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Bifunctional Primary Amine-Squaramide Catalyzed Enantioselective Intramolecular Michael Addition of Keto-enones: A Convenient Process to the Stereocontrolled Construction of *trans*-Dihydrobenzofuran Skeletons

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A highly diasterero- and enantioselective intramolecular Michael addition of keto-enones has been realized. By using the (*R*,*R*)-1,2-diphenylethane-1,2-diamine-based bifunctional primary amine-squaramide catalyst, the reaction proceeded smoothly to generate the corresponding *trans*-2,3-disubstituted dihydrobenzofuran derivatives in excellent yields with good to excellent diastereo- and enantioselectivities (up to 97:3 *dr*, up to >99 % *ee*).

Introduction

The 2,3-dihydrobenzofuran (DHB) skeleton is widespread in many natural products and biologically active molecules.[1] The biological activities of these systems are well recognized,[2] and these diverse and intriguing properties, combined with their broad occurrence in nature, have motivated chemists to develop various approaches to construct DHBs.[3] However, methods for their preparation in a catalytic asymmetric fashion are limited and rely mainly on the application of transition-metal catalysis.[4]

In contrast to the great progress made in asymmetric organocatalysis during the past three decades,[5,6] with regard to the organocatalyzed asymmetric synthesis of DHBs with high enantioselectivity, only limited examples of the stereoselective construction of the DHB ring have emerged in the past several years. In 2006, Enders developed the first example of an organocatalyzed enantioselective construction of a DHB ring system through an L-proline-catalyzed intramolecular aldol reaction.[7] A second example involves a direct organocatalytic enantioselective α-arylation by treating aldehydes with quinones to generate DHB derivatives with excellent enantioselectivities.[8] The enantioselective construction of the DHB core skeleton of (–)-variabilin and (–)-glycinol was realized by Calter through a cinchona alkaloid catalyzed enantioselective interrupted Feist–Bénary reaction as the key step.[9] Jørgensen reported an anodic oxidation/organocatalytic protocol for the α-arylation of aldehydes with *N*-tosyl-4-aminophenol to generate DHBs in good yields with excellent enantiomeric excesses.[10] Another elegant organocatalytic approach to optically active DHBs, also developed by Jørgensen and co-authors, is the L-prolinol silyl ether catalyzed one-pot reaction cascade.[11] A highly enantio- and diastereoselective approach to *cis*-2,3-dihydrobenzofurans was achieved by Smith et al. through an isothiourea-promoted intramolecular Michael addition of aryloxyacetic acids that contain an enone moiety on the aromatic tether.[12] Our group has also developed an efficient method for the synthesis of optically active *trans*-DHBs through a primary amine-thiourea catalyzed intramolecular Michael addition of a ketone to a nitroolefin.[13] Most recently, Alemán presented the asymmetric synthesis of *trans*-dihydroarylfurans through a Friedel–Crafts/substitution domino reaction under squaramide catalysis.[14] Because of their inherent importance and the scarcity of organocatalytic methods reported for these structures, new organocatalytic strategies to prepare these substrates are highly desirable. In this context, we realized that although there are a number of reports of elegant catalytic enantioselective intermolecular Michael additions to chalcones, intramolecular catalytic asymmetric Michael additions of ketones to chalcones are unexplored.[15] Herein, we report the efficient asymmetric aminocatalysis of intramolecular Michael reactions of keto-enones.

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Results and Discussion

We initially investigated the intramolecular Michael addition of (*E*)-3-[2-(2-oxopropoxy)phenyl]-1-phenylprop-2-en-1-one (**4a**) by employing bifunctional primary amine-thiourea **1**,[16] primary amine-thiophosphonamide **2**,[17] and primary amine-squaramide **3**[18] as the catalyst candidates (see Figure 1). The results are summarized in Table 1.

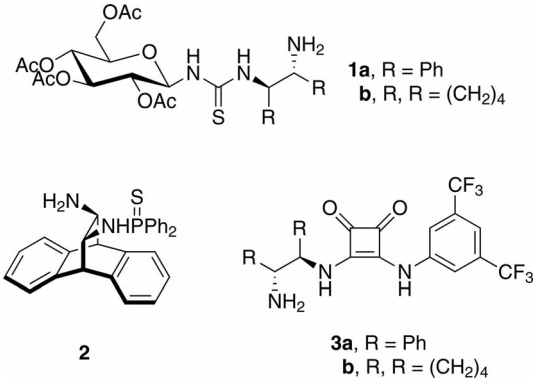
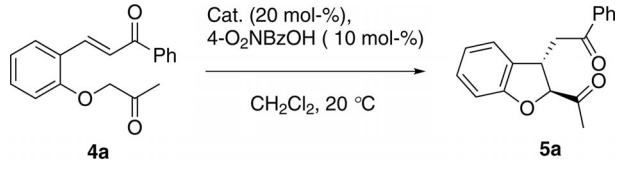


Figure 1. Catalyst candidates.

Table 1. Catalyst evaluation.[a]



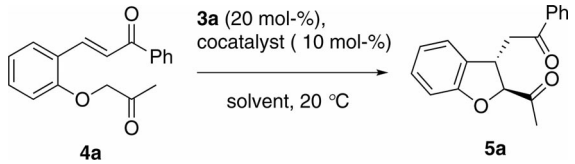
Entry	Catalyst	Time [h]	% Yield[b]	*trans*/*cis*[c]	% *ee*[d]
1	**1a**	2	88	95:5	9
2	**1b**	1.5	>99	89:11	84
3	**2**	2.5	>99	83:17	61
4	**3a**	20	98	94:6	94
5	**3b**	>7 d	53	89:11	87

[a] Reagents and conditions: keto-enone **4a** (0.3 mmol) in CH_2Cl_2 (1 mL) at 20 °C in the presence of catalyst (20 mol-%) and 4-nitrobenzoic acid (4-NO_2BzOH, 10 mol-%). [b] Yield of isolated product after chromatography on silica gel. [c] Determined by ^{1}H NMR analysis. [d] Determined by chiral HPLC analysis.

As shown in Table 1, bifunctional primary amine-thiourea **1** demonstrated high catalytic efficacy in the model reaction to generate the corresponding cyclization product **5a** in high yield within 2 h. However, the enantioselectivity was significantly influenced by the backbone of the thiourea, and 1,2-diphenylethane-1,2-diamine-based thiourea **1a**, which previously provided a high degree of enantioselectivity in the intramolecular Michael addition of keto-nitro olefins,[12] appeared to be ineffective in this transformation. The corresponding cyclization product **5a** was obtained almost in racemic form (see Table 1, Entry 1, 9%*ee*). The use of cyclohexane-1,2-diamine-derived thiourea **1b** resulted in a sharp increase of the *ee* value of product **5a** (see Table 1, Entry 2, 84%*ee*). Primary amine-thiophosphonamide **2** also worked well and gave *trans*-dihydrobenzofuran **5a** with an enantioselectivity of 61%*ee* (see Table 1, Entry 3). Although an obvious decrease in catalytic activity was observed for bifunctional squaramide catalyst **3**, it demonstrated a great advantage over the previous two types of catalysts with respect to the stereocontrol of the reaction. For example, in comparison to thiourea **1a**, the use of squaramide catalyst **3a**, which contained the same diamine scaffold, resulted in a dramatically increased enantioselectivity, but at the expense of the reaction time (see Table 1, Entry 4 vs. 1). Although squaramide **3b**, which contained a cyclohexane-1,2-diamine skeleton, was not sufficiently active to ensure the full conversion of **4a** over a week, the cyclization product was also obtained with a high level of stereocontrol (see Table 1, Entry 5, 87%*ee*).

