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Catalytic asymmetric synthesis of 3-aryl phthalides enabled by arylation–lactonization of 2-formylbenzoates†

Andressa M. M. Carlos, Rafael Stieler and Diogo S. Lüdtke *

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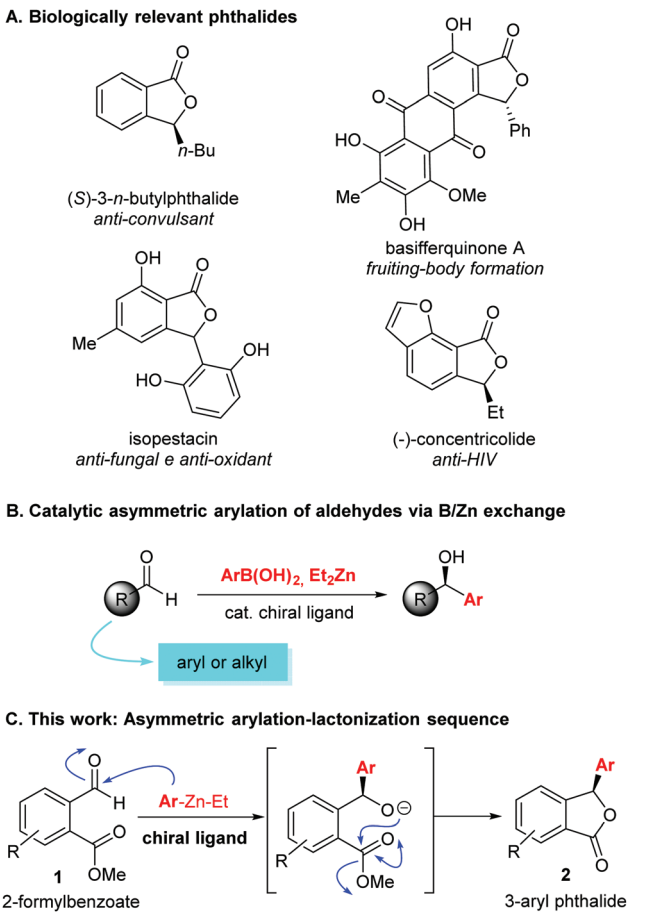
The catalytic asymmetric synthesis of 3-aryl phthalides is reported through a sequential asymmetric arylation–lactonization reaction. The reaction is enabled by a boron–zinc exchange to generate reactive arylating agents, which react with 2-formylbenzoates in the presence of a chiral amino naphthol ligand. The enantiodetermining step is the arylation of the aldehyde, which then undergoes a lactonization event to yield the corresponding phthalides in good yields and enantioselectivities.

Introduction

Optically active 3-substituted isobenzofuranones, commonly termed phthalides, are important structures in medicinal chemistry as well as in organic synthesis, and are frequently encountered in natural products. They are characterized by a bicyclic framework, with a benzene ring fused to a γ-lactone.[1] Several biologically relevant phthalides have been reported in the literature (Scheme 1A). For example, *n*-butylphthalide is marketed as an anti-convulsant drug for the treatment of ischemia-cerebralapoplexy,[2] while natural products basidifferquinone A,[3] isopestacin,[4] and concentricolide[5] have been reported to display fruiting bodies, and anti-fungal/anti-oxidant and anti-HIV activities, respectively. Despite their importance, the catalytic asymmetric synthesis of 3-substituted isobenzofuranones has been scarcely studied, most notably those bearing an aryl moiety at this position. Available methods are centered on the metal-catalyzed intramolecular cyclization of diketones,[6] organocatalyzed aldol-cyclization reactions,[7] and halogen-metal exchange-cyclization catalyzed by cobalt[8] or mediated by bimetallic Mg–Li reagents.[9] Rhodium[10] and ruthenium-catalyzed[11] additions of organoboronic acids to formylbenzoates have also been described.

Our research group has been involved in the development of stereoselective reactions using organozinc reagents,[12] with the development of catalytic asymmetric addition of arylzinc reagents to aldehydes[13] and diastereoselective arylations of chiral sugar[14] and amino-aldehydes,[15] and ketenimium ions.[16] Based on our experience in this subject, we hypothesized that a catalytic asymmetric arylation reaction, enabled by the



Scheme 1 Key precedents and this work.

