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New, Improved Procedure for the Synthesis of Structurally Diverse *N*-Spiro C_2-Symmetric Chiral Quaternary Ammonium Bromides

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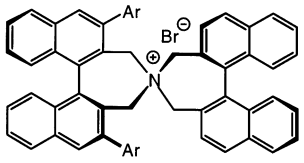
Abstract: Selective, direct ortho magnesiation of (*S*)-2,2′-bis(isopropoxycarbonyl)-1,1′-binaphthyl (**6**) has been achieved under mild conditions, using magnesium bis(2,2,6,6-tetramethylpiperamide) [$Mg(TMP)_2$]. In combination with the subsequent reaction with the appropriate electrophiles, bromine and iodine, this method constitutes a key step in establishing a new and concise synthetic route to a wide variety of *N*-spiro C_2-symmetric chiral quaternary ammonium bromides of type **1**.

In 1999 we introduced *N*-spiro C_2-symmetric chiral quaternary ammonium bromides of type **1** and demonstrated the effectiveness of (*S*,*S*)-**1c** [(*S*,*S*)-*β*-Np-NAS-Br] as a chiral phase-transfer catalyst in the enantioselective alkylation of protected glycine derivative, providing a practical method for the asymmetric synthesis of both natural and unnatural α-amino acids.[1] In the next year, we also disclosed a new catalyst (*S*,*S*)-**1b** [(*S*,*S*)-3,4,5-F_3-Ph-NAS-Br] possessing an electron-withdrawing 3,4,5-trifluorophenyl substituent and its successful utilization for the catalytic asymmetric synthesis of α,α-dialkyl-α-amino acids.[2] Although these chiral quaternary ammonium bromides can be assembled by a reliable procedure we recently published,[1e] more than 10 steps are required for preparation of the appropriately modified binaphthyl subunit; this could be an impediment to finding broad applications in academia as well as industry. Further, certain structural limitations pose a critical problem in every consideration of more precise molecular design. Accordingly, we undertook an exploration of an essentially new synthetic route to improve this situation. Herein we detail new procedures involving selective ortho magnesiation of 1,1′-binaphthyl-2,2′-dicarboxylic ester as a key step (Scheme 1), which enables the synthesis of a variety of chiral quaternary ammonium bromides of type **1**.



(*S*,*S*)-**1a** (Ar = 3,5-Me_2-Ph) [(*S*,*S*)-3,5-Me_2-Ph-NAS-Br]
b (Ar = 3,4,5-F_3-Ph) [(*S*,*S*)-3,4,5-F_3-Ph-NAS-Br]
c (Ar = *β*-Np) [(*S*,*S*)-*β*-Np-NAS-Br]

Since Ar-NAS-Br can be readily assembled under mildly basic conditions from (*S*)-bis-bromide **2** and *secondary* amine **3**, we focused our attention on the synthesis of **2**, which could be derivatized from the corresponding (*S*)-bis-ester **4** by simple reduction−bromination sequence. In considering the Suzuki−Miyaura cross-coupling reaction[3] for the introduction of aromatic substituent (Ar) to the 3,3′-position, (*S*)-3,3′-dibromo-1,1′-binaphthyl-2,2′-dicarboxylic ester **5a** appeared as a requisite compound to be prepared. For a straightforward synthesis of **5a**, direct ortho metalation of (*S*)-1,1′-binaphthyl-2,2′-dicarboxylic ester **6** was required, for which we chose magnesium bis(2,2,6,6-tetramethylpiperamide) [$Mg(TMP)_2$] as an appropriate base[4] and optimized the reaction conditions.[5]