With this promising catalyst **3a** in hand, other factors that may influence the reaction, such as solvent, acidic co-catalyst, catalyst loading, and reaction temperature, were thoroughly investigated by employing the intramolecular Michael addition of (*E*)-3-[2-(2-oxopropoxy)phenyl]-1-phenylprop-2-en-1-one (**4a**) as a model. The results are listed in Table 2.

Table 2. Optimization of reaction conditions.[a].



Entry	Solvent	Cocatalyst	Time [h]	% Yield[b]	*trans*/*cis*[c]	% *ee*[d]
1	CH_2Cl_2	4-NO_2BzOH	20	98	94:6	95
2	$CHCl_3$	4-NO_2BzOH	26	96	93:7	93
3	THF[e]	4-NO_2BzOH	49	76	96:4	95
4	$PhCH_3$	4-NO_2BzOH	96	84	94:6	93
5	CH_3OH	4-NO_2BzOH	>7 d	80	87:13	91
6	CH_2Cl_2	$PhCO_2H$	30	88	94:6	96
7	CH_2Cl_2	PhOH	>7 d	62	99:1	97
8	CH_2Cl_2	AcOH	10	96	95:5	97
9[f]	CH_2Cl_2	AcOH	80	80	98:2	97
10[g]	CH_2Cl_2	AcOH	12	95	95:5	97
11[h]	CH_2Cl_2	AcOH	24	90	95:5	97

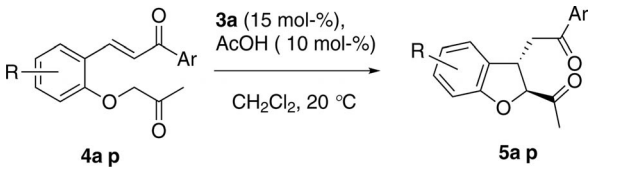
[a] Reagents and conditions: keto-enone **4a** (0.3 mmol) in solvent (1 mL) in the presence of catalyst **3a** and acidic cocatalyst (10 mol-%). [b] Yield of isolated product after chromatography on silica gel. [c] Determined by ^{1}H NMR analysis. [d] Determined by chiral HPLC analysis. [e] THF = tetrahydrofuran. [f] Reaction was carried out at 0 °C. [g] Catalyst **3a** (15 mol-%) was employed. [h] Catalyst **3a** (10 mol-%) was loaded.

Although the reaction proceeded smoothly in several conventional solvents (see Table 2) to afford the corresponding *trans*-dihydrobenzofuran **5a** with almost the same high *ee* values, performing the asymmetric intramolecular Michael addition in CH_2Cl_2 resulted in a slightly higher reaction efficiency and enantioselectivity (see Table 2, Entries 1–5). Moreover, an acidic cocatalyst was determined as essential to both the efficiency and enantioselectivity of the reaction. Acetic acid gave superior results with respect to reaction rate and enantioselectivity (see Table 2, Entry 8). Decreasing the reaction temperature from 20 to 0 °C led to a sluggish reaction with an unaltered enantioselectivity (see Table 2, Entry 9). Adjusting the catalyst loading had almost

no influence on the outcome of the enantioselectivity. The catalyst loading was successfully reduced to 15 mol-% without any detrimental effect to the reaction (see Table 2, Entry 10 vs. 8). The reaction also proceeded well with a catalyst loading of 10 mol-% without any erosion of the observed *ee* value, but at the expense of the reaction time (see Table 2, Entry 11).

With a set of optimized reaction conditions in hand (15 mol-% of bifunctional squaramide **3a** in combination with 10 mol-% of acetic acid as the catalyst at 20 °C in dichloromethane), we then explored the scope of the intramolecular Michael addition reaction with various keto-enones. The results are collected in Table 3.

Table 3. Substrate scope of **3a**-catalyzed asymmetric intramolecular Michael addition of keto-enones **4**.[a]



Entry	**5** (R, Ar)	Time [h]	% Yield[b]	*trans*/*cis*[c,d]	% *ee*[d]
1	**5a** (H, Ph)	12	95	95:5	97
2[e,f]	**5a** (H, Ph)	15	90 (85)	94:6 (>99:1)	96 (>99)
3	**5b** (5-F, Ph)	15	94	96:4	97
4	**5c** (5-Cl, Ph)	17	99	95:5	98
5	**5d** (5-Br, Ph)	17	99	95:5	95
6	**5e** (5,7-Cl_2, Ph)	30	95	96:4	97
7	**5f** (5-Me, Ph)	7	99	97:3	97
8	**5g** (6-Me, Ph)	6	99	93:7	98
9	**5h** (5-*t*Bu, Ph)	10	90	94:6	96
10	**5i** (H, 3-FC_6H_4)	8	90	97:3	98
11	**5j** (H, 4-FC_6H_4)	9	98	96:4	97
12	**5k** (H, 4-ClC_6H_4)	8.5	94	95:5	97
13	**5l** (H, 4-BrC_6H_4)	8	90	97:3	98
14	**5m** (H, 2,4-$Cl_2C_6H_3$)	6	66	76:24	88:94
15	**5n** (H, 4-$MeOC_6H_4$)	12	99	90:10	95
16	**5o** (H, 4-MeC_6H_4)	6	99	90:10	95
17	**5p** (H, 2-furyl)	5	98	95:5	>99

[a] Reagents and conditions: keto-enone (0.3 mmol) in CH_2Cl_2 (1 mL) at 20 °C in the presence of catalyst (15 mol-%) and AcOH (10 mol-%). [b] Yield of isolated product after chromatography on silica gel. [c] Determined by ^1H NMR analysis. [d] Determined by chiral HPLC analysis. [e] Performed on 10 mmol scale. [f] Data in parenthesis was obtained after a single recrystallization.

As shown in Table 3, this transformation has a broad substrate scope. Keto-enones that were derived from both electron-rich and electron-deficient salicylaldehydes with various substitution patterns participated in the intramolecular Michael addition to give *trans*-DHBs in excellent yields with excellent diasteroselectivities (*trans*/*cis*, 93:7–97:3) and enantioselectivities (from 95 to >98%*ee*; see Table 3, Entries 1–9). With respect to keto-enones prepared from substituted acetophenone and salicylaldehyde, substrates with an electron-withdrawing group substituent generally gave cyclization products with high diastereo- and enantioselectivities (see Table 3, Entries 10–13), whereas introducing an electron-donating group to the benzene ring led to a slightly decreased *trans*/*cis* ratio and *ee* value (see Table 3, Entries 15 and 16). Keto-enone **4m**, which is 2,4-dichlorophenyl-substituted, is an exception, as the bulky nature of this substrate resulted in an obvious decrease in the diastereo- and enantioselectivity (see Table 3, Entry 14). Moreover, 2-acetofuran-based keto-enone **4p** also work well to generate the corresponding dihydrobenzofuran **5p** in quantitative yield with an excellent stereochemical outcome (see Table 3, Entry 17; *trans*/*cis*, 95:5; >99%*ee*). In addition, the reaction was carried out on a gram scale to give the isolated product in excellent yield with an almost unaltered stereochemical outcome, which demonstrates the potential application of this method for preparative purposes (see Table 3, Entry 1 vs. 2). The absolute configuration of product **5a** was unequivocally established as (*S*,*S*) by X-ray crystal structure analysis (see Figure 2), and the remaining configurations were assumed by analogy.[19]

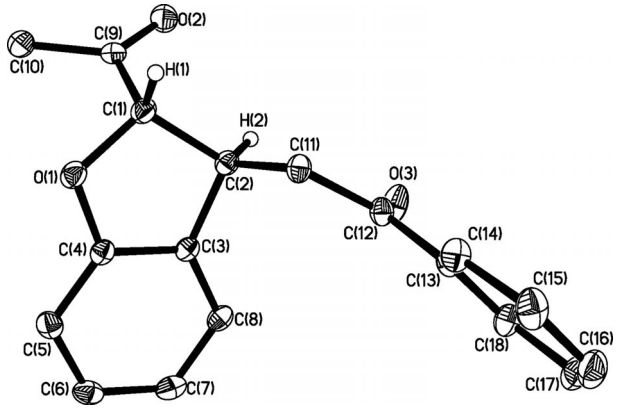


Figure 2. X-ray crystal structure of the major diastereomer of compound **5a**. Most of hydrogen atoms have been omitted for clarity.

