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Iridium-catalyzed asymmetric hydrogenation of 2-substituted 1,4-benzodioxines

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ABSTRACT

An Ir-catalyzed asymmetric hydrogenation of 2-substituted 1,4-benzodioxines was developed for the preparation of chiral 1,4-benzodioxanes, which are present in numerous biologically active compounds and natural products. Our *tropos* biphenyl phosphine-oxazoline ligand is essential for obtaining good ee. A broad range of substrates were tolerable to the reaction conditions and gave the corresponding hydrogenation products in excellent yields and with moderate to good enantioselectivities using the Ir-complex of our *tropos* phosphine-oxazoline ligand.

1. Introduction

The 1,4-benzodioxane framework has attracted considerable interest because it is a core structural motif in a variety of biologically active compounds and natural products (Fig. 1).[1] For example, Piperoxan is an α-adrenergic blocking agent with considerable stimulating activity and is used to diagnose pheochromocytoma and also acts as an antihypertension agent.[1a] 2-Aryl-1,4-benzodioxanes are subunits of this structure and exhibit important bioactivity. Skeleton **4** belongs to a class of leuketriiene A4 hydrolase inhibitor compounds.[1b] Isovanillyl sweetening agents,[1c] which are 500 times sweeter than sucrose, also contain the 1,4-benzodioxine moiety. Numerous lignans also containing the 2-aryl-1,4-benzodioxane nucleus represent a class of natural products with cytotoxic and hepatoprotective activities.[1d-f] Therefore, reliable and efficient synthetic methodologies for the preparation of these chiral skeletons are highly desired. However, most of the present synthetic methodologies rely on the use of chiral starting materials or large amounts of chirality inducing reagents which are not efficient with regards to atom economy.[2]

It is well-known that the asymmetric catalysis of suitable substrates is an efficient approach towards the synthesis of chiral 1,4-benzodioxanes, with clear advantages with regards to structural diversity and the ability to use only amounts of a chiral source. Asymmetric allylic substitution has been utilized for the preparation of chiral 2-vinyl-1,4-benzodioxanes by several groups.[3] Recently, two newly developed enantioselective reactions for the construction of this chiral skeleton have been reported (Scheme 1).[4,5] The Cai group reported a Pd-catalyzed asymmetric desymmetrization of diols to form chiral 1,4-benzodioxanes bearing a hydroxymethyl group at the 2-position.[4] Tang et al. developed an asymmetric alkene aryloxyarylation catalyzed by a Pd/Antphos catalyst system, yielding chiral 1,4-benzodioxanes possessing tetrasubstituted carbon stereocenters.[5] However, the preparation of chiral 2-aryl-1,4-benzodioxanes using these two methodologies has not been reported using asymmetric catalysis. Asymmetric hydrogenation has attracted considerable attention since the advent of asymmetric catalysis.[6] Although Ir-catalyzed asymmetric hydrogenation was developed later than Rh and Ru-catalysis, such catalyst systems have gained popularity due to their ability to catalyze the asymmetric hydrogenation of unfunctionalized olefins.[7] Ir-catalyzed asymmetric hydrogenation

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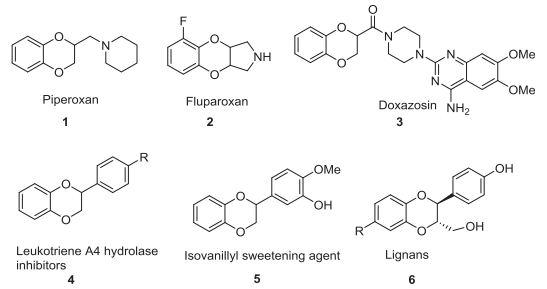
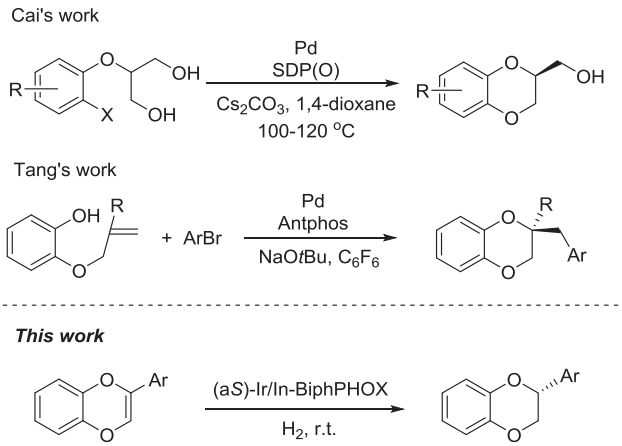


Fig. 1. Example compounds containing the 1,4-benzodioxane fragment.



