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FULL PAPER

Enantiodivergent synthesis of axially chiral biphenyls from σ-symmetric 1,1'-biphenyl-2,6-diol derivatives by single lipase-catalyzed acylative and hydrolytic desymmetrization

Kengo Kasama[a], Hiroshi Aoyama[a] and Shuji Akai*[a]

Abstract: The enzymatic acylative desymmetrization of σ-symmetric 2'-halo-1,1'-biphenyl-2,6-diols was achieved for the first time using commercially available *Burkholderia cepacia* lipase immobilized on diatomaceous earth to give (*S*)-mono esters. The hydrolytic desymmetrization of the corresponding diacetates was also achieved using the same lipase to give (*R*)-mono esters. Our results therefore demonstrate that a single lipase can conduct the enantiodivergent synthesis of axially chiral biphenyl compounds in high chemical and optical yields.

Introduction

Axially chiral biaryl compounds have received increasing attention in organic chemistry because of their abundance, their important roles in natural products and biologically active molecules, and their use as chiral catalysts and chiral ligands of transition metal catalysts.[1,2] Therefore, the asymmetric synthesis of these biaryl compounds has been intensively studied, with reported methods including the enantioselective coupling of phenols and their congeners using optically active transition metal catalysts[3] and organo-catalysts.[4] In addition, the kinetic resolution (KR) and dynamic kinetic resolution (DKR) of racemic biaryl compounds using metal catalysts[5] and organo-catalysts[6] to produce biaryl compounds have also been reported.

In contrast, due to excellent enantio- and chemo-selectivities of enzymes under mild conditions, the enzymatic asymmetric synthesis of axially chiral biaryls is also highly attractive.[7] Among the various enzymes examined to date, lipases are commonly employed in such enzymatic transformations due to their high stabilities, high catalytic activities in both aqueous and organic media, ease of handling, and lack of a requirement for cofactors. Indeed, they are able to catalyze not only hydrolysis but also (trans)esterification reactions.[8] Although the lipase-catalyzed acylative KR of axially chiral 1,1'-biaryl-2,2'-diols has been reported, there remained room for improvement in terms of the reaction rate and the substrate scope.[9] We previously addressed these issues by the dramatic acceleration of the lipase-catalyzed esterification of biaryl diols using a weak inorganic base, namely Na_2CO_3.[10a] We also reported a solution for the inherent limitation of KR (i.e., a maximum 50% yield of each enantiomer) by achieving DKR through the combination of KR with in situ racemization to produce optically pure 1,1'-biaryl-2,2'-diols in up to 98% yields.[10b]

The lipase-catalyzed asymmetric desymmetrization of σ-symmetric biaryl diols and their esters can also be employed to obtain axially chiral biaryl compounds in up to quantitative yields, with Matsumoto et al. reporting some excellent examples of the hydrolytic desymmetrization of σ-symmetric 1,1'-biphenyl-2,6-diyl diesters.[11] They also described the preparation of both enantiomers by the use of different lipases.[11a] Very recently, the *N*-heterocyclic-carbene-catalyzed atroposelective acylation of σ-symmetric 2'-amino-1,1'-biphenyl-2,6-diols was reported.[12] However, to the best of our knowledge, the atroposelective desymmetrization of σ-symmetric biaryl diols **1** by enzymatic esterification has yet to be reported. We also expect that the enantiodivergent synthesis of both enantiomers will be possible through the use of a single lipase since lipases can conduct both the esterification and hydrolysis of σ-symmetric biaryl compounds (**1** and **3**) through very similar transition states, in which the only difference is the R^2 substituent (R^2 = H for **1** and Ac for **3**) (Figure 1).

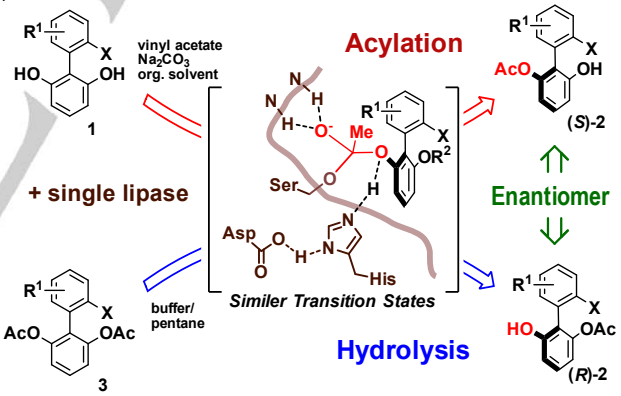

Figure 1. A concept of the enantiodivergent synthesis of both enantiomers (*S*)- and (*R*)-**2** by atroposelective desymmetrization of σ-symmetric biphenyl compounds **1** and **3** using a single lipase

Thus, in this study, our attention was focused on the preparation of 2'-halo-1,1'-biphenyl diol derivatives **2**, since the halogen atoms present on the benzene ring can be easily converted into other substituents, thereby enabling the preparation of a wider range of multi-substituted biphenyls.[5a,b] As such, we herein present the first example of the lipase-catalyzed acylative desymmetrization of σ-symmetric 1,1'-biphenyl-2,6-diols **1** using the commercially available *Burkholderia cepacia* lipase immobilized on diatomaceous earth (Amano PS-IM)[13,14] in the presence of Na_2CO_3. We also report the hydrolytic desymmetrization of diesters **3** using the same lipase. With these two types of desymmetrization reaction in hand, the enantiodivergent synthesis of both enantiomers of optically active mono acetates **2** (98–99% ee) is also carried out.

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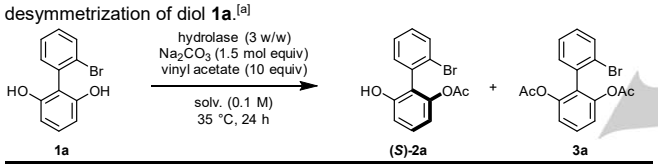
Results and Discussion

As a model compound for the enzymatic acylative desymmetrization reaction, we selected 2'-bromo-1,1'-biphenyl-2,6-diol **1a**. After screening a range of commercially available hydrolases under typical conditions[10a] [**1a** (5 mg, 0.02 mmol), hydrolase (3 w/w), vinyl acetate (10 equiv), Na_2CO_3 (1.5 mol equiv), organic solvent (0.1 M), 35 °C, 24 h (Table 1)], we were pleased to find that *Pseudomonas fluorescens* lipase (Amano AK), *Pseudomonas* sp. lipase (Toyobo LIP301), and *Burkholderia cepacia* lipase (Amano PS-IM) efficiently catalyzed the atroposelective acylation of **1a** to give the optically pure monoester (*S*)-**2a** (97–99% ee, >60% ratio based on HPLC analysis) along with diester **3a** (4–17% ratio based on HPLC analysis) (entries 7–9). Among them, PS-IM produced a perfect conversion and gave the highest ratio (88%) of (*S*)-**2a**. Using PS-IM, we also examined a number of other reaction solvents, but no improvements in the yield or the optical purity of (*S*)-**2a** were observed compared to those obtained using toluene (entries 10–13), and so a combination of PS-IM and toluene was selected for the reaction.