Instituto de Química, Universidade Federal do Rio Grande do Sul, UFRGS, Av. Bento Gonçalves 9500, 91501-970 Porto Alegre, RS, Brazil. E-mail: dsludtke@iq.ufrgs.br; Tel: +55 51 3308 9637

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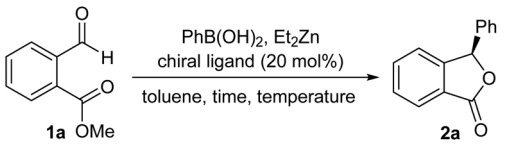
boron/zinc exchange of arylboronic acids with Et_2Zn,[17] which has been well described for aryl and alkyl aldehydes (Scheme 1B), would serve as a tool for the development of a sequential asymmetric arylation–lactonization reaction, ultimately leading to a catalytic asymmetric synthesis of 3-aryl phthalides (Scheme 1C).[18]

Results and discussion

Our initial investigation began with a ligand screening in the enantioselective arylation of methyl 2-formylbenzoate (**1a**), with the transferable phenyl group generated by the B/Zn exchange reaction between phenylboronic acid and diethylzinc (Table 1). Chiral amino alcohols bearing pyrrolidine,[19] aziridine,[20] Trost's ProPhenol,[21] and amino naphthol[22] backbones have been evaluated (Fig. 1).

The initial experiments revealed that **L1** resulted in a very low yield and ee for the desired product **2a** (entry 1), while a much better enantioselectivity of 73% was observed using the aziridino methanol ligand **L2**, despite the still moderate yield of 45% (entry 2). Trost's ProPhenol ligand resulted in a very low conversion and racemic product. More promising results have been achieved with ligands from the amino naphthol family **L4–L7**. The simplest ligand **L4** was able to deliver the desired phthalide **2a** in 57% yield and a good enantioselectivity of 55% (entry 4). Gratifyingly, when the bulkier ligand **L5**, bearing an *ortho*-tolyl substituent (instead of a phenyl in **L4**), resulted in an improved ee of 80%, while maintaining the yield (entry 5). Additional changes of the ligand at the aryl or *N*-R moieties didn't result in additional improvements (entries 6 and 7). With these results in hand, we proceeded to further optimization studies using **L5** as the ligand of choice. Changes have been made in time and temperature at which the reaction was performed. Gratifyingly, when the reaction was performed at lower temperatures, significant improvement of the enantioselectivity was observed (entries 8–11). Carrying out the reaction at 0 °C in the presence of 20 mol% of **L5** resulted in product **2a** in 83% and 80% ee (entry 8). An additional decrease in the temperature to −5 °C resulted in an additional increase in the enantioselectivity of the arylation reaction and 3-phenyl phthalide **2a** was isolated with 91% ee, with the best yield of 80% obtained after 5 h (entry 11). An attempt at lowering the ligand loading to 10 mol% resulted in a decrease in both yield and enantiomeric excess (entry 12). Decreasing the temperature even further didn't result in product formation after 5 h (entry 13).

Table 1 Optimization of the chiral ligand



Entry	Ligand	T (°C)	t (h)	Yield[a] (%)	ee[b] (%)
1	**L1**	25	24	16	31 (*S*)
2	**L2**	25	24	45	73 (*S*)
3	**L3**	25	24	28	0
4	**L4**	25	24	57	55 (*R*)
5	**L5**	25	24	69	80 (*R*)
6	**L6**	25	24	25	53 (*R*)
7	**L7**	25	24	28	50 (*R*)
8	**L5**	0	24	83	80 (*R*)
9	**L5**	−5	24	73	91 (*R*)
10	**L5**	0	2	56	83 (*R*)
11	**L5**	−5	5	80	91 (*R*)
12[c]	**L5**	−5	5	75	85 (*R*)
13	**L5**	−20	5	NR	ND

[a] Isolated yields. [b] Determined by HPLC using the chiral stationary phase. [c] Reaction using 10 mol% of **L5**. NR = no reaction. ND = not determined.

