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Dynamic Kinetic Resolution of 2-Hydroxybiaryl Atropisomers via Lipase-Catalyzed Enantioselective *O*-Acylation

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The increasing interest in axially chiral biaryl moieties, which are prevalent in chiral ligands, organocatalysts, and bioactive molecules, has raised the need for developing novel efficient synthetic methods for these types of molecules. In addition to the currently available methods, such as kinetic resolution, desymmetrization and enantio- and diastereo-selective biaryl coupling, we herein report a lipase-catalyzed dynamic kinetic resolution (DKR) of racemic 2-hydroxybiaryls through enantioselective *O*-acylation. This method features the production of enantiomerically enriched atropisomers (89%–98% ee) in 91%–99% yields from eleven racemates. Notably, the DKR proceeds without any racemization catalyst since *in situ*-racemization was achieved by easy rotation about the biaryl axis of the substrates. The enzymatic *O*-acylation then furnished conformationally stable biaryl-containing esters, in which the increased steric bulkiness of the *O*-acyl moiety suppresses the rotation, i.e., racemization, under the reaction conditions of 35–50 °C. This experimental study was accompanied by a computational determination of the rotational barrier of substrates and products. The choice of suitable substrates with a significant difference in their rotational barrier compared to that of their products turned out to be the key to an efficient implementation of this method.

Introduction

The importance of axially chiral biaryl compounds, characterized by the hindered rotation about a single bond between two (hetero)aromatic rings, has grown significantly over recent decades. The atropisomerism embraces a unique structural feature found in many natural products and synthetic molecules, and molecules containing this structural feature exhibit a range of medicinal properties.[1,2] Biaryl atropisomers are a promising group of compounds in drug discovery research because of their unique three-dimensional spread, which is different from typical pharmaceuticals containing central chirality.[3] Among them, polyketide-derived viridotoxin acts as an antibacterial,[4] allocolchicine acts against gout,[5,6] and gossypol exhibits potential anti-neoplastic activity[7] (Figure 1a). In addition, axially chiral biaryls are widely used as chiral ligands for transition-metal catalysts and organocatalysts with broad

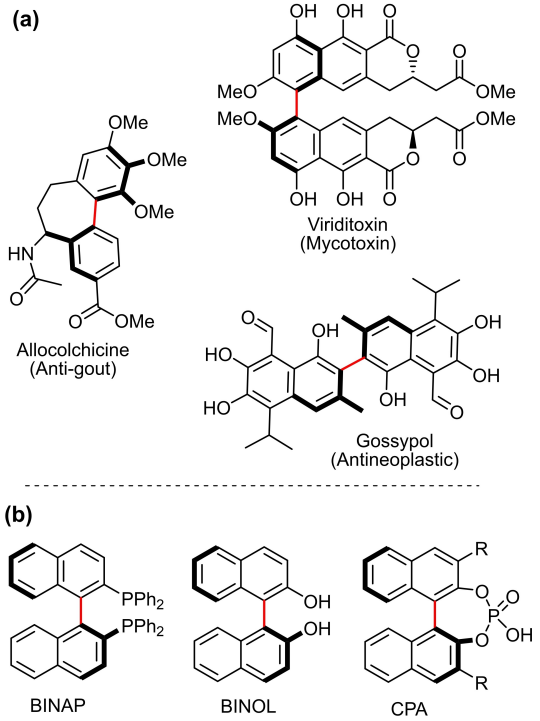

Figure 1. Some representative atropisomers in (a) bioactive natural products and (b) chiral ligands and catalysts.

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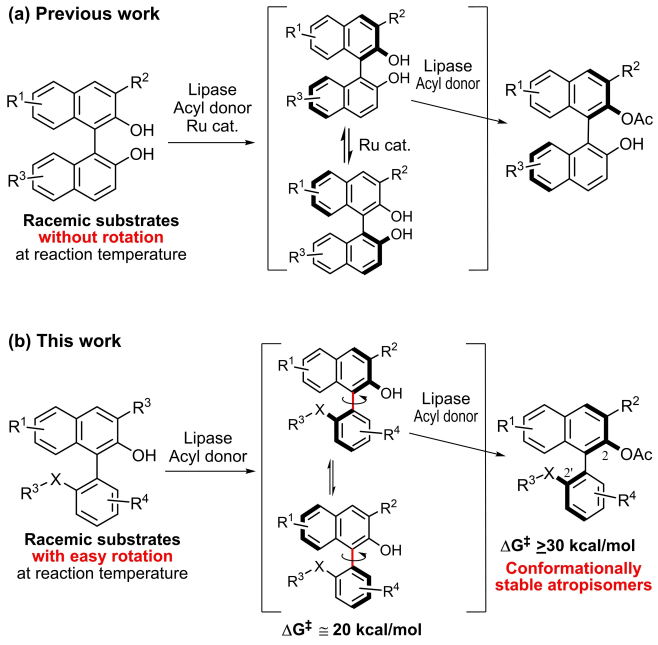
applicability in asymmetric catalysis.[8–10] For instance, BINAP and BINOL are well-known chiral ligands whereas chiral phosphoric acid (CPA) and its derivatives serve as organocatalysts (Figure 1b).