Table 1. Screening of hydrolases and solvents for the acylative desymmetrization of diol **1a**.[a]



1a **(*S*)-2a** **3a**

Entry	Hydrolase[b]	Solvent	Conversion,[c] %	(*S*)-**2a** Ratio,[d] %	(*S*)-**2a** Ee,[e] %	**3a** Ratio,[d] %
1	PLE	toluene	0	0	-	0
2	PPL	toluene	0	0	-	0
3	lipase AY	toluene	0	0	-	0
4	CAL-A	toluene	0	0	-	0
5	CAL-B	toluene	2	2	99	0
6	lipase AH	toluene	7	7	82	0
7	lipase AK	toluene	61	57	97	4
8	LIP301	toluene	95	78	99	17
9	lipase PS-IM	toluene	99	88	98	11
10	lipase PS-IM	heptane	89	84	83	5
11	lipase PS-IM	*i*Pr_2O	79	75	93	4
12	lipase PS-IM	CH_2Cl_2	64	62	96	2
13	lipase PS-IM	MeCN	27	26	94	1

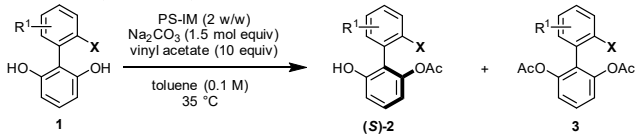
[a] Reaction scale; **1a** (5 mg, 0.02 mmol), enzyme (15 mg). [b] PLE = pig liver esterase, PPL = porcine pancreatic lipase, lipase AY = *Candida rugosa* lipase, CAL-A = *Candida antarctica* lipase A, CAL-B = *Candida antarctica* lipase B, lipase AH = *Burkholderia cepacia* lipase, lipase AK = *Pseudomonas fluorescens* lipase, LIP301 = *Pseudomonas* sp. lipase, PS-IM = *Burkholderia cepacia* lipase. [c] Ratio of the compounds (**2a** + **3a**) out of the total of **1a**, **2a** and **3a** determined by HPLC analysis using a Daicel CHIRALPAK IE column, detection: 254 nm. [d] Ratio of **3a** out of the total of **1a**, **2a** and **3a** determined by HPLC analysis shown in footnote c. [e] Optical purity (ee %) was determined by HPLC analysis shown in footnote c.

A similar reaction was then conducted using **1a** on the 0.50 mmol scale with a slightly reduced quantity of PS-IM (0.27 g, 2.0 w/w) in addition to *Burkholderia cepacia* lipase immobilized on diatomaceous earth,[14] Na_2CO_3 (1.5 mol equiv), and vinyl acetate (10 equiv) in toluene (0.1 M). In this case, complete conversion was achieved within 17 h at 35 °C, and optically pure (*S*)-**2a** was obtained in 91% yield after purification by column chromatography (Table 2, entry 1). We also reaffirmed the significant acceleration of the enzymatic acylation of **1a** by Na_2CO_3, since a similar reaction in the absence of Na_2CO_3 required 48 h to reach 98% conversion (entry 2).

Examples of similar desymmetrization reactions of other σ-symmetric biphenyl diols **1** (see Table 2) demonstrate the good substrate scope of our method, in which the reactions of 2'-halogenated diols **1b**–**1e** (0.50 mmol) reached complete conversion in 13–26 h at 35 °C to give optically pure monoesters (*S*)-**2b**–**2e** (98–99% ee) in 76–91% isolated yields (entries 3–6). In general, substrates bearing smaller substituent(s) on the upper phenyl moiety, such as **1a**, **1b**, **1d**, and **1e**, had a tendency to react faster, although a similar reaction of **1f** bearing three substituents on the upper phenyl moiety resulted in 77% conversion in 24 h at 35 °C. Such a low reactivity was improved by conducting the reaction with a higher loading of PS-IM (3 w/w) and at a higher temperature (50 °C) to achieve 99% conversion in 26 h to give (*S*)-**2f** (94% isolated yield, 99% ee) (entry 7).

In all cases, the corresponding diacetates **3b**–**3f** were also obtained. In particular, 2'-chloro compounds **1b** and **1e** produced **3b** and **3e**, respectively, in higher ratios (17–18%) than those obtained for other substrates (4–7%). We also examined the time course of the PS-IM-catalyzed second esterification reaction (**2b** → **3b**) using a racemic **2b** and found that **3b** was gradually formed over time along with an increase in the optical purity of (*S*)-**2b**. Thus, after 24 h at 35 ºC, (*S*)-**2b** (41% yield, 77% ee) was obtained (Figure 2). This result demonstrated that PS-IM conducted the kinetic resolution of racemic **2b** under the desymmetrization conditions employed herein, in which the esterification of (*R*)-**2b** took place preferentially. This phenomenon contributes to the formation of optically pure mono ester (*S*)-**2b**.

Table 2. Acylative desymmetrization of various diols **1a-f**.[a]



Entry	Substrate **1**	Reaction time, h	Conversion,[b] %	(*S*)-**2** Isolated yield, %	(*S*)-**2** Ee,[c] %	**3** Isolated yield, %
1	**1a** X = Br	17	98	(*S*)-**2a**, 91	99	**3a**, 7
2[d]	**1a**	48	98	(*S*)-**2a**, 90	99	**3a**, 3
3	**1b** X = Cl	16	99	(*S*)-**2b**, 82	98	**3b**, 17
4	**1c** X = I	24	96	(*S*)-**2c**, 89	99	**3c**, 5
5	**1d**	14	99	(*S*)-**2d**, 91	99	**3d**, 6
6	**1e**	13	99	(*S*)-**2e**, 76	99	**3e**, 18
7[e]	**1f**	26	99	(*S*)-**2f**, 94	99	**3f**, 4

[a] Each reaction was conducted by using 0.50 mmol of **1**. [b] Same as footnote c in Table 1. [c] Determined by HPLC analysis using a Daicel CHIRALPAK IE column as mentioned in footnote c in Table 1. [d] In the absence of Na_2CO_3. [e] Conducted using PS-IM (3 w/w) at 50 °C.

