-contiguous stereogenters, giving the chiral *trans*-4-substituted 3-alkoxycarbonylbutyrolactone derivatives with up to 95% of enantioselectivities. The asymmetric hydrogenation reaction could proceed smoothly at gram scale without any loss of reactivity and enantioselectivity. In addition, the synthetic utility of the chiral reductive products has been demonstrated through useful building blocks.

INTRODUCTION

3,4-Disubstituted dihydrofuran-2(3*H*)-one derivatives widely exist in natural products and drug molecules. For example, cinnamomumolide **A** is an active ingredient of a traditional Chinese medicine (Figure 1).[1] The lactone wikstromol **B**,[2] was found to be antileukemic in vivo, and compound podophyllotoxin **C** has been approved as an anticancer agent and is in use currently.[3] Consequently, the development of efficient protocols for these privileged scaffolds has attracted considerable attention, and many high enantioselective asymmetric versions have been achieved through multiple-step reactions,[4] substrate induction,[5] and chiral auxiliary.[6] Catalytic asymmetric syntheses were also developed. In 1999, Zhang's group reported a highly enantioselective palladium-catalyzed carbonylation of allylic alcohol under CO/H_2 atmosphere (Scheme 1a).[7] Later, a stereoselective reduction of 2-butenolides to chiral butanolides by reductases was discovered by Hamada group (Scheme 1b).[8] In 2013, Zhang and co-workers observed an iridium-catalyzed asymmetric hydrogenative desymmetrization of mesocyclic anhydrides, giving the 3,4-disubstituted dihydrofuran-2(3*H*)-ones with up to 99% ee (Scheme 1c).[9] Recently, Furuta and co-workers have reported a stereoselective intramolecular C−H insertion into *α*-aryl-*α*-diazoacetates with chiral dirhodium(II) carboxylate catalysts, affording a variety of *α*,*β*-diaryl-*γ*-lactones with high diastereo- and enantioselectivities (Scheme 1d).[10] Although these achievements, the development of new and efficient synthetic methods to access the chiral 3,4-disubstituted dihydrofuran-2(3*H*)-one is still of considerable interest. Among these processes, catalytic asymmetric hydrogenation of readily available tetrasubstituted olefin 3,4-disubstituted furan-2(5*H*)-ones is undoubtedly one of the most direct and effective accesses to these very important classes of building blocks.

Palladium is widely used in asymmetric hydrogenation of ketones,[11] imines[12] and heteroaromatic compounds.[13] In previous studies, we reported a palladium-catalyzed asymmetric hydrogenation of trisubstituted *α*,*β*-unsaturated ketones, and up to 89% ee was obtained.[14] In addition, when the palladium activated hydrogen gas to generate the active species Pd−H, it also simultaneously afforded an equivalent amount of trifluoroacetic acid,[15] which would further activate the C═C double bond of the substrate through the hydrogen bonding interaction with the C═O group of *α*,*β*-unsaturated ester. Recently, our group has reported an enantioselective palladium-catalyzed hydrogenation of *α*,*β*-unsaturated lactones by regulating the temperature, affording the hydrogenation products of C═C reduction and products of both C═C bond and ester group reduction, respectively.[16] Inspired by the above pioneering work, we envisioned that asymmetric hydrogenation of tetrasubstituted *α*,*β*-unsaturated esters might be realized using the chiral palladium catalyst under the acidic condition, and we constructed two contiguous stereogenic centers in one step. Herein, we report a palladium-catalyzed asymmetric hydrogenation of tetrasubstituted olefins 4-substituted 3-alkoxycarbonyl-furan-2(5*H*)-ones for facile

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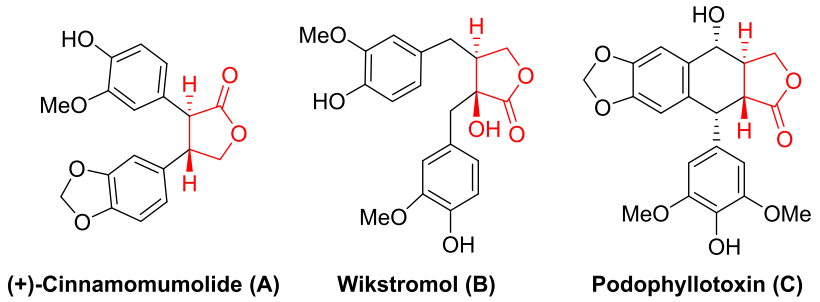
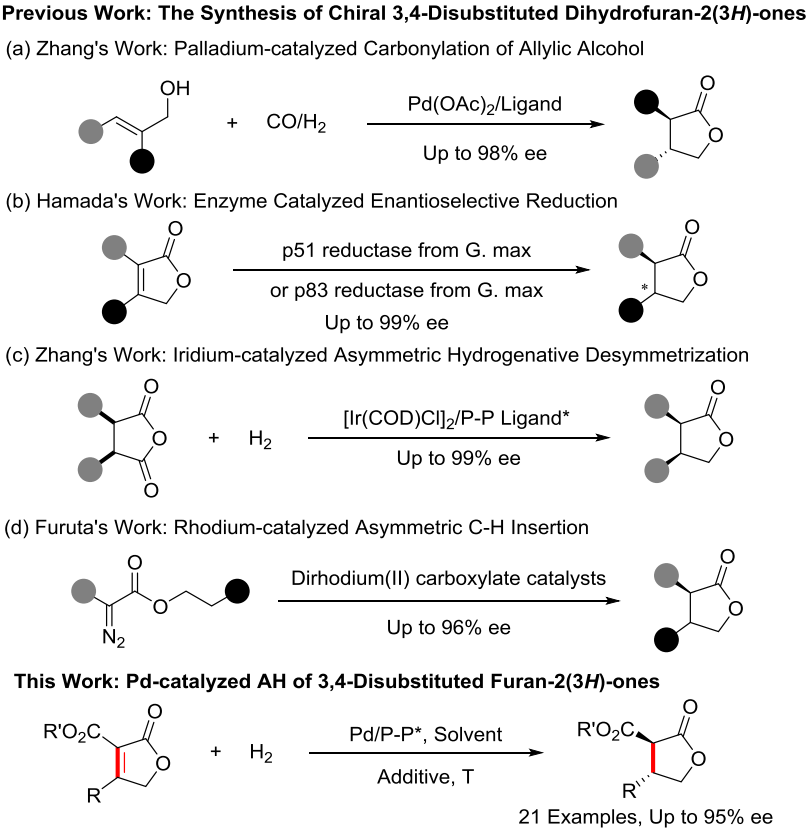


Figure 1. Some Bioactive Molecules Containing a Dihydrofuran-2(3*H*)-one Motif.

Scheme 1. Transition-Metal-Catalyzed Asymmetric Hydrogenation of Tetrasubstituted Olefins



synthesis of chiral *trans*-4-substituted 3-alkoxycarbonylbutyrolactone derivatives with high yields and stereoselectivities.

RESULTS AND DISCUSSION

To investigate the proposed hypothesis, we commenced asymmetric hydrogenation using **1a** as a model substrate. Some experimental results of condition optimization are summarized in Table 1. In the beginning, the hydrogenation was carried out in solvent 2,2,2-trifluoroethanol with Pd-$(OCOCF_3)_2$/(*S*,*S*)-QuinoxP* as a catalyst at 60 °C in the presence of 600 psi H_2. The hydrogenative product **2a'** could be obtained in full conversion, 69% enantioselectivity, and >20:1 diastereoselectivity (Table 1, entry 1). Considering that the additive Brϕnsted acids usually improve the reactivity and enantioselectivity in palladium-catalyzed asymmetric hydrogenation,[17] the effects of some additive Brϕnsted acids on the reactivity and enantioselectivity were investigated, and the experimental results indicated that weak acid benzoic acid was optimal with regard to enantioselectivity (entries 2−5). Next, we started to investigate the amount of benzoic acid and found that 20 mol % of benzoic acid gave the best result (entries 6−7). Next, the impact of different solvents was examined (entries 8−10), and hexafluoroisopropanol (HFIP) delivered similar yield and enantioselectivity (entry 8). No desirable product was observed in aprotic toluene. To further improve the enantioselectivity, the mixture solvents were screened (entries 11−13), and TFE/THF (2:1) gave the best enantioselectivity. Then, a variety of chiral bisphosphine ligands were evaluated, and high reactivity, albeit low enantioselectivity, was obtained with **L2, L3**, and **L4** (entries 14−16). Excellent enantioselectivity was observed with Ph-BPE **L5** (entry 17). The ligand *i*-Pr-BPE **L6** (entry 18) was also investigated under the above conditions, and a 21% ee value was obtained. The hydrogenation could be also conducted under lower temperatures (entries 19−20), and little improved ee values were observed. Then, the catalyst loading was screened, and it was found that 2 mol % chiral palladium catalyst was optimal. Because of the keto−enol

