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Highly asymmetric synthesis of (+)-corsifuran A. Elucidation of the electronic requirements in the Ruthenium–NHC catalyzed hydrogenation of benzofurans

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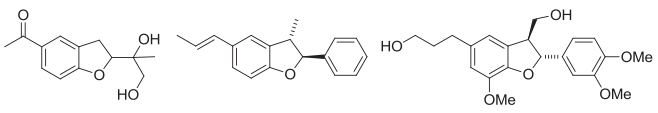
ABSTRACT

A short and efficient synthesis of *ent*-corsifuran A by a highly asymmetric hydrogenation of a benzofuran precursor is reported. In addition, the electronic influence of the substituents on the asymmetric hydrogenation of benzofurans is provided. Whereas the hydrogenation of electron-deficient benzofurans was achieved under very mild conditions, the presence of electron-donating groups in the benzofuran required harsher reaction conditions for achieving full conversion to the 2,3-dihydrobenzofuran.

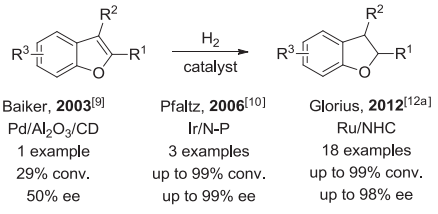
1. Introduction

Heterocyclic compounds are commonly present in a wide range of natural products and biologically active building blocks.[1] Among them, oxygenated metabolites have attracted the attention of many chemists due to their potent activities and structural diversity. In particular, the 2,3-dihydrobenzofuran skeleton represents the core of many interesting compounds.[2] Remarkable examples of this class are the antileukaemic agent megapodiol,[3] (+)-conocarpan, which exhibits insecticidal, antifungal and antitrypanosomal activity,[4] as well as the antitumoral neo-lignane (2*R*,3*S*)-3,4′-di-*O*-methylcedrusin (Scheme 1).[5]



Scheme 1. Selection of natural products containing 2,3-dihydrobenzofuran rings.

In the literature numerous reports can be found regarding the synthesis of 2,3-dihydrobenzofurans.[6] One might think that asymmetric hydrogenation from the corresponding substituted benzofuran should be the most straightforward route for their synthesis. However, the asymmetric hydrogenation of *O*-heterocycles has proven to be more troublesome than the one of *N*-heterocycles.[7] Often, partial decomposition of the furan ring to 2-ethylcyclohexanol and β-cyclohexylethyl alcohol is observed.[8] Nevertheless, a few examples can be found regarding the asymmetric hydrogenation of benzofurans: The heterogeneous reduction of 2-benzofuran carboxylic acid from Baiker and co-workers using a combination of Pd/Al_2O_3 with cinchonidine derivatives,[9] the highly enantioselective hydrogenation of some benzofurans with pyridine–phosphinite iridium complexes by Pfaltz and co-workers,[10] and our recent application of a ruthenium-*N*-heterocyclic carbene[11] (NHC)-complex with high levels of enantioselectivity and broad substrate scope (Scheme 2).[12]



Scheme 2. Asymmetric hydrogenation of benzofurans.

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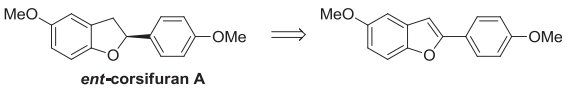
2. Results and discussion

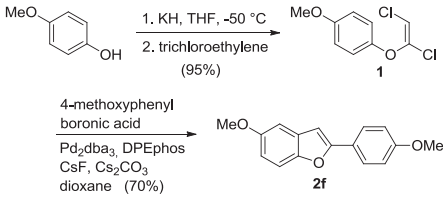
Encouraged by our previous results, we decided to test the efficiency of our developed ruthenium–NHC complex in the synthesis of a natural product. Therefore, we chose as target molecule corsifuran A,[13] a metabolite derived from stilbenoid precursors and isolated from the Mediterranean liverwort *Corsinia coriandrina*, which can be readily obtained from its benzofuran precursor (Scheme 3).



***ent*-corsifuran A**

Scheme 3. Proposed synthetic approach for corsifuran A.

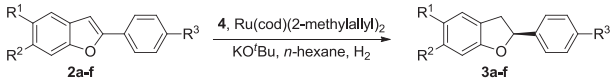
Corsifuran A has been synthesized twice in racemic form[13,14] and once in asymmetric fashion, but with very low to moderate yield.[15] For our approach, we prepared the benzofuran precursor **2f** by a literature known procedure starting from very simple and commercially available 4-methoxyphenol, trichloroethylene and 4-methoxyphenylboronic acid (Scheme 4).[16]



Scheme 4. Synthesis of benzofuran **2f**.

To our surprise, when we applied our general reaction conditions for the asymmetric hydrogenation of benzofurans to **2f**, we obtained (+)-corsifuran A (**3f**)[17] with low conversion (38%, Table 1). This observation is in sharp contrast to our previous work, where we observed that alkyl substituents on the carbocyclic ring of the benzofuran do not affect the reactivity. Thus, when 6-(*tert*-butyl)-2-phenylbenzofuran (**2b**) was submitted to hydrogenation conditions, the corresponding 2,3-dihydrobenzofuran **3b** was obtained with no change of the enantiomeric ratio or reactivity compared to the 2-phenylbenzofuran **2a**.

Table 1
Hydrogenation of some arylated benzofurans[a]

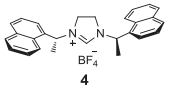


Substrate	R^1	R^2	R^3	T [°C]	$p(H_2)$ [bar]	Yield [%][b]	e.r.[c]
2a	H	H	H	25	10	>99	99:1
2b	H	*t*-Bu	H	25	10	>99	99:1
2c	H	H	F	25	10	>99	99:1
2d	H	H	CF_3	25	10	>99	98.5:1.5
2e	H	H	OMe	40	60	>99	99:1
2f	OMe	H	OMe	40	60	38	99:1

[a] General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.015 mmol), KO^{t}Bu (0.045 mmol) and **4** (0.03 mmol) were stirred at 70 °C in *n*-hexane (2 mL) for 12 h, after which it was added to substrate (**2a**–**f**, 0.30 mmol), and hydrogenation was performed under conditions shown in each case for 16 h.

[b] Given are isolated yields.

[c] e.r. was determined by HPLC on a chiral stationary phase.



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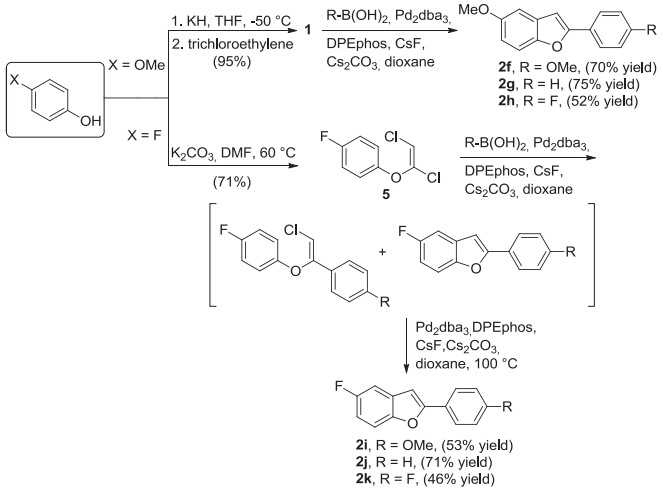
On the other hand, we also found out that the electronic properties of the 2-phenyl-substituted benzofurans have a significant influence on the reactivity. When the phenyl ring contained electron-withdrawing groups, such us fluorine (**2c**) or trifluoromethyl (**2d**) in *para* position, the reaction proceeded smoothly at 10 bar of hydrogen pressure and at room temperature, with full conversion and very good enantiomeric ratio. However, when the phenyl ring bears electron-donating substituents, like a methoxy group (**2e**), low conversion to the desired product was observed under the mild standard conditions, and 60 bar of hydrogen and 40 °C were required to obtain full conversion, maintaining an excellent enantiomeric ratio of 99:1 (Table 1). Therefore, the presence of the methoxy group in the carbocyclic ring on the precursor for our synthesis of corsifuran A (**2f**) also played a key role on the reactivity towards the hydrogenation process.

