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Facile synthesis of C_2-symmetric chiral binaphthyl ketone catalysts

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Abstract

C_2-Symmetric chiral binaphthyl ketones, efficient catalysts for asymmetric epoxidation, have been synthesized through an intramolecuar Ullmann reaction and/or a lipase-catalyzed enantioselective hydrolysis of the 11-membered cyclic binaphthyl acetate.

Keywords: epoxidation; Ullmann reactions; biaryls; enzymes and enzyme reactions.

Optically active epoxides have received considerable attention as useful chiral building blocks for drugs and natural products. The asymmetric epoxidation of olefins with chiral dioxiranes, generated in situ from the corresponding ketones, has recently emerged as a prominent synthetic method for the optically active epoxides.[1,2] Yang has developed C_2-symmetric chiral binaphthyl ketones **1** and has demonstrated their efficiency for the dioxirane-mediated catalytic asymmetric epoxidation.[2] The ketones **1a** (X=H) and **1b** (X=Cl) have been synthesized via condensation of optically active 1,1′-binaphthyl-2,2′-dicarboxylic acid derivatives with 1,3-dihydroxyacetone or 3-chloro-2-chloromethyl-1-propene, respectively. However, the methods are unsatisfactory for practical use because of the following drawbacks: (1) a poor yield (28%) for the condensation step in the synthesis of the unsubstituted ketone **1a** even by the use of Mukaiyama reagent and a high dilution method (ca. 300 volume of solvent per weight of the substrate was employed);[2a] (2) preparation of the optically active 1,1′-binaphthyl-2,2′-dicarboxylic acid derivatives requires very toxic brucine or quinine for the resolution.[3] We describe herein a facile synthesis of the ketones **1a** and **1b** by means of an intramolecular Ullmann reaction and/or a lipase-catalyzed kinetic resolution.

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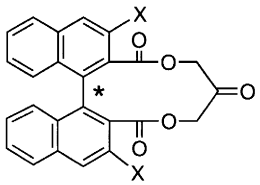


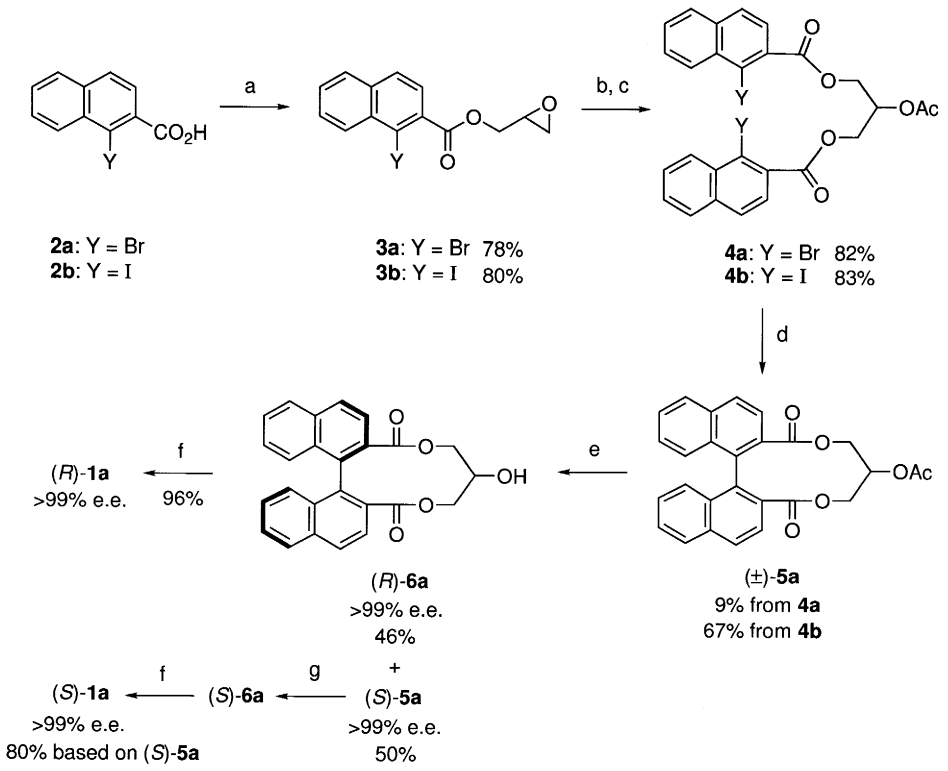
1a: X = H
1b: X = Cl

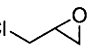
We first investigated synthesis of the unsubstituted ketone **1a** (Scheme 1). The intramolecular Ullmann reaction of a dibromide **4a** was attempted to improve the condensation step in the synthesis of **1a**. The dibromide **4a** was readily prepared in two steps from 1-bromo-2-naphthoic acid **2a** through sequential addition of two molecules of **2a** to epichlorohydrin.[4] Addition of the dibromide **4a** in DMF to a suspension of copper powder[5] in refluxing DMF for 6 h and an additional refluxing for 1 h provided the cyclized product (±)-**5a** in only 9% yield accompanied by considerable side reactions such as reductive cleavage of the bromo group. In order to improve the yield, we then employed more reactive diiodide **4b** derived from 1-iodo-2-naphthoic acid **2b**.[6] As expected, the cyclization of the diiodide **4b** gave the desired product (±)-**5a** in good yield (67%) using the same reaction procedure as with **4a**. It should be noted that the reaction can provide the 11-membered ring system without the need for high dilution methods (the total volume of the reaction solvent (DMF) is 40 v/w).