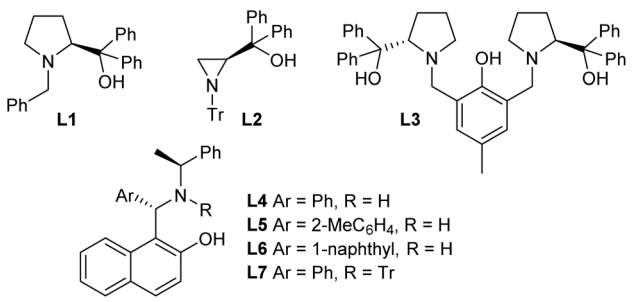
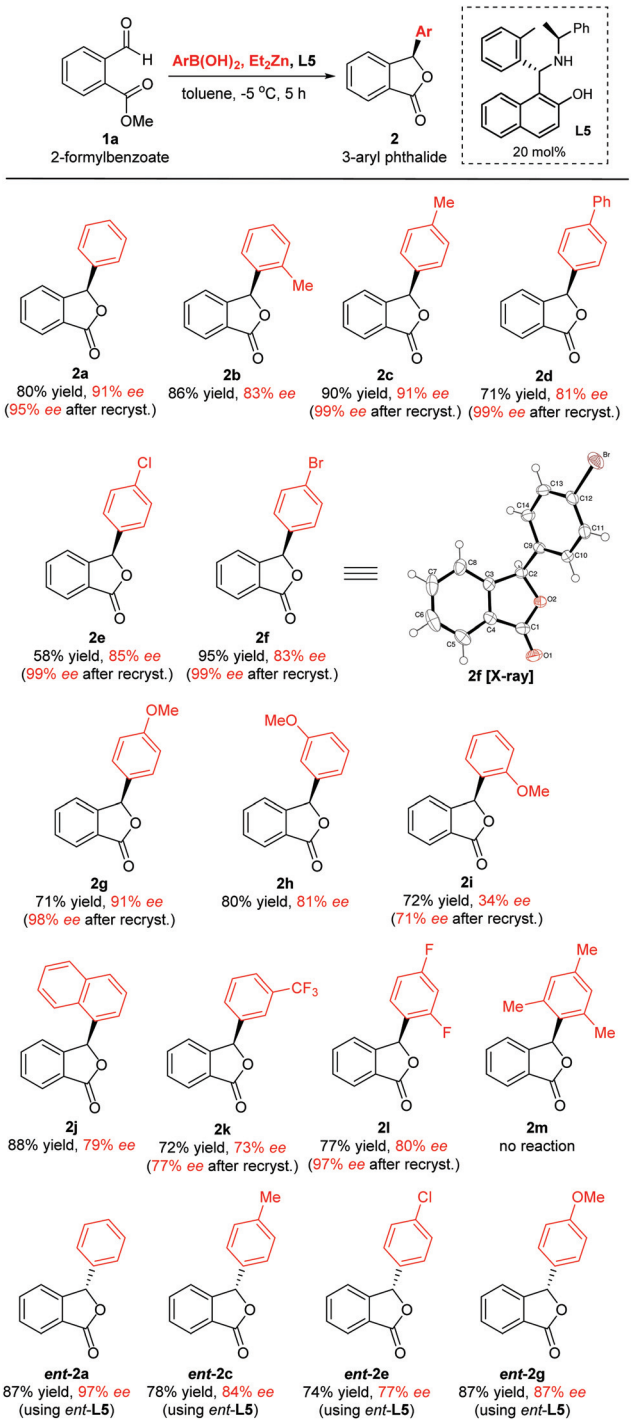


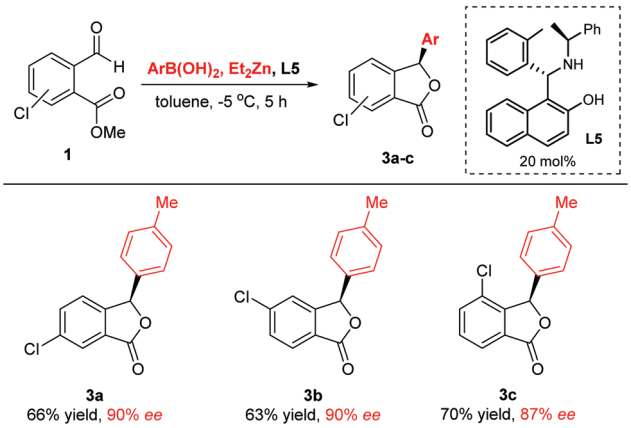
Fig. 1 Structure of the chiral ligands used in this work.

After establishing the optimal conditions for the phthalide synthesis, we proceeded to examine the reaction scope in respect of the arylboronic acid (Scheme 2).

