Efficient Synthesis of 1,1′-Binaphthyl and 2,2′-Bi-*o*-tolyl-2,2′-bis(oxazoline)s and Preliminary Use for the Catalytic Asymmetric Allylic Oxidation of Cyclohexene

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Chiral C_2-symmetric bis(oxazoline)s have been successfully employed as ligands with various metals in numerous catalytic asymmetric processes. These include cyclopropanation,[2] aziridination,[3] allylic substitution,[4] hydrosilylation,[5] imine additions,[6] Diels−Alder,[7] aldol,[8] and Wacker-type cyclization[9] reactions. In addition we and Pfaltz have recently used bis(oxazoline) copper complexes as catalysts for the asymmetric allylic oxidation of simple olefins using *tert*-butyl perbenzoate.[10] While the linker between the oxazolines in the past have consisted of a methylene unit, derived from a malonyl precursor, or a pyridyl unit, recently Corey reported the synthesis of a unique biaryl-linked ligand, 1,1′-bis-*o*-tolyl-2,2′-bis(oxazoline), for use in a highly selective intramolecular copper-catalyzed cyclopropanation reaction leading to (−)-sirenin.[11] This new catalyst was shown to superior to a variety of known metal·ligand combinations including the standard methylene bis(oxazoline)s. The synthesis of this new ligand required the use of a preparative chiral HPLC separation on the racemic bitolyl dicarboxylic acid precursor. The prohibitive cost of this step and our desire to apply this new class of ligands to the allylic oxidation reaction prompted the effort to develop an efficient synthetic route to biarylbis(oxazoline)s that would not depend on a chiral separation or a tedious resolution.[12] To this end, new asymmetric

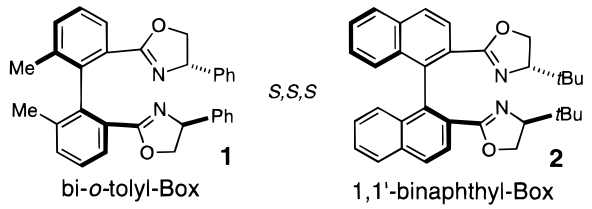
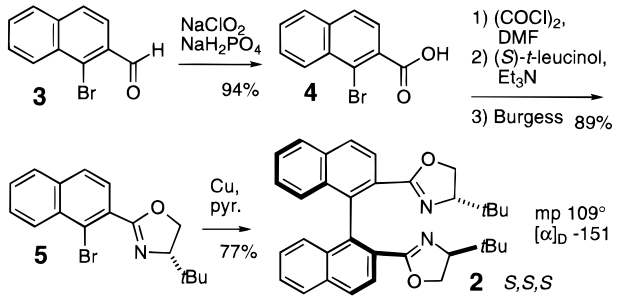


Figure 1.

Scheme 1



versions of the Ullman coupling reaction[13] were applied to produce two biarylbis(oxazoline)s, bi-*o*-tolyl diphenyl **1** and binaphthyl di-*tert*-butyl **2** (Figure 1).

Our route began with the efficient use of sodium chlorite with added sodium phosphate and 2-methylbutene[14] with 1-bromo-2-naphthaldehyde **3**[11] to produce the acid **4** in 94% yield (Scheme 1). Previous oxidations reported using transition metal oxides are uniformly low for this step.[12,15] The next three operations were performed without purification or isolation of the intermediates. Treatment of **4** with oxalyl chloride and catalytic DMF produced the acid chloride that was then treated with (*S*)-*tert*-leucinol and triethylamine to give the amide. The crude material was then treated with the Burgess reagent {[(methoxycarbonyl)sulfamoyl]triethylammonium hydroxide} according to the conditions of Corey giving oxazoline **5** in 89% overall yield.[9b,11] Alternative procedures using the dimesylate or the dichloride intermediate were found to be lower yielding in this case.[8,13a] Coupling with activated copper following the procedure of Meyers was then performed to access bi-*o*-tolyl-bis(oxazoline) **2** in 77% isolated yield as a white solid (mp 109 °C, $[\alpha]_D$ −151).[13a] This compound was an intermediate on the route to the enantiopure *S*-(−)-diacid dimethyl ester[16] and was not characterized previously. The coupling produced only the *S*,*S*,*S*-atropisomer (>30:1) together with only a small amount (<5%) of the reduced, debrominated byproduct as reported earlier. When the oxazoline side chain is changed from *tert*-butyl to the less sterically demanding phenyl or isopropyl groups, the coupling selectivity drops to 2:1 and 4:1.[13a] Recently Hayashi has reported a route to binaphthyl bis(oxazoline)s that uses racemic binaphthyl dicarboxylic acid and requires the separation of diastereomeric amides prior to bis(oxazoline) formation.[17]

