Facile and Highly Enantioselective Synthesis of Axially Chiral Biaryls by Enzymatic Desymmetrization

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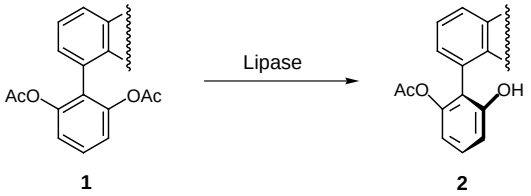
Abstract: The axially chiral biaryls **2** were obtained in high enantioselectivity by desymmetrization of the σ-symmetric biaryl diacetates **1** by lipase-catalyzed hydrolysis.

Key words: asymmetrization, hydrolysis, enzyme, axial chirality, biaryl

Axially chiral non-racemic biaryls are of current interest due to their importance as chiral ligands and auxiliaries in asymmetric synthesis. Also, they constitute a structural feature of many natural products.[1,2]

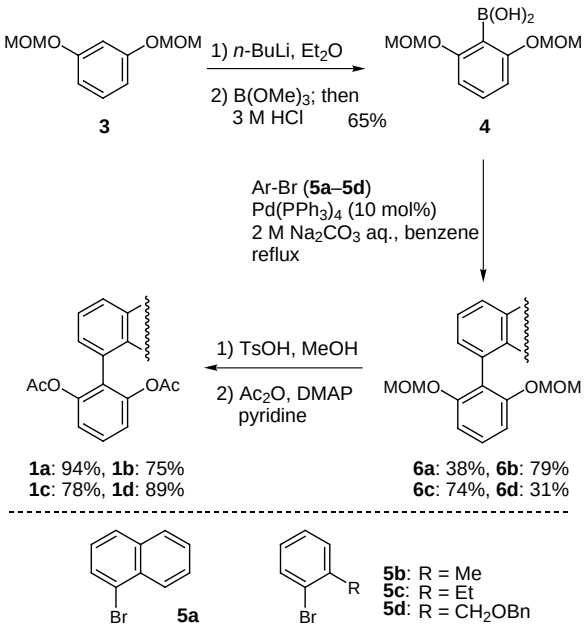
Among the approaches to such chiral biaryls, ones based on the desymmetrization of achiral biaryl derivatives, e.g. the palladium-catalyzed cross-coupling of 2-aryl-1,3-phenylene ditriflates by Hayashi[3a] and the acetalization of 2,2',6,6'-biphenyltetrol with L-menthone by Harada,[3b] are unique and convenient in terms of the ready accessibility to the achiral precursors. Surprisingly, however, there have been no reports on the application of an enzyme to such desymmetrization,[4] although the ability of enzymes to recognize the axial chiralities of a biaryl has been well documented in the kinetic resolution of racemic biaryls.[5]

In this communication, we wish to report the first example of the enzymatic asymmetric desymmetrization of biaryl compounds: The σ-symmetric biaryl diacetate **1** can be efficiently desymmetrized by lipase-catalyzed hydrolysis to give the chiral biaryls **2** in high enantioselectivity (Equation 1).



Equation 1

Substrates for the enzymatic hydrolysis, the diacetates **1a**–**1d**, were synthesized via the Suzuki coupling reaction[6] of the boronic acid **4** with the bromoarenes **5a**–**5d**, respectively (Scheme).



Scheme

The boronic acid **4** was easily prepared from the resorcinol derivative **3** via (1) lithiation, (2) trapping by $B(OMe)_3$, (3) acid workup, and (4) purification of the crude material by trituration with hexane. A single batch of the operations starting from 50 g of **3** gave 40 g of colorless, pure crystals of **4** [mp 79–80 °C]. The biaryl bond formations with the boronic acid **4** and the bromoarenes, **5a**–**5d**, proceeded in moderate to good yields under the standard conditions of the Suzuki coupling. Removal of the MOM groups under acidic conditions followed by acetylation gave the diacetates **1a**–**1d** in high yields.

