The Asymmetric Ullmann Reaction. 2. The Synthesis of Enantiomerically Pure C_2-Symmetric Binaphthyls

Todd D. Nelson and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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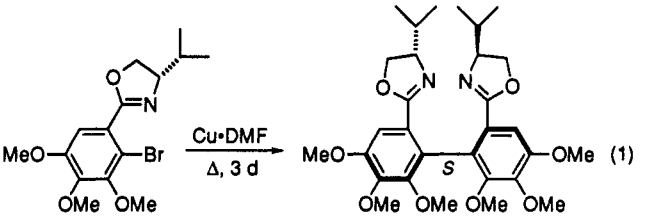
Although the synthesis of symmetric biphenyls by the intermolecular copper-mediated homocoupling of aromatic halides (Ullmann reaction)[1-3] was initially reported in 1901,[4] almost no effort has been devoted to the asymmetric variant of this process. The sole report of an intermolecular[5] attempt at an asymmetric Ullmann coupling resulted in very poor diastereoselectivities (2–13% de).[6]

Our interest in asymmetric biaryl syntheses has recently led to a report[7-9] of the successful synthesis of biaryl **2**, which was obtained in a thermodynamically controlled manner, mediated by copper. In this manner, the dia-



1 **2**

isolated yield 60 %
100 % de

stereomeric ratio of **2** was 70:30 after 12 h and 93:7 after 72 h and appeared to have involved a diastereomeric copper complex of **2**. Thus, the kinetic preference leading to **2** was indeed poorly selective, whereas the thermodynamic factors were favorable. We have now examined binaphthyl in a similar situation and, knowing full well that binaphthyls have a very high barrier to rotation,[10,11] felt that once the coupling was achieved, the stereoselectivity would be resistant to any further change and there would be little opportunity to duplicate the effect seen for **2**.

Commercially available 1-bromo-2-naphthoic acid (**3**)[12] was transformed into three different chiral oxazolines **4a–c** using readily available enantiopure amino alcohols.[13] The method employed to carry out this transformation involved preparation of the acid chloride of **3** followed by introduction of the appropriate amino alcohol and then cyclization of the intermediate amide to the oxazolines **4a–c**. The latter were obtained in 60–80% overall yield from **3**.

In order to evaluate the behavior of these (bromonaphthyl)oxazolines in asymmetric Ullmann reactions, each was treated with activated copper powder[14] (3–7 mmol of oxazoline per 1 g of Cu) in refluxing pyridine overnight. The resulting binaphthyls (**5a–c**) were accompanied by small amounts (<10%) of the debrominated naphthalene derivative, **6**.

The diastereomeric ratio of products was found to be sensitive to the size of the 4-substituent in the oxazoline ring since the *tert*-butyl group gave the highest level of selective Ullmann coupling. The assessment of these ratios

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(3) For reviews on asymmetric biaryl formation see: (a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, 29, 1977. (b) Bringmann, G.; Walter, R.; Weirich, R. In *Houben Weyl*, E22, C2, in press. (c) Recent contributions in this area include a chiral Ni-catalyzed cross coupling of a naphthyl Grignard reagent with a naphthyl bromide: Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 153. Other recent contributions in this area include: (d) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6989. (e) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6993. (f) Meyers, A. I.; Meier, A.; Rawson, D. J. *Tetrahedron Lett.* **1992**, *34*, 853. (g) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090. (h) Hattori, T.; Hotta, H.; Suzuki, T.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 613. (i) Bringmann, G.; Hartung, T. *Synthesis* **1992**, 433. (j) Tanaka, M.; Mitsuhashi, H.; Wakamatsu, T. *Tetrahedron Lett.* **1992**, *33*, 4161. (k) Tanaka, M.; Mukaiyama, C.; Mitsuhashi, H.; Wakamatsu, T. *Tetrahedron Lett.* **1992**, *33*, 4165. (l) Baker, R. W.; Pocock, G. R.; Sargent, M. V.; Twiss, E. *Tetrahedron: Asymmetry* **1993**, *4*, 2423. (m) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732.

