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Synthesis and Stereodynamics of Highly Constrained 1,8-Bis(2,2′-dialkyl-4,4′-diquinolyl)naphthalenes

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Received October 20, 2003

The syn and anti isomers of axially chiral 1,8-diquinolylnaphthalenes have been synthesized via Pd-catalyzed Stille coupling of 1,8-dibromonaphthalene and 2-alkyl-4-trimethylstannylquinolines. Optimization of the cross-coupling reaction allowed the preparation of highly constrained 1,8-bis-(2,2′-dimethyl-4,4′-diquinolyl)naphthalene, **2**, and 1,8-bis(2,2′-diisopropyl-4,4′-diquinolyl)naphthalene, **3**, in 42% and 41% yield, respectively. Employing $Pd(PPh_3)_4$ and CuO as the cocatalysts in the coupling reaction of 1,8-dibromonaphthalene and 2-alkyl-4-trimethylstannylquinolines proved to be superior over other catalysts such as $PdCl_2$(dppf), $Pd_2(dba)_3$/P(t-Bu)$_3$, and POPd. The C_2-symmetric anti isomers of **2** and **3** were found to be more stable than the corresponding meso syn isomer. The ratio of the two enantiomeric anti conformers to the syn conformer was determined as 7.9:1 for **2** and 8.6:1 for **3** by NMR and HPLC analysis. The atropisomers of **2** and **3** were found to be stable to rotation about the chiral axis at room temperature and all three stereoisomers of **2** were isolated by semipreparative HPLC on a Chiralpak AD column. The diastereoisomers of **3** were separated via preferential crystallization of the anti isomers from diethyl ether. Slow syn/anti interconversion was observed for both atropisomers at enhanced temperature, and the diastereomerization and enantiomerization processes were monitored by NMR and HPLC. The Gibbs activation energy, $\Delta G^{\ddagger}$, for the isomerization of **2** was determined as 116.0 (112.1) kJ/mol for the conversion of the anti (syn) to the syn (anti) isomer at 71.0 °C. The rotational energy barrier of **3** was determined as 115.2 (111.1) kJ/mol for the conversion of the anti (syn) to the syn (anti) isomer at 66.2 °C.

Introduction

The development of sterically congested aromatic compounds exhibiting unique stereochemical, electronic, and photochemical properties has paved the way toward new optoelectronic devices, rotors, and chemical sensors.[1] In particular, the stereodynamics of axially chiral 1,8-disubstituted naphthalenes have received considerable attention during recent years.[2] Alkyl,[3] aryl,[4] and hetaryl[5] groups have been introduced into the naphthalene frame-

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10.1021/jo0355471 CCC: $27.50
Published on Web 02/14/2004

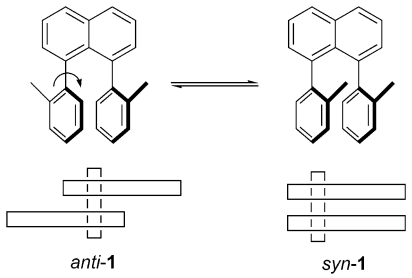

FIGURE 1. Structure of **1** exhibiting antiparallel (anti isomer) or parallel (syn isomer) 2-methylphenyl moieties.

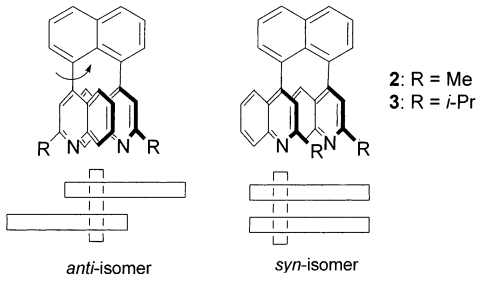

FIGURE 2. Structures of the syn and anti isomers of 1,8-diquinolylnaphthalenes **2** and **3**.

work to study the energy barrier to rotation about the naphthyl−alkyl or naphthyl−aryl bond and intramolecular interactions between stacked alkyl and aryl groups. We have recently reported the synthesis and conformational stability of 1,8-dipyridylnaphthalenes using variable-temperature NMR spectroscopy and computer simulation of elution profiles obtained by dynamic HPLC.[6] Incorporation of ortho- or meta-substituted aryl moieties into both peri positions of naphthalene results in two C_2-symmetric anti isomers and one meso syn isomer. It is broadly accepted that the peri aryl rings are coplanar and almost perpendicular to the naphthalene moiety in the ground state. Accordingly, 1,8-bis(2,2′-dimethyl-1,1′-diphenyl)naphthalene, **1**, exists as a mixture of atropisomeric syn and anti isomers (Figure 1). Interconversion of the isomers of **1** requires one phenyl ring to rotate about the chiral naphthyl−phenyl axis. Thus, the edge of the rotating ring will be directed toward the adjacent phenyl moiety in the transition state. In general, isomerization of **1** can proceed via two T-shaped transition states exhibiting the methyl ring of the rotating phenyl moiety either pointed toward or away from the other phenyl ring. The latter is expected to afford significantly less steric hindrance and should be favored. It is assumed that both phenyl rings are significantly splayed away from each other to minimize steric repulsion between the hydrogens in position 5 and 6 of the rotating 2-methylphenyl ring and the adjacent phenyl moiety in the transition state. Despite the significant steric hindrance to isomerization that one would expect for 1,8-diarylnaphthalenes, rotation about the chiral axis of **1** has been reported to proceed fast. The atropisomers of **1** exhibit an energy barrier to isomerization of 100 kJ/mol and are not stable to interconversion at room temperature.[7]