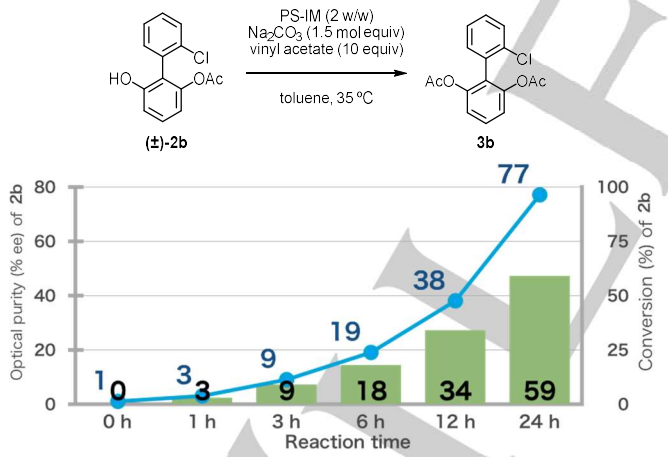
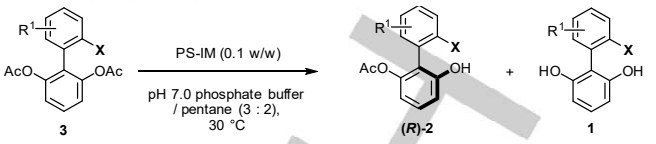


Figure 2. Time-course of the PS-IM-catalyzed kinetic resolution of racemic **2b**. -●- optical purity (% ee) of **2b**, ■ conversion (%) of **2b**.

We subsequently examined the feasibility of the hydrolytic desymmetrization reaction of diacetates **3** by PS-IM. Optimization of the reaction conditions using **3a** in a mixture of pH 7.0 phosphate buffer (or water) and an organic solvent or in the aqueous media only (for details, see: Supporting Information) gave perfect conversion in 16 h producing optically pure (*R*)-**2a** in 99% isolated yield under the following conditions; **3a** (0.50 mmol), PS-IM (0.1 w/w), a 3:2 (v/v) mixture of pH 7.0 phosphate buffer and pentane, 30 °C (Table 3, entry 1). When ion-exchanged water was used instead of pH 7.0 phosphate buffer with or without pentane, overhydrolysis to give **1a** was observed, and the yield of (*R*)-**2a** was a little bit lower than that obtained by using the buffer.

Table 3. Hydrolytic desymmetrization of various diacetates **3a-f**.[a]



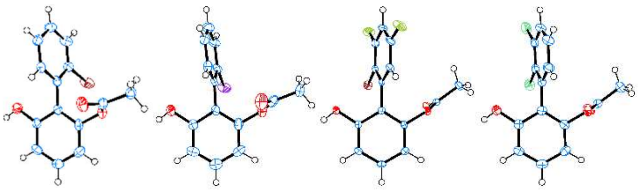
Entry	Substrate **3**	Time, h	Conversion,[b] %	(*R*)-**2** Isolated yield, %	(*R*)-**2** Ee,[c] %	**1** Isolated yield, %
1	**3a** X = Br	18	99	(*R*)-**2a**, 99	99	**1a**, 0
2	**3b** X = Cl	16	99	(*R*)-**2b**, 99	99	**1b**, 0
3[d]	**3c** X = I	37	95	(*R*)-**2c**, 85	99	**1c**, 0
4	**3d**	15	99	(*R*)-**2d**, 96[e]	99	**1d**, 0
5	**3e**	16	98	(*R*)-**2e**, 98	99	**1e**, 0
6[f]	**3f**	30	99	(*R*)-**2f**, 94	99	**1f**, 4

[a] Each reaction was conducted by using 0.50 mmol of **1**. [b] Same as footnote c in Table 1. [c] Determined by HPLC analysis using a Daicel CHIRALPAK IE column as mentioned in footnote c in Table 1. [d] Conducted using PS-IM (0.2 w/w) at 40 °C. [e] Contaminated with 2% of **1d** (^{1}H NMR analysis). [f] Conducted using PS-IM (0.2 w/w) at 50 °C in a mixture of pH 7.0 phosphate buffer (6.0 mL) and pentane (4.0 mL).

This method was then applied to other diacetates **3b**–**3f**, and the results are presented in Table 3. The reaction was highly chemoselective, exclusively yielding monoacetates (*R*)-**2b**–**2f**, and the formation of diols **1** was generally not observed (entries 1–3 and 5), with the exception of entries 4 and 6 (up to 4%). It should be noted that the optical purities of products (*R*)-**2** were 99% ee in all cases. Similar to the acylation reactions, smaller halogen substituents at the C2' position gave a faster reaction (entries 1 and 2). In the case of iodo compound **3c** only 17% conversion was achieved in 24 h. However, upon modifying the reaction conditions through the use of PS-IM (0.2 w/w) at 40 °C, 95% conversion was achieved in 37 h to give an 85% isolated yield of (*R*)-**2c** (entry 3). Although a similar reaction of **3f** was slow under the standard conditions, we found that conducting the hydrolysis reaction using PS-IM (0.2 w/w) along with double the volume of each reaction medium at 50 °C allowed the reaction to reach completion in 30 h, giving (*R*)-**2f** in 94% yield with >99% ee (entry 7).

It should also be noted that in all cases, the esterification and hydrolysis reactions produced enantiomers of each other as confirmed unambiguously by chiral HPLC analysis. The absolute configurations of **2a**, **2c, 2d**, and **2e**, obtained by the acylation reaction, were determined to be *S* by X-ray diffraction analysis

(Figure 3), and the others were estimated to be the same based on by similar enantiodiscrimination ability of the lipase.



(*S*)-**2a** (*S*)-**2c** (*S*)-**2d** (*S*)-**2e**

Figure 3. X-Ray structure of the products (*S*)-**2a,** (*S*)-**2c**, (*S*)-**2d**, and (*S*)-**2e** obtained by the enzymatic acylation reaction.[15]

Conclusions

We herein reported the lipase-catalyzed acylative desymmetrization of σ-symmetric 1,1'-biphenyl-2,2'-diols **1** for the first time, in which the addition of Na_2CO_3 was critical to accelerate the enzymatic acylation reaction. We also accomplished the hydrolytic desymmetrization of the corresponding diacetates **3** using the same lipase as that employed for the above acylation reactions (i.e., *Burkholderia cepacia* lipase (Amano PS-IM)). Through the combination of these two reactions (i.e., acylation and hydrolysis) using a single lipase, we demonstrated the first enantiodivergent synthesis of axially chiral biphenyls **2** in a particularly high optical purity (≥98% ee). In addition, the presence of reactive halogen and hydroxyl groups at the C2' and C2 positions, respectively, allows the installation of a range of substituents,[5a,b] thereby rendering biphenyls **2** valuable precursors for the preparation of both enantiomers of optically pure axially chiral multisubstituted biphenyls, which are important as synthetic intermediates of bioactive molecules, chiral catalysts, and chiral ligands.

Based on our previous study using *Pseudomonas* sp. lipase (Toyobo LIP301)[10a] and our current observations using *Burkholderia cepacia* lipase (Amano PS-IM), the acceleration effect of Na_2CO_3 on the lipase-catalyzed acylation of phenolic hydroxyl groups seems to be generally applicable.

Further studies into expanding the substrate scope of these reactions and the synthetic applications of the products are in progress in our laboratory, and the results will be presented in due course.

