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ARTICLE

Enantioselective Addition of Arylboronic Acids to Methyl 2-Formylbenzoates by using a Ruthenium/Me-BIPAM Catalyst for Synthesis of Chiral 3-Aryl-isobenzofuranones

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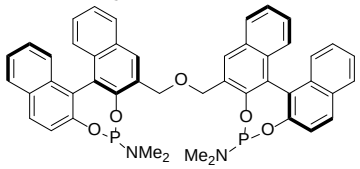
Abstract text goes here. The abstract should be a single paragraph that summarises the content of the article

Ruthenium/Me-BIPAM-catalyzed asymmetric addition of arylboronic acids to methyl 2-formylbenzoates afforded chiral 3-aryl-isobenzofuranones. [$RuCl_2$(*p*-cymene)]$_2$/Me-BIPAM and $RuCl_2(PPh_3)_3$/Me-BIPAM catalyst systems tolerate a variety of functional groups and give high yields with high enantioselectivities.

Optically active 3-substituted isobenzofuranones are important structures in medicinal chemistry as well as in synthetic chemistry.[1,2] Recently, various methods for the synthesis of these chiral compounds have been developed.[3] Reported methods include lactonization followed by the hydrogenation of the corresponding ketones,[4] intramolecular ketone hydroacylation,[5] aldol reaction,[6] addition reaction,[7] and cyclization reaction.[8]

Over the past decade, transition metal-catalyzed addition reactions of arylboronic acids with 2-formylbenzoates have become useful tools for accessing 3-aryl-isobenzofuranones.[9] However, to our knowledge, there have been only a few reports on the synthesis of optically active 3-aryl-isobenzofuranones using this strategy.[10]

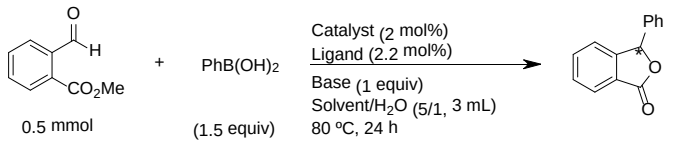
We have already developed a bidentate chiral phosphoramidite (Me-BIPAM) and have used it in ruthenium-catalyzed asymmetric addition of arylboronic acids to various carbonyl compounds.[11] Herein, we report the synthesis of optically active 3-aryl-isobenzofuranones by using enantioselective addition of arylboronic acids to methyl 2-formylbenzoates.



(*R*,*R*)-*O*-linked-Bisphosphoramidite
(*R*,*R*)-Me-BIPAM

Our initial investigation began by screening catalysts to evaluate their ability to promote enantioselective arylation of methyl 2-formylbenzoate with phenylboronic acid. As shown in Table 1, when [$RuCl_2$(*p*-cymene)]$_2$, $RuCl_2(PPh_3)_3$ or $RuCl_2$(nbd)$(MeCN)_2$ with Me-BIPAM, which were used in our

Table 1. Reaction Coditions[a]



entry	catalyst	ligand	base	solvent	Yield[b] (%)	ee[c] (%)
1	[$RuCl_2$(*p*-cymene)]$_2$	(*R*,*R*)-Me-BIPAM	K_2CO_3	toluene	96	94
2[d]	[$RuCl_2$(*p*-cymene)]$_2$	(*R*,*R*)-Me-BIPAM	K_2CO_3	toluene	96	97
3[d]	[$RuCl_2$(*p*-cymene)]$_2$	(*R*,*R*)-Me-BIPAM	KF	toluene	99.5	97
4[d]	[$RuCl_2$(*p*-cymene)]$_2$	(*R*,*R*)-Me-BIPAM	KOH	toluene	74	96
5[d]	[$RuCl_2$(*p*-cymene)]$_2$	(*R*,*R*)-Me-BIPAM	K_2CO_3	DCE	52	93
6	$RuCl_2(PPh_3)_3$	(*R*,*R*)-Me-BIPAM	K_2CO_3	toluene	96	93
7[d]	$RuCl_2(PPh_3)_3$	(*R*,*R*)-Me-BIPAM	K_2CO_3	toluene	98	96
8	$RuCl_2$(nbd)$(MeCN)_2$	(*R*,*R*)-Me-BIPAM	K_2CO_3	toluene	96	93
9[e]	$RuCl_2(PPh_3)_3$	(*R*,*R*)-Me-BIPAM	K_2CO_3	toluene	67	91
10	[$RuCl_2$(*p*-cymene)]$_2$	(*R*)-BINAP	K_2CO_3	toluene	26	-12
11	[$RuCl_2$(*p*-cymene)]$_2$	(*R*)-Monophos	K_2CO_3	toluene	70	78

[a]Reactions were carried out at 50-80 °C for 18 h by using methyl 2-formylbenzoates 1a (0.5 mmol), 2a (0.75 mmol), Ru catalyst (0.01 mmol), ligand (0.011 mmol), K_2CO_3 (0.5 mmol) and toluene/H_2O (5/1, 3.0 mL). [b]Isolated yield. [c]The ee value of 3 was determined by chiral HPLC analysis. [d] 50 °C, 18 h. [e] MeCN (20 mol %) was added