The reaction proceeded efficiently for a number of different arylating groups bearing both electron-donating and electron-withdrawing groups, typically at a synthetically useful level of enantioselectivity. For example, the arylation of **1a** using arylating agents with different substitution patterns such as *p*-Me (**2c**), *p*-Ph (**2d**), *p*-Cl (**2e**), *p*-Br (**2f**), *p*-OMe (**2g**), and 2,4-difluoro (**2l**) was well tolerated and the corresponding aryl phthalides were obtained in good yields and enantioselectivities ranging from 80% to 91% ee. Notably, a single recrystallization of the 3-aryl phthalide **2** in chloroform/petroleum ether resulted in a significant enantioenrichment of the compounds, with products **2a** and **2c–g**, and **2l** being obtained in >95% ee. Worth pointing out is that the mass recovery after recrystallization is always of >80%, in both 0.3 mmol and 1 mmol scales, which renders this process useful for preparative purposes. Steric effects have also been examined and the reaction is slightly less enantioselective when *ortho* substituents are present at the arylation agent. Hence, product **2b**, obtained by the transfer of a *o*-tolyl group, was obtained in 83% ee, while product **2i**, with an *o*-OMe was isolated in a diminished ee of 34%. The presence of two *ortho* methyl groups causes more severe steric hindrance and hampers the formation of the desired product **2m**. Finally, aryl phthalides with the opposite absolute configuration can also be prepared by the use of the enantiomer of the chiral ligand **L5**, and the corresponding products *ent*-**2a**, *ent*-



Scheme 2 Scope of the reaction.



Scheme 3 Arylation using substituted formyl benzoates.

2c, *ent*-**2e**, and *ent*-**2g** were obtained in comparable yields and enantioselectivities.

The absolute configuration of the 3-aryl phthalides was assigned as being (*R*), based on the single crystal X-ray diffraction studies of compound **2f** (Scheme 2, see the ESI† for crystallographic details). The absolute configurations of the remaining compounds have been assigned by analogy, assuming that the mechanism is the same for the transfer of the aryl groups, or by comparison of retention times in chiral stationary phase HPLC for known compounds (see the ESI† for details).

Further studies with variations in the substitution pattern of the electrophile have also been carried out. Substituted 2-formyl benzoates bearing a chlorine substituent were evaluated under the optimized reaction conditions, using *p*-tolylboronic acid as the aryl source (Scheme 3). The corresponding 3-aryl phthalides **3a–c** were obtained in good yields and high enantioselectivities ranging from 87% to 90% ee, indicating that the position of the substituent at the aryl ring has little influence on the efficiency of the arylation reaction.

Conclusions

In summary, we have developed an efficient, catalytic enantioselective synthesis of 3-aryl phthalides by a combination of an asymmetric arylation of an aldehyde with a lactonization reaction. The enantiodetermining event is the asymmetric addition of an arylzinc reagent to a 2-formylbenzoate. The products were obtained in good to excellent enantioselectivities, and we have shown that the ee of the products could be enriched to very high enantiopurity by a simple recrystallization in an ordinary chloroform/petroleum ether solvent mixture. The method developed is preparatively useful and shall find utility in the synthesis of novel chiral aryl phthalides.

Experimental section

General information

Air- and moisture-sensitive reactions were conducted in flame- or oven-dried glassware equipped with tightly fitted rubber septa and under a positive pressure of dry argon. Reagents and solvents were handled by using standard syringe techniques. Temperatures above room temperature were maintained by the

use of a mineral oil bath heated on a hotplate. Column chromatography was performed using silica gel (230–400 mesh) following the methods described by Still.[23] Thin layer chromatography (TLC) was performed using supported silica gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or treated with acid vanillin followed by heating. NMR spectra were recorded either with a 300 or 400 MHz instrument in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of residual $CHCl_3$ or tetramethylsilane (TMS) as a reference. The data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hz, and integrated intensity. ^{13}C NMR spectra were recorded at 75 and 100 MHz in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak $CDCl_3$. Abbreviations to denote the multiplicity of a particular signal are: s (singlet), d (doublet), t (triplet), dd (double doublet), m (multiplet), q (quartet), and br (broad singlet). ESI-QTOF-MS measurements were performed in the positive ion mode (m/z 50–2000 range). Optical rotations were measured using a digital polarimeter using 10 cm cells and are reported as $[\alpha]_D^{20}$, concentration (g per 100 mL), and solvent. Formyl benzoates **1** and amino naphthol **L5** were prepared according to literature procedures.[24,22d]

