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Axially Chiral Bifunctional 8,8′-Biquinolyl: Synthesis of 7,7′-Dihydroxymethyl-8,8′-biquinolyl via Pd-Catalyzed Double C−H Oxidation of 7,7′-Dimethyl-8,8′-biquinolyl

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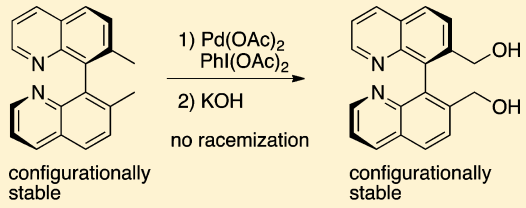
Supporting Information

ABSTRACT: Bifunctional C_2-symmetric 7,7′-dihydroxymethyl-8,8′-biquinolyl (**2**) was synthesized in short steps via (i) Cu/Pd-catalyzed homo coupling of 7-methyl-8-bromoquinoline and (ii) Pd(II)-catalyzed double C−H oxidation. Axial chirality of **2** and its synthetic precursor 7,7′-dimethyl-8,8′-biquinolyl (**3**) is stable. Optically active **2** was obtained through separation of racemic **2** by chiral column HPLC or Pd(II)-catalyzed double C−H oxidation of optically active **3**. The absolute stereochemistry of enantiomers of **2** and **3** was determined using the exciton chirality method.



Due to the stability of the axial chirality of the biaryl bond, 2,2′-disubstituted-1,1′-binaphthyl is an efficient scaffold for chiral ligands.[1] 1,1′-Binaphthyl-2,2′-diol (BINOL) is known to be one of the most effective asymmetric ligands and is used in various fields such as chiral recognition and for chiral materials (Figure 1).[2] For the stability of axial chirality in

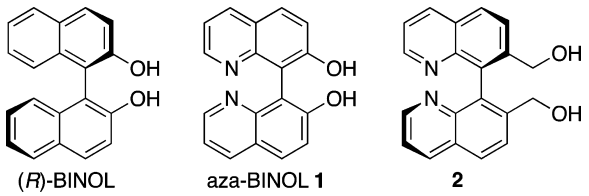


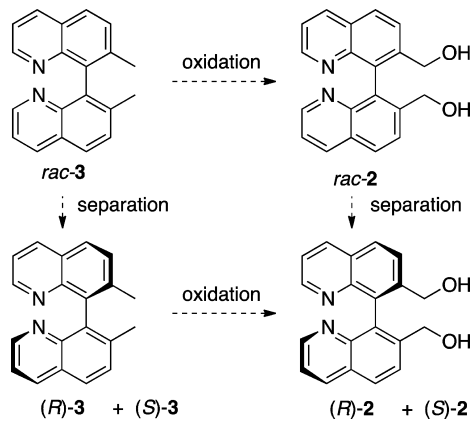
Figure 1. BINOL and bifunctional biquinolinediol **1** and **2**.

BINOL, the peri C−H bonds in the 8,8′-positions on the 1,1′-binaphthyl skeleton are important for inducing a high rotational barrier around the biaryl bond.[1] Various modifications of BINOL have been examined to increase the efficiency of chiral reagents, such as partial hydrolysis[3] or the introduction of fluorine[4] to BINOL. The aza-analogue **1** (aza-BINOL, 7,7′-dihydroxy-8,8′-biquinolyl), wherein the 8,8′-C−H positions in BINOL are replaced by nitrogen, is expected to be a bifunctional chiral source; however, it has not been used for this purpose because of the low rotational barrier around the aza-BINOL biaryl bond.[5] The low rotational barrier of **1** is due to the low repulsion between the sp^2 nitrogen atoms and between the sp^2 nitrogen and hydroxy group.

We envisioned that 7,7′-dihydroxymethyl-8,8′-biquinolyl (**2**), where the hydroxy groups are replaced by hydroxymethyl groups in aza-BINOL **1**, is a configurationally stable bifunctional biquinoline with the potential to be a new chiral reagent. We then examined the synthesis of biquinolinediol **2** and its configurational stability.

We planned to synthesize biquinolinediol **2** by the oxidation of dimethylbiquinoline **3** (Scheme 1). Optically active **2** could be synthesized from optically active **3** if **3** is configurationally stable or it could be obtained by the optical resolution of a racemic mixture of **2**.

