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An expedient synthesis of enantioenriched substituted (2-benzofuryl) arylcarbinols via tandem Rap–Stoermer and asymmetric transfer hydrogenation reactions

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ABSTRACT

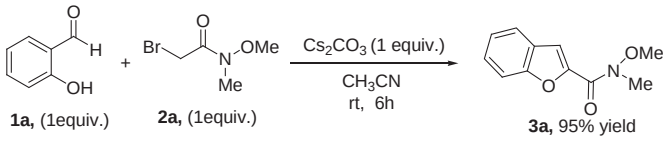
An expedient synthesis of enantioenriched substituted (benzofuran-yl)-aryl and heteroaryl carbinols, is described. A key feature of this protocol is synthesis of functionally varied benzofuran scaffolds via a Rap–Stoermer reaction/catalytic asymmetric transfer hydrogenation (ATH) using substituted salicylaldehyde and α-haloaryl, heteroaryl ketones.

1. Introduction

Benzofuran structural moiety is present in numerous biologically active natural products.[1] These privileged pharmacophore containing molecules exhibit therapeutical properties over wide range of targets.[2] Owing to their prevalence in natural products as well as pharmaceuticals have stimulated significant interest in the synthesis of benzofuran containing heterocycles. A flurry of synthetic methods has been appeared in the literature for the synthesis of benzofurans and their derivatives.[3] Among them, Rap–Stoermer reaction appears to be a versatile straightforward approach for the synthesis of functionally varied benzofuran scaffolds.[3h,4] It was observed that the racemic substituted (benzofuran-yl)-phenyl carbinols and related compounds reduced blood lipids in both laboratory animals[5] and patients.[6] This prompted us to initiate a programme for the synthesis of enantioenriched substituted (benzofuran-yl)-aryl and heteroaryl carbinols in substantial amount.

2. Results and discussion

Initially, we have evaluated base mediated reaction of salicylaldehyde **1a** with 2-bromo-*N*-methoxy-*N*-methylacetamide **2a** employing solvent,[4a] solvent-free,[4a] and microwave-assisted conditions.[4b] The desired product *N*-methoxy-*N*-methybenzofuran-2-carboxamide **3a** was obtained in poor yield. Additionally, the reaction mixture TLC analysis showed multiple spots. In Rap–Stoermer reaction, the choice of base and solvent was found to be critical; hence we screened a number of bases (NaOAc, KOAc, K_2CO_3, K_3PO_4, $CsOH\cdot H_2O$, Cs_2CO_3) and solvents (toluene, CH_2Cl_2, $CHCl_3$, DMF, EtOAc, CH_3CN), but found that Cs_2CO_3 and acetonitrile gave the desired product **3a** in 95% yield (Scheme 1). The Cs_2CO_3 and EtOAc system also resulted in the desired product **3a** but slightly less yield (90%).



1a, (1equiv.) **2a,** (1equiv.) **3a,** 95% yield

Scheme 1.

The generality and scope of this protocol were evaluated using above optimized conditions and the results are summarized in Table 1. From the Table 1, it appears that the nature of acyl substitution has no effect on coupling reaction; hence the benzofuryl derivative products were obtained with excellent yields (entry 1, 3, and 4). Remarkably, 1-mercapto-benzaldehyde **1b** with *N*-methoxy-*N*-methyl α-bromoacetamide **2a** underwent coupling and the corresponding product **3d** furnished 92% indicating the efficiency of this protocol.

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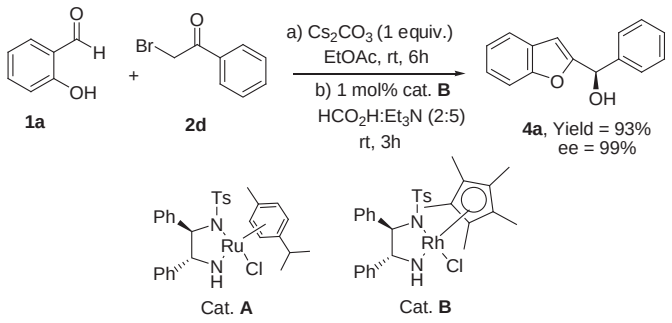
Table 1
Synthesis of various (benzofuran-yl)-*N*-substituted amide and keto derivatives as well as (benzothiophen-yl)-*N*-substituted amide[a,b,c]