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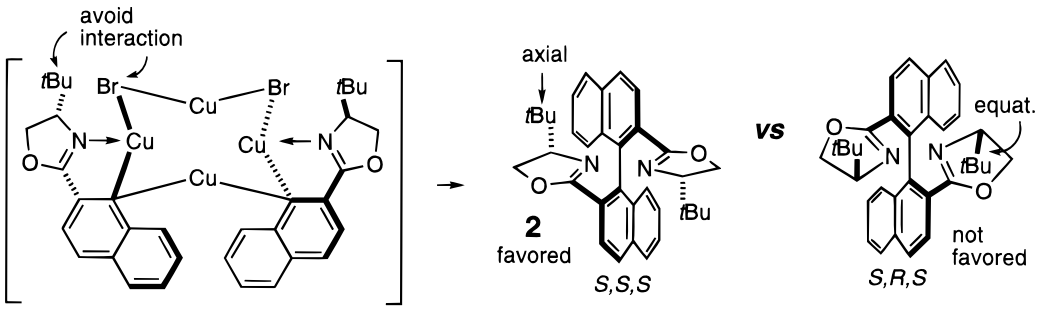
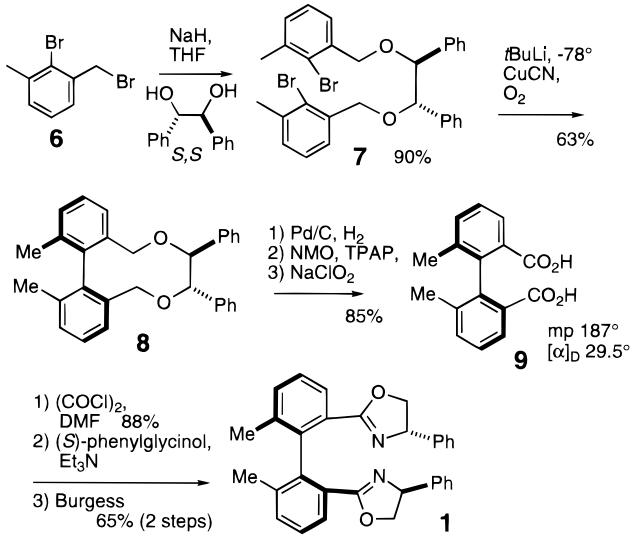


Figure 2.

The recent work of van Koten with the isolation and characterization of well defined arylcopper−copper bromide aggregates can now be used to suggest a model for the origin of the selectivity for the asymmetric intermolecular Ullman process.[18] Unlike previous mechanisms that have suggested a diarylcopper(III) intermediate,[19] the bis-diamine X-ray structures indicate a diaryl-C_{ipso}-bonded copper(I) structure with additional copper halide forming a ring of either 6 or 8 atoms depending on the stoichiometry of the added copper. Applying this copper(I) aggregate intermediate to the asymmetric binaphthyl coupling, the selectivity then appears to be controlled by the interaction of the flanking *tert*-butyl groups with the bridged bromine ligands (Figure 2). The transition state leading to the observed *S*,*S*,*S* isomer is formed avoiding this interaction. This is achieved by aligning the forming biaryl carbon−carbon bond in a parallel orientation to the flanking *tert*-butyl groups. This pseudo-diaxial alignment of the *tert*-butyl groups in the transition state will avoid nonbonded interactions with the copper−bromide aggregate. The alternative equatorial alignment, leading to the *S*,*R*,*S* isomer, forcing the *tert*-butyl groups out toward the copper−halide aggregate would be a higher energy process.