Thus, (*S*)-1,1′-binaphthyl-2,2′-dicarboxylic acid[6] was converted to the corresponding isopropyl ester **6**[7] in the usual manner. Treatment of **6** with 3 equiv of freshly prepared $Mg(TMP)_2$ in THF at room temperature for 10 h and subsequent reaction with bromine (6 equiv) at −78 °C to room temperature furnished (*S*)-3,3′-dibromo-2,2′-bis(isopropoxycarbonyl)-1,1′-binaphthyl (**5a**) in 60% yield (entry 1 in Table 1),[8] and the use of 4 equiv of $Mg(TMP)_2$ and 8 equiv of bromine improved the yield to 88% (entry 2). Further, we found that 3 h of stirring was critical for complete magnesiation and at least 8 equiv of bromine was optimal (entries 3−5). As expected, use of other electrophiles such as iodine became feasible, affording an alternative candidate for the next coupling reaction in 83% yield (entry 6). This method represents the potential utility of relatively unfamiliar $Mg(TMP)_2$ for the selective metalation of aromatic compounds possessing labile functionalities.[4b]

With this efficient method in hand, various aromatic substituents could be installed on the 3,3′-position of **5**

(1) (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. See also: (b) Ooi, T.; Kameda, M.; Tannai, H.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 8339. (c) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551. (d) Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640. (e) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.

(2) (a) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. See also: (b) Ooi, T.; Takeuchi, M.; Maruoka, K. *Synthesis* **2001**, 1716.

(3) For review, see: Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147 and references therein.

(4) (a) Eaton, P. E.; Lee, C.-H.; Xiiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (b) Henderson, K. W.; Kerr, W. J. *Chem. Eur. J.* **2001**, *7*, 3430.

(5) Use of LiTMP in place of $Mg(TMP)_2$ in the reaction with **6** gave totally unsatisfactory results. For instance, treatment of **6** with 2.2 equiv of LiTMP in THF at 0 °C for 2 h and subsequent reaction with bromine (2.2 equiv) at −78 °C to room temperature resulted in almost total recovery of starting **6**, while both attempts to use 3 equiv of LiTMP and to perform the lithiation at room temperature gave a deteriorated mixture.

(6) (a) Ohta, T.; Ito, M.; Inagaki, K.; Takaya, H. *Tetrahedron Lett.* **1993**, *34*, 1615. See also: (b) Seki, M.; Yamada, S.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **2000**, 1677.

(7) Attempted reactions with the corresponding methyl and ethyl esters under similar conditions afforded the desired products in less than 20% yields (^{1}H NMR).

(8) Concomitant formation of monobromination product was observed (ca. 25%). Magnesiation of **6** under more concentrated condition (0.62 M) or at higher temperature (50 °C) did not lead to the improvement of the chemical yield of **5a**, as long as 3 equiv of $Mg(TMP)_2$ was used.

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SCHEME 1

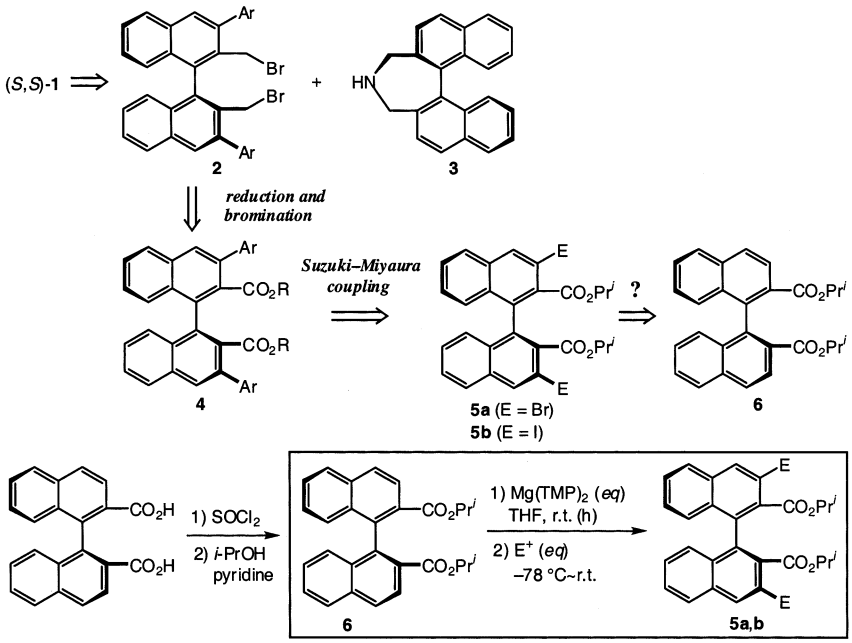
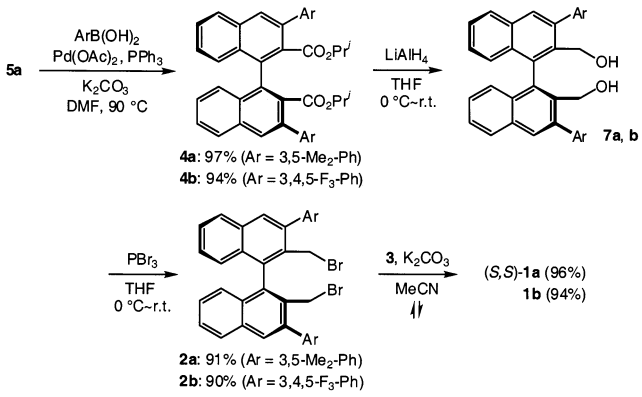