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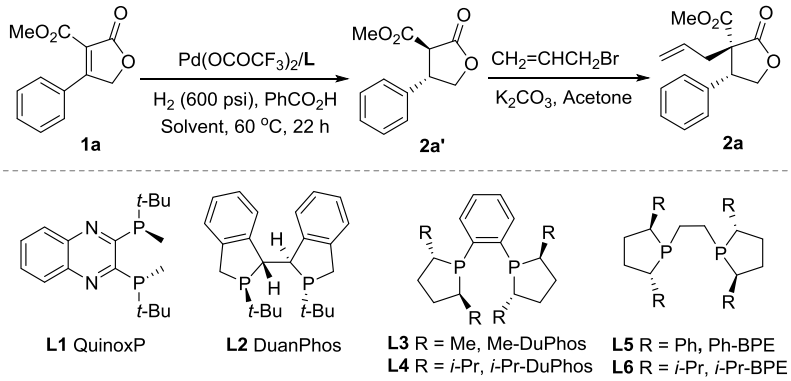
Table 1. Optimization of Pd-Catalyzed Asymmetric Hydrogenation



entry[a]	solvent	temp (°C)	additive	L	conv. (%)[b]	E_e (%)[c]
1	TFE	60		**L1**	>95	69
2	TFE	60	benzoic acid	**L1**	>95	72
3	TFE	60	acetic acid	**L1**	>95	69
4	TFE	60	*L*-tartaric acid	**L1**	>95	70
5	TFE	60	*D*-tartaric acid	**L1**	>95	70
6[d]	TFE	60	benzoic acid	**L1**	>95	69
7[e]	TFE	60	benzoic acid	**L1**	>95	71
8	HFIP	60	benzoic acid	**L1**	>95	66
9	THF	60	benzoic acid	**L1**	<5	72
10	toluene	60	benzoic acid	**L1**		
11	TFE/THF (1:1)	60	benzoic acid	**L1**	>95	76
12	TFE/THF (2:1)	60	benzoic acid	**L1**	>95	79
13	TFE/THF (5:1)	60	benzoic acid	**L1**	>95	75
14	TFE/THF (2:1)	60	benzoic acid	**L2**	>95	78
15	TFE/THF (2:1)	60	benzoic acid	**L3**	>95	37
16	TFE/THF (2:1)	60	benzoic acid	**L4**	>95	4
17	TFE/THF (2:1)	60	benzoic acid	**L5**	>95	89
18	TFE/THF (2:1)	60	benzoic acid	**L6**	>95	21
19	TFE/THF (2:1)	50	benzoic acid	**L5**	>95	91
20	TFE/THF (2:1)	40	benzoic acid	**L5**	>95	92
21[f,g],	TFE/THF (2:1)	40	benzoic acid	**L5**	>95 (94)	92

[a]Substrate **1a** (0.2 mmol, 1.0 equiv), palladium trifluoroacetate (0.01 mmol, 3.3 mg), ligand (0.012 mmol), benzoic acid (0.04 mmol, 20 mol %), TFE (4.0 mL), 60 °C, 22 h. The diastereoselectivity of all products >20/1. [b]Determined by ^{1}H NMR using pyrazine as internal standard. [c]Determined by HPLC. [d]The additive was 0.02 mmol. [e]The additive was 0.1 mmol. [f]The reaction was conducted at 0.4 mmol scale, and $Pd(OCOCF_3)_2$ (0.008 mmol, 2.0 mol %). [g]Isolated yield after protection with allyl bromide.

tautomerism of the hydrogenative products, for a more accurate characterization, the in situ alkylation of **2a'** was conducted with allyl bromide with excellent diastereoselectivity and yield (entry 21). Thus, the optimal reaction condition was identified (entry 21): substrate **1** (0.4 mmol), chiral palladium catalyst (2.0 mol %), benzoic acid (20 mol %), H_2 (600 psi), TFE/THF (2/1), and 40 °C.

With optimal reaction conditions in hand, the substrate scope of this asymmetric hydrogenation was examined. First, the variations of the ester substituents were studied (Table 2). Asymmetric hydrogenation of ethyl ester (**1b**), benzyl ester (**1c**), and isopropyl ester (**1d**) afforded **2b** (89% yield, 87% ee), **2c** (94% yield, 88% ee), and **2d** (87% yield, 82% ee), respectively. The best result was obtained with methyl ester substrate **2a** (94% yield, 92% ee). Next, the steric properties of the substituents on the aryl group of *R* were varied; when *R* was *o*-methylphenyl (**1e**), lower enantioselectivity was furnished with excellent yield **2e** (90% yield, 39% ee). Marginal influences on the hydrogenation were observed with the *m*-methylphenyl **1f** (88% yield, 90% ee) and *p*-methylphenyl **1g** (88% yield, 90% ee) substrates. Either electron-donating or electron-withdrawing substituents on the aryl group could also achieve excellent results (**1h**−**1k**). **1l**, which possessed a biphenyl, obtained excellent yield and 88% ee value. 2-Naphthyl-substituted substrate **1m** also proceeded in high 99% yield and 89% of enantioselectivity. Notably, 3,4-dimethyl-, 3,5-dimethyl-, or 3,4-dichloride-substituted substrates (**1n**−**1p**) had little influence. When 2,3-dihydrobenzo-[*b*][1,4]dioxine **1q** and heteroaryl **1r** were introduced, high yields were observed, albeit slightly decreased enantioselectivity was observed with **1r**. As for the alkyl-substituted substrates **1s**−**1u**, high enantioselectivities could also be obtained. The absolute configuration of **2l** was assigned as (3*R*,4*R*)-**2l** by X-ray diffraction analysis, and the absolute configuration of all other products was assigned by analogy (for the details, please see the Supporting Information).

To showcase the utility of this methodology, the gram scale experiment and elaborations of the product were investigated as shown in Scheme 2. First, when **1a** was conducted at 5.0 mmol scale, 91% ee and 98% yield were observed with the identified activity and enantioselectivity. Moreover, Heck reaction of (−)-**2a** with methyl 4-bromobenzoate using

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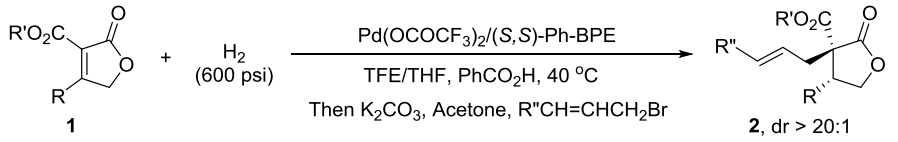
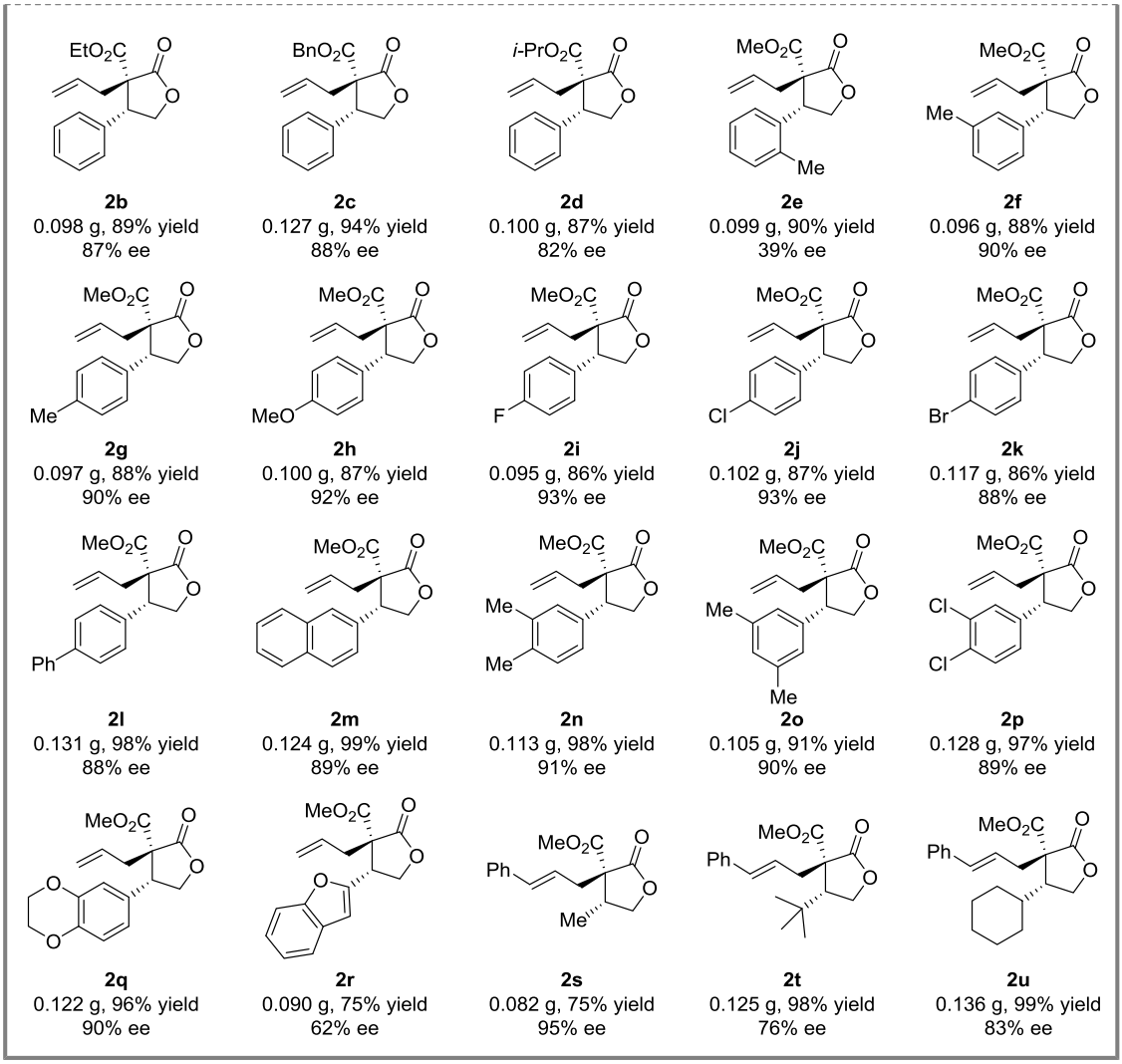
Table 2. Substrate Scope for Asymmetric Hydrogenation of 1