Due to the decreased selectivity for the intermolecular Ullman when other ligands besides *tert*-butyl are used, a more flexible route to access alternatively substituted diaryl bis(oxazoline)s was investigated using an intramolecular variant. Diol **6**, readily obtained using a Sharpless asymmetric dihydroxylation reaction with AD-mix-α reagent on *trans*-stilbene,[20] was converted to diether **7** (Scheme 2). Treatment with *tert*-butyllithium followed by the addition of copper(I) cyanide and dry oxygen at −78 °C, following the conditions of Lipshutz, gave the di-*o*-tolyl intermediate **8** in 63% yield as a single isomer.[13b] The original substrate used to establish this process was the analogous dinaphthyl diether. The selectivity can be explained by examining the energies of the diastereomeric *S*,*S*,*S* and *S*,*R*,*R* ground state structures. The observed *S*,*S*,*S* isomer is shown by MM2 representations to be favored by ∼1 kcal (Figure 3).[21] Placement of the two phenyl groups in equatorial positions in a chair-twist chair transition state is preferred leading to **8**. Alternative diaxial arrangement of the phenyls lead to the opposite atropisomer. The copper intermediate leading to biaryl formation, prior to oxygen exposure, is envisioned to be a six-membered diaryl C_{ipso}-copper(I)−Li_2-(CN) cyclic aggregate, as determined by ab initio calculation[22] analogous to the copper(I) bromide structure discussed above. The synthesis was completed by hydrogenation, oxidation with TPAP to the dialdehyde,[23] and treatment with sodium chlorite giving the intermediate *S*-diacid **9** in 85% combined yield (Scheme 2). Treatment with oxalyl chloride, *S*-phenylglycinol, followed by the Burgess reagent, then gave the desired bis(oxazoline) target **1** in high overall yield. The main advantage of the intramolecular Ullman route to the diacid intermediate is flexibility, allowing for either enantiomeric form depending on the AD reaction and the incorporation of various amino alcohols at the final stage of the synthesis.

Scheme 2



As an initial investigation, **1** was used with copper(I) as a ligand (10 mol %) in the catalytic asymmetric allylic oxidation of cyclohexene (5 equiv) (Scheme 3). The new, more reactive oxidant, *tert*-butyl *p*-nitroperbenzoate was used as the limiting reagent.[10a] After reacting at −20 °C for 5 d in acetonitrile, the *S*-benzoate ester was isolated in 76% yield and 73% ee,[24] demonstrating increased reactivity in addition to improved selectivity over the previously reported use of a *S*,*S*-methylene-linked phenylglycine-derived bis(oxazoline) ligand.[10b]

Experimental Section

General Procedures. Unless otherwise specified, materials were used as obtained from commercial sources. THF and ethyl

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(24) The selectivity was determined by integration of the ^{1}H NMR (500 MHz) signal for the *ortho*-protons of the benzoate using the chiral shift reagent Eu(hfc)$_3$ compared to the spectra of the racemic material.

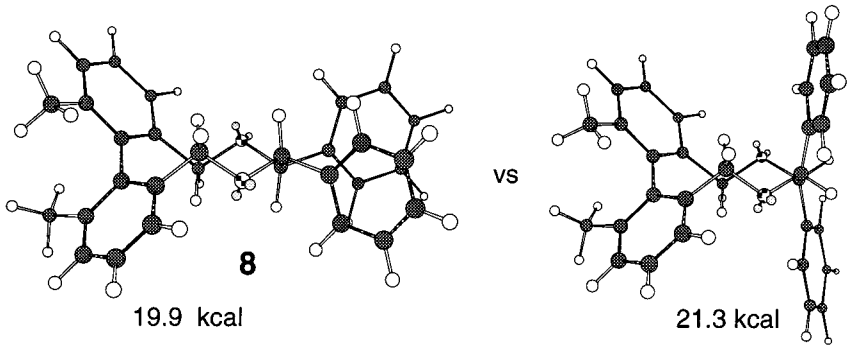
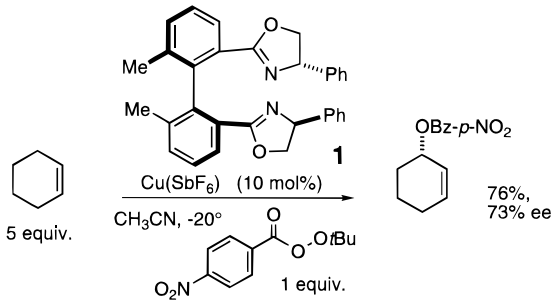


Figure 3.

