Palladium-Catalyzed Asymmetric Dihydroxylation of 1,3-Dienes with Catechols

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Summary of main observation and conclusion A palladium-catalyzed asymmetric dihydroxylation of 1,3-dienes with catechols is developed using chiral pyridinebis(oxazoline) ligand. Various chiral 2-substituted 1,4-benzodioxanes could be synthesized with moderate to high yields and enantioselectivities from readily available starting materials. The reaction is proposed to proceed through a cascade Wacker-type hydroxypalladation /asymmetric allylation process.

Background and Originality Content

Chiral 2-substituted 1,4-benzodioxane motifs have widely been found in bioactive natural products and molecules with significant biological activities, as exemplified by antidepressant MKC-242,[1] antihypertensive agent IDR-16084,[2] potent α_{1D}-adrenergicantagonist WB4101,[3] and the antihypertensive drug (*R*)-doxazosin[4] (Figure 1a). In the recent decades, global efforts have been devoted to this field, culminating in a variety of protocols to access chiral 2,3-dihydro-1,4-benzodioxane skeletons, including enzymatic[5] and chemical[6] resolution of racemic 1,4-benzodioxan-2-carboxylic acid derivatives and asymmetric synthesis from chiral pools.[7] In 2001, Buchwald reported a palladium-catalyzed intramolecular C-O bond formation reaction using a chiral alcohol substrate to synthesize 1,4-benzodioxane derivatives.[8] Cai and co-workers provided a highly enantioselective synthesis of 2-hydroxymethyl-1,4-benzodioxanes via Pd-catalyzed asymmetric C–O coupling reaction.[9] Recently, Zhang, Yang and co-workers reported an Ir-catalyzed asymmetric hydrogenation of benzo[b][1,4]dioxine derivatives,[10] and Zhang's group established a process enabled by a chiral rhodium catalyst to give high yields and excellent enantioselectivities.[11] Although these processes are robust for the construction of the 1,4-benzodioxane structures, they still have drawbacks, such as the use of relatively complex substrates or chiral starting materials. Asymmetric hydrogenation reactions also rely on the pre-synthesis of the benzo[*b*][1,4]dioxine core. Thus, catalytic approaches to access chiral 1,4-benzodioxane from simple and inexpensive starting materials are highly desirable.

Recently, our group has developed Pd(II)-catalyzed asymmetric aminohydroxylation and diamination reactions of 1,3-dienes with *N*-tosyl-2-aminophenol derivatives and ureas, respectively, via a cascade aza-Wacker/asymmetric allylation process.[12,13] Zhang and co-workers also reported the palladium-catalyzed diamination[14] and aminohydroxylation[15] reactions of 1,3-dienes. We envisioned that in the presence of an appropriate chiral Pd(II) catalyst, catechols and 1,3-dienes might undergo a cascade Wacker-type[16] hydroxypalladation/asymmetric allylation process,[17] thus providing a general and efficient synthesis of chiral 1,4-benzodioxanes from simple starting materials (Fig. 1b). Compared to our previous work using *N*-tosyl-2-aminophenol substrates,[12] the main challenge is to ensure both the reactivity of the Wacker-type process and the enantioselectivity of the asymmetric allylation step, given the fact that phenol groups are less reactive than aryl *N*-tosylamide group under our reaction conditions.[12]

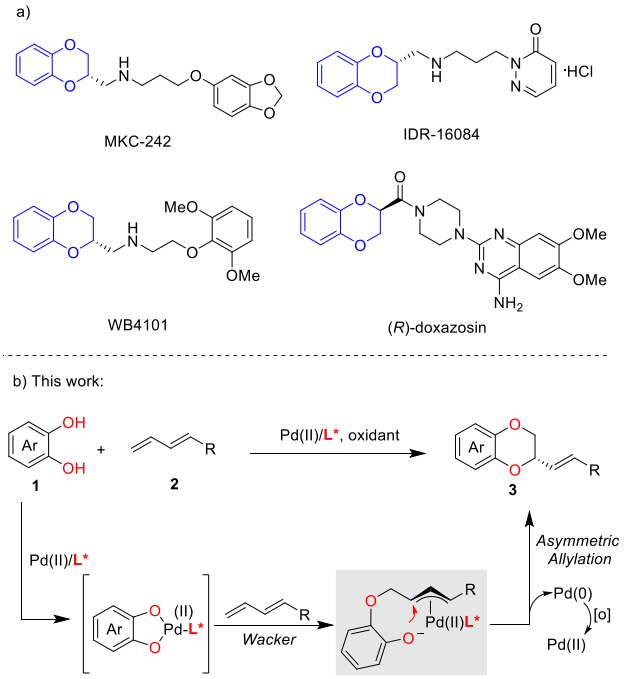


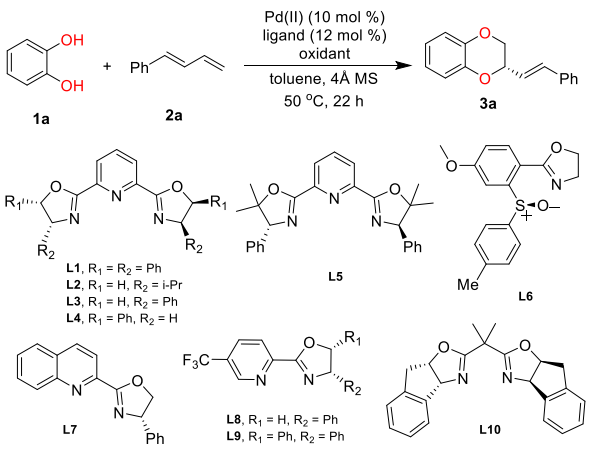
Figure 1 Representative bioactive compounds containing 2,3-dihydro-1,4-benzodioxane skeleton (a) and our synthetic approach (b).