Scheme 1. Synthetic Plan of Optically Active Biquinolinediol 2



Dimethylbiquinoline **3** was synthesized from *o*-toluidine in 7 steps by reported procedures (Scheme 2).[6]

We developed an alternative synthetic method for dimethylbiquinoline **3** from commercially available 7-methylquinoline (**8**) in 2 steps via homocoupling of bromoquinoline **9** (Scheme 3). Bromoquinoline **9** was synthesized quantitatively by the bromination of **8** with NBS in sulfuric acid.[7] When Ullmann coupling of **9** was attempted by treatment with Cu

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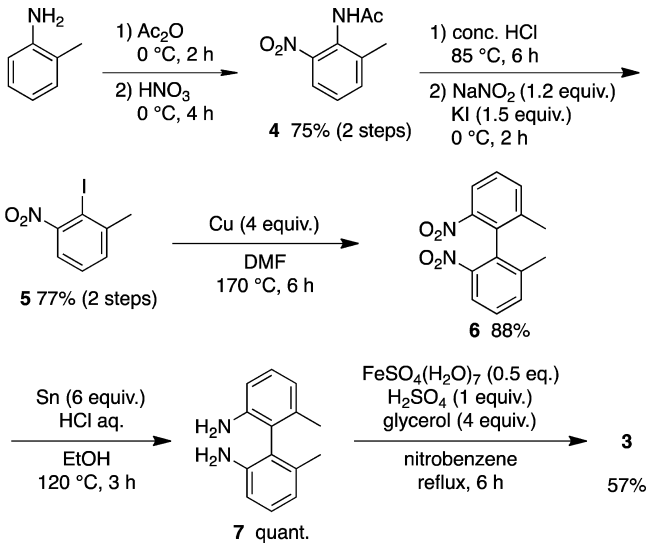
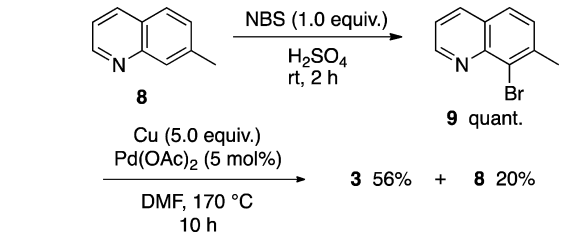
Scheme 2. Synthesis of Dimethylbiquinoline 3 from *o*-Toluidine



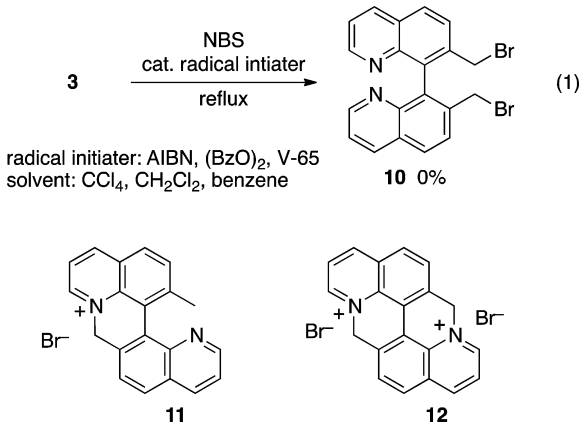
Scheme 3. Preparation of Dimethylbiquinoline 3 from 7-Methylquinoline (8)



powder in DMF at reflux temperature, reduction product **8** was primarily obtained, and the desired homocoupled product **3** was obtained in 33% yield. The yield of **3** increased to 56% by treating with Cu powder in the presence of a catalytic amount of $Pd(OAc)_2$,[8] and the yield of the reduction product **8** decreased to 20%. Although homocoupling of 7-unsubstituted-8-halo-quinoline has been successful by treating with a Ni catalyst (cat. $NiCl_2$, PPh_3, Zn),[9,10] it was not efficient for the homocoupling of **9**.

Chiral column HPLC analysis of **3** (DAICEL CHIRALPAK AD-H (4.6 × 250 mm), hexane/*i*PrOH = 9/1, 0.2 mL/min, retention time: first eluent 38.5 min, second eluent 45.3 min) showed the existence of two rotamers, and each rotamer was collected by preparative chiral column HPLC (DAICEL CHIRALPAK AD-H). The configuration of the first and second eluates were assigned as (*S*)-**3** (92% ee) and (*R*)-**3** (98% ee), respectively, using the exciton chirality method[11] (vide infra).