Scheme 3



ether were distilled prior to use from sodium benzophenone ketyl. Methylene chloride and amine reagents were distilled from calcium hydride. Column chromatography was performed on silica gel 60 (230−400 mesh) eluting with distilled hexanes and ethyl acetate. TLC was performed using silica gel 60 F_{254} plates with visualization by UV irradiation and standard staining. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded on a QE-300 instrument. Optical rotations were measured at 589 nm. Melting points are uncorrected. Mass spectral analyses were performed in the chemistry department at Purdue University.

1-Bromo-2-napthoic Acid (4). To a mixture of 1-bromo-2-napthaldehyde **3** (3.0 g, 12.7 mmol) and *tert*-butyl alcohol (200 mL) was added 2-methyl-2-butene (10 mL). A 100 mL aqueous solution of $NaClO_2$ (10 g, 116.4 mmol) and $NaH_2PO_4 \cdot H_2O$ (12.1 g, 87.8 mmol) was added dropwise over a period of 20 min. This resulted in a clear solution which was allowed to stir overnight at rt. The *tert*-butyl alcohol was removed by rotary evaporation and the mixture was treated with 50 mL of H_2O and washed with two 50 mL portions of hexane. The aqueous layer was then acidified to pH 1 and extracted (3×) with 50 mL of ether. The organic extracts were combined, and solvent was removed by rotary evaporation to afford the acid **4** (2.99 g, 94% yield) as a white solid: mp 185−187 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.52 (d, J = 8 Hz, 1 H), 7.87 (d, J = 8 Hz, 1 H), 7.70−7.63 (m, 4 H); ^{13}C ($CDCl_3$, 50 MHz) δ 172.3, 136.2, 134.2, 133.0, 129.5, 129.1, 128.7, 128.4, 126.9, 124.7; IR (KBr) 2944 (b) 1696, 1662.

Naphthyloxazoline Bromide (5). To 50 mL of CH_2Cl_2 was added 1-bromo-2-napthoic acid **4** (2.0 g, 7.96 mmol). The mixture was allowed to stir for 10 min. Oxalyl chloride (2.83 mL, 31.9 mmol) was added dropwise followed by three drops of DMF. The mixture turned clear and was allowed to stir overnight at ambient temperature under N_2. The solvent was removed by rotary evaporator, and the residue was pumped under high vacuum for 10 min. The solid was treated with CH_2Cl_2 (100 mL), and the solution was cooled to −10 °C. In a separate flask were combined (*S*)-*tert*-butyl leucinol[25] (1.03 g, 8.76 mmol), triethylamine (7 mL), and CH_2Cl_2 (50 mL) which were also cooled to −10 °C. The acid chloride solution was next added dropwise by cannula into the flask containing the leucinol, and the solution was allowed to warm to rt. After stirring overnight under N_2, the solvent was removed, and the solid was treated with a saturated solution of brine (50 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried with $MgSO_4$, and solvent was removed by rotary evaporator and high vacuum. The crude residue was then dissolved in THF (50 mL) and Burgess reagent [(methoxycarbonyl)sulfamoyl]triethylammonium hydroxide (1.9 g, 7.96 mmol) was added. The solution was allowed to stir under N_2 overnight at ambient temperature. The solvent was then removed by rotary evaporation to afford a yellow oil. Purification using radial chromatography (5−30% EtOAc/hexane) produced (2.29 g, 89%) of a light yellow solid: mp 65−67 °C. $[\alpha]^{23}_D$ = −55.1° (c = 3.06, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.40 (2 H, d, J = 8 Hz), 7.82−7.78 (m, 2H), 7.65−7.50 (m, 3H), 4.39 (dd, 10 Hz, 8.2 Hz, 1H), 4.31 (t, 8.4 Hz, 1H), 4.16 (dd, 10.0 Hz, 8 Hz, 1 Hz), 1.04 (s, 9H); ^{13}C ($CDCl_3$, 50 MHz) δ 164.3, 135.3, 132.8, 129.3, 128.7, 128.7, 128.40, 128.2, 128.2, 127.4, 123.6, 77.3, 69.7, 34.5, 26.6; IR (KBr, cm^{-1}) 3051, 2864, 1659, 1472, 1239, 1104.