The development of fluorescent chiral 1,8-dihetarylnaphthalenes exhibiting conformational stability at room temperature and the ability to undergo coordination to metal ions or hydrogen bonding to organic compounds could afford a new class of stereoselective sensors, ligands for Lewis acid-catalyzed asymmetric reactions, and thermally stable chiroptical switches that undergo photoenantiomerization upon irradiation of circularly polarized light.[8] However, the preparation of 1,8-diarylnaphthalenes exhibiting enhanced steric hindrance to rotation about the chiral axis has proven to be difficult. The preparation of a highly congested 1,8-diarylnaphthalene framework is impeded by severe steric repulsion during aryl−aryl bond formation, which results in very low yields and an efficient synthetic route toward sterically crowded 1,8-diarylnaphthalene derivatives exhibiting conformational stability at room temperature has proven to be difficult.[9] We have recently reported the synthesis of selectively substituted 1,8-diacridylnaphthalenes exhibiting a rotational energy barrier of at least 180 kJ/mol.[10] On the basis of CPK models and our studies with 1,8-dipyridyl- and 1,8-diacridylnaphthalenes, we assumed that incorporation of 2-substituted quinolyl moieties into the peri positions of naphthalene would afford rigid and fluorescent bidentate diheteroarylnaphthalenes exhibiting conformational stability at 25 °C and dynamic behavior at higher temperature, which could provide a new class of stereodynamic sensors utilizing fluorescence spectroscopy and induced circular dichroism in the presence of a chiral compound. Herein, we report the synthesis and stereodynamics of highly constrained 1,8-bis(2,2′-dimethyl-4,4′-diquinolyl)naphthalene, **2**, and 1,8-bis(2,2′-diisopropyl-4,4′-diquinolyl)naphthalene, **3** (Figure 2).

Experimental Section

All commercially available reagents, solvents, and chloroquinolines **4** and **5** were used without further purification. 1,8-Dibromonaphthalene was prepared from 1,8-diaminonaphthalene as described in the literature.[11] All reactions were carried out under nitrogen atmosphere and under anhydrous conditions. Organostannanes are highly toxic and should only be used in a vented hood and when wearing eye and skin protection. Products were purified by flash chromatography on SiO_2 (particle size 0.032−0.063 mm). GC/MS was performed on a 15 m DB-1 column. Atmospheric pressure chemical ionization (APCI) mass spectra were collected on a YMC-Pack CN column (4.6 × 250 mm) using an HPLC/MSD system equipped with electrospray and atmospheric pressure chemical ionization MS detection and hexanes/EtOH = 9:1 as the mobile phase. All analytical and preparative HPLC separations of **2** were conducted on a Chiralpak AD column (4.6 × 250 mm) at a flow rate of 1 mL/min with UV detection at 254 nm. Preparative separations were performed by repetitive injections of 100-μL portions of **2** dissolved in hexanes/EtOH = 1:1 at a concentration of approximately 20 mg/mL. For analytical separations, **2** was dissolved in the same diluent at a concen-

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tration of 1 mg/mL and 10-μL portions were injected. The HPLC selectivity factor, α, for the enantioseparation of **2** was determined as 1.68. Retention factors R_f were determined as 2.87 and 4.81 for the enantiomers of **2** and as 3.65 for the syn isomer of **2**. NMR spectra were obtained at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) with $CDCl_3$ as the solvent. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS). All kinetic experiments of **2** were conducted in a closed vessel designed for high-pressure experiments with hexanes/EtOH = 1:1 as the solvent. The vessel was submerged in an ethylene glycol bath and the temperature was measured with a calibrated digital thermometer. The samples were cooled to room temperature prior to analysis by HPLC. Kinetic studies of **3** were conducted in deuterated dimethyl sulfoxide (DMSO) (for convenience of NMR measurements).

A. Synthesis of 1,8-(2,2′-Disubstituted-4,4′-diquinolyl)-naphthalenes: 1,8-Bis(2,2′-dimethyl-4,4′-diquinolyl)naphthalene (2). A solution of 1,8-dibromonaphthalene (0.10 g, 0.34 mmol), $Pd(PPh_3)_4$ (44 mg, 11.2 mol %), and CuO (0.10 g, 1.3 mmol) in 4 mL of anhydrous dimethylformamide (DMF) was stirred at 100 °C under N_2. After 5 min, 2-methyl-4-trimethylstannylquinoline **9** (0.36 g, 1.2 mmol) in 2 mL of DMF was added. The reaction was stirred for 13 h, cooled to room temperature, and quenched with 10% NH_4OH. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated under vacuum. Purification by flash chromatography (hexanes/ethyl acetate/triethylamine) yielded **2** (59 mg, 0.14 mmol, 42%) as a white oil.

^{1}H NMR (anti and syn diastereomers exhibit the same spectra) δ 1.86 (s, 6H), 6.27 (s, 2H), 7.28−7.39 (m, 6H), 7.58−7.68 (m, 4H), 7.89 (d, J = 8.4 Hz, 2H), 8.12 (dd, J = 1.1 and 8.4 Hz, 2H). ^{13}C NMR δ 24.8, 123.1, 125.6, 125.9, 126.2, 128.9, 129.2, 129.9, 130.8, 135.1, 135.4, 147.1, 147.6, 157.7. EI-MS (70 eV) m/z (%) 410 (100, M^+), 395 (5, M^+ − Me), 268 (10, M^+ − methylquinolyl), 253 (7, M^+ − quinolyl), 143 (11, methylquinolyl). LC-APCI-MS m/z (%) 411 [100, $(M + H)^+$]. Anal. Calcd for $C_{30}H_{22}N_2$: C, 87.77; H, 5.90; N, 6.33. Found: C, 87.38; H, 6.43; N, 5.93.

1,8-Bis(2,2′-diisopropyl-4,4′diquinolyl)naphthalene (3). This compound was prepared from 1,8-dibromonaphthalene (0.90 g, 3.1 mmol) and 2-isopropyl-4-trimethylstannylquinoline **10** (4.0 g, 12.0 mmol) by the Stille coupling procedure described for **2**. Purification by chromatography on silica gel (100:20:1 hexanes/ethyl acetate/triethylamine) gave **3** (585 mg, 1.3 mmol, 41%) as yellow crystals, mp 214−218 °C.