Entry	Substrate	α-haloketone	Product	Yield%
1	**1a**	**2b**, X = O **2c**, X = NBoc	**3b** , X = O **3c** , X = NBoc	95 93
2	**1b**	**2a**	**3d**	92
3	**1a**	**2d**	**3e**	96
4	**1a**	**2e**	**3f**	95

[a] All reactions were carried out with substrate (1 mmol), α-haloketones (1 mmol) using base Cs_2CO_3 (1 equiv) in acetonitrile (5 mL) at ambient temperature stirring 6 h.
[b] All products were fully characterized.
[c] Unoptimized isolated yields.

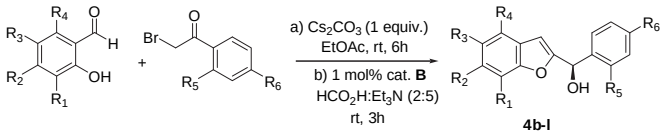
Having realized optimum conditions for synthesis of benzofuryl derivative; further, we envisaged to generate optically active carbinols via a Rap–Stoermer reaction/catalytic asymmetric transfer hydrogenation (ATH).[7] At the outset, we have selected salicylaldehyde **1a** and **2d** as test substrates and carried out the reaction under standard protocol (vide infra). After 6 h, the reaction mixture was filtered and the filtrate was evaporated. To the resulting residue, 2-propanol was added followed by 2 mol % of *R*,*R*-diamine–Ru catalyst **A** and heated to 60 °C for 10 h (Scheme 2). The anticipated product **4a** was not observed. While, the same reaction with HCOOH/Et_3N azeotropic mixture (2:5) as hydrogen source, in EtOAc at room temperature for 3 h resulted in the desired carbinol **4a** in 96% yield with 82% enantiomeric ratio. Further, enantioenrichment of **4a** was achieved under similar conditions using 1 mol % of *R*,*R*-diamine–Rh catalyst **B** in place of catalyst **A**. Fortunately, employing EtOAc as solvent in both reactions (i.e., Rap–Stoermer reaction and ATH reaction) under otherwise identical conditions furnished the required product **4a** in 93% yield with 99% ee (Scheme 2). The absolute configuration of new stereogenic center was assigned as *R* by comparison of sign of rotation {$[\alpha]_D^{23}$ −7.9° (*c* 1.0, $CHCl_3$); lit.[8] $[\alpha]_D^{23}$ +3.5° (*c* 0.041, $CHCl_3$)}, which is also in agreement with Noyori's protocol,[9] i.e., *R*,*R*-diamine–Rh induces *R*-configuration, while *S*,*S*-diamine–Rh generates *S*-configuration.



Scheme 2.

To test the generality and efficiency of this methodology, we subjected various substituted salicylaldehydes with α-bromoaryl ketones and our results are shown in Table 2.

Table 2
Synthesis of enantioenriched substituted (benzofuran-yl)-phenylcarbinols[a,b,c]



Entry	Product	R_1	R_2	R_3	R_4	R_5	R_6	Yield%	ee%
1	**4b**	OMe	H	H	H	H	H	96	99
2	**4c**	OMe	H	H	H	H	OMe	91	99
3	**4d**	OMe	H	H	H	H	Cl	87	95
4	**4e**	OMe	H	H	H	H	F	84	80
5	**4f**	OMe	H	H	H	H	OBn	92	82
6	**4g**	H	H	H	H	OMe	OMe	91	99
7	**4h**	H	OBn	H	OBn	H	H	89	85
8	**4i**	H	H	*t*-Bu	H	H	H	86	94
9	**4j**	*t*-Bu	H	*t*-Bu	H	H	H	78	90
10	**4k**	H	H	H	H	H	OH	83	92
11	**4l**	H	H	Br	H	H	H	84	88

[a] All reactions were carried out with substrate (1 mmol), α-haloketones (1.1 mmol) using base Cs_2CO_3 (1 equiv) in EtOAc (5 mL) at ambient temperature stirring 6 h using 1 mol % of *Cat. A* and HCOOH/Et_3N (2:5) in EtOAc (5 mL) at rt stirring 3 h.
[b] All products were fully characterized.
[c] Enantiomeric excess was analyzed on chiral column OD-H (250×4.6 mm, 5 μm, $UV_{254\ nm}$, hexane/2-propanol (80:20)) using recemates for comparison.