Results and Discussion

Our investigation started with a reaction between catechol **1a** and (*E*)-buta-1,3-dien-1-ylbenzene **2a** catalyzed by a palladium complex (Table 1). Initially, the reaction was carried out at 50 °C for 22 hours in the presence of 10 mol % of $Pd(OAc)_2$, 2,5-dimethylbenzoquinone (DMBQ) and 4Å molecular sieves in toluene without a ligand. Encouragingly, the racemic reaction provided **3a** in 10 % yield (entry 1). Next, a number of chiral ligands were evaluated for the reaction. Gratifyingly, the pyridinebis(oxazoline) (pybox) ligand **L1**, the optimal ligand used in our asymmetric aminohydroxylation reaction,[12a] exhibited high reactivity and enantioselectivity (entry 2, 82% yield and 89:11 e.r.). Variation of the substituents on the pybox ligands[18] all led to unproductive reactions (entries 3-5), indicating that the diphenyl substituents on the pybox ligand are crucial to achieve high reactivity and enantioselectivity. Interestingly, varying one of the phenyl group to dimethyl group provided the same enantioselectivity and slightly lower yield (entry 6, **L5**). None of chiral sulfoxide-oxazoline ligand **L6**,[19] Quinox **L7**, electron-poor pyridine-oxazoline ligands **L8**-**L9**, and bisoxazoline **L10** was able to accelerate the reaction, although some of the ligands such as **L7**

exerted a considerable effect on the stereocontrol. Afterwards, a number of solvents were tested and their consequences were unsatisfactory (shown in the Supporting Information). The oxidant also had considerable effect on both the yield and the enantioselectivity of the dihydroxylation reaction (entries 12-14), and 2,5-dimethylbenzoquinone still proved to be the optimal one (entry 2). Next, different palladium sources were examined, and it was found that Pd_2dba_3 could give higher enantioselectivity, which might be related to the effect of counter anions (entries 15-16). Performing the reaction at 40 or 70 °C led to the decrease in both the yield and enantioselectivity (entries 17-18). The yield also dropped when a less amount of diene was employed (entry 19).

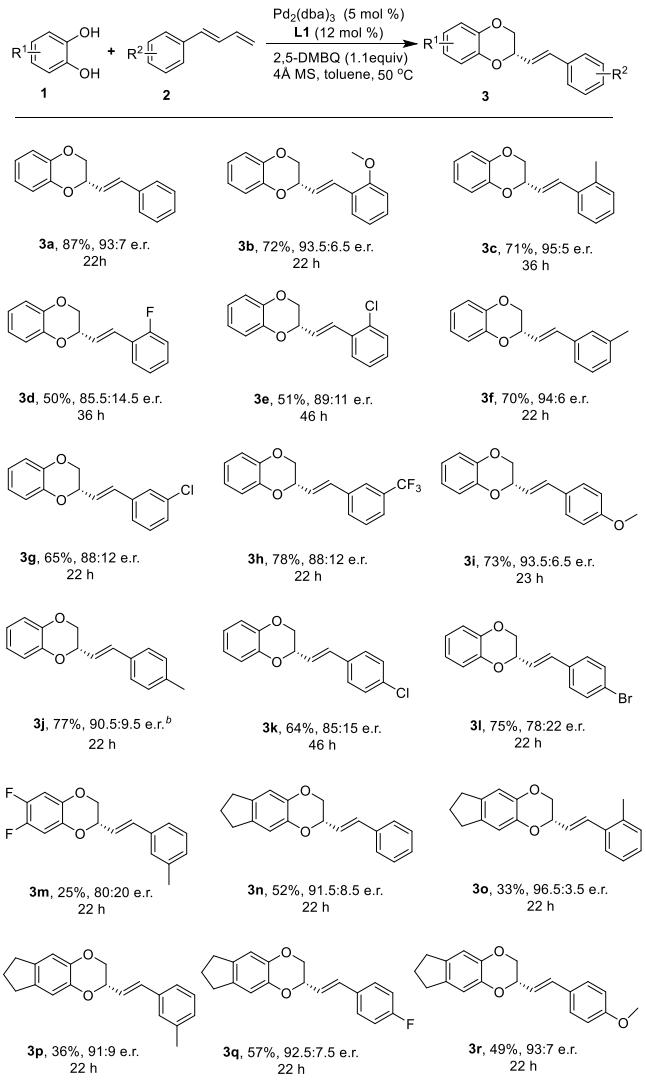
Table 1 Optimization of the reaction conditions [a]



Entry	Pd	Ligand	**3a**(%)[b]	e.r.(**3a**)[c]
1	$Pd(OAc)_2$	--	10	50:50
2	$Pd(OAc)_2$	**L1**	82	89:11
3	$Pd(OAc)_2$	**L2**	<5	80.5:19.5
4	$Pd(OAc)_2$	**L3**	<5	58:42
5	$Pd(OAc)_2$	**L4**	<5	64:36
6	$Pd(OAc)_2$	**L5**	78	89:11
7	$Pd(OAc)_2$	**L6**	<5	58:42
8	$Pd(OAc)_2$	**L7**	<5	74.5:25.5
9	$Pd(OAc)_2$	**L8**	<5	--
10	$Pd(OAc)_2$	**L9**	<5	--
11	$Pd(OAc)_2$	**L10**	<5	--
12[d]	$Pd(OAc)_2$	**L1**	33	89:11
13[e]	$Pd(OAc)_2$	**L1**	7	66:34
14[f]	$Pd(OAc)_2$	**L1**	5	76:24
15	$Pd(acac)_2$	**L1**	88	80:20
16[g]	**$Pd_2(dba)_3$**	**L1**	**87**	**93:7**
17[h]	$Pd_2(dba)_3$	**L1**	77	92:8
18[i]	$Pd_2(dba)_3$	**L1**	54	90.5:9.5
19[j]	$Pd_2(dba)_3$	**L1**	60	92:8