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(8) A more detailed account of the oxazoline-mediated, intermolecular "thermodynamic" Ullmann coupling has been accomplished: Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.*, in press.

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(10) For references to rotational barriers of 1,1'-binaphthyl derivatives see: (a) Kranz, M.; Clark, T.; Schleyer, P. v. R. *J. Org. Chem.* **1993**, *58*, 3317. (b) Lilgefors, T.; Carter, R. E. *Tetrahedron* **1978**, *34*, 1611.

(11) Although thermally stable under neutral conditions, some 2,2'-disubstituted 1,1'-binaphthyls have considerably lower rotational barriers under acidic and/or basic conditions. See, for example: (a) Oi, S.; Kawagoe, K.; Miyano, S. *Chem. Lett.* **1993**, 79. (b) Kyba, E. P.; Gokel, G. W.; Jong, F. d.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173.

(12) For the preparation of 1-bromo-2-naphthoic acid see: (a) Kim, J.-I.; Schuster, G. B. *J. Am. Chem. Soc.* **1992**, *114*, 9309. (b) Weber, E.; Csöregh, I.; Stensland, B.; Czugler, M. *J. Am. Chem. Soc.* **1984**, *106*, 3297.

(13) Reduction of less expensive amino acids was also readily accomplished using the following procedures: (a) Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Organic Syntheses;* Wiley: New York, 1990; Collect. Vol. VII, p 530. (b) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, 58, 3568.

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(15) For comparison in the 300-MHz ^{1}H NMR of the crude coupling mixtures, authentic nonhalogenated naphthyloxazolines were prepared from 2-naphthoic acid and the appropriate amino alcohol.

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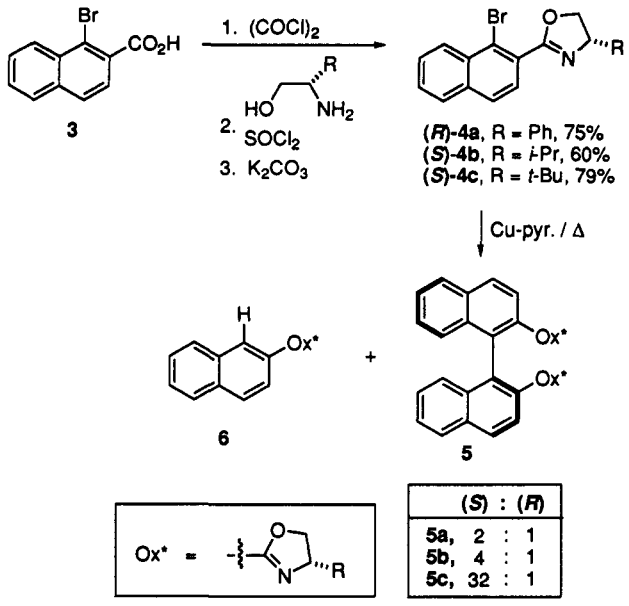

was initially determined by ^{1}H NMR spectral data, which indicated that for the isopropyl derivative **5b** the appropriate isopropyl resonances integrated to a 4:1 ratio, while the *tert*-butyl group in **5c** appeared as a clear single peak. This indicated that the ratio of diastereomeric products was at least 95:5. In an effort to determine more quantitatively the efficiency of the coupling of **4c** to **5c**, the crude mixture of the latter was transformed into the dicarbinol **8**, which involved partial ring opening to the ester amide **7** followed by reduction to the dicarbinol. This oxazoline removal sequence has been used previously for related systems.[3d-g] Treatment of dicarbinol **8** with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher's reagent)[16] led to the diastereomeric esters **9**, which were subsequently examined by ^{1}H NMR spectroscopy. When compared to a 1:1 mixture of diastereomers, obtained from racemic **8**, the AB quartets centered at δ 4.93 and 4.84 (benzylic methylene protons) gave the observed ratio of stereoisomers, **5a–c**, by integration.