A series of sterically and electronically differentiated salicylaldehydes and α-haloaryl ketones were subjected to this protocol. We were pleased to see that *o*-methoxy (**4g**, Table 2, entry 6) and *p*-methoxy (**4c**, Table 2, entry 2) aryl keto substrates underwent coupling/reduction efficiently and led to the products 91% yield with 99% ee, respectively. *p*-Chloro aryl keto substrate (Table 2, entry 3) also reduced with same efficacy and the anticipated product **4d** was obtained with 95%ee in an acceptable yield (87%), whereas, *p*-fluoro aryl keto substrate (Table 2, entry 4) gave **4e** in moderate ee (80%) and yield. 2-Hydroxy-1-naphthal **1c** and **2d** also reacted and the corresponding product **4m** was isolated in 90% yield with 99% ee (Table 3, entry 1). The reaction of 3-methoxy

Table 3
Synthesis of enantioenriched substituted (benzofuran-yl)-aryl and heteroaryl carbinols[a,b,c]

Entry	Substrate	α-haloketone	Product[a]	Yield%	ee%
1	**1c**	**2d**	**4m**	90	99
2	**1d**	**2f**	**4n**	87	99
3	**1a**	**2f**	**4o**	92	94
4	**1a**	**2g**	**4p**	85	87

[a] All reactions were carried out with substrate (1 mmol), α-haloketones (1 mmol) using base Cs_2CO_3 (1 equiv) in EtOAc (5 mL) at ambient temperature stirring 6 h using 1 mol % of *Cat. A* and HCOOH/Et_3N (2:5) in EtOAc (5 mL) at rt stirring 3 h.
[b] All products were fully characterized.
[c] Enantiomeric excess was analyzed on chiral column OD-H (250×4.6 mm, 5 μm, $UV_{254\ nm}$, Hexane/2-propanol (80:20)) using recemates for comparison.

salicylaldehyde **1d** with 2-thienyl derivative **2f** led to the expected product **4n** with high ee and yield indicating insignificant influence of *o*-methoxy group on metal center (Table 3, entry 2). In the similar vein, α-bromofuryl ketone **2g** with **1a** also furnished the product **4p** in 85% yield and with 87% ee (Table 3, entry 4).

3. Conclusion

In conclusion, we have developed a convenient tandem protocol for the synthesis of enantioenriched substituted (benzofuran-yl)-aryl and heteroaryl-carbinols via Rap-Stoermer reaction/catalytic asymmetric transfer hydrogenation (ATH) from corresponding substituted salicylaldehyde and α-haloaryl ketones. Further work is under progress for the synthesis of structurally diversified benzofuran scaffolds using analogous protocol.

4. Experimental section

4.1. General

All reactions were conducted under inert atmosphere, if argon mentioned. Apparatus used for the reactions are perfectly oven dried. THF was distilled from sodium benzophenone ketyl, and CH_2Cl_2, CH_3CN from CaH_2. ^1H NMR spectra were recorded at 200, 300, 400, 500, and ^{13}C NMR 50, 75, 100 MHz in $CDCl_3$ solutions unless otherwise mentioned, δ in parts per million, J in hertz. IR (FT-IR) spectrometer measured as a neat film. Mass spectral data were obtained using MS (ESI), HRMS data obtained using quadrupole time-of-flight (QTOF) mass spectrometer (QSTAR XL, Applied Biosystems MDS Sciex, Foster City, USA). Optical rotations are measured on a Horiba rectangular 20 polarimeter. HPLC was carried on a Shimadzu LC-10AT vp dual pump system. Column chromatography was carried out on silica gel, grade 60–120, and 100–200 mesh.

4.2. Typical experimental procedure for preparation of benzofuran and benzothiophene derivatives

To a stirred solution of bromo compound(1.0 mmol) in CH_3CN (10 mL) was added Cs_2CO_3 (1.0 mmol) under N_2 atmosphere, after stirred the reaction mixture for 10 min the aldehyde (1.0 mmol) was added, and the resulting reaction mixture was stirred for 6 h at room temperature. Filtered the reaction mixture through a pad of Celite and the filtrate was concentrated under reduced pressure, and the crude residue was purified by silica gel column chromatography.