(*S,S,S*)-1,1′-Binaphthyl-2,2′-*tert*-Butylbis(oxazoline) (2). Naphthyloxazoline bromide **5** (100 mg, 0.31 mmol) was azeotroped three times with benzene (5 mL) in a 10 mL roundbottom flask. To this were added activated Cu (0.5 g, 7.9 mmol) and dry freshly distilled pyridine (3 mL). The mixture was heated to reflux and allowed to react overnight. Upon cooling, the pyridine was removed by rotary evaporation and high vacuum. The residue was treated with CH_2Cl_2, and the copper was filtered through glass wool. The CH_2Cl_2 solution was treated with 20% NH_4OH (50 mL) and saturated aqueous NH_4Cl (10 mL) several times until loss of blue color from the aqueous layer. The organic layer was then dried with $MgSO_4$ and solvent was removed. The residue was then dissolved in EtOAc and filtered through a 2.5 cm plug of silica eluting with EtOAc. Solvent was removed, and the product was separated using radial chromatography (1 mm rotor, 5−50% EtOAc/hexane). The product was pumped under high vacuum to afford a white foam which solidified upon standing under vacuum (60 mg, 77%): mp 109−113 °C; $[\alpha]^{23}_D$ = −150.8 (c 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.13 (2 H, d, J = 8 Hz), 7.93 (2 H, d, J = 8.5 Hz), 7.88 (2 H, d, J = 8.0 Hz), 7.44 (2 H, t, J = 7.5 Hz), 7.19 (2 H, t, J = 7 Hz), 7.13 (2 H, d, J = 8.5 Hz), 3.6−3.78 (6H, m), 0.49 (18H, s); ^{13}C ($CDCl_3$, 50 MHz): d 163.9, 134.7, 133.6, 128.1, 127.8, 127.7, 127.1, 126.6, 126.1, 76.5, 68.6, 34.0, 25.9; IR (KBr, cm^{-1}) 3051, 1649, 1473, 1234, 1109; HRMS: Calcd for $C_{34}H_{36}N_2O_2$: 504.2777. Found: 504.2782.

2-Bromo-1-((2-((2-bromo-3-methylbenzyl)oxy)-1,2-diphenylethoxy)methyl)-3-methylbenzene (7). Sodium hydride (1.86 g, 77.5 mmol) was placed in a flame-dried round bottom flask (250 mL) containing THF (50 mL) and (*S,S*)-stilbenediol **6** (1.66 g, 7.75 mmol). The mixture was stirred for 30 min at rt. Then, 2-bromo-3-(bromomethyl)toluene (4.5 g, 17.05 mmol) in THF (50 mL) was slowly cannulated into the reaction flask containing the diol **6** and sodium hydride. The mixture was then refluxed overnight and benzylamine (2 or 3 drops) was added to the reaction flask and allowed to reflux for an additional 2 h. The flask was then cooled to rt and carefully quenched with methanol (10 mL), extracted with ethyl acetate (3 × 40 mL), washed with cold water (30 mL), HCl solution (10%), and again with cold water (40 mL), and dried over $MgSO_4$. After evaporation of the solvent, the pure product **7** was obtained (4.65 g, 93% yield): mp 78−80 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.46 (d, 2H), 7.32−6.92 (m, 14H), 4.73 (s, 2H), 4.52 (d, 4H), 2.35 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.92, 138.72, 138.43, 129.86, 128.63, 128.43, 128.30, 128.15, 127.33, 126.67,

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125.06, 86.21, 71.53, 23.85; IR (neat): 3061, 2916, 1332, 1109, 1088 cm^{-1}; $[\alpha]_D$ +44.85 (*c* 1.2, $CHCl_3$).