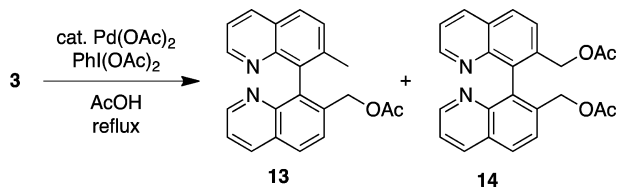
Next, we conducted the transformation of dimethylbiquinoline **3** to 7,7′-dihydroxymethyl-8,8′-biquinolyl **2** using the racemic compound. First, we intended to synthesize **2** by bromination of the benzylic positions of **3** followed by successive substitution of the bromide with oxygen nucleophiles, similar to the synthesis of 2,2′-dihydroxymethyl-1,1′-binaphthyl from 2,2′-dimethyl-1,1′-binaphthyl.[12] Although radical bromination was attempted for **3** under various reaction conditions, the formation of dibromide **10** failed, and high-polar compounds were formed (eq 1). The high-polar compounds could be quinolinium salts such as **11** and **12**, formed by the benzylic bromination of **3** followed by intramolecular cyclization.[13]



The recent developments in heteroatom-directed metal-catalyzed oxidation of C−H bonds are remarkable.[14] Pd-$(OAc)_2$-catalyzed oxidation combined with $PhI(OAc)_2$ as a reoxidant is recognized as a reliable method which enables the introduction of an acetoxy group.[15] Various directing groups are utilized for the $Pd(OAc)_2/PhI(OAc)_2$ oxidation. Among them, the pyridyl group is an efficient directing group.[15a] Recently, Blakemore succeeded in the synthesis of the diacetate of aza-BINOL **1** by the double aryl C−H bond oxidation of 8,8′-biquinolyl with $Pd(OAc)_2/PhI(OAc)_2$ which proceeds via a six-membered palladacycle intermediate.[10] We expected that acetoxy groups could be introduced at the benzylic positions of **3** if a similar quinoline-nitrogen directed C−H bond oxidation proceeded at one of the extended carbon positions.

Oxidation of dimethylbiquinoline **3** was examined by treatment with 20 mol % $Pd(OAc)_2$ and 2.5 equiv of $PhI(OAc)_2$ in acetic acid at reflux temperature (Table 1, run 1).[16] The desired diacetate **14** was obtained in 16% yield after stirring the mixture for 16 h, and the monoacetate **13** was obtained in 44% yield. The yield of diacetate **14** increased with increasing amounts of $PhI(OAc)_2$ (runs 1−3). Diacetate **14** was obtained in 63% yield with 8 equiv of $PhI(OAc)_2$ for a prolonged reaction time (38 h, run 4). A lower loading of

Table 1. Double C−H Oxidation of 3 with $Pd(OAc)_2$/$PhI(OAc)_2$



run	$Pd(OAc)_2$ (mol %)	$PhI(OAc)_2$ (equiv)	time (h)	yield (%) 3	13	14
1	20	2.5	16	12	44	16
2	20	5	16	6	63	24
3	20	8	16	0	42	38
4	20	8	38	0	24	63
5	10	8	38	10	34	35
6	5	8	38	19	44	20
7	20	20	7	0	0	74

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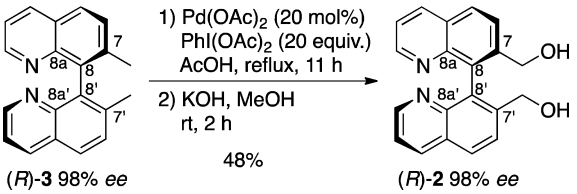
$Pd(OAc)_2$ led to a decrease in the yield of the desired double C−H activation product **14**, and **3** was recovered (runs 5 and 6). In the $Pd(OAc)_2/PhI(OAc)_2$-mediated reaction of **3**, the color of the reaction mixture gradually turned black, and the reaction rate slowed as measured by TLC monitoring. When additional $PhI(OAc)_2$ was added to the black reaction mixture, the color of the mixture changed to orange, and the progress of the reaction was monitored by TLC. The oxidation reaction was then conducted by adding an extra 2.0 equiv of $PhI(OAc)_2$ whenever the reaction mixture turned black, and **14** was obtained in 74% yield by treating with an overall 20 equiv of $PhI(OAc)_2$ (run 7).

