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One-Pot Asymmetric Synthesis of Substituted Tetrahydrofurans *via* a Multicatalytic Benzoin/Michael/Acetalization Cascade

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Abstract: A sequential benzoin/Michael/acetalization tandem reaction catalyzed by NHC and amine together has been developed to assemble aromatic aldehydes and enals into chiral tetrahydrofuran derivatives bearing multiple functional groups and stereogenic centers with high stereoselectivity of up to 95:5 *dr* and 96% *ee*. The high yield and stereocontrol of this process may be due to both acid-promoted symmetrization of racemic acyloins and iminium ion activation of enals.

Keywords: asymmetric synthesis; domino reactions; heterocycles; multicomponent reactions; organocatalysis

Introduction

Developing multicomponent cascade reactions in which densely functionalized scaffolds are assembled in one pot has become an increasingly fruitful area of research.[1] This approach can be particularly powerful when two catalytic entities are combined,[2] since this can enable transformations and stereocontrol that would be impossible in the presence of either catalyst on its own.

One efficient combination involves N-heterocyclic carbene (NHC) catalysis,[3] an elegant organocatalytic method for forming new bonds through umpolung, in concert with either sequential transition metal catalysis[4] or cooperative Lewis acid catalysis.[5] This catalytic combination should be used under carefully controlled conditions to prevent self-quenching and mutual interference between the two catalysts.[6] Very recently, Rovis,[7a,b] Enders,[7c] Jørgensen,[7d,e] Córdova,[7f] Xu[7g] and Melchiorre[7h] have taken advantage of the inherent basicity and compatibility of chiral amines and NHCs to develop a model of consecutive amine–NHC catalysis to stereoselectively access complex molecules.[7] Conversely, few studies have examined the reverse catalytic sequence of NHC followed by amine for the asymmetric synthesis of enantioenriched architectures.[8]

The NHC-catalyzed benzoin condensation is an atom-economical method of generating α-hydroxy ketones, which are highly valuable synthons that occur naturally in various furan-based biologically active compounds (Figure 1).[9] Several groups have reported the synthesis of racemic tetrahydrofuran derivatives *via* benzoin-triggered multicomponent tandem reactions under alkaline conditions with low yield and no stereocontrol.[10] However, we are unaware of studies exploring whether an analogous approach based on sequential NHC–amine catalysis could generate these

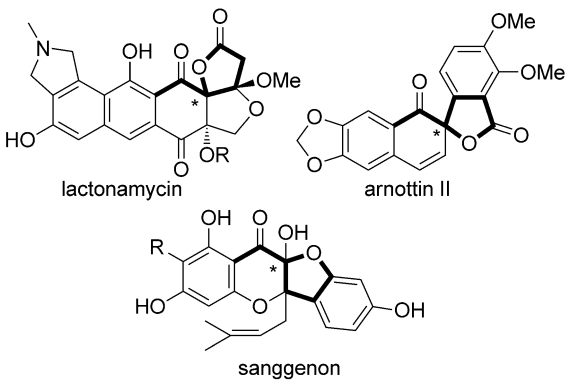
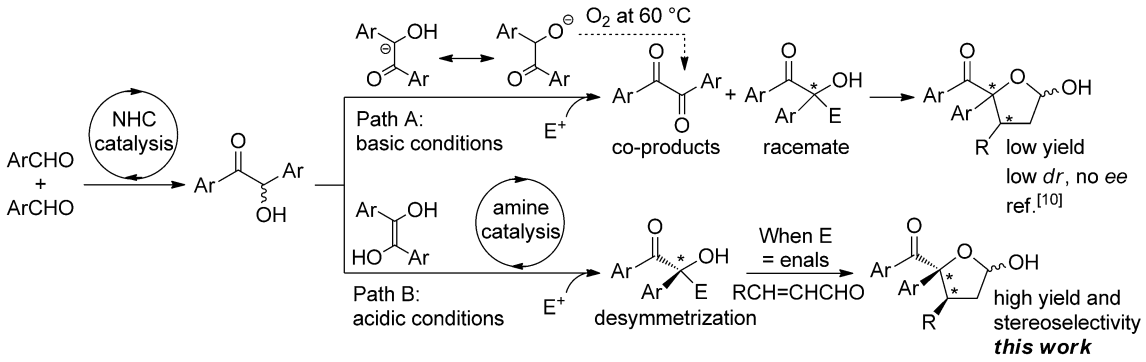


Figure 1. Examples of natural products containing the acyloin moiety.



Scheme 1. Synthetic strategy.

polysubstituted oxa-cyclic compounds efficiently and stereoselectively.

Results and Discussion

Previous studies and our own preliminary experiments suggested that this approach was vulnerable to a significant side reaction, even in an air atmosphere, in which oxidation of the base-promoted anion intermediate afforded dicarbonyl co-products in high yield (Scheme 1, Path A).[10] To avoid this path, we envisioned that adding an acid to the acyloin would induce the formation of stable and symmetrical enediol intermediates, thereby assuring a steady supply of nucleophiles for the subsequent enantio- and diastereoselective domino reaction. We know that chiral secondary amines can catalyze the stereoselective conjugate Michael addition of various nucleophiles to α,β-unsaturated aldehydes, and that this addition depends on acid-promoted iminium ion activation.[11] Therefore we decided to investigate a benzoin/Michael/acetalization cascade catalyzed by NHC and amine to asymmetrically generate pharmaceutically important tetrahydrofuran derivatives bearing multiple stereocenters (Path B).[12] In this process, the acid promoted both the symmetrization of racemic acyloins and the iminium ion activation of enals, which we predicted would lead to high yield and stereoselectivity. If successful, this approach would allow the enantioselective construction of chiral quaternary centers,[13] provide a novel cascade for asymmetric synthesis, and broaden the useful scope of sequential dual catalysis.[14]

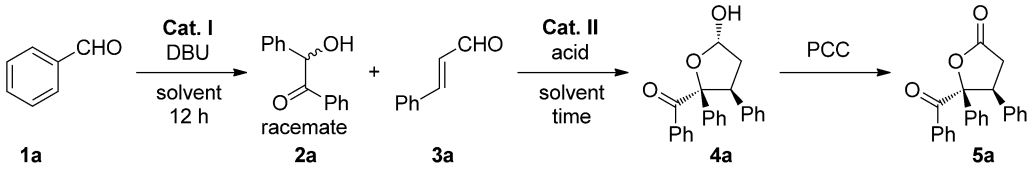
We first tested our hypothesis using aromatic aldehyde **1a** and NHC precatalyst **I** (Table 1). Based on reports of NHC-catalyzed intermolecular benzoin condensation,[15] we tested imidazolium-, thiazolium- and triazolium-based precatalysts **Ia**–**Id**. We screened numerous conditions, including base, temperature, time and concentrations; complete optimisation results are presented in Table S1 (Supporting Information). Acyloin was produced in good yield using pre-catalyst **Id** and DBU in acetonitrile or THF at room temperature.