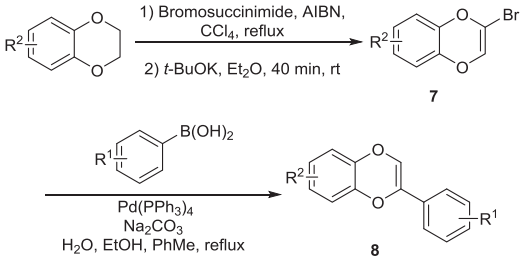
Scheme 1. Synthesis of chiral 1,4-benzodioxane via asymmetric catalysis.

of cyclic compounds has become an efficient protocol for the synthesis of chiral cyclic compounds.[6i,8] The Ir-catalyzed asymmetric hydrogenation of 2-substituted 1,4-benzodioxines provides an attractive route to the preparation of chiral 2-aryl-1,4-benzodioxanes. Herein, we report such a methodology using an Ir-complex of our chiral axially-unfixed biphenyl phosphine-oxazoline ligand (Scheme 1).[9]

2. Results and discussion

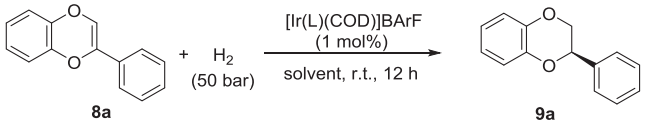
2-Substituted 1,4-benzodioxines could be prepared easily in 3 steps from 1,4-benzodioxane.[10] After a photo-induced dibromination and an elimination reaction, compound **7** could be prepared in large quantities. Cross-coupling of **7** with a series of arylboronic acids gave different 2-substituted 1,4-benzodioxines in moderate to high yields (Scheme 2).

Our study began with the asymmetric hydrogenation of 2-phenyl 1,4-benzodioxines **8a** (Table 1). Firstly, different Ir-complexes of different phosphine-oxazoline ligands were screened (entries 1–8).



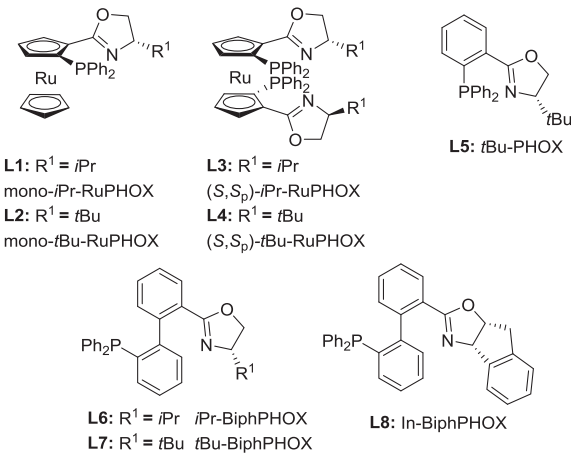
Scheme 2. Synthesis of substrates.

Table 1
Reaction optimization.[a]



Entry	Solvent	Ligand	Yield (%)[b]	ee (%)[c]
1	DCM	**L1**	trace	–
2	DCM	**L2**	>99	−82
3	DCM	**L3**	17	−10
4	DCM	**L4**	>99	−83
5	DCM	**L5**	>99	5
6	DCM	**L6**	91	81
7	DCM	**L7**	>99	70
8	DCM	**L8**	>99	90
9	DCE	**L8**	>99	88
10	Toluene	**L8**	ND[k]	–
11	THF	**L8**	NR[k]	–
12	MeOH	**L8**	NR[k]	–
13[d]	DCM	**L8**	>99	90
14[e]	DCM	**L8**	>99	90
15[f]	DCM	**L8**	91	88
16[g]	DCM	**L8**	87	90
17[h]	DCM	**L8**	ND[k]	–
18[i]	DCM	**L8**	66	88
19[j]	DCM	**L8**	ND[k]	–

[a] Reaction conditions: ratio of substrate/catalyst (S/C) = 100, 2 mL solvent, H_2 (50 bar).
[b] Determined by ^1H NMR spectroscopy.
[c] Enantioselectivity was determined by HPLC using a chiral column.
[d] H_2 (20 bar).
[e] H_2 (10 bar).
[f] H_2 (5 bar).
[g] 4Å MS (50 mg) as an additive.
[h] HOAc (0.1 equiv.) as an additive.
[i] Na_2CO_3 (0.1 equiv.) as an additive.
[j] I_2 (0.1 equiv.) as an additive.



[k] ND = a complex mixture not determined; NR = no reaction.

The type of ligand greatly influences this catalytic reaction (entries 2–8). When planar chiral ruthenocene-derived P-N ligands were used,[11] ligands bearing the sterically bulky *t*Bu group on the oxazoline ring(s) gave hydrogenated product **9a** in excellent conversion and good ee, while those bearing an *i*Pr group exhibited poor catalytic activity and enantio-inducing ability (entry 2 vs 1, 4 vs 3). Ligands bearing bis-(phosphine-oxazoline) groups provided similar behaviour to those bearing a mono-(phosphine-oxazoline) moiety (entry 1 vs 3, 2 vs 4). This suggests that these two (phosphine-oxazoline) functionalities present in **L3** and **L4** do not interact with each