The desired 7,7′-dihydroxymethyl-8,8′-biquinolyl (**2**) was obtained in quantitative yields by the hydrolysis of **14** with methanolic KOH (rt, 2 h).

Two rotamers of **2** were detected by chiral column HPLC (DAICEL CHIRALPAK AD-H (4.6 × 250 mm), hexane/*i*PrOH = 4/1, 0.6 mL/min, retention time: first eluent 33.9 min, second eluent 51.6 min), and each of the rotamers was collected as enantiomerically pure form, by preparative chiral column HPLC (DAICEL CHIRALPAK AD-H). The configuration of the first and second eluted rotamers of **2** were assigned (*S*) and (*R*), respectively, using the exciton chirality method (vide infra).

Next, double $Pd(OAc)_2/PhI(OAc)_2$ oxidation of enantiomer of dimethylbiquinoline **3** and the successive hydrolysis were examined (Scheme 4). (*R*)-**3** (98% ee) was successfully transformed to (*R*)-**2** (98% ee) without racemization.

Scheme 4. Reaction with Optically Active 3



We determined the absolute stereochemistry of separated enantiomers **2** and **3** using the exciton chirality method, which is one of the efficient methods for chirality determination.[11] To apply the exciton chirality method to binaphtyl-type compounds, information on the ground state dihedral angle of the biaryl parts is required because the sign of sprit-type Cotton effects is sensitive to the dihedral angle.[17]

We employed a geometry optimization of **2** and **3** with a semiempirical PM3 method,[18] and dihedral angles of two quinoline planes in **2** and **3** were found to be <90° (**2**: 87 and 85° for the dihedral C(7)−C(8)−C(8′)−C(7′) and C(8a)−C(8)−C(8′)−C(8a′), respectively; **3**: 88 and 87° for the dihedral C(7)−C(8)−C(8′)−C(7′) and C(8a)−C(8)−C(8′)−C(8a′), respectively; carbon numbering is shown in Scheme 4), allowing **2** and **3** to be studied using the exciton chirality method.

In Figures S1 and S2, CD and UV spectra for **3** and **2** are shown, respectively. In the UV spectrum of **3**, absorption was observed at 233 nm, assigned to a Platt singlet transition state of ^1B_b (Figure S1). In the CD spectrum of enantiomers of **3**, exciton coupling between long-axes polarized ^1B_b was observed, and two extrema with opposite signs were detected at 238 and 227 nm. In the CD spectrum of the first chiral column HPLC (vide supra) eluted compound of **3** (92% ee), a positive Cotton effect was observed (split CD extrema: $\Delta\varepsilon_{238}$ + 129; $\Delta\varepsilon_{227}$ − 82). Therefore, its absolute configuration was assigned to (*S*), and the second eluted compound of **3** (98% ee) was assigned to the (*R*)-isomer, which showed a negative Cotton effect.

The absolute configuration of **2** was assigned in a similar fashion to **3**. In the UV spectrum of **2**, the absorption observed at 233 nm was assigned to the Platt singlet transition state of ^1B_b (Figure S2). In the CD spectrum of enantiomerically pure **2**, exciton coupling between long-axes polarized ^1B_b was observed, and two extrema with opposite signs were detected at 238 and 226 nm. In the CD spectra of the first chiral column HPLC (vide supra) eluted compound of **2**, a positive Cotton effect induced by exciton coupling between ^1B_b was observed (split CD extrema: $\Delta\varepsilon_{238}$ + 117; $\Delta\varepsilon_{226}$ − 74); therefore, its absolute configuration was assigned as (*S*), and the second eluted compound **2** was assigned to the (*R*)-isomer, which showed a negative Cotton effect.

The axial chirality of **2** and **3** was found to be stable at room temperature for at least 2 months, and racemization of separated optically active **2** and **3** was not observed in toluene at reflux temperature for 48 h.