[a] Unless noted otherwise, the reaction of **1a** (0.1 mmol) and **2a** (0.5 mmol) were carried out with Pd (0.01 mmol), ligand (0.012 mmol), 2,5-DMBQ (0.1 mmol) and 4Å molecular sieves (40 mg) in toluene (0.5 mL) at 50 °C for 22h. [b] The yields were determined by ^{1}H-NMR analysis of the crude product based on internal standard. [c] The e.r. value of **3a** was determined by HPLC analysis. [d] 2,6-DMBQ was used instead of 2,5-DMBQ. [e] BQ was used instead of 2,5-DMBQ. [f] O_2 (1 atm) was used instead of 2,5-DMBQ. [g] When $Pd_2(dba)_3$ was used, the amount of DMBQ was 0.11 mmol. [h] The reaction was carried out at 40 °C. [i] The reaction was carried out at 70 °C. [j] The amount of **2a** was 0.3 mmol.

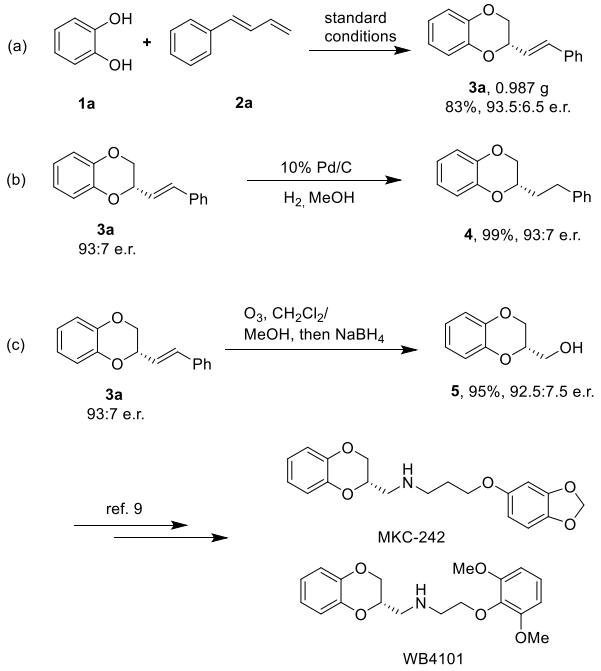
Table 2 Substrate scope [a]



[a] Unless noted otherwise, the reaction of **1** (0.1 mmol) and **2** (0.5 mmol) were carried out with Pd_2dba_3 (0.005 mmol), **L1** (0.012 mmol), 2,5-DMBQ (0.11 mmol) and 4Å molecular sieves (40 mg) in toluene (0.5 mL) at 50 °C . [b] Pd_2dba_3 (0.01 mmol), **L1** (0.024 mmol) were used.

With the optimized conditions in hand, we explored possible variations of the substrate. Firstly, we evaluated a variety of (*E*)-1-aryl-1,3-butadienes for the reaction with catechol **1a**. As shown in Table 2, various aryl groups, bearing either electron-donating or –withdrawing substituents, could be well tolerated. For example, ortho-, meta- and para-methyl or chloro substituted substrates all provided corresponding products with good yields and enantioselectivities. Notably, in the case of **3c**, 95:5 er could be achieved. Generally, (*E*)-1-aryl-1,3-butadienes bearing electron-donating groups led to higher yield and enantioselectivity than those with electron-withdrawing substituents. We next turned our attention to the generality of this dihydroxylation reaction for catechols. An electron-withdrawing group-substituted pyrocatechol, 4,5-difluorobenzene-1,2-diol (**3n**), only provided the product in a low yield and moderate enantioselectivity. The reaction of 2,3-dihydro-1H-indene-5,6-diol with the diene **2a** gave a higher yield and stereoselectivity (**3o**). Then, this catechol derivative was subjected to the reactions with a number of other dienes (**3p**-**3s**). Among them, the highest enantiomeric ratio (96.5:3.5) could be obtained for the reaction yielding **3p**.

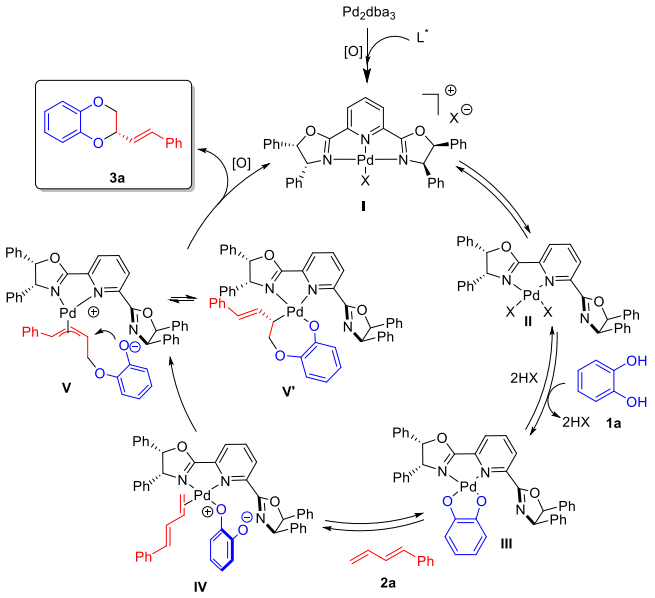
Scheme 1 Gram-scale reaction and synthetic applications of the products.