^{1}H NMR (anti isomer) δ 0.80 (d, J = 6.9 Hz, 6H), 0.98 (d, J = 6.9 Hz, 6H), 2.34 (sept, J = 6.9 Hz, 2H), 6.34 (s, 2H), 7.18 (dd, J = 1.1 and 8.2 Hz, 2H), 7.23−7.29 (m, 4H), 7.54 (ddd, J = 1.4, 6.7, and 8.4 Hz, 2H), 7.62 (dd, J = 7.1 and 8.2 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 8.13 (dd, J = 1.4 and 8.4 Hz, 2H). ^{1}H NMR (syn isomer) δ 1.26 (d, J = 6.9 Hz, 2H), 1.31 (d, J = 6.9 Hz, 2H), 2.98 (sept, J = 6.9 Hz, 2H), 6.69−6.79 (m, 4H), 6.77 (s, 2H), 7.54 (ddd, J = 1.4, 6.7, and 8.4 Hz, 2H), 7.62 (dd, J = 7.1 and 8.2 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 8.12 (dd, J = 1.4 and 8.4 Hz, 2H). ^{13}C NMR δ (mixture of syn and anti isomers) 21.1, 21.2, 22.5, 22.7, 36.1, 36.2, 119.8, 120.1, 125.1, 125.3, 125.3, 125.4, 125.6, 125.9, 126.1, 126.4, 126.6, 128.4, 129.2, 129.3, 129.4, 129.5, 129.6, 130.49, 130.6, 130.9, 131.1, 131.6, 134.4, 135.7, 146.7, 147.9, 148.2, 164.9, 165.5. EI-MS m/z (%) 466 (100, M^+), 451 (94, M^+ − Me), 436 (5, M^+ − 2Me), 423 (23, M^+ − i-Pr), 253 (5, M^+ − isopropylquinolyl). LC-APCI-MS m/z (%) 467 [100, $(M + H)^+$]. Anal. Calcd for $C_{34}H_{30}N_2$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.27; H, 7.23; N, 5.87.

4-Chloro-2-isopropylquinoline (6). A solution of 0.7 M isopropyllithium in n-pentane (73.4 mL, 51.4 mmol) was added under nitrogen to a solution of 4-chloroquinoline **4** (7.0 g, 42.8 mmol) in 130 mL of anhydrous tetrahydrofuran (THF) at −78 °C. After 1 h, the reaction was quenched with 10% NH_4OH, allowed to come to room temperature and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo. The residue was dissolved in 50 mL of acetone, and an aqueous solution of cerium(IV) ammonium nitrate (65.3 g, 120 mmol, 100 mL H_2O) was added. Acetone was removed after the dark red solution had turned to light yellow. The mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$, and the solvents were removed under reduced pressure. Flash chromatography on silica gel (75:25:1 hexanes/CH_2Cl_2/triethylamine) of the crude residue gave **7** (5.0 g, 57%) as a yellow oil.

^{1}H NMR δ 1.39 (d, J = 6.9 Hz, 6H), 3.23 (sept, J = 6.9 Hz, 1H), 7.43 (s, 1H), 7.58 (ddd, J = 1.4, 7.0, and 8.2 Hz, 1H), 7.73 (ddd, J = 1.4, 7.0, and 8.4 Hz, 1H), 8.06 (ddd, J = 0.5, 1.4, and 8.4 Hz, 1H), 8.18 (ddd, J = 0.5, 1.4, and 8.2 Hz, 1H). ^{13}C NMR δ 22.5, 37.3, 119.3, 123.8, 125.0, 126.5, 129.2, 130.1, 142.5, 148.5, 167.5. EI-MS (70 eV) m/z (%) 205 (30, M^+), 190 (100, M^+ − Me), 162 (15, M^+ − i-Pr), 127 (17, M^+ − i-Pr − Cl). Anal. Calcd for $C_{12}H_{12}ClN$: C, 70.07; H, 5.88; N, 6.81. Found: C, 69.96; H, 5.75; N, 6.64.

4-Iodo-2-methylquinoline (7). To a solution of 4-chloro-2-methylquinoline **5** (5.0 g, 28.1 mmol) in 50 mL of THF was added 4 M HCl in 1,4-dioxane (7.7 mL, 30.8 mmol). After 5 min, the solvent was removed and the precipitate was dried under reduced pressure. The hydrochloride salt and NaI previously dried at 120 °C under vacuum (21.1 g, 0.14 mol) were suspended in 150 mL of anhydrous acetonitrile and refluxed for 24 h. After this mixture was cooled to room temperature, an aqueous solution of 10% K_2CO_3 and 5% $NaHSO_3$ was added. After the mixture was extracted with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The residue was chromatographed on silica gel (100:20:1 hexanes/ethyl acetate/triethylamine as the eluent) to give **9** (6.1 g, 80%) as white crystals, mp 109−111 °C.

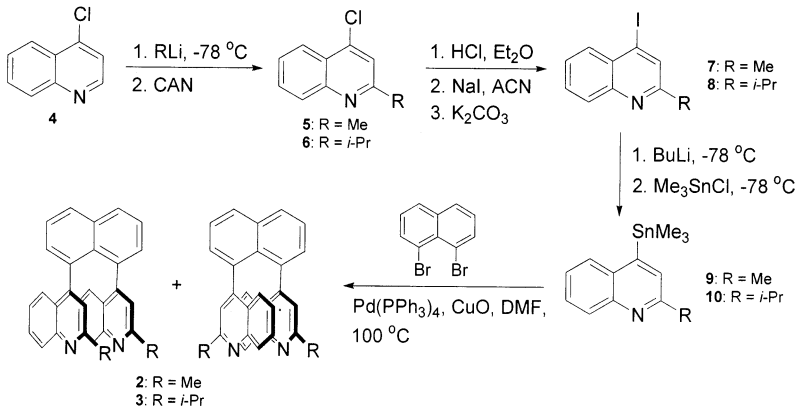
^{1}H NMR δ 2.70 (s, 3H), 7.56 (ddd, J = 1.4, 6.9, and 8.2 Hz, 1H), 7.71 (ddd, J = 1.4, 6.9, and 8.4 Hz, 1H), 7.91 (s, 1H), 7.94 (dd, J = 1.4 and 8.4 Hz, 1H), 7.97 (dd, J = 1.4 and 8.2 Hz, 1H). ^{13}C NMR δ 24.6, 112.1, 127.1, 128.4, 129.1, 130.3, 131.3, 133.3, 147.3, 158.6. EI-MS (70 eV) 269 (100, M^+), 142 (93, M^+ − I), 127 (33, M^+ − I − Me). Anal. Calcd for $C_{10}H_8IN$: C, 44.64; H, 3.00; N, 5.21. Found: C, 44.98; H, 2.78; N, 5.09.

4-Iodo-2-isopropylquinoline (8). 4-Chloro-2-isopropylquinoline **6** (4.5 g, 22.0 mmol) was converted to its hydrochloride salt by adding 4 M HCl in 1,4-dioxane (6.1 mL, 24.2 mmol). The salt was isolated as described for **7**. It was then suspended with dry NaI (16.5 g, 67.5 mmol) in anhydrous acetonitrile and the mixture was refluxed for 24 h. Following the workup procedure described for **7** and purification by flash chromatography (100:10:1 hexanes/ethyl acetate/triethylamine) afforded **8** (5.5 g, 84%) as a yellow oil.