Due to their numerous uses and advantages, many strategies have been developed for constructing axially chiral biaryls.[11–19] The available synthetic methodologies can broadly be classified into three types: (1) Enantio- or diastereoselective biaryl coupling using transition metals or organocatalysts (Class A);[12,13,17,18,20] (2) conversion of racemic or prochiral biaryl compounds into optically enriched ones (Class B);[15,21–28] and (3) construction of biaryl compounds via aromatization of non-aromatic compounds (Class C).[29–31] Kinetic resolution (KR) of racemic compounds with high rotational barrier and desymmetrization of symmetric biaryls[24,32] are among the most traditional examples in Class B.[14,15,33,34] In 2018, we have reported dynamic kinetic resolution (DKR) of racemic 2,2′-dihydroxybiaryls, such as BINOL and substituted BINOLs, by the combination of commercial lipase for KR and a ruthenium complex for racemization (Scheme 1a).[35]

In addition, DKR of biaryl compounds with ease of racemization due to their low rotational barrier provides an alternative to obtain enantiomerically enriched biaryls.[11,16] The most significant feature of this method compared to the DKR in Scheme 1a is that substrates rapidly racemize at the reaction temperature without using a racemization catalyst, but the products do not. Therefore, this method produces conformationally stable atropisomers. In general, steric bulkiness of substituent(s) in proximity to the chiral axis mainly contributes to the rotational stability around the aryl–aryl single bond, and the molecules with the rotational free energy barrier ($\Delta G^{\ddagger}$) below and around 20 kcal/mol can rotate rapidly at 25 °C, while those with $\Delta G^{\ddagger}$ above and about 30 kcal/mol exhibit sufficient atropisomerical stability at the same temperature.[36–39] So far, typical examples of this kind of DKR are based on the introduction of substituent(s) to the C2-position by bromination,[23,40,41] and C–C bond formation via aromatic C–H activation.[11,28,42] The increase of the steric bulkiness of the existing C2-functional groups via biaryl lactone/lactam opening,[43,44] cross coupling,[45] *O*-acylation,[46] and transamination reactions[47] is another strategy for this type of DKR. In those cases, organocatalysts and transition-metal catalysts have been primarily utilized to achieve the above-mentioned C2-functionalizations.

Taking advantage of the high enantio-differentiating ability of lipases, we planned to develop a DKR method using lipase for the esterification of easily rotatable 2-hydroxybiphenyl derivatives as the critical and only step of this transformation. This method could allow an efficient synthesis of conformationally stable biaryl atropisomers in high yield and high enantiomeric purity without the need for using any racemization catalyst (Scheme 1b). The size of the C2- and C2′-substituents of substrates and that of products have critical impacts on the racemization rate, and computational calculation of the rotational barrier of substrates and their esters aided in selecting/designing suitable substrates for such a DKR. In addition, the size of substrates must fit into the active site of the lipase for the desired acylation. Based on our previous success of the lipase–Ru co-catalyzed DKR of BINOLs[35] and the lipase-catalyzed desymmetrization of σ-symmetrical biphenyl derivatives,[48] we speculated that biaryl molecules, made of naphthyl and phenyl moieties bonded together, would be suitable for the above-mentioned DKR. Herein we report the DKR of easily rotating racemic 2-hydroxybiaryls using readily available commercial lipases.



Scheme 1. Our research group's DKRs of racemic 2-hydroxybiaryls to generate enantiomerically enriched atropisomers: (a) Previous work and (b) this work.