With the diacetates in hand, we examined several commercially available lipases for the hydrolysis of **1a**. Thus, **1a** (50 mg) was treated with the lipases (10 mg) in a 3:2-mixture of pH 7 phosphate buffer (0.1 M)–acetone at 30 °C. As shown in Table, it turned out that CAL and PCL were effective for the purpose. Both enzymes gave the mono-acetate (+)-**2a** in high enantioselectivity in high

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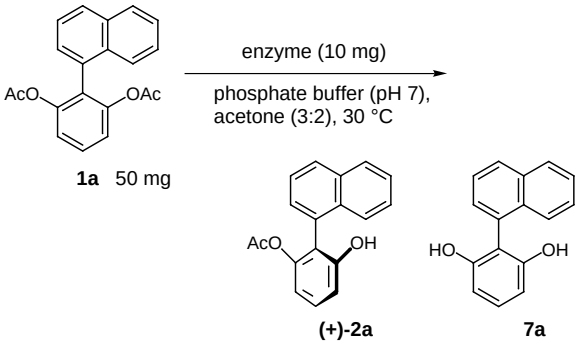
Table Hydrolysis of **1a** using Various Lipases

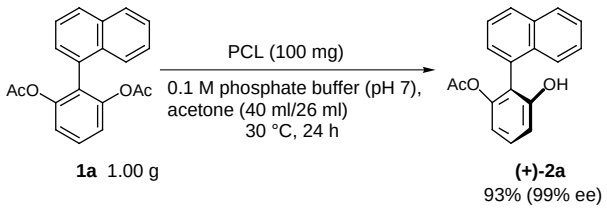


Run	Enzyme[a]	Period/day	Yield % (+)-**2a** (ee/%)	Recovery of **1a**	**7a**
1	PFL	2	82 (79)	7	5
2	CRL	2	4 (80)	93	0
3	PPL	2.5	12 (94)	60	2
4	PLE	2.5	12 (95)	51	20
5	CAL	2.5	72 (97)	11	3
6	PCL	1	94 (98)	1	1

[a] PFL: *Pseudomonas fluorescence* lipase (Amano Pharm. Co., lipase AK), CRL: *Candida rugosa* lipase (Amano Pharm. Co., lipase AY), PPL: porcine pancreas lipase (Sigma, Type II), PLE: pig liver esterase (Sigma), CAL: *Candida antarctica* lipase (Roche Diagnostics, Chirazyme L-2), PCL: *Pseudomonas cepacia* lipase (Amano Pharm. Co., lipase PS)

yield,[7] while the reaction rate was slower with CAL than that with PCL. By contrast, the enantioselectivity was unsatisfactory with PFL, and the reaction rate was too slow with CRL, PPL, or PLE.

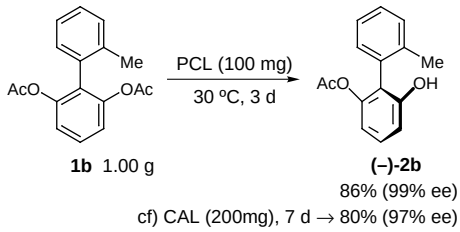
Equation 2 shows the 1g scale reaction with PCL under the optimized conditions (100 mg catalyst), where (+)-**2a** with 99% ee was obtained in 93% yield.[7]



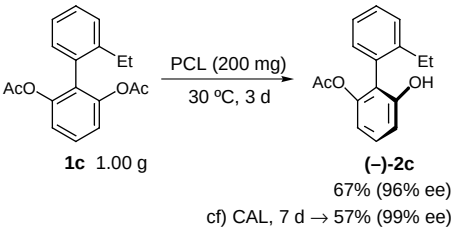
Equation 2

The reactions of diacetates **1b**–**1d** were carried out under the similar conditions by employing PCL and CAL as the catalyst (Equations 3–5).