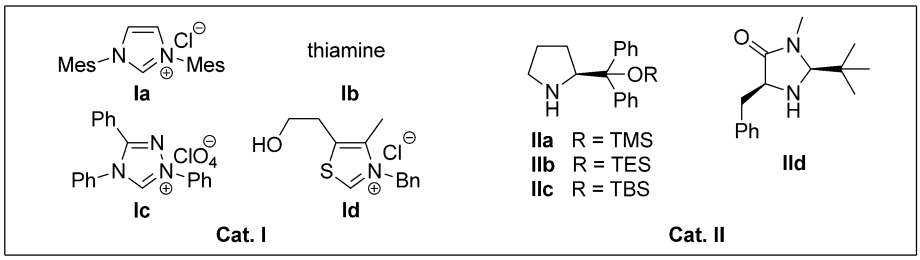
With the racemate **2a** in hand, we then explored the feasibility of subsequent Michael/acetalization. First we acidified the basic mixture and induced formation of the symmetrical enediol nucleophile, after which we added the chiral secondary amine catalyst **II** and enal **3**. Using this approach, we obtained hemiacetal **4a** in moderate yield from **2a** and cinnamyl aldehyde **3a** using the Jørgensen–Hayashi catalyst **IIa** and acetic acid (Table 1, entry 1). Direct oxidation of the hemiacetal with PCC gave the more stable corresponding γ-lactone **5a** as a 85:15 mixture of diastereomers, with 86% *ee* for the major isomer. Interestingly, this facile conversion may provide an alternative strategy for generating chiral cyclic α-acyloxycarbonyl compounds.[16]

The reaction gave lower yields of the desired product when we used other secondary amine catalysts (**IIb**–**IId**; entries 2–4). Screening identified the additive 4-fluorobenzoic acid and the solvent THF as giving the highest yield and stereoselectivity (entries 5–9). To our delight, increasing the reaction temperature to 60 °C improved the diastereoselectivity to 90:10, and significantly shortened the time required for completion (entry 10). Apparently, hemiacetal formation is under thermodynamic control in these experimental conditions.

Using the optimized reaction conditions, we proceeded to investigate the substrate scope (Table 2). The process showed a broad scope, but efficiencies and stereoselectivities varied with the electronic nature of the aromatic aldehydes **1**. Products were generated in higher yield and with greater enantioselectivity from aromatic aldehydes **1** bearing electron-withdrawing groups (Table 2, entries 2–7) than from those with neutral or electron-donating groups (entries 1 and 8). Heteroaryl aldehydes participated efficiently, giving even higher yields and diastereoselectivities than aryl aldehydes (entries 9 and 10). To extend the scope of the reaction further, we explored other enals **3**. The position and electronic properties of substituents on the aromatic ring of aryl-substituted

Table 1. Optimization of reaction conditions.[a]





Entry	Cat. **II**	Solvent	Additive	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**IIa**	MeCN	AcOH	16	40	85:15	86
2	**IIb**	MeCN	AcOH	>24	32	85:15	85
3	**IIc**	MeCN	AcOH	>24	30	87:13	85
4	**IId**	MeCN	AcOH	8	34	75:25	82
5	**IIa**	toluene	AcOH	8	40	85:15	90
6	**IIa**	THF	AcOH	8	45	85:15	89
7	**IIa**	THF	BzOH	16	32	90:10	90
8	**IIa**	THF	TFA	4	50	80:20	91
9	**IIa**	THF	*p*-FBA	4	65	85:15	90
10[e]	**IIa**	THF	*p*-FBA	2	62	90:10	92

[a] Unless otherwise noted, reactions were performed with precatalyst **I** (0.1 mmol), DBU (0.1 mol) and **1a** (1.6 mmol) in solvent (2 mL) at room temperature, after which acidic additive (0.2 mmol), catalyst **II** (0.1 mmol) and **3a** (0.4 mmol) were added.
[b] Yield of isolated **5a**.
[c] Calculated based on ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by HPLC using a chiral stationary phase.
[e] Reaction performed at 60 °C.

α,β-unsaturated aldehydes did not appear to significantly affect reaction efficiency (entries 11–14). Even the less reactive acrolein and crotonaldehyde participated in the reaction, giving products with moderate enantioselectivity (entries 15 and 16), albeit with lower *dr* for **5p**. Unfortunately, the reaction did not proceed with α-substituted or γ-branched enals.[17] When this catalytic cascade reaction was conducted on a larger scale, similar good results were observed (Table 2, entry 17).

The absolute configuration of **5a** was determined by X-ray crystallographic analysis,[18] while that of other products was tentatively assigned by analogy.

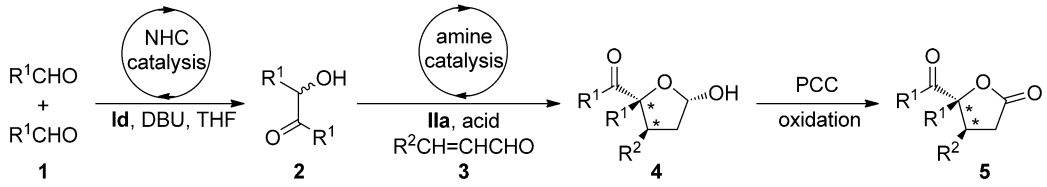
We propose a transition-state model to explain the high diastereo- and enantioselectivity of the reaction (Scheme 2). The symmetrical enediol approaches the β-position of the chiral iminium ion intermediate, while avoiding steric repulsion from the bulky diphenylsiloxymethyl group on the pyrrolidine ring and β-substituent of the enal. As a result, a carbon-carbon bond forms preferentially between the *Re* face of the enediol and the *Si* face of the iminium ion to provide the adduct and subsequent hemiacetal in the *S*,*S* configuration in high optical purity.