The reported sign of rotation for the previously prepared binaphthyldicarbinol (**8**),[17] when compared to the major atropisomer obtained in this study, indicated that dicarbinol **8** possessed the *S*-absolute stereochemistry about the chiral axis. *This result, which produced a 97:3 ratio of the chiral binaphthyldicarbinol (8), represents another useful example of an asymmetric, intermolecular Ullmann reaction.*

In order to reach enantiomerically pure binaphthyl, the diester amide **7c** (containing ~3% of the minor diastereomer) was crystallized from ethyl acetate and further purified by radial chromatography to afford diastereomerically pure **7c** in a 57% overall yield from (bromonaphthyl)oxazoline (**4c**). Transesterification using methanolic sodium methoxide gave the dimethyl ester **10** in an 88% yield.[18] The enantiomeric purity of dimethyl ester **10** was obtained via chiral HPLC analysis. Racemic dimethyl ester **10** was prepared for comparison purposes by Ullmann reaction of methyl 1-bromonaphthoate with copper.[12] The assay indicated that the dimethyl ester **10** was >99% enantiomerically pure, which corresponded to >99% de for the amido ester **7c**.

A sample of ester amide **7c**, prepared without purification from the Ullmann coupling mixture of bromo oxazoline **4c**, was transesterified to the dimethyl ester **10**. Chiral HPLC analysis indicated a 97:3 enantiomeric ratio. This agrees well with the 97:3 diastereomeric ratio obtained by examination of the ^{1}H NMR spectrum for the Mosher ester **9c** prepared from **8** (*vide supra*).

The stereoselectivity observed for this process can be rationalized by examining the transition states and copper intermediates (Figure 1, complex **A**, **B**). It has been suggested that a Cu(III) intermediate is the transient species prior to biaryl carbon–carbon bond formation.[19] On the basis of this hypothesis, one may envision the two diastereomeric copper complexes (**A**, **B**) forming prior to the aryl–aryl bond connection. Complex **B** depicts a crowded system in which the two oxazoline rings are in close proximity and the R-ring substituents are brought close to each other. The larger the R substituent, the more steric, nonbonded interactions come into play. Thus, the 4-*tert*-butyloxazoline in **4c** leads to the highest degree of selectivity (97:3) since the alternative complex **A** appears to be free of any severe nonbonded interactions. Thus, one would predict that **A** would be the major biaryl stereoisomer on the basis of thermodynamic preference in the transition state, and this is, indeed, what is observed. It should also be noted that the ratio of binaphthyls **5**, on heating, did not change, thus attesting to the stability toward bond rotation.

In summary, we have succeeded in implementing an intermolecular, thermodynamically controlled asymmetric Ullmann reaction. The diester (*S*)-**10** has been previously described as arising from (*S*)-2,2′-dihydroxy-1,1′-binaphthyl[20] by esterification of the corresponding diacid of **10** (that was prepared by various chemical resolutions)[21] or by an intramolecular Ullmann coupling of chiral naphthylnaphthoates.[5] It is to be noted that the present route to dimethyl ester **10** is, to our knowledge, the first that did not employ the chiral binaphthyl 1,1′-diol of Noyori.[5,20] The enantiomerically pure binaphthyl diester **10** or its corresponding diacid have been employed as a chiral stationary phase in HPLC and GC,[22] as a selective chiral host for selective inclusion of chiral alcohols,[23] and as a chiral ligand for palladium-catalyzed 1,6-enyne cyclizations.[24]

(16) (a) The dicarbinol **7** was prepared by treatment of a THF solution of ester amide **6** with lithium aluminum hydride. The Mosher esters **8** were prepared by using the Sharpless protocol (ref 16b). (b) For the preparation of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher's acid chloride) and the corresponding Mosher's esters see: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(17) Maigrot, N.; Mazaleyrat, J.-P. *Synthesis* **1985**, 317.

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(21) (a) Oi, S.; Matsuzaka, Y.; Yamashita, J. Miyano, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 956. (b) Kanoh, S.; Hongoh, Y.; Motoi, M.; Suda, H. *Bull Chem. Soc. Jpn.* **1988**, *61*, 1032.