^{1}H NMR δ 1.39 (d, J = 6.9 Hz, 6H), 3.19 (sept, J = 6.9 Hz, 1H), 7.55 (ddd, J = 1.4, 6.9, and 8.3 Hz, 1H), 7.70 (ddd, J = 1.4, 6.9, and 8.3 Hz, 1H), 7.95−7.98 (m, 2H). ^{13}C NMR δ 22.5, 36.8, 112.2, 127.1, 128.8, 129.5, 130.1, 130.8, 130.9, 131.3, 147.4, 167.3. EI-MS (70 eV) 297 (21, M^+), 282 (60, M^+ − Me), 170 (3, M^+ − I), 155 (20, M^+ − I − Me), 127 (18, M^+ − I − i-Pr). Anal. Calcd for $C_{12}H_{12}IN$: C, 48.51; H, 4.07; N, 4.71. Found: C, 48.91; H, 3.91; N, 4.64.

2-Methyl-4-trimethylstannylquinoline (9). A solution of 4-iodo-2-methylquinoline **7** (5.0 g, 18.5 mmol) in 100 mL of anhydrous diethyl ether was cooled to −78 °C under nitrogen. To the solution was added 1.6 M n-BuLi in hexanes (13.9 mL, 22.2 mmol) dropwise over a period of 15 min. After 30 min, a 1.0 M solution of Me_3SnCl in hexanes (27.8 mL, 27.8 mmol) was added. The resulting mixture was allowed to come to room temperature, stirred for 5 h, quenched with 10% NH_4OH, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the orange residue by flash chromatography (100:20:1 hexanes/CH_2Cl_2/triethylamine) afforded **9** (4.5 g, 80%) as a yellow solid. GC/MS revealed contamination of the product with 4-methylquinoline that could not be separated by chromatography.

SCHEME 1. Synthesis of 1,8-Diquinolylnaphthalenes 2 and 3



The stannane was therefore employed in the Stille coupling with 1,8-dibromonaphthalene without further purification.

^{1}H NMR δ 0.49 (s, 9H), 2.72 (s, 3H), 7.42 (s, 1H), 7.48 (ddd, J = 1.4, 6.9, and 8.1 Hz, 1H), 7.66 (ddd, J = 1.4, 6.9, and 8.3 Hz, 1H), 7.72 (ddd, J = 0.6, 1.4, and 8.1 Hz, 1H), 8.03 (ddd, J = 0.6, 1.4, and 8.4 Hz, 1H). ^{13}C NMR δ −8.4, 25.3, 125.3, 128.7, 129.3, 129.6, 130.4, 131.8, 147.0, 153.8, 157.0. EI-MS (70 eV) 307 (19, M^+), 292 (100, M^+ − Me), 262 (44, M^+ − 3Me), 142 (19, M^+ − Me_3Sn), 115 (14, M^+ − Me_3Sn − HCN).

2-Isopropyl-4-trimethylstannylquinoline (10). 4-Iodo-2-isopropylquinoline **8** (5.2 g, 17.5 mmol) was dissolved in 70 mL of anhydrous ether and cooled to −78 °C under nitrogen. A solution of *n*-BuLi in hexanes (13.0 mL, 1.6 M in hexanes) was added dropwise and the mixture was stirred for 30 min. To this solution, Me_3SnCl (26.0 mL, 1.0 M in hexanes) was added at once. The reaction mixture was allowed to come to room temperature and stirred for 5 h. Quenching with 10% NH_4OH was followed by a workup procedure described for **9**. Purification by flash chromatography (150:10:1 hexanes/ethyl acetate/triethylamine) afforded **10** (4.2 g, 72%) as a viscous yellow oil.

^{1}H NMR δ 0.48 (s, 9H), 1.41 (d, J = 6.9 Hz, 6H), 3.23 (sept, J = 6.9 Hz, 1H), 7.46 (s, 1H), 7.48 (ddd, J = 1.4 and 6.9 Hz, 1H), 7.66 (ddd, J = 1.4, 6.9, and 8.4 Hz, 1H), 7.71 (dd, J = 1.4 and 8.0 Hz, 1H), 8.06 (dd, J = 1.4 and 8.4 Hz, 1H). ^{13}C NMR δ −8.4, 22.7, 37.3, 125.3, 127.7, 128.6, 129.3, 130.0, 132.2, 147.0, 153.9, 165.0. EI-MS (70 ev) *m*/*z* (%) 335 (24, M^+), 320 (100, M^+ − Me), 305(9, M^+ − 2Me), 290 (31, M^+ − Me), 275 (3, M^+ − 4Me), 170 (32, M^+ − Me_3Sn), 155 (11, M^+ − Me − Me_3Sn). Anal. Calcd for $C_{15}H_{21}NSn$: C, 53.93; H, 6.34; N, 4.19. Found: C, 53.67; H, 6.70; N, 4.19.

B. Kinetic Investigations of 1,8-Bis(2,2′-disubstituted-4,4′-diquinolyl)naphthalenes 2 and 3. We were able to use enantiopure samples to study the isomerization of **2**. Separation of the stereoisomers of **2** was performed on an HPLC column (Chiralpak AD, mobile phase 95:5 hexanes/ethanol). The more strongly retained enantiomer was dissolved in the mobile phase at a concentration of 1 mg/mL and heated at 71.0 °C in a high-pressure flask for 1 h. The solution was then cooled to room temperature and analyzed by HPLC with individual response factors for the syn and anti diastereoisomers. The procedure was repeated 17 times to monitor the changes in the concentration of the three stereoisomers as a function of time until equilibrium was reached after 46 h. Crystallization from diethyl ether allowed us to separate the diastereoisomers of diquinolylnaphthalene **3**. The stereodynamics of **3** were studied by ^{1}H NMR spectroscopy at 66.2 °C with a racemic mixture of *anti*-**3** in DMSO-d_6 (1 mg/mL). The temperature of the sample was allowed to equilibrate for 10 min prior to the first NMR experiment. Integration of the well-resolved methyl signals of the syn and anti isomers of **3** allowed us to monitor the isomerization process. All isomerization reactions investigated were found to obey reversible first-order kinetics.