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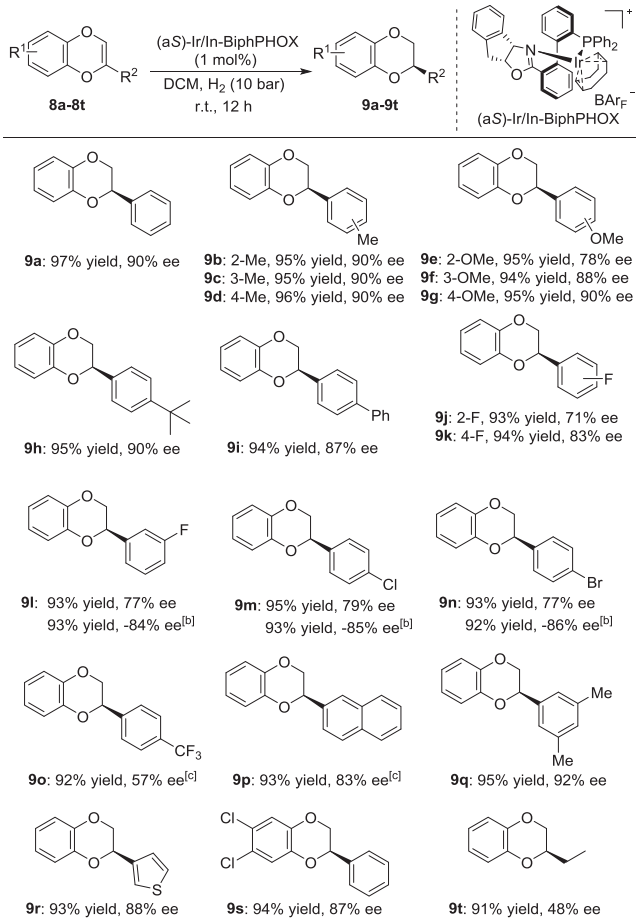
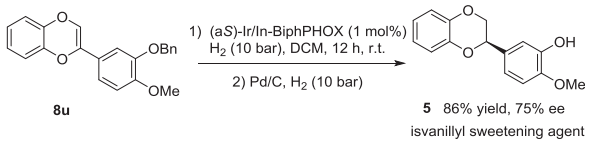
other. The well-known ligand, *t*Bu-Phox, also afforded the desired product in high conversion but with very low ee (entry 5). These results suggest that the planar chirality that is present in ligands **L2** and **L4** is important for obtaining good results in the hydrogenation reaction. Further screening of ligands bearing a biphenyl backbone developed by our group exhibit another interesting phenomenon; the axially-chiral backbone also has a significant influence on this reaction and possesses the opposite enantio-inducing ability compared to ligands bearing a planar chiral backbone. Ligands **L6-L8** gave the reduced product **9a** in excellent conversions with 70–90% ees. The effect of the substituents on the oxazoline rings of **L6**-**L8** on ee also differs from the planar chiral ligands **L1**-**L4**. Ligand **L6** bearing an *i*Pr on the oxazoline gave product **9a** with better ee than that of **L7** bearing a *t*Bu group (entry 6 vs 7). The best ee was obtained with the Ir-complex of ligand **L8** bearing a chiral indane-fused oxazoline (entry 8). The above results indicate that the backbones of the phosphine-oxazoline ligands have a dramatic effect on the configuration of the hydrogenation product (**L2** vs **L5** vs **L7**). Different solvents were also tested. Hydrogenation in the solvent DCE afforded **9a** with a similar result to that of carrying out the hydrogenation in DCM (entry 9). Other solvents, such as MeOH, EtOH, and toluene, did not give the desired product or gave a complex mixture (entries 10–12). Different hydrogen pressures were also investigated, and the optimal pressure was found to be 10 bar (entries 13–15). The addition of additives, including 4 Å molecular sieves, acids, bases and I_2, did not further improve the ee. Therefore, the best conditions were found to be using [Ir(**L8**)COD]BArF as a catalyst precursor and carrying out the reaction under 10 bar of hydrogen in DCM solvent at room temperature for 12 h.

With the optimized conditions in hand, different 2-substituted 1,4-benzodioxines were examined, as shown in Scheme 3. The results showed that substrates bearing both electron-rich and electron-neutral mono-substituted aryl groups gave the corresponding products with excellent yields and with almost identical enantioselectivities (Scheme 3, **9a-9i**). However, increasing the electron-withdrawing ability of the substituents on the phenyl group led to a concomitant decrease in ee (**9j-9o**). Substrate bearing a OMe group at the *ortho* position gave its corresponding product with lower ee (**9e**), while a Me group at the same position did not affect the ee (**9b**). This may be due to the coordinating effect of OMe group. It should be noted that the bromide substituent is also tolerable to the hydrogenation conditions thus allowing for further functionalization. Substrates bearing fused-ring aryl, heteroaryl and disubstituted aryl groups at the C2 position also gave their corresponding products with excellent yields and good enantioselectivities (**9p**-**9r**). Product **9q** was obtained with the best ee. A substrate bearing chlorine atoms on the benzene ring of the 1,4-benzodioxane was successfully hydrogenated, yielding **9s** with good results. Finally, an alkyl substituted substrate **8t** was also used for this hydrogenation; however, the desired product was obtained with only 48% ee. The absolute configuration of **9s** was determined to be (*R*) by X-ray analysis.[12] Since the Ir/mono-*t*Bu-RuPHOX complex is able to provide hydrogenation products with opposite configuration and with relatively high ee, we decided to test this catalyst for several substrates. Interestingly, we found that the Ir/mono-*t*Bu-RuPHOX catalyst exhibited better enantioinducing ability compared to Ir/In-BiphPHOX for substrates bearing electron-withdrawing groups (**9l**-**9n**). Compound **5**, which is a sweetening agent, was prepared via a sequence process of asymmetric hydrogenation and hydrogenative deprotection of **8u** (Scheme 4).