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(23) Weber, E.; Csöregh, I.; Stensland, B.; Czugler, M. *J. Am. Chem. Soc.* **1984**, 106, 3297.

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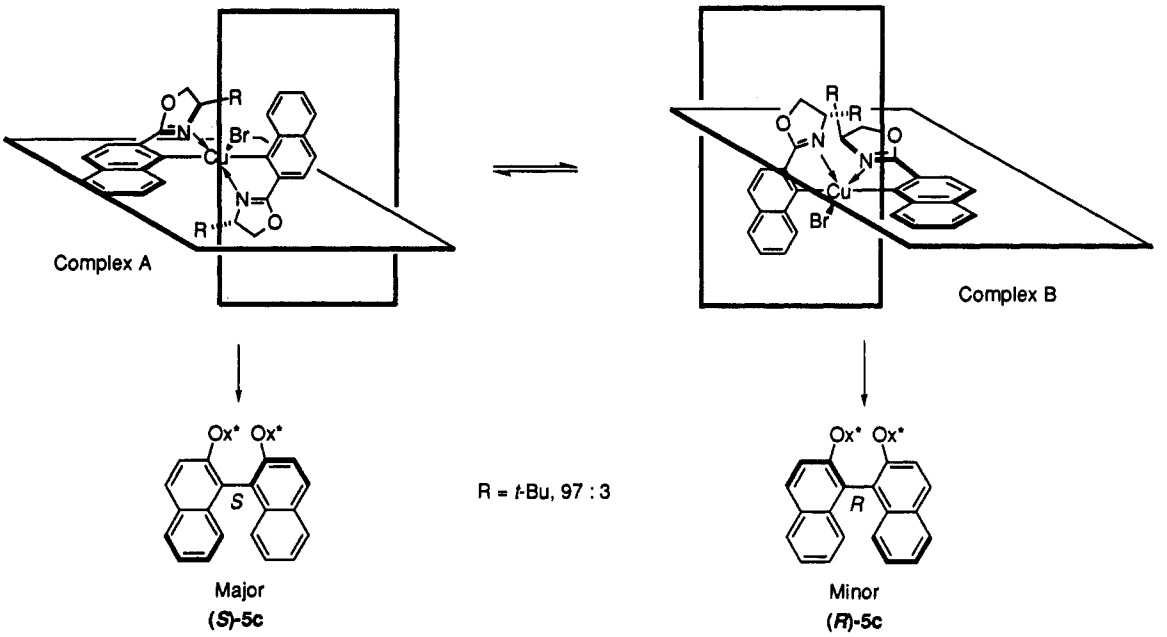
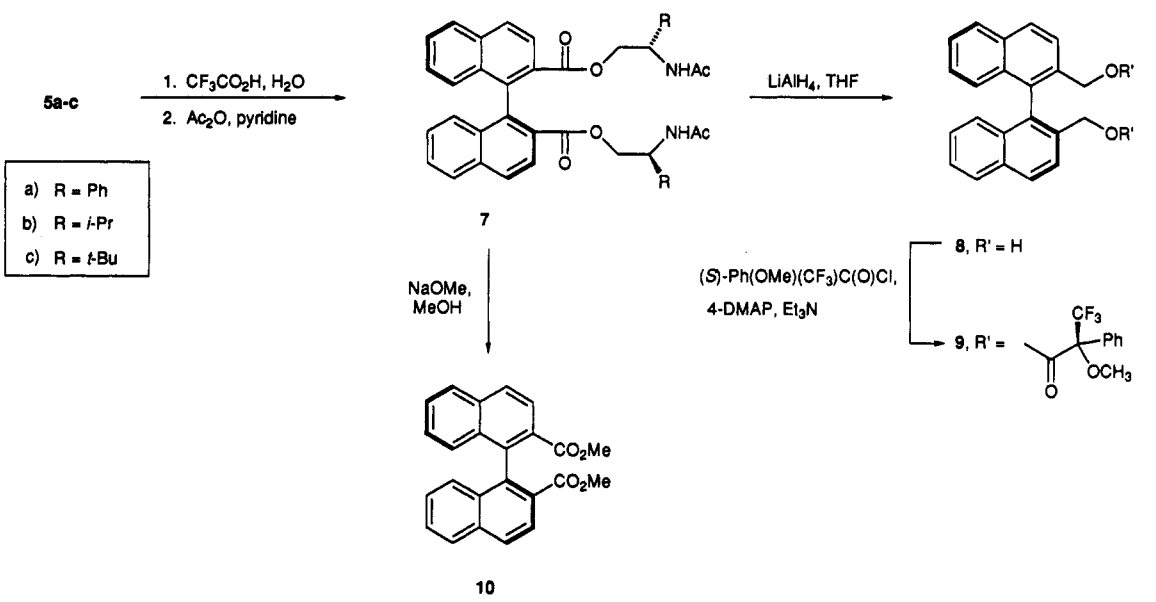