In conclusion, we achieved the synthesis of bifunctional C_2 symmetric 7,7′-dihydroxymethyl-8,8′-biquinolyl (**2**) via (i) Cu/Pd-catalyzed homo coupling of 8-bromoquinoline and (ii) Pd(II)-catalyzed double C−H oxidation. Axial chirality of **2** is stable, and optically active **2** was obtained by the separation of racemic **2** or 7,7′-dimethyl-8,8′-biquinolyl (**3**), the precursor of the Pd(II)-catalyzed C−H functionalization, by chiral column HPLC. Pd-catalyzed C−H activation reaction enables to synthesize **2** which could not be synthesized by traditional method.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under a nitrogen atmosphere. ^1H NMR (400 MHz, 500 MHz) and $^{13}C\{^1H\}$ NMR (100 MHz, 126 MHz) spectra were recorded in $CDCl_3$ [TMS (for ^1H, δ = 0) or $CDCl_3$ (for ^{13}C, δ = 77.0) was used as an internal standard]. HRMS-FAB spectra were obtained with a double focusing sector detector. Enantiomeric excess was determined by HPLC analysis using chiral column (DAICEL CHIRALPAK AD-H) with hexane/2-propanol as the solvent. PM3 calculation was conducted with Spartan 14.

Materials. DMF and toluene were distilled from CaH_2 and stored over 4A molecular sieves. Acetic acid was distilled from $KMnO_4$. $PhI(OAc)_2$ was recrystallized with hexane.

Typical Procedure and Spectroscopic Data of Products. *Preparation of 7,7′-Dimethyl-8,8′-biquinoline (3) by Reported Procedure (Scheme 2).*[6] *o*-Toluidine (9.96 g, 94.1 mmol) was added in acetic anhydryde (65 mL) at 0 °C, and the mixture was stirred for 2 h at 0 °C. Then, nitric acid (12.6 mL, 188 mmol) was added slowly for 1 h, and the mixture was stirred for 3 h. The mixture was poured into ice, and the thus formed solid was collected by vacuum filtration. The residue was solved in the solution of H_2O (540 mL), EtOH (119 mL), KOH (60.0 g), and the mixture was stirred for 1 h at room temperature. Solid was separated by vacuum filtration, and the filtrate was purified by recrystallization (hexane/EtOAc) to give 2-acetylamide-3-methyl nitrobenzene (**4**) (11.5 g, 70.6 mmol) in 75% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (br, 1H), 7.83 (d, 1H, J = 8.1 Hz), 7.51 (d, 1H, J = 8.1 Hz), 7.28 (dd, 1H, J = 8.0, 7.9 Hz), 2.32 (s, 3H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.3, 144.9, 138.3, 136.1, 129.7, 126.4, 122.8, 23.8, 19.8. A solution of **4** (22.9 g, 141 mmol) in conc. HCl (150 mL) was heated at 85 °C, and the mixture was stirred for 6 h. The reaction flask was cooled to 0 °C and was added dropwise solution of $NaNO_2$ (12.1 g, 176 mmol) in H_2O (44 mL) for 1 h. After stirring the mixture for 1 h, the mixture was poured into solution of KI (34.1 g, 200 mmol) in ice water, and

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the mixture was stirred for 2 h. Aqueous $NaHSO_4$ was added to the mixture, and the mixture was stirred for 1 h. Solid was separated by vacuum filtration and was purified by recrystallization (hexane/EtOAc) to give 2-iodo-3-methyl nitrobenzene (**5**) (28.5 g, 109 mmol) in 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 2H, J = 7.4 Hz), 7.35 (dd, 1H, J = 8.0, 7.2 Hz), 2.58 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.2, 132.3, 128.6, 121.8, 92.4, 29.7. To a solution of **5** (1.52 g, 5.78 mmol) in DMF (12 mL) was added Cu powder (1.51 g, 23.7 mmol), and the mixture was stirred for 2 h at reflux. The reaction quenched with sat. $NaHCO_3$ aq and basified with 2 M NaOH aq. The mixture was filtered through a Celite pad. The organic materials were extracted with EtOAc (3 × 20 mL), washed with H_2O (3 × 50 mL), and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford crude compound, which was purified by recrystallization (hexane/EtOAc) to give 3,3′-dimethyl-2,2′-binitrobenzene (**6**) (692 mg, 2.54 mmol) in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 2H, J = 8.2 Hz), 7.57 (d, 2H, J = 7.5 Hz), 7.46 (dd, 2H, J = 8.0, 7.9 Hz), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.1, 138.3, 135.2, 131.4, 128.6, 122.3, 19.8. To a solution of **6** (400 mg, 1.47 mmol) in conc. HCl (9.6 mL) and EtOH (5.0 mL) was added Sn powder (994 mg, 8.82 mmol), and the mixture was stirred for 2 h at reflux. The reaction mixture was poured into ice water and basified with 2 M NaOH aq. After removing EtOH in vacuo. The resulting suspention was filtered through a Celite pad. Organic materials were extracted with CH_2Cl_2 (3 × 30 mL) from the filtrate, and the organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford crude compound, which was purified by recrystallization (hexane/EtOAc) to give 3,3′-dimethyl-2,2′-bianiline (**7**) (311 mg, 1.47 mmol), quantitatively. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, 2H, J = 8.0, 7.5 Hz), 6.72 (d, 2H, J = 7.5 Hz), 6.64 (d, 2H, J = 8.0 Hz), 3.45 (brs, 4H), 1.97 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.2, 137.9, 128.4, 122.2, 120.1, 112.8, 19.5. To a solution of **7** (2.81 g, 13.2 mmol) in nitrobenzene (10 mL) and conc. H_2SO_4 (2.8 mL) were added $FeSO_4(H_2O)_7$ (1.83 g, 6.50 mmol) and glycerol (4.86 g, 53.0 mmol), and the mixture was stirred for 6 h at reflux. The reaction mixture was poured into ice water, basified with sat. $NaHCO_3$ aq, and filtered through a Celite pad. The filtrate was acidified with 2 M HCl aq and extracted with H_2O (3 × 50 mL). After the aqueous layer was basified with 2 M NaOH aq, the layer was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford crude compound, which was purified by column chlomatography (silica gel, hexane/EtOAc = 2/1) to give **3** (2.14 g, 7.52 mmol) in 57% yield.