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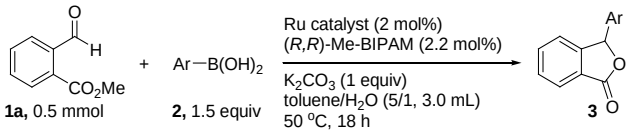
previous works, were used for this reaction, addition products were obtained in high yields with high enantioselectivities (entries 2, 7 and 8). Use of KOH and DCE resulted in lower yields (entries 4 and 5). Among the chiral ligands screened, the use of (R)-BINAP (entry 10) and monodentate phosphoramidite, (R)-MonoPhos (entry 11) resulted in lower enantioselectivities, -12% ee and 78% ee, respectively.[11]

We then studied the substrate scope for various arylboronic acids with $[RuCl_2(p\text{-cymene})]_2$- or $RuCl_2(PPh_3)_3$-Me-BIPAM catalyst (Table 1). Arylboronic acids with electron-donating and -withdrawing groups at *para*- and *meta*-positions afforded 3-aryl-isobenzofuranones in high yields with high enantioselectivities in the range of 91–97% ee. The addition of *para*-biphenylboronic acid and 3-thienylboronic acid resulted in a high yield with high enantioselectivities when the temperature was increased and the solvent ratio of toluene/H_2O was changed (entries 5 and 12). The structure of **3al** was confirmed unequivocally by its X-ray crystal structure (entry 12). The absolute configuration of the product was assigned as *S* enantiomer from X-ray crystallographic analysis of the compound of **3al** (Figure 1).[13]

From the above results, $[RuCl_2(p\text{-cymene})]_2$ with (*R,R*)-Me-BIPAM catalyst gave higher enantioselectivities for the electron-donating arylboronic acids, but $RuCl_2(PPh_3)_3$ with (*R,R*)-Me-BIPAM catalyst gave higher yields and enantioselectivities for the electron-withdrawing arylboronic acids. The structure of $[RuCl_2(p\text{-cymene})]_2$ with (*R,R*)-Me-BIPAM showed cationic complex,[14] but the structure of $RuCl_2(PPh_3)_3$ with (*R,R*)-Me-BIPAM complex showed neutral complex.[11c] The difference in reactivity between $[RuCl_2(p\text{-cymene})]_2$ and $RuCl_2(PPh_3)_3$ catalyst is correlated with the electronic effect of the arylruthenium intermediates.

Table 2. Substrate Scope for the Arylboronic Acids[a]

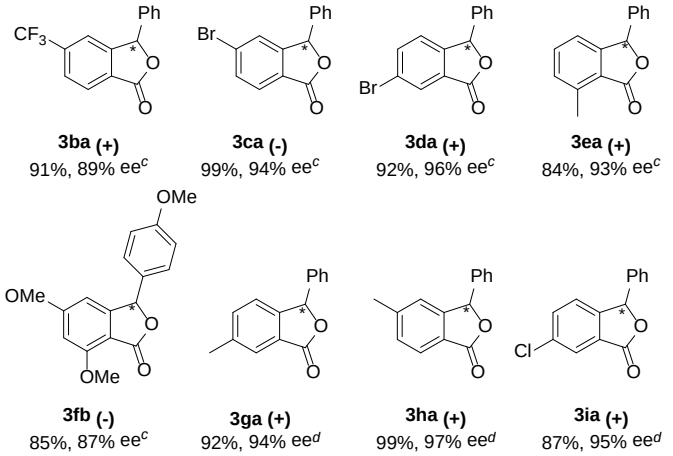


entry	Ar = (Ar-B(OH)$_2$)	catalyst	yield (%)[b]	ee (%)[c]
1	C_6H_5	$[RuCl_2(p\text{-cymene})]_2$	96 (**3aa**)	97 (*S*)
2[d]	4-$MeOC_6H_4$	$[RuCl_2(p\text{-cymene})]_2$	80 (**3ab**)	96 (*S*)
3[d]	4-MeC_6H_4	$[RuCl_2(p\text{-cymene})]_2$	99 (**3ac**)	95 (*S*)
4	4-CH_2=CHC_6H_4	$[RuCl_2(p\text{-cymene})]_2$	93 (**3ad**)	95 (+)
5[e]	4-PhC_6H_4	$RuCl_2(PPh_3)_3$	87 (**3ae**)	94 (+)
6	4-FC_6H_4	$RuCl_2(PPh_3)_3$	98 (**3af**)	95 (+)
7	4-ClC_6H_4	$RuCl_2(PPh_3)_3$	97 (**3ag**)	96 (*S*)
8	4-$CF_3C_6H_4$	$RuCl_2(PPh_3)_3$	74 (**3ah**)	91 (*S*)
9	2-naphthyl	$RuCl_2(PPh_3)_3$	92 (**3ai**)	93 (*S*)
10	3, 5-MeC_6H_4	$RuCl_2(PPh_3)_3$	99 (**3aj**)	96 (*S*)
11	3-ClC_6H_4	$RuCl_2(PPh_3)_3$	84 (**3ak**)	93 (*S*)
12[f]	3-thienyl	$RuCl_2(PPh_3)_3$	92 (**3al**)	91 (*S*)