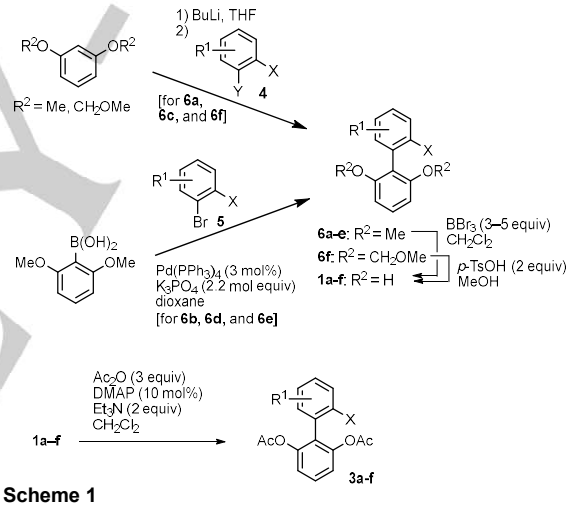
Experimental Section

General considerations

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) absorption spectra were recorded on a SHIMADZU FTIR-8400S spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on JEOL JNM-ECA500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) and JEOL JNM-ECS400 (^{13}C: 101 MHz and ^{19}F: 376 MHz) instruments. Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in δ (ppm) relative to the residual nondeuterated solvent signal for ^{1}H ($CHCl_3$: δ = 7.26 ppm, DMSO: δ = 2.50 ppm, acetone: 2.05 ppm) and relative to the solvent signal for ^{13}C ($CDCl_3$: δ = 77.0 ppm), and those of ^{19}F NMR spectra reported in δ (ppm) relative to hexafluorobenzene ($CDCl_3$: -164.9 ppm) as an internal standard. The mass spectra (MS) were measured on a JEOL JMS-S3000 (MALDI) with a TOF mass analyser. HPLC analyses were carried out using a JASCO LC-2000Plus system (HPLC pump: PU-2080, UV detector: MD-2018) equipped with a Daicel CHIRALPAK IE column with a size of 4.6 mm x 250 mm. Optical rotations were measured on a JASCO P-1020 polarimeter. The lipase from *Burkholderia cepacia* immobilized on diatomaceous earth (commercial name; Lipase PS IM Amano) was gifted from Amano Enzyme Inc. and used as received. Kanto silica gel 60N was used for column chromatography. In general, the anhydrous reactions were carried out in anhydrous solvents.

Preparation of substrates 1 and 3

The preparation of **1** and **3** were performed as shown in Scheme 1. 1,3-Bis(methoxymethyl)benzene was prepared according to the reported procedure.[16] Other chemicals were purchased and used as received.



Scheme 1

2'-Bromo-2,6-dimethoxy-1,1'-biphenyl (6a): 6a was synthesized from 1,3-dimethoxybenene and 1-bromo-2-chlorobenzene **4a** according to the reported procedure.[17] Its ^{1}H NMR data ([D$_6$]DMSO) are in good agreement with those reported.[16] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.33-7.37 (m, 2H), 7.18-7.24 (m, 2H), 6.66 (d, *J* = 8.0 Hz, 2H), 3.74 (s, 6H).

2'-Iodo-2,6-dimethoxy-1,1'-biphenyl (6c): 6c was synthesized from 1,3-dimethoxybenene and 1,3-diiodobenzene **4b** according to the reported procedure.[17] Its spectroscopic data are in good agreement with those reported.[18]

2'-Chloro-2,6-dimethoxy-1,1'-biphenyl (6b); a typical procedure for the coupling of bromobenzene 5 and (2,6-dimethoxyphenyl)-boronic acid to give biphenyl 6 (Procedure A): A mixture of 1-bromo-2-chlorobenzene (**5b**) (1.0 g, 5.2 mmol), (2,6-dimethoxy-phenyl)boronic acid (1.1 g, 6.3 mmol), $Pd(PPh_3)_4$ (0.30 g, 0.16 mmol), and K_3PO_4 (2.4 g, 11.5 mmol) in 1,4-dioxane (0.1 M) was stirred at 90 °C for 4 h. After being cooled to ambient temperature, the mixture

was concentrated in vacuo. Water and CH_2Cl_2 were added to the residue, and the product was extracted with CH_2Cl_2 three times. The combined organic layer was washed with water, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes/EtOAc = 10:1) to give **6b** (1.08 g, 83% yield). A colourless solid. Mp. 134-136 °C. ^{1}H NMR (500 MHz, [D$_6$]acetone) δ 7.44-7.46 (m, 1H), 7.30-7.36 (m, 3H), 7.20-7.22 (m, 1H), 6.74 (d, J = 8.0 Hz, 2H), 3.70 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 134.6, 133.8, 132.4, 129.4, 129.1, 128.4, 126.2, 117.0, 104.0, 56.0. IR (neat) v 1586 cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{14}H_{15}{}^{35}ClO_2$ [M+H]$^+$: 249.0677, found: 249.0676.

2,3-Dichloro-2',6'-dimethoxy-1,1'-biphenyl (6e): By following **Procedure A** (reaction time: 2 h), 1-bromo-2,3-dichlorobenzene (**5e**) (0.90 g, 4.0 mmol) was converted to **6e** (0.94 g, 83% yield). A colourless solid. Mp. 124-126 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.0, 2.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.15 (dd, J = 8.0, 2.0 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 3.74 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 136.2, 133.1, 132.8, 130.6, 129.7, 129.2, 126.7, 116.7, 103.9, 55.9. IR (neat) v 1591 cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{14}H_{12}{}^{35}Cl_2O_2$ [M]$^+$: 283.0287, found: 283.0290.

2'-bromo-1,1'-biphenyl-2,6-diol (1a): **1a** was synthesized according to the reported procedure.[19] Its spectroscopic data are in good agreement with those reported.[19]

2'-Chloro-1,1'-biphenyl-2,6-diol (1b); a typical procedure for the demethylation of 6 to give 1 (Procedure B): A 1.0 M solution of BBr_3 (20 mL, 20 mmol) in CH_2Cl_2 was dropwise added to an ice-cold solution of **6b** (1.0 g, 4.0 mmol) in CH_2Cl_2 (0.07 M) over 10 min. The resulting solution was stirred at ambient temperature overnight and cooled again to 0 ºC. MeOH (1.0 mL) was added, Water and CH_2Cl_2 were added to the residue, and the mixture was extracted with CH_2Cl_2 three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc = 4:1) to give **1b** (0.67 g, 83% yield). A colourless solid. Mp. 145-146 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.61-7.63 (m, 1H), 7.39-7.46 (m, 3H), 7.20 (t, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 2H), 4.61 (s, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.5, 135.8, 133.0, 130.7, 130.2, 130.1, 128.0, 113.4, 107.9. Two ^{13}C signals are overlapped. IR (neat) v 3401. 1622, 1592 cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{12}H_{10}{}^{35}ClO_2$ [M+H]$^+$: 221.0364, found: 221.0364.