At this point, in the context of our current studies related to the characterization and mechanistic behaviour of these ruthenium–NHC complexes for the hydrogenation of arenes, we decided to study the influence of the electronic properties of the substituent on the benzofuran on reactivity. The ruthenium catalyst formed from NHC precursor **4**[18] already showed its versatility by reducing substituted quinoxalines and benzofurans with high levels of regio- and enantioselectivity. Thus, insight into the electronic requirements of the substrate could help us to design a more reactive or selective second generation catalyst or to find other suitable substrates to be reduced.

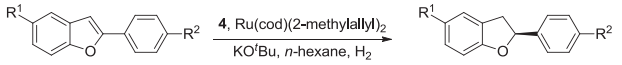
First of all, in order to determine, if the lower reactivity of the electron-donating substituted benzofurans is caused by deactivation of the catalyst, we run competition experiments. Therefore, we mixed 2-(*p*-methoxyphenyl) benzofuran (**2e**) and 2-(*p*-trifluoromethylphenyl) benzofuran (**2d**) in a 1:1 ratio and submitted to hydrogenation at 10 bar of hydrogen pressure and room temperature. After 3 h the reaction was stopped and showed 89% conversion of **2d** and almost only starting material recovered for **2e** (8% conversion).[19] Interestingly, when the reaction was carried out at 60 bar of hydrogen and 40 °C, after 3 h both compounds were reduced completely to the corresponding 2,3-dihydrobenzofuran. This indicates that the presence of the less reactive benzofuran **2e** is not affecting the activity of the catalyst towards **2d** and the need of harsher conditions for the electron-donating substituted benzofurans might be explained in terms of the high electron density of the substrate. To probe this hypothesis, we synthesized a series of benzofurans varying systematically the substitution pattern with fluorine, methoxy group and hydrogen to test them under hydrogenation conditions. All compounds were obtained using the methodology described for **2f** in Scheme 1, but starting from 4-methoxyphenol or 4-fluorophenol and the corresponding boronic acid in each case. It must be mentioned that in the case of the 4-fluorophenol a different procedure was required to form the corresponding vinyl ether, because of the lower nucleophilicity of the potassium phenolate in the formation of dichlorovinyl ether **5**. Subsequent palladium catalyzed reaction gave a mixture of the Suzuki coupling product and benzofuran, which was submitted again to the same reaction conditions to give the desired product, albeit in low yields (Scheme 5).

Once synthesized, we tested the different substituted benzofurans under our recently established hydrogenation conditions. As we can conclude from the results shown in Table 2, the activity of our ruthenium catalyst can be influenced by both factors, the electronic properties of the phenyl substituent and the ones from the group in the carbocyclic ring of the benzofuran. As we discussed before, our catalyst was able to smoothly reduce 2-phenyl benzofurans containing electron-withdrawing groups at 10 bar of hydrogen pressure and room temperature (entry 1–2). However, electron-donating substituted benzofurans required harsher conditions (60 bar of hydrogen pressure, 40°, entry 3). When we removed electron density from the benzofuran by adding a fluorine atom to the carbocyclic ring, the reactivity maintained the same (entries 4–6) but resulted on a slight decrease on the enantiomeric



Scheme 5. Synthesis of benzofurans **2f**–**k**.

Table 2
Hydrogenation of different substituted benzofurans[a]



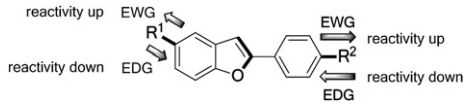
Entry	Substrate	R^1	R^2	Conditions	Yield[c] [%]	e.r.[d]
1	**2c**	H	F	A	>99	99:1
2	**2a**	H	H	A	>99	99:1
3	**2e**	H	OMe	B	>99	99:1
4	**2k**	F	F	A	>99	98:2
5	**2i**	F	H	A	>99	98:2
6	**2j**	F	OMe	B	>99	96:4
7	**2h**	OMe	F	A	>99	99:1
8	**2g**	OMe	H	B	>99	99:1
9	**2f**	OMe	OMe	B[b]	80	99:1

[a] General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.015 mmol), KO*t*-Bu (0.045 mmol) and **4** (0.03 mmol) were stirred at 70 °C in *n*-hexane (2 mL) for 12 h, after which it was added to substrate (0.30 mmol), and hydrogenation was performed under conditions shown in each case for 16 h. **Conditions A**: 10 bar H_2, 25 °C, **Conditions B**: 60 bar H_2, 40 °C.
[b] Reaction carried out with 20% catalyst loading.
[c] Given are isolated yields.
[d] e.r. was determined by HPLC on a chiral stationary phase.

ratio. Interestingly, when we tested more electron-rich substrates, which present a methoxy group on the carbocyclic ring of the benzofuran, only the 2-(4-fluorophenyl)-5-methoxybenzofuran (entry 7) was able to react at 10 bar of hydrogen pressure and room temperature. In the latter case, the corsifuran A precursor (entry 9) required the use of 20% catalyst loading to obtain 80% conversion to the enantiomer of the desired natural product, showing the strong influence of both methoxy substituents.

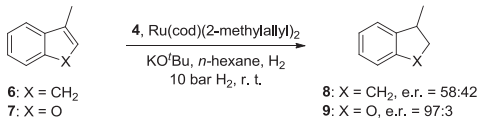
With these results, we can conclude that the hydrogenation is favoured for electron-deficient substrates. The electronic properties of the phenyl ring have a stronger influence on the reactivity than the ones on the carbocyclic ring, if we compare entries 6 and 7, where the 2-(4-fluorophenyl)-5-methoxybenzofuran (entry 7) reacted at 10 bar and room temperature, whereas the opposite substitution pattern (5-fluoro-2-(4-methoxyphenyl)benzofuran) (entry 6) required harsher conditions. Thus, the presence of electron-donating (EDG) or electron-withdrawing groups (EWG) affect the reactivity of the benzofuran, as shown in Scheme 6.

Trying to go further in our understanding of the catalyst activity, we studied the influence of the oxygen of the benzofuran ring on the hydrogenation process. Therefore, we prepared 3-methylindene (**6**) to compare the reactivity with the 3-methylbenzofuran (**7**). Interestingly, when we performed the hydrogenation of 3-



Scheme 6. Influence of the electronic properties of the substituents on the asymmetric hydrogenation of benzofurans.

methyl–indene at 10 bar of hydrogen and room temperature, we obtained full conversion like in the case of 3-methylbenzofuran, but with a dramatic drop of the enantiomeric ratio from 93:7 to 58:42 (Scheme 7). Therefore, the presence of the oxygen seems crucial for high levels of asymmetric induction, but not for the reactivity. A coordination of the oxygen to the ruthenium catalyst might be beneficial to obtain high levels of enantioselectivity.



Scheme 7. Hydrogenation of 3-methyl-indene and 3-methylbenzofuran.

3. Conclusion

In conclusion, we show a short and efficient synthesis of *ent*-corsifuran A, the unnatural (+)-enantiomer, by a highly asymmetric hydrogenation of a benzofuran precursor. Also, a study on the electronic influence of the substituents on the asymmetric hydrogenation of benzofurans is provided. Whereas the hydrogenation of electron-deficient benzofurans was achieved under very mild conditions, the presence of electron-donating groups in the benzofuran required harsher reaction conditions to achieve full conversion to the 2,3-dihydrobenzofuran. We also found out that the oxygen atom of the benzofuran is required to reach high levels of enantioselectivity on the reaction. Further studies focussed on catalyst characterization, application on the synthesis of other interesting natural products and hydrogenation of other challenging substrates are ongoing.

