Enantioselective Synthesis of Biaryl Compounds via Suzuki–Miyaura Cross-Coupling Using a Palladium Complex of 7′-Butoxy-7-(diphenylphosphino)-8,8′-biquinolyl: Investigation of a New Chiral Ligand Architecture

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Abstract: 7,7′-Dihydroxy-8,8′-biquinolyl was converted to the title phosphine in four-steps via Mitsunobu monoetherification, trifylation, phosphination, and phosphine oxide reduction (63% overall yield). Enantiomerically pure phosphine was combined with Pd_2dba_3 and investigated for the synthesis of axially chiral biaryl compounds from Ar^1Br and $Ar^2B(OH)_2$ in the presence of K_3PO_4 in toluene solvent (6 examples, 4–97% yield, 4–74% ee). The analogous carbocyclic ligand 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl (MOP) was studied for comparative purposes and found to be effective for the synthesis of hindered 2,2′-disubstituted 1,1′-binaphthyls (78–83% yield, 20–38% ee).

Key words: asymmetric catalysis, atropisomerism, azaBINOL, cross-coupling, quinolines

The continued development of synthetically useful enantioselective processes is stimulated by the introduction of new stereoinductive elements that may offer heightened selectivity as compared to known technologies. Axially chiral molecules have featured prominently as controlling ligands for metal-mediated asymmetric catalysis, particularly systems based on the all carbocyclic 1,1′-binaphthyl scaffold such as BINOL[1] and BINAP.[2] By contrast, with the notable exception of the QUINAP (**1**) family of ligands,[3] axially chiral heterocyclic frameworks are rarely exploited for the same purpose in spite of the fact that such molecules may provide unique chelation modes. Within this arena, and given our continuing interest in biquinolyl derivatives,[4] 7-phosphino-8,8′-biquinolyls such as **2** were identified as an intriguing new type of N,P-ligand worthy of investigation (Figure 1). Various bidentate chiral ligands (e.g., **1**) have been introduced that chelate a metal atom between a suitably bridged pair of N- and P-atoms for effective stereoinduction;[5] however, the topology of **2** is unlike any of them. The relative orientation of the N- and P-lone pairs in **2** is such that both σ-donors cannot simultaneously engage in conventional end-on overlap with the same metal center; rather, the N-atom lone pair may engage only in a weak side-on interaction as indicated (**2**·[M]). In this manner, one can envision that the advantages of both monodentate (high reactivity) and bidentate (high stereoselectivity) ligand types might be derivable from ligand **2** by facile coordination changes. To explore the above premise, herein, we describe a synthesis of **2** from azaBINOL (**4**), its evaluation in a valuable Pd-catalyzed cross-coupling process, and comparison of **2** with the analogous carbocyclic ligand MOP (**3**).

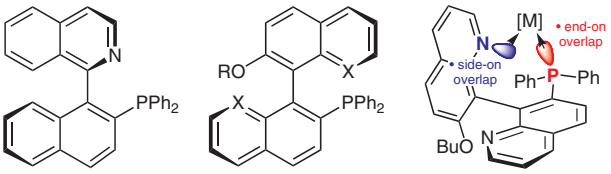
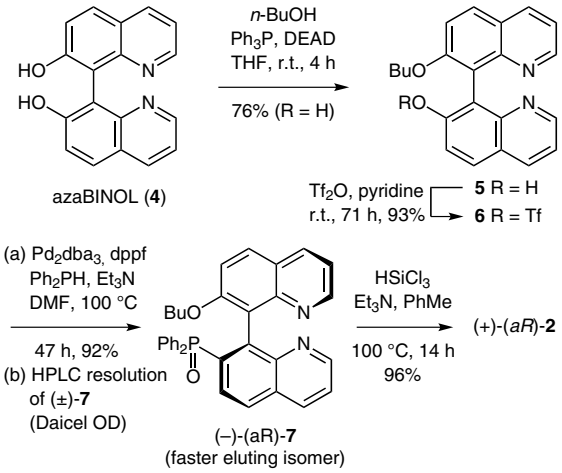


Figure 1 1-(2-Diphenylphosphino-1-naphthyl)isoquinoline (QUINAP, **1**), 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl (MOP, **3**), 7′-butoxy-7-(diphenylphosphino)-8,8′-biquinolyl (**2**), and a hypothetical metal chelation mode (*aS*)-**2**·[M] involving the latter

The synthesis of 7-phosphino-8,8′-biquinolyl (**2**) began with monoetherification of azaBINOL (**4**); a material obtained from 8-chloroquinoline in two or three steps (Scheme 1).[6] Alkylation of one hydroxyl group in **4** was desired to improve solubility of all subsequent intermediates and to simplify incorporation of the phosphorus atom. It was discovered that Williamson conditions (i.e., **4**, base, *n*-BuBr) resulted in exclusive formation of the diether no matter the reaction stoichiometry, while the illustrated Mitsunobu protocol resulted in generation of the mono-



Scheme 1 Synthesis of (+)-(*aR*)-**2** from 7,7′-dihydroxy-8,8′-biquinolyl ('azaBINOL', **4**)

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ether (**5**) in good yield.[7] Triflylation of the remaining free phenol in **5** followed by Pd-catalyzed substitution with diphenylphosphine led to a mixture of phosphine **2** and its oxide **7**, unless quite stringent measures were taken to avoid adventitious exposure to oxygen.[8] For this reason, and the finding (±)-**7** was much easier to resolve than (±)-**2**, the reaction was run in the presence of air to cleanly obtain the oxide as the only product. The identity of (±)-**7** was unequivocally established by single-crystal X-ray diffraction analysis of the crystalline racemate (Figure 2).[9]