palladium catalyst system[18] resulted in the formation of (+)-**3** in 85% yield and 91% ee. The chiral (−)-**2a** was treated with lithium chloride in dimethyl sulfoxide (DMSO) to afford the *trans*-3,4-disubstituted butyrolactone (+)-**4** with 84% yield.[19]

CONCLUSIONS

In conclusion, we have successfully developed palladium-catalyzed asymmetric hydrogenation of functionalized 4-substituted 3-alkoxycarbonylfuran-2(5*H*)-ones for the facile construction of two contiguous stereogenic centers. This methodology showed good functional group tolerance, and a broad range of highly enantiomerically enriched chiral 4-substituted 3-alkoxycarbonylbutyrolactones could be conveniently prepared with up to 95% ee. Efforts to expand the application of this palladium catalyst system to other substrates are underway in our laboratory.

EXPERIMENTAL SECTION

All reactions were carried out under an atmosphere of nitrogen using 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{^{1}H} NMR, and ^{19}F{^{1}H} NMR spectra were recorded at room temperature in $CDCl_3$ on a 400 MHz instrument with tetramethylsilane as the 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 high-performance liquid chromatography (HPLC) analysis, using the 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 thin-layer chromatography (TLC) analysis. High-resolution mass spectrometry (HRMS) electrospray ionization-time-of-flight (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.

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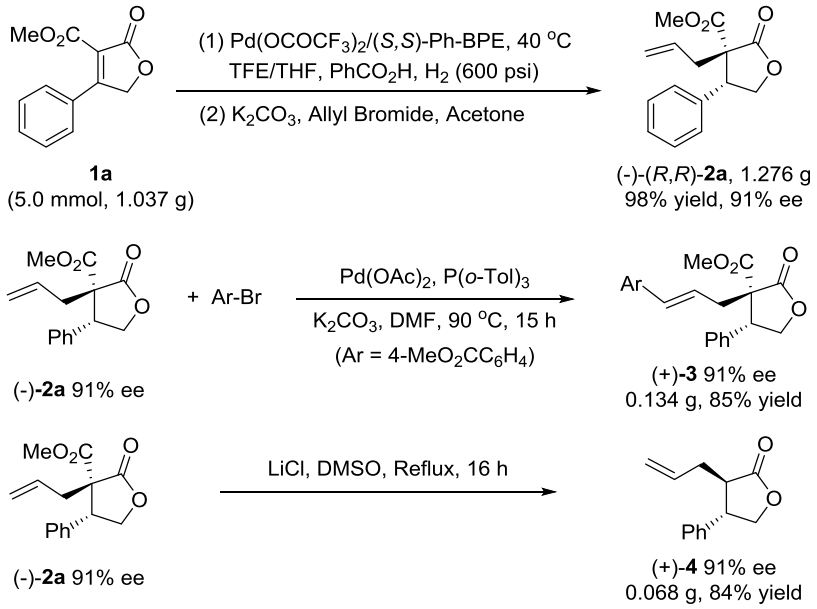
Scheme 2. Scale-Up Experiment and Transformations of Chiral Product 2a



Synthesis of Substrates 1. The substrates 4-aryl- or 4-alkyl-substituted 3-alkoxycarbonylfuran-2(5*H*)-ones **1** were conveniently synthesized through 3 steps in one pot from the commercially available aryl methyl ketones or alkyl methyl ketones according to the similar procedure.[20] The substrate benzyl 2-oxo-4-phenyl-2,5-dihydrofuran-3-carboxylate **1c** was prepared by transesterification of compound **1a** with benzyl alcohol.[21] Among them, substrates **1a**, **1g**−**1h**, **1j**, **1k**, and **1s** are the known compounds.[20,22]

General Procedure. A mixture of aryl methyl ketones or alkyl methyl ketones (10.0 mmol) and [hydroxyl(tosyloxy)iodo]benzene (4.314 g, 11.0 mmol) in acetonitrile (30 mL) was refluxed for 1.5 h. After successful formation of α-tosyloxyketone (monitored by TLC), potassium monoalkyl malonate (12.0 mmol) was added and the reaction mixture was refluxed for 4−5 h until complete consumption of the α-tosyloxyketone (monitored by TLC). Then, the mixture was cooled to room temperature, potassium carbonate (0.829 g, 6.0 mmol) was added, and the mixture was refluxed for another 1.5 h. After completion of the reaction (monitored by TLC), the mixture was quenched with hydrochloric acid (3 N, 15 mL) and extracted 3 times with dichloromethane (50 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under the reduced pressure. The residue was purified by flash column chromatography on silica gel using hexanes/ethyl acetate (5/1) as eluent to give the desired product 4-aryl- or 4-alkyl-substituted 3-alkoxycarbonylfuran-2(5*H*)-ones **1**.

The 4-aryl- or 4-alkyl-substituted 3-alkoxycarbonylfuran-2(5*H*)-ones **1** could be further purified by recrystallization with dichloromethane/hexanes.

*Ethyl 2-Oxo-4-phenyl-2,5-dihydrofuran-3-carboxylate (**1b**).* 1.307 g, 56% yield, yellow solid, mp 97−98 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.44 (m, 5H), 5.17 (s, 2H), 4.37 (q, *J* = 7.0 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.6, 164.2, 162.4, 132.1, 129.3, 129.1, 127.8, 119.7, 70.5, 62.0, 14.0. HRMS Calculated for $C_{13}H_{13}O_4$ $[M + H]^+$ 233.0808, found: 233.0809.

*Benzyl 2-Oxo-4-phenyl-2,5-dihydrofuran-3-carboxylate (**1c**).* 0.483 g (5 mmol scale), 33% yield, white solid, mp 117−118 °C, new compound, R_f = 0.58 (hexanes/ethyl acetate/dichloromethane 5/1/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.28 (m, 10H), 5.34 (s, 2H), 5.15 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 164.5, 162.1, 134.8, 132.1, 129.1, 128.6, 128.6, 127.8, 119.4, 70.6, 67.6. HRMS Calculated for $C_{18}H_{15}O_4$ $[M + H]^+$ 295.0965, found: 295.0967.

*Isopropyl 2-Oxo-4-phenyl-2,5-dihydrofuran-3-carboxylate (**1d**).* 0.896 g, 36% yield, yellow viscous liquid, new compound, R_f = 0.60 (hexanes/ethyl acetate 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.45 (m, 5H), 5.28−5.22 (m, 1H), 5.16 (s, 2H), 1.30 (d, *J* = 6.3 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.6, 163.3, 162.0, 132.0, 129.3, 129.1, 127.8, 120.1, 70.4, 70.0, 21.6. HRMS Calculated for $C_{14}H_{15}O_4$ $[M + H]^+$ 247.0965, found: 247.0966.