Results and Discussion

Compound **1a** was selected as a model substrate for establishing this new DKR method. The rotational barriers for racemization of **1a** and its acetate **2a** were estimated by DFT calculation prior to the experimental study. The calculated $\Delta G^{\ddagger}$ value ($\Delta G^{\ddagger}_{calc}$) for the optimized transition states (TS) was 23.9 kcal/mol for **1a** and 29.8 kcal/mol for **2a** (Figure 2). The $\Delta G^{\ddagger}_{calc}$ of another TS for **1a** where OH and OEt are distally located was 7.8 kcal/mol higher than that shown in Figure 2 (see also Supporting Information). These results suggested that **1a** would rotate rapidly at room temperature, thereby facilitating the racemization. On the other hand, its acetate **2a** has a sufficiently high rotational barrier so that **2a** would be conformationally stable. The computational results were in good agreement with the experimental results, i.e., the $\Delta G^{\ddagger}_{exp}$ for **1a** is 24.3 kcal/mol at 25 °C in heptane and its half-life time ($t_{1/2}$) is 9.2 h; $\Delta G^{\ddagger}_{exp}$ for **2a** is 28.9 kcal/mol at 50 °C in heptane with $t_{1/2} = 4.9\times10^{2}$ h (for detailed information, see Supporting Information). Thus, **1a** seems to be a suitable substrate for our envisioned DKR.

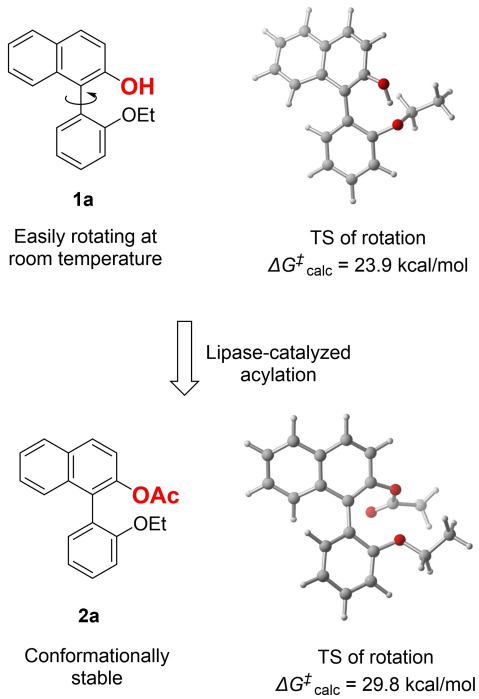
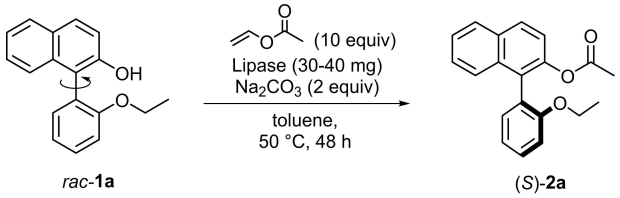


Figure 2. Calculated rotational energy barriers ($\Delta G^{\ddagger}_{calc}$) of **1a** and **2a**; calculations were performed at B3LYP/631G** in gas phase.

Table 1. Screening of lipases for esterification of *rac*-**1a**.[a]



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

Entry	Immobilized lipase	% NMR-yield and % ee of (*S*)-**2a**[b]
1	*Candida antarctica* lipase A (CHIRAZYME L-5)	Not detected
2	*Candida antarctica* lipase B (Novozyme 435)	23%, 94% ee
3	*Pseudomonas fluorescens* lipase (AK "Amano" IM)	20%, 88% ee
4	*Pseudomonas* sp. lipase (Toyobo LIP300)	24%, 98% ee
5	*Burkholderia cepacia* lipase (PS "Amano")	54%, 94% ee
6	*Burkholderia cepacia* lipase (PS "Amano" IMH)	76%, 93% ee

[a] 0.04 mmol of *rac*-**1a** was used. [b] The yield was calculated by ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. The enantiomeric excess was determined by HPLC analysis using a chiral column (for details, see: Supporting Information).