General procedure for the aryl transfer reaction

Under an atmosphere of argon, 1.5 M solution of Et_2Zn (7.2 equiv., 3.6 mmol, 2.4 mL) was slowly added to a solution of arylboronic acid (2.4 equiv., 1.2 mmol) in dry toluene (2 mL). The mixture was stirred at 60 °C for 1 h and after this time, it was cooled at room temperature and a solution of 20 mol% of ligand **L5** in 1 mL of dry toluene was added. The reaction mixture was stirred for 15 min followed by the addition of the aldehyde (0.5 mmol). After stirring at −5 °C for 5 h the reaction mixture was carefully quenched by the addition of 1 M HCl. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and the solvent was evaporated in a vacuum. The crude product was purified by flash chromatography using hexane : ethyl acetate.

(*R*)-3-Phenylisobenzofuran-1(3*H*)-one $C_{14}H_{10}O_2$ (2a). White solid. R_f = 0.4 (hexane/EtOAc 90 : 10). $[\alpha]_D^{20}$ = −45.4 (*c* 0.34, DCM). **Melting point** = 152–154 °C. Purified by column chromatography (hexane/EtOAc 90 : 10) to give the product in 80% yield (89 mg) and 91% ee. **HPLC**: (Chiralcel OD, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 8.63 min, (*R*) = 11.14 min. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 6.40 (s, 1H), 7.26–7.41 (m, 6H), 7.55 (t, J = 7.5 Hz, 1H), 7.64 (td, J = 7.5 Hz, J = 1.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 82.6, 122.8, 125.50, 125.55, 126.9, 128.9, 129.23, 129.29, 134.2, 136.3, 149.6, 170.4. **HRMS (ESI$^+$):** Calcd for $C_{14}H_{10}O_2$ $[M + H]^+$ requires 211.0759; found 211.0758.

***Ent*-2a:** Purified by column chromatography (hexane/EtOAc 90 : 10) to give the product in 87% yield and 97% ee. $[\alpha]_D^{20}$ = +43.98 (*c* 0.98, DCM). **HPLC**: (Chiralcel OD, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 9.34 min, (*R*) = 12.19 min.

(*R*)-3-*o*-Tolylisobenzofuran-1(3*H*)-one $C_{15}H_{12}O_2$ (2b). White solid. R_f = 0.3 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = +27.4 (*c* 0.94, EtOAc). **Melting point** = 118–120 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 86% yield (96 mg) and 83% ee. **HPLC**: (Chiralcel OD, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 9.61 min, (*R*) = 12.82 min. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.50 (s, 3H), 6.69 (s, 1H), 6.92 (d, J = 7.6 Hz, 1H), 7.11–7.15 (m, 1H), 7.26–7.28 (m, 2H), 7.34 (dd, J = 7.6 Hz, J = 0.8 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.67 (td, J = 7.5 Hz, J = 1,1 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 19.2, 80.4, 122.9, 125.6, 126.32, 126.35, 127.1, 129.25, 129.29, 131.0, 134.0, 134.1, 137.0, 149.2, 170.5. **HRMS (ESI$^+$):** Calcd for $C_{15}H_{12}O_2$ $[M + H]^+$ requires 225.0916; found 225.0918.

(*R*)-3-*p*-Tolylisobenzofuran-1(3*H*)-one $C_{15}H_{12}O_2$ (2c). White solid. R_f = 0.3 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = −7.72 (*c* 0.22, DCM). **Melting point** = 127–130 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 90% yield (101 mg) and 91% ee. **HPLC**: (Chiralcel OD, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 7.82 min, (*R*) = 9.61 min. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 2.35 (s, 3H), 6.37 (s, 1H), 7.14–7.19 (m, 4H), 7.32 (d, J = 7.6 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.64 (td, J = 7.5 Hz, 1.1 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 21.3, 82.6, 122.8, 125.5, 125.6, 126.9, 129.2, 129.5, 133.3, 134.2, 139.3, 149.7, 170.5. **HRMS (ESI$^+$):** Calcd for $C_{15}H_{12}O_2$ $[M + H]^+$ requires 225.0916; found 225.0917.

***Ent*-2f:** Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 78% yield (88 mg) and 84% ee. $[\alpha]_D^{20}$ = +50.12 (*c* 0.78, DCM). **HPLC**: (Chiralcel OD, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 9.30 min, (*R*) = 12.12 min.