To illustrate the synthetic potential of our approach, we smoothly converted the chiral hemiacetal **4** into several versatile building blocks beside the γ-lactone (Scheme 3). The hemiaminal **4a** was dehydroxylated by treatment with Et_3SiH and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 as solvent at −20 °C, providing the chiral tetrahydrofuran **6**. The hydroxy group of **4a** was also acetylated to give **7**. Directly treating the tetrahydropyranol **4a** with allyltrimethylsilane or cyanotrimethylsilane in the presence of $TiCl_4$ generated the corresponding polysubstituted tetrahydrofurans **8** and **9** with three stereogenic centers *via* S_N1 reactions.

Conclusions

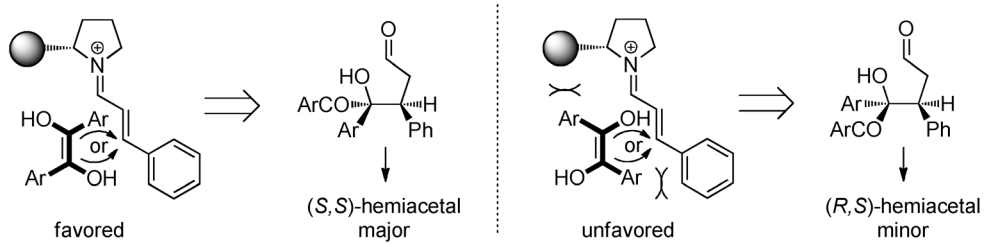
In summary, we have developed an unprecedented sequential organocatalytic reaction involving a benzoin/

Table 2. Investigating the scope of the cascade reaction.[a]

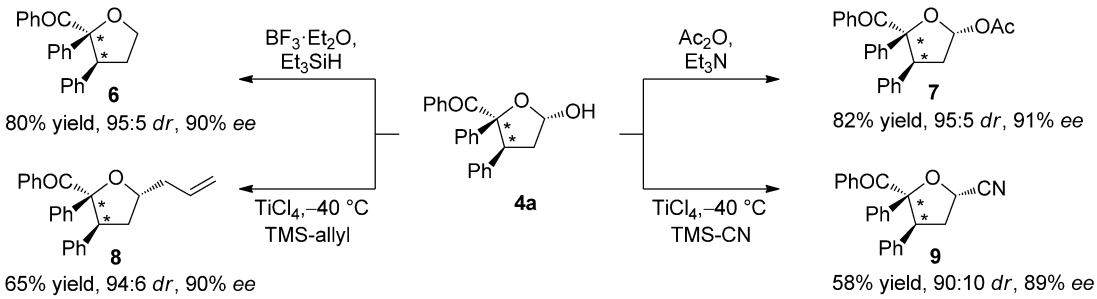


Entry	R^1	R^2	Product	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	Ph	Ph	**5a**	62	90:10	92
2	2-ClC_6H_4	Ph	**5b**	65	92:8	91
3	4-ClC_6H_4	Ph	**5c**	73	84:16	90
4	3-BrC_6H_4	Ph	**5d**	68	93:7	96
5	4-BrC_6H_4	Ph	**5e**	70	90:10	93
6	4-FC_6H_4	Ph	**5f**	68	90:10	95
7	2,4-$Cl_2C_6H_3$	Ph	**5g**	63	95:5	92
8	4-*i*-PrC_6H_4	Ph	**5h**	55	94:6	90
9	2-furyl	Ph	**5i**	76	95:5	86
10	2-thienyl	Ph	**5j**	74	95:5	87
11	Ph	4-ClC_6H_4	**5k**	67	82:18	90
12	Ph	4-BrC_6H_4	**5l**	64	90:10	92
13	Ph	3-FC_6H_4	**5m**	61	92:8	91
14	Ph	4-MeC_6H_4	**5n**	60	87:13	88
15	4-ClC_6H_4	H	**5o**	47	–	61
16	Ph	CH_3	**5p**	58[e]	52:48	75/71
17[f]	Ph	Ph	**5a**	58	90:10	90

[a] See entry 10 and footnote[a] in Table 1.
[b] Yield of isolated **5**.
[c] Based on chiral HPLC analysis.
[d] Calculated from ^1H NMR analysis of the crude reaction mixture.
[e] Calculated from two isolated isomers.
[f] The scaled-up reaction: **1a** (8 mmol), **3a** (2 mmol), **Id** (0.5 mmol), **IIa** (0.5 mmol).



Scheme 2. Proposed mechanism to explain the high stereoselectivity.



Scheme 3. Chemical transformations of **4a**.

Michael/acetalization cascade for the asymmetric assembly of aromatic aldehydes and enals into tetrahydrofuran derivatives bearing multiple functional groups and stereogenic centers. The reaction proceeds with high stereoselectivity of up to 95:5 *dr* and 96% *ee*. The high yield and diastereomeric ratio may be due to the fact that acid promotes not only the iminium ion activation of enals but also the symmetrization of racemic acyloins. The mild reaction conditions, short reaction times, and high tolerance for various functional groups makes this strategy an attractive method for the construction of enantioenriched heterocyclic compounds. Our laboratory is conducting further studies into asymmetric domino reactions involving sequential NHC-amine catalysis.

Experimental Section

NMR data was obtained for ^{1}H at 400 MHz, and for ^{13}C at 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. ESI HR-MS was recorded on a Waters SYNAPT G2. In each case, the enantiomeric ratio was determined by HPLC analysis on a chiral column in comparison with authentic racemates, using a Daicel Chiralpak AD-H Column (250×4.6 mm), Daicel Chiralpak OD-H Column (250×4.6 mm), Daicel Chiralpak AS-H Column (250×4.6 mm) or Kromasil AmyCoat Column (250×4.6 mm). UV detection was monitored at 220 nm or 254 nm. Optical rotation data were examined in EtOH solution at 20 °C. Column chromatography was performed on silica gel (200–300 mesh) eluting with ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates. UV light and I_2 were used to visualize products. Melting points were determined on a Mel-Temp apparatus and are uncorrected. All chemicals were from Adamas-beta and were used without purification unless otherwise noted.