4. Experimental

4.1. General

Unless otherwise noted, all reactions were carried out under an atmosphere of argon in flame-dried glassware. The solvents used were purified by distillation over the drying agents indicated in parentheses and were transferred under argon: *n*-hexane (CaH_2), THF (Na-benzophenone), CH_2Cl_2 (CaH_2). Commercially available chemicals were obtained from Acros Organics, Aldrich Chemical Co., Strem Chemicals, Alfa Aesar, ABCR and TCI Europe and used as received unless otherwise stated. NMR spectra were recorded on a Bruker ARX-300, AV-300 or AV-400 MHz ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or in the solvent indicated. Chemical shifts (δ) are quoted in parts per million downfield of tetramethylsilane and were referenced to the residual chloroform and $CDCl_3$, ^1H NMR: 7.26 ppm, ^{13}C NMR: 77.00 ppm, respectively. Coupling constants (J) are quoted in Hertz. Infrared spectra were recorded on a Varian Associated FTIR 3100 Excalibur with ATR unit. The wave numbers (ν) of recorded IR-signals are quoted in cm^{-1}. ESI mass spectra were recorded on a Bruker Daltonics MicroTof. Specific rotation was measured on a Perkin Elmer 341 polarimeter at 20 °C using a quartz glass cell (100 mm path length). HPLC analysis was performed on an Agilent Technologies 1200 series HPLC with a Daicel Chemical Industries LTD chiral AD-

H and OJ-H column. Analytical thin layer chromatography was performed on Polygram SIL G/UV254 plates. Visualization was accomplished with short wave UV light and/or $KMnO_4$ staining solution followed by gentle heating. Flash column chromatography was performed on Merck silica gel (40–63 mesh) by using standard laboratory techniques. Solvents used for flash column chromatography were distilled before use. GC/MS Spectra were recorded with an Agilent Technologies 7890A GC-system with Agilent 5975C VL MSD or 5975 inert Mass Selective Detector and a HP-5MS column (0.25 mm×30 m, Film: 0.25 μm); Method 50_40: T_0=50 °C, T_1=290 °C, ramp=40 °C/min, t=4 min.

4.2. Preparation of the benzofurans 2a–k

*4.2.1. 2-Phenylbenzofuran (**2a**).* Following a modified procedure by Suzuki et al.,[20] in a dry Schlenk benzofuran-2-boronic acid (200 mg, 1.23 mmol), iodobenzene (126 μL, 1.12 mmol), $Pd(OAc)_2$ (24 mg, 0.11 mmol) and Na_2CO_3 (237 mg, 2.24 mmol) were placed under Argon, and acetone (6.6 mL) and water (7.7 mL) were added. The reaction mixture was stirred at room temperature until full consumption of the starting material was indicated by TLC (8 h). The reaction mixture was quenched with water and extracted with dichloromethane (3×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated to dryness in vacuo. The crude compound was purified by flash chromatography (silica, pentane/EtOAc 98:2) to afford 2-phenylbenzofuran (**2a**) as a white solid with 97% yield (211 mg, 1.08 mmol); R_f (pentane): 0.24; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.90 (dd, J=8.4, 1.2 Hz, 2H), 7.64–7.59 (m, 1H), 7.56 (dd, J=8.0, 0.7 Hz, 1H), 7.52–7.44 (m, 2H), 7.42–7.35 (m, 1H), 7.29 (m, 2H), 7.06 (d, J=0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=156.1, 155.0, 130.6, 129.4, 128.9, 128.7, 125.1, 124.4, 123.1, 121.0, 111.3, 101.4; ESI-MS: calculated for $[C_{14}H_{10}O+H]^+$: 195.0804, found: 195.0809; GC–MS: R_t (50_40): 8.8 min; EI: 82 (13), 97 (11), 165 (53), 194 (100), 195 (16); ATR-FTIR (cm^{-1}): 3043, 1683, 1560, 1485, 1455, 1441, 1258, 1207, 1169, 1101, 1038, 1020, 918, 882, 806, 765, 740, 689, 613.

*4.2.2. 2-Phenyl-6-(tert-butyl)benzofuran (**2b**).* To 3-(*tert*-butyl) phenol (1.75 g, 11.7 mmol) in an ammonium hydroxide solution (25%, 60 mL), KI (9.71 g, 58.5 mmol) and I_2 (3.55 g, 14.0 mmol) dissolved in water (30 mL) were added. The mixture was stirred at rt for 14 h, after which it was heated to 90 °C for 2 h. After cooling to room temperature the mixture was extracted with CH_2Cl_2 (5×20 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After purification by flash chromatography 2-iodo-5-(*tert*-butyl)phenol was obtained in 78% yield (2.51 g, 9.10 mmol). R_f (pentane/EtOAc 94:6): 0.2; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.55 (d, J=8.4 Hz, 1H), 7.04 (d, J=2.2 Hz, 1H), 6.73 (dd, J=8.4, 2.2 Hz, 1H), 5.23 (m, 1H), 1.29 (s, 9H); the spectral data is consistent with the literature.[21] Following a modified procedure by Kotschy et al.[22] phenylacetylene (0.66 mL, 6.00 mmol) was added to a screw capped tube equipped with 2-iodo-5-(*tert*-butyl)phenol (828 mg, 3.00 mmol), $(Pd(OAc)_2$ (34.0 mg, 0.15 mmol), P(*t*-Bu)$_3$·HBF_4 (65.0 mg, 0.23 mmol), CuI (29.0 mg, 0.15 mmol) and diisopropylamine (3.6 mL, 26 mmol) in THF (10 mL). The reaction mixture was stirred for 21 h at 40 °C. The brown suspension was filtered over a plug of silica and washed with CH_2Cl_2. After concentration the crude product was purified by flash column chromatography (pentane) to obtain **2b** as white crystalline powder (293 mg, 1.17 mmol, 39%). R_f (pentane): 0.23; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.94–7.88 (m, 2H), 7.64–7.62 (m, 1H), 7.55 (d, J=8.2 Hz, 1H), 7.53–7.45 (m, 2H), 7.42–7.34 (m, 2H), 7.03 (d, J=0.9 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 155.8, 155.4, 148.4, 130.8, 128.9, 128.4, 126.7, 124.9, 120.9, 120.3, 108.0, 101.2, 35.1, 31.8; ESI-MS: calculated $[C_{15}H_{12}O+Na]^+$: 231.0780, found: 231.0779; GC–MS: R_t (50_40): 8.8 min; EI: 77 (13), 89 (13), 131 (47), 178 (25), 179 (13), 207 (100), 208 (89), 209 (14); ATR-FTIR (cm^{-1}): 2961, 1604, 1487, 1448, 1361, 1290, 1238, 1175, 1076, 1021, 934, 915, 826, 763, 691, 660.

*4.2.3. 2-(4-Fluorophenyl)benzofuran (**2c**).* Compound **2c** was synthesized following the procedure described for the preparation of 2-phenylbenzofuran (**2a**) using 1-fluoro-4-iodobenzene (129 μL, 1.12 mmol). 2-(4-fluorophenyl) benzofuran (**2c**) was obtained as a white solid in 93% yield (221 mg, 1.04 mmol). R_f (pentane): 0.57; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.75 (m, 2H), 7.49 (m, 1H), 7.43 (m, 1H), 7.23–7.12 (m, 2H), 7.05 (m, 2H), 6.87 (d, J=0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.7, 161.3, 155.1, 155.0, 129.3, 126.9, 126.9, 126.8, 124.4, 123.1, 121.0, 116.2, 115.9, 111.3, 101.1, 101.1; GC–MS: R_t (50_40): 8.7 min; EI: 183 (57), 212 (100), 213 (15); ATR-FTIR (cm^{-1}): 3608, 3053, 1608, 1570, 1499, 1450, 1410, 1351, 1224, 1156, 1098, 1030, 1009, 926, 884, 839, 801, 749, 625.