Results and Discussion

Synthesis of Highly Constrained 1,8-Bis(2,2′-dialkyl-4,4′-quinolyl)naphthalenes. We envisioned a synthetic approach toward 1,8-diquinolylnaphthalenes **2** and **3** involving a cross-coupling reaction of a 1,8-dihalonaphthalene with 2-alkyl-4-quinolyl boronic acids, Grignards and stannanes, respectively, as the key step. We decided to prepare the quinolyl precursors for Suzuki, Kharasch, and Stille couplings from 2-alkyl-4-iodoquinolines since 2-methyl-4-chloroquinoline **5** is commercially available and due to our previous finding that 2-isopropyl-4-chloroquinoline **6** can be prepared in 57% yield by Ziegler alkylation of 4-chloroquinoline **4** with isopropyllithium at −78 °C followed by oxidation with CAN. Initial attempts to replace the chloride by iodide with sodium iodide and acetic acid in refluxing acetone or DMF failed, but 2-methyl-4-iodoquinoline **7** was obtained in 24% yield with acetonitrile as the solvent. We were pleased to find that employing the hydrochloride salt of 4-chloroquinoline **5** in the nucleophilic aromatic substitution by iodide increased the yield of **7** to 80%. Similarly, 2-isopropyl-4-iodoquinoline **8** was prepared in 84% yield (Scheme 1). Formation of 2-methyl-4-quinolylmagnesium iodide with either magnesium or isopropylmagnesium chloride[12] and subsequent Ni(acac)$_2$-catalyzed Kharasch coupling with 1,8-diiodonaphthalene[13] afforded the monocoupling product only. Our initial studies with quinolyl-derived boronic acids revealed an inherently low solubility, which can be attributed to the zwitterionic nature of these compounds. As a consequence, purification and use of these compounds in Suzuki coupling reactions is limited and formation of the desired coupling products was not observed with 2-methyl-4-quinolylboronic acid or the corresponding pinacolato derivative. We therefore focused on the synthesis of 2-alkyl-4-trimethylstannylquinolines that would allow the preparation of 1,8-diquinolylnaphthalenes via Stille coupling. Lithiation of **7** and **8** with butyllithium at −78 °C and subsequent treatment with trimethylstannyl chloride afforded 2-methyl-4-trimethylstannylquinoline **9** and 2-isopropyl-4-trimethylstannylquinoline **10** in 88% and 74% yield, respectively. Employing 1,8-diiodonaphthalene and stannane **9** in the coupling reaction catalyzed by $Pd(PPh_3)_4$, $PdCl_2$(dppf), or

(12) Rottlaender, M.; Boymond, L.; Berillon, L.; Leprete, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Queguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.* **2000**, 767−770.

(13) See ref 4e.

TABLE 1. Results of Pd-Catalyzed Cross-Coupling Reactions Using 1,8-Dibromonaphthalene[a]

entry	stannane	product	catalyst	additives	conditions	yield (%)
1	9	2	$Pd(PPh_3)_4$	CuO	100 °C/8 h	26
2	9	2	$Pd(PPh_3)_4$	CuO	100 °C/13 h	42
3	9	2	$Pd(PPh_3)_4$	CuO, Cy_2NMe	100 °C/13 h	21
4	9	2	$PdCl_2$(dppf)	CuO	100 °C/13 h	35
5	9	2	POPd	CuO	100 °C/13 h	21
6	9	2	$Pd_2(dba)_3$/ $P(t\text{-}Bu)_3$	CsF	100 °C/13 h	25
7	10	3	$Pd(PPh_3)_4$	CuO	100 °C/13 h	41

[a] Cy, cyclohexyl; dba, dibenzylideneacetone; dppf, diphenylphosphinoferrocenyl; POPd, palladium phosphinous acid $[(t\text{-}Bu)_2P(OH)]_2PdCl_2$.

POPd in DMF at 140 °C did not result in the formation of 1,8-diquinolylnaphthalenes **2**. Since we were able to recover high amounts of stannane **9** but no 1,8-diiodonaphthalene, we concluded that **9** needs to be further activated to undergo transmetalation. The use of CsF for activation of fluorophilic stannanes for Stille coupling has recently been reported by Fu and co-workers.[14] We were pleased to find that the desired cross-coupling reaction between stannane **9** and 1,8-dibromonaphthalene proceeded when $Pd_2(dba)_3/P(t\text{-}Bu)_3$ was employed as the catalyst in the presence of CsF. However, the coupling product was formed in only 25% yield and a lot of starting material was recovered. Further screening of various catalysts and optimization of reaction conditions revealed that Pd-catalyzed Stille cross-coupling between 2-alkyl-4-trimethylstannylquinolines and 1,8-dibromonaphthalene occurs with remarkable yields in the presence of CuO.[15] Thus, 1,8-bis(2,2′-dimethyl-4,4′-diquinolyl)naphthalene **2** and 1,8-bis(2,2′-diisopropyl-4,4′-diquinolyl)-naphthalene **3** were prepared in 42% and 41% yield by utilizing $Pd(PPh_3)_4$/CuO in DMF at 100 °C (Table 1). Increasing the reaction time from 8 to 13 h results in a substantial increase of yield of coupling product **2** (entries 1 and 2). The palladium−phosphinous acid complex $[(t\text{-}Bu)_2P(OH)]_2PdCl_2$, POPd has successfully been used in a variety of cross-coupling reactions and is known for its robustness, ease of use, and tolerance to N-donors including hetaryls such as quinolines.[16] However, employing POPd in the coupling reaction affords only 21% yield of Stille product **2** (entry 5). In our hands, $Pd(PPh_3)_4$ proved to be superior over other catalysts such as $PdCl_2$(dppf), $Pd_2(dba)_3/P(t\text{-}Bu)_3$, and POPd (entries 2 and 4−6). Attempts to facilitate the catalyst regeneration, i.e., reductive elimination, by addition of methyldicyclohexylamine did not improve yields (entry 3).