TABLE 1. Optimization of the Reaction Parameter for Ortho Magnesiation of 6 and Subsequent Trapping with Electrophiles[a]

entry	$Mg(TMP)_2$ (equiv)	condition (h)	E^+ (equiv)	yield[b] (%)	product
1	3	10	Br_2 (6)	60	**5a**
2	4	10	Br_2 (8)	88	**5a**
3	4	3	Br_2 (8)	89	**5a**
4	4	3	Br_2 (6)	76	**5a**
5	4	3	Br_2 (9)	89	**5a**
6	4	3	I_2 (8)	83	**5b**

[a] The magnesiation was carried out by adding a THF solution of **6** to $Mg(TMP)_2$ in THF−hexane at 0 °C followed by stirring at room temperature. Then, electrophile (E^+) was introduced at −78 °C, and the mixture was allowed to warm to room temperature and stirred there for 1 h. [b] Isolated yield.

SCHEME 2



by well-established Suzuki−Miyaura cross coupling.[3] For instance, the reaction of **5a** with 3,5-dimethylphenylboronic acid in the presence of $Pd(OAc)_2$, PPh_3, and K_2CO_3 in DMF at 90 °C for 8 h gave rise to the desired coupling product **4a** in 97% yield. Reduction of **4a** with $LiAlH_4$ in THF at room temperature for 4 h afforded (*S*)-3,3′-bis(3,5-dimethylphenyl)-2,2′-bis(hydroxymethyl)-1,1′-binaphthyl (**7a**), which without purification was treated with PBr_3 in THF at 0 °C to room temperature for 1 h, producing the (*S*)-bis-bromide **2a** in 91% yield (2 steps). It should be noted that this type of bis-bromide **2** having several benzylic protons was inaccessible by the previous procedure because of the difficulty of selective radical bromination.[1e] Assembly of **2a** with **3** was conducted in refluxing acetonitrile, using K_2CO_3 as a base, giving the chiral quaternary ammonium bromide (*S*,*S*)-**1a** in 96% yield (Scheme 2). Similarly, (*S*,*S*)-**1b** also can be prepared as shown in Scheme 2.

In summary, we have developed a new synthetic route to the structurally diverse *N*-spiro C_2-symmetric chiral quaternary ammonium bromide [Ar-NAS-Br] with selective, direct magnesiation of 1,1′-binaphthyl-2,2′-dicarboxylic esters as a key step. This procedure should facilitate large-scale access to this type of compound and hopefully accelerate the research using them as chiral phase-transfer catalysts.