Conclusions

In summary, we have developed a highly diastereo- and enantioselective organocatalytic asymmetric intramolecular Michael addition of a keto-enone to give *trans*-dihydrobenzofurans with two contiguous stereocenters in high yields with up to 97:3 *dr* and up to >99%*ee*. Hence, this reaction provides a convenient and scalable process for the syntheses of pharmaceutically valuable *trans*-dihydrobenzofurans.

Experimental Section

General Methods: All reagents and solvents were commercial grade and purified prior to use when necessary. The NMR spectroscopic data were recorded with a Varian 400 MHz instrument. Chemical shifts are recorded relative to the solvent peaks as an internal standard set to δ = 7.26 and 77.0 ppm ($CHCl_3$, $CDCl_3$, respectively). Specific rotations were measured with a Perkin–Elmer 341MC polarimeter. Enantiomeric excesses (*ee*) were determined by using an HP-1100 instrument (chiral column; mobile phase: hexane/*i*PrOH). HRMS was performed with a Varian QFT-ESI instrument. Melting points were determined with a Taike X-4 melting point apparatus.

Synthesis of Squaramide Catalyst 3a {3-[(1*R*,2*R*)-2-Amino-1,2-diphenylethylamino]-4-[3,5-bis(trifluoromethyl)phenylamino]-cyclobut-3-ene-1,2-dione}: To a solution of dimethyl squarate (284 mg, 2.00 mmol) in CH_2Cl_2 (8 mL) was added 3,5-bis(trifluoromethyl) benzenamine (2.0 mmol). The resulting mixture was stirred at room temperature until the amine was completely consumed (monitored by TLC). Then, the reaction mixture was filtered, and the filtrate was washed with HCl (1 M aqueous solution). The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated to afford the monosquaramide intermediate. To a solution of the (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (1.00 mmol) in MeOH (4 mL) was added the monosquaramide (1.00 mmol). The reaction mixture was stirred at room temperature until the raw material was completely consumed (monitored by TLC). After removal of the solvent, the residue was purified through column chromatography on silica gel (200–300 mesh; petroleum ether/ethyl acetate, 5:1) to give the desired squaramide catalyst (343 mg, 66% yield) as a white solid; m.p. 215–218 °C. $[a]_D^{20}$ = +13.6 [*c* = 1.5, DMSO (dimethyl sulfoxide)]. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.41 (br. s, 4 H), 4.47 (d, *J* = 4.8 Hz, 1 H), 5.37 (d, *J* = 4.4 Hz, 1 H), 7.18–7.29 (m, 4 H, Ar), 7.37–7.44 (m, 6 H, Ar), 7.66 (s, 1 H, Ar), 8.07 (s, 2 H, Ar) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 59.4, 63.4, 114.6, 117.9, 121.8, 124.5, 126.5, 127.0, 127.4, 128.0, 128.5, 131.2, 131.5, 140.3, 141.1, 142.4, 162.5, 169.6, 180.5, 184.1 ppm. HRMS (ESI): calcd. for $C_{26}H_{19}F_6N_3NaO_2$ [M + Na]$^+$ 542.1274; found 542.1278.

General Procedure for the Preparation of Keto-enone 4: To a suspension of K_2CO_3 (1.38 g, 10 mmol) and the 2-hydroxyl-substituted chalcones (5 mmol) in acetone (60 mL) was added 1-bromopropan-2-one (1.03 g, 7.5 mmol) at 0 °C. The resulting mixture was warmed to room temperature and stirred until the starting material was completely consumed (observed by TLC). After removal of solvent under reduced pressure, the crude product was purified by column chromatography to furnish the corresponding keto-enone **4** as a white solid.

(*E*)-3-[2-(2-Oxopropoxy)phenyl]-1-phenylprop-2-en-1-one (4a): White solid (62% yield); m.p. 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 4.66 (s, 2 H), 6.79 (d, *J* = 8.0 Hz, 1 H, Ar), 7.06 (t, *J* = 8.0 Hz, 1 H, Ar), 7.06 (t, *J* = 8.0 Hz), 7.36 (dd, *J* = 1.2, 8.0 Hz, 1 H, Ar), 7.50–7.61 (m, 3 H, Ar), 7.69 (dd, *J* = 1.2, 8.0 Hz, 1 H, Ar), 7.79 (d, *J* = 16.0 Hz, 1 H), 8.09 (d, *J* = 7.2 Hz, 2 H, Ar), 8.16 (d, *J* = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.8, 73.2, 111.9, 121.9, 123.6, 124.3, 128.5, 128.6, 129.8, 131.7, 132.7, 138.3, 139.7, 156.7, 191.0, 204.5 ppm. HRMS (ESI): calcd. for $C_{18}H_{16}O_3Na$ [M + Na]$^+$ 303.0992; found 303.0985.

(*E*)-3-[2-(2-Oxopropoxy)-5-fluorophenyl]-1-phenylprop-2-en-1-one (4b): White solid (65% yield); m.p. 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 4.63 (s, 2 H), 6.73 (d, *J* = 4.4, 9.2 Hz, 1 H, Ar), 7.03–7.08 (m, 1 H, Ar), 7.38 (dd, *J* = 3.2, 8.8 Hz, 1 H, Ar), 7.51 (t, *J* = 8.0 Hz, 2 H, Ar), 7.60 (t, *J* = 7.2 Hz, 1 H, Ar), 7.73 (d, *J* = 16.0 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H, Ar), 80.9 (d, *J* = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.6, 37.3, 113.3 (d, *J* = 8.1 Hz), 115.4 (d, *J* = 23.5 Hz), 117.8 (d, *J* = 23.6 Hz), 124.4, 125.7 (d, *J* = 7.3 Hz), 128.5, 128.6, 132.9, 138.0, 138.3, 152.9, 157.4 (d, *J* = 240.7 Hz), 190.5, 204.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}FO_3Na$ [M + Na]$^+$ 321.0897; found 321.0902.

(*E*)-3-[2-(2-Oxopropoxy)-5-chlorophenyl]-1-phenylprop-2-en-1-one (4c): White solid (72% yield); m.p. 129–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 4.65 (s, 2 H), 6.72 (d, *J* = 8.8 Hz, 1 H, Ar), 7.30 (dd, *J* = 2.4, 8.8 Hz, 1 H, Ar), 7.51–7.62 (m, 3 H, Ar), 7.64 (d, *J* = 2.4 Hz, 1 H, Ar), 7.76 (d, *J* = 16.0 Hz, 1 H), 8.08 (d, *J* = 16.0 Hz, 1 H), 8.09 (dd, *J* = 1.6, 6.8 Hz, 2 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.7, 73.4, 113.3, 124.4, 125.9, 127.0, 128.6, 129.0, 131.0, 132.9, 138.0, 155.2, 190.4, 203.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}ClO_3Na$ [M + Na]$^+$ 337.0602; found 337.0609.

(*E*)-3-[2-(2-Oxopropoxy)-5-bromophenyl]-1-phenylprop-2-en-1-one (4d): White solid (75% yield); m.p. 147–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 4.64 (s, 2 H), 6.66 (d, *J* = 8.8 Hz, 1 H, Ar), 7.44 (dd, *J* = 2.4, 8.8 Hz, 1 H, Ar), 7.51–7.62 (m, 3 H, Ar), 7.75 (d, *J* = 15.6 Hz), 7.78 (d, *J* = 2.4 Hz, 1 H, Ar), 8.05 (d, *J* = 15.6 Hz, 1 H), 8.09 (d, *J* = 6.8 Hz, 2 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.7, 73.3, 113.7, 114.3, 124.5, 126.4, 128.6, 128.7, 131.9, 132.9, 133.9, 137.9, 138.0, 155.7, 190.4, 203.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}BrO_3Na$ [M + Na]$^+$ 381.0097; found 381.0101.