*Methyl 2-Oxo-4-(o-tolyl)-2,5-dihydrofuran-3-carboxylate (**1e**).* 1.705 g, 72% yield, yellow solid, mp 72−73 °C, new compound, R_f = 0.45 (hexanes/ethyl acetate 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40−7.35 (m, 1H), 7.33−7.27 (m, 2H), 7.14−7.12 (m, 1H), 4.99 (s, 2H), 3.75 (s, 3H), 2.27 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 171.9, 168.7, 161.1, 135.0, 130.8, 130.2, 130.1, 126.6, 126.0, 121.3, 72.0, 52.5, 19.7. HRMS Calculated for $C_{13}H_{13}O_4$ $[M + H]^+$ 233.0808, found: 233.0807.

*Methyl 2-Oxo-4-(m-tolyl)-2,5-dihydrofuran-3-carboxylate (**1f**).* 1.245 g, 53% yield, yellow solid, mp 145−146 °C, new compound, R_f = 0.60 (hexanes/ethyl acetate 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37−7.30 (m, 4H), 5.16 (s, 2H), 3.89 (s, 3H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.6, 165.3, 162.8, 139.0, 133.0, 129.1, 129.1, 128.3, 125.0, 119.1, 70.7, 52.8, 21.4. HRMS Calculated for $C_{13}H_{13}O_4$ $[M + H]^+$ 233.0808, found: 233.0806.

*Methyl 2-Oxo-4-(4-fluorophenyl)-2,5-dihydrofuran-3-carboxylate (**1i**).* 1.412 g, 60% yield, pure yellow solid, mp 125−126 °C, new compound, R_f = 0.48 (hexanes/ethyl acetate 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62−7.59 (m, 2H), 7.21−7.17 (m, 2H), 5.17 (s, 2H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 166.1, 163.9 (d, $^1J_{F-C}$ = 195.5 Hz), 162.7, 130.4 (d, $^3J_{F-C}$ = 9.1 Hz), 125.4 (d, $^4J_{F-C}$ = 3.4 Hz), 118.9, 116.5 (d, $^2J_{F-C}$ = 21.9 Hz), 70.5, 52.8. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ − 105.52. HRMS Calculated for $C_{12}H_{10}FO_4$ $[M + H]^+$ 237.0558, found: 237.0556.

*Methyl 2-Oxo-4-([1,1′-biphenyl]-4-yl)-2,5-dihydrofuran-3-carboxylate (**1l**).* 1.666 g, 57% yield, yellow solid, mp 160−161 °C, new compound, R_f = 0.38 (hexanes/ethyl acetate 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74−7.69 (m, 2H), 7.67−7.59 (m, 4H), 7.52−7.46 (m, 2H), 7.45−7.40 (m, 1H), 5.22 (s, 2H), 3.93 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.7, 164.8, 162.9, 145.1, 139.4, 129.1, 128.5, 128.5, 127.7, 127.2, 118.7, 70.6, 52.9. HRMS Calculated for $C_{18}H_{15}O_4$ $[M + H]^+$ 295.0965, found: 295.0966.

*Methyl 2-Oxo-4-(naphthalen-2-yl)-2,5-dihydrofuran-3-carboxylate (**1m**).* 1.553 g, 58% yield, orange solid, mp 123−124 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.94−7.88 (m, 3H), 7.68−7.51 (m, 3H), 5.30 (s, 2H), 3.92 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)

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δ: 169.7, 165.2, 162.9, 134.7, 132.7, 129.0, 129.0, 128.6, 128.6, 127.9, 127.4, 126.5, 124.2, 119.2, 70.7, 52.9. HRMS Calculated for $C_{16}H_{13}O_4$ $[M + H]^+$ 269.0808, found: 269.0811.

*Methyl 2-Oxo-4-(3,4-dimethylphenyl)-2,5-dihydrofuran-3-carboxylate (**1n**).* 1.309 g, 53% yield, yellow solid, mp 100−101 °C, new compound, R_f = 0.61 (hexanes/ethyl acetate 5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32−7.27 (m, 2H), 7.26−7.21 (m, 1H), 5.16 (s, 2H), 3.90 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.9, 165.2, 163.1, 142.0, 137.6, 130.4, 128.8, 126.7, 125.6, 118.0, 70.6, 52.7, 20.0, 19.9. HRMS Calculated for $C_{14}H_{15}O_4$ $[M + H]^+$ 247.0965, found: 247.0964.

*Methyl 2-Oxo-4-(3,5-dimethylphenyl)-2,5-dihydrofuran-3-carboxylate (**1o**).* 0.538 g (6.6 mmol scale), 33% yield, yellow solid, mp 102−103 °C, new compound, R_f = 0.65 (hexanes/ethyl acetate 5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24:7.04 (m, 3H), 5.15 (s, 2H), 3.89 (s, 3H), 2.36 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.8, 165.6, 162.9, 138.9, 134.0, 129.0, 125.5, 118.7, 70.8, 52.7, 21.3. HRMS Calculated for $C_{14}H_{15}O_4$ $[M + H]^+$ 247.0965, found: 247.0965.

*Methyl 2-Oxo-4-(3,4-dichlorophenyl)-2,5-dihydrofuran-3-carboxylate (**1p**).* 0.743 g, 23% yield, yellow solid, mp 151−152 °C, new compound, R_f = 0.49 (hexanes/ethyl acetate 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68−7.67 (m, 1H), 7.59−7.57 (m, 1H), 7.44−7.41 (m, 1H), 5.15 (s, 2H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 168.8, 163.1, 162.1, 136.6, 133.7, 131.2, 129.8, 128.9, 127.2, 120.4, 70.4, 53.0. HRMS Calculated for $C_{12}H_9Cl_2O_4$ $[M + H]^+$ 286.9872 (^{35}Cl) and 288.9845 (^{37}Cl), found: 286.9876 (^{35}Cl) and 288.9843 (^{37}Cl).

*Methyl 2-Oxo-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2,5-dihydrofuran-3-carboxylate (**1q**).* 0.789 g, 29% yield, yellow solid, mp 146−147 °C, new compound, R_f = 0.34 (hexanes/ethyl acetate 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.01 (m, 2H), 6.94−6.92 (m, 1H), 5.12 (s, 2H), 4.31 (d, J = 9.4 Hz, 4H), 3.91 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 170.0, 164.0, 163.2, 147.4, 143.8, 122.1, 121.9, 118.0, 117.3, 117.2, 70.4, 64.7, 64.2, 52.8. HRMS Calculated for $C_{14}H_{13}O_6$ $[M + H]^+$ 277.0707, found: 277.0708.

*Methyl 2-Oxo-4-(benzofuran-2-yl)-2,5-dihydrofuran-3-carboxylate (**1r**).* 1.593 g (20 mmol scale), 31% yield, orange solid, mp 196−197 °C, new compound, R_f = 0.49 (hexanes/ethyl acetate 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (s, 1H), 7.36−7.32 (m, 1H), 7.57−7.47 (m, 2H), 7.36−7.32 (m, 1H), 5.37 (s, 2H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.1, 162.2, 156.5, 155.7, 145.8, 128.8, 128.0, 124.3, 123.4, 118.4, 114.6, 111.8, 68.9, 52.7. HRMS Calculated for $C_{14}H_{11}O_5$ $[M + H]^+$ 259.0601, found: 259.0598.

*Methyl 2-Oxo-4-(tert-butyl)-2,5-dihydrofuran-3-carboxylate (**1t**).* 2.488 g (20 mmol scale), 63% yield, white solid, mp 78−79 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (s, 2H), 3.87 (s, 3H), 1.27 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 175.9, 170.3, 163.9, 120.6, 70.2, 52.8, 34.4, 28.5. HRMS Calculated for $C_{10}H_{15}O_4$ $[M + H]^+$ 199.0965, found: 199.0967.

*Methyl 2-Oxo-4-cyclohexyl-2,5-dihydrofuran-3-carboxylate (**1u**).* 0.818 g, 36% yield, white solid, mp 114−115 °C, new compound, R_f = 0.42 (hexanes/ethyl acetate 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.84 (s, 2H), 3.89 (s, 3H), 3.56−3.28 (m, 1H), 1.92−1.75 (m, 5H), 1.48−1.35 (m, 2H), 1.31−1.18 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 183.0, 169.4, 161.9, 117.4, 69.2, 52.3, 38.3, 31.1, 25.7, 25.6. HRMS Calculated for $C_{12}H_{17}O_4$ $[M + H]^+$ 225.1121, found: 225.1115.

Procedure for the Synthesis of Substrate 1c. A mixture of methyl 2-oxo-4-phenyl-2,5-dihydrofuran-3-carboxylate **1a** (1.091 g, 5 mmol), benzyl alcohol (1.081 g, 10 mmol), and *p*-toluenesulfonic acid monohydrate (95.1 mg, 0.5 mmol) in toluene (30 mL) was refluxed for 24 h. After successful formation of benzyl ester (monitored by TLC), the mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexanes/ethyl acetate/dichloromethane (5/1/0.5) as eluent to give the desired product benzyl 2-oxo-4-phenyl-2,5-dihydrofuran-3-carboxylate **1c**.