*4.2.1. N-Methoxy-N-methylbenzofuran-2-carboxamide (**3a**).* R_f (20% EtOAc/Hex) 0.45; ^1H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J=7.8 Hz, 1H, ArH), 7.51 (d, J=8.2 Hz, 1H, ArH), 7.40 (s, 1H, ArH), 7.34 (t, J=7.3 Hz, 1H, ArH), 7.20 (t, J=7.3 Hz, 1H, ArH), 3.78 (s, 3H, OMe), 3.34 (s, 3H, NMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 154.7, 146.4, 127.4, 127.1, 123.4, 122.6, 113.7, 112.2, 61.4, 33.2; MS (ESI) m/z 206 $(M+H)^+$; HRMS (ESI) m/z 206.0815 (calcd for $C_{11}H_{12}NO_3$: 206.0817); IR (neat): 2935, 1647, 1552, 1417, 1184, 983, 744 cm^{-1}.

*4.2.2. N-Methoxy-N-methylbenzo[b]thiophene-2-carboxamide (**3b**).* R_f (30% EtOAc/Hex) 0.40; ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J=7.9 Hz, 1H, ArH), 7.48 (d, J=8.3, 1H, ArH), 7.38 (dd, J=1.1, 7.1 Hz, 1H, ArH), 7.34 (s, 1H, ArH), 7.27 (t, J=7.1 Hz, 1H, ArH), 3.89–3.83 (m, 4H, OCH_2), 3.75 (t, J=4.9 Hz, 4H, NCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 154.6, 148.7, 126.5, 123.6, 122.2, 112.4, 111.8, 66.9; MS (ESI) m/z 232 $(M+H)^+$; HRMS (ESI) m/z 232.0980 (calcd for $C_{13}H_{14}NO_3$: 232.0973); IR (neat): 2987, 2867, 1668, 1600, 1433, 1243, 1113, 1028, 765 cm^{-1}.

*4.2.3. tert-Butyl 4-(benzofuran-2-carbonyl) piperazine-1-carboxylate (**3c**).* R_f (30% EtOAc/Hex) 0.35; ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J=7.5 Hz, 1H, ArH), 7.48 (d, J=8.3, 1H, ArH), 7.39 (m, 1H, ArH), 7.34 (s, 1H, ArH), 7.28 (m, 1H, ArH), 3.87–3.78 (m, 4H, $BocNCH_2$), 3.56–3.52 (m, 4H, NCH_2), 1.48 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 154.6, 148.8, 126.5, 123.6, 122.2, 112.5, 111.7, 80.3, 43.8, 43.5, 28.3; MS (ESI) m/z 331 $(M+H)^+$; IR (neat): 2975, 2863, 1691, 1563, 1411, 1006, 742 cm^{-1}.

*4.2.4. N-Methoxy-N-methylbenzo[b]thiophene-2-carboxamide (**3d**).* R_f(20% EtOAc/Hex) 0.55; ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H, ArH), 7.84 (dd, J=7.8, 17.5 Hz, 2H, ArH), 7.41–7.34 (m, 2H, ArH), 3.83 (s, 3H, OMe), 3.41 (s, 3H, NMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 142.5, 137.9, 133.1, 131.2, 126.4, 125.1, 124.5, 122.2, 61.7, 33.1; MS (ESI) m/z 222 $(M+H)^+$; HRMS (ESI) m/z 222.0578 (calcd for $C_{11}H_{12}NO_2S$: 222.0588); IR (neat): 2938, 1680, 1629, 1383, 1176, 1001, 754 cm^{-1}.

*4.2.5. Benzofuran-2-yl(phenyl)methanone (**3e**).* R_f (10% EtOAc/Hex) 0.50; ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J=8.1 Hz, 2H, ArH), 7.70 (d, J=7.9 Hz, 1H, ArH), 7.61 (t, J=8.1 Hz, 2H, ArH), 7.53 (s, 1H, ArH), 7.54–7.45 (m, 3H, ArH), 7.29 (dd, J=7.3, 15.1 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.4, 155.7, 152.2, 137.1, 132.8, 128.7, 128.2, 127.0, 124.0, 123.3, 116.5, 112.5; MS (ESI) m/z 223 $(M+H)^+$; HRMS (ESI) m/z 223.0753 (calcd for $C_{15}H_{11}O_2$: 223.0759); IR (neat): 3140, 3056, 1641, 1543, 1329, 1215, 970, 744, 692 cm^{-1}.