(*R*)-3-(*p*-Biphenyl)isobenzofuran-1(3*H*)-one $C_{20}H_{14}O_2$ (2d). White solid. R_f = 0.3 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = +23.6° (*c* 0.22, DCM). **Melting point** = 209–212 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 71% yield (102 mg) and 81% ee. **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 12.02 min, (*R*) = 14.43 min. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 6.45 (s, 1H), 7.34–7.39 (m, 4H), 7.44 (t, J = 7.5 Hz, 2H), 7.55–7.61 (m, 5H), 7.67 (td, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 82.4, 122.8, 125.66, 125.70, 127.1, 127.4, 127.67, 127.69, 128.8, 129.4, 134.4, 135.2, 140.2, 149.9, 170.4. **HRMS (ESI$^+$):** Calcd for $C_{20}H_{14}O_2$ $[M + H]^+$: requires 287.1072; found 287.1072.

(*R*)-3-(*p*-Chlorophenyl)isobenzofuran-1(3*H*)-one $C_{14}H_9ClO_2$ (2e). White solid. R_f = 0.3 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = −34.7 (*c* 0.22, DCM). **Melting point** = 156–159 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 58% yield (71 mg) and 85% ee. **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 9.13 min, (*R*) = 10.36 min. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 6.38 (s, 1H), 7.20–7.24 (m, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.34–7.38 (m, 2H), 7.58 (t, J = 7.5 Hz 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ = 81.7, 122.7, 125.4, 125.7, 128.3, 129.1, 129.5, 134.4, 134.8,

135.2, 149.1, 170.2. **HRMS (ESI$^+$)**: Calcd for $C_{14}H_9ClO_2$ $[M + H]^+$: requires 245.0369; found 245.0370.

***Ent*-2b**: Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 74% yield (91 mg) and 77% ee. $[\alpha]_D^{20}$ = +40.88 (*c* 0.56, DCM). **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 8.64 min, (*R*) = 9.86 min.

(*R*)-3-(*p*-Bromophenyl)isobenzofuran-1(3*H*)-one $C_{14}H_9BrO_2$ (2f). White solid. R_f = 0.3 (hexane/EtOAc 90 : 10). $[\alpha]_D^{20}$ = −20.7 (*c* 0.72, DCM). **Melting point** = 169–172 °C. Purified by column chromatography (hexane/EtOAc 90 : 10) to give the product in 95% yield (137 mg) and 83% ee. **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 9.44 min, (*R*) = 10.62 min. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 6.37 (s, 1H), 7.17–7.19 (m, 2H), 7.33 (dq, *J* = 7.7 Hz, *J* = 0.8 Hz, 1H), 7.52–7.54 (m, 2H), 7.57–7.61 (m, 1H), 7.68 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 81.7, 122.6, 123.3, 125.33, 125.65, 128.5, 129.5, 132.0, 134.4, 135.4, 149.0, 170.1. **HRMS (ESI$^+$)**: Calcd for $C_{14}H_9{}^{79}BrO_2$ $[M + H]^+$: requires 288.9864; found 288.9864; calcd for $C_{14}H_9{}^{81}BrO_2$ $[M + H]^+$: requires 290.9845; found 290.9822.

(*R*)-3-(*p*-Methoxyphenyl)isobenzofuran-1(3*H*)-one $C_{15}H_{12}O_3$ (2g). White solid. R_f = 0.4 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = +28.5° (*c* 0.53, DCM). **Melting point** = 144–147 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 71% yield (85 mg) and 91% ee. **HPLC**: (Chiralcel OD, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 13.63 min, (*R*) = 16.58 min. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 3.81 (s, 3H); 6.37 (s, 1H); 6.89 (d, *J* = 8.4 Hz, 2H); 7.17 (d, *J* = 8.4 Hz, 2H); 7.31 (d, *J* = 7.6 Hz, 1H); 7.56 (t, *J* = 7.5 Hz, 1H); 7.64 (t, *J* = 7.5 Hz, 1H); 7.96 (d, *J* = 7.6 Hz, 1H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 55.2, 82.6, 114.2, 122.8, 125.3, 125.7, 128.1, 128.6, 129.1, 134.1, 149.6, 160.3, 170.4. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_{12}O_3$ $[M + H]^+$: requires 241.0865; found 241.0862.

***Ent*-2g**: Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 87% yield (105 mg) and 87% ee. $[\alpha]_D^{20}$ = −6.76 (*c* 0.69, DCM). **HPLC**: (Chiralcel OD, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 12.44 min, (*R*) = 15.72 min.