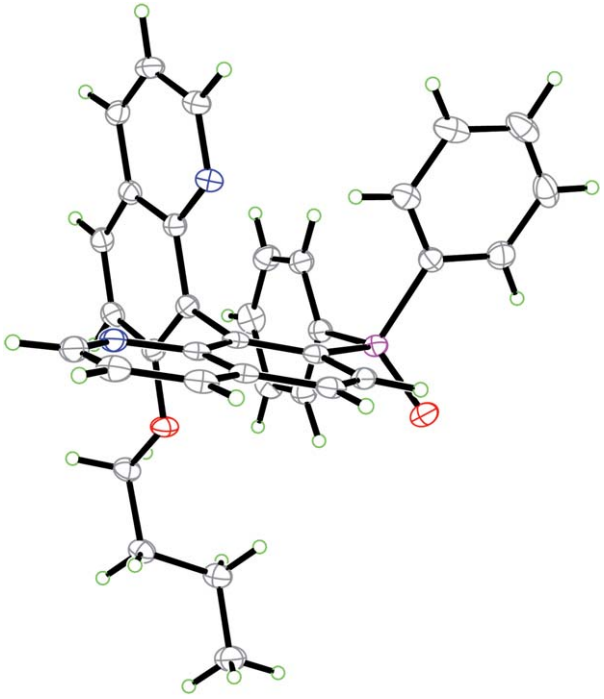


Figure 2 ORTEP diagram for phosphine oxide (±)-**7**; 50% probability ellipsoids are plotted for non-hydrogen atoms

Phosphine oxide **7** was resolved by preparative HPLC on a chiral stationary phase (Daicel OD column) into its configurationally stable enantiomeric atropisomers. In a previous work,[4a] it was established that structurally related 8,8′-biquinolyls and 1,1′-binaphthyls share the same exciton couplet chirality phase in their electronic CD spectra. On this basis, the dextrorotary isomer of biquinolyl **7**[10] is tentatively assigned as having (*aS*)-configuration because its CD spectrum revealed opposite exciton chirality[11] to that shown by the analogous carbocyclic phosphine oxide prepared (with aq H_2O_2) from a bought sample of (+)-(*aR*)-MOP (**3**)[12] (Figure 3). Reduction of phosphine oxide (–)-**7** with trichlorosilane[13] resulted in its nonracemizing conversion to phosphine (+)-**2**. In line with our earlier observations, it was found that phosphine **2** is very susceptible to aerial oxidation, especially in solution. This material could, however, be stored without transformation to **7** in the solid state and it was established that phosphine **2** is configurationally stable to at least 110 °C.[14]

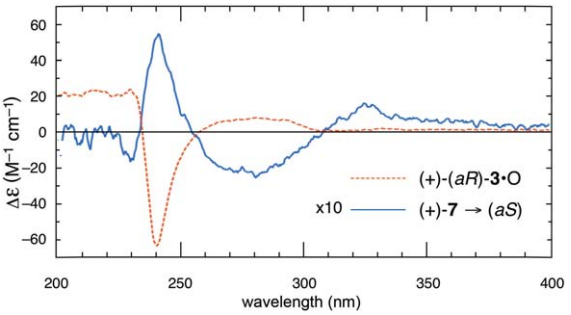
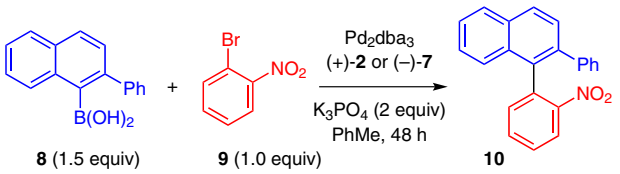


Figure 3 Comparison of electronic CD spectra for phosphine oxides (+)-**7** and (+)-(*aR*)-MOP-oxide (**3**·O) collected from MeOH solutions (0.30 mM and 0.17 mM, respectively). Phosphine oxide (+)-**7** was assigned as having (*aS*)-configuration because this material shows an opposite exciton chirality phase to that exhibited by (+)-(*aR*)-MOP-oxide.

With biquinolyl phosphine **2** in hand its efficacy as an activating and controlling ligand in the Pd-catalyzed synthesis of biaryl derivatives from aryl bromides and arylboronic acids via Suzuki–Miyaura cross-coupling was evaluated.[15] This useful approach to the enantioselective synthesis of axially chiral biaryls was first described by Cammidge[16a] and Buchwald[16b,c] and it has emerged as a valuable benchmark for the study of new ligands because of the difficulty of obtaining high ee and the challenge associated with forming sterically congested C–C bonds.[17] We began our investigation with the synthesis of an α-phenylnaphthalene **10** from boronic acid **8** and bromobenzene **9**, a cross-coupling reaction previously explored by Buchwald et al. and achieved in 86% yield and 73% ee using a 2-amino-2′-phosphino-1,1′-binaphthyl ligand in combination with Pd_2dba_3 as precatalyst, K_3PO_4 as base, and toluene as solvent at 70 °C (48 h).[16b] Evaluation of ligand (+)-**2** under the same reaction conditions afforded biaryl **10** in comparable yield and 55% ee (Table 1, entry 1). An improvement in yield was noted by use of higher Pd and ligand loadings (entries 1–3) and, as expected, stereoselectivity was raised to the detriment of the rate of reaction by conducting the cross-coupling at lower temperature (entries 3–5). Given the ready conversion of (+)-**2** to (–)-**7** in air, we assessed the likely effect of phosphine oxide contamination on reaction outcome by deliberately doping phosphine (+)-**2** with variable quantities of its oxide (–)-**7** (entry 3 vs. entries 6–8). It was evident that the free phosphine was a more active ligand than the phosphine oxide and the presence of (–)-**7** barely compromized yield and stereoselectivity until the molar ratio of **7**:**2** exceeded 1:1. Beyond this level and efficacy began to suffer markedly, an effect understandable given that it was found that (–)-**7** alone favored formation of the opposite enantiomer of **10** as compared to (+)-**2** (cf. entries 3 and 8). Lastly, cross-coupling was found to occur to a modest degree in the absence of (+)-**2** [or (–)-**7**] (entry 9). In the event that the active metal-ligand complex (**2**·[Pd]) is kinetically labile to dissociation, a nonligand controlled re-

action necessarily leading to racemic product could therefore operate and in doing so erode maximal ee.[18]

Table 1 Enantioselective Synthesis of Biaryl **10** Using Phosphine Ligand (+)-**2** with and without Addition of Phosphine Oxide (–)-**7**[a]