(*E*)-3-[2-(2-Oxopropoxy)-3,5-dichlorophenyl]-1-phenylprop-2-en-1-one (4e): White solid (74% yield); m.p. 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 4.53 (s, 2 H), 7.44 (d, *J* = 2.4 Hz, 1 H, Ar), 7.50–7.61 (m, 3 H, Ar), 7.58 (d, *J* = 2.4 Hz, 1 H, Ar), 7.62 (d, *J* = 16.0 Hz, 1 H), 7.96 (d, *J* = 16.0 Hz, 1 H), 8.03 (d, *J* = 7.2 Hz, 2 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.7, 77.6, 125.8, 126.5, 128.6, 128.8, 129.2, 130.6, 131.6, 133.3, 136.7, 137.5, 152.0, 189.7, 203.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{14}Cl_2O_3Na$ [M + Na]$^+$ 371.0212; found 371.0208.

(*E*)-3-[2-(2-Oxopropoxy)-5-methylphenyl]-1-phenylprop-2-en-1-one (4f): White solid (66% yield); m.p. 117–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.34 (s, 3 H), 4.62 (s, 2 H), 6.68 (d, *J* = 8.4 Hz, 1 H, Ar), 7.16 (d, *J* = 8.4 Hz, 1 H, Ar), 7.49–7.59 (m, 4 H, Ar), 7.76 (d, *J* = 16.0 Hz, 1 H), 8.09 (d, *J* = 7.2 Hz, 2 H, Ar), 8.14 (d, *J* = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.4, 26.7, 73.4, 111.9, 123.3, 124.0, 128.5, 128.6, 130.0, 131.2, 132.2, 132.6, 138.4, 139.8, 154.8, 191.0, 204.9 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}O_3Na$ [M + Na]$^+$ 317.1148; found 317.1145.

(*E*)-3-[2-(2-Oxopropoxy)-4-methylphenyl]-1-phenylprop-2-en-1-one (4g): White solid (68% yield); m.p. 95–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 2.37 (s, 3 H), 4.64 (s, 2 H), 6.59 (s, 1 H, Ar), 6.87 (d, *J* = 8.0 Hz, 1 H, Ar), 7.49–7.60 (m, 4 H, Ar), 7.76 (d, *J* = 16.0 Hz, 1 H), 8.09 (d, *J* = 7.6 Hz, 2 H, Ar), 8.13 (d, *J* = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.9, 26.7, 73.1, 112.7, 121.5, 122.5, 122.7, 128.5, 129.7, 132.5, 138.4, 139.8, 142.7, 156.7, 191.1, 204.6 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}O_3Na$ [M + Na]$^+$ 317.1148; found 317.1151.

(*E*)-3-[2-(2-Oxopropoxy)-5-*tert*-butylphenyl]-1-phenylprop-2-en-1-one (4h): White solid (72% yield); m.p. 95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9 H), 2.31 (s, 3 H), 4.64 (s, 2 H), 6.72 (d, *J* = 8.4 Hz, 1 H, Ar), 7.38 (dd, *J* = 2.4, 8.4 Hz, 1 H, Ar), 7.50–7.61 (m, 3 H, Ar), 7.66 (d, *J* = 2.4 Hz, 1 H, Ar), 7.80 (d, *J* = 16.0 Hz, 1 H), 8.09 (d, *J* = 6.4 Hz, 2 H, Ar), 8.12 (d, *J* = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.7, 31.4, 34.2, 73.3, 111.6, 123.6, 127.1, 128.5, 128.6, 128.7, 132.6, 138.4, 140.6, 144.6, 154.7, 191.3, 204.7 ppm. HRMS (ESI): calcd. for $C_{22}H_{24}O_3Na$ [M + Na]$^+$ 359.1618; found 359.1617.

(*E*)-3-[2-(2-Oxopropoxy)phenyl]-1-(3-fluorophenyl)prop-2-en-1-one (4i): White solid (64% yield); m.p. 129–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 4.68 (s, 2 H), 6.79 (d, *J* = 8.4 Hz, 1 H, Ar), 7.07 (t, *J* = 7.6 Hz, 1 H, Ar), 7.29 (dd, *J* = 1.6, 8.0 Hz, 1 H, Ar), 7.38 (dt, *J* = 1.6, 8.4 Hz, 1 H, Ar), 7.48–7.53 (m, 1 H, Ar), 7.67 (dd, *J* = 1.6, 7.6 Hz, 1 H, Ar), 7.77–7.81 (m, 1 H, Ar), 7.81 (d, *J* = 15.6 Hz, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H, Ar), 8.15 (d, *J* = 15.6 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.7, 73.1, 112.0, 115.4 (d, *J* = 22.3 Hz), 119.7 (d, *J* = 21.3 Hz),

121.9, 123.2, 124.1, 124.3, 130.2, 131.9, 140.6, 156.9, 162.9 (d, J = 247.8 Hz), 189.7, 204.0 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}FO_3Na$ $[M + Na]^+$ 321.0897; found 321.0903.

(*E*)-3-[2-(2-Oxopropoxy)phenyl]-1-(4-fluorophenyl)prop-2-en-1-one (4j): White solid (69% yield); m.p. 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 4.69 (s, 2 H), 6.80 (d, J = 8.4 Hz, 1 H, Ar), 7.07 (t, J = 7.6 Hz, 1 H, Ar), 7.19 (t, J = 8.4 Hz, 2 H, Ar), 7.37 (dt, J = 1.6, 8.4 Hz, 1 H, Ar), 7.67 (dd, J = 1.2, 7.6 Hz, 1 H, Ar), 7.87 (d, J = 15.6 Hz, 1 H), 8.13 (d, J = 15.6 Hz, 1 H), 8.15–8.19 (m, 2 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.6, 73.2, 111.9, 115.5 (d, J = 21.7 Hz), 121.9, 123.4, 124.3, 130.3, 131.2, 131.3, 131.7, 140.6, 156.8, 165.6 (d, J = 254.0 Hz), 189.3, 203.9 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}FO_3Na$ $[M + Na]^+$ 321.0897; found 321.0897.

(*E*)-3-[2-(2-Oxopropoxy)phenyl]-1-(4-chlorophenyl)prop-2-en-1-one (4k): White solid (66% yield); m.p. 123–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 4.69 (s, 2 H), 6.79 (d, J = 8.4 Hz, 1 H, Ar), 7.06 (t, J = 7.6 Hz, 1 H, Ar), 7.37 (dt, J = 1.6, 8.4 Hz, 1 H, Ar), 7.49 (d, J = 8.4 Hz, 2 H, Ar), 7.66 (d, J = 8.0 Hz, 1 H, Ar), 7.86 (d, J = 16.0 Hz, 1 H), 8.08 (d, J = 8.4 Hz, 2 H, Ar), 8.12 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.6, 73.1, 111.9, 121.9, 123.3, 124.2, 128.9, 129.6, 130.1, 130.4, 131.8, 136.6, 139.1, 140.4, 156.9, 189.7, 203.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}ClO_3Na$ $[M + Na]^+$ 337.0602; found 337.0596.