*Separation of **3** by Chiral Column HPLC.* Chiral column HPLC analysis of **3** (DAICEL CHIRALPAK AD-H (4.6 × 250 mm), hexane/*i*PrOH = 9/1, 0.2 mL/min, retention time: first eluent 38.5 min, second eluent 45.3 min) showed the existence of two rotamers. Racemic **3** (ca. 1 mg) was solved in mixed solvent (hexane/*i*PrOH = 9/1, 5 mL) and was separated two enantiomers (*S*)-**3** and (*R*)-**3** by chiral column preparative HPLC (column: DAICEL CHIRAL PAK AD-H; eluent: hexane/*i*PrOH = 9/1). The configurations of the first and second eluates were assigned as (*S*)-**3** (92% ee) and (*R*)-**3** (98% ee), respectively, using the exciton chirality method (see text).

*7,7′-Dimethyl-8,8′-biquinoline (**3**).* Mp 219−223 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, 2H, J = 4.2, 1.8 Hz), 8.16 (dd, 2H, J = 8.2, 1.8 Hz), 7.82 (d, 2H, J = 8.3 Hz), 7.57 (d, 2H, J = 8.3 Hz), 7.28 (dd, 2H, J = 8.2, 4.2 Hz), 2.06 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 150.2, 147.3, 138.1, 137.1, 135.9, 129.4, 127.1, 126.8, 119.9, 20.6. IR (ATR) 3028, 1489, 802. HRMS(FAB$^+$) m/z (M + H)$^+$ calcd for $C_{20}H_{17}N_2$ 285.1392, found 285.1384. UV−vis (MeOH) λ_{max} 320 nm (ε 6400), 233 (43600), 208 (45200). For (*S*)-**3** (92% ee): $[\alpha]_D^{25}$ = −34 (*c* 1.0, $CHCl_3$). CD (MeOH) λ_{ext} 238 nm ($\Delta\varepsilon$ + 129), 227 (−82). For (*R*)-**3** (98% ee): $[\alpha]_D^{25}$ = +44 (*c* 1.0, $CHCl_3$). CD (MeOH) λ_{ext} 238 nm ($\Delta\varepsilon$ −155), 227 (+74).

*8-Bromo-7-methylquinoline (**9**).*[7] To a solution of 7-methylquinoline (**8**) (10.8 g, 75 mmol) in conc. H_2SO_4 (150 mL) was added NBS (13.5 g, 75.3 mmol) at 0 °C, and the mixture was stirred for 2 h at room temperature. The reaction flask poured into iced water, and basified with 2 M NaOH aq. The organic materials were extracted with EtOAc (3 × 200 mL) and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford crude compound, which was purified by column chlomatography (Silicagel, hexane/EtOAc = 6/1) to give **9** (16.7 g, 75 mmol), quantitatively.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (dd, 1H, J = 4.2, 1.7 Hz), 7.89 (dd, 1H, J = 8.2, 1.7 Hz), 7.43 (d, 1H, J = 8.3 Hz), 7.30 (dd, 1H, J = 8.2, 4.2 Hz), 7.29 (d, 1H, J = 8.3 Hz), 2.60 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.4, 150.3, 145.0, 139.6, 135.8, 128.8, 127.1, 126.1, 125.3, 120.4, 23.8.