It should be noted that two subsequent catalytic cycles are required to afford 1,8-diquinolylnaphthalenes **2** and **3** from 1,8-dibromonaphthalene and the corresponding 2-alkyl-4-trimethylstannanes **9** or **10**. An overall yield of 42% obtained for **2** therefore corresponds to an averaged yield of 65% for each individual coupling step. In all coupling reactions utilizing stannyl **9**, substantial formation of 1-methyl-8-(2-methyl-4-quinolyl)naphthalene **11** was observed.[17] Even under optimized reaction conditions, coupling byproduct **11** was obtained in 15% yield. We assume that the first catalytic cycle consisting of an oxidative addition of 1,8-dibromonaphthalene to Pd, transmetalation, and reductive elimination to regenerate the catalyst proceeds smoothly. By contrast, completion of the second Stille coupling between bulky intermediate 1-bromo-8-(2-methyl-4-quinolyl)naphthalene **12** and another stannane **9** is subject to severe steric hindrance. As a consequence, the transfer of a methyl group instead of the bulky 2-methyl-4-quinolyl moiety becomes a significant transmetalation side reaction. As a result, a substantial amount of less sterically hindered **11** is formed after reductive elimination (Scheme 2). Accordingly, employing stannane **10** in the Stille coupling with 1,8-dibromonaphthalene gave 1,8-bis(2,2′-diisopropyl-4,4′-diquinolyl)naphthalene **3** in 41% yield and 1-methyl-8-(2-isopropyl-4-quinolyl)naphthalene in 27% yield.

The Stille coupling of 1,8-dibromonaphthalene and 2-alkyl-4-trimethylstannanes **9** or **10** affords a mixture of syn and anti isomers. Kinetic investigations of the conformational stability of atropisomers **2** and **3** revealed that isomerization should occur fast under Stille coupling reaction conditions, vide infra. As a consequence of enhanced repulsion between the alkyl moieties in position 2 of the quinoline rings in the syn isomer, one would expect the anti isomer of **2** and **3** to be thermodynamically more stable. Accordingly, the ratio of the two enantiomeric anti conformers to the syn conformer was determined as 7.9:1 for **2** and 8.6:1 for **3** by HPLC and NMR analysis, respectively.[18] The observed ratio corresponds to a difference in Gibbs free energy of the anti and syn isomers, ΔG, of 3.4 kJ/mol for **2** and 3.6 kJ/mol for **3** according to the Boltzmann equation (eq 1):[19]

$$n_1/2n_2 = \exp(-\Delta G°/RT) \qquad (1)$$

Kinetic Investigations of 1,8-Diquinolylnaphthalenes 2 and 3. Rotation of a quinolyl ring about a chiral

(14) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348, and references therein.

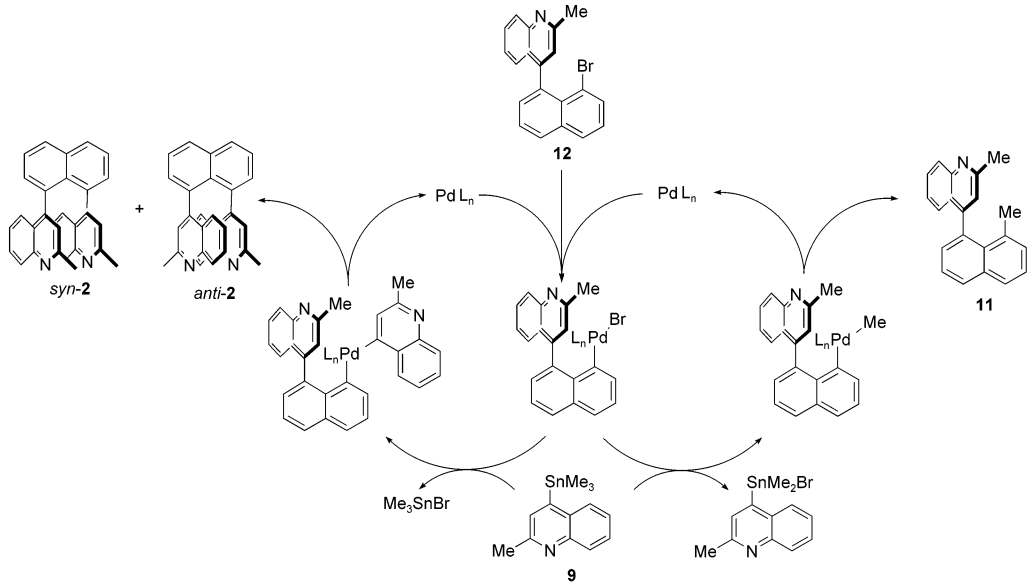
(15) Gronowitz, S.; Bjoerk, P.; Malm, J.; Hoernfeldt, A.-B. *J. Organomet. Chem.* **1993**, 460, 127−129.

(16) (a) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513−1516. (b) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677−8681. (c) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643−3650.

(17) The structure of 1-methyl-8-(2-alkyl-4-quinolyl)naphthalene, **11**, was determined by ^{1}H NMR, GC/MS, and LC/MS/APCI.

(18) The anti/syn ratio of the coupling product mixture of **3** was determined by integration of the well-resolved ^{1}H NMR signals of the isopropyl protons. By contrast, the diastereoisomers of **2** exhibit superimposable NMR spectra. The isomer ratio of **2** was therefore determined by chiral HPLC analysis of the product mixture of **2** on a Chiralpak AD column. Preparative separation of pure anti and syn isomers of **2** allowed us to determine the individual UV response factors of each atropisomer for quantification. The determination of the syn and anti conformations of **2** was based on the successful separation of the enantiomers of *anti*-**2** by chiral HPLC. From our studies with **2** we conclude that the thermodynamically favored isomer of **3** has the anti conformation. The syn and anti conformations of **3** were also investigated by ^{1}H NMR with a chiral lanthanide shift reagent. The formation of diastereomeric complexes of the C_2-symmetric anti isomers of **3** exhibiting anisochronous signals was observed in the presence of (+)-Eu(tfc)$_3$, whereas the signals of the methyl protons of the meso form are downfield-shifted but remain isochronous; see Supporting Information.

SCHEME 2. Possible Transmetalation Pathways during the Second Catalytic Cycle of the Pd-Catalyzed Stille Coupling of 1-Bromo-8-(2-methyl-4-quinolyl)naphthalene 12 and Stannane 9



quinolyl/naphthyl axis causes interconversion of the three stereoisomers of **2** and **3** (Figure 3). We were pleased to find that the stereoisomers are conformationally stable at room temperature but expected isomerization to occur at higher temperature.