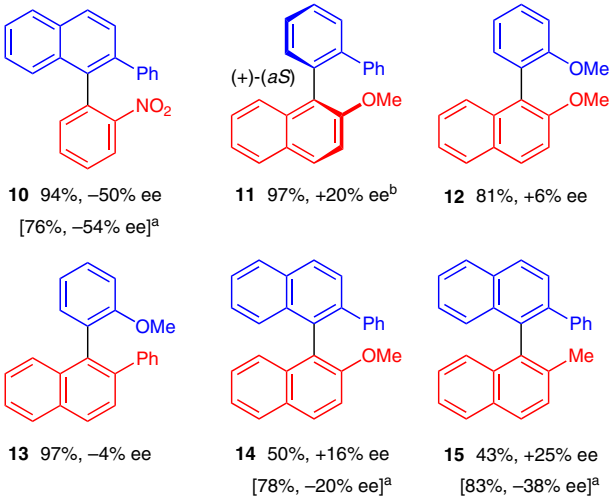
8 (1.5 equiv) **9** (1.0 equiv) **10**

Entry	Pd(0)[b] mol%	(+)-**2** mol%	(–)-**7** mol%	Temp (°C)	Yield (%)	ee (%)[c]
1	2.5	3.0	0.0	70	80	–55
2	5.0	6.0	0.0	70	90	–52
3	**10.0**	**12.0**	**0.0**	**70**	**94**	**–50**
4	10.0	12.0	0.0	45	16	–58
5[d]	10.0	12.0	0.0	23	4	–74
6	10.0	6.0	6.0	70	92	–43
7	10.0	3.0	9.0	70	62	–37
8	10.0	0.0	12.0	70	<20	+54
9	20.0	0.0	0.0	70	22	na

[a] Compounds (+)-**2** and (–)-**7** share the same (*aR*)-configuration.
[b] Mol% of Pd (e.g., 10 mol% Pd = 5 mol% Pd_2dba_3).
[c] Sign of enantiomeric excess (ee) value indicates sign of optical rotation $[\alpha]_D$ ($CHCl_3$) for generated biaryl product **10**; na: not available.
[d] Reaction time: 96 h.

With optimal reaction conditions for the enantioselective synthesis of **10** using ligand (+)-**2** identified, the same protocol was applied to access three further α-phenylnaphthalenes possessing a trio of nontrivial substituents flanking the chiral axis **11**–**13** and it was then extended to two 1,1′-binaphthyl compounds fully substituted about the central bond (**14**, **15**) (Figure 4). In targeting biaryls **11**–**13**, high yield was realized but the products exhibited low ee (≤20%) and, in the case of **11** and **12**, significantly higher enantioselectivities have been realized before from the same precursors using alternate chiral ligands.[19] Pleasingly, sterically encumbered biaryls **14** and **15** were generated in good yield albeit with only modest enantioselectivity.

To gauge whether the presence of biquinolyl N-atoms within phosphine (+)-**2** had a meaningful effect on the Suzuki–Miyaura process, three of the cross-couplings previously evaluated were reassessed with (+)-MOP (**3**) as ligand (Figure 4, data in square brackets). To the best of our knowledge, application of MOP to the atroposelective synthesis of biaryls is limited to a few reports[20] and it has never before been evaluated for the synthesis of fully *ortho*-substituted compounds such as **14** and **15**. The monodentate Pd-ligand **3**[12,21] was less effective than (+)-**2** for the generation of **10** but it provided the challenging targets **14** and **15** with improved efficacy. Indeed, the



10 94%, –50% ee [76%, –54% ee][a]
11 97%, +20% ee[b]
12 81%, +6% ee
13 97%, –4% ee
14 50%, +16% ee [78%, –20% ee][a]
15 43%, +25% ee [83%, –38% ee][a]

Figure 4 Yield and enantioselectivity for biaryl molecules **10**–**15** prepared from an aryl bromide (1.0 equiv, source of lower aryl moiety shown in red) and an aryl boronic acid (1.5 equiv, source of upper aryl moiety shown in blue) using the conditions described in Table 1, entry 3 [i.e., Pd_2dba_3 (5 mol%), (+)-(*aR*)-**2** (12 mol%), K_3PO_4 (2 equiv), toluene, 70 °C, 48 h]; sign of enantiomeric excess (ee) value indicates sign of optical rotation $[\alpha]_D$ ($CHCl_3$) for biaryl products. [a] Data in square brackets were obtained by substituting (+)-(*aR*)-MOP (**3**) for (+)-(*aR*)-**2**. [b] Reaction carried out at 45 °C instead of 70 °C; absolute configuration of (+)-(*aS*)-**11** reported.[17a]

yield realized for the synthesis of **15** (83%) compares very favorably to that reported by Buchwald et al. using a more complicated 2-(9-phenanthrenyl)phenyl phosphine ligand (90%).[22]

Of note, while ligands (+)-(*aR*)-**2** and (+)-(*aR*)-**3** were found to favor generation of the same levorotary form of triortho-substituted biaryl **10**, the fully *ortho*-substituted biaryls **14** and **15** were produced in dextrorotary form with (+)-(*aR*)-**2** but in levorotary form using (+)-(*aR*)-**3**.[23] These data indicate that phosphines **2** and **3** do not behave as simple isosteric analogues of one another, but rather that their differing carbocyclic/heterocyclic characters can lead to distinct stereoinduction modes. That being said, it would be speculation to attribute the origin of the differing behavior to the putative N,P-ligating mode introduced above in the absence of structural characterization of **2**·[Pd] complexes.

In summary, a new type of phosphine ligand based on an axially chiral biquinolyl scaffold was prepared and demonstrated to offer modest efficacy for the enantioselective synthesis of biaryl compounds via Suzuki–Miyaura cross-coupling. Although grossly similar in structure to the well known binaphthyl ligand MOP, differences in the sense of stereoinduction offered by biquinolyl (**2**) and binaphthyl (**3**) phosphines indicates that these two ligand systems are not simple analogues of each other. Finally, the comparative study using MOP (**3**) revealed that this widely available phosphine warrants further exploration for the assembly of hindered C–C bonds via Suzuki–Miyaura reaction.[24]

Efforts to structurally characterize Pd and other metal complexes derived from 8,8′-biquinoyl phosphine **2** and related quinoline containing biaryl molecules are in progress. This work and investigations of further applications of axially chiral heterocyclic biaryls in asymmetric synthesis will be reported in due course.