Next, we investigated the suitability of lipases to enantioselectively acylate *rac*-**1a**. Inspired by our previous work on lipase-catalyzed kinetic resolution of 2-hydroxylbiaryl compounds,[32] the esterification reaction of *rac*-**1a** was initially carried out with a series of commercially available immobilized lipases in the presence of vinyl acetate and Na_2CO_3 (Table 1). In terms of the reaction conversion and enantiomeric purity of the corresponding acetate (*S*)-**2a**, we found that lipases belonging to the *Pseudomonas* and *Burkholderia* families are suitable for **1a** (entries 3–6). In contrast, screening of other lipases belonging to other classes, such as lipases from porcine pancreas and *Candida rugosa*, did not provide **2a**. It is worth noting that the yield of (*S*)-**2a** was well over 50% with high enantiomeric purity (93% ee) (Table 1, entry 6), indicating the success of DKR with rapid racemization. By NMR analysis of crude products, we also confirmed that unreacted **1a** was recovered and there were no side products in all entries. Based on the highest yield of (*S*)-**2a** at the reaction time of 48 h, *Burkholderia cepacia* lipase (trade name: lipase PS "Amano" IMH) was selected for further investigation.

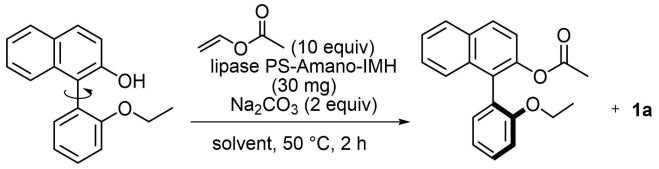
We next investigated the solvent effect. Thus, esterification of *rac*-**1a** using lipase PS-Amano-IMH was conducted for 2 h in a range of solvents (Table 2). In polar solvents, we observed the formation of racemic **2a** (entries 1 and 2), whereas very slow reaction progress was observed in acetone and CH_2Cl_2 (entries 3 and 4). In contrast, the reaction was much faster in *i*-Pr_2O, cyclohexane and *n*-heptane than that in toluene while maintaining high enantioselectivity (entries 5–8). Among them, *n*-heptane turned out to be the most suitable solvent.

We also examined the impact of the acyl moiety bulkiness of the acyl donors, using vinyl esters having longer or bulky alkyl chains. However, no better findings were obtained (for details, see Supporting Information).

Our next attempt was to understand the impact of reaction temperature on the lipase-catalyzed esterification of *rac*-**1a** (Table 3), since the temperature has a significant influence on the rotational stability of both substrate and product.[38] We observed a slow reaction at low temperatures (15–25 °C), while (*S*)-**2a** was obtained with 96% ee and (*R*)-**1a** was recovered with 11–15% ee after 48 h (entries 1 and 2). In contrast, both esterification and racemization of **1a** were sufficiently fast at 35 °C to give (*S*)-**2a** (96% yield) in 95% ee along with recovered **1a** (4% yield) as a racemate after 24 h (entry 3). Both reactions proceeded much faster at 50 °C, and (*S*)-**2a** (94% ee) was obtained quantitatively within 17 h while maintaining the high enantiomeric excess even at this elevated temperature (entry 4). Furthermore, the addition of Na_2CO_3 seems to be crucial,[32] as the reaction progress was much slower in the absence of Na_2CO_3 (entry 5). We assume that the presence of base enhances the reaction by the formation of a more nucleophilic oxyanion or anion-line species from **1a**.

With the optimal reaction conditions (entry 4 in Table 3) in hand, we studied the substrate scope of this protocol (Table 4). The substrates *rac*-**1a**–**1i** with substituents of different electronic and steric nature at either the C6 or C7 position of the naphthalene moiety were subjected to the DKR, and all of them reacted smoothly to produce enantiomerically enriched acetates (*S*)-**2a**–**2i** (88%–98% ee) in high isolated yields (91%–99%). In particular, as seen in examples (*S*)-**2b**, **2e**, and **2g**, the differences in the electronic properties of the substituents have

Table 2. Solvent effects on lipase-catalyzed esterification of *rac*-**1 a**.[a]

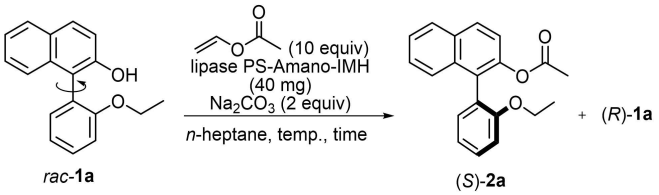


rac-**1a** (*S*)-**2a**

Entry	Solvent	% NMR-yield[b] of (*S*)-**2 a**	% Ee[b]	
			(*S*)-**2 a**	**1 a**
1	DMSO	25	0	2
2	*N,N*-Dimethylacetamide	17	2	0
3	Acetone	0	–	–
4	CH_2Cl_2	Trace	67	0
5	*i*-Pr_2O	9	96	4
6	Toluene	3	>99	0
7	Cyclohexane	10	97	0
8	*n*-Heptane	20	98	4

[a] 0.04 mmol of *rac*-**1 a** was used. [b] Same as footnote b in Table 1.