Diether 8. Copper(I) cyanide (0.65 g, 7.3 mmol) was placed in a flame-dried two-necked round bottom flask (500 mL) equipped with two rubber septa and a stirring bar. The flask was again gently dried with a heat gun under vacuum and allowed to cool to rt under N_2. THF (125 mL) was added and the mixture cooled to −78 °C. In another 250 mL round bottom flask, compound **7** (4.15 g, 7.16 mmol) was dissolved in THF (110 mL) and cooled to −78 °C, and *tert*-butyllithium (1.5 M, 28.6 mmol) was slowly added, giving an orange solution. The reaction mixture was stirred for 1 h at this temperature, and this solution of the dilithium compound was cannulated to the flask containing CuCN at −78 °C. The mixture was then warmed to −40 °C, and a yellow solution was obtained. The reaction mixture was then recooled to −78 °C. The N_2 flow was then stopped, and dry O_2 (passed through a trap at −78 °C) was bubbled into the reaction mixture for 2 h where upon the solution turned to a dark color. The mixture was allowed to warm to 0 °C, and the flow of O_2 was continued for an additional 1 h. The reaction mixture was then quenched with methanol (5 mL) and saturated aqueous $NaHSO_3$. The reaction was then allowed to warm to rt, poured into a solution of 10% NH_4OH in NH_4Cl (15 mL), stirred for 0.5 h, extracted with ethyl acetate (3 × 80 mL), and added over $MgSO_4$. After evaporation of the solvent, the crude yellow product obtained was purified by column chromatography (1−3% ethyl acetate/hexane) to obtain a white solid−oil product **8** (1.9 g, 63% yield): ^1H NMR (200 MHz, $CDCl_3$): δ 7.65−6.76 (m, 16H), 4.62−4.46 (m, 3H), 4.45−4.23 (m, 3H), 2.28 (3H, s), 1.85 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.86, 139.04, 138.84, 137.01, 129.90, 128.46, 128.29, 128.11, 128.05, 127.85, 127.61, 87.56, 70.40, 20.71; IR (KBr): 3062, 2913, 1329, 1100 cm^{-1}; $[\alpha]_D$ −15.41 (*c* 1.85, $CHCl_3$).

(*S*)-2,2′-Bis(hydroxymethyl)-6,6′-dimethylbiphenyl. Compound **8** (1.9 g, 4.52 mmol) was dissolved in a round bottom flask (50 mL) containing methanol (25 mL). Then a catalytic amount of Pd/C (10%, 5 mg) was added to the reaction flask, and H_2 was slowly bubbled into the flask for 1 d with stirring. The mixture was filtered and evaporation of the solvent afforded a yellow solid product. A white solid product was obtained after purification by column chromatography (0.95 g, 87% yield): mp 116−118 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 7.43−7.13 (m, 6H), 4.32 (d, 2H), 4.11 (d, 2H), 2.46 (s, 1H), 1.83 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 130.44, 128.64, 128.41, 128.0, 62.19, 20.48; IR (KBr): 3383, 3050, 2988, 1420, 1264 cm^{-1}; $[\alpha]_D = -30.0$ (*c* 0.4, chloroform).