[a]Reactions were carried out at 50-80 °C for 18 h by using methyl 2-formylbenzoates 1a (0.5 mmol), 2 (0.75 mmol), Ru catalyst (0.01 mmol), ligand (0.011 mmol), K_2CO_3 (0.5 mmol) and toluene/H_2O (5/1, 3.0 mL). [b]Isolated yield. [c]The *ee* value of 3 was determined by chiral HPLC analysis. [d] 6 h. [e] 80 °C, toluene/H_2O (20/1, 3 mL). [f] 80 °C, toluene/H_2O (10/1, 3 mL).

Next, we investigated the substrate scope with focus on substituents on the aromatic ring of methyl 2-formylbenzoates (Table 3). Arylation of methyl 2-formylbenzoates gave the corresponding products in high yields (84–99%) with excellent enantioselectivities (87–97% ee). The arylation product of 5,6-desmethylenedioxy-5-methoxy-aglalactone (**3fb**) which was isolated from the $CHCl_3$ soluble extract of the leaves and twigs of Aglaia ponapensis exhibit the NF-kB inhibitory activity.[12]

Table 3. Substrate Scope for the methyl 2-formylbenzoates[a, b]



3ba (+) 91%, 89% ee[c]
3ca (-) 99%, 94% ee[c]
3da (+) 92%, 96% ee[c]
3ea (+) 84%, 93% ee[c]
3fb (-) 85%, 87% ee[c]
3ga (+) 92%, 94% ee[d]
3ha (+) 99%, 97% ee[d]
3ia (+) 87%, 95% ee[d]

[a]Isolated yield. [b]The ee value of 3 was determined by chiral HPLC analysis. [c] $[RuCl_2(p\text{-cymene})]_2$ was used. [d] $RuCl_2(PPh_3)_3$ was used.

We propose a possible catalytic cycle of this reaction. The reaction may proceed through transmetalation of an arylboronic acid to a Ru/Me-BIPAM complex giving an Ar–[Ru]. Insertion of the C=O bond of methyl 2-formyl benzoates into the Ar–Ru bond gave the Ru–O intermediate, and then provided 3-aryl-isobenzofuranones by hydrolysis and lactonization (Figure 2). The enantioselectivity is determined at the step of insertion of the C=O bond into an aryl ruthenium intermediate. Thus, the *S* configuration in Tables 1–3 caused by (*R,R*)-Me-BIPAM is rationalized by the coordination of an methyl 2-formyl benzoate with its *si*-face. The *si*-coordination of the substrate is preferred without significant steric interaction to give the experimentally observed *S* enantiomer by parallel coordination of the C=O bond to the Ar-Ru bond for the subsequent insertion step (Figure 3).

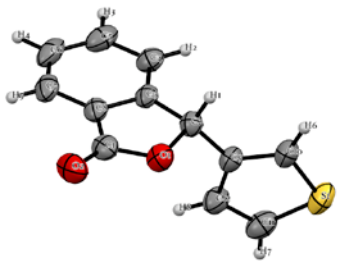


Figure 1. ORTEP diagram of 3al (ORTEP drawing at 50% ellipsoid probability)

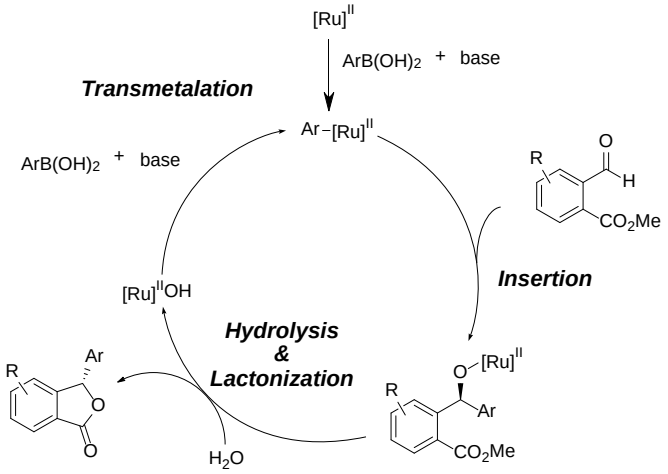


Figure 2. Proposed catalytic cycle

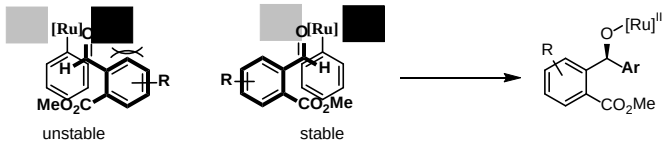


Figure 3. Proposed coordination model

Conclusions

In summary, we have developed a ruthenium/Me-BIPAM-catalyzed addition of arylboronic acids to methyl 2-formylbenzoates for enantioselective synthesis of 3-aryl-isobenzofuranones. Various substituted chiral 3-aryl-isobenzofuranones were obtained with excellent enantioselectivities (87-97 % ee).