Table 3. Effects of reaction temperature and reaction time on the lipase-catalyzed esterification of *rac*-**1 a**.[a]



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

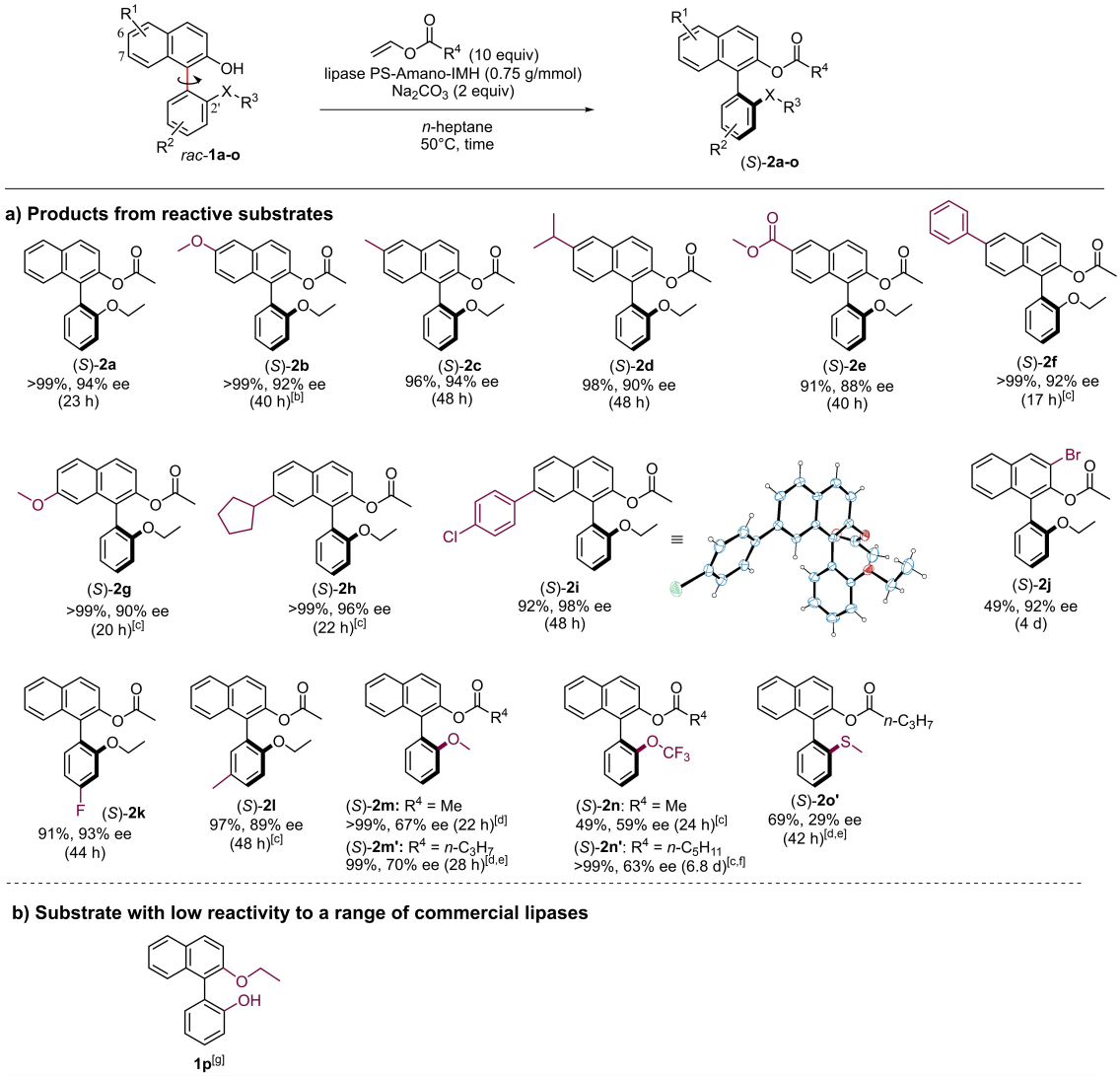
Entry	Temp. [°C]	Time [h]	% NMR-yield, % ee[b]	
			(*S*)-**2 a**	(*R*)-**1 a**[c]
1	15	48	16%, 96% ee	84%, 11% ee
2	25	48	48%, 96% ee	50%, 15% ee
3	35	24	96%, 95% ee	4%, 1% ee
4	50	17	>99%, 94% ee	–
5[d]	50	40	91%, 93% ee	5%, 2% ee