Preparative chromatographic separations were performed on silica gel 60 (35–75 μm) and reactions followed by TLC analysis using silica gel 60 plates (2–25 μm) with fluorescent indicator (254 nm) and visualized by UV or phosphomolybdic acid (PMA). All commercially available reagents were used as received (Aldrich). Anhydrous solvents were obtained from a Pure Process Technologies solvent purification system and dispensed under argon.[25] Melting points were recorded on a Mel-Temp melting point apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer Spectrum II FT-IR using KBr discs for solids or a thin film between NaCl plates for oils. NMR spectra were recorded on Bruker Avance spectrometers at the field strength specified from 5 mm diameter tubes. Chemical shift in ppm is quoted relative to residual solvent signals calibrated as follows for $CDCl_3$: δ_H ($CHCl_3$) = 7.26, δ_C = 77.2 ppm. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT spectral editing technique. Low- (MS) and high-resolution (HRMS) mass spectra were obtained using electrospray (ES), electron impact (EI), or chemical ionization (CI) techniques. Ion mass/charge (*m*/*z*) ratios are reported as values in atomic mass units. Chiral stationary phase (CSP) high performance liquid chromatography (HPLC) was executed on an Agilent 1100 series modular HPLC system equipped with standard Daicel Industries chiral columns as indicated. Circular dichroism (CD) spectra were recorded on a Jasco J-815 instrument at a scan rate of 100 nm min^{-1} from MeOH solutions in a cell with 1 mm path length.

7′-Butoxy-7-hydroxy-8,8′-biquinolyl (5)

A stirred suspension of 7,7′-dihydroxy-8,8′-biquinolyl (**4**;[6] 1.48 g, 5.13 mmol), Ph_3P (1.88 g, 7.18 mmol), and *n*-BuOH (2.40 mL, *d* = 0.810, 1.94 g, 26.2 mmol) in THF (52 mL) was treated with diethyl azodicarboxylate (DEAD, 3.10 mL, 40 wt% in toluene, *d* = 0.956, 1.19 g, 6.81 mmol) at r.t. The resulting mixture was stirred for 4 h at r.t. and then concentrated in vacuo. The residue was taken up in 2.0 M aq HCl (10 mL) and H_2O (20 mL) and the acidic aqueous solution of biquinolyl hydrochloride salts washed with EtOAc (3 × 30 mL). The pH of the aqueous phase was adjusted to 7.0 with 30 wt% aq KOH and the free bases of the biquinolyl components were extracted with EtOAc (4 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluting with 1–2% MeOH in CH_2Cl_2) to afford the monoether **5** (1.35 g, 3.92 mmol, 76%) as a yellow solid; mp 136–138 °C.

IR (KBr): 2933, 1610, 1501, 1428, 1307, 1085 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (dd, *J* = 4.3, 1.8 Hz, 1 H), 8.68 (dd, *J* = 4.3, 1.8 Hz, 1 H), 8.23 (dd, *J* = 8.2, 1.8 Hz, 1 H), 8.11 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.97 (d, *J* = 9.0 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.53 (d, *J* = 9.0 Hz, 1 H), 7.46 (d, *J* = 8.9 Hz, 1 H), 7.31 (dd, *J* = 8.3, 4.3 Hz, 1 H), 7.19 (dd, *J* = 8.1, 4.2 Hz, 1 H), 6.80–6.30 (br s, OH), 4.04–3.91 (m, 2 H), 1.30–1.20 (m, 2 H), 0.86 (sext, *J* = 7.1 Hz, 2 H), 0.63 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (0), 155.2 (0), 151.1 (1), 149.9 (1), 148.7 (0), 147.8 (0), 137.4 (1), 136.1 (1), 129.9 (1), 129.0 (1), 124.1 (0), 124.0 (0), 120.5 (1), 119.3 (0), 119.0 (1), 118.6 (0), 118.4 (1), 116.4 (1), 69.1 (2), 31.2 (2), 18.7 (2), 13.7 (3).

MS (ES+): *m*/*z* (%) = 345 (100, [M + H^+]).

HRMS (ES+): *m*/*z* calcd for $C_{22}H_{21}N_2O_2$: 345.1603; found: 345.1586.

7′-Butoxy-7-(trifluoromethylsulfonyloxy)-8,8′-biquinolyl (6)

A stirred solution of phenol **5** (1.00 g, 2.90 mmol) in anhydrous pyridine (12 mL) at 0 °C under argon was treated dropwise with neat Tf_2O (1.43 mL, *d* = 1.677, 2.40 g, 8.50 mmol). The mixture was allowed to warm to r.t. and stirred for 71 h and then concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluting with 3–5% MeOH in CH_2Cl_2) to afford triflate **6** (1.29 g, 2.71 mmol, 93%) as a yellow solid; mp 117–119 °C ($CHCl_3$).

IR (KBr): 2961, 1613, 1503, 1418, 1213, 1143, 964, 847 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (dd, *J* = 4.0, 1.2 Hz, 1 H), 8.71 (dd, *J* = 4.1, 1.4 Hz, 1 H), 8.26 (dd, *J* = 8.4, 1.4 Hz, 1 H), 8.15 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.99 (d, *J* = 8.9 Hz, 1 H), 7.97 (d, *J* = 9.0 Hz, 1 H), 7.65 (d, *J* = 9.0 Hz, 1 H), 7.49 (d, *J* = 9.1 Hz, 1 H), 7.42 (dd, *J* = 8.2, 4.1 Hz, 1 H), 7.23 (dd, *J* = 8.2, 4.2 Hz, 1 H), 4.05 (t, *J* = 6.5 Hz, 2 H), 1.42 (quint, *J* = 7.0 Hz, 2 H), 0.99 (sext, *J* = 7.4 Hz, 2 H), 0.66 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7 (0), 151.4 (1), 151.1 (1), 148.2 (0), 148.1 (0), 148.0 (0), 136.3 (1), 136.1 (1), 130.5 (1), 129.5 (1), 127.7 (0), 123.6 (0), 121.6 (1), 120.4 (1), 120.0 (0), 119.0 (1), 117.7 (0), 114.8 (1), 68.8 (2), 31.2 (2), 18.8 (2), 13.6 (3) (CF_3 not distinguishable).