Experimental Section

(*S*)-2,2′-Bis(isopropoxycarbonyl)-1,1′-binaphthyl (6). (*S*)-1,1′-Binaphthyl-2,2′-dicarboxylic acid[6] (1.71 g, 5.0 mmol) was placed in a dry two-neck flask with a stirring bar under argon atmosphere and $SOCl_2$ (5 mL) was introduced. The mixture was refluxed for 4 h and excess $SOCl_2$ was removed under reduced pressure. Then, *i*-PrOH (5 mL) and pyridine (1 mL) were added and the mixture was heated to reflux for 1 h. The resulting solution was washed with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (short-pass, EtOAc/hexane 1:4 as eluent) to give **6** (2.05 g, 4.70 mmol, 94%) as a white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (2H, d, J = 8.7 Hz), 8.01 (2H, d, J = 9.1 Hz), 7.92 (2H, d, J = 8.3 Hz), 7.50 (2H, ddd, J = 1.2, 6.7, 7.9 Hz), 7.24 (2H, ddd, J = 1.2, 6.7, 7.9 Hz), 7.13 (2H, d, J = 8.7 Hz), 4.75 (2H, sept, J = 6.3 Hz), 0.76 (6H, d, J = 6.3 Hz), 0.44 (6H, d, J = 6.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 139.5, 134.6, 133.1, 128.3, 127.6, 127.6, 127.5, 127.4, 126.5, 126.0, 67.7, 21.2, 20.8 ppm.

Preparation of Magnesium Bis(2,2,6,6-tetramethylpiperamide). To Mg turnings (55.0 mg, 2.25 mmol) in refluxing THF (2.25 mL), freshly distilled from sodium benzophenoneketyl,

was added 1,2-dibromoethane (198 μL, 2.25 mmol) dropwise to form a suspension of $MgBr_2$. A suspension of LiTMP in THF, prepared in a separate flask by the treatment of distilled 2,2,6,6-tetramethylpiperidine (759 μL, 4.5 mmol) in THF (2.25 mL) with a 1.6 M hexane solution of *n*-BuLi (2.81 mL, 4.5 mmol) at 0 °C for 30 min, was successively transferred to the $MgBr_2$ suspension. Additional stirring at 0 °C for 2 h gave a THF solution of $Mg(TMP)_2$ (clear brown solution). This solution of $Mg(TMP)_2$ is storable in a refrigerator in a Sure/Seal bottle and no loss of activity was observed after a month.

(*S*)-3,3′-Dibromo-2,2′-bis(isopropoxycarbonyl)-1,1′-binaphthyl (5a). To a THF solution of $Mg(TMP)_2$ prepared as described above (0.31 M, 6.5 mL, 2.0 mmol) was added **6** (213 mg, 0.5 mmol) in THF (2.0 mL) dropwise at 0 °C under argon atmosphere and the mixture was stirred for 3 h at room temperature. After being cooled to −78 °C, Br_2 (205 μL, 4.0 mmol) was added and stirring was continued for 1 h at room temperature. This mixture was then poured into cooled 1 N HCl, washed with saturated Na_2SO_3, and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane 1:20 to 1:10 as eluent) gave **5a** (260 mg, 0.445 mmol, 89%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (2H, s), 7.82 (2H, d, J = 8.3 Hz), 7.53 (2H, ddd, J = 1.2, 7.1, 8.3 Hz), 7.34 (2H, ddd, J = 1.2, 7.1, 8.3 Hz), 7.19 (2H, d, J = 7.9 Hz), 4.78 (2H, sept, J = 6.3 Hz), 0.78 (6H, d, J = 6.3 Hz), 0.67 (6H, d, J = 6.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 134.1, 134.0, 133.8, 132.1, 131.4, 127.9, 127.6, 127.1, 126.8, 115.8, 69.0, 21.1, 20.8 ppm.

(*S*)-3,3′-Diiodo-2,2′-bis(isopropoxycarbonyl)-1,1′-binaphthyl (5b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (2H, s), 7.78 (2H, d, J = 8.3 Hz), 7.51 (2H, m), 7.34 (2H, m), 7.17 (2H, d, J = 8.7 Hz), 4.76 (2H, sept, J = 6.3 Hz), 0.76 (6H, d, J = 6.3 Hz), 0.69 (6H, d, J = 6.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 139.3, 136.9, 134.2, 133.6, 131.8, 127.7, 127.6, 127.3, 126.5, 88.2, 69.0, 21.0, 20.8 ppm.