General Procedure for the Asymmetric Synthesis of γ-Lactone 5

The reaction was carried out with precatalyst **Id** (0.1 mmol), DBU (0.1 mol) and **1** (1.6 mmol) in THF (2.0 mL) at room temperature to afford the racemate acyloin **2**, after which 4-fluorobenzoic acid (0.2 mmol), diphenylprolinol TMS ether **IIa** (0.1 mmol) and enal **3** (0.4 mmol) were added in one-pot. The reaction mixture was stirred at 60 °C for a specified reaction time (about 6–8 h) until the reaction was completed (monitored by TLC). Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give hemiacetal **4**.

Hemiacetal **4** was oxidized to the stable corresponding γ-lactone **5** as follows. To a solution of **4** in dichloromethane (5 mL) was added PCC (107.8 mg, 0.5 mmol). The mixture was stirred for 2 h at 50 °C. The solid was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate = 15:1) to give γ-lactone **5**.

(4*S*,5*S*)-5-Benzoyl-4,5-diphenyldihydrofuran-2(3*H*)-one (5a): Obtained as a white solid; yield: 85 mg (62%) for two steps after flash chromatography. The *dr* value was calculated to be 90:10 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 92% by HPLC (AmyCoat column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{major} = 9.77 min, t_{minor} = 11.73 min; mp 138–139 °C; $[\alpha]_D^{20}$: −138.9 (*c* 0.12 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.6 Hz, 2H), 7.46–7.43 (m, 1H), 7.32–7.26 (m, 2H), 7.11–7.07 (m, 8H), 6.94 (s, 2H), 4.88 (t, J = 5.6 Hz, 1H), 3.03 (dd, J_1 = 18.0 Hz, J_2 = 8.8 Hz, 1H), 2.88 (dd, J_1 = 18.0 Hz, J_2 = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.29, 175.24, 137.31, 135.33, 133.59, 133.42, 130.95, 128.79, 128.45, 128.27, 128.19, 128.07, 127.26, 124.68, 95.07, 47.94, 35.53; ESI-HR-MS: *m/z* = 365.1152, calcd. for $C_{23}H_{18}O_3$ + Na: 365.1154.

(4*S*,5*S*)-5-(2-Chlorobenzoyl)-5-(2-chlorophenyl)-4-phenyldihydrofuran-2(3*H*)-one (5b): Obtained as a white solid; yield: 107 mg (65%) for two steps after flash chromatography. The *dr* value was calculated to be 92:8 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 91% by HPLC (Amycoat column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 220 nm): t_{major} = 9.97 min, t_{minor} = 11.09 min; mp 144–145 °C; $[\alpha]_D^{20}$: −156.3 (*c* 0.03 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 7.2 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.26–7.21 (m, 1H), 7.12–6.93 (m, 10H), 5.05 (d, J = 8.8 Hz, 1H), 3.62 (dd, J_1 = 18.0 Hz, J_2 = 9.2 Hz, 1H), 2.71 (d, J = 18.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.46, 175.25, 139.28, 134.30, 134.02, 133.48, 131.81, 131.11, 130.70, 129.80, 129.70, 129.32, 128.21, 127.93, 127.38, 126.77, 125.48, 94.29, 45.32, 37.97; ESI-HR-MS: *m/z* = 433.0371, calcd. for $C_{23}H_{16}Cl_2O_3$ + Na: 433.0374.

(4*S*,5*S*)-5-(4-Chlorobenzoyl)-5-(4-chlorophenyl)-4-phenyldihydrofuran-2(3*H*)-one (5c): Obtained as a white solid; yield: 120 mg (73%) for two steps after flash chromatography. The *dr* value was calculated to be 84:16 by ^{1}H NMR analysis and the enantiomeric excess was determined to be 90% by HPLC (Chiralpak OD-H column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{major} = 17.29 min, t_{minor} = 20.24 min; mp 114–115 °C; $[\alpha]_D^{20}$: −176.4 (*c* 0.1 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.4 Hz, 2H), 7.31–7.29 (m, 2H), 7.11–7.09 (m, 5H), 6.98–6.93 (m, 4H), 4.85 (dd, J_1 = 8.0 Hz, J_2 = 5.6 Hz, 1H), 3.03 (dd, J_1 = 18.0 Hz, J_2 = 8.4 Hz, 1H), 2.87 (dd, J_1 = 18.0 Hz, J_2 = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.84, 174.65, 140.29, 136.89, 134.49, 133.76, 132.27, 131.61, 128.79, 128.76, 128.63, 128.35, 127.62, 126.07, 94.48, 47.75, 35.38; ESI-HR-MS: *m/z* = 433.0378, calcd. for $C_{23}H_{16}Cl_2O_3$ + Na: 433.0374.

(4*S*,5*S*)-5-(3-Bromobenzoyl)-5-(3-bromophenyl)-4-phenyldihydrofuran-2(3*H*)-one (5d): Obtained as a white solid; yield: 136 mg (68%) for two steps after flash chromatography. The *dr* value was calculated to be 93:7 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 96% by HPLC (Chiralpak OD-H column, 10% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 220 nm): t_{minor} = 13.18 min, t_{major} = 15.51 min; mp 126–127 °C; $[\alpha]_D^{20}$: −175.0 (*c* = 0.10 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.60–7.56 (m, 1H), 7.25–7.23 (m, 1H), 7.20–7.16 (m, 2H), 7.11 (m,

3H), 7.00–6.91 (m, 4H), 4.84 (t, $J=6.8$ Hz, 1H), 3.03 (dd, $J_1=18.0$ Hz, $J_2=8.4$ Hz, 1H), 2.88 (dd, $J_1=18.0$ Hz, $J_2=5.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=193.60$, 174.52, 137.25, 136.73, 136.55, 135.04, 133.47, 131.57, 130.07, 129.94, 129.60, 128.59, 128.32, 127.78, 127.70, 123.26, 122.92, 122.68, 94.20, 47.94, 35.24; ESI-HR-MS: m/z=520.9361, calcd. for $C_{23}H_{16}Br_2O_3$+Na: 520.9364.