Screening of a number of chiral HPLC columns revealed that the three isomers of **2** are well separated on a Chiralpak AD column. The high selectivity of this column allowed us to separate the two anti isomers and the syn isomer of **2** by semipreparative HPLC. Slow syn/anti interconversion of **2** was observed at elevated temperature and the diastereomerization and enantiomerization process of **2** in hexanes at 71.0 °C was monitored by chiral HPLC at room temperature.[20] Integration and quantification with individual UV response factors of *anti*-**2** and *syn*-**2** allowed us to calculate the change of the isomer composition over time (Figure 4a). The concentration of *syn*-**2** increased quickly to 7.5% within the first 3 h and then changed very slowly since its conversion to the anti isomers increased significantly relative to its rate of formation. The fast initial increase of the concentration of the intermediate syn isomer followed by a slow increase to its final concentration at equilibrium is indicative of consecutive, reversible reactions. After 46 h, a steady state, i.e., constant concentrations of all isomers of **2**, was observed. The final composition at equilibrium was determined as 44.4% of each chiral anti isomer and 11.2% of the meso syn isomer. The

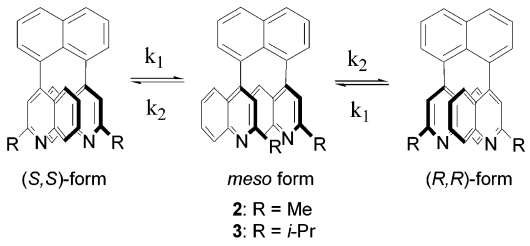


FIGURE 3. Interconversion of anti and syn isomers of **2** and **3**.

mathematical solution for the kinetics of consecutive, first-order, reversible reactions involving three species such as the syn/anti intereconversion of **2** has been reported by Vriens.[21] Curve-fit analysis with eq 2 allowed determination of the rate constant for the anti to syn isomerization, k_1 (Figure 4b):

$$x = C_1 e^{D_1 k_1 t} + C_2 e^{D_2 k_1 t} + \frac{\alpha}{K_1 K_2 E_2} \qquad (2)$$

where k_1 = rate constant of the anti to syn interconversion, K_1 = equilibrium constant for the formation of the syn isomer, K_2 = equilibrium constant for the formation of either anti isomer, and α = ratio of forward rate constants (k_2/k_1) for the consecutive, reversible, first-order reactions. C_1, C_2, D_1, D_2, and E_2 are constants.[22]

Having determined the syn/anti ratio and thus the equilibrium constants for the isomerization of **2**, we were able to determine the rate constants for the reversible isomerization reactions, k_1 and k_2, as 3.45×10^{-5} s^{-1} for the anti → syn and as 1.38×10^{-4} s^{-1} for the syn → anti interconversion, respectively. As expected, the observed isomerizations proved to obey first-order kinetics. The Gibbs activation energy, $\Delta G^{\ddagger}$, for the isomerization of **2** was calculated from the Eyring equation as 116.0 (112.1) kJ/mol for the conversion of the anti (syn) to the syn (anti) isomer.

The diastereoisomers of **3** were resolved via preferential crystallization of the anti isomers from diethyl ether, but attempts to separate the enantiomers of *anti*-**3** by chiral HPLC were not successful. Initially, we attempted to study the conformational stability of **3** by variable-temperature NMR monitoring of diastereotopic signals

(19) The factor 2 in eq 1 accounts for the two enantiomeric anti isomers of **2** and **3**.

(20) See Supporting Information for the HPLC analysis of the interconversion of one isolated anti isomer of **2** to its syn diastereoisomer and subsequently to its enantiomer.

(21) Vriens, G. N. *Ind. Eng. Chem.* **1954**, 669−671.

(22) See Supporting Information for mathematical treatment of the kinetics of consecutive, reversible, first-order reactions.

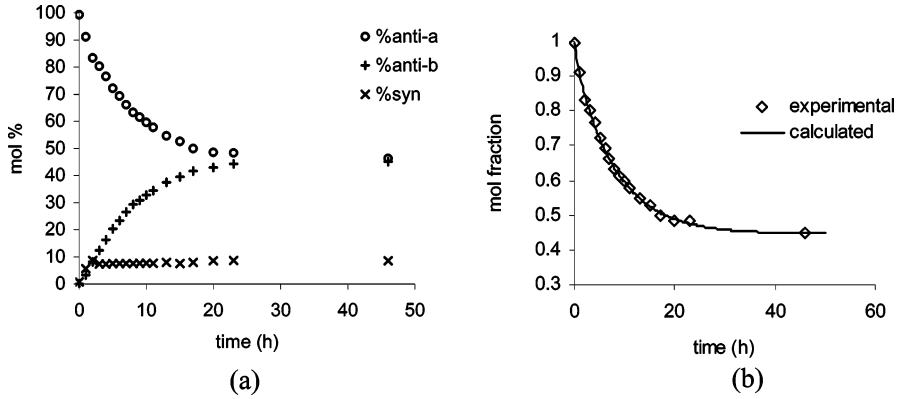


FIGURE 4. (a) Plot of mole percent vs time for the isomerization of **2** at 71.0 °C determined by HPLC analysis with a Chiralpak AD column. *Anti*-**a** and *anti*-**b** refer to the enantiomers of **2**. (b) Calculated curve fit based on eq 2 using the mol fraction of *anti*-**2a**.

of the isopropyl groups. However, no sign of coalescence was observed at 135 °C. We therefore decided to perform similar kinetic studies as outlined for **2**, using NMR spectroscopy to monitor the diastereoisomerization of **3** in DMSO at 66.2 °C. Mathematical treatment of the interconversion of two nondistinguishable anti isomers that isomerize via an intermediate syn isomer gave eq 3.[21] The change of diastereoisomer composition monitored by NMR is shown in Figure 5a.[23] By use of eq 3, the rate constant for the anti → syn isomerization, k_1, was determined as 2.56×10^{-5} s^{-1}. The rate constant for the syn → anti interconversion, k_2, was calculated as 1.10×10^{-4} s^{-1} (Figure 5b). At equilibrium a mixture of 10.4% *syn*-**3** and 89.6% *anti*-**3** was observed. The rotational energy barrier of **3** was determined according to the known equilibrium constant $K = k_1/k_2$ and the Eyring equation as 115.2 (111.1) kJ/mol for the conversion of the anti (syn) to the syn (anti) isomer.