Figure 1.

Scheme 1



Experimental Section[25]

Naphthyloxazoline Bromide (*S*)-4c. A mixture of 4.89 g (19.5 mmol) of 1-bromo-2-naphthoic acid, 8.7 mL (99 mmol) of oxalyl chloride, 100 mL of CH_2Cl_2, and 6 drops of DMF was stirred overnight at rt under Ar. The solvent was removed *in vacuo*, and the residue was dissolved in 50 mL of CH_2Cl_2 and added to a cooled (0 °C) solution of 2.5 g (21.5 mmol, 1.1 equiv) of *tert*-leucinol, 10 mL of Et_3N, and 100 mL of CH_2Cl_2. This mixture was stirred overnight at rt under Ar and then diluted with water. The organic portion was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was dissolved in 100 mL of CH_2Cl_2, 10.0 mL of $SOCl_2$ was added, and the mixture was stirred at rt for 8 h. The reaction mixture was cooled to 0 °C and quenched with H_2O and then 4 N NaOH(aq). The organic portion was dried ($MgSO_4$), and the solvent was removed *in vacuo*. To the residue was added 300 mL of CH_3CN, 25 mL of H_2O, and 62 g of K_2CO_3, and the mixture was heated at reflux for 3 d. After the mixture was cooled, the CH_3CN was removed by rotary evaporation and the residue was extracted with CH_2Cl_2. Purification of oxazoline (*S*)-**4c** by silica gel chromatography (hexane to 50% hexane/EtOAc) afforded 5.13 g (79%) of the oxazoline as a viscous, light yellow oil: R_f 0.6 (1:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 4.15 (dd, J = 10.2, 8.1 Hz, 1H), 4.31 (t, $J \approx$ 8.3 Hz, 1H), 4.42 (dd, J = 10.2, 8.6 Hz, 1H), 7.50–7.63 (m, 3H), 7.78–7.83 (m, 2H), 8.40 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.0, 34.0, 69.2, 76.8, 123.1, 126.8, 127.6, 127.7, 127.9, 128.2, 128.2, 128.8, 132.3, 134.8, 163.7; FT-IR (film) 1665 cm^{-1}; MS *m/z* (EI, 70 eV) 333 (7, M^+ + 2), 331 (9, M^+), 276 (92), 274 (90), 221 (31), 219 (32), 167 (100), 126 (56), 41 (60); $[\alpha]^{25}_D$ −56.4° (c = 3.52, CH_2Cl_2). Anal. Calcd for $C_{17}H_{18}ONBr$: C, 61.45; H, 5.46. Found: C, 61.38; H, 5.47.