MS (ES+): *m*/*z* (%) = 477 (100, [M + H^+]).

HRMS (ES+): *m*/*z* calcd for $C_{23}H_{20}F_3N_2O_4S$: 477.1096; found: 477.1094.

7′-Butoxy-7-(diphenyloxyphosphino)-8,8′-biquinolyl (7)

A 30 mL thick-walled glass reaction tube equipped with a Teflon screw-fitting stopper (a ‘sealed tube’ apparatus) was opened to air and charged with a stir bar, triflate **6** (566 mg, 1.19 mmol), tris(dibenzylideneactone)dipalladium (Pd_2dba_3, 53 mg, 0.058 mmol, 5 mol%), and 1,1′-bis(diphenylphosphino)ferrocene (dppf, 71 mg, 0.128 mmol, 11 mol%). Et_3N (0.24 mL, *d* = 0.726, 174 mg, 1.73 mmol), Ph_2PH (0.22 mL, *d* = 1.07, 235 mg, 1.26 mmol), and DMF (12 mL) were then added and the Teflon stopper screwed back into place to create a tight seal. Stirring was initiated to effect dissolution and the tube partially submerged in a 100 °C oil bath above a magnetic stirrer-hotplate (note: the entire apparatus was set-up behind a large plastic blast shield). The contents of the sealed tube were stirred in this manner for 47 h and then allowed to cool to r.t. before the stopper was cautiously removed. The reaction mixture was filtered and the solids washed with EtOAc (2 × 5 mL). The filtrate and combined washings were partitioned between EtOAc (20 mL) and H_2O (30 mL) and the layers separated. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic phases washed with sat. aq NH_4Cl (3 × 40 mL), brine (20 mL), then dried (Na_2SO_4), and concentrated in vacuo. The residue was further purified by column chromatography (SiO_2, eluting with 3–5% MeOH in $CHCl_2$) to afford the racemic phosphine oxide (±)-**7** (577 mg, 1.09 mmol, 92%) as a viscous yellow-brown oil that solidified on standing. Recrystallization from toluene gave pale yellow plates suitable for X-ray diffraction analysis[9] (Figure 2); mp 136–138 °C (toluene).

IR (KBr): 2926, 1611, 1502, 1437, 1308, 1273, 1175, 1116 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (dd, *J* = 4.1, 1.7 Hz, 1 H), 8.45 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1 H), 8.00 (dd, *J* = 11.3, 8.6 Hz, 1 H), 7.92 (dd, *J* = 8.6, 2.7 Hz, 1 H), 7.85 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.62–7.55 (m, 3 H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.32 (tm, *J* = 7.5 Hz, 1 H), 7.25–7.17 (m, 5 H), 7.08 (d, *J* = 9.0 Hz, 1 H), 7.05–7.00 (m, 3 H), 3.95–3.90 (m, 1 H), 3.88–3.81 (m, 1 H), 1.43–1.35 (m, 2 H), 0.98–0.85 (m, 2 H), 0.62 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5 (0), 150.8 (1), 150.0 (1), 148.5 (0), 147.7 (0, d, *J* = 14 Hz), 142.6 (0, d, *J* = 8 Hz), 136.0 (1), 135.6 (1), 133.7 (0, d, *J* = 103 Hz), 133.2 (0, d, *J* = 104 Hz), 132.2 (1, d, *J* = 10 Hz, 2 C), 131.7 (1, d, *J* = 10 Hz, 2 C), 131.1 (1, d, *J* = 2 Hz), 130.8 (1, d, *J* = 2 Hz), 129.9 (0, d, *J* = 3 Hz), 129.8 (1, d, *J* = 11

Hz), 129.7 (1, 2 C), 127.7 (1, d, J = 12 Hz, 2 C), 127.4 (1, d, J = 12 Hz, 2 C), 127.4 (0, d, J = 13 Hz), 123.1 (0), 122.4 (1), 122.3 (0, d, J = 5 Hz), 118.4 (1), 114.5 (1), 68.4 (2), 31.3 (2), 18.8 (2), 13.7 (3).

MS (ES+): m/z (%) = 529 (100, [M + H$^+$]).

HRMS (ES+): m/z calcd for $C_{34}H_{30}N_2O_2P$: 529.2045; found: 529.2029.

X-ray Diffraction Analysis of (±)-7 (Figure 2)[9]

Diffraction intensities for phosphine oxide (±)-**7** were collected at 100(2) K on a Bruker Apex2 CCD diffractometer with a Incoatec $I\mu S$ source (CuK radiation = 1.54178 Å). Space group was determined based on systematic absences. Absorption corrections were applied by SADABS. Structure was solved by direct methods and Fourier techniques and refined on F^2 using full matrix least-squares procedures. All non-H atoms were refined with anisotropic thermal parameters. All H atoms were found on the residual density and refined with isotropic thermal parameters. All calculations were performed by the Bruker SHELXTL (v. 6.10) package.[26]

$C_{34}H_{29}N_2O_2P$, M = 528.56, 0.12 × 0.07 × 0.02 mm, T = 100 K, monoclinic, space group $P2_1/n$, a = 13.1020(6) Å, b = 11.2950(5) Å, c = 18.4184(9) Å, = 107.347(2), V = 2601.7(2) Å^3, Z = 4, D_c = 1.349 Mg/m^3, μ = 1.216 mm^{-1}, $F(000)$ = 1112, $2\theta_{max}$ = 126.96°, 32878 reflections, 4061 independent reflections [R_{int} = 0.0461], $R1$ = 0.0340, $wR2$ = 0.0896 and GOF = 1.027 for 4061 reflections (468 parameters) with $I>2(I)$, $R1$ = 0.0373, $wR2$ = 0.0921 and GOF = 1.027 for all reflections, max/min residual electron density +0.228/–0.434 eÅ^3.