Experimental

Genetal methods

^{1}H–NMR spectra were recorded on a JEOL ECX-400 (400 MHz) or JEOL ECS-400 (400 MHz) in $CDCl_3$ with tetramethylsilane (δ = 0.00) as internal standard. Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). ^{13}C–NMR spectra were recorded on a JEOL ECX-400 (100MHz) in $CDCl_3$ (δ = 77.00) with tetramethylsilane as an internal standard (δ = 0.0). Chemical shifts are reported in part per million (ppm). HPLC analysis was directly performed with chiral stationary phase column, Chiralpak AD–H or Chiralcel OD–H purchased from DAICEL Co., Ltd. High resolution mass spectra (HRMS) were recorded on a JEOL JMS 700TZ mass spectrometer at the Center for Instrumental Analysis, Hokkaido University. Optical rotations were measured on a HORIBA SEPA–300 digital polarimeter. Kanto Chemical silica gel 60N (particle size 0.063–0.210 mm) was used for flash column chromatography. $RuCl_3 \cdot xH_2O$ was purchased from Furuya Metal Co., Ltd. $[RuCl_2(p\text{-cymene})]_2$,[15] $RuCl_2(PPh_3)_3$[16] and $RuCl_2(nbd)(MeCN)_2$[17] were prepared by the literature procedure. BIPAM ligand (Me-BIPAM) were prepared according to our previous procedure.[18] Me-BIPAM was commercially available from Wako Pure Chemical Industries, Ltd. Phthalide was purchased from commercial source and substituted phthalides were synthesized according to known literature.[19]

Preparation of 2-formylbenzoates[20]

To a solution of phthalides (2.0 mmol) in 10 mL dry benzene was added NBS (0.41g, 2.2 mmol) and AIBN (16.4 mg, 0.1 mmol) was added at room temperature. Then the mixture was refluxed at 85 ºC overnight. It was cooled to room temperature and purified by flash chromatograph (silica gel, petroleum ether and ethyl acetate as eluent). The product was then suspended in 20 mL of H_2O and heated to 100 ºC. After 1 h, the mixture was cooled to room temperature and then extracted with EtOAc (3×30 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a corresponding 2-formylbenzoic acid as a solid. To a solution of the corresponding 2-formylbenzoic acid in acetone were added Me_2SO_4 (0.126 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol). After stirring for 2 h at room temperature, the mixture was refluxed for 1 h and cooled to ambient temperature, filtered and washed with acetone (3×15 mL). The combined filtrates were concentrated in vacuo and the residue was purified by flash chromatography (silica gel, eluent: petroleum/ethyl acetate = 20:1) to give methyl 2-formylbenzoate.

General Procedure for Ruthenium/Me-BIPAM catalyzed Asymmetric Arylation of 2-formylbenzoate with Arylboronic Acids

A flask was charged with Ruthenium catalyst (0.01 mmol, 2 mol%) and Me-BIPAM (0.011 mmol, 2.2 mol%) under nitrogen atmosphere. Toluene (2.5 ml) was added and the mixture was stirred at room temperature for 30 min. Phenylboronic acid (0.75 mmol), 2-formylbenzoate (0.5 mmol), K_2CO_3 (0.5 mmol) and H_2O (0.5 ml) were then added to this catalyst solution. The reaction mixture was then heated at 50 °C for 18 h. The mixture was quenched with aqueous saturated NH_4Cl, extracted with AcOEt, dried over $MgSO_4$, filtered off, and the solvents were evaporated. The crude product was purified by flash column chromatography (Hexane/AcOEt = 7/1 to 5/1) to afford pure 3-aryl-ahydroxy-benzofuran-2-one.

(*S*)-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3aa).[11a,21] White solid; mp 151–153 ºC; 96% yield (103 mg); $[\alpha]_D^{24}$ = +43.0 (*c* 0.50, $CHCl_3$), 97% ee [lit. $[\alpha]_D$ = +45.3 (*c* 0.10, $CHCl_3$, 71% ee (*S*))[11a]], [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 23.4 min (major) and 30.9 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.55 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.36 (m, 2H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.28 (m, 2H), 6.40 (s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.42, 149.53, 136.25, 134.23, 129.23, 129.14, 128.82, 126.81, 125.41, 125.34, 122.76, 82.57; MS (EI) *m/z* 77.02 (30), 105.03 (100), 133.02 (12), 152.06 (12), 165.07 (34), 181.06 (16), 210.06 (78); HRMS (EI) *m/z* calcd for $C_{14}H_{10}O_2$ $[M]^+$: 210.06808, found: 210.06768.