*4.2.4. 2-(4-(Trifluoromethyl) phenyl)benzofuran (**2d**).* Compound **2d** was synthesized following the procedure described for the preparation of 2-phenylbenzofuran (**2a**) using 1-iodo-4-(trifluoromethyl) benzene (165 μL, 1.12 mmol). 2-(4-(Trifluoromethyl) phenyl) benzofuran (**2d**) was obtained as a white solid in 82% yield (241 mg, 0.92 mmol); R_f (pentane): 0.44; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.96 (m, 2H), 7.70 (d, J=8.2 Hz, 2H), 7.57 (m, 2H), 7.37–7.24 (m, 2H), 7.14 (d, J=0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 155.3, 154.3, 133.8, 130.4, 130.0, 128.9, 126.0, 125.9, 125.8, 125.2, 125.1, 123.4, 122.4, 121.5, 111.5, 103.4; GC–MS: R_t (50_40): 8.6 min; EI: 165 (28), 262 (100), 263 (17); ATR-FTIR (cm^{-1}): 3066, 1615, 1453, 1414, 1324, 1257, 1188, 1164, 1106, 1067, 1030, 1007, 920, 885, 840, 812, 748, 688, 592.

*4.2.5. 2-(4-Methoxyphenyl)benzofuran (**2e**).* Compound **2e** was synthesized following the procedure described for the preparation of 2-phenylbenzofuran (**2a**) using 4-iodoanisole (262 mg, 1.12 mmol). 2-(4-Methoxyphenyl) benzofuran (**2e**) was obtained as a white solid in 98% yield (246 mg, 1.09 mmol); R_f (pentane): 0.80; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.72 (m, 2H), 7.43 (m, 2H), 7.15 (m, 2H), 6.89 (m, 2H), 6.80 (d, J=0.8 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.1, 156.17, 154.8, 129.6, 126.5, 123.9, 123.5, 123.0, 120.7, 114.4, 111.1, 99.8, 55.5; ESI-MS: calculated $[C_{15}H_{12}O_2+H]^+$: 225.0910, found: 225.0916; GC–MS: R_t (50_40): 9.6 min; EI: 165 (21), 178 (16), 208 (100), 209 (15); ATR-FTIR (cm^{-1}): 3045, 2962, 2835, 1606, 1566, 1502, 1446, 1301, 1244, 1172, 1112, 1022, 925, 835, 799, 779, 741, 620, 518.

*4.2.6. 5-Methoxy-2-(4-methoxyphenyl)benzofuran (**2f**).* KH (820 mg, 10.5 mmol) was suspended in THF (40 mL) and 4-methoxyphenol (10 mmol, 1.2 g) dissolved in THF (12 mL) was added dropwise. The mixture was allowed to stir for 1 h. The suspension was cooled to −50 °C and then trichloroethylene (15 mmol, 1.3 mL) was added dropwise, after which the reaction was warmed to room temperature and stirred overnight. The reaction was diluted with petroleum ether and quenched with ice-cold water. The layers were separated and the aqueous phase was extracted twice with petroleum ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated to dryness in vacuo. The crude compound was purified by flash chromatography (silica, pentane/EtOAc 95:5) to afford (*E*)-1-((1,2-dichlorovinyl)oxy)-4-methoxybenzene (**1**) as a yellow oil in 95% yield (2.1 g, 9.5 mmol); R_f (pentane/EtOAc 99:1)= 0.38; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.02 (m, 2H), 6.90 (m, 2H), 5.89 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 156.7, 147.7, 140.8, 118.6, 114.8, 102.6, 55.7; the spectral data is consistent with the literature.[16] 4-Methoxyphenyl boronic acid (319 mg, 2.1 mmol), $Pd_2(dba)_3$ (45 mg, 0.05 mmol), DPEphos (0.1 mmol, 53,8 mg), CsF (911 mg, 6 mmol) and Cs_2CO_3 (1.9 g, 6 mmol) were placed in a dry Schlenk and purged with argon for 15 min. Then, a solution of **1** in 1,4-dioxane (5 mL) was added and the solution was stirred at 100 °C

overnight. The cooled reaction mixture was quenched with water and extracted with dichloromethane. The aqueous layer was extracted twice more with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated to dryness in vacuo. The crude compound was purified by flash chromatography (silica, pentane) to afford (**2f**) as a pale yellow solid in 70% yield (356 mg, 1.4 mmol) R_f (pentane/EtOAc 99:1): 0.30; ^{1}H NMR (300 MHz, CDCl3): δ=7.77 (m, 2H), 7.39 (d, J=8.9 Hz, 1H), 7.02 (d, J=2.5 Hz, 1H), 6.97 (m, 2H), 6.86 (dd, J=8.9, 2.6 Hz, 1H), 6.83 (d, J=0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.1, 156.9, 156.1, 149.8, 130.2, 126.5, 123.5, 114.3, 112.4, 111.5, 103.3, 99.9, 56.0, 55.5; GC–MS: R_t (50_40): 10.3 min; EI: 127 (8), 139 (12), 168 (13), 211 (14), 239 (51), 254 (100), 255 (17); ATR-FTIR (cm^{-1}): 3002, 2944, 2841, 1605, 1593, 1505, 1469, 1438, 1312, 1248, 1206, 1180, 1143, 1113, 1024, 938, 913, 831, 789, 734, 634, 525.

*4.2.7. 5-Methoxy-2-phenylbenzofuran (**2g**).* Compound **2g** was synthesized from the 1,2-dichloro vinyl ether **1** following the procedure described for the preparation of 5-methoxy-2-(4-methoxyphenyl) benzofuran (**2f**) using phenyl boronic acid (256 mg, 2.1 mmol). 5-methoxy-2-phenylbenzofuran (**2g**) was obtained as a white solid in 75% yield (336 mg, 1.5 mmol); R_f (pentane/EtOAc 99:1): 0.46; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.87 (m, 2H), 7.47–7.43 (m, 3H), 7.38 (m, 1H), 7.06 (d, J=2.6 Hz, 1H), 6.97 (d, J=0.9 Hz, 1H), 6.92 (dd, J=8.9, 2.6 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 156.8, 156.1, 150.0, 130.6, 129.9, 128.9, 128.6, 124.9, 113.1, 111.7, 103.4, 101.6, 55.9; GC–MS: R_t (50_40): 9.5 min; EI: 127 (9), 152 (33), 153 (22), 181 (17), 224 (100), 225 (16); ATR-FTIR (cm^{-1}): 3004, 2940, 2835, 1603, 1471, 1447, 1431, 1338, 1304, 1276, 1203, 1144, 1072, 1030, 915, 843, 812, 803, 759, 737, 683, 659, 619, 539.

*4.2.8. 2-(4-Fluorophenyl)-5-methoxybenzofuran (**2h**).* Compound **2h** was synthesized from the 1,2-dichloro vinyl ether **1** following the procedure described for the preparation of 5-methoxy-2-(4-methoxyphenyl) benzofuran (**2f**) using 4-fluorophenyl boronic acid (294 mg, 2.1 mmol). 2-(4-fluorophenyl)-5-methoxybenzofuran (**2h**) was obtained as a white solid in 52% yield (252 mg, 1.04 mmol); R_f (pentane/EtOAc 99:1): 0.42; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.83–7.78 (m, 2H), 7.41 (d, J=8.9 Hz, 1H), 7.13 (dd, J=8.8, 8.8 Hz, 2H), 7.03 (d, J=2.5 Hz, 1H), 6.92 (d, J=2.6 Hz, 1H), 6.90 (m, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.6, 161.3, 156.2, 155.9, 149.9, 129.8, 126.9, 126.9, 126.8, 126.7, 116.1, 115.8, 113.1, 111.7, 103.4, 101.3, 101.3, 55.9; GC–MS: R_t (50_40): 9.4 min; EI: 155 (10), 170 (31), 171 (28), 199 (18), 206 (18), 242 (100), 243 (18); ATR-FTIR (cm^{-1}): 3112, 3017, 2962, 2838, 1603, 1589, 1504, 1459, 1419, 1346, 1248, 1174, 1126, 1039, 1021, 920, 867, 830, 791, 634, 599.