*Benzyl 2-Oxo-4-phenyl-2,5-dihydrofuran-3-carboxylate (**1c**).* 0.483 g (5 mmol scale), 33% yield, white solid, mp 117−118 °C, new compound, R_f = 0.58 (hexanes/ethyl acetate/dichloromethane 5/1/0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.28 (m, 10H), 5.34 (s, 2H), 5.15 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 164.5, 162.1, 134.8, 132.1, 129.1, 128.6, 128.6, 127.8, 119.4, 70.6, 67.6. HRMS Calculated for $C_{18}H_{15}O_4$ $[M + H]^+$ 295.0965, found: 295.0967.

General Procedure for Pd-Catalyzed Asymmetric Hydrogenation of 4-Substituted 3-Alkoxy- Carbonylfuran-2(5*H*)-Ones. Palladium trifluoroacetate (0.008 mmol, 2.7 mg), ligand (*S,S*)-Ph-BPE (0.0096 mmol, 4.9 mg), and acetone (1.0 mL) were placed in a dried Schlenk tube under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. Then, the solvent was removed under vacuum to give the chiral catalyst. This catalyst was taken into a glovebox filled with nitrogen and dissolved in 2,2,2-trifluoroethanol (2.67 mL). To the mixture of substrates **1** (0.4 mmol) and benzoic acid (9.8 mg, 0.08 mmol) in tetrahydrofuran (1.33 mL) was added the above catalyst solution, and then the mixture was transferred to an autoclave, where hydrogen gas was charged (600 psi). The autoclave was stirred at 40 °C (bath oil temperature) for 20−40 h. After release of the hydrogen gas (before the autoclave was opened, the hydrogen should be released carefully in the fume hood), the autoclave was opened and the mixture was concentrated under the reduced pressure. Then, solid potassium carbonate (0.8 mmol, 110.6 mg), allyl bromide or cinnamyl bromide (0.8 mmol), and acetone (2.0 mL) were added. The mixture was stirred at ambient temperature for 24 h. The reaction mixture was quenched with hydrochloric acid (3 *N*, 1.0 mL), extracted 3 times with dichloromethane, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Then, purification was performed through column chromatography on silica gel using hexanes/ethyl acetate (10/1) as the eluent to give the chiral reductive products **2**.

The racemates of **2** could be prepared through the above hydrogenation procedure with racemic Ph-BPE or achiral 1,2-bis(dicyclohexylphosphino)ethane as a ligand or hydrogenation with heterogeneous Pd/C in methanol.

*(−)-Methyl 3-Allyl-2-oxo-4-phenyltetrahydrofuran-3-carboxylate (**2a**).* 0.098 g, 94% yield, colorless viscous liquid, new compound, R_f = 0.65 (hexanes/ethyl acetate 5/1), 92% ee, $[\alpha]^{20}_D$ = −44.32 (*c* 1.78, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 3H), 7.19−7.12 (m, 2H), 5.83−5.69 (m, 1H), 5.41−5.32 (m, 2H), 4.75 (dd, J = 10.9, 8.9 Hz, 1H), 4.55 (t, J = 8.5 Hz, 1H), 3.93 (dd, J = 10.9, 8.2 Hz, 1H), 3.53 (s, 3H), 2.95−2.86 (m, 1H), 2.66 (dd, J = 14.6, 9.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.0, 168.4, 133.9, 132.1, 129.0, 128.5, 127.9, 121.6, 69.2, 59.7, 52.5, 47.0, 35.4. HPLC: Chiralcel OJ-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 25.8 min (major) and 28.4 min. HRMS Calculated for $C_{15}H_{17}O_4$ $[M + H]^+$ 261.1121, found: 261.1119.

*(−)-Ethyl 3-Allyl-2-oxo-4-phenyltetrahydrofuran-3-carboxylate (**2b**).* 0.098 g, 89% yield, colorless viscous liquid, new compound, R_f = 0.68 (hexanes/ethyl acetate 5/1), 87% ee, $[\alpha]^{20}_D$ = −47.71 (*c* 1.66, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 3H), 7.21−7.14 (m, 2H), 5.84−5.70 (m, 1H), 5.40−5.32 (m, 2H), 4.77 (dd, J = 10.9, 8.8 Hz, 1H), 4.56 (t, J = 8.4 Hz, 1H), 4.02−3.89 (m, 3H), 2.96−2.88 (m, 1H), 2.73−2.63 (m, 1H), 1.07 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.1, 167.9, 134.0, 132.2, 128.9, 128.4, 127.9, 121.5, 69.1, 61.9, 59.6, 46.8, 35.5, 13.8. HPLC: Chiralcel OD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 12.0 and 14.4 min (major). HRMS Calculated for $C_{16}H_{19}O_4$ $[M + H]^+$ 275.1278, found: 275.1280.

*(−)-Benzyl 3-Allyl-2-oxo-4-phenyltetrahydrofuran-3-carboxylate (**2c**).* 0.127 g, 94% yield, white solid, mp 98−99 °C, new compound, R_f = 0.68 (hexanes/ethyl acetate 5/1), 88% ee, $[\alpha]^{20}_D$ = −66.57 (*c* 2.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.21 (m, 6H), 7.18−7.10 (m, 2H), 7.09−7.01 (m, 2H), 5.84−5.71 (m, 1H), 5.42−5.30 (m, 2H), 4.95 (dd, J = 52.9, 12.2 Hz, 2H), 4.70 (dd, J = 11.1, 8.8 Hz, 1H), 4.52 (t, J = 8.4 Hz, 1H), 3.93 (dd, J = 11.0, 8.2 Hz, 1H), 2.99−2.89 (m, 1H), 2.68 (dd, J = 14.6, 9.7 Hz, 1H). $^{13}C\{^1H\}$ NMR

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(100 MHz, $CDCl_3$) δ: 173.9, 167.8, 134.5, 133.7, 132.1, 129.0, 128.7, 128.6, 128.4, 128.4, 127.9, 121.6, 69.2, 67.6, 59.7, 47.0, 35.4. HPLC: Chiralcel OD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 15.1 and 17.6 min (major). HRMS Calculated for $C_{21}H_{21}O_4$ $[M + H]^+$ 337.1434, found: 337.1435.

*(−)-Isopropyl 3-Allyl-2-oxo-4-phenyltetrahydrofuran-3-carboxylate (**2d**).* 0.100 g, 87% yield, colorless viscous liquid, new compound, R_f = 0.69 (hexanes/ethyl acetate 5/1), 82% ee, $[\alpha]^{20}_D$ = −41.76 (*c* 1.42, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.28 (m, 3H), 7.22−7.14 (m, 2H), 5.85−5.68 (m, 1H), 5.40−5.30 (m, 2H), 4.86−4.70 (m, 2H), 4.55 (t, *J* = 8.4 Hz, 1H), 3.93 (dd, *J* = 10.9, 8.1 Hz, 1H), 2.97−2.88 (m, 1H), 2.71−2.66 (m, 1H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.93 (d, *J* = 6.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.3, 167.5, 134.1, 132.3, 128.9, 128.3, 127.9, 121.4, 70.1, 69.1, 59.6, 46.6, 35.6, 21.6, 21.3. HPLC: Chiralcel OD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 10.3 and 12.1 min (major). HRMS Calculated for $C_{17}H_{21}O_4$ $[M + H]^+$ 289.1434, found: 289.1436.

*(−)-Methyl 3-Allyl-2-oxo-4-(o-tolyl)tetrahydrofuran-3-carboxylate (**2e**).* 0.099 g, 90% yield, colorless viscous liquid, new compound, R_f = 0.55 (hexanes/ethyl acetate 5/1), 39% ee, $[\alpha]^{20}_D$ = −8.56 (*c* 1.88, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.22−7.13 (m, 4H), 5.92−5.77 (m, 1H), 5.37−5.27 (m, 2H), 4.64−4.51 (m, 2H), 4.10 (t, *J* = 8.0 Hz, 1H), 3.42 (s, 3H), 2.93−2.86 (m, 1H), 2.73 (dd, *J* = 14.6, 8.6 Hz, 1H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.3, 168.8, 137.1, 134.1, 131.6, 131.1, 128.1, 126.7, 126.3, 121.1, 71.1, 60.6, 52.3, 44.0, 37.4, 20.3. HPLC: Chiralcel OD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 13.6 and 28.1 min (major). HRMS Calculated for $C_{16}H_{19}O_4$ $[M + H]^+$ 275.1278, found: 275.1280.