[a] Reaction conditions: ratio of substrate/catalyst (S/C) = 100, 2 mL solvent, Ir/In-BiphPHOX as catalyst, H_2 (10 bar), 12 h. [b] Reaction conditions: Ir/mono-*t*Bu-RuPHOX (1 mol%) instead of Ir/In-BiphPHOX as catalyst, H_2 (30 bar), 12 h [c] Reaction time was 24 h.

Scheme 3. Scope of substrates.



Scheme 4. Transformations of hydrogenation product.

3. Conclusions

In summary, we have developed an Ir-catalyzed asymmetric hydrogenation of 2-substituted 1,4-benzodioxines for the preparation of chiral 1,4-benzodioxanes. The ligand backbone is essential for obtaining good results, and our *tropos* biphenyl phosphine-oxazoline ligand and planar chiral ruthenocene-derived phosphine-oxazoline ligand provided the hydrogenation products in good ees with opposite configurations. A broad range of substrates were tested and gave the corresponding hydrogenation products in excellent yields and with moderate to good enantioselectivities using the Ir-complex of our *tropos* phosphine-oxazoline ligand.

4. Experimental section

4.1. General

All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques, unless otherwise noted.[1]H NMR

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(400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on a Varian MERCURY plus-400 spectrometer with TMS as an internal standard. HRMS was performed at the Analysis Center of Shanghai Jiao Tong University. Optical rotations were measured with a SPSI SGW-1 polarimeter. Enantioselectivity was performed on a Shimadzu LC-2010 HPLC system and using Daicel Chiralcel columns with n-hexane/i-propyl alcohol as an eluent. Chiralpak OJ-H, Chiralpak AD-H were purchased from Daicel Chiral Technologies (China) Co., Ltd.. Column chromatography was performed using 200–300 mesh silica gel. Melting points were measured with SGW X-4 micro melting point apparatus. All commercially available substrates were used as received.

4.2. General procedure for Ir-Catalyzed asymmetric hydrogenation

Under nitrogen atmosphere, the catalyst ([Ir(**L8**)(COD)]BArF, 3.20 mg, 0.002 mmol, 0.01 equiv.) and substrate **8** (0.2 mmol, 1.0 equiv.) were placed in a 5 mL tube equipped with a magnetic stirrer bar. This tube was then put into an argon-filled autoclave. DCM (2.0 mL) was added to the mixture under a nitrogen atmosphere. The autoclave was then closed, purged three times with hydrogen (less than the pressure needed), and finally pressurized to 10 bar. The reaction mixture was stirred at r.t. for 12 h. The hydrogen gas was slowly released and the solvent was removed by vacuum evaporation. The residue was purified by preparative TLC on silica gel to give the product **9**. The ee was determined by chiral HPLC. The absolute configuration of **9s** was determined by X-ray crystallographic analysis.

4.2.1. (R)-2-Phenyl-2,3-dihydrobenzo[b][1,4]dioxine (**9a**)

White solid; 97% yield; m. p. 54.5–55.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.26 (m, 5H, ArH), 7.02–7.00 (m, 1H, ArH), 6.97–6.94 (m, 1H, ArH), 6.92–6.88 (m, 2H, ArH), 5.14 (dd, J = 9.2, 2.4 Hz, 1H), 4.37 (dd, J = 11.2, 2.4 Hz, 1H), 4.05 (dd, J = 11.6, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 143.2, 136.6, 128.9, 126.7, 121.7, 117.7, 117.3, 75.2, 69.5; HRMS (ESI): calcd for $C_{14}H_{13}O_2$ $[M+H]^+$: 213.0916, found 213.0919; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 12.0 min (S), t_{R2} = 18.6 min (R)]; ee = 90%; $[\alpha]^D_{25}$ = −64.71 (c = 0.50, $CHCl_3$).

4.2.2. (R)-2-(o-Tolyl)-2,3-dihydrobenzo[b][1,4]dioxine (**9b**)

White solid; 95% yield; m. p. 31.3–32.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.46 (m, 1H, ArH), 7.31–7.20 (m, 3H, ArH), 7.01–6.93 (m, 2H, ArH), 6.91–6.87 (m, 2H, ArH), 5.32 (dd, J = 9.2, 2.4 Hz, 1H), 4.34 (dd, J = 11.6, 2.4 Hz, 1H), 3.99 (dd, J = 11.6, 9.2 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 143.2, 135.3, 134.5, 130.8, 128.7, 126.8, 126.5, 121.71, 121.69, 117.8, 117.2, 72.3, 68.5, 19.2; HRMS (ESI): calcd for $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1072, found 227.1079; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 7.3 min (S), t_{R2} = 11.2 min (R)]; ee = 89%; $[\alpha]^D_{25}$ = −56.52 (c = 0.74, $CHCl_3$).