Resolution of Phosphine Oxide (±)-7 via CSP HPLC

The racemate of phosphine oxide **7** was resolved using a Daicel Chiralcel OD semi-preparative column (250 mm × 10 mm I.D.) with a chiral stationary phase of cellulose tris(3,5-dimethylphenylcarbamate) on 10 μm SiO_2. Multiple chromatographic runs were performed, for each run, 150 μL of a 70 mg mL^{-1} solution of (±)-**7** in 10% *i*-PrOH in hexanes was injected onto the above column. Isocratic elution using a solvent blend of 10% *i*-PrOH in hexanes and a flow rate of 3.0 mL min^{-1} was performed with UV detection at 254 nm. The faster eluting enantiomer, (–)-(*aR*)-**7**, was collected from 28–39 min, and the slower eluting isomer, (+)-(*aS*)-**7**, was collected from 42–60 min. The atropisomers were obtained with >98% ee using this method. An enantiopure sample of (–)-(*aR*)-**7** exhibited: $[\alpha]_D^{20}$ –29.5 (c = 1.17, $CHCl_3$).

(+)-7′-Butoxy-7-(diphenylphosphino)-8,8′-biquinolyl [(+)-2]

A stirred solution of phosphine oxide (–)-**7** (17 mg, 0.032 mmol) in toluene (2.0 mL) at r.t. under argon was treated with Et_3N (53 mL, d = 0.726, 38 mg, 0.38 mmol) and $HSiCl_3$ (26 mL, d = 1.34, 35 mg, 0.26 mmol). The resulting mixture was heated to 100 °C and stirred for 14 h. After this time, the mixture was allowed to cool and then partitioned between sat. aq $NaHCO_3$ (10 mL) and EtOAc (10 mL) and the layers separated. The aqueous phase was extracted with EtOAc (10 mL) and the combined organic extracts washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluting with 2–6% MeOH in CH_2Cl_2) to yield phosphine (+)-**2** (15.8 mg, 0.031 mmol, 96%) as a yellow solid; mp 145–147 °C (EtOAc); $[\alpha]_D^{20}$ +61.3 (c = 0.77, $CHCl_3$, >98% ee).

CSP HPLC analysis: Daicel Chiracel OD (250 mm × 10 mm I.D.), eluting with 10% *i*-PrOH in hexanes at 3.0 mL min^{-1} and monitored by UV at 254 nm. Retention times: (+)-**2** = 11.9 min, (–)-**2** = 28.6 min.

IR (KBr): 3050, 2957, 1610, 1501, 1434, 1308, 1272, 1083, 835, 744, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (d, J = 2.8 Hz, 1 H), 8.54 (d, J = 3.1 Hz, 1 H), 8.15 (d, J = 8.2 Hz, 1 H), 8.09 (d, J = 8.1 Hz, 1 H), 7.90 (d, J = 9.0 Hz, 1 H), 7.80 (d, J = 8.4 Hz, 1 H), 7.47 (dd, J = 8.3, 2.1 Hz, 1 H), 7.39 (d, J = 9.0 Hz, 1 H), 7.33 (dd, J = 8.1, 4.2 Hz, 1 H), 7.28–7.19 (m, 10 H), 7.12 (dd, J = 8.1, 4.1 Hz, 1 H), 3.89 (q, J = 8.3 Hz, 1 H), 3.79 (dt, J = 8.7, 6.2 Hz, 1 H), 1.31–1.20 (m, 2 H), 0.96–0.83 (m, 2 H), 0.61 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3 (0), 150.5 (1), 150.3 (1), 148.6 (0), 147.8 (0, d, J = 9 Hz), 139.7 (0, d, J = 11 Hz), 138.3 (0, d, J = 14 Hz), 138.0 (0, d, J = 13 Hz), 136.1 (1), 135.9 (1), 133.7 (1, d, J = 1 Hz, 2 C), 133.5 (1, d, J = 2 Hz, 2 C), 131.1 (1), 129.2 (1), 128.7 (0), 128.2 (1, d, J = 1 Hz, 2 C), 128.1 (1, d, J = 1 Hz, 2 C), 128.1 (1, 2 C), 127.6 (1), 124.8 (0, d, J = 1 Hz), 123.5 (0), 121.4 (1), 118.6 (1), 114.9 (1), 68.5 (2), 31.3 (2), 18.8 (2), 13.7 (3) (1 quaternary carbon signal obscured).

MS (ES+): m/z (%) = 513 (100, [M + H$^+$]).

HRMS (ES+): m/z calcd for $C_{34}H_{30}N_2OP$: 513.2096; found: 513.2082.

Suzuki–Miyaura Coupling; 2-Phenyl-1-(2-nitrophenyl)naphthalene (10); Typical Procedure (Table 1, entry 3, and Figure 4)

A 15 mL thick-walled glass reaction tube equipped with a Teflon screw-fitting stopper (a 'sealed tube' apparatus) was opened and charged with a stir bar, 1-bromo-2-nitrobenzene (**9**; 20 mg, 0.099 mmol), 2-phenyl-1-naphthylboronic acid (**8**; 37 mg, 0.149 mmol), ligand (+)-**2** (6 mg, 0.012 mmol, 12 mol%), tris(dibenzylideneacetone)dipalladium (Pd_2dba_3, 4.5 mg, 0.0049 mmol, 5 mol%), and K_3PO_4 (42 mg, 0.199 mmol). A rubber septum was applied and the vessel was flushed with argon gas, then anhydrous toluene (0.50 mL) added via syringe. The septum was carefully replaced with the Teflon stopper, which was screwed on tight to seal the reaction tube. The contents of the vessel were sonicated for 30 s and then the tube partially submerged in a 70 °C oil bath above a magnetic stirrer-hotplate (note: the entire apparatus was set up behind a large plastic blast shield). The contents of the sealed tube were stirred in this manner for 48 h and then allowed to cool to r.t. before the stopper was cautiously removed. The reaction mixture was filtered and the solids washed with EtOAc (3 × 5 mL). The filtrate and combined washings were concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluting with 11–33% CH_2Cl_2 in hexanes) to afford biaryl **10** (30.6 mg, 0.094 mmol, 94%, 50% ee) as a yellow solid: mp 141–143 °C ($CHCl_3$); $[\alpha]_D^{20}$ –30.2 (c = 2.41, $CHCl_3$, 50% ee). ^{1}H and ^{13}C NMR spectral data were in agreement with those reported by Buchwald et al.[16b]

CSP HPLC analysis: Daicel Chiracel OD (250 mm × 4.6 mm I.D.), eluting with 5% *i*-PrOH in hexanes at 0.5 mL min^{-1} and monitored by UV at 254 nm. Retention times: (+)-**10** = 17.9 min, (–)-**10** = 21.6 min.