We then examined the lipase-catalyzed kinetic resolution of the acetate (±)-**5a**. Although recognition of the axial chirality in biaryls by enzymes has scarcely been studied,[8] treatment of (±)-**5a** with Lipoprotein lipase (Toyobo Co., Ltd) at 30°C for 48 h in a mixed solvent of toluene and 0.1 M Tris-HCl buffer (pH 7.5) (1:1) was found to selectively hydrolyze (*R*)-**5a** to give an alcohol (*R*)-**6a** in enantiopure form (>99% e.e.,[9] 46% yield) and the recovery of a homochiral acetate (*S*)-**5** (>99% e.e.,[8] 50% yield) (E-value=670). The alcohol (*R*)-**6a** was cleanly oxidized with MnO_2 at ambient temperature to provide the desired ketone (*R*)-**1a** (>99% e.e.[10]) in 96% yield.[11] The antipode (*S*)-**1a** was prepared through aminolysis of the acetate (*S*)-**5a** followed by the oxidation with MnO_2 (>99% e.e.,[10] 80% yield, two steps).

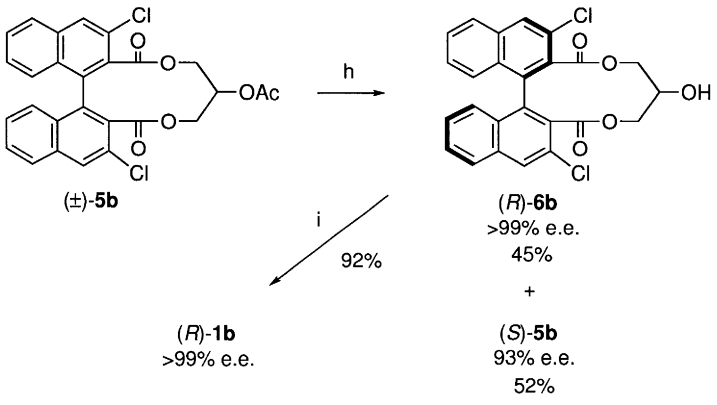
The present synthetic method based on the enzymatic resolution was applicable to the synthesis of a 3,3′-dichloro derivative (*R*)-**1b**, a better epoxidation catalyst for some olefins (Scheme 2).[2b] Although the racemic acetate (±)-**5b** could not be obtained through the intramolecular Ullmann reaction shown in Scheme 1, it was prepared from a racemic ketone (±)-**1b**[2b,12] by reduction of the carbonyl group followed by acetylation (1. $NaBH_4$; 2. Ac_2O, Et_3N, DMAP (cat.), 86% (two steps)). The compound (±)-**5b** was allowed to react with Lipoprotein lipase (Toyobo Co., Ltd) at 30°C for 48 h in a mixed solvent of toluene and 0.1 M Tris-HCl buffer (pH 7.5) (1:1) provided an alcohol (*R*)-**6b** in high enantioselectivity (>99% e.e.,[9] 45% yield) while the homochiral acetate (*S*)-**5b** was recovered in 52% yield (93% e.e.[9]) (E-value=85). The alcohol (*R*)-**6b** was oxidized with MnO_2 to provide the desired ketone (*R*)-**1b** (>99% e.e.[10]) in 92% yield.[13]

In conclusion, efficient syntheses of C_2-symmetric chiral binaphthyl ketones **1a** and **1b** were accomplished by the use of the intramolecular Ullmann reaction of the diiodide **4b** (for the synthesis of **1a**) and the lipase-catalyzed kinetic resolution of the acetates (±)-**5a** and (±)-**5b**. The present synthesis is efficient in terms of the high enantioselectivities and the versatilty of the enzymatic reactions. Both unsubstituted and 3,3′-dichloro binaphthyl ketones **1a** and **1b** are readily accessible in enantiopure form through the Lipoprotein lipase-catalyzed kinetic resolution. Further efforts to improve the present synthesis are in progress and will be reported elsewhere in due course.



a:  , NaH, *n*-Hex_4NBr; b: **2**, NaOH, *n*-Bu_4NHSO_4, c: Ac_2O, Et_3N, DMAP; THF; d: Cu, DMF (40 v/w); e: Lipoprotein lipase, 0.1 M Tris-HCl buffer (pH 7.5), toluene; f: MnO_2, toluene; g: $MeNH_2$, MeOH.

Scheme 1.



h: Lipoprotein lipase, 0.1 M Tris-HCl buffer (pH 7.5), toluene; i: MnO_2, toluene.

Scheme 2.