(*R*)-3-(*m*-Methoxyphenyl)isobenzofuran-1(3*H*)-one $C_{15}H_{12}O_3$ (2h). Yellow oil. R_f = 0.2 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = −26.95 (*c* 1.52, DCM). Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 80% yield (96 mg) and 48% ee. **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 8.13 min, (*R*) = 8.44 min. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 3.77 (s, 3H), 6.37 (s, 1H), 6.78–6.80 (m, 1H), 6.87–6.91 (m, 2H), 7.28–7.36 (m, 2H), 7.53–7.57 (m, 1H), 7.64 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.95 (d, *J* = 7.96 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 55.2, 82.4, 112.3, 114.5, 118.9, 122.7, 125.3, 125.4, 129.2, 129.9, 134.2, 137.8, 149.4, 159.8, 170.4. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_{12}O_2$ $[M + H]^+$: requires 241.0865; found 241.0866.

(*R*)-3-(*o*-Methoxyphenyl)isobenzofuran-1(3*H*)-one $C_{15}H_{12}O_3$ (2i). White solid. R_f = 0.3 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = −95.9 (*c* 0.50, DCM). **Melting point** = 100–103 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 72% yield (86 mg) and 34% ee. **HPLC**: (Chiralcel AS-H, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 20.80 min, (*R*) = 18.37 min. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 3.91 (s, 3H), 6.85 (s, 1H), 6.91 (td, *J* = 7.5 Hz, *J* = 0.9 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 7.08 (dd, *J* = 7.6 Hz, *J* = 1.7 Hz, 1H), 7.30–7.34 (m, 1H), 7.44 (dd, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.61 (td, *J* = 7.5 Hz, *J* = 1.1 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 55.5, 78.0, 110.9, 120.7, 122.8, 124.9, 125.3, 125.5, 126.8, 128.9, 130.0, 134.0, 150.3, 156.9, 170.9 pp. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_{12}O_3$ $[M + H]^+$: requires 241.0865; found 241.0865.

(*R*)-3-(Naphthalen-1-yl)isobenzofuran-1(3*H*)-one $C_{18}H_{12}O_2$ (2j). White solid. R_f = 0.3 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = +4.46 (*c* 0.51, DCM). **Melting point** = 154–157 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 88% yield (115 mg) and 79% ee. **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 15.46 min, (*R*) = 25.56 min. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.23–7.27 (m, 2H); 7.38 (d, *J* = 8.1 Hz, 1H); 7.39–7.45 (m, 1H); 7.54–7.68 (m, 4H); 7.87 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 8.1 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 79.6, 122.8, 123.1, 124.4, 125.2, 125.9, 126.0, 126.1, 126.9, 129.0, 131.2, 131.8, 133.9, 134.1, 149.2, 170.5. **HRMS (ESI$^+$)**: Calcd for $C_{18}H_{12}O_2$ $[M + H]^+$ requires 261.0916; found 261.0918.

(*R*)-3-(*m*-(Trifluoromethyl)phenyl)isobenzofuran-1(3*H*)-one $C_{15}H_9F_3O_2$ (2k). White solid. R_f = 0.3 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = −47.4 (*c* 1.04, EtOAc). **Melting point** = 98–100 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 72% yield (100 mg) and 73% ee. **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 6.73 min, (*R*) = 8.51 min. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 6.45 (s, 1H), 7.35 (dd, *J* = 7.7 Hz, *J* = 0.8 Hz, 1H), 7.47–7.55 (m, 2H), 7.58–7.71 (m, 4H), 8.00 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 81.5, 122.6, 123.62 (q, $^4J_{C-F}$ = 3.8 Hz), 123.64 (q, J_{C-F} = 271.1 Hz), 125.3, 125.8, 126.0 (q, J_{C-F} = 3.7 Hz), 129.5, 129.7, 130.1, 131.3 (q, J_{C-F} = 32.6 Hz), 134.5, 137.5, 148.8, 170.0. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_9F_3O_2$ $[M + H]^+$: requires 279.0633; found 279.0639.