*4.2.9. 5-Fluoro-2-(4-methoxyphenyl)benzofuran (**2i**).* K_2CO_3 (4.1 g, 30 mmol) and 4-fluorophenol (10 mmol, 1.1 g) were suspended in dry DMF (7.5 mL) in a round bottomed flask and heated at 60 °C. The mixture was allowed to stir for 30 min and then trichloroethylene (30 mmol, 2.6 mL) was added dropwise. The reaction was heated overnight at 70 °C. The cooled down mixture was portioned between water and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated to dryness in vacuo. The crude compound was purified by flash chromatography (silica, pentane/EtOAc 98:2) to afford (*E*)-1-((1,2-dichlorovinyl) oxy)-4-fluorobenzene (**5**) as a yellow oil in 71% yield (1.4 g, 7.1 mmol); R_f (pentane/EtOAc 99:1): 0.80; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.10–7.02 (m, 4H), 5.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 161.2, 158.0, 149.9, 149.8, 140.3, 118.8, 118.7, 116.7, 116.3, 103.7; GC–MS: R_t (50_40): 8.7 min; EI: 75 (37), 83 (19), 95 (68), 130 (22), 143 (100), 144 (8), 145 (32), 206 (44), 208 (28), 209 (5); ATR-FTIR (cm^{-1}): 3105, 1631, 1498, 1273, 1182, 1069, 1012, 832, 805, 733, 692, 612, 510. 4-methoxyphenyl boronic acid (319 mg, 2.1 mmol), $Pd_2(dba)_3$ (45 mg, 0.05 mmol), DPEphos (0.1 mmol, 53,8 mg), CsF (911 mg, 6 mmol) and Cs_2CO_3 (1.9 g, 6 mmol) were placed in a dry Schlenk and purged with argon for 15 min. Then, a solution of **5** in 1,4-dioxane (5 mL) was added and the solution was stirred at 100 °C overnight. The cooled reaction mixture was quenched with water and extracted with dichloromethane. The aqueous layer was extracted twice more with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated to dryness in vacuo. The crude compound was purified by flash chromatography (silica, pentane) to afford (**2i**) as a white solid in 53% yield (257 mg, 1.1 mmol) R_f (pentane/EtOAc 99:1): 0.54; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.78 (m, 2H), 7.41 (dd, J=8.9, 4.1 Hz, 1H), 7.20 (dd, J=8.6, 2.6 Hz, 1H), 7.00–6.94 (m, 3H), 6.84 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.9, 160.2, 157.8, 157.7, 150.8, 130.3, 130.2, 126.5, 122.9, 114.3, 111.5, 111.4, 111.3, 111.0, 106.2, 105.8, 99.8, 99.7, 55.3; GC–MS: R_t (50_40): 9.5 min; EI: 133 (15), 170 (26), 199 (42), 207 (39), 227 (68), 242 (100), 243 (16); ATR-FTIR (cm^{-1}): 3066, 1619, 1591, 1461, 1442, 1344, 1255, 1208, 1188, 1127, 1073, 1041, 1022, 951, 915, 866, 800, 761, 736, 688, 662, 601.

*4.2.10. 5-Fluoro-2-phenylbenzofuran (**2j**).* Compound **2j** was synthesized from the 1,2-dichloro vinyl ether **5** following the procedure described for the preparation of 5-fluoro-2-(4-methoxyphenyl) benzofuran (**2i**) using phenyl boronic acid (256 mg, 2.1 mmol). 5-fluoro-2-phenylbenzofuran (**2j**) was obtained as a white solid in 71% yield (301 mg, 1.42 mmol); R_f (pentane/EtOAc 99:1): 0.82; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.77 (m, 2H), 7.40–7.26 (m, 4H), 7.17–7.13 (m, 1H), 6.95–6.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.8, 157.7, 157.6, 151.1, 130.1, 130.0, 129.9, 128.8, 128.8, 124.9, 112.0, 111.8, 111.7, 111.6, 106.5, 106.1, 101.4, 101.3; GC–MS: R_t (50_40): 8.8 min; EI: 183 (48), 207 (9), 212 (100), 213 (10); ATR-FTIR (cm^{-1}): 3066, 1619, 1591, 1461, 1442, 1344, 1255, 1208, 1188, 1127, 1073, 1041, 1022, 951, 915, 866, 800, 761, 736, 688, 662, 601.

*4.2.11. 5-Fluoro-2-(4-fluorophenyl)benzofuran (**2k**).* Compound **2k** was synthesized from the 1,2-dichloro vinyl ether **5** following the procedure described for the preparation of 5-fluoro-2-(4-fluorophenyl)benzofuran (**2i**) using 4-fluorophenyl boronic acid (294 mg, 2.1 mmol). 5-fluoro-2-(4-fluorophenyl)benzofuran (**2k**) was obtained as a white solid in 46% yield (212 mg, 0.92 mmol); R_f (pentane/EtOAc 99:1)=0.51; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.83–7.79 (m, 2H), 7.44–7.40 (m, 1H), 7.22 (dd, J=8.5, 2.6 Hz, 1H), 7.14 (m, 2H), 7.00 (ddd, J=9.1, 9.1, 2.6 Hz, 1H), 6.89 (d, J=0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.4, 161.9, 160.7, 158.3, 156.9, 151.2, 130.2, 130.0, 127.0, 126.9, 126.9, 126.6, 126.5, 116.2, 115.9, 111.9, 111.8, 106.6, 106.3, 101.3, 101.2, 101.2, 101.2; GC–MS: R_t (50_40): 8.7 min; EI: 181 (8), 201 (56), 230 (100), 231 (16); ATR-FTIR (cm^{-1}): 3066, 1615, 1453, 1414, 1324, 1257, 1188, 1164, 1106, 1067, 1030, 1007, 920, 885, 840, 812, 748, 688, 592.

*4.2.12. 3-Methyl-indene (**6**).* Following the procedure by Adamczyk and Netzel,[23] to a solution of methylmagnesium bromide (5 mL of a 3 M solution, 15 mmol) in 25 mL of dry THF at 0 °C under argon atmosphere was added 2-indanone (1.4 g, 10 mmol) dissolved in THF over a period of 20 min. The reaction was stirred at room temperature overnight, quenched with 25 mL of 15% aqueous HCl solution at -78 °C, and stirred for additional 8 h to complete the dehydration of the intermediate alcohol. The solution was extracted with diethyl ether, washed with brine and dried with anhydrous $MgSO_4$. The crude product was purified by flash chromatography (silica, pentane) to afford **6** as a colourless oil in 83% yield (1.08 g, 8.3 mmol); R_f (pentane)=0.72; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.53 (dd, J=7.3, 0.9 Hz, 1H), 7.44–7.37 (m, 2H), 7.31–7.26 (m, 1H), 6.28 (ddd, J=1.8, 1.8, 1.8 Hz, 1H), 3.39 (dd, J=2.2, 2.2 Hz, 2H), 2.25 (ddd, J=2.2, 2.2 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 146.2,

114.4, 140.0, 128.8, 126.1, 124.5, 123.7, 118.9, 37.8, 13.2. The spectral data is consistent with the literature.[23]