(*S*)-3-(4-methoxyphenyl)-1,3-dihydro-2-benzofuran-1-one (3ab).[11a,21] White solid; mp 141–144 ºC; 80% yield (96 mg); $[\alpha]_D^{24}$ = -8.9 (*c* 0.50, $CHCl_3$), 96% ee [lit. $[\alpha]_D$ = -27.8 (*c* 0.10, $CHCl_3$, 67% ee (*S*))[11a]], [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 30.2 min (major) and 40.6 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.3 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.37 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.43, 160.24, 149.63, 134.17, 129.17, 128.66, 128.11, 125.71, 125.35, 122.85, 114.17, 82.60, 55.19; MS (EI) *m/z* 43.98 (23), 77.02 (32), 104.01 (53), 135.02 (52), 152.03 (48), 165.04 (30), 181.03 (32), 195.05 (30), 209.02 (23), 240.03 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_3$ $[M]^+$: 240.07864, found: 240.07806.

(*S*)-3-(4-methylphenyl)-1,3-dihydro-2-benzofuran-1-one (3ac).[11a,21] White solid; mp 128–132 ºC; >99% yield (117 mg); $[\alpha]_D^{25}$ = +15.0 (*c* 0.50, $CHCl_3$), 95% ee [lit. $[\alpha]_D$ = +10.3 (*c* 0.10, $CHCl_3$, 77% ee (*S*))[11a]], [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, tR = 19.3 min (major) and 25.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.55 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.36 (m, 2H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.28 (m, 2H), 6.40 (s, 1H); ^{13}C NMR (100 MHz, CD2Cl2): δ = 170.49, 149.68, 139.16, 134.18, 133.24, 129.48, 129.14, 126.89, 125.49, 125.36, 122.77, 82.63, 21.08; MS (EI) *m/z* 77.03 (22), 91.04 (20), 104.01 (37), 119.03 (65), 133.01 (12), 152.04 (20), 165.04 (60), 178.05 (18), 195.05 (7), 209.03 (100), 224.05 (84); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_2$ $[M]^+$: 224.08373, found: 224.08311.

(+)-3-(4-ethenylphenyl)-1,3-dihydro-2-benzofuran-1-one (3ad). White solid; mp 139–142 ºC; 93% yield (111 mg); $[\alpha]_D^{25}$ = +23.0 (*c* 0.50, $CHCl_3$), 95% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 21.6 min (major) and 27.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.3 Hz, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 7.8 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.70 (dd, *J* = 11.0 Hz 17.8 Hz, 1H), 6.39 (s, 1H), 5.76 (d, *J* = 17.8 Hz, 1H), 5.28 (d, *J* = 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.43, 149.49, 135.88, 135.61, 134.28, 129.29, 127.12, 126.63, 125.51, 125.42, 122.76, 114.93, 82.38; MS (EI) *m/z* 77.04 (27), 104.03 (43), 131.05 (38), 191.09 (20), 209.06 (10), 236.08 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{12}O_2$ $[M]^+$: 236. 08373, found: 236.08326.

(+)-3-(4-phenylphenyl)-1,3-dihydro-2-benzofuran-1-one (3ae).[21] White solid; mp 249–251 ºC; 87% yield (125 mg); $[\alpha]_D^{25}$ = +31.0 (*c* 0.50, $CHCl_3$), 94% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 38.3 min (major) and 50.2 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.62–7.55 (m, 5H), 7.44 (t, *J* = 7.3 Hz 7.8 Hz, 2H), 7.39–7.34 (m, 4H), 6.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.61, 149.71, 142.40, 140.36, 129.53, 128.95, 127.81, 127.58, 127.23, 125.81, 125.75, 123.00, 82.62; MS (EI) *m/z* 43.99 (13), 77.03 (22), 104.01 (43), 132.00 (9), 152.04 (26), 181.04 (39), 209.03 (9), 241.06 (35), 286.06 (100), 224.05 (xx); HRMS (EI) *m/z* calcd for $C_{20}H_{14}O_2$ $[M]^+$: 286.09938, found: 286.09876.

(+)-3-(4-fluorophenyl)-1,3-dihydro-2-benzofuran-1-one (3af).[22] White solid; mp 121–124 ºC; 98% yield (112 mg); $[\alpha]_D^{25}$ = +18.0 (*c* 0.50, $CHCl_3$), 95% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 21.1 min (major) and 25.9 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.3 Hz, 1H), 7.68 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.58 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.28–7.24 (m, 2H), 7.07 (t, *J* = 8.7 Hz, 1H), 6.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.19, 163.02 (d, $J_{C\text{-}F}$ = 247.5 Hz), 149.25, 134.36, 132.17, 129.40, 128.96 (d, $J_{C\text{-}F}$ = 8.8 Hz), 125.50, 125.41, 122.76, 115.85 (d, $J_{C\text{-}F}$ = 21.3 Hz), 81.87; MS (EI) *m/z* 77.04 (20), 105.03 (100), 123.02 (26), 133.03 (11), 170.05 (11), 183.06 (54), 199.05 (6), 228.06 (57); HRMS (EI) *m/z* calcd for $C_{14}H_9FO_2$ $[M]^+$: 228.05866, found: 228.05819.