Naphthyloxazoline Bromide (*S*)-4b. This oxazoline was prepared in an analogous fashion to bromide (*S*)-**4c** by substituting (*S*)-valinol for (*S*)-*tert*-leucinol and by utilizing the following amounts of requisite reagents: 0.879 g (3.50 mmol) of 1-bromo-2-naphthoic acid, 0.9 mL (10.3 mmol, 2.9 equiv) of oxalyl chloride, 386 mg (3.74 mmol, 1.1 equiv) of L-valinol, 3 mL (41 mmol, 12 equiv) of $SOCl_2$, and 5.1 g of K_2CO_3. Purification by radial chromatography (4-mm rotor, 10% EtOAc/hexane to EtOAc)

(25) For details concerning the general Expermental Section see: Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1011.

afforded 648 mg (60%) of the oxazoline (*S*)-**4b** as a viscous, light yellow oil: R_f 0.5 (1:1 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.87–2.02 (m, 1H), 4.16–4.25 (m, 1H), 4.51–4.25 (m, 2H), 7.49–7.80 (m, 5H), 8.38 (d, J = 8.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.2, 18.8, 32.6, 70.4, 73.0, 123.1, 126.8, 127.6, 127.6, 127.8, 128.1, 128.1, 128.6, 132.2, 134.8, 163.7; FT-IR (film) 1666 cm^{-1}; MS *m/z* (EI, 70 eV) 319 (11, M^+ + 2), 317 (11, M^+), 276 (72), 274 (73), 248 (9), 246 (9), 221 (27), 219 (27), 167 (100), 126 (63); $[\alpha]^{25}_D$ −53.3° (*c* = 5.77, CH_2Cl_2). Anal. Calcd for $C_{16}H_{16}ONBr$: C, 60.39; H, 5.03. Found: C, 60.30; H, 5.07.

Naphthyloxazoline Bromide (*S*)-4a. This oxazoline was prepared in an analogous fashion to bromide (*S*)-**4c** by substituting (*R*)-phenylglycinol for (*S*)-*tert*-leucinol and by utilizing the following amounts of requisite reagents: 0.399 g (1.59 mmol) of 1-bromo-2-naphthoic acid (**2**), 0.42 mL (4.8 mmol) of oxalyl chloride, 0.245 g (1.8 mmol) of phenyl glycinol, 0.40 mL (4.8 mmol) of $SOCl_2$, and 10 g of K_2CO_3. Purification by radial chromatography (4-mm rotor, hexane to 20% hexane/EtOAc) afforded 0.420 g (75%) of the oxazoline (*S*)-**4a** as a viscous, light yellow oil that solidified upon standing: R_f 0.5 (1:1 ethyl acetate/hexane). A sample was triturated from Et_2O/hexane: mp 74–74.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (t, J = 8.4 Hz, 1H), 4.89 (dd, J = 10.2, 8.4 Hz, 1H), 5.50 (dd, J = 10.2, 8.4 Hz, 1H) 7.27–7.87 (m, 10H), 8.44 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) (one degeneracy found in aromatic region) δ 70.6, 75.2, 123.4, 126.8, 126.9, 127.7, 127.8, 127.8, 128.0, 128.2, 128.3, 128.8, 132.3, 135.0, 142.1, 165.2; ^{13}C NMR (75.5 MHz, CD_3OD) (one degeneracy found in aromatic region) δ 71.2, 76.9, 123.8, 127.4, 128.0, 128.8, 129.0, 129.29, 129.34, 129.5, 129.6, 129.9, 133.3, 136.5, 143.1, 167.9; ^{13}C NMR (75.5 MHz, acetone-d_6) (one degeneracy found in aromatic region) δ 71.3, 75.8, 123.3, 127.6, 127.8, 128.2, 128.5, 128.9, 129.2, 129.3, 129.4, 129.8, 132.89, 135.85, 143.7, 165.2; FT-IR (film) 1660 cm^{-1}; $[\alpha]^{23}_D$ −41.3° (*c* = 5.80, CH_2Cl_2). Anal. Calcd for $C_{19}H_{14}ONBr$: C, 64.79; H, 4.01. Found: C, 64.63; H, 3.94.