4.2.3. (R)-2-(m-Tolyl)-2,3-dihydrobenzo[b][1,4]dioxine (**9c**)

Colorless oil; 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, J = 7.6 Hz, 1H, ArH), 7.25–7.18 (m, 3H, ArH), 7.01–6.97 (m, 1H, ArH), 6.96–6.92 (m, 1H, ArH), 6.91–6.86 (m, 2H, ArH), 5.09 (dd, J = 8.8, 2.4 Hz, 1H), 4.34 (dd, J = 11.2, 2.4 Hz, 1H), 4.03 (dd, J = 11.6, 8.8 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 143.2, 138.7, 136.5, 129.7, 128.8, 127.3, 123.8, 121.7, 117.7, 117.2, 75.3, 69.5, 21.6; HRMS (ESI): calcd for $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1072, found 227.1066; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 9.7 min (S), t_{R2} = 14.4 min (R)]; ee = 90%; $[\alpha]^D_{25}$ = −45.94 (c = 0.58, $CHCl_3$).

4.2.4. (R)-2-(p-Tolyl)-2,3-dihydrobenzo[b][1,4]dioxine (**9d**)

White solid; 96% yield; m. p. 33.4–34.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.30 (m, 2H, ArH), 7.25–7.21 (m, 2H, ArH), 6.99–6.96 (m, 1H, ArH), 6.95–6.92 (m, 1H, ArH), 6.90–6.87 (m, 2H, ArH), 5.09 (dd, J = 8.8, 2.4 Hz, 1H), 4.33 (dd, J = 11.6, 2.4 Hz, 1H), 4.03 (dd, J = 11.6, 9.2 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 143.2, 138.8, 133.6, 129.6, 126.6, 121.7, 121.6, 117.7, 117.2, 75.1, 69.5, 21.4; HRMS (ESI): calcd for $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1072, found 227.1067; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 10.8 min (S), t_{R2} = 19.1 min (R)]; ee = 90%; $[\alpha]^D_{25}$ = −67.36 (c = 0.29, $CHCl_3$).

4.2.5. (R)-2-(2-Methoxyphenyl)-2,3-dihydrobenzo[b][1,4]dioxine (**9e**)

White solid; 95% yield; m. p. 64.6–65.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.48 (m, 1H, ArH), 7.35–7.11 (m, 1H, ArH), 7.06–6.99 (m, 2H, ArH), 6.95–6.90 (m, 2H, ArH), 6.89–6.86 (m, 2H, ArH), 5.52 (dd, J = 8.4, 2.4 Hz, 1H), 4.45 (dd, J = 11.2, 2.4 Hz, 1H), 3.91 (dd, J = 11.2, 8.8 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 144.3, 143.4, 129.6, 127.1, 124.9, 121.6, 121.5, 121.1, 117.7, 117.2, 110.5, 70.3, 68.4, 55.5; HRMS (ESI): calcd for $C_{15}H_{15}O_3$ $[M+H]^+$: 243.1021, found 243.1024; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 8.1 min (S), t_{R2} = 10.6 min (R)]; ee = 78%; $[\alpha]^D_{25}$ = −61.88 (c = 0.57, $CHCl_3$).

4.2.6. (R)-2-(3-Methoxyphenyl)-2,3-dihydrobenzo[b][1,4]dioxine (**9f**)

Colorless oil; 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, J = 8.0 Hz, 1H, ArH), 7.01–6.97 (m, 3H, ArH), 6.95–6.87 (m, 4H, ArH), 5.10 (dd, J = 8.8, 2.4 Hz, 1H), 4.35 (dd, J = 11.6, 2.4 Hz, 1H), 4.02 (dd, J = 11.6, 8.8 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 143.9, 143.2, 138.1, 130.0, 121.73, 121.72, 118.9, 117.7, 117.3, 114.3, 112.2, 75.1, 69.5, 55.5; HRMS (ESI): calcd for $C_{15}H_{15}O_3$ $[M+H]^+$: 243.1021, found 243.1026; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 12.8 min (S), t_{R2} = 16.1 min (R)]; ee = 88%; $[\alpha]^D_{25}$ = −53.74 (c = 0.93, $CHCl_3$).

4.2.7. (R)-2-(4-Methoxyphenyl)-2,3-dihydrobenzo[b][1,4]dioxine (**9g**)

Colorless oil; 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.33 (m, 2H, ArH), 6.99–6.92 (m, 4H, ArH), 6.90–6.86 (m, 2H, ArH), 5.07 (dd, J = 8.8, 2.4 Hz, 1H), 4.31 (dd, J = 11.6, 2.4 Hz, 1H), 4.03 (dd, J = 11.2, 8.8 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 144.1, 143.2, 128.7, 128.1, 121.7, 121.6, 117.7, 117.2, 114.3, 74.9, 69.5, 55.5; HRMS (ESI): calcd for $C_{15}H_{15}O_3$ $[M+H]^+$: 243.1021, found 243.1019; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 17.6 min (S), t_{R2} = 27.0 min (R)]; ee = 90%; $[\alpha]^D_{25}$ = −37.63 (c = 0.62, $CHCl_3$).

4.2.8. (R)-2-(4-(tert-Butyl)phenyl)-2,3-dihydrobenzo[b][1,4]dioxine (**9h**)

White solid; 95% yield; m. p. 56.0–57.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (t, J = 8.4 Hz, 2H, ArH), 7.35 (t, J = 8.8 Hz, 2H, ArH), 6.99–6.85 (m, 4H, ArH), 5.10 (dd, J = 8.8, 2.4 Hz, 1H), 4.35 (dd, J = 11.6, 2.4 Hz, 1H), 4.05 (dd, J = 11.6, 8.8 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 144.2, 143.2, 133.5, 126.5, 125.9, 121.7, 121.6, 117.7, 117.2, 75.1, 69.4, 34.8, 31.4; HRMS (ESI): calcd for $C_{18}H_{21}O_3$ $[M+H]^+$: 269.1542, found 269.1541; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 95/5, 210 nm, 0.5 mL/min. t_{R1} = 13.6 min (S), t_{R2} = 14.3 min (R)]; ee = 90%; $[\alpha]^D_{25}$ = −36.67 (c = 0.72, $CHCl_3$).