*4.2.13. 3-Methylbenzofuran (**7**).* Following the procedure of Nielek and Lesiak,[24] 2-hydroxyacetophenone (1.20 mL, 10.0 mmol), ethylbromoacetate (1.55 mL, 14.0 mmol) and K_2CO_3 (5.53 g, 40.0 mmol) were suspended in dry acetone (10 mL) and the mixture was refluxed for 60 h. On completion, the reaction mixture was cooled to rt and filtered. The filter cake was washed with EtOAc and the filtrate was concentrated under reduced pressure to afford the desired product. The crude product was used without further purification. To a solution of the obtained ethyl ester (1 equiv) in EtOH (4 mL) was added NaOH (3 N, 6 mL) and the resulting mixture was stirred for 2 h. Reaction progress was monitored by TLC. On completion, EtOH was removed in vacuo, the residual aqueous mixture was cooled to 0 °C and treated with conc. HCl until pH 1–2. The resulting precipitate was collected by filtration and washed with water to afford on drying the desired product. The crude product was used without further purification. A suspension of the carboxylic acid (472 mg, 2.40 mmol) and NaOAc (1.20 g, 14.6 mmol) in Ac_2O (1.37 mL, 14.6 mmol) was warmed to reflux and stirred for 18 h. On completion, the reaction mixture was cooled to rt and poured onto ice. The aqueous suspension was extracted with Et_2O (3×) and the combined organic phases dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the compound was purified by column chromatography (pentane) yielding 3-methylbenzofurane (**7**) (225 mg, 1.70 mmol, 17% over 3 steps) as a colourless, volatile liquid. R_f (pentane)=0.42; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.55–7.51 (m, 1H), 7.48–7.43 (m, 1H), 7.41–7.39 (m, 1H), 2.25 (d, J=1.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 155.3, 141.5, 128.9, 124.2, 122.3, 119.5, 115.7, 111.4, 8.1; GC–MS: R_t (50_40): 7.9 min; EI: 51 (15), 77 (18), 78 (11), 103 (17), 131 (100), 132 (67); ATR-FTIR (cm^{-1}): 3059, 2949, 2923, 2861, 2362, 1587, 1453, 1281, 1187, 1089, 856, 743, 631, 537.

4.3. Asymmetric hydrogenation of benzofurans 2a–k

*4.3.1. General procedure for the asymmetric hydrogenation of benzofurans **2a**–**k**.* To a flame-dried screw capped tube equipped with a magnetic stir bar was added [Ru(cod)(2-methylallyl)$_2$] (4.8 mg, 0.015 mmol), imidazolium salt **4** (14.1 mg, 0.03 mmol) and dry KO^{t}Bu (5.0 mg, 0.045 mmol) in a glove box. The mixture was suspended in hexane (2 mL) and stirred at 70 °C for 12 h under argon. Then the mixture was transferred under argon to a glass vial containing benzofuran (0.3 mmol) and a magnetic stirring bar. The glass vial was placed in a 150 mL stainless-steel reactor. The autoclave was carefully pressurized/depressurized with hydrogen gas three times before a pressure of 10 bar was adjusted. The hydrogenation was performed at 25 °C for a predetermined period of time. After the autoclave was depressurized carefully, the crude mixture was filtered through a plug of silica using a mixture of pentane:EtOAc (9:1) yielding analytically pure compound. The enantiomeric ratio of all compounds was determined by HPLC on a chiral stationary phase.

4.3.2. Characterization of the products.

*4.3.2.1. (S)-2-Phenyl-2,3-dihydrobenzofuran (**3a**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h. The product was obtained as colourless oil (58.8 mg, 0.3 mmol, quantitative); 99:1 e.r $[\alpha]_D^{24}$=−40.0 (c 1.00, CH_2Cl_2), R_F (pentane): 0.81; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.29–7.17 (m, 5H), 7.05 (m, 2H), 6.75 (m, 2H), 5.62 (dd, J=9.2, 8.5 Hz, 1H), 3.49 (dd, J=15.6, 9.5 Hz, 1H), 3.08 (dd, J=15.6, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.8, 142.1, 128.8, 128.3, 128.1, 126.6, 125.9, 124.9, 120.8, 109.5, 84.1, 38.5; GC–MS: R_t (50_40): 8.6 min; EI: 51 (14), 63 (13), 77 (13), 82 (10), 89 (19), 115 (10), 118 (10), 152 (18), 165 (35), 167 (22), 177 (12), 178 (12), 179 (15), 181 (15), 194 (24), 195 (60), 196 (100), 197 (16); ATR-FTIR (cm^{-1}): 3033, 2915, 1596, 1478, 1461, 1365, 1327, 1308, 1229, 1172, 1099, 1077, 1015, 973, 930, 861, 746, 696, 601, 534; HPLC (AD-H, elute: hexane/*i*-PrOH=97/3, detector: 230 nm, flowrate: 1 mL/min), $t_{1(major)}$=5.0 min, $t_{2(minor)}$=5.5 min.

*4.3.2.2. (S)-6-(tert-Butyl)-2-phenyl-2,3-dihydrobenzofuran (**3b**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h. The product was obtained as colourless oil (75.7 mg, 0.30 mmol, quantitative). 99:1 e.r. $[\alpha]_D^{24}$=−88.7 (c 0.53, CH_2Cl_2), R_F (pentane): 0.62; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.49–7.35 (m, 5H), 7.16 (dd, J=7.4, 0.9 Hz, 1H), 6.97 (m, 2H), 5.79 (t, J=8.9 Hz, 1H), 3.63 (dd, J=15.5, 9.4 Hz, 1H), 3.23 (ddd, J=15.5, 8.5, 0.9 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.9, 152.3, 142.2, 128.7, 128.1, 125.9, 124.3, 123.6, 117.7, 106.8, 84.5, 38.3, 34.9, 31.6; GC–MS: R_t (50_40): 9.3 min; EI: 91 (16), 237 (100), 238 (18), 252 (63), 253 (13); ATR-FTIR (cm^{-1}): 3031, 2961, 2906, 2867, 1621, 1589, 1493, 1457, 1423, 1363, 1309, 1261, 1221, 1181, 1125, 1077, 1026, 976, 940, 861, 811, 758, 697, 645, 602, 541; HPLC (AD-H, elute: hexane/*i*-PrOH=99/1, detector: 230 nm, flowrate: 1.0 mL/min), $t_{1(major)}$=5.7 min, $t_{2(minor)}$=7.7 min.

*4.3.2.3. (S)-2-(4-Fluorophenyl)-2,3-dihydrobenzofuran (**3c**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h. The product was obtained as white solid (64.2 mg, 0.30 mmol, quantitative). 99:1 e.r. $[\alpha]_D^{24}$=−32.4 (c 1.00, CH_2Cl_2), R_F (pentane/EtOAc 98:2): 0.65; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40 (m, 2H), 7.20 (m, 2H), 7.07 (m, 2H), 6.91 (m, 2H), 5.75 (dd, J=8.8, 8.7 Hz, 1H), 3.64 (dd, J=15.6, 9.4 Hz, 1H), 3.20 (dd, J=15.6, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.2, 160.9, 159.5, 137.9, 137.8, 128.4, 127.7, 127.6, 126.4, 125.0, 120.9, 115.8, 115.5, 109.5, 83.5, 38.6; GC–MS: R_t (50_40): 8.4 min; EI: 165 (20), 170 (8), 183 (20), 185 (14), 195 (10), 199 (13), 213 (45), 214 (100), 215 (15); ATR-FTIR (cm^{-1}): 3047, 2917, 1605, 1511, 1479, 1460, 1328, 1222, 1157, 1096, 1015, 976, 920, 862, 832, 746, 719, 623, 587, 540; HPLC (OJ-H, elute: hexane/*i*-PrOH=95/5, detector: 230 nm, flowrate: 1 mL/min), $t_{1(minor)}$=9.8 min, $t_{2(major)}$=18.4 min.