Ullmann Coupling and Oxazoline Opening to Ester Amide 7c. A mixture of 4.31 g (12.97 mmol) of naphthyloxazoline bromide (*S*)-**4c** (azeotroped three times with benzene) and 1.99 g of freshly activated copper[14] in 4.0 mL of freshly distilled pyridine was heated at reflux for 24 h. After being cooled, the mixture was diluted with CH_2Cl_2 and washed with aqueous ammonia repeatedly until the copper had been completely removed. The organic portion was washed with water and dried ($MgSO_4$) and the solvent removed *in vacuo* to give a tan solid that was used without further purification. Crude ^{1}H NMR (300 MHz, $CDCl_3$) integration of the *tert*-butyl resonance from the major atropisomer **5c** (δ 0.47) and the reduced starting material **6c** (δ 0.97) gave an indication of the coupled to reduced starting material ratio (93:7). Resonance from the *tert*-butyl group of the minor coupled atropisomer was absent or degenerate with the major isomer.

To a THF solution (100 mL) of the solid residue was added 5 mL of water, 11 mL of trifluoroacetic acid, and 55 g of Na_2SO_4, and this suspension was stirred overnight at rt. After filtration, the solvent was removed *in vacuo*, and the brown residue was dissolved in 200 mL of CH_2Cl_2. To this solution was added 12 mL of pyridine and 20 mL of acetic anhydride and the mixture stirred at rt overnight. The mixture was washed with 1 N HCl (3 × 100 mL) and then water (100 mL) and dried ($MgSO_4$) and the solvent removed *in vacuo* leaving a brown solid, which was crystallized from ethyl acetate (two crops) and then purified by radial chromatography (8-mm rotor, 5% ethyl acetate/hexane to ethyl acetate) to afford 2.30 g (57%) of the diastereomerically pure (>99% de) ester amide **7c** as a colorless solid. The supernatant from the crystallization was also purified by radial chromatography, to give an additional 0.55 g (14%) of ester amide **7c** as a colorless solid (mp 106–112 °C), and then slow bubbling that ceased at 128 °C, R_f 0.2 (ethyl acetate). The diastereomeric purity was assayed by the transesterification to the dimethyl ester **10** followed by chiral HPLC analysis (*vide infra*). A small amount of residual ethyl acetate was present, as evidenced by the ^{1}H NMR spectrum: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 9H), 1.86 (s, 3H), 3.85–3.80 (m, 2H), 4.07–3.98 (m, 1H), 6.85 (d, J = 8.5 Hz, 1 *-NH*), 7.28 (t, $J \approx$ 7.5 Hz, 1H), 7.57 (t, $J \approx$ 7.5 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 8.14–8.01 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.4 (q), 26.7 (q, 3C), 33.8 (s), 55.9 (d), 64.2 (t), 125.7 (d), 126.8 (d), 126.9 (s), 127.2 (d), 127.8 (d), 128.0 (d), 128.1 (d), 132.8 (s), 134.8 (s), 140.3 (s), 166.6 (s), 170.1 (s); HRMS *m/z* calcd for $C_{38}H_{44}N_2O_6$ (M^+) 624.3199, found 624.3207.

(*S*)-Dimethyl 1,1′-Binaphthyl-2,2′-dicarboxylate ((*S*)-10). To a solution of 159.5 mg (0.255 mmol) of ester amide **7c** in 3 mL of methanol and 3 mL of THF was added 5 mL of a sodium methoxide solution (prepared by the addition of 0.23 g of Na to 10 mL of MeOH). After being stirred for 1.5 d, the mixture was neutralized with methanolic acetic acid and the solvent was removed by rotary evaporation. The residue was dissolved in water and CH_2Cl_2, the organic portion was dried ($MgSO_4$), and the solvent was evaporated. Purification by silica gel chromatography (hexane to 50% hexane/ethyl acetate) afforded 83 mg (88%) of the dimethyl ester (*S*)-**10** as a colorless solid: mp 154.4–155.5 °C (lit.[18] mp 154–155 °C); $[\alpha]$ −17° (*c* < 0.3, MeOH) (lit.[18] $[\alpha]$ −18° (*c* = 1.2, MeOH)). The diester was shown to be enantiomerically pure (>99% ee) by chiral HPLC analysis: Chiralcel OD column, 0.5 mL/min, 9:1 hexane:2-propanol, λ = 254 nm, t_R = 18 min.

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Supplementary Material Available: Spectral data (^{1}H and ^{13}C NMR) of all intermediates **4–9** (38 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.