4.3. Typical experimental procedure for preparation of enantioenriched carbinols

To a stirred solution of bromo compound (1.0 mmol) in EtOAc (5 mL) was added Cs_2CO_3 (1.0 mmol) under N_2 atmosphere. After stirred the reaction mixture for 10 min, salicylaldehyde (1.0 mmol) was added and the resulting reaction mixture was stirred at room temperature. After 6 h, the reaction mixture was filtered through a pad of Celite and the filtrate was transferred to a round bottom flask under N_2 atmosphere. To this reaction mixture *Cat. B* (1 mol %)[10] was added followed by NEt_3/HCOOH (5:2) azeotropic mixture (0.2 mL). The resulting reaction mixture was stirred for 3 h at room temperature and then filtered through a small pad silica gel, the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography.

*4.3.1. (R)-Benzofuran-2-yl(phenyl)methanol (**4a**).* The crude residue was purified by silica gel column chromatography eluting with 10% EtOAc in Hexane afforded the compound **4a** (0.52 g, 93%) as a yellowish solid, mp 54–56 °C, $[\alpha]_D^{23}$ −7.9 (*c* 1.0, $CHCl_3$); R_f (10% EtOAc/Hex) 0.40; ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.42 (m, 3H, ArH), 7.41–7.30 (m, 4H, ArH), 7.24–7.12 (m, 2H, ArH), 6.46 (s, 1H,=CH), 5.90 (s, 1H, CHOH), 2.40 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 154.9, 140.2, 128.6, 128.4, 126.8, 124.3, 122.8, 121.1, 111.3, 104.0, 70.6; MS (ESI) m/z 247 $(M+Na)^+$; HRMS (ESI) m/z 247.0745 (calcd for $C_{15}H_{12}NaO_2$: 247.0734); IR (neat): 3404, 3028, 2933, 1607, 1498, 1307, 1239, 1017, 798 cm^{-1}.

*4.3.2. (R)-(7-Methoxybenzofuran-2-yl)(phenyl)methanol (**4b**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 80/20) to give **4b** (768 mg, 96% yield). $[\alpha]_D^{23}$ +8.1 (*c* 2.2, $CHCl_3$); R_f (20% EtOAc/Hex) 0.40; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50–7.43 (m, 2H, ArH), 7.39–7.29 (m, 2H, ArH), 7.24 (s, 1H, ArH), 7.07–7.03 (m, 1H, ArH), 6.71 (dd, J=2.2, 6.4 Hz, 1H, ArH), 6.40 (s, 1H,=CH), 5.91 (s, 1H, CHOH), 3.97 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 145.2, 144.8, 140.2, 128.6, 128.5, 128.3, 126.8, 123.5, 113.7, 106.4, 104.3, 70.5, 56.0; MS (ESI) m/z 277 $(M+Na)^+$; HRMS (ESI) m/z 277.0852 (calcd for $C_{16}H_{14}NaO_3$: 277.0840); IR (neat): 3433, 3022, 2924, 1602, 1498, 1309, 1173, 1017, 765 cm^{-1}.

*4.3.3. (R)-(7-Methoxybenzofuran-2-yl)(4-methoxyphenyl)methanol (**4c**).* The crude residue was purified by column chromatography on

silica gel (hexanes/EtOAc: 75/25) to give **4c** (1.14 g, 91% yield). $[\alpha]_D^{23}$ +6.9 (*c* 1.5, $CHCl_3$); R_f (30% EtOAc/Hex) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34(d, *J*=8.49 Hz, 2H, ArH), 7.08–7.01(m, 2H, ArH), 6.84 (d, *J*=8.6 Hz, 2H, ArH), 6.69 (dd, *J*=2.2, 6.4 Hz, 1H, ArH), 6.40 (s, 1H,=CH), 5.84 (s, 1H, CHOH), 3.95 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.65 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 159.2, 145.3, 144.3, 132.4, 129.1, 128.2, 123.5, 114.0, 113.5, 106.4, 104.2, 70.1, 55.9, 55.2; MS (ESI) *m*/*z* 307 $(M+Na)^+$; HRMS (ESI) *m*/*z* 307.0960 (calcd for $C_{17}H_{16}NaO_4$: 307.0946); IR (neat): 3418, 2932, 2841, 1612, 1513, 1248, 1031, 732 cm^{-1}.