(*S*)-2,2′-Bis(isopropoxycarbonyl)-3,3′-bis(3,5-dimethylphenyl)-1,1′-binaphthyl (4a). A mixture of **5a** (635 mg, 1.0 mmol), 3,5-dimethylphenylboronic acid (360 mg, 2.4 mmol), $Pd(OAc)_2$ (11.6 mg, 0.05 mmol), PPh_3 (40.1 mg, 0.15 mmol), and K_2CO_3 (419 mg, 3.0 mmol) in DMF (5.0 mL) was degassed and backfilled with argon. This mixture was heated at 90 °C for 8 h. After being cooled to room temperature, the resulting mixture was poured into saturated NH_4Cl and extracted with Et_2O. The organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (EtOAc/hexane 1:20 to 1:10 as eluent) afforded **4a** (616 mg, 0.97 mmol, 97%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, s), 7.90 (2H, d, J = 7.9 Hz), 7.52−7.48 (2H, m), 7.34−7.29 (4H, m), 7.16 (4H, s), 6.99 (2H, s), 4.50 (2H, sept, J = 6.3 Hz), 2.34 (12H, s), 0.57 (6H, d, J = 6.3 Hz), 0.55 (6H, d, J = 6.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 140.9, 137.5, 134.3, 133.1, 132.9, 131.9, 128.9, 128.8, 127.6, 127.6, 127.0, 126.5, 126.4, 67.8, 21.4, 20.9, 20.7 ppm.

(*S*)-2,2′-Bis(isopropoxycarbonyl)-3,3′-bis(3,4,5-trifluorophenyl)-1,1′-binaphthyl (4b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, d, J = 9.1 Hz), 7.92 (2H, s), 7.57 (2H, ddd, J = 1.2, 6.7, 7.9 Hz), 7.38 (2H, ddd, J = 1.2, 6.7, 7.9 Hz), 7.28 (2H, d, J = 8.3 Hz), 7.16−7.13 (4H, m), 4.55 (2H, sept, J = 6.3 Hz), 0.61 (6H, d, J = 6.3 Hz), 0.54 (6H, d, J = 6.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 150.8 (ddd, J_{C-F} = 249, 9.8, 4.1 Hz), 139.3 (dt, J_{C-F} = 252, 14.7 Hz), 136.8 (dt, J_{C-F} = 8.2, 4.9 Hz), 134.6, 134.3, 132.9, 132.2, 132.0, 129.3, 127.9, 127.8, 127.4, 112.9 (dd, J_{C-F} = 15.5, 5.8 Hz), 68.5, 20.9, 20.7 ppm.

(*S*)-2,2′-Bis(bromomethyl)-3,3′-bis(3,5-dimethylphenyl)-1,1′-binaphthyl (2a). To a suspension of $LiAlH_4$ (142 mg, 3.0 mmol) in THF (3.0 mL) was added **4a** (635 mg, 1.0 mmol) portionwise at 0 °C and the reaction mixture was stirred for 4 h at room temperature. Then, Et_2O (3 mL) was added and the reaction was quenched by the sequential treatment with H_2O (142 μL), 15% NaOH (142 μL), and H_2O (284 μL). After being stirred for 1 h at room temperature, this mixture was filtered through a pad of Celite and the filtrate was concentrated. Without further purification, this crude (*S*)-3,3′-bis(3,5-dimethylphenyl)-2,2′-bis(hydroxymethyl)-1,1′-binaphthyl (**7a**) was used for the subsequent bromination. An analytical sample was obtained by recrystallization from THF/hexane: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, s), 7.91 (2H, d, J = 7.5 Hz), 7.49−7.45 (2H, m), 7.30 (4H, s), 7.27−7.23 (2H, m), 7.07 (2H, s), 7.04 (2H, d, J = 8.7 Hz), 4.45 (2H, d, J = 11.7 Hz), 4.13 (2H, d, J = 11.7 Hz), 2.41 (12H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 140.9, 137.5, 136.3, 135.8, 132.8, 132.3, 129.5, 128.9, 127.9, 127.5, 126.4, 126.3, 126.2, 60.1, 21.5 ppm.