2'-Iodo-1,1'-biphenyl-2,6-diol (1c): By following **Procedure B**, **6c** (0.68 g, 2.0 mmol) was converted to **1c** (0.50 g, 79% yield). A colourless solid. Mp. 172-174 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, J = 8.0, 1.0 Hz, 1H), 7.53 (td, J = 8.0, 1.0 Hz, 1H), 7.37 (dd, J = 7.0, 2.0 Hz, 1H), 7.17-7.23 (m, 2H), 6.59 (d, J = 8.0 Hz, 2H), 4.55 (s, 2H)., ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1, 140.4, 136.6, 132.2, 130.9, 130.2, 129.5, 118.7, 107.9, 102.5. IR (neat) v 3405, 1622, 1590 cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{12}H_{10}IO_2$ [M+H]$^+$: 312.9719, found: 312.9720.

2'-Bromo-3',5'-difluoro-1,1'-biphenyl-2,6-diol (1d): 2'-Bromo-3',5'-difluoro-2,2'-dimethoxy-1,1'-biphenyl-2,6-diol **6d** was prepared from 1,2-dibromo-3,5-difluorobenzene **5d** (1.1 g, 4.0 mmol) by following **Procedure A** with the following modifications: Cs_2CO_3 was used instead of K_3PO_4 and the reaction was conducted for 13 h. Then, the crude product **6d** was subjected to **method B**, and the follwoing recrystallization of a crude product from $CHCl_3$ gave **1d** (0.50 g, 55% yield for 2 steps). A colourless solid. Mp. 188-190 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, J = 8.0 Hz, 1H), 6.96-7.03 (m, 2H), 6.56 (d, J = 8.0 Hz, 2H), 4.66 (s, 2H)., ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1 (dd, J_{CF} = 234, 13 Hz), 160.1 (dd, J_{CF} = 234, 13 Hz), 153.3, 136.6 (d, J_{CF} = 10 Hz), 130.6, 115.4 (dd, J_{CF} = 21, 4.0 Hz), 113.7, 108.2, 107.9 (dd, J_{CF} = 21, 4.0 Hz), 105.3 (t, J_{CF} = 26 Hz). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -105.7 (m, 1F), -117.5 (m, 1F). IR (neat) v 3397, 1622, 1587 cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{12}H_7{}^{79}BrF_2O_2$ [M]$^+$: 300.9670, found: 300.9673.

2',3'-Dichloro-1,1'-biphenyl-2,6-diol (1e): By following **Procedure B**, **6e** (0.85 g, 3.0 mmol) was converted to **1e** (0.68 g, 89% yield). A colourless solid. Mp. 62-65 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.0, 2.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.30 (dd, J = 8.0, 2.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 6.58 (d, J = 8.0 Hz, 2H), 4.66 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 134.5, 134.2, 132.9, 131.2, 131.0, 130.3, 128.1, 113.5, 108.0. IR (neat) v 3406, 1621, 1591 cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{12}H_9{}^{35}Cl_2O_2$ [M+H]$^+$: 254.9975, found: 254.9974.

2-Bromo-4,5-dimethoxy-2',6'-bis(methoxymethoxy)-1,1'-biphenyl (6f) and **2'-Bromo-4',5'-dimethoxy-1,1'-biphenyl-2,6-diol (1f):** To an ice-cold, stirred solution of 1,3-bis(methoxymethyl)benzene (3.6 g, 18.1 mmol) in Et_2O (40mL) was dropwise added *n*-BuLi (2.8 M solution in hexanes, 7.2 mL, 19.9 mmol) over 25 min. The reaction mixture was stirred at ambient temperature for 4 h and was cooled to 0 °C, to which was dropwise added 1,2-dibromo-4,5-dimethoxybenzene **4f** (5.4 g, 18.1 mmol) over 5 min with vigorous stirring. The mixture was stirred at 0 °C overnight, and MeOH (1.0 mL) and H_2O (40 mL) were added. The resulting mixture was extracted with EtOAc three times, and the combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc = 4:1) to give **6f** (5.0 g) which contained some impurities. Further purification of the product by column chromatography (hexanes/EtOAc = 4:1) produced pure **6f**. A colourless solid. Mp. 104-106 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J = 8.0 Hz, 1H), 7.13 (s, 1H), 6.90 (d, J = 8.0 Hz, 2H), 6.76 (s, 1H), 5.09 and 5.06 (ABq, J = 7.0 Hz, 4H), 3.91 (s, 3H), 3.83 (s, 3H), 3.37 (s, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 155.5, 148.6, 147.9, 129.4, 128.0, 121.2, 115.0, 114.9, 114.6, 108.7, 94.7, 56.04, 56.02, 55.99. IR (neat) v 1595 cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{18}H_{21}{}^{79}BrO_6Na$[M+Na]$^+$: 435.0414, found: 435.0414.

A solution of the aforementioned **6f** (5.0 g) and *p*-TsOH (2.3 g, 24 mmol) in MeOH (30 mL) was stirred at ambient temperature for 10 h and was concentrated under vacuo. The residue was purified by column chromatography (hexanes/EtOAc = 4:1 to 1:1) to give **1f** (3.9 g), which was recrystallized from MeOH to give pure **1f** (2.4 g, 40% yield for 2 steps). Colorless needles. Mp. 236-237 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.84 (s, 1H), 6.60 (d, J = 8.0 Hz, 2H), 4.68 (s, 2H), 3.94 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 150.5, 149.5, 130.1, 123.0, 116.33, 116.31, 115.1, 114.6, 107.7, 56.3, 56.2. IR (neat) v 3446, 1622, 1599. HRMS (MALDI) *m/z* calcd for $C_{14}H_{13}{}^{79}BrO_4Na$ [M+Na]$^+$: 346.9889, found: 346.9887.

2'-Bromo-1,1'-biphenyl-2,6-diyl diacetate (3a); a typical procedure for the acetylation of 1 to give 3 (Procedure C): A solution of **1a** (0.30 g, 1.1 mmol), Ac_2O (0.31 mL, 3.3 mmol, 3.0 equiv), 4-(dimethyamino)pridine (DMAP) (13.8 mg, 0.10 mmol, 0.1 equiv), and Et_3N (0.31 mL, 2.3 mmol. 2.0 equiv) in CH_2Cl_2 (0.1 M) was stirred at ambient temperature for 1 h and was concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc = 4:1) to give **3a** (0.31 g, 80% yield). A colourless solid. Mp. 81-83 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, J = 8.0, 1.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.32 (td, J = 8.0, 1.0 Hz, 1H),

7.23 (td, *J* = 8.0, 2.0 Hz, 1H), 7.18 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 1.94 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 168.8, 149.0, 133.64, 132.5, 131.8, 129.5, 129.3, 127.9, 126.9, 124.2, 120.2, 20.5. IR (neat) ν 1769 cm^{-1}. HRMS (MALDI) m/z calcd for $C_{16}H_{13}{}^{79}BrO_4Na$ [M+Na]$^+$: 370.9889, found: 370.9886.