3-(2,4-Difluorophenyl)isobenzofuran-1(3*H*)-one $C_{14}H_8F_2O_2$ (2l). White solid. R_f = 0.3(hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = −15.84 (*c* 0.50, DCM). **Melting point** = 113–116 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 77% yield (95 mg) and 80% ee. **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 7.67 min, (*R*) = 8.19 min. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 6.70 (s, 1H), 6.81–6.96 (m, 2H), 7.11 (td, *J* = 8.4 Hz, *J* = 6.3 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.69 (td, *J* = 7.6 Hz, *J* = 1.0 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 76.1 (d, $^4J_{C-F}$ = 3.5 Hz), 104.4 (t, *J* = 25.3 Hz), 111.9 (dd, $^2J_{C-F}$ = 21.6 Hz, $^1J_{C-F}$ = 3.7 Hz), 120.0 (d, $^3J_{C-F}$ = 13.2 Hz), 122.6 (d, J_{C-F} = 2.0 Hz), 125.4, 125.8, 129.0 (dd, $^3J_{C-F}$ = 10.0 Hz, $^4J_{C-F}$ = 4.9 Hz), 129.6, 134.5, 148.8, 160.81 (dd, ^1J = 251.1 Hz, ^3J = 12.2 Hz, 163.3 (dd, $^1J_{C-F}$ = 252.8, $^3J_{C-F}$ =

12.2 Hz), 170.1. **HRMS (ESI$^+$)**: Calcd for $C_{14}H_8F_2O_2$ $[M + H]^+$ requires 247.0571; found 247.0569.

(*R*)-5-Chloro-3-(*p*-tolyl)isobenzofuran-1(3*H*)-one $C_{15}H_{11}O_2Cl$ (3a). White solid. R_f = 0.4 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = +71.50 (*c* 0.40, DCM). **Melting point** = 139–141 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 66% yield (85 mg) and 90% ee. **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 1.0 mL min^{-1}, λ = 254 nm): (*S*) = 10.21 min, (*R*) = 12.67 min. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 2.36 (s, 3H), 6.33 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.29–7.31 (m, 1H) 7.52 (dd, *J* = 8.2 Hz, *J* = 1.7 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 21.2, 82.1, 123.2, 124.1, 126.7, 126.9, 129.7, 130.1, 132.6, 139.6, 141.0, 151.4, 169.3. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_{11}ClO_2$ $[M + H]^+$ requires 259.0526; found 259.0522. $[M + H - CH_3]^+$ requires 245.0369; found 245.0360.

(*R*)-6-Chloro-3-(*p*-tolyl)isobenzofuran-1(3*H*)-one $C_{15}H_{11}O_2Cl$ (3b). White solid. R_f = 0.4 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = −4.07 (*c* 0.59, DCM). **Melting point** = 121–124 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 63% yield (82 mg) and 92% ee. **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 0.8 mL min^{-1}, λ = 254 nm): (*S*) = 11.36 min, (*R*) = 14.89 min. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 2.35 (s, 3H), 6.35 (s, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 1.7 Hz, 1H), 7.60 (dd, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H), 7.91 (d, *J* = 1.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 21.2, 82.6, 124.1, 125.4, 127.0, 127.5, 129.7, 132.7, 134.5, 135.6, 139.6, 147.9, 169.0. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_{11}ClO_2$: $[M + H]^+$ requires 259.0526; found 259.0527. $[M + H - CH_3]^+$ requires 245.0369; found 245.0371.

(*R*)-7-Chloro-3-(*p*-tolyl)isobenzofuran-1(3*H*)-one $C_{15}H_{11}O_2Cl$ (3c). White solid. R_f = 0.3 (hexane/EtOAc 85 : 15). $[\alpha]_D^{20}$ = −109.70 (*c* 0.85, DCM). **Melting point** = 97–100 °C. Purified by column chromatography (hexane/EtOAc 85 : 15) to give the product in 70% yield (91 mg) and 87% ee. **HPLC**: (Chiralcel OD-H, hexane/i-PrOH = 85/15, flow rate = 0.8 mL min^{-1}, λ = 254 nm): (*S*) = 12.94 min, (*R*) = 17.22 min. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 2.35 (s, 3H), 6.30 (s, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.18–7.21 (m, 3H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 21.1, 81.3, 121.3, 122.2, 126.9, 129.6, 130.5, 132.8, 133.0, 135.1, 152.1, 139.5, 167.3. **HRMS (ESI$^+$)**: Calcd for $C_{15}H_{11}ClO_2$ $[M + H]^+$ requires 259.0526; found 259.0520. $[M + H - CH_3]^+$ requires 245.0369; found 245.0361.

Conflicts of interest

There are no conflicts to declare.

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