(4*S*,5*S*)-5-(4-Bromobenzoyl)-5-(4-bromophenyl)-4-phenyldihydrofuran-2(3*H*)-one (5e): Obtained as a white solid; yield: 140 mg (70%) for two steps after flash chromatography. The *dr* value was calculated to be 90:10 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 93% by HPLC (Amycoat column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 220 nm): $t_{major}=10.94$ min, $t_{minor}=13.64$ min; mp 143–144 °C; $[\alpha]_D^{20}$: −188.5 (*c* 0.052 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.76 (d, $J=8.4$ Hz, 2H), 7.47 (d, $J=8.0$ Hz, 2H), 7.26–7.24 (m, 3H), 7.11 (s, 3H), 6.91–6.89 (m, 3H), 4.84 (t, $J=6.4$ Hz, 1H), 3.03 (dd, $J_1=18.0$ Hz, $J_2=8.4$ Hz, 1H), 2.87 (dd, $J_1=$ 18.0 Hz, $J_2=5.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 193.85, 174.58, 136.83, 134.26, 132.31, 132.01, 131.78, 131.74, 129.19, 128.62, 128.36, 127.64, 126.34, 122.68, 94.50, 47.70, 35.37; ESI -HR-MS: *m/z*=520.9362, calcd. for $C_{23}H_{16}Br_2O_3$+Na: 520.9364.

(4*S*,5*S*)-5-(4-Fluorobenzoyl)-5-(4-fluorophenyl)-4-phenyldihydrofuran-2(3*H*)-one (5f): Obtained as a white solid; yield: 103 mg (68%) for two steps after flash chromatography. The *dr* value was calculated to be 90:10 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 95% by HPLC (Chiralpak OD-H column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): $t_{minor}=16.58$ min, $t_{major}=25.25$ min; mp 127–128 °C; $[\alpha]_D^{20}$: −102.4 (*c* 0.1 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.95$ (s, 2H), 7.10 (br s, 3H), 7.01–7.00 (m, 4H), 6.92 (m, 2H), 6.83–6.79 (m, 2H), 4.86 (t, $J=6.0$ Hz, 1H), 3.03 (dd, $J_1=18.0$ Hz, $J_2=8.4$ Hz, 1H), 2.88 (dd, $J_1=18.0$ Hz, $J_2=$ 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=193.59$, 174.82, 165.77 (d, $J_{C,F}=255$ Hz), 162.41 (d, $J_{C,F}=247$ Hz), 137.10, 133.78 (d, $J_{C,F}=9$ Hz), 131.14 (d, $J_{C,F}=4$ Hz), 129.72 (d, $J_{C,F}=3$ Hz), 128.65, 128.27, 127.50, 126.54 (d, $J_{C,F}=9$ Hz), 115.72 (d, $J_{C,F}=3$ Hz), 115.50 (d, $J_{C,F}=2$ Hz), 94.57, 47.81, 35.38; ESI-HR-MS: *m/z*=401.0968, calcd. for $C_{23}H_{16}F_2O_3$+Na: 401.0965.

(4*S*,5*S*)-5-(2,4-Dichlorobenzoyl)-5-(2,4-dichlorophenyl)-4-phenyldihydrofuran-2(3*H*)-one (5g): Obtained as a white solid; yield: 121 mg (63%) for two steps after flash chromatography. The *dr* value was calculated to be 95:5 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 92% by HPLC (Amycoat column; 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): $t_{major}=6.80$ min, $t_{minor}=9.08$ min; mp 148–149 °C; $[\alpha]_D^{20}$: −61.4 (*c* 0.12 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.49$ (d, $J=8.4$ Hz, 1H), 7.43 (s, 1H), 7.19–7.17 (m, 1H), 7.07–6.97 (m, 8H), 4.98 (d, $J=8.8$ Hz, 1H), 3.61 (dd, $J_1=18.0$ Hz, $J_2=9.2$ Hz, 1H), 2.82 (d, $J=18.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=192.09$, 174.73, 138.86, 137.85, 135.08, 134.85, 132.83, 132.17, 131.36, 131.33, 130.30, 129.68, 128.73, 128.46, 127.75, 127.25, 126.03, 93.71, 45.39, 37.76; ESI-HR-MS: m/z=500.9593, calcd. for $C_{23}H_{14}Cl_4O_3$+Na: 500.9595.

(4*S*,5*S*)-5-(4-Isopropylbenzoyl)-5-(4-isopropylphenyl)-4-phenyldihydrofuran-2(3*H*)-one (5h): Obtained as a white solid; yield: 94 mg (55%) for two steps after flash chromatography. The *dr* value was calculated to be 94:6 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 90% by HPLC (Amycoat column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): $t_{major}=6.43$ min, $t_{minor}=7.74$ min; mp 132–133 °C; $[\alpha]_D^{20}$: −130.2 (*c* 0.096 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.86$ (d, $J=8.4$ Hz, 2H), 7.17–7.15 (m, 2H), 7.04–7.03 (m, 3H), 6.96–6.88 (m, 6H), 4.82 (dd, $J_1=8.4$ Hz, $J_2=6.4$ Hz, 1H), 2.99 (dd, $J_1=18.0$ Hz, $J_2=8.8$ Hz, 1H), 2.90–2.83 (m, 2H), 2.77–2.71 (m, 1H), 1.20 (d, $J=2.0$ Hz, 3H), 1.18 (d, $J=1.6$ Hz, 3H), 1.11 (d, $J=3.2$ Hz, 3H), 1.10 (d, $J=3.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=195.06$, 175.47, 154.91, 148.99, 137.40, 132.71, 131.44, 131.32, 128.85, 127.86, 127.06, 126.39, 124.57, 95.20, 48.04, 35.40, 34.24, 33.60, 23.78, 23.77, 23.53, 23.47; ESI-HR-MS: *m/z*= 449.2090, calcd. for $C_{29}H_{30}O_3$+Na: 449.2093.