4.2.9. (R)-2-([1,1′-Biphenyl]-4-yl)-2,3-dihydrobenzo[b][1,4]dioxine (**9i**)

White solid; 94% yield, m. p. 71.5–72.3 °C; ^{1}H NMR (400 MHz,

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$CDCl_3$): δ 7.65–7.57 (m, 4H, ArH), 7.50–7.43 (m, 4H, ArH), 7.38–7.34 (m, 1H, ArH), 7.02–6.87 (m, 4H, ArH), 5.17 (dd, J = 9.2, 2.4 Hz, 1H), 4.39 (dd, J = 11.6, 2.4 Hz, 1H), 4.08 (dd, J = 11.6, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 143.2, 141.9, 140.7, 135.5, 129.0, 127.70, 127.67, 127.3, 127.1, 121.8, 117.7, 117.3, 75.0, 69.4; HRMS (ESI): calcd for $C_{20}H_{17}O_2$ $[M+H]^+$: 289.1229, found 289.1224; HPLC [Daicel Chiralcel AD-H, hexane/i-PrOH = 99/1, 210 nm, 0.5 mL/min. t_{R1} = 38.6 min (*R*), t_{R2} = 43.7 min (*S*)]; ee = 87%; $[\alpha]^D_{25}$ = −47.17 (c = 0.78, $CHCl_3$).

4.2.10. (R)-2-(2-Fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxine (9j)

White solid; 93% yield; m. p. 34.5–35.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.51 (m, 1H, ArH), 7.38–7.33 (m, 1H, ArH), 7.25–7.20 (m, 1H, ArH), 7.13–7.08 (m, 1H, ArH), 7.01–6.98 (m, 1H, ArH), 6.96–6.93 (m, 1H, ArH), 6.92–6.88 (m, 2H, ArH), 5.47 (dd, J = 8.4, 2.4 Hz, 1H), 4.43 (ddd, J = 11.2, 2.4, 0.8 Hz, 1H), 4.02 (ddd, J = 11.2, 8.6, 0.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (d, J = 246.0 Hz), 143.8, 143.2, 130.3 (d, J = 9.0 Hz), 128.1 (d, J = 4.0 Hz), 124.8 (d, J = 3.0 Hz), 124.0, 123.9, 121.8 (d, J = 5.0 Hz), 117.6, 117.4, 115.5 (d, J = 22.0 Hz), 69.5 (d, J = 3.0 Hz), 68.2 (d, J = 2.0 Hz); HRMS (ESI): calcd for $C_{14}H_{12}FO_2$ $[M+H]^+$: 231.0821, found 231.0823; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 6.4 min (*S*), t_{R2} = 9.3 min (*R*)]; ee = 71%; $[\alpha]^D_{25}$ = −63.58 (c = 0.48, $CHCl_3$).

4.2.11. (R)-2-(4-Fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxine (9k)

White solid; 94% yield; m. p. 56.7–57.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.39 (m, 2H, ArH), 7.14–7.09 (m, 2H, ArH), 7.00–6.88 (m, 4H, ArH), 5.11 (dd, J = 8.8, 2.4 Hz, 1H), 4.33 (dd, J = 11.6, 2.4 Hz, 1H), 4.00 (dd, J = 11.6, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1 (d, J = 246.0 Hz), 143.9, 143.1, 132.4 (d, J = 3.0 Hz), 128.5 (d, J = 8.0 Hz), 121.84, 121.80, 117.7, 117.3, 115.9 (d, J = 21.0 Hz), 74.6, 69.4; HRMS (ESI): calcd for $C_{14}H_{12}FO_2$ $[M+H]^+$: 231.0821, found 231.0824; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 10.3 min (*S*), t_{R2} = 17.6 min (*R*)]; ee = 83%; $[\alpha]^D_{25}$ = −46.72 (c = 0.46, $CHCl_3$).

4.2.12. (R)-2-(3-Fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxine (9l)

White solid; 93% yield; m. p. 80.7–81.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.36 (m, 1H, ArH), 7.21–7.15 (m, 2H, ArH), 7.09–7.04 (m, 1H, ArH), 7.01–6.98 (m, 1H, ArH), 6.95–6.88 (m, 3H, ArH), 5.13 (dd, J = 8.8, 2.4 Hz, 1H), 4.36 (dd, J = 11.6, 2.4 Hz, 1H), 4.00 (dd, J = 11.2, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2 (d, J = 245.0 Hz), 143.7, 143.1, 139.3 (d, J = 7.0 Hz), 130.5 (d, J = 8.0 Hz), 122.2 (d, J = 3.0 Hz), 121.91, 121.87, 117.7, 117.3, 115.8 (d, J = 21.0 Hz), 113.7 (d, J = 23.0 Hz), 74.5 (d, J = 2.0 Hz), 69.3; HRMS (ESI): calcd for $C_{14}H_{12}FO_2$ $[M+H]^+$: 231.0821, found 231.0825; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 9.2 min (*S*), t_{R2} = 11.2 min (*R*)]; ee = 77%; $[\alpha]^D_{25}$ = −54.33 (c = 0.50, $CHCl_3$); **(*S*)-9l**: HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 8.1 min (*S*), t_{R2} = 9.3 min (*R*)]; ee = −84%; $[\alpha]^D_{25}$ = 64.28 (c = 0.58, $CHCl_3$).