*4.3.2.4. (S)-2-(4-(Trifluoromethyl)phenyl)-2,3-dihydrobenzofuran (**3d**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h. The product was obtained as white solid (79.3 mg, 0.30 mmol, quantitative). 98.5:1.5 e.r. $[\alpha]_D^{24}$=−67.7 (c 1.00, CH_2Cl_2), R_F (pentane/EtOAc 98:2): 0.64; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.65 (d, J=8.2 Hz, 2H), 7.53 (d, J=8.3 Hz, 2H), 7.22 (m, 2H), 6.93 (m, 2H), 5.83 (dd, J=8.8, 8.6 Hz, 1H), 3.71 (dd, J=15.6, 9.6 Hz, 1H), 3.19 (dd, J=15.6, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.5, 146.3, 146.3, 130.9, 130.4, 130.0, 129.6, 128.5, 126.0, 125.9, 125.8, 125.7, 125.1, 122.4, 121.2, 109.6, 83.1, 38.6; GC–MS: R_t (50_40): 8.4 min; EI: 51 (12), 63 (13), 89 (17), 165 (40), 166 (12), 167 (17), 195 (21), 262 (23), 263 (23), 264 (100), 265 (16); ATR-FTIR (cm^{-1}): 2925, 1618, 1597, 1481, 1460, 1419, 1325, 1234, 1160, 1105, 1067, 1014, 985, 930, 862, 838, 794, 757, 676, 602, 570, 527; HPLC (AD-H, elute: hexane/*i*-PrOH=99/1, detector: 230 nm, flowrate: 0.5 mL/min), $t_{1(minor)}$=11.8 min, $t_{2(major)}$=12.6 min.

*4.3.2.5. (S)-2-(4-Methoxyphenyl)-2,3-dihydrobenzofuran (**3e**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h (in this case, hydrogenation was performed at 60 bar (H_2) and 40 °C). The product was obtained as white solid (67.9 mg, 0.30 mmol, quantitative). 99:1 e.r. $[\alpha]_D^{24}$=+15.6 (c 1.00, CH_2Cl_2), R_F (pentane/EtOAc 98:2): 0.69; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.18 (m, 2H), 7.01 (m, 2H), 6.75–6.68 (m, 4H), 5.54 (dd, J=8.9, 8.9 Hz, 1H), 3.63 (s, 3H), 3.41 (dd, J=15.7, 9.3 Hz, 1H), 3.05 (dd, J=15.7, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.6, 159.5, 133.9, 128.3, 127.4, 126.8, 124.9, 120.6, 114.1, 109.4, 84.1, 55.4, 38.3;

ESI-MS: calculated $[C_{15}H_{14}O_2+Na]^+$: 249.0886, found: 249.0884; GC–MS: R_t (50_40): 9.3 min; EI: 153 (10), 165 (24), 211 (24), 225 (12), 226 (100), 227 (17); ATR-FTIR (cm^{-1}): 3049, 3016, 2971, 2910, 2845, 1609, 1514, 1477, 1455, 1328, 1301, 1283, 1247, 1228, 1187, 1173, 1102, 1027, 1012, 1102, 1027, 1012, 973, 926, 863, 824, 741, 712, 659, 625, 586; HPLC (AD-H, elute: hexane/*i*-PrOH=99/1, detector: 230 nm, flowrate: 0.5 mL/min), $t_{1(minor)}$=26.6 min, $t_{2(major)}$=28.7 min.

*4.3.2.6. (S)-5-Methoxy-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran: (+)-Corsifuran A (**3f**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h (in this case, hydrogenation was performed at 60 bar (H_2) and 40 °C using 20% catalyst loading). The product was obtained as white solid (61.5 mg, 0.24 mmol, 80% yield). 99:1 e.r. $[\alpha]_D^{24}$=+12.7 (c 0.55, $CHCl_3$), R_F (pentane/EtOAc 99:1): 0.21; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.34 (m, 2H), 6.91–6.88 (m, 2H), 6.79–6.70 (m, 3H), 5.68 (dd, *J*=8.8, 8.8 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.55 (dd, *J*=15.8, 9.2 Hz, 1H), 3.24–3.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.4, 154.2, 153.7, 133.9, 127.7, 127.3, 113.9, 112.9, 111.1, 109.2, 84.2, 56.0, 55.3, 38.7; GC–MS: R_t (50_40): 9.9 min; EI: 152 (8), 241 (9), 254 (11), 256 (100), 257 (18); ATR-FTIR (cm^{-1}); ATR-FTIR (cm^{-1}): 3304, 2966, 2840, 1610, 1586, 1505, 1470, 1436, 1307, 1246, 1206, 1180, 1142, 1112, 1018, 941, 916, 831, 789, 758, 737, 634; HPLC (AD-H, elute: hexane/*i*-PrOH=97/3, detector: 230 nm, flowrate: 1.0 mL/min), $t_{1(major)}$=15.5 min, $t_{2(minor)}$=17.9 min.

*4.3.2.7. (S)-5-Methoxy-2-phenyl-2,3-dihydrobenzofuran (**3g**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h (in this case, hydrogenation was performed at 60 bar (H_2) and 40 °C). The product was obtained as white solid (67.8 mg, 0.30 mmol, quantitative). 99:1 e.r. $[\alpha]_D^{24}$=–12.9 (c 1.00, CH_2Cl_2), R_F (pentane/EtOAc 99:1): 0.32; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.45–7.33 (m, 5H), 6.82 (m, 2H), 6.73 (dd, *J*=8.7, 2.6 Hz, 1H), 5.76 (dd, *J*=8.7, 8.7 Hz, 1H), 3.79 (s, 3H), 3.64 (dd, *J*=15.7, 9.3 Hz, 1H), 3.22 (dd, *J*=15.7, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 154.4, 153.9, 142.1, 128.7, 128.1, 127.6, 125.9, 113.1, 111.3, 109.3, 84.3, 56.1, 38.9; GC–MS: R_t (50_40): 9.2 min; EI: 152 (10), 165 (39), 225 (14), 226 (100), 227 (17); ATR-FTIR (cm^{-1}): 3038, 2995, 2958, 2917, 2834, 1603, 1485, 1469, 1434, 1363, 1306, 1251, 1230, 1196, 1184, 1133, 1113, 1080, 1034, 1002, 961, 936, 916, 874, 806, 764, 735, 702, 627, 566, 546, 482; HPLC (AD-H, elute: hexane/*i*-PrOH=99/1, detector: 230 nm, flowrate: 0.5 mL/min), $t_{1(minor)}$=26.6 min, $t_{2(major)}$=28.7 min.

*4.3.2.8. (S)-2-(4-Fluorophenyl)-5-methoxy-2,3-dihydrobenzofuran (**3h**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h. The product was obtained as white solid (73.2 mg, 0.30 mmol, quantitative). 99:1 e.r. $[\alpha]_D^{24}$=–15.9 (c 1.00, CH_2Cl_2), R_F (pentane/EtOAc 99:1): 0.29; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.18 (m, 2H), 7.01 (m, 2H), 6.75–6.68 (m, 4H), 5.54 (dd, *J*=8.9, 8.9 Hz, 1H), 3.63 (s, 3H), 3.41 (dd, *J*=15.7, 9.3 Hz, 1H), 3.05 (dd, *J*=15.7, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 163.8, 161.3, 154.5, 153.7, 137.9, 127.7, 127.7, 127.6, 127.6, 127.4, 115.7, 115.5, 113.2, 111.3, 109.3, 83.7, 56.1, 39.0; GC–MS: R_t (50_40): 9.1 min; EI: 109 (10), 183 (37), 244 (100), 245 (16); ATR-FTIR (cm^{-1}): 3000, 2956, 2848, 1603, 1511, 1481, 1224, 1202, 1132, 1032, 973, 929, 879, 836, 807, 767, 737, 625, 566, 542, 523; HPLC (AD-H, elute: hexane/*i*-PrOH=99/1, detector: 210 nm, flowrate: 0.5 mL/min), $t_{1(major)}$=36.2 min, $t_{2(minor)}$=38.9 min.