[a] 0.04 mmol of *rac*-**1 a** was used. [b] Same as footnote b in Table 1. [c] Special attention was paid for the analytical measurement of the ee-value due to the easy rotation of **1 a** (for details, see Supporting Information). [d] Without Na_2CO_3.

little effect on the reaction rate, ester yield and enantiomeric purity. On the other hand, compound **1 j** with bromo at the C3 position afforded a 48% yield of (*S*)-**2 j** (92% ee) even though a prolonged reaction time (4 days) was required. The other substrates **1 k** and **1 l** having substituents at the phenyl moiety were also converted to the optically active acetates (*S*)-**2 k** (94% ee) and (*S*)-**2 l** (89% ee) in 91% and 97% isolated yields, respectively.

Similar substrates **1 m** and **1 n**, with a MeO or CF_3O group instead of the EtO group at the C2′ position of the phenyl moiety, provided the corresponding acetates (*S*)-**2 m** (>99% yield) and (*S*)-**2 n** (49% yield) but with moderate enantiomeric purity (67% ee and 59% ee, respectively). Therefore, the effect of the acyl moiety bulkiness was also examined. For **1 m**, the butyrate (*S*)-**2 m′** was obtained with similar yield (99%) and enantiomeric purity (70% ee). On the other hand, the yield of hexanoate (*S*)-**2 n′** was increased to quantitative with similar enantiomeric purity (63% ee) (for details, see Supporting Information). We believe that the lower enantiomeric purity of **2 n′** compared to that of **2 a** mainly depends on the difference between rotational barriers of the substrates and products. For instance, **1 n** has a relatively high rotational barrier ($\Delta G^{\ddagger}_{exp,50\,°C}$ = 26.8 kcal/mol), and its racemization is decelerated compared to that of **1 a** ($\Delta G^{\ddagger}_{exp,25\,°C}$ = 24.3 kcal/mol) which requires a longer reaction time (6.8 days) to completely consume **1 n**. On the other hand, the rotational barrier of **2 n′** ($\Delta G^{\ddagger}_{exp,50\,°C}$ = 28.9 kcal/mol) corresponds to that of **2 a** ($\Delta G^{\ddagger}_{exp,50\,°C}$ = 28.9 kcal/mol). The lower enantiomeric purity was due to simultaneous racemiza-

Table 4. Substrate scope of DKR of 2-hydroxybiaryls *rac*-**1**.[a]



[a] Unless otherwise noted, the reaction was conducted using *rac*-**1** (0.20 mmol), vinyl acetate (10 equiv), lipase PS-Amano-IMH (0.75 g/mmol) and Na_2CO_3 (2 equiv) in *n*-heptane at 50 °C for the reaction time indicated in the parentheses. The isolated yield of the ester (*S*)-**2** is shown, and the enantiomeric excess was determined as in footnote b in Table 1. [b] The reaction was conducted in cyclohexane instead of *n*-heptane. [c] 1.0 g/mmol of lipase PS-Amano-IMH was used. [d] The reaction was conducted at 35 °C. [e] The reaction was conducted using vinyl butyrate (10 equiv) instead of vinyl acetate. [f] The reaction was conducted using vinyl hexanoate (10 equiv) instead of vinyl acetate. [g] For details, see Supporting information.

tion during the reaction of that long duration. The DKR of **1n** was further investigated by changing the steric bulkiness of the acyl moiety, but no improved results were obtained.

A similar substrate **1o** with a MeS group at the C2′ position produced the butyrate **2o′** in 69% yield but with 29% ee (for some trials in DKR of **1o** using different acyl donors, see Supporting Information). Attempts to achieve the DKR of another type of 2-hydroxybiaryl compound **1p**, in which the positions of OH and EtO groups swapped with those in **1a**, did not produce any esters (see also Supporting Information).