(*S*)-3-(4-chlorophenyl)-1,3-dihydro-2-benzofuran-1-one (3ag).[5c,21] White solid; mp 156–159 ºC; 97% yield (118 mg); $[\alpha]_D^{25}$ = +25.0 (*c* 0.5, $CHCl_3$), 96% ee [lit. $[\alpha]_D^{22}$ = -32.2 (*c* 0.72, $CHCl_3$, 88% ee (*R*))[25]] [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 22.0 min (major) and 26.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.3 Hz, 1H), 7.67 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.58 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.37–7.31 (m, 3H), 7.24–7.21 (m, 2H), 6.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.18, 149.11, 135.14, 134.85, 134.42, 129.49, 129.10, 128.28, 125.63, 125.33, 122.70, 81.74; MS (EI) *m/z* 43.99 (28), 77.04 (32), 105.03 (100), 133.03 (15), 138.99 (21), 165.07 (60), 199.03 (5), 209.06 (90), 244.03 (29); HRMS (EI) *m/z* calcd for $C_{14}H_9FO_2$ $[M]^+$: 244.02911, found: 244.02859.

(*S*)-3-[4-(trifluoromethyl)phenyl]-1,3-dihydro-2-benzofuran-1-one (3ah).[21] White solid; mp 118–121 ºC; 74% yield (103 mg); $[\alpha]_D^{24}$ = +47.0 (*c* 0.50, $CHCl_3$), 91% ee [lit. $[\alpha]_D^{27}$ = +34.0 (*c* 0.50, CH_2Cl_2, 70% ee (*S*))[23]] [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 22.5 min (major) and 26.2 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.3 Hz, 1H), 7.70–7.64 (m, 3H), 7.59 (d, *J* = 7.3 Hz 7.8 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 6.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.11, 148.90, 140.44, 134.57, 131.32 (q, $J_{C\text{-}F}$ = 32.9 Hz), 129.69, 127.05, 125.96 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.83, 125.17, 123.70 (q, $J_{C\text{-}F}$ = 271.5 Hz), 122.67, 81.50; MS (EI) *m/z* 77.04 (18), 105.03 (100), 133.02 (13), 145.02 (8), 165.06 (18), 201.04 (8), 209.05 (18), 278.05 (21); HRMS (EI) *m/z* calcd for $C_{15}H_9F_3O_2$ $[M]^+$: 278.05546, found: 278.05473.

(*S*)-3-(naphthalen-2-yl)-1,3-dihydro-2-benzofuran-1-one (3ai).[9f,11a] White solid; mp 184–187 ºC; 92% yield (127 mg); $[\alpha]_D^{25}$ = +97.0 (*c* 0.50, $CHCl_3$), 93% ee [lit. $[\alpha]_D$ = +97.9 (*c* 0.10, $CHCl_3$, 83% ee (*S*))[11a]] [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 26.9 min (major) and 38.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.0 (d, *J* = 7.3 Hz, 1H), 7.85–7.82 (m, 4H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.58–7.49 (m, 3H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.24–7.22 (m, 1H), 6.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.59, 149.69, 134.36, 133.65, 133.55, 133.04, 129.41, 129.05, 128.06, 127.78, 126.81, 126.68, 125.69, 125.58, 125.75, 122.90, 82.89; MS (EI) *m/z* 43.99 (6), 77.03 (15), 104.02 (41), 127.04 (24), 132.01 (6), 155.04 (29), 202.07 (15), 215.08 (50), 231.07 (15), 260.07 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{12}O_2$ $[M]^+$: 260.08373, found: 260.08340.

(*S*)-3-(3,5-dimethylphenyl)-1,3-dihydro-2-benzofuran-1-one (3aj).[11a] White solid; mp 91–93 ºC; 99% yield (120 mg); $[\alpha]_D^{25}$ = +56.0 (*c* 0.50, $CHCl_3$), 96% ee [lit. $[\alpha]_D$ = +18.8 (*c* 0.07, $CHCl_3$, 67% ee (*S*)[9f]) [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 14.7 min (major) and 17.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.53 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 6.98 (s, 1H), 6.87 (s, 2H), 6.31 (s, 1H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.57, 149.79, 138.53, 136.14, 134.19, 130.80, 129.13, 125.40, 124.49, 122.77, 82.77, 21.82; MS (EI) *m/z* 43.99 (13), 77.03 (18), 104.02 (44), 133.05 (62), 152.05 (9), 165.05 (18), 179.07 (31), 195.06 (11), 215.08 (50), 223.05 (100), 238.08 (82); HRMS (EI) *m/z* calcd for $C_{16}H_{14}O_2$ $[M]^+$: 238.09938, found: 238.09888.