(*S*)-3,3′-Dimethyl-2,2′-biphenyl-1,1′-dicarboxylic Acid (9). The above diol intermediate (0.70 g, 2.89 mmol) was placed in a flame-dried round bottom flask (100 mL) equipped with a magnetic stirring bar. Methylene chloride (25 mL), molecular sieves (4 Å, 2.89 g), and NMO (1.02 g, 8.71 mmol) were added to the reaction flask and allowed to stir for 5 min. TPAP (0.11 g, 0.29 mmol) was then added to the reaction mixture and the reaction stirred for 15 min at rt. The reaction mixture was then passed through silica gel using ethyl acetate (150 mL), and evaporation of the solvent afforded a white solid of dialdehyde intermediate (0.65 g, 94% yield). This aldehyde (0.57 g, 2.40 mmol) was then dissolved in a round bottom flask (250 mL) containing *tert*-butyl alcohol (55 mL) and 2-methyl-2-butene (13.5 mL). A solution of sodium chlorite (2.52 g, 26.4 mmol) and sodium dihydrogen phosphate (2.52 g, 21.6 mmol) in water (21 mL) was slowly added to the reaction mixture. The pale yellow reaction mixture was stirred overnight, and the solution turned colorless after 3 h. Then solvent and volatiles were removed under reduced pressure, the residue was dissolved in water (15 mL), and extracted with *n*-hexanes (2 × 20 mL). The water layer was acidified to pH 3 with HCl and extracted with ethyl acetate (3 × 50 mL), washed with cold water (30 mL), saturated $NaHCO_3$ (aq), and cold water again. The organic layer was dried over $MgSO_4$, and evaporation of the solvent afforded yellow solid product diacid **9** (0.63 g, 97% yield): mp 187−190 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 9.56 (s, 2H), 7.86 (d, 2H), 7.57−7.11 (m, 4H), 1.83 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.96, 142.52, 136.82, 135.15, 129.39, 128.20, 127.35, 20.48; IR (KBr) δ 3445, 3051, 2978, 1701, 1415, 1264, 1186, 1156 cm^{-1}; $[\alpha]_D$ (*c* 1.0, chloroform).

(*S,S,S*)-2,2′-Bi-*o*-tolyl-1,1′-diphenylbis(oxazoline) (1). Diacid **9** (0.35 g, 1.3 mmol) was placed in a flame-dried round bottom flask (100 mL). Methylene chloride (25 mL) was then added to the reaction flask. Oxalyl chloride (1.64 g, 13.0 mmol) was added dropwise followed by two drops of DMF. The reaction mixture was stirred for 8 h at rt under N_2. The solvent was then removed under reduced pressure, and yellow oil diacid chloride was isolated (0.40 g, 88% yield). Without delay, a solution of this intermediate (0.40 g, 1.30 mmol) in methylene chloride (15 mL) was cooled to −40 °C. In a separate flask, a mixture of (*S*)-phenylglycinol (0.36 g, 2.6 mmol) and triethylamine (1 mL) in methylene chloride (15 mL) was cooled to −40 °C. The diacid chloride solution was then added dropwise by cannula into the flask containing phenylglycinol, and the solution was allowed to warm after 30 min with stirring overnight under N_2. The solvent was removed, and the solid obtained was treated with saturated solution of brine (10 mL) and extracted with methylene chloride. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure to obtain the crude residue. This was then dissolved in THF (10 mL) and Burgess Reagent (0.63 g, 2.65 mmol) was added to the solution. The solution was allowed to stir under N_2 overnight at rt. The solvent was then removed under reduced pressure to obtain a crude yellow residue. Purification using radial chromatography (1 mm rotor, 5−35% ethyl acetate/hexane) produced a white oil−solid product (0.40 g, 65% yield): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.83 (d, 2H, J = 8 Hz), 7.52−7.13 (m, 10H), 7.12−6.91 (m, 4H), 5.13 (t, 2H, J = 8.5 Hz), 4.38 (t, 2H, J = 8.5 Hz), 3.85 (t, 2H, J = 8.5 Hz), 1.98 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.2, 141.9, 140.1, 138.9, 136.5, 128.9, 128.1, 127.9, 127.5, 77.5, 70.3, 20.5; IR (neat): 3061, 2967, 2895, 1949, 1882, 1804, 1643, 1487, 1451, 1347, 1150 cm^{-1}; HRMS: Calcd for $C_{32}H_{28}O_2N_2$: 473.2229. Found: 473.2209. $[\alpha]_D = +26.2$ (*c* 4.20, $CHCl_3$).

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Supporting Information Available: ^1H and ^{13}C NMR spectra for the intermediates and biaryl bis(oxazoline)s **1** and **2** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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