*4.3.4. (R)-(4-Chlorophenyl)(7-methoxybenzofuran-2-yl)methanol (**4d**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 85/15) to give **4d** (800 mg, 87% yield). $[\alpha]_D^{23}$ +10.5 (*c* 4.0, $CHCl_3$); R_f (15% EtOAc/Hex) 0.35; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, *J*=8.4 Hz, 2H, ArH), 7.33 (d, *J*=8.4 Hz, 2H, ArH), 7.26 (d, *J*=7.7 Hz, 1H, ArH), 6.73 (dd, *J*=1.7, 7.1 Hz, 1H, ArH), 6.40 (s, 1H,=CH), 5.90 (s, 1H, CHOH), 3.97 (s, 3H, OMe), 2.59 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 145.3, 144.2, 138.6, 133.8, 129.5, 128.6, 128.0, 126.7, 123.5, 113.4, 106.5, 104.4, 69.6, 55.8; MS (ESI) *m*/*z* 311 $(M+Na)^+$; HRMS (ESI) *m*/*z* 311.0459 (calcd for $C_{16}H_{13}NaO_3Cl$: 295.0746); IR (neat): 3367, 2936, 2842, 1592, 1490, 1270, 1091, 779 cm^{-1}.

*4.3.5. (R)-(4-Fluorophenyl)(7-methoxybenzofuran-2-yl)methanol (**4e**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 85/15) to give **4e** (730 mg, 84% yield). $[\alpha]_D^{23}$ −3.8 (*c* 3.0, $CHCl_3$); R_f (20% EtOAc/Hex) 0.35; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (dd, *J*=5.4, 8.4 Hz, 2H, ArH), 7.06–6.91 (m, 4H, ArH), 6.67 (dd, *J*=1.3, 7.3 Hz, 1H, ArH), 6.32 (s, 1H,=CH), 5.81 (s, 1H, CHOH), 3.87 (s, 3H, OMe), 3.52 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1, 160.8, 158.6, 145.1, 136.0, 135.9, 129.5, 128.6, 128.4, 123.5, 115.4, 115.1, 113.4, 106.4, 104.2, 69.7, 55.8; MS (ESI) *m*/*z* 295 $(M+Na)^+$; HRMS (ESI) *m*/*z* 295.0756 (calcd for $C_{16}H_{13}NaO_3F$: 295.0746); IR (neat): 3388, 2936, 2844, 1599, 1500, 1222, 1094, 730 cm^{-1}.

*4.3.6. (R)-(4-(Benzyloxy)phenyl)(7-methoxybenzofuran-2-yl)methanol (**4f**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 80/20) to give **4f** (1.05 g, 92% yield). $[\alpha]_D^{23}$ +5.3 (*c* 1.5, $CHCl_3$); R_f(30% EtOAc/Hex) 0.35; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.24 (m, 15H, Ar), 7.05–7.02 (m, 2H, ArH), 6.93 (d, *J*=8.6 Hz, 2H, ArH), 6.71 (dd, *J*=2.4, 6.4 Hz, 1H, ArH), 6.42 (s, 1H,=CH), 5.86 (s, 1H, CHOH), 5.05 (s, 2H, OCH_2), 3.98 (s, 3H, OMe), 2.38 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 158.8, 145.3, 144.2, 136.9, 132.6, 129.9, 128.5, 128.2, 127.9, 127.4, 123.4, 114.8, 113.4, 106.2, 104.0, 70.0, 69.9, 55.8; MS (ESI) *m*/*z* 383 $(M+Na)^+$; HRMS (ESI) *m*/*z* 383.1266 (calcd for $C_{23}H_{20}NaO_4$: 383.1259); IR (neat): 3409, 3034, 2933, 1609, 1502, 1309, 1237, 1173, 1017, 784 cm^{-1}.