(*E*)-3-[2-(2-Oxopropoxy)phenyl]-1-(4-bromophenyl)prop-2-en-1-one (4l): White solid (72% yield); m.p. 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 4.68 (s, 2 H), 6.79 (d, J = 8.4 Hz, 1 H, Ar), 7.06 (t, J = 7.6 Hz, 1 H, Ar), 7.37 (dt, J = 1.6, 8.0 Hz, 1 H, Ar), 7.64–7.67 (m, 3 H, Ar), 7.85 (d, J = 15.6 Hz, 1 H), 8.00 (d, J = 8.8 Hz, 2 H, Ar), 8.12 (d, J = 15.6 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.6, 73.1, 111.9, 121.9, 123.2, 124.1, 127.8, 129.7, 130.2, 131.8, 131.9, 137.1, 140.4, 156.9, 189.9, 203.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}BrO_3Na$ $[M + Na]^+$ 381.0097; found 381.0103.

(*E*)-3-[2-(2-Oxopropoxy)phenyl]-1-(2,4-dichlorophenyl)prop-2-en-1-one (4m): White solid (74% yield); m.p. 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (s, 3 H), 4.58 (s, 2 H), 6.75 (d, J = 8.4 Hz, 1 H, Ar), 7.05 (t, J = 7.6 Hz, 1 H, Ar), 7.23 (d, J = 16.4 Hz, 1 H), 7.35–7.40 (m, 2 H, Ar), 7.46 (d, J = 8.4 Hz, 1 H, Ar), 7.48 (d, J = 2.0 Hz, 1 H, Ar), 7.64 (dd, J = 1.6, 7.6 Hz, 1 H, Ar), 7.87 (d, J = 16.4 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.6, 73.1, 112.0, 122.0, 123.6, 126.8, 127.2, 129.1, 130.1, 130.4, 132.3, 132.4, 136.7, 137.6, 141.5, 156.6, 193.1, 204.6 ppm. HRMS (ESI): calcd. for $C_{18}H_{14}Cl_2O_3Na$ $[M + Na]^+$ 371.0212; found 371.0214.

(*E*)-3-[2-(2-Oxopropoxy)phenyl]-1-(4-methoxyphenyl)prop-2-en-1-one (4n): White solid (62% yield); m.p. 131–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 3.89 (s, 3 H), 4.66 (s, 2 H), 6.78 (d, J = 8.4 Hz, 1 H, Ar), 6.99 (d, J = 8.8 Hz, 2 H, Ar), 7.05 (t, J = 7.6 Hz, 1 H, Ar), 7.35 (dt, J = 1.6, 8.4 Hz, 1 H, Ar), 7.67 (dd, J = 1.6, 7.6 Hz, 1 H, Ar), 7.84 (d, J = 16.0 Hz, 1 H), 8.12 (d, J = 8.8 Hz, 2 H, Ar), 8.13 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.7, 55.5, 73.2, 111.9, 113.8, 121.8, 123.5, 124.5, 129.9, 130.9, 131.2, 131.4, 138.9, 156.7, 163.3, 189.1, 204.5 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}O_4Na$ $[M + Na]^+$ 333.1097; found 333.1102.

(*E*)-3-[2-(2-Oxopropoxy)phenyl]-1-*p*-tolylprop-2-en-1-one (4o): White solid (70% yield); m.p. 115–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 2.45 (s, 3 H), 4.65 (s, 2 H), 6.78 (d, J = 8.4 Hz, 1 H, Ar), 7.06 (t, J = 7.6 Hz, 1 H, Ar), 7.32 (d, J = 8.4 Hz, 2 H, Ar), 7.36 (t, J = 7.2 Hz, 1 H, Ar), 7.67 (d, J = 7.6 Hz, 1 H, Ar), 7.78 (d, J = 16.0 Hz, 1 H), 8.01 (d, J = 8.4 Hz, 2 H, Ar), 8.15 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 26.7, 73.2, 111.9, 121.9, 123.6, 124.5, 128.7, 129.3, 129.7, 131.5, 135.7, 139.2, 143.5, 156.7, 190.4, 204.6 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}O_3Na$ $[M + Na]^+$ 317.1148; found 317.1155.

(*E*)-3-[2-(2-Oxopropoxy)phenyl]-1-(furan-2-yl)prop-2-en-1-one (4p): White solid (58% yield); m.p. 147–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 4.68 (s, 2 H), 6.61 (dd, J = 1.6, 7.6 Hz, 1 H, Ar), 7.05 (d, J = 7.6 Hz, 1 H, Ar), 7.35 (d, J = 8.0 Hz, 1 H, Ar), 7.51 (t, J = 3.6 Hz, 1 H, Ar), 7.65–7.67 (m, 2 H, Ar), 7.79 (d, J = 16.0 Hz, 1 H), 8.16 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.7, 73.1, 111.9, 112.5, 117.9, 121.9, 123.1, 124.2, 130.6, 131.7, 139.0, 146.6, 153.9, 156.9, 178.5, 204.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}O_4Na$ $[M + Na]^+$ 293.0784; found 293.0778.

General Procedure for the Primary Amine-Squaramide 3a Catalyzed Asymmetric Intramolecular Michael Addition of Keto-enone 4: Keto-enone **4** (0.3 mmol), glacial acetic acid (0.03 mmol), and primary amine-squaramide catalyst **3a** (0.045 mmol) were dissolved in dichloromethane (1 mL). The resulting solution was stirred at 20 °C until the keto-enone was completely consumed (monitored by TLC). After completion of the reaction, the mixture was directly purified by column chromatography on silica gel [100–200 mesh; petroleum ether (PE)/EtOAc, 15:1] to afford the desired product **5**. The enantiomeric excess of the pure product was determined by chiral HPLC analysis.

(2*S*,3*S*)-2-Acetyl-3-(1-oxo-1-phenylethyl)-2,3-dihydrobenzofuran (5a): White solid (95% yield; *trans*/*cis*, 95:5; 97%*ee* for *trans* isomer); m.p. 74–78 °C. $[\alpha]_D^{20}$ = +84.4 (c = 1.0, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 0.15 H, *cis* isomer), 2.36 (s, 2.85 H, *trans* isomer), 3.45 (dd, J = 6.8, 11.2 Hz, 2 H), 4.18 (dd, J = 6.4, 12.8 Hz, 0.95 H, *trans* isomer), 4.45 (dd, J = 6.4, 16.0 Hz, 0.05 H, *cis* isomer), 4.78 (d, J = 5.6 Hz, 0.95 H, *trans* isomer), 5.21 (d, J = 10.0 Hz, 0.05 H, *cis* isomer), 6.88–6.92 (m, 2 H, Ar), 7.17–7.21 (m, 2 H, Ar), 7.47 (t, J = 8.0 Hz, 2 H, Ar), 7.59 (t, J = 7.6 Hz, 1 H, Ar), 7.97 (d, J = 7.6 Hz, 1.90 H, Ar, *trans* isomer), 7.90 (d, J = 7.2 Hz, 0.10 H, Ar, *cis* isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.1, 40.7, 44.4, 90.6, 109.9, 121.5, 124.9, 128.1, 128.5, 128.7, 129.0, 133.5, 136.4, 158.8, 197.5, 207.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{16}O_3Na$ $[M + Na]^+$ 303.0992; found 303.0990. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t (retention time) = 33.65 (minor, *trans* isomer) and 36.84 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-5-fluoro-3-(1-oxo-1-phenylethyl)-2,3-dihydrobenzofuran (5b): White solid (94% yield; *trans*/*cis*, 96:4; 97%*ee* for *trans* isomer); m.p. 84–87 °C. $[\alpha]_D^{20}$ = +88.0 (c = 1.0, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 0.12 H, *cis* isomer), 2.36 (s, 2.88 H, *trans* isomer), 3.45 (dd, J = 1.2 and 6.8 Hz, 2 H), 4.17 (dd, J = 6.4, 12.8 Hz, 2 H), 4.80 (d, J = 6.0 Hz, 0.95 H, *trans* isomer), 5.22 (d, J = 9.6 Hz, 0.05 H, *cis* isomer), 6.80–6.93 (m, 3 H, Ar), 7.48 (t, J = 7.6 Hz, 2 H, Ar), 7.60 (t, J = 7.6 Hz, 1 H, Ar), 7.96–7.98 (m, 2 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.1, 40.7, 44.0, 91.0, 110.0 (d, J = 8.5 Hz), 112.2 (d, J = 25.2 Hz), 128.0, 128.7, 129.9 (d, J = 8.8 Hz), 133.6, 136.1, 154.6, 157.8 (d, J = 238.4 Hz), 197.2, 206.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}FO_3Na$ $[M + Na]^+$ 321.0897; found 321.0900. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 31.31 (minor, *trans* isomer) and 38.01 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-5-chloro-3-(1-oxo-1-phenylethyl)-2,3-dihydrobenzofuran (5c): White solid (99% yield, *trans*/*cis*, 95:5; 98%*ee* for *trans* isomer); m.p. 93–95 °C. $[\alpha]_D^{20}$ = +31.8 (c = 1.0, ethyl acetate). ^{1}H

NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 0.15 H, *cis* isomer), 2.36 (s, 2.85 H, *trans* isomer), 3.45 (dd, J = 4.0 and 6.8 Hz, 2 H), 4.16 (dd, J = 6.4, 12.8 Hz, 1 H), 4.81 (d, J = 5.6 Hz, 0.96 H, *trans* isomer), 5.23 (d, J = 10.0 Hz, 0.04 H, *cis* isomer), 6.83 (d, J = 8.4 Hz, 1 H, Ar), 7.13–7.17 (m, 2 H, Ar), 7.48 (t, J = 8.0 Hz, 2 H, Ar), 7.60 (t, J = 7.2 Hz, 1 H, Ar), 7.91 (d, J = 7.2 Hz, 0.10 H, Ar, *cis* isomer), 7.97 (d, J = 7.2 Hz, 1.90 H, Ar, *trans* isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.2, 40.6, 44.1, 91.0, 110.8, 125.2, 126.3, 128.1, 128.8, 128.9, 130.5, 133.7, 136.2, 157.5, 197.2, 206.5 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}ClO_3Na$ [M + Na]$^+$ 337.0602; found 337.0598. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 31.11 (minor, *trans* isomer) and 35.94 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-5-bromo-3-(1-oxo-1-phenylethyl)-2,3-dihydrobenzofuran (5d): White solid (99% yield; *trans*/*cis*, 95:5; 95%*ee* for *trans* isomer); m.p. 96–98 °C. $[\alpha]_D^{20}$ = +12.2 (c = 1.0, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 0.15 H, *cis* isomer), 2.36 (s, 2.85 H, *trans* isomer), 3.45 (dd, J = 4.4 and 6.4 Hz, 2 H), 4.16 (dd, J = 6.4, 12.8 Hz, 1 H), 4.81 (d, J = 5.6 Hz, 0.95 H, *trans* isomer), 5.22 (d, J = 9.6 Hz, 0.05 H, *cis* isomer), 6.79 (d, J = 8.4 Hz, 1 H, Ar), 7.27–7.31 (m, 2 H, Ar), 7.48 (t, J = 8.0 Hz, 2 H, Ar), 7.60 (t, J = 7.2 Hz, 1 H, Ar), 7.91 (d, J = 7.2 Hz, 0.10 H, Ar, *cis* isomer), 7.97 (d, J = 7.2 Hz, 1.90 H, Ar, *trans* isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.2, 40.5, 44.1, 90.9, 111.4, 113.4, 128.0, 128.1, 128.8, 131.0, 131.8, 133.7, 136.2, 158.0, 197.2, 204.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}BrO_3Na$ [M + Na]$^+$ 381.0097; found 381.0098. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 32.73 (minor, *trans* isomer) and 38.19 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-5,7-dichloro-3-(1-oxo-1-phenylethyl)-2,3-dihydrobenzofuran (5e): White solid (95% yield; *trans*/*cis*, 96:4; 97%*ee* for *trans* isomer); m.p. 127–130 °C. $[\alpha]_D^{20}$ = +38.8 (c = 1.0, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 0.12 H, *cis* isomer), 2.39 (s, 2.88 H, *trans* isomer), 3.46 (dd, J = 2.0, 6.8 Hz, 2 H), 4.24 (dd, J = 6.4, 12.8 Hz, 1 H), 4.89 (d, J = 6.0 Hz, 0.96 H, *trans* isomer), 5.20 (d, J = 10.0 Hz, 0.04 H, *cis* isomer), 7.09 (s, 1 H, Ar), 7.20 (d, J = 1.6 Hz, 1 H, Ar), 7.49 (t, J = 7.6 Hz, 2 H, Ar), 7.61 (t, J = 7.6 Hz, 1 H, Ar), 7.90 (d, J = 7.2 Hz, 0.08 H, Ar, *cis* isomer), 7.96 (d, J = 7.2 Hz, 1.92 H, Ar, *cis* isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.4, 41.2, 43.9, 91.2, 115.9, 123.8, 126.7, 128.1, 128.8, 128.9, 131.7, 133.8, 136.0, 153.6, 196.8, 205.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{14}Cl_2O_3Na$ [M + Na]$^+$ 371.0212; found 371.0208. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 24.12 (minor, *trans* isomer) and 31.07 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-5-methyl-3-(1-oxo-1-phenylethyl)-2,3-dihydrobenzofuran (5f): Pale yellow oil (99% yield; *trans*/*cis*, 97:3; 97%*ee* for *trans* isomer). $[\alpha]_D^{20}$ = +25.8 (c = 2.7, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, 3 H), 2.28 (s, 0.09 H, *cis* isomer), 2.34 (s, 2.91 H, *trans* isomer), 3.44 (dd, J = 6.8 and 12.0 Hz, 2 H), 4.13 (dd, J = 6.4, 12.4 Hz, 1 H), 4.75 (d, J = 5.6 Hz, 0.97 H, *trans* isomer), 5.19 (d, J = 9.6 Hz, 0.03 H, *cis* isomer), 6.79 (d, J = 8.8 Hz, 1 H, Ar), 6.95–6.99 (m, 2 H, Ar), 7.48 (t, J = 7.6 Hz, 2 H, Ar), 7.59 (t, J = 7.6 Hz, 1 H, Ar), 7.91 (d, J = 7.2 Hz, 0.06 H, Ar, *cis* isomer), 7.97 (d, J = 7.6 Hz, 1.94 H, Ar, *trans* isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.8, 26.1, 40.8, 44.4, 90.8, 109.4, 125.4, 128.1, 128.5, 128.7, 129.4, 130.9, 133.5, 136.4, 156.7, 197.6, 207.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}O_3Na$ [M + Na]$^+$ 317.1148; found 317.1149. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 28.87 (minor, *trans* isomer) and 30.77 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-6-methyl-3-(1-oxo-1-phenylethyl)-2,3-dihydrobenzofuran (5g): Pale yellow oil (99% yield; *trans*/*cis*, 93:7; 98%*ee* for *trans* isomer). $[\alpha]_D^{20}$ = +53.3 (c = 2.5, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 0.21 H, *cis* isomer), 2.32 (s, 3 H), 2.35 (s, 2.79 H, *trans* isomer), 3.42 (dd, J = 6.8, 8.8 Hz, 2 H), 4.12 (dd, J = 6.8, 12.8 Hz, 1 H), 4.77 (d, J = 5.2 Hz, 0.93 H, *trans* isomer), 5.20 (d, J = 9.6 Hz, 0.07 H, *cis* isomer), 6.71 (d, J = 7.6 Hz, 1 H, Ar), 6.74 (s, 1 H, Ar), 7.47 (t, J = 7.6 Hz, 2 H, Ar), 7.58 (t, J = 7.6 Hz, 1 H, Ar), 7.90 (d, J = 7.2 Hz, 0.14 H, Ar, *cis* isomer), 7.96 (d, J = 7.2 Hz, 1.86 H, Ar, *cis* isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.5, 26.1, 40.6, 44.5, 90.9, 110.6, 122.2, 124.5, 125.5, 128.1, 133.5, 136.4, 139.3, 159.1, 197.6, 207.3 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}O_3Na$ [M + Na]$^+$ 317.1148; found 317.1141. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 31.14 (minor, *trans* isomer) and 36.70 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-5-*tert*-butyl-3-(1-oxo-1-phenylethyl)-2,3-dihydrobenzofuran (5h): Pale yellow oil (90% yield; *trans*/*cis*, 94:6; 96%*ee* for *trans* isomer). $[\alpha]_D^{20}$ = +14.8 (c = 7.1, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 0.54 H, *cis* isomer), 1.26 (s, 8.46 H, trans isomer), 2.30 (s, 0.18 H, *cis* isomer), 2.35 (s, 2.82 H, *trans* isomer), 3.45 (dd, J = 6.4, 12.4 Hz, 2 H), 4.16 (dd, J = 6.8, 12.8 Hz, 1 H), 4.77 (d, J = 5.2 Hz, 0.94 H, *trans* isomer), 5.21 (d, J = 9.6 Hz, 0.06 H, *cis* isomer), 6.83 (d, J = 8.4 Hz, 1 H, Ar), 7.18–7.22 (m, 2 H, Ar), 7.47 (t, J = 7.6 Hz, 2 H, Ar), 7.59 (t, J = 7.6 Hz, 1 H, Ar), 7.89 (d, J = 7.2 Hz, 0.12 H, Ar, *cis* isomer), 7.97 (d, J = 7.2 Hz, 1.88 H, Ar, *cis* isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.2, 31.6, 34.4, 41.0, 44.4, 90.9, 109.1, 121.7, 125.9, 128.0, 128.1, 128.7, 133.5, 136.6, 144.6, 156.5, 197.8, 207.3 ppm. HRMS (ESI): calcd. for $C_{22}H_{24}O_3Na$ [M + Na]$^+$ 359.1618; found 359.1616. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 13.57 (minor, *trans* isomer) and 14.82 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-3-[1-oxo-1-(3-fluorophenyl)ethyl]-2,3-dihydrobenzofuran (5i): Pale yellow oil (90% yield; *trans*/*cis*, 97:3; 98%*ee* for *trans* isomer). $[\alpha]_D^{20}$ = +71.8 (c = 2.2, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 0.09 H, *cis* isomer), 2.35 (s, 2.91 H, *trans* isomer), 3.41 (dd, J = 6.8 and 9.2 Hz, 2 H), 4.16 (dd, J = 6.4, 12.8 Hz, 1 H), 4.76 (d, J = 5.6 Hz, 1 H), 6.88–6.92 (m, 2 H, Ar), 7.16–7.21 (m, 2 H, Ar), 7.62 (d, J = 8.8 Hz, 2 H, Ar), 7.83 (d, J = 8.8 Hz, 2 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.1, 40.5, 44.4, 90.5, 109.9, 114.8 (d, J = 22.3 Hz), 120.5 (d, J = 21.4 Hz), 121.5, 123.8, 124.8, 128.3, 129.0, 130.4 (d, J = 7.6 Hz), 138.4 (d, J = 6.2 Hz), 158.7, 162.8 (d, J = 248.4 Hz), 196.3, 207.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}FO_3Na$ [M + Na]$^+$ 321.0897; found 321.0892. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 28.42 (minor, *trans* isomer) and 29.95 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-3-[1-oxo-1-(4-fluorophenyl)ethyl]-2,3-dihydrobenzofuran (5j): Pale yellow oil (98% yield; *trans*/*cis*, 96:4; 97%*ee* for *trans* isomer). $[\alpha]_D^{20}$ = +68.3 (c = 2.3, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 0.12 H, *cis* isomer), 2.35 (s, 2.88 H, *trans* isomer), 3.42 (dd, J = 6.4 and 9.6 Hz, 2 H), 4.17 (dd, J = 6.4, 12.8 Hz, 1 H), 4.77 (d, J = 5.6 Hz, 0.96 H, *trans* isomer), 45.21 (d, J = 9.6 Hz, 0.04 H, *cis* isomer), 6.88–6.92 (m, 2 H, Ar), 7.12–7.21 (m, 4 H, Ar), 7.98–8.01 (m, 2 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.1, 40.6, 44.1, 90.5, 109.8, 115.8 (d, J = 21.8 Hz), 121.4, 124.8, 128.3, 128.9, 130.6, 130.7, 132.7, 132.8, 158.7, 165.8 (d, J = 255.5 Hz), 4.3, 121.3, 124.0, 128.0, 129.3, 129.6, 129.9, 131.8, 156.8, 206.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}FO_3Na$ [M + Na]$^+$ 321.0897; found 321.0902. HPLC analy-