IR (KBr): 3059, 2924, 1610, 1524, 1351, 826, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.92 (m, 3 H), 7.60–7.34 (m, 6 H), 7.29 (dd, J = 7.6, 1.3 Hz, 1 H), 7.20–7.14 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2 (0), 141.3 (0), 138.3 (0), 134.8 (0), 134.4 (1), 133.5 (0), 132.83 (0), 132.75 (1), 131.8 (0), 129.7 (1, 2 C), 128.6 (1), 128.53 (1), 128.47 (1), 128.2 (1), 128.0 (1, 2 C), 127.04 (1), 126.95 (1), 126.1 (1), 125.4 (1), 124.5 (1).

1-(2-Biphenyl)-2-methoxynaphthalene (11)

1-Bromo-2-methoxynaphthalene (24 mg, 0.101 mmol) and biphenyl-2-boronic acid (30 mg, 0.151 mmol) were coupled according to the typical procedure given above (with a reaction temperature of 45 °C) using (+)-**2** as ligand to yield the title biaryl (+)-(*aS*)-**11** (30 mg, 0.097 mmol, 97%, 20% ee) as a colorless oil; $[\alpha]_D^{20}$ +9.0 (c = 1.42, $CHCl_3$, 20% ee). ^{1}H and ^{13}C NMR spectral data were in agreement with those reported by Tu et al.[27]

CSP HPLC analysis: Daicel Chiracel OJ (250 mm × 4.6 mm I.D.), eluting with 5% *i*-PrOH in hexanes at 0.5 mL min^{-1} and monitored by UV at 254 nm. Retention times: (–)-**11** = 17.8 min, (+)-**11** = 29.6 min.

IR (neat): 3056, 2933, 1621, 1593, 1509, 1380, 1333, 1262, 1070, 808, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 9.0 Hz, 2 H), 7.60–7.48 (m, 4 H), 7.41–7.31 (m, 3 H), 7.14 (d, *J* = 9.0 Hz, 1 H), 7.11–7.03 (m, 5 H), 3.54 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7 (0), 143.2 (0), 142.0 (0), 135.0 (0), 134.0 (0), 132.0 (1), 130.0 (1), 129.2 (1), 129.0 (0), 128.8 (1, 2 C), 128.1 (1), 127.9 (1), 127.4 (1, 2 C), 127.3 (1), 126.5 (1), 126.4 (1), 125.4 (1), 124.6 (0), 123.5 (1), 113.3 (1), 56.2 (3).

1-(2-Methoxyphenyl)-2-methoxynaphthalene (12)

1-Bromo-2-methoxynaphthalene (21 mg, 0.089 mmol) and 2-methoxyphenylboronic acid (20.5 mg, 0.135 mmol) were coupled according to the typical procedure given above using (+)-**2** as ligand to yield the title biaryl (+)-**12** (19 mg, 0.072 mmol, 81%, 6% ee) as a yellow oil; $[\alpha]_D^{20}$ +1.6 (*c* = 1.78, $CHCl_3$, 6% ee). ^{1}H and ^{13}C NMR spectral data were in agreement with those reported by Tu et al.[27]

CSP HPLC analysis: Daicel Chiracel OJ (250 mm × 4.6 mm I.D.), eluting with 1% *i*-PrOH in hexanes at 1.2 mL min^{-1} and monitored by UV at 254 nm. Retention times: (–)-**12** = 13.3 min, (+)-**12** = 19.8 min.

IR (neat): 3058, 2935, 1622, 1594, 1495, 1433, 1269, 1068, 810, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 9.1 Hz, 1 H), 7.85–7.80 (m, 1 H), 7.45 (dt, *J* = 8.3, 1.7 Hz, 1 H), 7.39 (d, *J* = 9.1 Hz, 2 H), 7.35–7.30 (m, 2 H), 7.24 (dd, *J* = 7.4, 1.7 Hz, 1 H), 7.12 (dm, *J* = 7.4 Hz, 1 H), 7.09 (d, *J* = 8.2 Hz), 3.85 (s, 3 H), 3.71 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9 (0), 154.4 (0), 133.8 (0), 132.6 (1), 129.2 (0), 129.2 (1), 129.0 (1), 128.0 (1), 126.3 (1), 125.5 (0), 125.4 (1), 123.6 (1), 122.3 (0), 120.7 (1), 114.3 (1), 111.5 (1), 57.1 (3), 55.9 (3).

1-(2-Methoxyphenyl)-2-phenylnaphthalene (13)

1-Bromo-2-phenylnaphthalene (25.5 mg, 0.090 mmol) and 2-methoxyphenylboronic acid (20.5 mg, 0.135 mmol) were coupled according to the typical procedure given above using (+)-**2** as ligand to yield the title biaryl (–)-**13** (27 mg, 0.087 mmol, 97%, 4% ee) as a colorless oil; $[\alpha]_D^{20}$ – 4.3 (*c* = 1.76, $CHCl_3$, 4% ee).

CSP HPLC analysis: Daicel Chiracel OJ (250 mm × 4.6 mm I.D.), eluting with 1% *i*-PrOH in hexanes at 1.0 mL min^{-1} and monitored by UV at 254 nm. Retention times: (+)-**13** = 9.5 min, (–)-**13** = 16.2 min.