(*S*)-3-(3-chlorophenyl)-1,3-dihydro-2-benzofuran-1-one (3ak).[11c,21] White solid; mp 118–121 ºC; 84% yield (107 mg); $[\alpha]_D^{24}$ = +54.0 (*c* 0.50, $CHCl_3$), 93% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 22.6 min (major) and 31.5 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.3 Hz 7.8 Hz, 1H), 7.58 (d, *J* = 7.3 Hz 7.8 Hz, 1H), 7.36–7.30 (m, 3H), 7.27–7.26 (m, 1H), 7.21–7.19 (m, 1H), 6.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.12, 148.95, 138.38, 134.82, 134.48, 130.25, 129.58, 129.38, 126.85, 125.72, 125.25, 124.99, 122.72, 81.60; MS (EI) *m/z* 77.03 (21), 105.02 (100), 133.01 (16), 152.05 (11), 165.05 (21), 209.04 (50), 244.01 (26); HRMS (EI) *m/z* calcd for $C_{14}H_9ClO_2$ $[M]^+$: 244.02911, found: 244.02872.

(*S*)-3-(thiophen-3-yl)-1,3-dihydro-2-benzofuran-1-one (3al).[21] White solid; mp 112–116 ºC; 92% yield (99 mg); $[\alpha]_D^{25}$ = -34.0 (*c* 0.50, $CHCl_3$), 91% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 30.2 min (major) and 39.9 min (minor)]; ^{1}H NMR (400

MHz, $CDCl_3$): δ = 7.96 (d, J = 7.3 Hz, 1H), 7.69 (t, J = 7.3 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.36–7.33 (m, 2H), 6.96–6.34 (m, 1H), 6.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.15, 148.89, 137.06, 134.23, 129.37, 129.13, 125.79, 125.61, 125.57, 124.41, 122.77, 78.34; MS (EI) *m/z* 77.04 (20), 82.99 (2), 105.03 (59), 110.99 (37), 133.03 (7), 171.02 (59), 187.01 (10), 216.02 (100); HRMS (EI) *m/z* calcd for $C_{12}H_8O_2S$ $[M]^+$: 216.02450, found: 216.02450.

(+)-3-phenyl-5-(trifluoromethyl)-1,3-dihydro-2-benzofuran-1-one (3ba). White solid; mp 152–155 ºC; 91% yield (127 mg); $[\alpha]_D^{25}$ = +29.0 (*c* 0.5, $CHCl_3$), 89% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 18.9 min (major) and 29.1 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.42–7.41 (m, 3H), 7.30–7.26 (m, 2H), 6.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.92, 149.99, 136.08 (q, $J_{C\text{-}F}$ = 32.9 Hz), 135.26, 129.70, 129.19, 128.74, 126.91, 126.70 (dd, $J_{C\text{-}F}$ = 2.8 Hz 3.8Hz), 126.39, 125.95 (q, $J_{C\text{-}F}$ = 273.4 Hz), 120.23 (q, $J_{C\text{-}F}$ = 3.8 Hz), 82.71; MS (EI) *m/z* 77.05 (34), 105.05 (93), 145.04 (34), 165.09 (47), 172.03 (75), 201.07 (19), 233.08 (12), 249.08 (12), 278.08 (100); HRMS (EI) *m/z* calcd for $C_{15}H_9F_3O_2$ $[M]^+$: 278.05546, found: 278.05451.

(-)-5-bromo-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3ca).[24] White solid; mp 171–173 ºC; 99% yield (143 mg); $[\alpha]_D^{25}$ = -49.0 (*c* 0.50, $CHCl_3$), 94% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 23.3 min (major) and 32.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.41–7.39 (m, 3H), 7.29–7.24 (m, 2H), 6.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.38, 151.29, 135.53, 132.91, 129.49, 129.46, 129.02, 126.81, 126.78, 126.18, 124.34, 81.95; MS (EI) *m/z* 77.03 (14), 105.02 (100), 152.05 (9), 165.05 (23), 184.92 (16), 210.92 (3), 289.95 (23); HRMS (EI) *m/z* calcd for $C_{14}H_9BrO_2$ $[M]^+$: 287.97859, found: 287.97765.

(+)-6-bromo-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3da).[25] White solid; mp 109–112 ºC; 92% yield (133 mg); $[\alpha]_D^{24}$ = +19.0 (*c* 0.50, $CHCl_3$), 96% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 28.8 min (major) and 47.0 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 1.4 Hz, 1H), 7.76 (dd, J = 1.83 Hz 8.2 Hz, 1H), 7.41–7.37 (m, 3H), 7.28–7.21 (m, 3H), 6.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.85, 148.29, 137.37, 135.67, 129.55, 129.07, 128.58, 127.67, 126.93, 124.46, 123.41, 82.63; MS (EI) *m/z* 43.99 (19), 75.01 (27), 105.02 (100), 152.05 (16), 165.05 (48), 184.92 (35), 210.92 (8), 289.95 (55); HRMS (EI) *m/z* calcd for $C_{14}H_9BrO_2$ $[M]^+$: 287.97859, found: 287.97776.