The palladium-catalyzed asymmetric dihydroxylation reaction of 1,3-dienes with catechols could be readily utilized for gram-scale synthesis, without notable erosion of the yield and enantioselectivity (Scheme 1a). The chiral 2-substituted 1,4-benzodioxane products could also undergo further transformations. The alkene moiety in **3a** could be readily hydrogenated to give compound **4** in 99% yield (Scheme 1b). Ozonolysis and reduction workup of **3a** furnished a chiral alcohol **5** in an excellent yield and with maintained enantioselectivity. The compound **5** could be then readily transformed to a number of bioactive compounds, such as MKC-242 and WB4101, following a reported procedure (Scheme 1c).[9]

As shown in Scheme 2, possible catalytic cycle for the Pd(II)-catalyzed asymmetric dihydroxylation of 1,3-dienes with catechols was proposed according to previous related reports.[12,14-15] First, Pd_2dba_3 is oxidized by DMBQ to form Pd(II) complex **I** bearing a three-coordinated Pybox ligand. The Pd(II)-complex could exist as an equilibrium mixture of tri- and bidentate isomers **I** and **II** in solution.[20] Subsequently, the five-membered palladacycle **III** could be generated, which might then be converted to an intermediate **IV** via ligand exchange. Through a hydroxypalladation process, the intermediate **IV** then transforms into π-allyl-Pd intermediate **V**, which might exist in equilibrium with η^1-allyl complex **V'**. Finally, back attack of the oxygen nucleophile on the π-allyl palladium moiety would generate product **3a**. Alternatively, the *syn*-oxygenation process of **V'** is also a possible pathway to form **3a**.[17,21] A possible explanation for the excellent *E*-selectivity of the reaction is the σ-interconversion during complexation of the palladium-ligand,[22, 23] and the *E*-π-palladium complex, which leads to the *E*-product, is more stable due to steric hindrance.

Scheme 2 Proposed mechanism.



Conclusions

In summary, we have developed a palladium-catalyzed asymmetric dihydroxylation of 1,3-dienes with catechols utilizing chiral pyridinebis(oxazoline) ligand. The reaction is proposed to proceed via a cascade Wacker-type hydroxypalladation /asymmetric allylation process. This methodology provides a direct and straightforward synthesis to prepare chiral 2-substituted 1,4-benzodioxane motifs in moderate to good yield and enantioselectivity from readily available starting materials.

Experimental

General Information. NMR spectra were recorded on a Bruker-400 MHz spectrometer. Chemical shifts (δ) are given in ppm relative to TMS. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). The high resolution mass spectra were recorded on a Thermo LTQ Orbitrap XL (ESI^+) or a P-SIMS-Gly of Bruker DaltonicsInc (EI^+). Infrared spectra were recorded on a Nicolet MX-1E FT-IR spectrometer. Enantiomeric excesses were performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump, UV detection monitored at 254 nm or 220nm). Chiralpak OD-H columns were purchased from Daicel Chemical Industries, LTD. Optical rotations were determined at 589 nm (sodium D line) by using a Perkin-Elmer-343 polarimeter.

General Experimental Procedure. To a flame-dried and Ar-purged Schlenk tube (10 mL) were added Pd_2dba_3 (0.005 mmol, 4.6 mg), **1** (0.1 mmol, 11.0 mg), **L1** (0.012mmol, 6.3 mg), 2, 5-DMBQ (0.11 mmol, 15.0 mg), 4Å (40 mg) and a stirring bar. The Schlenk tube was then evacuated and filled with argon. This cycle was repeated three times and followed by addition of 1, 3-diene **2** (0.5 mmol) and toluene (0.5 mL) via syringe. The mixture was stirred at 50 °C for 22 h. After that, the mixture was filtrated by silica gel and washed with EtOAc (3 ×10 mL). The combined organic layers were concentrated under vacuum. After ^{1}H-NMR analysis, the residue was purified by flash column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1) to afford the **3**.

(*S,E*)-2-styryl-2,3-dihydrobenzo[*b*][1,4]dioxine **(3a).** Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 2H), 7.28 – 7.22 (m, 2H), 7.19 (dt, *J* = 20.9, 9.9 Hz, 1H), 6.91 – 6.85 (m, 1H), 6.85 – 6.76

(m, 3H), 6.74 (d, *J* = 15.6 Hz, 1H), 6.14 (dd, *J* = 16.0, 6.6 Hz, 1H), 4.79 – 4.59 (m, 1H), 4.23 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.90 (dd, *J* = 11.3, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.16, 142.00, 134.83, 133.25, 127.62, 127.30, 125.68, 122.04, 120.61, 120.42, 116.38, 116.07, 72.66, 66.80; IR (CH_2Cl_2) γ 3027, 2922, 1593, 1493, 1465, 1264, 1064, 967, 743 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{16}H_{14}O_2$: 239.1072, found: 239.1055; $[\alpha]_D^{20}$ = 30.4 (c = 0.68, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 93:7 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 8.34 min, t_R (minor) = 6.71 min; the absolute configuration was determined to be *S* based on the absolute configuration of compound **5**.