2'-Chloro-1,1'-biphenyl-2,6-diyl diacetate (**3b):** By following **Procedure C**, **1b** (0.22 g, 1.0 mmol) was converted to **3b** (0.30 g, 98% yield). A colourless solid. Mp. 71-73 °C. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.44-7.47 (m, 2H), 7.27-7.33 (m, 2H), 7.19 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 1.95 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 168.8, 149.1, 134.2, 131.7, 131.4, 129.4, 129.3, 126.3, 126.2, 120.2, 20.47. Two ^{13}C signals are overlapped. IR (neat) ν 1771, 1639, 1615 cm^{-1}. HRMS (MALDI) m/z calcd for $C_{16}H_{13}{}^{35}ClO_4Na$ [M+Na]$^+$: 327.0395 , found: 327.0397.

2'-Iodo-1,1'-biphenyl-2,6-diyl diacetate (3c): By following **Procedure C**, **1c** (0.31 g, 1.0 mmol) was converted to **3c** (0.38 g, 95% yield). A colourless solid. Mp. 122-124 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) *δ* 7.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.36 (td, *J* = 8.0, 1.0 Hz, 1H), 7.11-7.15 (m, 3H), 7.05 (td, *J* = 8.0, 2.0 Hz, 1H), 1.93 (s, 6H)., ^{13}C-NMR (126 MHz, $CDCl_3$) *δ* 168.7, 148.8, 138.8, 137.9, 130.9, 129.4, 129.3, 127.7, 120.3, 99.7, 20.49. Two ^{13}C signals are overlapped. IR (neat) ν 1768, 1613 cm^{-1}. HRMS (MALDI) m/z calcd for $C_{16}H_{13}IO_4Na$ [M+Na]$^+$: 418.9751, found: 418.9748.

2'-Bromo-3',5'-difluoro-1,1'-biphenyl-2,6-diyl diacetate (3d): By following **Procedure C**, **1d** (0.31 g, 1.0 mmol) was converted to **3d** (0.38 g, quantitative yield). A colourless solid. Mp. 116-118 °C. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.49 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.94 (td, *J* = 8.0, 3.0 Hz, 1H), 6.79-6.82 (m, 1H), 2.01 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 168.5, 161.2 (dd, J_{CF} = 242, 12 Hz), 159.1 (dd, J_{CF} = 242, 12 Hz), 148.7, 137.0 (d, J_{CF} = 9 Hz), 130.0, 125.7, 120.3, 114.4 (dd, J_{CF} = 22, 4 Hz), 106.6 (dd, J_{CF} = 22, 4 Hz), 104.6 (t, J_{CF} = 26 Hz), 20.6. ^{19}F NMR (376 MHz, $CDCl_3$) *δ* -102.8 (m, 1F), -114.1 (m, 1F). IR (neat) ν 1775, 1615, 1589 cm^{-1}. HRMS (MALDI) m/z calcd for $C_{16}H_{11}{}^{79}BrO_4F_2Na$ [M+Na]$^+$: 406.9701, found: 406.9698.

2',3'-Dichloro-1,1'-biphenyl-2,6-diyl diacetate (3e): By following **Procedure C**, **1e** (0.26 g, 1.0 mmol) was converted to **3e** (0.32 g, 95% yield). A colourless solid. Mp. 102-104 °C. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.45-7.50 (m, 2H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.11 (dd, *J* = 8.0, 2.0 Hz, 1H), 1.97 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 168.7, 148.8, 138.8, 137.9, 130.9, 129.4, 129.3, 127.7, 120.3, 99.7, 20.49. Two ^{13}C signals are overlapped. IR (neat) ν 1771, 1613, 1583 cm^{-1}. HRMS (MALDI) m/z calcd for $C_{16}H_{12}{}^{35}Cl_2O_4Na$ [M+Na]$^+$: 361.0005, found: 361.0003.

2'-Bromo-4',5'-dimethoxy-1,1'-biphenyl-2,6-diyl diacetate (3f): By following **Procedure C, 1f** (1.0 g, 3.1 mmol) was converted to **3f** (1.16 g, 92% yield). A colourless solid. Mp. 160-162 °C. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.44 (t, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.10 (s, 1H), 6.68 (s, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 2.00 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 168.9, 149.3, 149.1, 147.8, 129.2, 127.8, 125.4, 120.2, 114.9, 114.3, 114.0, 56.11, 56.06, 20.6. IR (neat) ν 1765, 1599, 1509 cm^{-1}. HRMS (MALDI) m/z calcd for $C_{18}H_{17}{}^{79}BrO_6Na$ [M+Na]$^+$: 431.0101, found: 431.0100.

A general procedure for lipase-catalyzed acylative desymmetrization of 1 (Procedure D): To a solution of biaryl diol **1** (0.50 mmol) in toluene (0.1 M) was added PS-IM (2.0 w/w), vinyl acetate (0.46 mL, 5.0 mmol) and Na_2CO_3 (50 mg, 0.75 mmol) at 35 °C. The progress of the reaction was monitored by HPLC analysis of an aliquot of the reaction mixture. After the consumption of **1**, the mixture was filtered through a pad of Celite with EtOAc, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc = 8:1) to give (*S*)-**2**.

(*S*)-2'-Bromo-6-hydroxy-1,1'-biphenyl-2-yl acetate [(*S*)-2a]: By following **Procedure D**, **(*S*)-2a** (138 mg, 90% yield) was obtained from **1a** (133 mg, 0.50 mmol). A colourless solid. Mp. 95-97 °C. $[\alpha]_D^{22}$ +37.8 (*c* 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.74 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.41 (td, *J* = 8.0, 1.0 Hz, 1H), 7.28-7.35 (m, 3H), 6.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.73 (s, 1H), 1.93 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 169.1, 153.6, 148.7, 133.3, 132.7, 132.4, 130.4, 129.8, 127.8, 125.2, 121.3, 114.5, 113.4, 20.5. IR (neat) ν 3429, 1738, 1619, 1590 cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{14}H_{11}{}^{79}BrO_3Na$ [M+Na]$^+$: 328.9784, found: 328.9783. Its optical purity (>99% ee) was determined by HPLC analysis at 20 °C using a CHIRALPAK IE column (hexanes/2-propanol = 97.5:2.5; flow rate: 1.0 mL/min; UV detection: 220 nm; retention times: 13.1 min (*R*), 14.7 min (*S*)).