*Preparation of 7,7′-Dimethyl-8,8′-biquinoline (**3**) by Homo Coupling of **9** (Scheme 3).* To a solution of **9** (1.05 g, 4.74 mmol) in DMF (11 mL) was added $Pd(OAc)_2$ (56.0 mg, 0.25 mmol) and Cu powder (1.51 g, 24.8 mmol), and the mixture was stirred for 10 h at reflux (170 °C). The reaction was quenched with 2 M NaOH aq, and the organic materials were extracted with EtOAc (3 × 50 mL) and dried with anhydrous sodium sulfate. The solvent was removed in vacuo to afford crude compound, which was purified by column chlomatography (Silicagel, hexane/EtOAc = 2/1) to give **3** (380 mg, 1.34 mmol) in 56% and **8** (138 mg, 0.96 mmol) in 20% yield.

*Pd-Catalyzed Double C−H Oxidation of 7,7′-Dimethyl-8,8′-biquinoline (**3**).* To a solution of **3** (49.0 mg, 0.17 mmol) in AcOH (3.4 mL) was added $Pd(OAc)_2$ (7.6 mg, 0.034 mmol) and $PhI(OAc)_2$ (354 mg, 1.1 mmol), and the mixture was stirred at reflux. $PhI(OAc)_2$ (113 mg, 0.35 mmol) was added 6 times by ca. 1 h to the reaction mixture when the color of reaction mixture became black and the progress of the reaction was not observed by TLC. The reaction lasted after 7 h and was quenched with sat. $NaHCO_3$ aq. The organic materials were extracted with CH_2Cl_2 (3 × 10 mL), washed with brine, and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford crude compound, which was purified by column chlomatography (silica gel, $CHCl_3$/MeOH = 19/1) to give **14** (51 mg, 0.13 mmol) in 74%.

*7,7′-Diacethoxymethyl-8,8′-biquinoline (**14**).* Mp 165−167 °C (dec). ^{1}H NMR δ 8.73, (dd, 2H, J = 4.2, 1.8 Hz), 8.20 (dd, 2H, J = 8.2, 1.7 Hz), 7.96 (d, 2H, J = 8.5 Hz), 7.77 (d, 2H, J = 8.5 Hz), 7.35 (dd, 2H, J = 8.2, 4.2 Hz), 4.90 (d, 2H, J = 13.1 Hz), 4.78 (d, 2H, J = 13.1 Hz), 1.94 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.5, 150.6, 147.0, 136.1, 135.6, 128.4, 128.1, 126.3, 121.1, 77.2, 64.6, 20.7. IR (KBr) 3051, 1740, 1371 cm^{-1}. HRMS (FAB$^+$) m/z (M + H)$^+$ calcd for $C_{24}H_{21}N_2O_4$ 401.1501, found: 401.1499.

*7-Acethoxymethyl-7′-methyl-8,8′-biquinoline (**13**).* Mp 169−172 °C (dec). ^{1}H NMR δ 8.75 (dd, 1H, J = 4.2, 1.8 Hz), 8.69 (dd, 1H, J = 4.2, 1.8 Hz), 8.20 (dd, 1H, J = 8.2, 1.7 Hz), 8.17 (dd, 1H, J = 8.2, 1.7 Hz), 7.94 (d, 1H, J = 8.5 Hz), 7.84 (d, 1H, J = 8.4 Hz), 7.77 (d, 1H, J = 8.5 Hz), 7.57 (d, 1H, J = 8.4 Hz), 7.34 (dd, 1H, J = 8.2, 4.2 Hz), 7.28 (dd, 1H, J = 8.2, 4.2 Hz), 4.88 (d, 1H, J = 13.0 Hz), 4.75 (d, 1H, J = 13.0 Hz), 2.08 (s, 3H) 1.93 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.5, 150.6, 150.2, 147.3, 146.9, 138.8, 137.7, 136.0, 136.0, 135.6, 135.1, 129.3, 128.1, 127.8, 127.6, 126.7, 126.5, 121.0, 120.0, 64.8, 20.8, 20.7. IR (ATR) 2884, 1736, 842 cm^{-1}. HRMS (FAB$^+$) m/z (M + H)$^+$ calcd for $C_{22}H_{19}N_2O_2$ 343.1447, found: 343.1478.