(*S,E*)-2-(2-methoxystyryl)-2,3-dihydrobenzo[*b*][1,4]dioxine (**3b**) Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.15-7.22 (1H), 7.07 (d, *J* = 16.2 Hz, 1H), 6.90 – 6.81 (m, 2H), 6.81 – 6.74 (m, 4H), 6.19 (dd, *J* = 16.2, 6.9 Hz, 1H), 4.81 – 4.58 (m, 1H), 4.25 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.93 (dd, *J* = 11.3, 8.2 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.97, 142.32, 142.04, 128.56, 128.41, 126.28, 123.78, 122.59, 120.53, 120.31, 119.60, 116.43, 116.01, 109.85, 73.25, 66.96, 54.40; IR (CH_2Cl_2) γ 3043, 2923, 2852, 1593, 1492, 1464, 1266, 1246, 1196, 1051, 1027, 975, 747 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{17}H_{16}O_3$: 269.1178, found: 269.1177; $[\alpha]_D^{20}$ = 16.2 (c = 0.39, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 94:6 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 9.30 min, t_R (minor) = 8.79 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(2-methylstyryl)-2,3-dihydrobenzo[*b*][1,4]dioxine **(3c).** Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.44 (m, 1H), 7.18-7.22 (m, 3H), 7.07 (d, *J* = 15.9 Hz, 1H), 7.00 – 6.95 (m, 1H), 6.90 (m, 3H), 6.13 (dd, *J* = 15.9, 6.6 Hz, 1H), 4.83 (t, *J* = 7.1 Hz, 1H), 4.34 (dd, *J* = 11.3, 2.4 Hz, 1H), 4.03 (dd, *J* = 11.3, 7.9 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.19, 142.05, 134.79, 134.02, 131.15, 129.37, 127.16, 125.14, 124.75, 123.41, 120.61, 120.42, 116.40, 116.07, 72.82, 66.91, 18.73.; IR (CH_2Cl_2) γ 3040, 2922, 1593, 1493, 1265, 1248, 1027, 967, 745 cm^{-1} ; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{17}H_{16}O_2$: 253.1229, found: 253.1220; $[\alpha]_D^{20}$ = 13.0 (c = 0.32, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 95:5 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 7.84 min, t_R (minor) = 7.12 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(2-fluorostyryl)-2,3-dihydrobenzo[*b*][1,4]dioxine **(3d).** Yield: 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (td, J = 7.7, 1.6 Hz, 1H), 7.21 – 7.14 (m, 1H), 7.07 – 7.01 (m, 1H), 7.01 – 6.95 (m, 1H), 6.94 – 6.86 (m, 2H), 6.86 – 6.78 (m, 3H), 6.27 (dd, *J* = 16.2, 6.5 Hz, 1H), 4.80 – 4.68 (m, 1H), 4.26 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.93 (dd, *J* = 11.3, 8.0 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.94 (d, *J* = 250.37 Hz), 142.11, 142.02, 128.63 (d, *J* = 8.5 Hz), 126.77(d, *J* = 3.52Hz), 125.81 (d, *J* = 3.4 Hz), 124.77 (d, *J* = 5.5 Hz), 123.17(d, *J* = 3.60Hz), 122.72 (d, *J* = 12.0 Hz), 120.66, 120.48, 116.42, 116.10, 114.85 (d, *J* = 22.0 Hz), 72.73, 66.76; IR (CH_2Cl_2) γ 3042, 2922, 2854, 1593, 1493, 1265, 1246, 1065, 968, 748 cm^{-1} ; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{16}H_{13}FO_2$: 257.0978, found: 257.0978; $[\alpha]_D^{20}$ = 17.5 (c = 0.29, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 85.5:14.5 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 5.90 min, t_R (minor) = 5.55 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(2-methoxystyryl)-2,3-dihydrobenzo[*b*][1,4]dioxine **(3e)**. Yield: 51%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 1H), 7.40 – 7.34 (m, 1H), 7.25 – 7.19 (m, 3H), 6.99 – 6.94 (m, 1H), 6.93 – 6.86 (m, 3H), 6.23 (dd, *J* = 16.0, 6.6 Hz, 1H), 4.89 – 4.82 (m, 1H), 4.35 (dd, *J* = 11.3, 2.4 Hz, 1H), 4.03 (dd, *J* = 11.3, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.11, 143.06, 134.14, 133.47, 130.49, 129.84, 129.33, 127.02, 126.94, 126.07, 121.72, 121.54, 117.49, 117.15, 73.63, 67.77; IR (CH_2Cl_2) γ 3038, 2924, 1593, 1493, 1264, 1246, 1036, 960, 746 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{16}H_{13}ClO_2$: 273.0682, found: 273.0680; $[\alpha]_D^{20}$ = 10.8 (c = 0.22, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 89:11 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 7.73 min, t_R (minor) = 6.83 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(3-methylstyryl)-2,3-dihydrobenzo[*b*][1,4]dioxine **(3f)**. Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.13 (m, 3H), 7.05 – 6.99 (m, 1H), 6.90 – 6.85 (m, 1H), 6.85 – 6.81 (m, 1H), 6.81 – 6.76 (m, 2H), 6.72 (dd, *J* = 16.0, 1.1 Hz, 1H), 6.14 (dd, *J* = 16.0, 6.6 Hz, 1H), 4.74 – 4.67 (m, 1H), 4.24 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.92 (dd, *J* = 11.3, 8.0 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.20, 142.02, 137.21, 134.80, 133.39, 128.11, 127.52, 126.38, 122.87, 121.84, 120.61, 120.40, 116.40, 116.07, 72.73, 66.85, 20.34; IR (CH_2Cl_2) γ 3041, 2963, 2922, 1593, 1493, 1264, 1063, 966, 747 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{17}H_{16}O_2$: 253.1229, found: 253.1229; $[\alpha]_D^{20}$ = 29.9 (c = 0.36, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 94:6 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 6.84 min, t_R (minor) = 5.83 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(3-chlorostyryl)-2,3-dihydrobenzo[*b*][1,4]dioxine **(3g).** Yield: 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.32 (m, 1H), 7.21 – 7.16 (m, 3H), 6.91 – 6.85 (m, 1H), 6.85 – 6.76 (m, 3H), 6.70 (dd, *J* = 16.0, 1.1 Hz, 1H), 6.17 (dd, *J* = 16.0, 6.3 Hz, 1H), 4.77 – 4.69 (m, 1H), 4.25 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.91 (dd, *J* = 11.3, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.01, 141.96, 136.73, 133.60, 131.68, 128.86, 127.22, 125.58, 123.91, 123.67, 120.70, 120.53, 116.38, 116.12, 72.33, 66.66; IR (CH_2Cl_2) γ 3042, 2917, 2850, 1593, 1492, 1263, 1038, 963, 746 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{16}H_{13}ClO_2$: 273.0682, found: 273.0677; $[\alpha]_D^{20}$ = 31.0 (c = 0.36, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 88:12 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 8.50 min, t_R (minor) = 6.69 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(3-(trifluoromethyl)styryl)-2,3-dihydrobenzo[*b*][1,4] dioxine **(3h).** Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.63 – 7.39 (m, 3H), 7.02 – 6.79 (m, 5H), 6.33 (dd, *J* = 16.0, 6.2 Hz, 1H), 4.99 – 4.69 (m, 1H), 4.35 (dd, *J* = 11.3, 2.4 Hz, 1H), 4.02 (dd, *J* = 11.3, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.17, 143.16, 136.87, 132.73, 131.29 (q, *J* = 32.34 Hz), 130.01, 130.00, 129.30, 125.39, 124.96 (q, *J* = 3.76 Hz), 123.50 (q, *J* = 3.82 Hz), 122.79, 121.92, 121.75, 117.56, 117.33, 73.45, 67.81; IR (CH_2Cl_2) γ 3044, 2919, 2850, 1593, 1493, 1264, 1128, 1072, 965, 747 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{17}H_{13}ClO_2$: 307.0946, found: 307.0953; $[\alpha]_D^{20}$ = 27.0 (c = 0.36, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 88:12 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 6.48 min, t_R (minor) = 5.94 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(4-methoxystyryl)-2,3-dihydrobenzo[*b*][1,4]dioxine **(3i).** Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 2H), 6.98 – 6.94 (m, 1H), 6.94 – 6.90 (m, 1H), 6.90 – 6.84 (m, 4H), 6.78 (d, *J* = 15.9 Hz, 1H), 6.10 (dd, *J* = 16.0, 6.9 Hz, 1H), 4.77 (dddd, *J* = 8.1, 6.9, 2.4, 1.2 Hz, 1H), 4.32 (dd, *J* = 11.3, 2.4 Hz, 1H), 4.00 (dd, *J* = 11.3, 8.1 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.91, 143.42, 143.18, 134.16, 128.75, 128.14, 121.74, 121.53, 120.83, 117.55, 117.21, 114.18, 74.09, 68.09, 55.43; IR (CH_2Cl_2) γ 3041, 2962, 2923, 2853, 1655, 1608, 1493, 1261, 1020, 800, 746 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{17}H_{16}O_3$: 269.1178, found: 269.1174; $[\alpha]_D^{20}$ = 26.4 (c = 0.37, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 94:6 e.r.