(*S*)-2'-Chloro-6-hydroxy-1,1'-biphenyl-2-yl acetate [(*S*)-2b]: By following **Procedure D**, **(*S*)-2b** (108 mg, 82% yield) was obtained from **1b** (110 mg, 0.50 mmol). A colourless solid. Mp. 87-88 °C. $[\alpha]_D^{24}$ +47.6 (*c* 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.54-7.56 (m, 1H), 7.29-7.41 (m, 4H), 6.91 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.79 (s, 1H), 1.93 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 169.1, 153.8, 148.9, 135.0, 132.4, 130.5, 130.2, 130.1, 129.8, 127.2, 119.5, 114.5, 113.4, 20.5. IR (neat) ν 3438, 1738, 1615, 1591 cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{14}H_{11}{}^{35}ClO_3Na$ [M+Na]$^+$: 285.0289, found: 285.0289. Its optical purity (99% ee) was determined by HPLC analysis at 20 °C using a CHIRALPAK IE column (hexanes/2-propanol = 97.5:2.5; flow rate: 1.0 mL/min; UV detection: 254 nm; retention times: 13.0 min (*R*), 14.1 min (*S*)).

(*S*)-6-hydroxy-2'-iodo-1,1'-biphenyl-2-yl acetate [(*S*)-2c]: By following **Procedure D**, **(*S*)-2c** (160 mg, 90% yield) was obtained from **1c** (156 mg, 0.50 mmol). A colourless solid. Mp. 117-121 °C. $[\alpha]_D^{22}$ +30.8 (*c* 0.49, $CHCl_3$). ^{1}H NMR (500 MHz, [D_6]acetone) *δ* 8.45 (s, 1H), 7.95 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.42 (td, *J* = 8.0, 1.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.10 (td, *J* = 8.0, 2.0 Hz, 1H), 6.88 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.70 (dd, *J* = 8.0, 1.0 Hz, 1H), 1.84 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) *δ* 169.1, 153.4, 148.6, 139.7, 137.0, 131.6, 130.3, 129.9, 128.7, 124.6, 114.5, 113.5, 101.1, 20.5. IR (neat) ν 3434, 1738, 1615 cm^{-1}. HRMS (MALDI) m/z calcd for $C_{14}H_{11}IO_3Na$ [M+Na]$^+$: 376.9645, found: 376.9646. Its optical purity (99% ee) was determined by HPLC analysis at 20 °C using a CHIRALPAK IE column (hexanes/2-propanol = 97.5:2.5; flow rate: 1.0 mL/min; UV detection: 254 nm; retention times: 13.0 min (*R*), 14.5 min (*S*)).

(*S*)-2'-Bromo-3',5'-difluoro-6-hydroxy-1,1'-biphenyl-2-yl acetate [(*S*)-2d]: By following **Procedure D**, **(*S*)-2d** (156 mg, 91% yield) was obtained from **1d** (151 mg, 0.50 mmol). A colourless solid. Mp. 136-140 °C. $[\alpha]_D^{23}$ +19.6 (*c* 0.44, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.35 (t, *J* = 8.0 Hz, 1H), 6.98 (td, *J* = 8.0, 3.0 Hz, 1H), 6.86-6.90 (m, 2H), 6.81 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.78 (s, 1H), 2.00 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) *δ* 169.1, 161.6 (dd, J_{CF} = 250, 12 Hz), 159.7 (dd, J_{CF} = 250, 12 Hz), 153.5, 148.6, 136.7 (d, J_{CF} = 10 Hz), 130.3, 119.6, 114.83 (dd, J_{CF} = 21, 4.0 Hz), 114.81, 113.6, 107.2 (dd, J_{CF} = 21, 4.0 Hz), 104.9 (t, J_{CF} = 26 Hz), 20.6. ^{19}F NMR (376 MHz, $CDCl_3$) *δ* -101.9 (m, 1F), -113.4 (m, 1F). IR (neat) ν 3415, 1738, 1619, 1588 cm^{-1}. HRMS (FAB$^+$) m/z calcd for $C_{14}H_{10}{}^{79}BrF_2O_3$ [M+H]$^+$: 342.9781, found: 342.9776. Its optical purity (>99% ee) was determined by HPLC analysis at 20 °C using a CHIRALPAK IE column (hexanes/2-

propanol = 98.75:1.25; flow rate: 1.0 mL/min; UV detection: 220 nm; retention times: 12.2 min (*R*), 13.7 min (*S*)).

(*S*)-2',3'-Dichloro-6-hydroxy-1,1'-biphenyl-2-yl acetate [(*S*)-2e]: By following **Procedure D**, **(*S*)-2e** (113 mg, 76% yield) was obtained from **1e** (128 mg, 0.50 mmol). A colourless solid. Mp. 136-138°C. $[\alpha]_D^{23}$ +48.7 (*c* 0.50, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.55 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.28-7.36 (m, 2H), 7.21 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.90 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.81 (s, 1H), 1.96 (s, 3H)., ^{13}C NMR (126 MHz, CDCl3) *δ* 169.1, 153.6, 148.8, 133.8, 133.4, 133.1, 130.8, 130.4, 130.0, 127.6, 119.5, 114.7, 113.5, 20.6. IR (neat) v 3415, 1737, 1617, 1589 cm^{-1}. HRMS (MALDI) m/z calcd for $C_{14}H_{10}{}^{35}Cl_2O_3Na$ $[M+Na]^+$: 318.9899, found: 318.9897. Its optical purity (>99% ee) was determined by HPLC analysis at 20 °C using a CHIRALPAK IE column (hexanes/2-propanol = 97.5:2.5; flow rate: 1.0 mL/min; UV detection: 220 nm; retention times: 18.9 min (*R*), 22.3 min (*S*)).

(*S*)-2'-Bromo-6-hydroxy-4',5'-dimethoxy-1,1'-biphenyl-2-yl acetate [(*S*)-2f]: **(*S*)-2f** (172 mg, 94% yield) was obtained from **1f** (163 mg, 0.50 mmol) by following **Procedure D** with the following modifications: Using PS-IM (488 mg, 3 w/w) at 50 °C for 26 h and the column chromatography (hexanes/EtOAc = 4:1 to 2:1). An amorphous colourless solid. Mp. 43-55 °C. $[\alpha]_D^{25}$ +11.4 (*c* 0.56, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.32 (t, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 6.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.75-6.77 (m, 2H), 4.87 (s, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 169.4, 154.0, 149.9, 149.1, 148.8, 129.9, 124.1, 121.3, 115.7, 115.3, 114.6, 114.4, 113.5, 56.30, 56.28, 20.8. IR (neat) v 3448, 3012, 2938, 2842, 1762, 1599, 1509 cm^{-1}. HRMS (MALDI) m/z calcd for $C_{16}H_{15}{}^{79}BrO_5Na$ $[M+Na]^+$: 388.9995, found: 388.9994. Its optical purity (>99% ee) was determined by HPLC analysis at 20 °C using a CHIRALPAK IE column (hexanes/2-propanol = 92.5:7.5; flow rate: 1.0 mL/min; UV detection: 254 nm; retention times: 11.0 min (*R*), 12.1 min (*S*)).