(+)-7-methyl-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3ea) Colorless oil; 84% yield (94 mg); $[\alpha]_D^{25}$ = +54.0 (*c* 0.50, $CHCl_3$), 93% ee [HPLC condition: ChiralCel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 18.1 min (major) and 24.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (t, J = 7.2 Hz 7.6 Hz, 1H), 7.39–7.35 (m, 3H), 7.30–7.26 (m, 3H), 7.12 (d, J = 7.2 Hz, 1H), 6.33 (s, 1H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.67, 150.14, 139.54, 136.74, 133.96, 130.83, 129.07, 128.83, 126.87, 122.89, 120.13, 81.72, 17.32; MS (EI) *m/z* 77.05 (15), 91.07 (23), 119.06 (100), 147.06 (10), 165.09 (27), 224.11 (54); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_2$ $[M]^+$: 224. 08373, found: 224.08290.

(-)-5,7-dimethoxy-3-(4-methoxyphenyl)-1,3-dihydro-2-benzofuran-1-one (3fb).[12] White solid; mp 138–142 ºC; 85% yield (127 mg); $[\alpha]_D^{25}$ = -13.0 (*c* 0.50, $CHCl_3$), 87% ee [lit. $[\alpha]_D^{22}$ = -13 (*c* 1.1, $CHCl_3$)[16]] [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 114.8 min (minor) and 127.6 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (s, 1H), 7.19 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 6.43 (s, 1H), 6.26 (s, 1H), 6.18 (s, 1H), 3.98 (s, 3H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.16, 166.66, 159.97, 159.08, 154.64, 128.41, 113.98, 106.15, 98.76, 98.22, 81.08, 55.80, 55.71, 55.04; MS (EI) *m/z* 43.99 (35), 77.05 (13), 106.03 (14), 135.03 (23), 165.04 (67), 255.05 (33), 270.06 (51), 300.08 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{16}O_5$ $[M]^+$: 300.09977, found: 300.09907.

(+)-6-methyl-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3ga).[25] White solid; mp 103–106 ºC; 92% yield (103 mg); $[\alpha]_D^{25}$ = +25.0 (*c* 0.50, $CHCl_3$), 95% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 19.5 min (major) and 26.3 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.38–7.36 (m, 3H), 7.28–7.26 (m, 2H), 7.21 (d, J = 7.8 Hz, 1H), 6.37 (s, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.61, 147.01, 139.55, 136.54, 135.42, 129.10, 128.81, 126.84, 125.59, 125.40, 122.47, 82.52, 21.16; MS (EI) *m/z* 41.04 (16), 91.05 (16), 105.02 (13), 119.04 (100), 147.03 (13), 165.05 (25), 178.06 (9), 224.06 (52); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_2$ $[M]^+$: 224. 08373, found: 224.08364.

(+)-5-methyl-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3ha).[25] White solid; mp 138–141 ºC; 99% yield (111 mg); $[\alpha]_D^{25}$ = +4.0 (*c* 0.50, $CHCl_3$), 97% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 19.7 min (major) and 24.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.8 Hz, 1H), 7.41–7.34 (m, 4H), 7.29–7.26 (m, 2H), 7.11 (s, 1H), 6.35 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.54, 150.18, 145.59, 136.52, 130.45, 129.11, 128.84, 126.82, 125.23, 123.01, 122.80, 82.35, 21.96; MS (EI) *m/z* 43.99 (16), 77.03 (14), 91.05 (20), 119.04 (100), 147.03 (12), 165.05 (26), 178.06 (9), 195.06 (6), 224.06 (45); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_2$ $[M]^+$: 224. 08373, found: 224.08364.

(+)-6-chloro-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3ia). White solid; mp 102–106 ºC; 87% yield (106 mg); $[\alpha]_D^{25}$ = +17.0 (*c* 0.50, $CHCl_3$), 95% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 25.5 min (major) and 43.5 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 1.8 Hz, 1H), 7.61 (dd, J = 1.8 Hz 7.9 Hz, 1H), 7.39 (t, J = 3.1 Hz, 3H), 7.29–7.23 (m, 3H), 6.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.00, 147.79, 135.72, 134.62, 129.53, 129.07, 127.39, 126.92, 125.50, 124.18, 82.58; MS (EI) *m/z* 77.04 (25), 105.03 (100), 138.99 (27), 165.07 (31), 181.06 (7), 199.03 (5), 209.06 (5), 244.03 (67); HRMS (EI) *m/z* calcd for $C_{14}H_9ClO_2$ $[M]^+$: 244.02911, found: 244.02842.

Notes and references

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