(CHIRALPAK OD-H, hexane/i-PrOH = 99/1, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 33.89 min, t_R (minor) = 33.16 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(4-methylstyryl)-2,3-dihydrobenzo[*b*][1,4]dioxine **(3j).** Yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.93 – 6.85 (m, 1H), 6.85 – 6.81 (m, 1H), 6.81 – 6.76 (m, 2H), 6.72 (d, *J* = 16.0 Hz, 1H), 6.10 (dd, *J* = 16.0, 6.8 Hz, 1H), 4.83 – 4.58 (m, 1H), 4.24 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.92 (dd, *J* = 11.3, 8.1 Hz, 1H), 2.27 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.30, 143.09, 138.34, 134.36, 133.14, 129.39, 126.68, 122.01, 121.65, 121.45, 117.46, 117.12, 73.89, 67.96, 21.29; IR (CH_2Cl_2) γ 3043, 2920, 1593, 1493, 1265, 1249, 1061, 969, 747 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{17}H_{16}O_2$: 253.1229, found: 253.1222; $[\alpha]_D^{20}$ = 33.9 (c = 0.32, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 90:10 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 99/1, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 12.96 min, t_R (minor) = 11.46 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(4-chlorostyryl)-2,3-dihydrobenzo[*b*][1,4]dioxine **(3k).** Yield: 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 4H), 6.98 – 6.85 (m, 4H), 6.22 (dd, *J* = 16.0, 6.5 Hz, 1H), 4.82 – 4.77 (m, 1H), 4.33 (dd, *J* = 11.3, 2.4 Hz, 1H), 4.00 (dd, *J* = 11.3, 7.9 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.12, 143.04, 134.43, 134.06, 132.99, 128.88, 127.95, 123.83, 121.74, 121.56, 117.43, 117.16, 73.54, 67.77; IR (CH_2Cl_2) γ 3042, 2921, 1593, 1493, 1264, 1249, 1090, 1064, 968, 748 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{16}H_{13}ClO_2$: 273.0682, found: 273.0673; $[\alpha]_D^{20}$ = 35.6 (c = 0.25, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 85:15 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 99.7/0.3, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 26.56 min, t_R (minor) = 29.27 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(4-bromostyryl)-2,3-dihydrobenzo[*b*][1,4]dioxine **(3l)**. Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.36 – 7.16 (m, 2H), 6.99 – 6.92 (m, 1H), 6.92 – 6.83 (m, 3H), 6.76 (d, *J* = 16.0 Hz, 1H), 6.22 (dd, *J* = 16.0, 6.4 Hz, 1H), 4.78 (dd, *J* = 9.4, 4.0 Hz, 1H), 4.31 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.99 (dd, *J* = 11.3, 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.22, 143.15, 134.99, 133.15, 131.95, 128.36, 124.07, 122.36, 121.86, 121.69, 117.55, 117.29, 73.65, 67.85; IR (CH_2Cl_2) γ 3041, 2922, 2869, 1592, 1490, 1262, 1071, 1008, 967, 747 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{16}H_{13}BrO_2$: 317.0177, found: 317.0172; $[\alpha]_D^{20}$ = 20.6 (c = 0.46, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 78:22 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 99.7/0.3, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 39.54 min, t_R (minor) = 43.14 min; the absolute configuration was assigned by analogy.