4.2.13. (R)-2-(4-Chlorophenyl)-2,3-dihydrobenzo[b][1,4]dioxine (9m)

Colorless oil; 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.35 (m, 4H, ArH), 7.00–6.88 (m, 4H, ArH), 5.11 (dd, J = 8.8, 2.4 Hz, 1H), 4.33 (dd, J = 11.6, 2.4 Hz, 1H), 3.99 (dd, J = 11.2, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 143.1, 135.1, 134.8, 129.1, 128.0, 121.9, 121.8, 117.7, 117.3, 74.5, 69.3; HRMS (ESI): calcd for $C_{14}H_{12}ClO_2$ $[M+H]^+$: 247.0526, found 247.0527; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 9.8 min (*S*), t_{R2} = 14.4 min (*R*)]; ee = 78%; $[\alpha]^D_{25}$ = −43.41 (c = 0.53, $CHCl_3$); **(*S*)-9m**: HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 8.8 min (*S*), t_{R2} = 12.5 min (*R*)]; ee = −85%; $[\alpha]^D_{25}$ = 52.36 (c = 0.60, $CHCl_3$).

4.2.14. (R)-2-(4-Bromophenyl)-2,3-dihydrobenzo[b][1,4]dioxine (9n)

Colorless oil; 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.54 (m, 2H, ArH), 7.32–7.29 (m, 2H, ArH), 6.99–6.87 (m, 4H, ArH), 5.10 (dd, J = 8.4, 2.4 Hz, 1H), 4.33 (dd, J = 11.6, 2.4 Hz, 1H), 3.98 (dd, J = 11.6, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 143.1, 135.6, 132.1, 128.3, 122.9, 121.9, 121.8, 117.6, 117.3, 74.6, 69.2; HRMS (ESI): calcd for $C_{14}H_{12}BrO_2$ $[M+H]^+$: 291.0021, found 291.0023; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 10.9 min (*S*), t_{R2} = 14.6 min (*R*)]; ee = 76%; $[\alpha]^D_{25}$ = −36.59 (c = 0.63, $CHCl_3$); **(*S*)-9n**: HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 10.1 min (*S*), t_{R2} = 13.2 min (*R*)]; ee = −86%; $[\alpha]^D_{25}$ = 44.21 (c = 0.65, $CHCl_3$).

4.2.15. (R)-2-(4-(Trifluoromethyl)phenyl)-2,3-dihydrobenzo[b][1,4]dioxine (9o)

White solid; 92% yield; m. p. 59.6–60.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.0 Hz, 2H, ArH), 7.56 (d, J = 8.4 Hz, 2H, ArH), 7.02–6.89 (m, 4H, ArH), 5.21 (dd, J = 8.8, 2.4 Hz, 1H), 4.38 (dd, J = 11.6, 2.4 Hz, 1H), 4.02 (dd, J = 11.6, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 143.1, 140.6, 131.1 (q, J = 32.0 Hz), 126.9, 125.9 (q, J = 4.0 Hz), 124.1 (q, J = 271.0 Hz), 122.02, 121.96, 117.7, 117.4, 74.5, 69.2; HRMS (ESI): calcd for $C_{15}H_{12}F_3O_2$ $[M+H]^+$: 281.0789, found 281.0797; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 7.6 min (*S*), t_{R2} = 8.7 min (*R*)]; ee = 57%; $[\alpha]^D_{25}$ = −40.11 (c = 0.50, $CHCl_3$).

4.2.16. (R)-2-(Naphthalen-2-yl)-2,3-dihydrobenzo[b][1,4]dioxine (9p)

White solid; 93% yield; m. p. 47.1–47.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93–7.85 (m, 4H, ArH), 7.53–7.49 (m, 3H, ArH), 7.06–7.03 (m, 1H, ArH), 6.98–6.95 (m, 1H, ArH), 6.93–6.90 (m, 2H, ArH), 5.30 (dd, J = 9.2, 2.4 Hz, 1H), 4.44 (dd, J = 11.2, 2.4 Hz, 1H), 4.12 (dd, J = 11.6, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 143.2, 133.9, 133.6, 133.3, 128.8, 128.2, 127.9, 126.63, 126.61, 126.0, 124.0, 121.8, 117.7, 117.3, 75.3, 69.5; HRMS (ESI): calcd for $C_{18}H_{15}O_2$ $[M+H]^+$: 263.1072, found 263.1075; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 18.6 min (*S*), t_{R2} = 22.9 min (*R*)]; ee = 83%; $[\alpha]^D_{25}$ = −45.10 (c = 0.76, $CHCl_3$).