*Synthesis of 7,7′-Dihydroxymethyl-8,8′-biquinoline (**2**) by Hydrolysis of **14**.* To a solution of **14** (64.0 mg, 0.16 mmol) in MeOH (2.0 mL) was added KOH (53.0 mg, 0.96 mmol), and the mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. NH_4Cl aq, and MeOH was removed in vacuo. The organic materials were extracted with CH_2Cl_2 (3 × 10 mL) and dried with anhydrous sodium sulfate. The solvent was removed in vacuo to afford crude compound, which was purified by column chromatography (silica gel, $CHCl_3$/MeOH = 19/1) to give **2** (49.9 mg, 0.16 mmol), quantitatively.

*Separation of **2** by Chiral Column HPLC.* Chiral column HPLC analysis of **2** (DAICEL CHIRALPAK AD-H (4.6 × 250 mm), hexane/*i*PrOH = 4/1, 0.6 mL/min, retention time: first eluent 33.9 min, second eluent 51.6 min) showed the existence of two rotamers. Racemic **2** (ca. 1 mg) was solved in mixed solvent (hexane/*i*PrOH = 4/1, 20 mL) and was separated two enantiomers (*S*)-**3** and (*R*)-**3** by chiral column preparative HPLC (column: DAICEL CHIRAL PAK AD-H; eluent: hexane/*i*PrOH = 4/1). The configurations of the first

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and second eluates were assigned as (*S*)-**2** (>99% ee) and (*R*)-**3** (>99%ee), respectively, using the exciton chirality method (see text).

*7,7′-Dihydroxymethyl-8,8′-biquinoline (**2**).* Mp 202−210 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, 2H, J = 4.2, 1.8 Hz), 8.26 (dd, 2H, J = 8.2, 1.8 Hz), 8.01 (d, 2H, J = 8.4 Hz), 7.89 (d, 2H, J = 8.4 Hz), 7.38 (dd, 2H, J = 8.2, 4.2 Hz), 4.28 (s, 4H), 3.19 (brs, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.6, 147.3, 141.3, 136.8, 134.9, 128.6, 128.4, 128.2, 121.1, 64.1. IR (KBr) 3327, 2899, 1502 cm^{-1}. HRMS (FAB$^+$) m/z (M + H)$^+$ calcd for $C_{20}H_{17}N_2O_2$ 317.1290, found: 317.1299. UV−vis (MeOH) λ_{max} 318 nm (ε 6500), 233 (46800), 208 (48800). For (*S*)-**2** (92% ee): $[\alpha]_D^{25}$ = −34 (c 1.0, $CHCl_3$). CD (MeOH) λ_{ext} 238 nm ($\Delta\varepsilon$ + 117), 226 (−74). For (*R*)-**2** (>99% ee): $[\alpha]_D^{25}$ = +33 (c 1.0, $CHCl_3$). CD (MeOH) λ_{ext} 238 nm ($\Delta\varepsilon$ −116), 226 (+50).

*Double C−H Oxidation and Successive Hydrolysis of Optically Active Biquinoline (R)-**3** (Scheme 4).* To a solution of (*R*)-**3** (98% ee, 5.0 mg, 0.017 mmol) in AcOH (1.0 mL) were added $Pd(OAc)_2$ (0.8 mg, 0.0036 mmol) and $PhI(OAc)_2$ (43.8 mg, 0.136 mmol), and the mixture was stirred at reflux. The reaction mixture was added $PhI(OAc)_2$ (10.9 mg, 0.034 mmol) was added to the mixture each hour, and the reaction lasted for 7 h. The solvent was removed in vacuo to afford crude compound, which was dissolved in MeOH (1.0 mL). KOH (9.5 mg, 0.16 mmol) was added, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. NH_4Cl aq and MeOH was removed in vacuo. The organic materials were extracted with CH_2Cl_2 (3 × 10 mL) and dried with anhydrous sodium sulfate. The solvent was removed in vacuo to afford crude compound, which was purified by column chlomatography (Silicagel, $CHCl_3$/MeOH = 19/1) to give (*R*)-**2** (98% ee, 2.6 mg, 0.0082 mmol) in 48%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00534.

NMR spectra, chiral HPLC chart, CD/UV spectra, and Cartesian coordinates of computational data (PDF)

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Notes

The authors declare no competing financial interest.

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