*(−)-Methyl 3-Allyl-2-oxo-4-(m-tolyl)tetrahydrofuran-3-carboxylate (**2f**).* 0.096 g, 88% yield, colorless viscous liquid, new compound, R_f = 0.58 (hexanes/ethyl acetate 5/1), 90% ee, $[\alpha]^{20}_D$ = −34.28 (*c* 2.08, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.20 (m, 1H), 7.17−7.10 (m, 1H), 6.98−6.90 (m, 2H), 5.84−5.69 (m, 1H), 5.41−5.31 (m, 2H), 4.78−4.70 (m, 1H), 4.52 (t, *J* = 8.5 Hz, 1H), 3.94−3.83 (m, 1H), 3.55 (s, 3H), 2.94−2.84 (m, 1H), 2.66 (dd, *J* = 14.6, 9.6 Hz, 1H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.0, 168.4, 138.7, 133.8, 132.1, 129.2, 128.8, 128.6, 124.9, 121.5, 69.3, 59.7, 52.4, 47.1, 35.4, 21.5. HPLC: Chiralcel OD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, retention time 15.6 and 18.8 min (major). HRMS Calculated for $C_{16}H_{19}O_4$ $[M + H]^+$ 275.1278, found: 275.1277.

*(−)-Methyl 3-Allyl-2-oxo-4-(p-tolyl)tetrahydrofuran-3-carboxylate (**2g**).* 0.097 g, 88% yield, colorless viscous liquid, new compound, R_f = 0.55 (hexanes/ethyl acetate 5/1), 90% ee, $[\alpha]^{20}_D$ = −38.87 (*c* 1.86, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.18−7.12 (m, 2H), 7.06−7.00 (m, 2H), 5.82−5.69 (m, 1H), 5.39−5.32 (m, 2H), 4.72 (dd, *J* = 11.0, 8.8 Hz, 1H), 4.52 (t, *J* = 8.5 Hz, 1H), 3.89 (dd, *J* = 11.0, 8.2 Hz, 1H), 3.56 (s, 3H), 2.93−2.85 (m, 1H), 2.65 (dd, *J* = 14.6, 9.6 Hz, 1H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.1, 168.4, 138.3, 132.2, 130.7, 129.7, 127.7, 121.5, 69.3, 59.7, 52.5, 46.8, 35.4, 21.1. HPLC: Chiralcel OD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, retention time 15.9 and 20.9 min (major). HRMS Calculated for $C_{16}H_{19}O_4$ $[M + H]^+$ 275.1278, found: 275.1269.

*(−)-Methyl 3-Allyl-4-(4-methoxyphenyl)-2-oxotetrahydrofuran-3-carboxylate (**2h**).* 0.100 g, 87% yield, colorless viscous liquid, new compound, R_f = 0.46 (hexanes/ethyl acetate 5/1), 92% ee, $[\alpha]^{20}_D$ = −37.72 (*c* 1.14, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.09−7.04 (m, 2H), 6.90−6.85 (m, 2H), 5.82−5.69 (m, 1H), 5.38−5.31 (m, 2H), 4.69 (dd, *J* = 11.0, 8.8 Hz, 1H), 4.52 (t, *J* = 8.5 Hz, 1H), 3.88 (dd, *J* = 11.0, 8.2 Hz, 1H), 3.80 (s, 3H), 3.57 (s, 3H), 2.92−2.85 (m, 1H), 2.64 (dd, *J* = 14.6, 9.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.1, 168.5, 159.6, 132.2, 129.0, 125.6, 121.4, 114.4, 69.4, 59.6, 55.3, 52.5, 46.5, 35.3. HPLC: Chiralcel OD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 18.0 and 21.0 min (major). HRMS Calculated for $C_{16}H_{19}O_5$ $[M + H]^+$ 291.1227, found: 291.1213.

*(−)-Methyl 3-Allyl-4-(4-fluorophenyl)-2-oxotetrahydrofuran-3-carboxylate (**2i**).* 0.095 g, 86% yield, yellow viscous liquid, new compound, R_f = 0.52 (hexanes/ethyl acetate 5/1), 93% ee, $[\alpha]^{20}_D$ = −44.05 (*c* 1.90, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.19−7.10 (m, 2H), 7.10−6.99 (m, 2H), 5.84−5.67 (m, 1H), 5.39−5.31 (m, 2H), 4.70 (dd, *J* = 10.9, 8.9 Hz, 1H), 4.54 (t, *J* = 8.5 Hz, 1H), 3.91 (dd, *J* = 10.9, 8.2 Hz, 1H), 3.56 (s, 3H), 2.96−2.85 (m, 1H), 2.64 (dd, *J* = 14.6, 9.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.7, 168.3, 162.6 (d, $^1J_{F-C}$ = 247.0 Hz), 132.0, 129.7 (d, $^4J_{F-C}$ = 3.4 Hz), 129.5 (d, $^3J_{F-C}$ = 8.1 Hz), 121.6, 116.0 (d, $^2J_{F-C}$ = 21.3 Hz), 69.2, 59.6, 52.6, 46.4, 35.4. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ − 112.99. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, retention time 11.9 min (major), and 14.2 min. HRMS Calculated for $C_{15}H_{16}FO_4$ $[M + H]^+$ 279.1027, found: 279.1026.

*(−)-Methyl 3-Allyl-4-(4-chlorophenyl)-2-oxotetrahydrofuran-3-carboxylate (**2j**).* 0.102 g, 87% yield, yellow viscous liquid, new compound, R_f = 0.54 (hexanes/ethyl acetate 5/1), 93% ee, $[\alpha]^{20}_D$ = −33.58 (*c* 1.84, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 2H), 7.15−7.05 (m, 2H), 5.80−5.68 (m, 1H), 5.41−5.29 (m, 2H), 4.69 (dd, *J* = 10.8, 8.9 Hz, 1H), 4.54 (t, *J* = 8.5 Hz, 1H), 3.91 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.56 (s, 3H), 2.95−2.86 (m, 1H), 2.64 (dd, *J* = 14.6, 9.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 173.6, 168.2, 134.4, 132.5, 131.9, 129.2, 121.7, 69.0, 59.6, 52.6, 46.4, 35.5. HPLC: Chiralcel OD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 17.5 and 18.8 min (major). HRMS Calculated for $C_{15}H_{16}ClO_4$ $[M + H]^+$ 295.0732 (^{35}Cl) and 297.0708 (^{37}Cl), found: 295.0736 (^{35}Cl) and 297.0710 (^{37}Cl).

*(−)-Methyl 3-Allyl-4-(4-bromophenyl)-2-oxotetrahydrofuran-3-carboxylate (**2k**).* 0.117 g, 86% yield, yellow viscous liquid, new compound, R_f = 0.70 (hexanes/ethyl acetate 3/1), 88% ee, $[\alpha]^{20}_D$ = −26.58 (*c* 2.34, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.42 (m, 2H), 7.07−6.99 (m, 2H), 5.81−5.68 (m, 1H), 5.39−5.31 (m, 2H), 4.69 (dd, *J* = 10.8, 8.9 Hz, 1H), 4.54 (t, *J* = 8.5 Hz, 1H), 3.89 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.57 (s, 3H), 2.95−2.87 (m, 1H), 2.64 (dd, *J* = 14.6, 9.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 173.6, 168.2, 140.0, 132.2 131.9, 129.5, 122.6, 121.7, 68.9, 59.5, 52.7, 46.5, 35.4. HPLC: Chiralcel OD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 19.1 and 23.8 min (major). HRMS Calculated for $C_{15}H_{16}BrO_4$ $[M + H]^+$ 339.0226 (^{79}Br) and 341.0208 (^{81}Br), found: 339.0229 (^{79}Br) and 341.0206 (^{81}Br).

*(−)-(3R,4R)-Methyl 4-([1,1′-biphenyl]-4-yl)-3-allyl-2-oxotetrahydrofuran-3-carboxylate (**2l**).* 0.131 g, 98% yield, white solid, mp 170−171 °C, new compound, R_f = 0.44 (hexanes/ethyl acetate 5/1), 88% ee, $[\alpha]^{20}_D$ = −16.95 (*c* 2.62, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.54 (m, 4H), 7.48−7.41 (m, 2H), 7.40−7.33 (m, 1H), 7.25−7.19 (m, 2H), 5.85−5.72 (m, 1H), 5.44−5.34 (m, 2H), 4.78 (dd, *J* = 10.9, 8.9 Hz, 1H), 4.57 (t, *J* = 8.5 Hz, 1H), 3.97 (dd, *J* = 10.9, 8.2 Hz, 1H), 3.58 (s, 3H), 2.98−2.89 (m, 1H), 2.70 (dd, *J* = 14.6, 9.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 173.9, 168.4, 141.3, 140.1, 132.8, 132.1, 128.9, 128.3, 127.7, 127.6, 127.0, 121.6, 69.3, 59.7, 52.6, 46.8, 35.5. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 13.2 min (major) and 15.3 min. HRMS Calculated for $C_{21}H_{21}O_4$ $[M + H]^+$ 337.1434, found: 337.1437. Confirmed by X-ray analysis, CCDC number: 2131830.