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5. The copper powder (particle size: 100–200 mesh) was purchased from Kanto Chemicals Co., Inc. and used without further purification.
6. 1-Iodo-2-naphthoic acid **2b** was prepared from 1-bromo-2-hydroxymethylnaphthalene[7] through iodination [(i) *n*-BuLi (2.2 equiv.), THF, −60°C, 10 min, (ii) I_2, −50–60°C, 1.5 h (80%)] followed by oxidation of the hydroxymethyl group to the carboxylic acid [1. MnO_2, toluene (63%); 2. $NaClO_2$, H_2O_2, NaH_2PO_4, CH_3CN, H_2O (95%)].
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8. Enzymatic kinetic resolution of 2,2′-dihydroxy-1,1′-binaphthyl was reported: (a) Kazlauskas, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 4953. (b) Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.* **1989**, *53*, 1879.
9. The e.e.s of the products were determined by HPLC: Chiralcel OD (Daicel), *n*-hexane:2-propanol=10:1, 1 mL/min, 40°C, 224 nm.
10. IR, ^{1}H NMR and MS spectra of the products **1a** and **1b** are in good accordance with those of the literature.[2a,b] The mp and specific rotation of **1a** and **1b** are not reported. Absolute configuration and optical purities of the products **1a** and **1b** were determined by comparing the retention time in the chiral HPLC with those of the authentic samples prepared according to the literature.[2a,b] HPLC: Chiralcel OD (Daicel), *n*-hexane:2-propanol=10:1, 1 mL/min, 40°C, 224 nm.
11. (*R*)-**6a**: mp 256–257°C; IR (KBr) 1744, 1720, 1592 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.11 (d, *J*=8.4 Hz, 1H), 4.03 (dd, *J*=1.3, 12.4 Hz, 1H), 4.25–4.35 (m, 1H), 4.57 (dd, *J*=8.3, 10.7 Hz, 1H), 4.85 (dd, *J*=3.2, 12.4 Hz, 1H), 7.17 (d, *J*=8.6 Hz, 2H), 7.31 (d, *J*=7.4 Hz, 2H), 7.49–7.56 (m, 2H), 7.65 (dd, *J*=8.5, 11.4 Hz, 2H), 7.93–8.02 (m, 4H); MS (*m/z*) 398 (M^+); $[\alpha]_D^{25}$ −230 (*c*, 1.01, $CHCl_3$). (*S*)-**5a**: mp 256°C; IR (KBr) 1746 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 4.00 (d, *J*=13.1 Hz, 1H), 4.15 (dd, *J*=7.2, 10.9 Hz, 1H), 4.66 (dd, *J*=9.8, 10.8 Hz, 1H), 4.99 (d, *J*=3.9, 13.1 Hz, 1H), 5.32–5.42 (m, 1H), 7.18–7.34 (m, 4H), 7.49–7.71 (m, 4H), 7.93–8.04 (m, 4H); MS (*m/z*) 440 (M^+); $[\alpha]_D^{25}$ +171 (*c*, 1.0, $CHCl_3$).
12. Reported synthesis of (±)-**1b** involves condensation of 3,3′-dichloro-1,1′-binaphthyl-2,2′-dicarboxylic acid with 3-chloro-2-chloromethyl-1-propene and oxidative cleavage of the double bond.[2b] While the yield of the cyclization is moderate (60% yield), that of the oxidation step is poor (21% yield).
13. (*R*)-**6b**: mp >300°C; IR (KBr) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (d, *J*=1.1 Hz, 1H), 4.07 (dd, *J*=12.3 Hz, 1H), 4.19 (dd, *J*=6.5, 10.3 Hz, 1H), 4.41 (m, 1H), 4.57 (dd, *J*=8.8, 10.2 Hz, 1H), 4.91 (dd, *J*=3.4, 12.2 Hz, 1H), 6.91 (d, *J*=8.5 Hz, 2H), 7.28 (t, *J*=7.7 Hz, 2H), 7.53 (t, *J*=7.6 Hz, 2H), 7.85 (d, *J*=8.2 Hz, 2H), 8.05 (d, *J*=2.8 Hz, 1H); MS (*m/z*) 467 (M^+); $[\alpha]_D^{21}$ −97 (*c*, 0.1, $CHCl_3$). (*S*)-**5b**: mp 300°C (dec); IR (KBr) 1747 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.08 (s, 3H), 4.02 (d, *J*=13.0 Hz, 1H), 4.23 (dd, *J*=7.2, 10.8 Hz, 1H), 4.42 (dd, J=10.1, 10.7 Hz, 1H), 4.87 (dd, *J*=3.8, 13.1 Hz, 1H), 5.37–5.56 (m, 1H), 6.78 (d, *J*=8.5 Hz, 1H), 7.39 (ddd, *J*=1.1, 7.0, 7.7 Hz, 2H), 7.66 (ddd, *J*=1.0, 6.9, 7.5 Hz, 2H), 8.10 (d, *J*=8.2 Hz, 2H), 8.45 (s, 2H); MS (*m/z*) 509 (M^+); $[\alpha]_D^{21}$ +71 (*c*, 1.01, $CHCl_3$).