sis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 45.49 (minor, *trans* isomer) and 48.61 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-3-[1-oxo-1-(4-chlorophenyl)ethyl]-2,3-dihydrobenzofuran (5k): Pale yellow oil (94% yield; *trans*/*cis*, 95:5; 97%*ee* for *trans* isomer). $[\alpha]_D^{20}$ = +45.2 (*c* = 2.1, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 0.15 H, *cis* isomer), 2.35 (s, 2.85 H, *trans* isomer), 3.41 (dd, *J* = 6.8, 9.6 Hz, 2 H), 4.16 (dd, *J* = 6.4, 12.8 Hz, 1 H), 4.76 (d, *J* = 5.6 Hz, 0.95 H, *trans* isomer), 5.20 (d, *J* = 9.6 Hz, 0.05 H, *cis* isomer), 6.88–6.92 (m, 2 H, Ar), 7.16–7.21 (m, 2 H, Ar), 7.45 (d, *J* = 8.4 Hz, 2 H, Ar), 7.90 (d, *J* = 8.4 Hz, 2 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.2, 40.7, 44.3, 90.6, 109.9, 121.6, 124.9, 128.3, 129.1, 129.5, 134.7, 140.1, 158.8, 196.3, 207.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}ClO_3Na$ [M + Na]$^+$ 337.0602; found 337.0596. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 48.67 (minor, *trans* isomer) and 54.36 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-3-[1-oxo-1-(4-bromophenyl)ethyl]-2,3-dihydrobenzofuran (5l): Pale yellow oil (90% yield; *trans*/*cis*, 97:3; 98%*ee* for *trans* isomer). $[\alpha]_D^{20}$ = +59.6 (*c* = 3.1, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 0.09 H, *cis* isomer), 2.36 (s, 2.91 H, *trans* isomer), 3.43 (dd, *J* = 6.8, 8.8 Hz, 2 H), 4.17 (dd, *J* = 6.4, 12.8 Hz, 1 H), 4.77 (d, *J* = 6.0 Hz, 0.97 H), 5.20 (d, *J* = 9.6 Hz, 0.03 H), 6.88–6.93 (m, 2 H, Ar), 7.17–7.22 (m, 2 H, Ar), 7.27–7.31 (m, 1 H, Ar), 7.43–7.48 (m, 1 H, Ar), 7.64–7.67 (m, 1 H, Ar), 7.74 (d, *J* = 8.0 Hz, 1 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.2, 40.6, 44.2, 90.5, 109.9, 121.5, 124.9, 128.3, 128.8, 129.0, 129.6, 132.0, 136.1, 158.7, 196.5, 207.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}BrO_3Na$ [M + Na]$^+$ 381.0097; found 381.0095. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 59.88 (minor, *trans* isomer) and 63.78 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-3-[1-oxo-1-(2,4-dichlorophenyl)ethyl]-2,3-dihydrobenzofuran (5m): Pale yellow oil (66% yield; *trans*/*cis*, 76:24; 88%*ee* for *trans* isomer, 94%*ee* for *cis* isomer). $[\alpha]_D^{20}$ = +23.4 (*c* = 2.6, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 0.72 H, *cis* isomer), 2.33 (s, 2.28 H, *trans* isomer), 3.26, (dd, *J* = 6.8, 10.4 Hz, 0.48 H, *cis* isomer), 3.42 (dd, *J* = 6.8, 8.8 Hz, 1.52 H, *trans* isomer), 4.15 (dd, *J* = 6.8, 12.8 Hz, 0.76 H, *trans* isomer), 4.42 (dd, *J* = 7.2, 16.4 Hz, 0.24 H, *cis* isomer), 4.76 (d, *J* = 5.6 Hz, 0.76 H, *trans* isomer), 5.16 (d, *J* = 9.6 Hz, 0.24 H, *cis* isomer), 6.86–6.92 (m, 2 H, Ar), 7.15–7.21 (m, 2 H, Ar), 7.29–7.33 (m, 1 H, Ar), 7.42–7.52 (m, 2 H, Ar) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.2 (*trans* isomer), 28.6 (*cis* isomer), 40.1 (*cis* isomer), 40.9 (*trans* isomer), 43.4 (*cis* isomer), 48.3 (*trans* isomer), 87.6 (*cis* isomer), 90.3 (*trans* isomer), 109.9 (*trans* isomer), 110.0 (*cis* isomer), 121.5 (*cis* isomer), 121.6 (*trans* isomer), 124.3 (*cis* isomer), 124.8 (*trans* isomer), 127.4 (*cis* isomer), 127.5 (*trans* isomer), 128.0 (*trans* isomer), 128.5 (*cis* isomer), 129.0 (*cis* isomer), 129.1 (*trans* isomer), 130.4 (*cis* isomer), 130.5 (*trans* isomer), 130.6 (*trans* isomer), 130.9 (*cis* isomer), 132.0 (*cis* isomer), 132.3 (*trans* isomer), 136.6 (*trans* isomer), 136.8 (*cis* isomer), 137.7 (*cis* isomer), 138.0 (*trans* isomer), 158.6 (*cis* isomer), 158.7 (*trans* isomer), 199.0 (*cis* isomer), 199.2 (*trans* isomer), 207.4 (*trans* isomer), 209.1 (*cis* isomer) ppm. HRMS (ESI): calcd. for $C_{18}H_{14}Cl_2O_3Na$ [M + Na]$^+$ 371.0212; found 371.0214. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 16.58 (major, *cis* isomer), 20.61 (minor, *cis* isomer), 29.76 (minor, *trans* isomer), and 32.87 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-3-[1-oxo-1-(4-methoxyphenyl)ethyl]-2,3-dihydrobenzofuran (5n): Pale yellow oil (99% yield; *trans*/*cis*, 90:10; 95%*ee* for *trans* isomer). $[\alpha]_D^{20}$ = +44.4 (*c* = 4.8, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 0.30 H, *cis* isomer), 2.35 (s, 2.70 H, *trans* isomer), 3.39 (dd, *J* = 6.8, 8.8 Hz, 2 H), 3.85 (s, 0.30 H, *cis* isomer), 3.86 (s, 2.70 H, *trans* isomer), 4.15 (dd, *J* = 6.4, 12.8 Hz, 0.90 H, *trans* isomer), 4.44 (d, *J* = 6.8, 16.0 Hz, 0.10 H, *cis* isomer), 4.78 (d, *J* = 5.6 Hz, 0.90 H, *trans* isomer), 5.21 (d, *J* = 9.6 Hz, 0.10 H, *cis* isomer), 6.87–6.94 (m, 4 H, Ar), 7.15–7.19 (m, 2 H, Ar), 7.88 (d, *J* = 8.8 Hz, 0.20 H, Ar, *cis* isomer), 7.94 (d, *J* = 8.8 Hz, 1.80 H, Ar, *trans* isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.1, 40.8, 44.0, 55.4, 90.6, 109.8, 113.8, 121.4, 124.9, 128.6, 128.9, 129.5, 130.3, 158.8, 163.7, 196.0, 207.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}O_4Na$ [M + Na]$^+$ 333.1097; found 333.1091. HPLC analysis (Chiralpak AD column; hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 51.81 (minor, *trans* isomer) and 55.34 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-3-[1-oxo-1-(4-methylphenyl)ethyl]-2,3-dihydrobenzofuran (5o): Pale yellow oil (99% yield; *trans*/*cis*, 90:10; 95%*ee* for *trans* isomer). $[\alpha]_D^{20}$ = +73.7 (*c* = 2.7, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 0.30 H, *cis* isomer), 2.36 (s, 2.70 H, *trans* isomer), 2.42 (s, 3 H), 3.42 (dd, *J* = 6.8, 11.6 Hz, 2 H), 4.17 (dd, *J* = 6.4, 12.8 Hz, 0.90 H, *trans* isomer), 4.45 (dd, *J* = 6.4, 16.4 Hz, 0.10 H, *cis* isomer), 4.78 (d, *J* = 5.6 Hz, 0.90 H, *trans* isomer), 5.21 (d, *J* = 9.6 Hz, 0.10 H, *cis* isomer), 6.86–6.92 (m, 2 H, Ar), 7.17–7.20 (m, 2 H, Ar), 7.27 (d, *J* = 8.0 Hz, 2 H, Ar), 7.80 (d, *J* = 8.0 Hz, 0.20 H, Ar, *cis* isomer), 7.87 (d, *J* = 8.0 Hz, 1.80 H, Ar, *trans* isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.6, 26.1, 40.7, 44.2, 90.6, 109.8, 121.4, 124.9, 128.2, 128.5, 128.9, 129.4, 133.9, 144.4, 158.8, 197.1, 207.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}O_3Na$ [M + Na]$^+$ 317.1148; found 317.1148. HPLC analysis (Chiralpak AD column, hexane/2-propanol, 98:2; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 47.23 (minor, *trans* isomer) and 51.29 min (major, *trans* isomer).