A THF (ca. 3 mL) solution of **7a** (523 mg, 1.0 mmol) was cooled to 0 °C and PBr_3 (52.8 μL, 0.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h and poured into H_2O. Extractive workup was performed with EtOAc and the combined extracts were dried over Na_2SO_4. Removal of volatiles and purification of the residue by column chromatography on silica gel (EtOAc/hexane 1:10 as eluent) furnished **2a** (590 mg, 0.91 mmol, 91% in two steps) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 7.5 Hz), 7.89 (2H, s), 7.50 (2H, m), 7.28 (2H, m), 7.24 (4H, s), 7.15 (2H, d, J = 7.5 Hz), 7.08 (2H, s), 4.30 (2H, d, J = 10.1 Hz), 4.27 (2H, d, J = 10.1 Hz), 2.41 (12H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 140.2, 137.5, 136.3, 133.1, 132.2, 131.7, 130.0, 129.0, 127.7, 127.3, 127.2, 127.0, 126.2, 32.2, 21.5 ppm.

(*S*)-2,2′-Bis(hydroxymethyl)-3,3′-bis(3,4,5-trifluorophenyl)-1,1′-binaphthyl (7b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, d, J = 8.7 Hz), 7.93 (2H, s), 7.54−7.51 (2H, m), 7.45−7.42 (4H, m), 7.31−7.27 (2H, m), 6.97 (2H, d, J = 8.3 Hz), 4.32 (2H, d, J = 11.1 Hz), 4.15 (2H, d, J = 11.1 Hz), 1.59 (2H, br) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5 (ddd, J_{C-F} = 249, 9.8, 4.1 Hz), 139.3 (dt, J_{C-F} = 252, 15.2 Hz), 138.5, 136.8, 136.7 (m), 134.6, 132.7, 132.5, 129.9, 128.1, 127.2, 127.1, 126.0, 114.2 (dd, J_{C-F} = 15.6, 5.7 Hz), 59.7 ppm.

Chiral Ammonium Salt (*S*,*S*)-1a. A mixture of **2a** (324 mg, 0.5 mmol), chiral *secondary* amine **3** (147 mg, 0.5 mmol), and K_2CO_3 (139 mg, 1.0 mmol) in CH_3CN (3.0 mL) was heated and refluxed for 6 h. This mixture was poured into H_2O and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2 1:20 to 1:10 as eluent) to give (*S*,*S*)-**1a** (414 mg, 0.48 mmol, 96%) as a white solid: $[\alpha]^{27.3}_D$ 16.6° (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.36 (2H, s), 8.15 (2H, d, J = 8.3 Hz), 7.93 (2H, d, J = 7.9 Hz), 7.70−7.22 (4H, br), 7.70−7.66 (2H, m), 7.57−7.53 (2H, m), 7.45 (2H, s), 7.42 (2H, d, J = 8.3 Hz), 7.38−7.34 (2H, m), 7.26−7.22 (2H, m), 7.15 (4H, d, J = 7.9 Hz), 6.37 (2H, d, J = 7.9 Hz), 4.99 (2H, d, J = 13.9 Hz), 4.06 (2H, d, J = 13.9 Hz), 3.98 (2H, d, J = 12.9 Hz), 3.63 (2H, d, J = 12.9 Hz), 2.88−1.18 (12H, br) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 139.4, 139.2, 139.2, 136.2, 133.9, 133.8, 132.3, 130.9, 130.8, 130.3, 128.8, 128.6 (br), 128.3, 128.3, 128.0, 127.5, 127.4, 127.3, 127.3, 126.7, 125.0, 122.5, 62.1, 57.4, 21.7 ppm. Melted at 230 °C with decomposition.

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Supporting Information Available: Full spectroscopic characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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