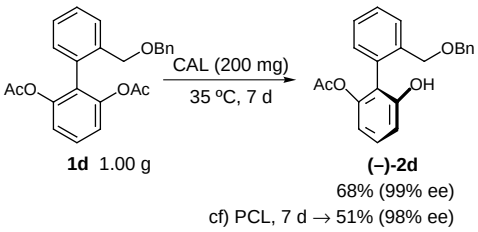
Both PCL and CAL exhibited high enantioselectivities in all cases.[7] However, in terms of the reaction rate, PCL was preferable in the reactions of **1b** and **1c**, and CAL was preferable in the reaction of **1d**.



Equation 3



Equation 4

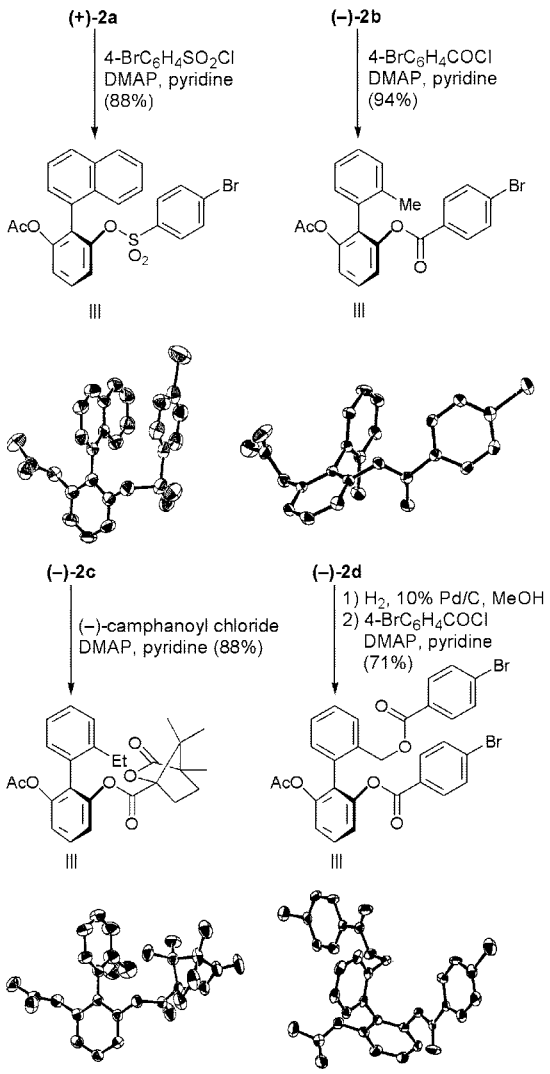


Equation 5

The chiral biaryls, **2a**–**2d**, thus obtained, were configurationally stable at room temperature. Even the compound **2b**, which should have the lowest barrier to the biaryl bond rotation among these compounds, underwent virtually no racemization during storage as a solution in $CHCl_3$ for one week or as crystals for some months.[8]

The absolute configurations of **2a**–**2d** were determined by X-ray crystallography after derivations as shown below (Figure). Thus, the sense of the stereoselection proved identical in all the cases. Namely, the *pro-R* acetates were predominantly hydrolyzed, although we can not give a rational explanation based on the enzyme structure.

In summary, the symmetric diacetates **1** were efficiently desymmetrized by hydrolysis with a suitable lipase, i.e. PCL or CAL, to give the corresponding mono-acetates **2** in high enantioselectivity. This desymmetrization will have considerable value as a synthetic method for axially chiral biaryls because of its convenience and high enantioselectivity.