A general procedure for lipase-catalyzed hydrolytic desymmetrization of 3 (Procedure E): To a solution of **3** (0.50 mmol) in a mixture of a solution pH 7.0 phosphate buffer (3.0 mL) and pentane (2.0 mL) was added PS-IM (0.10 w/w) at 30 °C. The progress of the reaction was monitored by HPLC analysis of an aliquot of the reaction mixture. After the consumption of **3**, the mixture was filtered through a pad of Celite with EtOAc and extracted with EtOAc for three times. Then the filtrate was concentrated under vacuo to give monoester (*R*)-**2**, whose purity was more than 98% based on ^1H NMR analysis.

(*R*)-2'-Bromo-6-hydroxy-1,1'-biphenyl-2-yl acetate [(*R*)-2a]: By following **Procedure E**, **(*R*)-2a** (153 mg, >99% yield) was obtained from **3a** (175 mg, 0.50 mmol). A colourless solid. Mp. 97-98 °C. $[\alpha]_D^{22}$ -37.8 (*c* 0.58, $CHCl_3$). Its ^1H NMR, ^{13}C NMR, and IR data are in good agreement with those for **(*S*)-2a**. HRMS (MALDI) *m/z* calcd for $C_{14}H_{11}{}^{79}BrO_3Na$ $[M+Na]^+$: 328.9784, found: 328.9784. Its optical purity (>99% ee) was determined by HPLC analysis as shown for **(*S*)-2a**.

(*R*)-2'-Chloro-6-hydroxy-1,1'-biphenyl-2-yl acetate [(*R*)-2b]: By following **Procedure E**, **(*R*)-2b** (131 mg, >99% yield) was obtained from **3b** (152 mg, 0.50 mmol). A colourless solid. Mp. 87-88 °C. $[\alpha]_D^{25}$ -46.7 (*c* 0.50, $CHCl_3$). Its ^1H NMR, ^{13}C NMR, and IR data are in good agreement with those for **(*S*)-2b**. HRMS (MALDI) *m/z* calcd for $C_{14}H_{11}{}^{35}ClO_3Na$ $[M+Na]^+$: 285.0289, found: 285.0291. Its optical purity (>99% ee) was determined by HPLC analysis as shown for **(*S*)-2b**.

(*R*)-6-Hydroxy-2'-iodo-1,1'-biphenyl-2-yl acetate [(*R*)-2c]: **(*R*)-2c** (150 mg, 85% yield) was obtained from **3c** (198 mg, 0.50 mmol) by following **Procedure E** with the following modification; the crude product was purified by column chromatography (hexanes/EtOAc = 8:1). A colourless solid. Mp. 117-121 °C. $[\alpha]_D^{22}$ -31.6 (*c* 0.58, $CHCl_3$). Its ^1H NMR, ^{13}C NMR, and IR data are in good agreement with those for **(*S*)-2b**. HRMS (MALDI) m/z calcd for $C_{14}H_{11}IO_3Na$ $[M+Na]^+$: 376.9645, found: 376.9642. Its optical purity (>99% ee) was determined by HPLC analysis as shown for **(*S*)-2c**.

(*R*)-2'-Bromo-3',5'-difluoro-6-hydroxy-1,1'-biphenyl-2-yl acetate [(*R*)-2d]: By following **Procedure E**, **(*R*)-2d** (162 mg, 94% yield) was obtained from **3d** (193 mg, 0.50 mmol). A colourless solid. Mp. 136-140 °C. $[\alpha]_D^{22}$ -19.9 (*c* 0.48, $CHCl_3$). Its ^1H NMR, ^{13}C NMR, ^{19}F NMR, and IR data are in good agreement with those for **(*S*)-2d**. HRMS (FAB^+) m/z calcd for $C_{14}H_{10}{}^{79}BrF_2O_3$ $[M+H]^+$: 342.9781 and 344.9762, found:342.9790 and 344.9772. Its optical purity (>99% ee) was determined by HPLC analysis as shown for **(*S*)-2d**.

(*R*)-2',3'-Dichloro-6-hydroxy-1,1'-biphenyl-2-yl acetate [(*R*)-2e]: By following **Procedure E**, **(*R*)-2e** (146 mg, 98% yield) was obtained from **3e** (170 mg, 0.50 mmol). A colourless solid. Mp. 136-138 °C. $[\alpha]_D^{23}$ -49.9 (*c* 0.58, $CHCl_3$). Its ^1H NMR, ^{13}C NMR, and IR data are in good agreement with those for **(*S*)-2e**. HRMS (MALDI) m/z calcd for $C_{14}H_{10}{}^{35}Cl_2O_3Na$ $[M+Na]^+$: 318.9899, found: 318.9899. Its optical purity (>99% ee) was determined by HPLC analysis as shown for **(*S*)-2e**.

(*R*)-2'-bromo-6-hydroxy-4',5'-dimethoxy-1,1'-biphenyl-2-yl acetate [(*R*)-2f]: **(*R*)-2f** (174 mg, 95% yield) was obtained from **3f** (205 mg, 0.50 mmol) by following **Procedure E** with the following modifications: Using PS-IM (41 mg, 0.20 w/w) and double volume of each solvent at 50 °C. A colourless solid. Mp. 52-57 °C. $[\alpha]_D^{22}$ -10.3 (*c* 0.70, $CHCl_3$). Its ^1H NMR, ^{13}C NMR, and IR data are in good agreement with those for **(*S*)-2f**. HRMS (MALDI) m/z calcd for $C_{16}H_{15}{}^{79}BrO_5Na$ $[M+Na]^+$: 388.9995, found: 388.9992. Its optical purity (>99% ee) was determined by HPLC analysis as shown for **(*S*)-2f**.

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Keywords: lipase • axial chirality • enantiodivergent synthesis• desymmetrization

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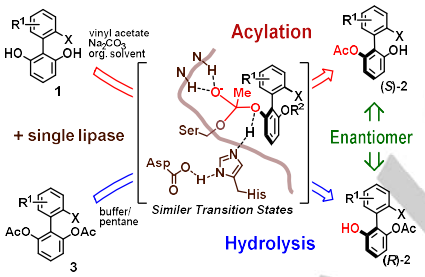
Layout 1:

FULL PAPER

Commercially available *Burkholderia cepacia* lipase was used for the acylative desymmetrization of σ-symmetric 2'-halo-1,1'-biphenyl-2,6-diols **1** and the hydrolytic desymmetrization of their diacetates **3** to achieve the enantiodivergent synthesis of axially chiral biphenyl monoacetates, (*S*)- and (*R*)-**2,** respectively, in high chemical and optical yields.



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Enantiodivergent synthesis of axially chiral biphenyls from σ-symmetric 1,1'-biphenyl-2,6-diol derivatives by single lipase-catalyzed acylative and hydrolytic desymmetrization