4.2.17. (R)-2-(3,5-Dimethylphenyl)-2,3-dihydrobenzo[b][1,4]dioxine (9q)

Colorless oil; 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04–6.87 (m, 7H, ArH), 5.04 (dd, J = 9.2, 2.4 Hz, 1H), 4.33 (dd, J = 11.2, 2.4 Hz, 1H), 4.02 (dd, J = 11.6, 9.2 Hz, 1H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 143.2, 138.6, 136.4, 130.6, 124.5, 121.7, 117.7, 117.2, 75.4, 69.6, 21.5; HRMS (ESI): calcd for $C_{16}H_{17}O_2$ $[M+H]^+$: 241.1229, found 241.1224; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 6.6 min (*S*), t_{R2} = 8.0 min (*R*)]; ee = 92%; $[\alpha]^D_{25}$ = −51.93 (c = 0.56, $CHCl_3$).

4.2.18. (R)-2-(Thiophen-3-yl)-2,3-dihydrobenzo[b][1,4]dioxine (9r)

Colorless oil; 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.39 (m, 1H, ArH), 7.38 (t, J = 2.8 Hz, 1H, ArH), 7.14 (dd, J = 5.2, 1.6 Hz, 1H), 6.98–6.86 (m, 4H, ArH), 5.26 (dd, J = 8.8, 2.4 Hz, 1H), 4.39 (dd, J = 11.2, 2.4 Hz, 1H), 4.11 (dd, J = 11.6, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 143.2, 137.7, 126.8, 125.8, 123.3, 121.77, 121.75, 117.6, 117.3, 71.8, 68.7; HRMS (ESI): calcd for $C_{12}H_{11}SO_2$ $[M+H]^+$: 219.0480, found 219.0474; HPLC [Daicel Chiralcel OJ-H,

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hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 20.3 min (*R*), t_{R2} = 22.7 min (*S*)]; ee = 88%; $[\alpha]^{D}_{25} = -22.11$ (c = 0.58, $CHCl_3$).

4.2.19. (R)-6,7-Dichloro-2-phenyl-2,3-dihydrobenzo[b][1,4]dioxine ***(9s)***

White solid; 94% yield; m. p. 69.0–69.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.38 (m, 5H, ArH), 7.09 (s, 1H, ArH), 7.04 (s, 1H, ArH), 5.11 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.36 (dd, *J* = 11.6, 2.4 Hz, 1H), 4.01 (dd, *J* = 11.6, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 142.4, 135.6, 129.2, 129.0, 126.6, 124.38, 124.35, 118.9, 118.5, 75.3, 69.3; HRMS (ESI): calcd for $C_{14}H_{11}Cl_2O_2$ $[M+H]^+$: 281.0136, found 281.0132; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 90/10, 210 nm, 1.0 mL/min. t_{R1} = 8.2 min (*S*), t_{R2} = 10.2 min (*R*)]; ee = 87%; $[\alpha]^{D}_{25} = -24.42$ (c = 0.80, $CHCl_3$).

4.2.20. (R)-2-Ethyl-2,3-dihydrobenzo[b][1,4]dioxine ***(9t)***

Colorless oil; 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89–6.81 (m, 4H, ArH), 4.24 (dd, *J* = 11.2, 2.0 Hz, 1H), 4.07–4.01 (m, 1H), 3.88 (dd, *J* = 11.2, 8.0 Hz, 1H), 1.78–1.57 (m, 2H), 1.07 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 143.4, 121.5, 121.2, 117.4, 117.1, 74.4, 67.9, 24.3, 9.6; HRMS (ESI): calcd for $C_{10}H_{13}O_2$ $[M+H]^+$: 165.0916, found 165.0912; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 95/5, 210 nm, 1.0 mL/min. t_{R1} = 5.7 min (*S*), t_{R2} = 5.9 min (*R*)]; ee = 48%; $[\alpha]^{D}_{25} = 20.29$ (c = 0.50, $CHCl_3$).

4.2.21. (R)-5-(2,3-Dihydrobenzo[b][1,4]dioxin-2-yl)-2-methoxyphenol ***(5)***

White solid; 92% yield; m. p. 88.7–89.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00–6.86 (m, 7H, ArH), 5.69 (s, 1H), 5.03 (dd, *J* = 9.2, 2.4 Hz, 1H), 4.31 (dd, *J* = 11.2, 2.4 Hz, 1H), 4.01 (dd, *J* = 11.6, 8.8 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 146.0, 144.1, 143.2, 129.8, 121.7, 121.6, 118.5, 117.7, 117.2, 113.0, 110.9, 74.9, 69.5, 56.2; HRMS (ESI): calcd for $C_{15}H_{15}O_4$ $[M+H]^+$: 259.0970, found 259.0971; HPLC [Daicel Chiralcel OJ-H, hexane/i-PrOH = 80/20, 210 nm, 1.0 mL/min. t_{R1} = 23.9 min (*S*), t_{R2} = 33.5 min (*R*)]; ee = 75%; $[\alpha]^{D}_{25} = -37.07$ (c = 0.50, $CHCl_3$).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.12.015.

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12. CCDC 1578630 [(R)-6,7-Dichloro-2-phenyl-2,3-dihydrobenzo[b][1,4]dioxine] contains the supplementary crystallographic data for this paper. Data are provided free of charge by The Cambridge Crystallographic Data Centre.