*4.3.2.9. (S)-5-Fluoro-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran (**3i**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h (in this case, hydrogenation was performed at 60 bar (H_2) and 40 °C). The product was obtained as white solid (73.2 mg, 0.30 mmol, quantitative). 96:4 e.r. $[\alpha]_D^{24}$=+1.5 (c 0.65, CH_2Cl_2), R_F (pentane/EtOAc 99:1): 0.25; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.33 (m, 2H), 6.91 (m, 3H), 6.85 (m, 1H), 6.74 (dd, *J*=8.7, 4.2 Hz, 1H), 5.73 (dd, *J*=8.9, 8.9 Hz, 1H), 3.82 (s, 3H), 3.59–3.53 (m, 1H), 3.21 (ddd, *J*=15.9, 8.4, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.7, 158.8, 156.5, 155.7, 155.6, 133.6, 128.2, 128.1, 127.4, 114.4, 114.2, 114.2, 112.2, 111.9, 109.5, 109.4, 84.7, 55.4, 38.6, 38.5; GC–MS: R_t (50_40): 9.2 min; EI: 44 (36), 207 (40), 229 (17), 243 (10), 244 (100), 245 (16); ATR-FTIR (cm^{-1}): 3019, 2968, 2904, 2842, 1611, 1583, 1512, 1475, 1438, 1355, 1305, 1288, 1247, 1223, 1180, 1123, 1031, 986, 922, 871, 812, 772, 744, 711, 638, 619, 577, 555, 518; HPLC (AD-H, elute: hexane/*i*-PrOH=97/3, detector: 230 nm, flowrate: 1.0 mL/min), $t_{1(major)}$=10.8 min, $t_{2(minor)}$=11.3 min.

*4.3.2.10. (S)-5-Fluoro-2-phenyl-2,3-dihydrobenzofuran (**3j**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h (in this case, hydrogenation was performed at 60 bar (H_2) and 40 °C). The product was obtained as white solid (64.2 mg, 0.30 mmol, quantitative). 98:2 e.r. $[\alpha]_D^{24}$=–37.6 (c 0.88, CH_2Cl_2), R_F (pentane/EtOAc 99:1): 0.36; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.42–7.32 (m, 5H), 6.91–6.76 (m, 3H), 5.78 (dd, *J*=9.3, 8.3 Hz, 1H), 3.62 (dd, *J*=15.9, 9.4 Hz, 1H), 3.25–3.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.3, 156.2, 155.7, 141.7, 128.8, 128.3, 127.9, 125.8, 114.5, 114.2, 112.3, 111.9, 109.6, 109.4, 84.7, 38.7, 38.7; R_t (50_40): 8.5 min; EI: 165 (24), 183 (23), 197 (14), 199 (15), 212 (16), 213 (44), 214 (100), 215 (16); ATR-FTIR (cm^{-1}): 3062, 2924, 2850, 1738, 1618, 1482, 1456, 1439, 1368, 1328, 1315, 1255, 1221, 1193, 1154, 1121, 1094, 1077, 1024, 968, 922, 910, 872, 811, 761, 743, 698, 662, 594, 539; HPLC (AD-H, elute: hexane/*i*-PrOH=99/1, detector: 210 nm, flowrate: 0.5 mL/min), $t_{1(major)}$=17.6 min, $t_{2(minor)}$=18.9 min.

*4.3.2.11. (S)-5-Fluoro-2-(4-fluorophenyl)-2,3-dihydrobenzofuran (**3k**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h. The product was obtained as white solid (69.7 mg, 0.30 mmol, quantitative). 98:2 e.r. $[\alpha]_D^{24}$=–95.4 (c 1.00, CH_2Cl_2), R_F (pentane/EtOAc 99:1): 0.33; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40–7.35 (m, 2H), 7.07 (dd, *J*=8.7, 8.7 Hz, 2H), 6.92–6.83 (m, 2H), 6.76 (dd, *J*=8.6, 4.3 Hz, 1H), 5.75 (dd, *J*=8.8, 8.8 Hz, 1H), 3.65–3.56 (m, 1H), 3.17 (ddd, *J*=15.9, 8.3, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.3, 161.0, 159.3, 156.2, 155.5, 155.5, 137.5, 137.4, 127.8, 127.7, 127.7, 127.6, 115.9, 115.6, 114.6, 114.3, 112.3, 111.9, 109.6, 109.5, 84.1, 38.8, 38.7, 38.7; GC–MS: R_t (50_40): 8.5 min; EI: 107 (17), 183 (30), 201 (19), 230 (12), 231 (33), 232 (100), 233 (15); ATR-FTIR (cm^{-1}): 2905, 1681, 1605, 1512, 1477, 1439, 1222, 1191, 1118, 1095, 1014, 974, 921, 864, 834, 819, 778, 740, 712, 615, 541; HPLC (OD-H, elute: hexane/*i*-PrOH=97/3, detector: 230 nm, flowrate: 1.0 mL/min), $t_{1(major)}$=6.8 min, $t_{2(minor)}$=7.5 min.

*4.3.2.12. 1-Methyl-2,3-dihydroindene (**8**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h. The product was obtained as colourless oil (39.6 mg, 0.30 mmol, quantitative). 58:42 e.r. $[\alpha]_D^{24}$=–2.1 (c 0.62, CH_2Cl_2), R_F (pentane): 0.64; ^{1}H NMR (300 MHz, $CDCl_3$): 7.23–7.13 (m, 4H), 3.25–3.13 (m, 1H), 2.91–2.83 (m, 2H), 2.33–2.28 (m, 1H), 1.61–1.53 (m, 1H), 1.29 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 126.2, 124.5, 123.3, 39.5, 34.9, 31.6, 20.0; GC–MS: R_t (50_40): 7.5 min; EI: 91 (13), 115 (33), 116 (10), 117 (100), 118 (11), 131 (9), 132 (29); ATR-FTIR (cm^{-1}): 3039, 2954, 2862, 1717, 1607, 1478, 1456, 1226, 752; HPLC (OJ-H, elute: hexane/*i*-PrOH=95/5, detector: 230 nm, flowrate: 0.5 mL/min), $t_{1(minor)}$=7.6 min, $t_{2(major)}$=7.8 min.

*4.3.2.13. 3-Methyl-2,3-dihydrobenzofuran (**9**).* Following the general procedure, the hydrogenation reaction was carried out for 16 h. The product was obtained as colourless oil (40.2 mg mg, 0.30 mmol, quantitative). 97:3 e.r. $[\alpha]_D^{24}$=+10.2 (c 0.50, CH_2Cl_2), R_F (pentane): 0.76; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.16 (m, 2H), 6.84 (ddd, *J*=7.4, 7.4, 0.9 Hz, 1H), 6.78 (d, *J*=8.0 Hz, 1H), 4.94 (ddd, *J*=8.8,

7.7, 6.2 Hz, 1H), 3.33 (dd, J=15.4, 8.8 Hz, 1H), 2.83 (dd, J=15.4, 7.7 Hz, 1H), 1.31 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.6, 128.1, 127.1, 125.1, 120.3, 109.4, 79.6, 37.2, 21.9; GC–MS: R_t (50_40): 6.3 min; EI: 51 (11), 63 (11), 65 (11), 77 (14), 91 (100), 119 (94), 134 (64); ATR-FTIR (cm^{-1}): 2963, 2928, 2873, 1597, 1481, 1461, 1377, 1329, 1226, 1165, 1100, 1017, 966, 835, 748; HPLC (AD-H, elute: hexane/*i*-PrOH=100/0, detector: 230 nm, flowrate: 0.5 mL/min), $t_{1(minor)}$=16.6 min, $t_{2(major)}$=17.2 min.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.109.

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