Figure

References

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(7) Enantiomeric purities of the biaryls **2a**-**2d** were determined by chiral HPLC analyses. Enantiomerically pure samples of **2a**–**2c** could be obtained by recrystallization. Data for the compounds **2a**–**2d** follow; (+)-**2a** (>99% *e.e.*): Mp 97–98 °C (hexane–EtOAc); $[\alpha]^{18}_{D}$ +101 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 3 H), 4.77 (s, 1 H), 6.83 (dd, 1 H, *J* = 8.3, 1.0 Hz), 7.00 (dd, 1 H, *J* = 8.3, 1.0 Hz), 7.3–7.6 (m, 6 H), 7.94 (dd, 2 H, *J* = 8.1, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 20.3, 113.2, 114.6, 119.8, 125.3, 125.6, 126.4, 126.9, 128.3, 128.5, 128.8, 129.3, 129.5, 131.8, 133.8, 149.4, 154.4, 169.3; IR (KBr) 3419, 1740 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.62; H, 5.37. HPLC (Daicel CHIRACEL OJ, 250 × 4.6 mm, hexane–*i*-PrOH = 9:1, 0.5 mL/min) retention time: 34.6 min for (+)-**2a** [43.1 min for (–)-**2a**].
(–)-**2b** (>99% *e.e.*): Mp 87–88 °C (hexane–EtOAc); $[\alpha]^{24}_{D}$ –17.6 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3 H), 2.13 (s, 3 H), 4.84 (s, 1 H), 6.73 (dd, 1 H, *J* = 8.3, 1.0 Hz), 6.90 (dd, 1 H, *J* = 8.3, 1.0 Hz), 7.1–7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 19.4, 20.4, 113.1, 114.3, 121.3, 126.3, 129.0, 129.1, 130.3, 130.6, 130.9, 138.3, 148.9, 153.8, 169.2; IR (KBr) 3422, 1761 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.59; H, 5.82. HPLC (Daisel CHIRACEL OD-H, 250 × 4.6 mm, hexane–^{i}PrOH = 9:1, 0.7 mL/min) retention time: 8.13 min for (–)-**2b** [7.68 min for (+)-**2b**].
(–)-**2c** (>99% *e.e.*): Mp 56–57 °C (hexane–EtOAc); $[\alpha]^{23}_{D}$ –41.5 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3 H, *J* = 7.6 Hz), 1.85 (s, 3 H), 2.43 (q, 2 H, *J* = 7.6 Hz), 4.74 (s, 1 H), 6.74 (dd, 1 H, *J* = 8.3, 1.3 Hz), 6.91 (dd, 1 H, *J* = 8.3, 1.3 Hz), 7.1–7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.8, 20.4, 25.9, 113.0, 114.3, 121.1, 126.4, 128.8, 129.1, 129.2, 129.5, 131.0, 144.2, 148.9, 153.9, 169.2; IR (KBr) 3438, 1744 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.86; H, 6.35. HPLC (Daisel CHIRACEL OD-H, 250 × 4.6 mm, hexane–*i*-PrOH = 9:1, 0.7 mL/min) retention time: 8.40 min for (–)-**2c** [7.83 min for (+)-**2c**].
(–)-**2d** (99% *e.e.*): Colorless oil; $[\alpha]_{D}^{23}$ –18.4 (*c* 1.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 3 H), 4.34 (s, 2 H), 4.45 (d, 1 H, *J* = 11.6 Hz), 4.53 (d, 1 H, *J* = 11.6 Hz), 6.22 (s, 1 H), 6.74 (dd, 1 H, *J* = 8.2, 1.0 Hz), 6.97 (dd, 1 H, *J* = 8.2, 1.0 Hz), 7.1–7.5 (m, 9 H), 7.5–7.6 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.3, 71.4, 73.1, 114.6, 115.2, 122.3, 127.8, 128.0, 128.4, 128.5, 128.8, 129.3, 130.1, 131.4, 131.7, 137.1, 137.3, 149.0, 154.8, 169.2; IR (KBr) 3422, 1758 cm^{-1}. Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.72; H, 5.96. HPLC (Daisel CHIRACEL OD-H, 250 × 4.6 mm, hexane–*i*-PrOH = 9:1, 0.5 mL/min) retention time: 12.9 min for (+)-**2d** and 14.5 min for (–)-**2d**.

(8) Upon heating in toluene at 60 °C, (+)-**2a** racemized 1% after 12 h, and 80 °C, 7% after 12 h.