The absolute stereochemistry of **2i** was unambiguously determined to be *S* by its X-ray crystallographic analysis.[49] Since lipase generally tends to exhibit the same enantioselectivity towards substrates with similar substructure around the reactive OH group, we infer that the conformation of all other esters **2** is also *S*. Circular dichroism (CD) spectra of **2a** as well as compounds **2m′** and **2n′** with slightly different substituents at the C2′ position are similar to that of **2i** (for details, see Supporting Information), which also infers the absolute stereochemistry of these compounds is *S*.

Conclusions

DKR of easily rotating racemic biaryl atropisomers **1** has been achieved by simple lipase-catalyzed enantioselective *O*-acyla-

tion without using racemization catalysts. Due to the high enantiomeric recognition ability of the lipase, the products **2** bearing an ethoxy group at the C2′-position were obtained with high enantiomeric purities (88–98% ee) and in excellent yields (up to >99%). This method has benefits such as mild reaction conditions (35–50 °C) and simple procedure, thus enabling an environmentally benign approach and facilitating an ease access to enantiomerically pure atropisomers. We are currently working on extending the substrate scope of this method based on the search for other lipases as well as the creation of lipase mutants.

Experimental Section

General procedure for DKR of biaryl compounds **1**: To a reaction vial containing *rac*-**1a**–**1o** (0.20 mmol), immobilized *Burkholderia cepacia* lipase (PS-Amano-IMH) (0.15–0.20 g), Na_2CO_3 (0.40 mmol), *n*-heptane (2.0 mL) and vinyl acetate (2.0 mmol) were added. The reaction mixture was allowed to stir at 50 °C for the reaction time indicated in Table 4. After the complete consumption of **1a**–**1o**, monitored by TLC, the resultant mixture was filtered through a short pad of silica gel and the eluent was concentrated *in vacuo*. The residue was purified by column chromatography (5–7% EtOAc in hexane) giving the corresponding ester **2a**–**2o**. The enantiomeric purity of the product was determined by HPLC analysis using a chiral column.

(*S*)-1-(2-Ethoxyphenyl)naphthalen-2-yl acetate (**2a**): Following the general DKR procedure, the compound (*S*)-**2a** (61 mg, 0.20 mmol, >99% yield, 94% ee) was synthesized from *rac*-**1a** (52 mg, 0.20 mmol) using the lipase (156 mg). A white semi solid, $[\alpha]_D^{21} = +21.05^\circ$ (c = 0.15, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.46–7.43 (m, 1H), 7.42–7.36 (m, 2H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.19 (d, *J* = 6.3 Hz, 1H), 7.06–7.03 (m, 2H), 3.99–3.93 (m, 2H), 2.01 (s, 3H), 1.09 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 157.1, 146.2, 133.6, 132.3, 132.0, 129.6, 129.0, 128.3, 127.9, 126.6, 126.5, 125.6, 124.6, 121.9, 120.7, 112.8, 64.4, 21.1, 14.8. IR (NaCl): ν 1759 cm^{-1}. HRMS (MALDI) *m/z*: calcd for $C_{20}H_{18}O_3Na$ [(M + Na)$^+$]: 329.1148; found: 329.1147. HPLC (UV 220 nm, chiral column Daicel IBN-3, *i*-PrOH/hexane = 5/95, flow rate = 1 mL/min): t_1 = 5.8 min (major, 97.1%), t_2 = 6.3 min (minor, 2.9%).

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Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Acylation · Asymmetric synthesis · Atropisomerism · Biaryls · Density functional calculations · Dynamic kinetic resolution · Lipases

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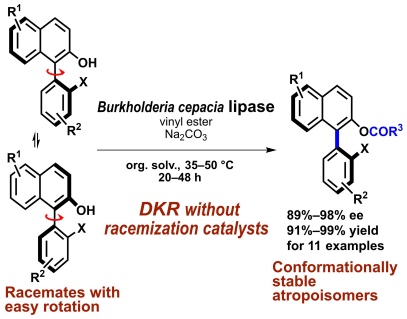
RESEARCH ARTICLE

Enantiomerically pure atropisomers were synthesized by lipase-catalyzed dynamic kinetic resolution of racemic 2-hydroxybiaryls, which is characterized by low rotational barriers of the substrates and sufficiently high rotational barriers of products, thus eliminating the need for racemization catalysts. Computational calculation to design suitable substrates was instrumental in this work.



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