$$\ln \frac{\{2A_0S_0 - S_0x_{eq} + A_0^2 - x(S_0 + x_{eq})\}x_{eq}}{(2A_0S_0 - S_0x_{eq} + A_0^2)(x_{eq} - x)} = \frac{(2A_0S_0 - 2S_0x_{eq} + A_0^2 - x_{eq}^2)}{(S_0 + x_{eq})}k_1t \quad (3)$$

$$A_0 = [anti\text{-}\mathbf{3a}]_0 = [anti\text{-}\mathbf{3b}]_0,\ S_0 = [syn\text{-}\mathbf{3}]_0$$

where $x = A_0 - A_t$ (concentration of A at time t).

$$A = \frac{\{2A_0S_0 - S_0x_{eq} + A_0^2 - x(S_0 + x_{eq})\}x_{eq}}{(2A_0S_0 - S_0x_{eq} + A_0^2)(x_{eq} - x)}$$

As mentioned above, isomerization proceeds via a T-shaped transition state exhibiting the alkyl group of the rotating quinolyl ring pointing toward the adjacent quinolyl moiety. One might expect that 1,8-bis(2,2′-diisopropyl-4,4′-diquinolyl)naphthalene **3** would exhibit a higher conformational stability than 1,8-bis(2,2′-dimethyl-4,4′-diquinolyl)naphthalene **2**, as a consequence of increased steric hindrance between the isopropyl group

(23) Note that, in contrast to our HPLC analysis of the isomerization of **2**, NMR analysis of the interconversion of **3** does not distinguish between its anti isomers, and thus requires a different mathematical treatment to afford k_1 and k_2.

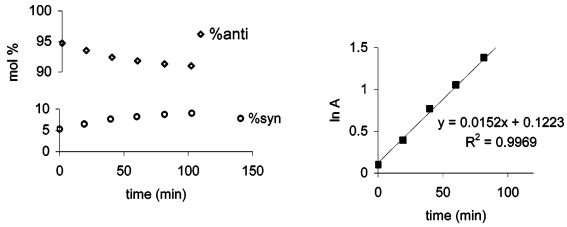


FIGURE 5. (a) Plot of mole percent vs time for the diastereoisomerization of **3** at 66.2 °C determined by ^{1}H NMR integration of the methyl groups of *anti*- and *syn*-**3**. (b) Plot of ln *A* against time for the first-order isomerization of **3** at 66.2 °C as defined in eq 3.

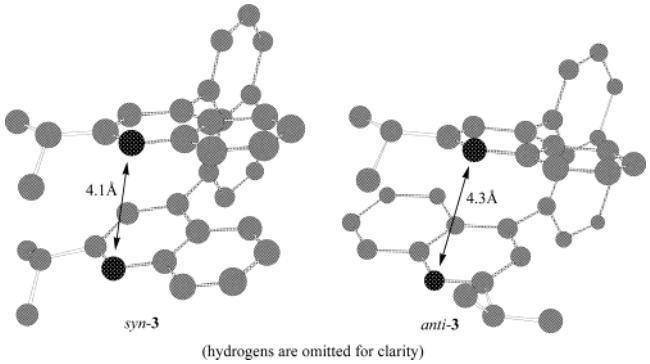


FIGURE 6. Ground states of *syn*- and *anti*-**3** optimized by PM3 calculations.

of the rotating ring and the peri-quinolyl ring during the rotation. However, the rotational energy barrier for 1,8-bis(2,2′-dimethyl-4,4′-diquinolyl)naphthalene **2** was observed to be slightly higher than for its diisopropyl analogue **3**. We assume that steric and electronic repulsion between the 2-alkylquinolyl groups in the cofacial ground state of **2** and **3** are at least as important as steric effects in the transition state. The steric repulsion between the isopropyl group and the peri-quinolyl ring of **3** might result in a significant destabilization of the syn and anti ground states (Figure 6). The slightly lower Gibbs standard activation energy observed for the isomerization of **3** might thus be attributed to a higher destabilization of the ground states of both isomers, which

possibly overcompensates the increased steric hindrance in the T-shaped transition state of **3**. However, electronic factors are also likely to exhibit significant effects on the conformationally stability of diquinolylnaphthalenes.

Conclusions

An efficient synthetic route toward highly congested 1,8-diquinolylnaphthalenes via CuO-promoted Stille cross-coupling of 1,8-dibromonaphthalene and 4-alkyl-9-trimethylstannylquinolines has been developed. The syn and anti isomers of 1,8-bis(2,2′-dimethyl-4,4′-diquinolyl)-naphthalene **2** and 1,8-bis(2,2′-diisopropyl-4,4′-diquinolyl)-naphthalene **3** have been isolated for investigation of their stereodynamic properties. The rotational energy barrier to anti/syn and syn/anti isomerization of **2** was determined as 116.0 (112.1) kJ/mol by chiral HPLC analysis of the enantiomerization and diastereomerization of enantiopure **2** at 71 °C. NMR Analysis of the diastereomerization of racemic *anti*-**3** to its syn isomer revealed an energy barrier of 115.2 (111.1) kJ/mol for the conversion of the anti (syn) to the syn (anti) isomer at 66.2 °C. All isomerizations were found to obey reversible first-order kinetics. The slightly lower conformational stability of **3** was attributed to destabilization of the ground state as a consequence of increased steric repulsion between the cofacial 2-isopropylquinolyl rings. Because of their unique geometry and stereodynamic properties, C_2-symmetric 1,8-dihetarylnaphthalenes such as *anti*-**3** are promising candidates for the development of new enantioselective sensors and chiral switches. Chiral recognition studies with 1,8-diquinolylnaphthalenes as stereodynamic sensors are currently underway in our laboratories.

Acknowledgment. C.W. gratefully acknowledges the National Science Foundation for a CAREER award. We thank Mark Olsen, GlaxoSmithKline Pharmaceuticals, for LC/APCI/MS analysis of compounds **2**, **3**, and **11**. The generous supply of POPd by Combiphos Catalysts, Inc., New Jersey, is acknowledged.

Supporting Information Available: HPLC chromatograms obtained for monitoring the isomerization of **2**, derived equations for reversible reactions obeying first-order kinetics and NMR analysis of the isomers of **3** using Eu(tfc)$_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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