(*S,E*)-6,7-difluoro-2-(3-methylstyryl)-2,3-dihydrobenzo[*b*][1,4] dioxine **(3m)**. Yield: 25%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 3H), 7.11 (d, *J* = 6.8 Hz, 1H), 6.82 – 6.69 (m, 3H), 6.17 (dd, *J* = 16.0, 6.6 Hz, 1H), 4.81 – 4.71 (m, 1H), 4.29 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.96 (dd, *J* = 11.4, 7.9 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.01, 143.44, 138.58 (d, *J* = 9.4 Hz), 135.61, 134.88, 129.33, 128.62, 127.44, 123.92, 122.10, 105.71(dd, *J* = 21.0, 26.6 Hz), 73.77, 67.76, 21.38; IR (CH_2Cl_2) γ 3043, 2923, 1513, 1208, 1165, 966, 776 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{17}H_{14}F_2O_2$: 289.1040, found: 289.1043; $[\alpha]_D^{20}$ = 17.8 (c = 0.13, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 80:20 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 7.99 min, t_R (minor) = 6.74 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-styryl-2,3,7,8-tetrahydro-6*H*-indeno[5,6-*b*][1,4] dioxine **(3n).** Yield: 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.1 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.30 – 7.24 (m, 1H), 6.80 (dd, *J* = 16.3, 11.3 Hz, 2H), 6.24 (dd, *J* = 16.0, 6.6 Hz, 1H), 4.75 (ddd, *J* = 6.7, 3.9, 1.0 Hz, 1H), 4.28 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.96 (dd, *J* = 11.3, 7.9 Hz, 1H), 2.82 (t, *J* = 7.4 Hz, 4H), 2.05 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.47, 140.34, 136.23, 136.01, 134.96, 133.05, 127.60, 127.23, 125.68, 122.40, 111.86, 111.55, 72.63, 66.85, 31.43, 31.41, 24.95; IR (CH_2Cl_2) γ 3027, 2927, 1590, 1488, 1450, 1324, 1285, 1155, 964, 744 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{19}H_{18}O_2$: 279.1385, found: 279.1381; $[\alpha]_D^{20}$ = 24.6 (c = 0.27, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 91:9 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 7.67 min, t_R (minor) = 6.58 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(2-methylstyryl)-2,3,7,8-tetrahydro-6*H*-indeno[5,6-*b*][1, 4]dioxine **(3o)**. Yield: 33%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.42 (m, 1H), 7.21 – 7.11 (m, 3H), 7.05 (d, *J* = 15.9 Hz, 1H), 6.82 (s, 1H), 6.77 (s, 1H), 6.13 (dd, *J* = 15.9, 6.6 Hz, 1H), 4.90 – 4.64 (m, 1H), 4.30 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.97 (dd, *J* = 11.3, 7.9 Hz, 1H), 2.82 (t, *J* = 7.4 Hz, 4H), 2.36 (s, 3H), 2.06 (p, *J* = 7.4 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.47, 140.34, 136.23, 136.01, 134.96, 133.05, 127.60, 127.23, 125.68, 122.40, 111.86, 111.55, 72.63, 66.85, 31.43, 31.41, 24.95; IR (CH_2Cl_2) γ 3042, 2926, 1637, 1485, 1439, 1320, 1246, 1155, 1028, 952, 738 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{20}H_{20}O_2$: 293.1542, found: 293.1533; $[\alpha]_D^{20}$ = 11.1 (c = 0.21, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 96.5:3.5 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 99/1, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 17.41 min, t_R (minor) = 15.96 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(3-methylstyryl)-2,3,7,8-tetrahydro-6*H*-indeno[5,6-*b*][1, 4]dioxine **(3p)**. Yield: 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 3H), 7.13 – 7.04 (m, 1H), 6.78 (d, *J* = 15.8 Hz, 3H), 6.22 (dd, *J* = 16.0, 6.7 Hz, 1H), 4.86 – 4.63 (m, 1H), 4.27 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.96 (dd, *J* = 11.3, 7.9 Hz, 1H), 2.82 (t, *J* = 7.4 Hz, 4H), 2.35 (s, 3H), 2.05 (p, *J* = 7.4 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.50, 140.34, 137.19, 136.22, 135.99, 134.90, 133.17, 128.03, 127.50, 126.36, 122.87, 122.18, 111.86, 111.55, 72.68, 66.88, 31.43, 31.41, 24.96, 20.34; IR (CH_2Cl_2) γ 3029, 2922, 2847, 1590, 1487, 1325, 1287, 1154, 1054, 966, 774 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{20}H_{20}O_2$: 293.1542, found: 293.1533; $[\alpha]_D^{20}$ = 29.4 (c = 0.20, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 91:9 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 6.85 min, t_R (minor) = 5.91 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(4-fluorostyryl)-2,3,7,8-tetrahydro-6*H*-indeno[5,6-*b*][1, 4]dioxine **(3q)**. Yield: 49%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 6.86 – 6.73 (m, 3H), 6.16 (dd, *J* = 16.0, 6.6 Hz, 1H), 4.86 – 4.56 (m, 1H), 4.28 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.96 (dd, *J* = 11.3, 7.8 Hz, 1H), 2.82 (t, *J* = 7.4 Hz, 4H), 2.06 (dq, *J* = 14.7, 7.4 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.70 (d, *J* = 247.8 Hz), 141.41(d, J = 10.0 Hz), 137.33, 137.12, 132.92, 132.20(d, *J* = 3.34 Hz), 128.32(d, *J* = 8.2 Hz), 123.23, 123.21, 115.73, 115.51, 112.89, 112.63, 73.59, 67.84, 32.48, 32.46, 26.00; IR (CH_2Cl_2) γ 3042, 2925, 2871, 1589, 1510, 1487, 1327, 1156, 1053, 969, 867 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{20}H_{17}FO_2$: 297.1291, found: 297.1273; $[\alpha]_D^{20}$ = 32.7 (c = 0.30, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 92.5:7.5 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 99/1, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 11.69 min, t_R (minor) = 12.60 min; the absolute configuration was assigned by analogy.