(4*S*,5*S*)-5-(Furan-2-carbonyl)-5-(furan-2-yl)-4-phenyldihydrofuran-2(3*H*)-one (5i): Obtained as a white solid; yield: 98 mg (76%) for two steps after flash chromatography. The *dr* value was calculated to be 95:5 by ^{1}H NMR analysis and the enantiomeric excess was determined to be 86% by HPLC (Chiralpak OD-H column, 20% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 220 nm), $t_{major}=22.59$ min, $t_{minor}=$ 28.17 min. m.p. 126–127 °C; $[\alpha]_D^{20}$: −116.4 (*c*=0.12 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.65$ (s, 1H), 7.32 (br s, 1H), 7.18 (br s, 4H), 7.09 (br s, 2H), 6.49 (s, 1H), 6.15 (d, $J=8.8$ Hz, 2H), 4.70 (t, $J=8.4$ Hz, 1H), 3.11–2.97 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=181.03$, 174.27, 149.14, 148.16, 147.95, 143.20, 136.25, 128.29, 128.24, 127.66, 123.13, 112.56, 110.58, 109.38, 89.67, 46.69, 34.42 ppm; ESI HRMS: calcd. For $C_{19}H_{14}O_5$+Na 345.0739, found 345.0743.

(4*S*,5*R*)-4-Phenyl-5-(thiophen-2-yl)-5-(thiophene-2-carbonyl)dihydrofuran-2(3*H*)-one (5j): Obtained as a white solid; yield: 105 mg (74%) for two steps after flash chromatography. The dr value was calculated to be 95:5 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 87% by HPLC on Chiralpak OD-H column (10% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): $t_{minor}=18.83$ min, $t_{major}=23.25$ min; mp 90–91 °C; $[\alpha]_D^{20}$: −90.8 (*c* 0.10 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.98$ (d, $J=3.6$ Hz, 1H), 7.66 (d, $J=$ 4.8 Hz, 1H), 7.16–7.05 (m, 7H), 6.75–6.72 (m, 1H), 6.60–6.59 (m, 1H), 4.75 (t, $J=7.2$ Hz, 1H), 3.06–2.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=187.83$, 174.24, 139.34, 138.10, 136.77, 136.63, 135.76, 128.70, 128.61, 128.18, 127.67, 127.10, 126.17, 126.09, 93.47, 48.18, 34.96; ESI-HR-MS: *m/z*=377.0280, calcd. for $C_{19}H_{14}O_3S_2$+Na: 377.0282.

(4*S*,5*S*)-5-Benzoyl-4-(4-chlorophenyl)-5-phenyldihydrofuran-2(3*H*)-one (5k): Obtained as a white solid; yield: 101 mg (67%) for two steps after flash chromatography. The *dr* value was calculated to be 82:18 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 90% by HPLC (Amycoat column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): $t_{major}=$ 12.18 min, $t_{minor}=16.32$ min; mp 123–124 °C; $[\alpha]_D^{20}$: −50 (*c* 0.10 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.89$ (d, $J=$ 8.0 Hz, 2H), 7.47–7.43 (m, 1H), 7.32–7.29 (m, 2H), 7.15 (br s, 3H), 7.06–7.04 (m, 4H), 6.86 (d, $J=7.6$ Hz, 2H), 4.85 (t, $J=7.6$ Hz, 1H), 3.01 (dd, $J_1=18.0$ Hz, $J_2=8.4$ Hz, 1H), 2.82 (dd, $J_1=18.0$ Hz, $J_2=6.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=194.03$, 173.71, 134.67, 134.01, 132.50, 132.41,

132.18, 129.91, 129.10, 127.65, 127.46, 127.26, 127.17, 123.58, 93.64, 46.37, 34.28; ESI-HR-MS: m/z = 399.0766, calcd. for $C_{23}H_{17}ClO_3$ + Na: 399.0764.

(4*S*,5*S*)-5-Benzoyl-4-(4-bromophenyl)-5-phenyldihydrofuran-2(3*H*)-one (5l): Obtained as a white solid; yield: 108 mg (64%) for two steps after flash chromatography. The *dr* value was calculated to be 90:10 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 92% by HPLC (Amycoat column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{major} = 12.79 min, t_{minor} = 17.69 min; mp 149–150 °C; $[\alpha]_D^{20}$: −89.3 (*c* 0.12 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.0 Hz, 2H), 7.46–7.43 (m, 1H), 7.32–7.28 (m, 2H), 7.21–7.15 (m, 5H), 7.04 (br s, 2H), 6.80 (d, J = 8.0 Hz, 2H), 4.83 (t, J = 7.6 Hz, 1H), 3.01 (dd, J_1 = 18.0 Hz, J_2 = 8.8 Hz, 1H), 2.81 (dd, J_1 = 18.0 Hz, J_2 = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.04, 174.70, 136.23, 135.02, 133.53, 133.44, 131.16, 130.94, 130.49, 128.70, 128.52, 128.30, 124.62, 121.37, 94.59, 47.48, 35.26; ESI-HR-MS: m/z = 399.0766, calcd. for $C_{123}H_{17}BrO_3$ + Na: 443.0259.

(4*S*,5*S*)-5-Benzoyl-4-(3-fluorophenyl)-5-phenyldihydrofuran-2(3*H*)-one (5m): Obtained as a white solid; yield: 88 mg (61%) for two steps after flash chromatography. The *dr* value was calculated to be 92:8 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 91% by HPLC (Amycoat column; 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{major} = 10.57 min, t_{minor} = 12.95 min; mp 129–130 °C; $[\alpha]_D^{20}$: −97.7 (*c* 0.13 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.0 Hz, 2H), 7.47–7.43 (m, 1H), 7.33–7.29 (m, 2H), 7.15–7.14 (m, 3H), 7.07–7.02 (m, 3H), 6.79–6.73 (m, 2H), 6.65 (d, J = 10.0 Hz, 1H), 4.88 (t, J = 7.2 Hz, 1H), 3.03 (dd, J_1 = 18.0 Hz, J_2 = 8.8 Hz, 1H), 2.86 (dd, J_1 = 18.0 Hz, J_2 = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.96, 174.70, 162.36 (d, $J_{C,F}$ = 244 Hz), 139.85 (d, $J_{C,F}$ = 7 Hz), 135.05, 133.53, 133.42, 130.97, 129.52, 128.62, 128.45, 128.30, 125.17, 124.57, 115.93 (d, $J_{C,F}$ = 21 Hz), 114.25 (d, $J_{C,F}$ = 21 Hz), 94.76, 47.59, 35.27; ESI-HR-MS: m/z = 383.1057, calcd. for $C_{23}H_{17}FO_3$ + Na: 383.1059.