*(−)-Methyl 3-Allyl-4-(naphthalen-2-yl)-2-oxotetrahydrofuran-3-carboxylate (**2m**).* 0.124 g, 99% yield, colorless solid, mp 113−114 °C, new compound, R_f = 0.78 (hexanes/ethyl acetate 3/1), 89% ee, $[\alpha]^{20}_D$ = −3.91 (*c* 2.56, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.87−7.77 (m, 3H), 7.64−7.59 (m, 1H), 7.54−7.46 (m, 2H), 7.27−7.22 (m, 1H), 5.88−5.74 (m, 1H), 5.47- 5.36 (m, 2H), 4.88 (dd, *J* = 10.8, 8.9 Hz, 1H), 4.62 (t, *J* = 8.5 Hz, 1H), 4.09 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.49 (s, 3H), 2.98−2.90 (m, 1H), 2.73 (dd, *J* = 14.6, 9.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.0, 168.4, 133.3, 133.0, 132.2, 131.4, 128.8, 127.8, 127.8, 127.1, 126.7, 126.6, 125.4, 121.6, 69.3, 59.9, 52.6, 47.2, 35.6. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time

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10.3 min (major) and 11.0 min. HRMS Calculated for $C_{19}H_{19}O_4$ $[M + H]^+$ 311.1278, found: 311.1275.

*(−)-Methyl 3-Allyl-4-(3,4-dimethylphenyl)-2-oxotetrahydrofuran-3-carboxylate (**2n**).* 0.113 g, 98% yield, colorless viscous liquid, new compound, R_f = 0.53 (hexanes/ethyl acetate 5/1), 91% ee, $[\alpha]^{20}_D$ = −31.24 (*c* 2.26, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.16−7.03 (m, 1H), 6.97−6.76 (m, 2H), 5.87−5.66 (m, 1H), 5.44−5.27 (m, 2H), 4.81−4.63 (m, 1H), 4.58−4.43 (m, 1H), 3.91−3.79 (m, 1H), 3.58 (s, 3H), 2.96−2.81 (m, 1H), 2.71−2.56 (m, 1H), 2.25 (s, 3H), 2.24 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.1, 168.5, 137.3, 137.0, 132.2, 131.0, 130.2, 129.2, 125.1, 121.5, 69.4, 59.6, 52.5, 46.8, 35.3, 19.9, 19.5. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, retention time 9.4 min (major) and 10.0 min. HRMS Calculated for $C_{17}H_{20}O_4K$ $[M + K]^+$ 327.0993, found: 327.0993.

*(−)-Methyl 3-Allyl-4-(3,5-dimethylphenyl)-2-oxotetrahydrofuran-3-carboxylate (**2o**).* 0.105 g, 91% yield, colorless viscous liquid, new compound, R_f = 0.55 (hexanes/ethyl acetate 5/1), 90% ee, $[\alpha]^{20}_D$ = −28.09 (*c* 2.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.74 (s, 2H), 5.85−5.66 (m, 1H), 5.41−5.31 (m, 2H), 4.72 (dd, *J* = 11.0, 8.9 Hz, 1H), 4.51 (t, *J* = 8.5 Hz, 1H), 3.92−3.79 (m, 1H), 3.57 (s, 3H), 2.95−2.82 (m, 1H), 2.64 (dd, *J* = 14.5, 9.6 Hz, 1H), 2.30 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.1, 168.5, 138.5, 133.7, 132.2, 130.1, 125.7, 121.5, 69.4, 59.7, 52.4, 47.1, 35.3, 21.4. HPLC: Chiralcel OD-3 column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, retention time 12.6 and 13.3 min (major). HRMS Calculated for $C_{17}H_{24}O_4N$ $[M + NH_4]^+$ 306.1700, found: 306.1708.

*(−)-Methyl 3-Allyl-4-(3,4-dichlorophenyl)-2-oxotetrahydrofuran-3-carboxylate (**2p**).* 0.128 g, 97% yield, colorless viscous liquid, new compound, R_f = 0.47 (hexanes/ethyl acetate 5/1), 89% ee, $[\alpha]^{20}_D$ = −16.68 (*c* 2.56, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.43 (m, 1H), 7.25−7.24 (m, 1H), 7.02−6.99 (m, 1H), 5.82−5.64 (m, 1H), 5.43−5.30 (m, 2H), 4.73−4.61 (m, 1H), 4.55 (t, *J* = 8.5 Hz, 1H), 3.89 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.61 (s, 3H), 2.92 (dd, *J* = 14.6, 5.0 Hz, 1H), 2.63 (dd, *J* = 14.6, 9.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 173.3, 168.0, 134.2, 133.2, 132.8, 131.8, 131.0, 129.8, 127.4, 121.9, 68.8, 59.5, 52.8, 46.1, 35.4. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 8.7 min (major) and 11.0 min. HRMS Calculated for $C_{15}H_{15}Cl_2O_4$ $[M + H]^+$ 329.0342 (^{35}Cl) and 331.0315 (^{37}Cl), found: 329.0346 (^{35}Cl) and 331.0316 (^{37}Cl).

*(−)-Methyl 3-Allyl-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-oxotetrahydrofuran-3-carboxylate (**2q**).* 0.122 g, 96% yield, colorless, viscous liquid, new compound, R_f = 0.32 (hexanes/ethyl acetate 5/1), 90% ee, $[\alpha]^{20}_D$ = −29.06 (*c* 2.44, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84−6.82 (m, 1H), 6.70−6.56 (m, 2H), 5.81−5.66 (m, 1H), 5.42−5.29 (m, 2H), 4.70−4.60 (m, 1H), 4.49 (t, *J* = 8.5 Hz, 1H), 4.25 (s, 4H), 3.86−3.78 (m, 1H), 3.62 (s, 3H), 2.88 (d, *J* = 18.6 Hz, 1H), 2.70−2.56 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 174.0, 168.4, 143.8, 143.7, 132.1, 126.6, 121.6, 120.7, 117.7, 116.8, 69.3, 64.3, 59.5, 52.6, 46.4, 35.2. HPLC: Chiralpak AS-H column, 220 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 47.2 and 51.0 min (major). HRMS Calculated for $C_{17}H_{19}O_6$ $[M + H]^+$ 319.1176, found: 319.1174.

*(−)-Methyl 3-Allyl-4-(benzofuran-2-yl)-2-oxotetrahydrofuran-3-carboxylate (**2r**).* 0.090 g, 75% yield, yellow viscous liquid, new compound, R_f = 0.38 (hexanes/ethyl acetate 5/1), 62% ee, $[\alpha]^{20}_D$ = −16.11 (*c* 1.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.52 (m, 1H), 7.43−7.41 (m, 1H), 7.30−7.26 (m, 1H), 7.24−7.20 (m, 1H), 6.57 (s, 1H), 5.83−5.71 (m, 1H), 5.43−5.32 (m, 2H), 4.75 (dd, *J* = 11.1, 8.7 Hz, 1H), 4.60 (t, *J* = 8.5 Hz, 1H), 4.16 (dd, *J* = 11.0, 8.3 Hz, 1H), 3.63 (s, 3H), 2.94 (dd, *J* = 14.3, 5.3 Hz, 1H), 2.80 (dd, *J* = 14.3, 9.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 173.4, 168.2, 155.0, 150.7, 131.7, 127.6, 124.8, 123.2, 122.1, 121.1, 111.1, 105.5, 67.7, 58.1, 53.0, 41.9, 35.5. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.6 mL/min, retention time 15.8 and 16.9 min (major). HRMS Calculated for $C_{17}H_{17}O_5$ $[M + H]^+$ 301.1071, found: 301.1072.

*(+)-Methyl 3-Cinnamyl-4-methyl-2-oxotetrahydrofuran-3-carboxylate (**2s**).* 0.082 g, 75% yield, colorless viscous liquid, new compound, R_f = 0.38 (hexanes/ethyl acetate 5/1), 95% ee, $[\alpha]^{20}_D$ = +4.27 (*c* 0.96, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.33 (m, 2H), 7.33−7.27 (m, 2H), 7.26−7.20 (m, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.20−6.06 (m, 1H), 4.35 (t, *J* = 8.3 Hz, 1H), 3.97 (dd, *J* = 10.6, 8.7 Hz, 1H), 3.79 (s, 3H), 2.95−2.68 (m, 3H), 1.01 (d, *J* = 6.9 Hz, 3H) $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.1, 169.0, 136.7, 135.5, 128.6, 127.7, 126.3, 123.3, 71.9, 57.8, 52.7, 37.2, 35.0, 11.9. HPLC: Chiralpak IB column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 10.1 min (major) and 11.1 min. HRMS Calculated for $C_{16}H_{19}O_4$ $[M + H]^+$ 275.1278, found: 275.1285.