*4.3.7. (R)-Benzofuran-2-yl(2,4-dimethoxyphenyl)methanol (**4g**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 75/25) to give **4g** (1.42 g, 91% yield); R_f (20% EtOAc/Hex) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.36 (m, 3H, ArH), 7.22–7.11 (m, 2H, ArH), 6.55–6.46 (m, 1H, ArH), 6.44 (s, 2H, ArH), 6.05 (s, 1H, CHOH), 3.83 (s, 3H, OMe), 3.80 (s, 3H, OMe), 2.81 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 157.7, 156.3, 156.2, 129.1, 127.6, 125.1, 124.7, 123.3, 120.9, 111.5, 110.9, 105.0, 100.6, 66.7, 55.6, 55.4; MS (ESI) *m*/*z* 307 $(M+Na)^+$; HRMS (ESI) *m*/*z* 307.0956 (calcd for $C_{17}H_{16}NaO_4$: 307.0946); IR (neat): 3565, 2932, 2841, 1609, 1459, 1209, 1034, 750 cm^{-1}.

*4.3.8. (R)-(4,6-Bis(benzyloxy)benzofuran-2-yl)(phenyl)methanol (**4h**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 70/30) to give **4h** (580 mg, 89% yield). $[\alpha]_D^{23}$ −6.7 (*c* 2.3, $CHCl_3$); R_f (35% EtOAc/Hex) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.26 (m, 15H, ArH), 6.59 (s, 1H, ArH), 6.48 (s, 1H, ArH), 6.36 (s, 1H,=CH), 5.80 (s, 1H, CHOH), 5.05 (s, 2H, OCH_2), 4.98 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 156.7, 156.0, 152.6, 140.3, 136.7, 128.4, 128.0, 127.5, 127.4, 126.7, 101.8, 96.0, 89.8, 70.5, 70.4, 70.1; MS (ESI) *m*/*z* 459 $(M+Na)^+$; HRMS (ESI) *m*/*z* 459.1588 (calcd for $C_{29}H_{24}NaO_4$: 459.1572); IR (neat): 3442, 3032, 2927, 2325, 1615, 1498, 1154, 1030, 738 cm^{-1}.

*4.3.9. (R)-(5-tert-Butylbenzofuran-2-yl)(phenyl)methanol (**4i**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 90/10) to give **4i** (675 mg, 86% yield); R_f (10% EtOAc/Hex) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.40 (m, 3H, ArH), 7.36–7.24 (m, 5H, ArH), 6.41 (s, 1H,=CH), 5.85 (s, 1H, CHOH), 2.48 (br s, 1H, OH), 1.34 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 153.0, 145.8, 140.3, 128.6, 128.3, 127.6, 126.7, 122.2, 117.2, 110.5, 104.1, 70.7, 34.6, 31.8; MS (ESI) *m*/*z* 281 $(M+H)^+$; IR (neat): 3412, 2922, 2838, 1609, 1502, 1248, 1026, 728 cm^{-1}.

*4.3.10. (R)-(5,7-Di-tert-butylbenzofuran-2-yl)(phenyl)methanol (**4j**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 90/10) to give 4j (559 mg, 78% yield). $[\alpha]_D^{23}$ −97.5 (*c* 0.4, $CHCl_3$); R_f (10% EtOAc/Hex) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.45 (m, 2H, ArH), 7.37–7.28 (m, 4H, ArH), 7.14 (d, *J*=1.8 Hz, 1H, ArH), 6.42 (s, 1H,=CH), 5.91 (d, *J*=3.7 Hz, 1H, CHOH), 2.31 (d, *J*=4.3 Hz, 1H, OH), 1.45 (s, 9H, *t*-Bu), 1.34 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 145.7, 140.7, 133.7, 128.3, 128.1, 126.8, 124.0, 122.5, 118.9, 115.1, 103.8, 70.6, 34.7, 34.3, 31.8, 29.0; MS (ESI) *m*/*z* 359 $(M+Na)^+$; IR (neat): 3415, 2924, 2833, 1605, 1499, 1027, 738 cm^{-1}.