(4*S*,5*S*)-5-Benzoyl-5-phenyl-4-(*para*-tolyl)dihydrofuran-2(3*H*)-one (5n): Obtained as a white solid; yield: 86 mg (60%) for two steps after flash chromatography. The *dr* value was calculated to be 87:13 by ^{1}H NMR analysis of the crude reaction mixture and the enantiomeric excess was determined to be 88% by HPLC on Chiralpak AD-H column (5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{major} = 11.13 min, t_{minor} = 12.73 min, mp 99–100 °C; $[\alpha]_D^{20}$: −118.0 (*c* 0.10 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.6 Hz, 2H), 7.45–7.41 (m, 1H), 7.31–7.27 (m, 2H), 7.12–7.11 (m, 3H), 7.065–7.056 (m, 2H), 6.87 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 4.83 (t, J = 7.2 Hz, 1H), 2.99 (dd, J_1 = 17.6 Hz, J_2 = 8.4 Hz, 1H), 2.84 (dd, J_1 = 18.0 Hz, J_2 = 6.0 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.40, 175.32, 136.91, 135.38, 134.15, 133.78, 133.36, 130.92, 128.74, 128.66, 128.44, 128.25, 128.17, 124.76, 95.06, 47.68, 35.64, 20.96; ESI-HR-MS: m/z = 379.1312, calcd. for $C_{24}H_{20}O_3$ + Na: 379.1310.

(*S*)-5-(4-Chlorobenzoyl)-5-(4-chlorophenyl)dihydrofuran-2(3*H*)-one (5o): Obtained as a white semisolid; yield: 63 mg (47%) for two steps after flash chromatography. The enantiomeric excess was determined to be 61% by HPLC (Chiralpak AS-H column, 2% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{major} = 18.24 min, t_{minor} = 20.52 min; $[\alpha]_D^{20}$: −83.3 (*c* 0.06 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.4 Hz, 2H), 7.39 (br s, 4H), 7.32 (d, J = 8.4 Hz, 2H), 3.46–3.39 (m, 1H), 2.61–2.56 (m, 2H), 2.32–2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.72, 175.03, 140.33, 137.65, 134.88, 132.13, 131.52, 129.64, 128.80, 125.17, 91.49, 34.17, 27.88; ESI-HR-MS: m/z = 357.0059, calcd. for $C_{17}H_{12}Cl_2O_3$ + Na: 357.0061.

(4*R*,5*S*)-5-Benzoyl-4-methyl-5-phenyldihydrofuran-2(3*H*)-one (5p): Obtained as a white semisolid; yield: 34 mg (30%) for two steps after flash chromatography. The enantiomeric excess was determined to be 75% by HPLC (Chiralpak OD-H column, 2% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 220 nm): t_{major} = 7.99 min, t_{minor} = 12.63 min; $[\alpha]_D^{20}$: −192.3 (*c* 0.05 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.40–7.36 (m, 4H), 7.26 (s, 2H), 3.09 (t, J = 6.4 Hz, 1H), 2.57 (dd, J_1 = 17.2 Hz, J_2 = 7.2 Hz, 1H), 2.26 (dd, J_1 = 17.2 Hz, J_2 = 9.2 Hz, 1H), 1.24 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.01, 174.83, 140.07, 136.55, 135.20, 133.69, 131.31, 129.34, 128.73, 126.60, 94.11, 42.83, 36.01, 16.48; ESI-HR-MS: m/z = 303.0995, calcd. for $C_{18}H_{16}O_3$ + Na: 303.0997.

(4*S*,5*S*)-5-Benzoyl-4-methyl-5-phenyldihydrofuran-2(3*H*)-one: The diastereomer of **5p** was obtained as a white semisolid; yield: 31 mg (28%) for two steps after flash chromatography. The enantiomeric excess was determined to be 71% by HPLC (Chiralpak AD-H column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{major} = 14.53 min, t_{minor} = 22.05 min; $[\alpha]_D^{20}$: +115.2 (*c* 0.06 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.4 Hz, 2H), 7.40–7.27 (m, 8H), 3.63 (m, 1H), 2.75 (dd, J_1 = 17.6 Hz, J_2 = 8.0 Hz, 1H), 2.28 (dd, J_1 = 17.6 Hz, J_2 = 4.8 Hz, 1H), 0.77 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.30, 174.58, 140.21, 134.93, 133.84, 132.17, 131.68, 129.50, 128.75, 125.90, 93.93, 36.81, 36.43, 16.52; ESI-HR-MS: m/z = 303.0995, calcd. for $C_{18}H_{16}O_3$ + Na: 303.0997.

Synthetic Transformations to Access Diverse Building Blocks

[(2*S*,3*S*)-2,3-Diphenyltetrahydrofuran-2-yl](phenyl)methanone (6): To a solution of **4a** (68.9 mg, 0.2 mmol) and triethylsilane (69.8 mg, 0.6 mmol) in DCM (5 mL) was added $BF_3{\cdot}Et_2O$ (84 μL, 0.66 mmol). The mixture was stirred at 0 °C for 12 h. The reaction was quenched with aqueous $NaHCO_3$, extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 40:1). The tetrahydrofuran derivative **6** was obtained as a white semisolid; yield: 53 mg (80%) after flash chromatography. The *dr* value was calculated to be 95:5 by ^{1}H NMR analysis and the enantiomeric excess was determined to be 90% by HPLC (Chiralpak AD-H column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{major} = 4.86 min, t_{minor} = 5.20 min; $[\alpha]_D^{20}$: −82.4 (*c* 0.21 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 7.6 Hz, 2H), 7.39–7.36 (m, 1H), 7.27–7.21 (m, 3H), 7.13–7.11 (m, 2H), 7.05–6.95 (m, 7H), 4.55 (t, J = 7.2 Hz, 1H), 4.43 (dt, J_1 = 8.4 Hz, J_2 = 4.4 Hz, 1H), 3.92 (dd, J_1 = 16.8 Hz, J_2 = 8.4 Hz, 1H), 2.43–2.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.13, 140.62, 138.63, 134.83, 132.56, 130.66, 129.26, 127.93, 127.84, 127.59, 127.08, 126.12, 125.67, 95.26, 67.89, 50.94,

32.95; ESI-HR-MS: $m/z = 351.1360$, calcd. for $C_{23}H_{20}O_2$+Na: 351.1361.