*(−)-Methyl 4-(tert-Butyl)-3-cinnamyl-2-oxotetrahydrofuran-3-carboxylate (**2t**).* 0.125 g, 98% yield, colorless viscous liquid, new compound, R_f = 0.52 (hexanes/ethyl acetate 5/1), 76% ee, $[\alpha]^{20}_D$ = −3.52 (*c* 2.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 4H), 7.27−7.22 (m, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.00−5.90 (m, 1H), 4.33−4.24 (m, 2H), 3.76 (s, 3H), 3.11−2.98 (m, 2H), 2.64 (dd, *J* = 11.3, 8.5 Hz, 1H), 0.98 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 175.4, 170.0, 136.8, 135.9, 128.6, 127.8, 126.4, 123.6, 68.0, 56.4, 52.7, 50.9, 36.4, 32.3, 27.9. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 8.4 min (major) and 10.7 min. HRMS Calculated for $C_{19}H_{25}O_4$ $[M + H]^+$ 317.1747, found: 317.1749.

*(+)-Methyl 3-Cinnamyl-4-cyclohexyl-2-oxotetrahydrofuran-3-carboxylate (**2u**).* 0.136 g, 99% yield, colorless viscous liquid, new compound, R_f = 0.61 (hexanes/ethyl acetate 5/1), 83% ee, $[\alpha]^{20}_D$ = +12.21 (*c* 2.72, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.35 (m, 2H), 7.33−7.29 (m, 2H), 7.27−7.22 (m, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.03−5.91 (m, 1H), 4.34 (t, *J* = 8.4 Hz, 1H), 4.07 (dd, *J* = 10.9, 8.7 Hz, 1H), 3.81 (s, 3H), 3.19−3.06 (m, 1H), 2.87 (dd, *J* = 14.5, 9.9 Hz, 1H), 2.57−2.45 (m, 1H), 2.05 (d, *J* = 12.3 Hz, 1H), 1.77−1.62 (m, 3H), 1.50- 1.46 (m, 1H), 1.32−1.12 (m, 4H), 1.05−0.87 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 175.5, 169.3, 136.7, 135.8, 128.6, 127.8, 126.4, 123.5, 70.4, 57.8, 52.8, 46.4, 39.0, 36.5, 31.2, 30.7, 26.0, 25.8, 25.8. HPLC: Chiralcel OD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, retention time 9.9 min (major) and 15.9 min. HRMS Calculated for $C_{21}H_{27}O_4$ $[M + H]^+$ 343.1904, found: 343.1902.

Experiment on Gram Scale. Palladium trifluoroacetate (0.1 mmol, 33.2 mg), ligand (*S,S*)-Ph-BPE (0.12 mmol, 60.8 mg), and acetone (10 mL) were placed in a dried Schlenk tube under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. Then, the solvent was removed under vacuum to give the chiral catalyst. This catalyst was taken into a glovebox filled with nitrogen and dissolved in 2,2,2-trifluoroethanol (30 mL). To the mixture of compound **1a** (5.0 mmol) and benzoic acid (1.0 mmol, 122.1 mg) in tetrahydrofuran (15 mL) was added the above catalyst solution, and then the mixture was transferred to an autoclave, which was charged with hydrogen gas (600 psi). The autoclave was stirred at 40 °C (bath oil temperature) for 40 h. After release of the hydrogen gas, the autoclave was opened, and the mixture was concentrated under the reduced pressure. Then, potassium carbonate (10 mmol, 1.380 g), allyl bromide (10 mmol,0.92 mL), and acetone (30 mL) were added. The new mixture was stirred at ambient temperature for 36 h. The reaction mixture was quenched with hydrochloric acid (HCl, 3 *N*, 5.0 mL), extracted three times with dichloromethane (15 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Then, purification was performed by column chromatography on silica gel using hexanes/ethyl acetate (15/1) as the eluent to give the chiral reductive product (−)-**2a** 1.276 g, 98% isolated yield, and 91% ee.

*Synthesis of (+)-Methyl 3-((E)-3-(4-(Methoxycarbonyl)phenyl)-allyl)-2-oxo-4-phenyltetrahydrofuran-3-carboxylate (**3**).* To a dried Schlenk tube under a nitrogen atmosphere were added compound (−)-**2a** (0.4 mmol, 104.0 mg), palladium acetate (0.02 mmol, 4.4 mg), P(*o*-Tol)$_3$ (0.04 mmol, 12.0 mg), potassium carbonate (1.2 mmol, 165.6 mg), methyl 4-bromobenzoate (1 mmol, 215.0 mg), and dry *N,N*-dimethylformamide (3.0 mL). The mixture was stirred at 90

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°C for 9 h. After completion of reaction (monitored by TLC), the mixture was cooled to room temperature, and water (10 mL) and ethyl acetate (10 mL) were added. The water layer was extracted with ethyl acetate (8.0 mL) three times. 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/acetone (5/1) as the eluent to give the Heck coupling product (+)-**3**. 0.134 g, 85% yield, yellow viscous liquid, new compound, R_f = 0.35 (hexanes/acetone 5/1), 91% ee, $[\alpha]^{20}_D$ = +127.77 (*c* 1.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.46−7.44 (m, 2H), 7.40−7.32 (m, 3H), 7.20−7.14 (m, 2H), 6.70 (d, *J* = 15.8 Hz, 1H), 6.34−6.23 (m, 1H), 4.77 (dd, *J* = 10.8, 9.1 Hz, 1H), 4.56 (t, *J* = 8.5 Hz, 1H), 3.95−3.89 (m, 4H), 3.58 (s, 3H), 3.08−3.03 (m, 4.8 Hz, 1H), 2.88 (dd, *J* = 14.7, 9.3 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 174.0, 168.2, 166.8, 141.0, 135.2, 133.7, 130.0, 129.3, 129.1, 128.6, 127.9, 126.3, 126.3, 69.3, 59.9, 52.7, 52.2, 47.8, 35.0. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 0.8 mL/min, retention time 29.2 min (major) and 38.3 min. HRMS Calculated for $C_{23}H_{23}O_6$ $[M + H]^+$ 395.1489, found: 395.1491.

*Synthesis of (+)-3-Allyl-4-phenyldihydrofuran-2(3H)-one (**4**).* A mixture of (−)-**2a** (0.4 mmol, 104.0 mg, 91% ee) and lithium chloride (1.2 mmol, 50.9 mg) in dimethyl sulfoxide (3 mL) and water (9.2 μL) was refluxed for 16.5 h. After full consumption of reactant (monitored by TLC), water (10 mL) and ethyl acetate (10 mL) were added, and the water layer was extracted 5 times with ethyl acetate (8.0 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel using hexanes/ethyl acetate (5/1) as an eluent to give the decarboxylation product (+)-**4**. 0.068 g, 84% yield, colorless viscous liquid, new compound, R_f = 0.52 (hexanes/ethyl acetate 8/1), 91% ee, $[\alpha]^{20}_D$ = +65.32 (*c* 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.34 (m, 2H), 7.34−7.28 (m, 1H), 7.26−7.24 (m, 2H), 5.91−5.54 (m, 1H), 5.32−4.96 (m, 2H), 4.55 (t, *J* = 8.7 Hz, 1H), 4.17 (t, *J* = 9.5 Hz, 1H), 3.51 (dd, *J* = 18.7, 10.2 Hz, 1H), 2.94−2.71 (m, 1H), 2.63−2.33 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 177.5, 138.1, 133.6, 129.2, 127.9, 127.5, 118.7, 72.2, 46.4, 46.2, 32.5. HPLC: Chiralpak AD-H column, 220 nm, 30 °C, *n*-Hexane/*i*-Pr- OH = 95/5, flow = 0.8 mL/min, retention time 10.7 min (major), and 11.5 min. HRMS Calculated for $C_{13}H_{15}O_2$ $[M + H]^+$ 203.1067, found: 203.1067.

Determination of the Absolute Configuration of Compound (+)-2l. To determine the absolute configuration of (−)-methyl 4-([1,1′-biphenyl]-4-yl)-3-allyl-2-oxotetrahydrofu-*ran*-3-carboxylate (**2l**): first, (−)-**2l** was upgraded to >99% ee by recrystallization with *n*-hexane/dichloromethane. Then, (−)-**2l** was completely dissolved in dichloromethane (1.0 mL), and *n*-hexane (2.0 mL) was added slowly at room temperature. The solvent diffused slowly, and the single crystal could be obtained after 2 days. The structure in Figure S1 showed that the absolute configuration is (3*R*,4*R*). The CCDC number is 2131830. These details can be obtained free of charge via www.ccdc.com.ac.uk/data_request/cif from Cambridge Crystallographic Data Centre.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.5c00042.

NMR spectra of products; copies of ^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} spectra of all new compounds (PDF)

Accession Codes

Deposition Number 2131830 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

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