(2*S*,3*S*)-2-Acetyl-3-[1-oxo-1-(furan-2-yl)ethyl]-2,3-dihydrobenzofuran (5p): Pale yellow oil (98% yield; *trans*/*cis*, 95:5; >99%*ee* for *trans* isomer). $[\alpha]_D^{20}$ = +73.1 (*c* = 2.8, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 0.15 H, *cis* isomer), 2.32 (s, 2.85 H, *trans* isomer), 3.29 (dd, *J* = 6.8, 18.4 Hz, 2 H), 4.13 (dd, *J* = 6.8, 12.8 Hz, 1 H), 4.78 (d, *J* = 5.6 Hz, 0.95 H, *trans* isomer), 5.16 (d, *J* = 9.6 Hz, 0.05 H, *cis* isomer), 6.54 (dd, *J* = 1.6, 3.6 Hz, 1 H, Ar), 6.86–6.90 (m, 2 H, Ar), 7.15–7.19 (m, 2 H, Ar), 7.22 (d, *J* = 3.2 Hz, 1 H, Ar), 7.54 (d, *J* = 0.80 Hz, 0.05 H, Ar, *cis* isomer), 7.58 (d, *J* = 0.8 Hz, 0.95 H, Ar, *trans* isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.1, 40.5, 43.9, 90.4, 109.8, 112.4, 117.5, 121.5, 124.9, 128.2, 129.0, 146.7, 152.4, 158.7, 186.6, 207.0 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}O_4Na$ [M + Na]$^+$ 293.0784; found 293.0782. HPLC analysis (Chiralpak OD column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 8.28 min (major, *trans* isomer).

Supporting Information (see footnote on the first page of this article): Copies of NMR and HRMS spectra as well as the chiral HPLC spectra of the prepared optically active *trans*-dihydrobenzofurans.

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