IR (neat): 3055, 2931, 1601, 1579, 1491, 1461, 1434, 1243, 1028, 823, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (t, *J* = 8.4 Hz, 2 H), 7.60 (t, *J* = 8.5 Hz, 2 H), 7.49 (tm, *J* = 8.0 Hz, 1 H), 7.41 (ddd, *J* = 8.2, 7.2, 1.0 Hz, 1 H), 7.31 (dt, *J* = 8.3, 1.7 Hz, 1 H), 7.24–7.15 (m, 5 H), 7.09 (dd, *J* = 7.4, 1.6 Hz, 1 H), 6.93 (t, *J* = 7.4 Hz, 1 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 3.54 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8 (0), 142.5 (0), 139.1 (0), 134.4 (0), 132.90 (1), 132.87 (1), 129.6 (1, 2 C), 128.9 (1), 128.2 (1), 128.2 (0), 128.1 (1), 127.8 (1), 127.5 (1, 2 C), 126.9 (1), 126.4 (1), 126.2 (1), 125.7 (1), 55. 4 (3) (3 quaternary carbon signals obscured).

MS (EI+): *m*/*z* (%) = 310 (100, $M^{\bullet+}$).

HRMS (EI+): *m*/*z* calcd for $C_{23}H_{18}O$: 310.1358; found: 310.1352.

2-Methoxy-2′-phenyl-1,1′-binaphthyl (14)

1-Bromo-2-methoxynaphthalene (24 mg, 0.101 mmol) and 2-phenyl-1-naphthylboronic acid (37 mg, 0.149 mmol) were coupled according to the typical procedure given above using (+)-**2** as ligand to yield the title biaryl (+)-**14** (18.3 mg, 0.051 mmol, 50%, 16% ee) as a colorless solid; $[\alpha]_D^{20}$ +6.2 (*c* = 1.62, $CHCl_3$, 16% ee).

CSP HPLC analysis: Daicel Chiracel AD (250 mm × 4.6 mm I.D.), eluting with 1% *i*-PrOH in hexanes at 0.5 mL min^{-1} and monitored by UV at 254 nm. Retention times: (–)-**14** = 13.9 min, (+)-**14** = 18.8 min.

IR (KBr): 3055, 2933, 1624, 1592, 1267, 1251, 1147, 1075, 809, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.5 Hz, 1 H), 7.96 (d, *J* = 8.2 Hz, 1 H), 7.85 (d, *J* = 9.0 Hz, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.46 (ddd, *J* = 8.0, 5.4, 2.5 Hz, 1 H), 7.30–7.18 (m, 5 H), 7.15–7.08 (m, 3 H), 7.04–7.00 (m, 3 H), 3.58 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9 (0), 142.4 (0), 140.4 (0), 134.6 (0), 133.3 (0), 133.1 (0), 132.0 (0), 129.6 (1), 128.9 (1, 2 C), 128.4 (1), 128.2 (1), 128.1 (1), 128.0 (1), 127.3 (1, 2 C), 126.9 (1), 126.6 (1), 126.4 (1, 2 C), 125.8 (1), 125.7 (1), 123.5 (1), 122.0 (0), 113.4 (1), 56.4 (3) (1 quaternary carbon signal obscured).

MS (EI+): *m*/*z* (%) = 360 (100, $M^{\bullet+}$).

HRMS (EI+): *m*/*z* calcd for $C_{27}H_{20}O$: 360.1514; found: 360.1524.

2-Methyl-2′-phenyl-1,1′-binaphthyl (15)

1-Bromo-2-methylnaphthalene (22 mg, 0.100 mmol) and 2-phenyl-1-naphthylboronic acid (37 mg, 0.149 mmol) were coupled according to the typical procedure given above using (+)-**2** as ligand to yield the title biaryl (+)-**15** (14.7 mg, 0.043 mmol, 43%, 25% ee) as a colorless oil; $[\alpha]_D^{20}$ +41.1 (*c* = 1.23, $CHCl_3$, 25% ee). ^{1}H and ^{13}C NMR spectral data were in agreement with those reported by Buchwald et al.[22]

CSP HPLC analysis: Daicel Chiracel OD-H (250 mm × 4.6 mm I.D.), eluting with 0.5% *i*-PrOH in hexanes at 0.2 mL min^{-1} and monitored by UV at 254 nm. Retention times: (–)-**15** = 26.3 min, (+)-**15** = 29.3 min.

IR (neat): 3054, 2920, 1595, 1507, 1494, 1444, 1029, 908, 824, 763, 733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.5 Hz, 1 H), 7.98 (d, *J* = 8.1 Hz, 1 H), 7.84 (d, *J* = 8.2 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 1 H), 7.69 (d, *J* = 8.5 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 1 H), 7.38 (dt, *J* = 8.4, 4.0 Hz, 1 H), 7.29 (d, *J* = 8.3 Hz, 1 H), 7.27–7.23 (m, 3 H), 7.15 (d, *J* = 8.5 Hz, 1 H), 7.10–7.00 (m, 5 H), 1.94 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9 (0), 139.5 (0), 134.9 (0), 134.8 (0), 134.7 (0), 134.2 (0), 133.0 (0), 132.9 (0), 131.8 (0), 129.0 (1, 2 C), 128.7 (1), 128.6 (1), 128.2 (1), 128.13 (1), 128.08 (1), 127.7 (1), 127.6 (1, 3 C), 126.9 (1), 126.6 (1, 2 C), 126.2 (1), 126.0 (1), 124.8 (1), 20.6 (3).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(10) As defined for polarimetry readings taken from $CHCl_3$ solution at 589 nm. All other signs of optical rotation indicated herein are likewise defined.

(11) Exciton coupling between the long-axes polarized ^1B_b transitions of biquinolyl (+)-**7** was revealed as a weak bisignate band of positive chirality phase. The couplet was composed of a positive maximum Cotton effect at 242 nm and a corresponding negative minimum at 231 nm ($\Delta\Delta\varepsilon = +6.8\ M^{-1}\ cm^{-1}$ at >98% ee). For discourse on exciton coupling in the biaryl series, see: (a) Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, *30*, 1671. (b) Rodger, A.; Nordén, B. *Circular Dichroism and Linear Dichroism*; Oxford University Press: New York, **1997**. (c) Berova, N.; Nakanishi, K. In *Circular Dichroism: Principles and Applications*; Berova, N.; Nakanishi, K.; Woody, R. W., Eds.; Wiley-VCH: New York, **2000**.

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