*4.3.11. (R)-(5-Bromobenzofuran-2-yl)(phenyl)methanol (**4l**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 90/10) to give **4l** (760 mg, 95% yield). $[\alpha]_D^{23}$ −7.3 (*c* 1.5, $CHCl_3$); R_f (10% EtOAc/Hex) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J*=1.8 Hz, 1H, ArH), 7.51 (dd, *J*=1.5, 5.2 Hz, 1H, ArH), 7.46–7.31 (m, 5H, ArH), 7.29 (d, *J*=1.8 Hz, 1H, ArH), 6.42 (s, 1H,=CH), 5.84 (s, 1H, CHOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 139.9, 139.7, 129.6, 128.7, 127.1, 126.7, 123.8, 122.9, 112.7, 104.2, 103.3, 70.6; HRMS (ESI) *m*/*z* 324.9838 (calcd for $C_{15}H_{11}NaO_2Br$: 324.9840); IR (neat): 3432, 3028, 2927, 1611, 1498, 1150, 748 cm^{-1}.

*4.3.12. (R)-Naphtho[2,1-b]furan-2-yl(phenyl)methanol (**4m**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 85/15) to give **4m** (716 mg, 90% yield). $[\alpha]_D^{23}$ −10.3 (*c* 2.0, $CHCl_3$); R_f (20% EtOAc/Hex) 0.60; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, *J*=8.1 Hz, 1H, ArH), 7.85 (d, *J*=7.9 Hz, 1H, ArH), 7.68–7.61 (m, 1H, ArH), 7.55 (d, *J*=8.8 Hz, 1H, ArH), 7.51–7.45 (m, 2H, ArH), 7.40–7.23 (m, 5H, ArH), 6.92 (s, 1H,=CH), 5.97 (s, 1H, CHOH), 2.62 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 152.6, 140.4, 130.3, 128.7, 128.6, 128.4, 127.7, 126.8, 126.3, 125.3, 124.5, 123.3, 112.4, 103.2, 70.8; MS (ESI) *m*/*z* 297 $(M+Na)^+$; IR (neat): 3416, 3058, 2924, 1630, 1454, 1049, 804, 745 cm^{-1}.

*4.3.13. (S)-(7-Methoxybenzofuran-2-yl)(thiophen-2-yl)methanol (**4n**).* The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc: 85/15) to give **4n** (716 mg, 90% yield). $[\alpha]_D^{23}$ −10.3 (*c* 2.0, $CHCl_3$); R_f (20% EtOAc/Hex) 0.40; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, *J*=3.7 Hz, 1H, ArH), 7.05 (d, *J*=2.2 Hz, 1H, ArH), 7.03 (s, 1H, ArH), 7.00 (d, *J*=3.0 Hz, 1H, ArH), 6.90 (dd, *J*=3.0, 4.5 Hz, 1H, ArH), 6.69 (dd, *J*=3.7, 6.0 Hz, 1H, ArH), 6.55 (s, 1H,=CH), 6.09 (s, 1H, CHOH), 3.91 (s, 3H, OMe), 3.36 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 145.2, 143.7, 291.5, 126.6, 125.7, 125.6, 123.5, 113.5, 106.2, 104.2, 66.5, 57.0; MS (ESI) *m*/*z* 283 $(M+Na)^+$; IR (neat): 3394, 2924, 2848, 1591, 1491, 1267, 1176, 778, 703 cm^{-1}.

*4.3.14. (S)-Benzofuran-2-yl(thiophen-2-yl)methanol (**4o**).* The crude residue was purified by column chromatography on silica

gel (hexanes/EtOAc: 85/15) to give **4o** (716 mg, 90% yield). $[\alpha]_D^{23}$ −10.3 (*c* 2.0, $CHCl_3$); R_f (20% EtOAc/Hex) 0.35; ^1H NMR (200 MHz, $CDCl_3$): δ 7.45 (d, *J*=7.5 Hz, 1H, ArH), 7.38 (d, *J*=8.3 Hz, 1H, ArH), 7.24–7.13 (m, 3H, ArH), 6.99 (d, *J*=3.0 Hz, 1H, ArH), 6.92 (dd, *J*=3.7, 5.2 Hz, 1H, ArH), 6.57 (s, 1H,=CH), 6.05 (br s, 1H, CHOH), 3.28 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 155.0, 143.8, 127.9, 126.8, 125.9, 124.5, 124.1, 122.9, 111.4, 104.0, 66.7; MS (ESI) *m*/*z* 253 $(M+Na)^+$; IR (neat): 3388, 2923, 2856, 1601, 1453, 1230, 1171, 748, 703 cm^{-1}.

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Supplementary data

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