(*S,E*)-2-(4-methoxystyryl)-2,3,7,8-tetrahydro-6*H*-indeno[5,6-*b*][1,4]dioxine **(3r)**. Yield: 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 2H), 6.92 – 6.84 (m, 2H), 6.77 (dd, *J* = 15.0, 10.4 Hz, 3H), 6.10 (dd, *J* = 16.0, 6.9 Hz, 1H), 4.77 – 4.70 (m, 1H), 4.28 (dd, *J* = 11.3, 2.4 Hz, 1H), 3.96 (dd, *J* = 11.3, 8.0 Hz, 1H), 3.82 (s, 3H), 2.82 (t, *J* = 7.4 Hz, 4H), 2.06 (p, *J* = 7.4 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.47, 140.34, 136.23, 136.01, 134.96, 133.05, 127.60,

127.23, 125.68, 122.40, 111.86, 111.55, 72.63, 66.85, 31.43, 31.41, 24.95; IR (CH_2Cl_2) ν 3031, 2931, 2845, 1606, 1512, 1487, 1326, 1250, 1155, 969, 764 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_{20}H_{20}O_3$: 309.1491, found: 309.1486; $[\alpha]_D^{20}$ = 29.8 (c = 0.31, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 93:7 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 220 nm), t_R (major) = 7.81 min, t_R (minor) = 7.20 min; the absolute configuration was assigned by analogy.

(*S*)-2-phenethyl-2,3-dihydrobenzo[*b*][1,4]dioxine **(4)**. Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 -7.26 (m, 2H), 7.23 -7.18 (m, 3H), 6.93 – 6.88 (m, 1H), 6.87 – 6.79 (m, 3H), 4.17 (dd, *J* = 11.2, 2.2 Hz, 1H), 4.12 – 4.05 (m, 1H), 3.88 (dd, *J* = 11.2, 7.6 Hz, 1H), 2.85 (dddd, *J* = 16.2, 13.9, 8.9, 6.6 Hz, 2H), 2.00 (ddd, *J* = 17.4, 8.7, 5.5 Hz, 1H), 1.92 – 1.78 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.30, 142.22, 140.02, 127.48, 127.46, 125.09, 120.42, 120.19, 116.29, 115.95, 70.93, 66.91, 31.46, 29.99; IR (CH_2Cl_2) ν 3026, 2925, 2869, 1592, 1493, 1454, 1268, 1099, 1043, 907, 748, 700 cm^{-1}; HRMS (ESI) m/z $(M+Na)^+$: calculated for $C_{16}H_{16}O_2$: 263.1064, found: 263.1064; $[\alpha]_D^{20}$ = -75.6 (c = 0.96, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 93:7 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30°C, 254 nm), t_R (major) = 8.00 min, t_R (minor) = 6.95 min; the absolute configuration was assigned by analogy.

(*S*)-(2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)methanol **(5)**. Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 – 6.82 (m, 4H), 4.33 – 4.23 (m, 2H), 4.16 – 4.07 (m, 1H), 3.94 – 3.80 (m, 2H), 2.29 – 2.11 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.06, 141.95, 120.63, 120.55, 116.26, 116.19, 72.37, 64.09, 60.75; IR (CH_2Cl_2) ν 3426, 3044, 2927, 2883, 1593, 1493, 1266, 1102, 1042, 940, 747 cm^{-1}; HRMS (ESI) m/z $(M+H)^+$: calculated for $C_9H_{10}O_3$: 167.0708, found: 167.0704; $[\alpha]_D^{20}$ = -28.9 (c = 0.32, $CHCl_3$); the product was analyzed by HPLC to determine the enantiomeric ratio: 92:8 e.r. (CHIRALPAK OD-H, hexane/i-PrOH = 95/5, flow rate: 1.0 mL/min, T = 30°C, 220 nm), t_R (major) = 14.65 min, t_R (minor) = 15.93 min; the absolute configuration of **5** was assigned to be *S* by comparing the optical rotation data with literature reports[24] (see details in the Supporting Information).

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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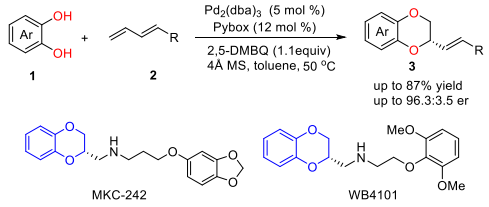

A Pd(II)-catalyzed asymmetric dihydroxylation of 1,3-dienes with catechols was developed for the efficient synthesis of chiral 1,4-benzodioxanes.

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