(2*R*,4*S*,5*S*)-5-Benzoyl-4,5-diphenyltetrahydrofuran-2-yl acetate (7): To a solution of **4a** (68.9 mg, 0.2 mmol) in DCM (4 mL) was added acetic anhydride (30.6 mg, 0.3 mmol) and triethylamine (30.4 mg 0.3 mmol). The mixture was stirred for 2 h at room temperature. When the reaction was complete, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 30:1). The acetylated derivative **7** was obtained as a white solid; yield: 63 mg (82%) after flash chromatography. The *dr* value was calculated to be 95:5 by ^{1}H NMR analysis and the enantiomeric excess was determined to be 91% by HPLC (Chiralpak AD-H column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{major} = 6.12 min, t_{minor} = 6.48 min; mp 104–105 °C; $[\alpha]_D^{20}$: −62.5 (*c* 0.12 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 7.6 Hz, 2H), 7.41–7.37 (m, 1H), 7.30–7.28 (m, 2H), 7.09–7.02 (m, 8H), 6.95–6.93 (m, 2H), 6.82–6.81 (m, 1H), 4.86 (t, J = 7.6 Hz, 1H), 2.61–2.48 (m, 2H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.55, 170.29, 139.34, 136.86, 134.65, 132.52, 130.83, 129.79, 129.11, 127.99, 127.92, 127.73, 126.44, 125.27, 97.88, 96.39, 49.63, 38.84, 20.46; ESI-HR-MS: m/z = 393.1465, calcd. for $C_{25}H_{22}O_3$+Na: 393.1467.

[(2*S*,3*S*,5*R*)-5-Allyl-2,3-diphenyltetrahydrofuran-2-yl]-(phenyl)methanone (8): $TiCl_4$ (55.0 μL, 0.5 mmol) and allyltrimethylsilane (79.5 μL, 0.5 mmol) were added to a solution of **4a** (68.9 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) at −70 °C under an argon atmosphere. The resulting mixture was slowly warmed up to −40 °C and stirred for 5 h before being quenched with Et_3N (0.4 mL) followed by addition of saturated aqueous $NaHCO_3$ solution (2 mL) at −40 °C. The resulting suspension was filtered through a celite pad. The aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with H_2O and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 40:1). The allyl-substituted tetrahydrofuran derivative **8** was obtained as a white semisolid; yield: 48 mg (65%) after flash chromatography. The *dr* value was calculated to be 94:6 by ^{1}H NMR analysis and the enantiomeric excess was determined to be 90% by HPLC (Chiralpak AD-H column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{major} = 4.33 min, t_{minor} = 4.56 min; $[\alpha]_D^{20}$: −65.8 (*c* 0.08 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.0 Hz, 2H), 7.38–7.35 (m, 1H), 7.27–7.23 (m, 2H), 7.13–7.12 (m, 2H), 7.05–6.97 (m, 8H), 5.67 (dt, J_1 = 17.2 Hz, J_2 = 7.2 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 4.86 (d, J = 17.2 Hz, 1H), 4.77 (t, J = 6.8 Hz, 1H), 4.67 (t, J = 6.4 Hz, 1H), 2.42–2.36 (m, 1H), 2.27–2.07 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.91, 140.25, 139.07, 135.11, 134.59, 132.37, 131.04, 129.27, 127.83, 127.80, 127.63, 126.99, 126.12, 125.62, 117.27, 95.59, 80.67, 51.06, 41.65, 38.14; ESI-HR-MS: m/z = 391.1073, calcd. for $C_{26}H_{24}O_2$+Na: 391.1674.

(2*S*,4*S*,5*S*)-5-Benzoyl-4,5-diphenyltetrahydrofuran-2-carbonitrile (9): $TiCl_4$ (55.0 μL, 0.5 mmol) and cyanotrimethylsilane (66.7 μL, 0.5 mmol) were added to a solution of **4a** (68.9 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) at −70 °C under an argon atmosphere. The resulting mixture was slowly warmed up to −40 °C and stirred for 5 h before being quenched with Et_3N (0.4 mL) followed by addition of saturated aqueous $NaHCO_3$ solution (2 mL) at −40 °C. The resulting suspension was filtered through a celite pad. The aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with H_2O and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 40:1). The cyano-substituted tetrahydrofuran derivative **9** was obtained as a white solid; yield: 41 mg (58%) after flash chromatography. The *dr* value was calculated to be 90:10 by ^{1}H NMR analysis and the enantiomeric excess was determined to be 89% by HPLC (Chiralpak AD-H column, 5% 2-propanol/*n*-hexane, 1 mL min^{-1}, UV 254 nm): t_{minor} = 5.03 min, t_{major} = 7.57 min; mp 148–149 °C; $[\alpha]_D^{20}$: +118.9 (*c* 0.04 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.2 Hz, 2H), 7.37–7.36 (m, 1H), 7.30–7.28 (m, 2H), 7.04–7.00 (m, 5H), 6.95 (br s, 3H), 6.69 (br s, 2H), 5.30–5.29 (m, 1H), 4.59 (t, J = 6.4 Hz, 1H), 1.75–1.70 (m, 1H), 1.61–1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.53, 140.12, 137.52, 135.30, 132.16, 130.65, 129.04, 128.63, 127.89, 127.82, 127.46, 127.14, 126.00, 125.17, 100.63, 95.33, 50.08, 38.95; ESI-HR-MS: m/z = 376.1310, calcd. for $C_{24}H_{19}NO_2$+Na: 376.1313.

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10 One-Pot Asymmetric Synthesis of Substituted Tetrahydrofurans *via* a Multicatalytic Benzoin/Michael/Acetalization Cascade

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