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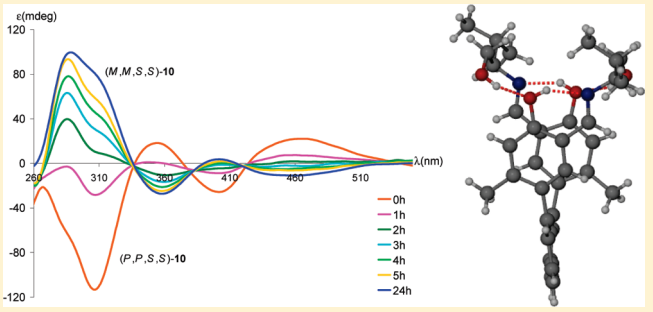
Synthesis, Conformational Stability, and Asymmetric Transformation of Atropisomeric 1,8-Bisphenolnaphthalenes

Marwan W. Ghosn and Christian Wolf*

Department of Chemistry, Georgetown University, Washington, D.C. 20057, United States

Supporting Information

ABSTRACT: Highly congested, axially chiral 1,8-bisphenolnaphthalenes have been synthesized in 75% overall yield by palladium-catalyzed Suzuki coupling of 1,8-diiodonaphthalene and 4-methoxy-2-methylphenylboronic acid followed by regioselective formylation and deprotection. The C_2-symmetric *anti*-stereoisomers of 1,8-bis(2′-methyl-4′-hydroxy-5′-formylphenyl)naphthalene, **5**, and its diimine analogues **9** and **10** were found to be significantly more stable than the corresponding *syn*-isomer. Crystallographic analysis revealed that this stereochemical preference results from a unique intramolecular hydrogen bonding motif and concomitant minimization of steric repulsion. Triaryl **5** proved stable to rotation about the chiral axes at room temperature and the enantiomers were isolated via formation of diastereomeric diimines with (*R*)-2-amino-1-propanol and (*R*)-2-amino-3-methyl-1-butanol, respectively, chromatographic separation, and mild hydrolysis. Slow *syn*/*anti*-interconversion of **5**, **9**, and **10** was observed at enhanced temperatures and the diastereomerization and enantiomerization processes were monitored by CD and NMR spectroscopy. The Gibbs activation energy, $\Delta G^{\ddagger}$, for the isomerization of **5** was determined as 103.7 (102.4) kJ/mol for the conversion of the *anti*-(*syn*-) to the *syn*-(*anti*-)isomer at 45.0 °C. Condensation of **5** with two chiral amino alcohols generates diimines that undergo quantitative asymmetric transformation of the first kind toward the thermodynamically favored (*P*,*P*,*R*,*R*)- or (*M*,*M*,*S*,*S*)-atropisomer, respectively. The incorporation of two imino alcohol units controls the outcome of this unidirectional atropisomerization, i.e. the central chirality of the amino alcohol used induces a rigid, axially chiral triaryl scaffold with perfect stereocontrol. Accordingly, the rotational energy barrier for the conversion of (*M*,*M*,*S*,*S*)-**9** to its *syn*-isomer is significantly increased and was determined as 115.7 kJ/mol at 58.0 °C.

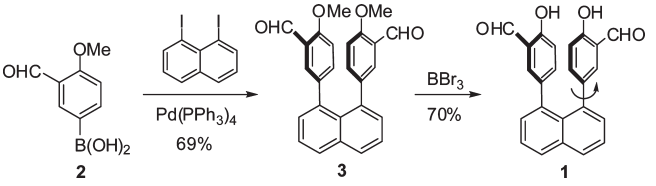


INTRODUCTION

The intriguing structure and dynamic stereochemistry of axially chiral compounds has fueled their use in asymmetric synthesis, chiral recognition, the design of microscopic devices such as molecular motors and switches, drug discovery, and other areas.[1] Undoubtedly, the exceptional diversity and the unique stereochemical, electronic, and photochemical properties of both conformationally stable and rapidly racemizing axially chiral biaryls and polyaryls have led to a wide variety of applications.[2] It is therefore not surprising that structural analysis along with the study of enantiomerization and diastereomerization processes of mono- and disubstituted naphthalenes have received significant attention.[3] Alkyl,[4] aryl,[5] and heteroaryl[6] groups have been introduced into the naphthalene framework to study the energy barrier to rotation about the naphthyl−alkyl or naphthyl−aryl bond and intramolecular interactions between proximate alkyl and aryl groups. In particular, the incorporation of two phenol rings into a rigid C_2-symmetric scaffold that is reminiscent of the successful BINOL motif has been of general interest due to potential applications in asymmetric catalysis and enantioselective sensing for a long time.[7]

In continuation of previously conducted studies with stereodynamic chiral biaryls and triaryls,[8] and 1,8-diheteroarylnaphthalene-derived sensors,[9] we recently prepared 1,8-bis(3′-formyl-4′-hydroxyphenyl)naphthalene, **1**, exhibiting two salicylaldehyde rings in the *peri*-positions of naphthalene via Suzuki coupling of 1,8-diiodonaphthalene and boronic acid **2** followed by deprotection of dialdehyde **3** (Scheme 1).[10]

Scheme 1. Synthesis of 1,8-Bis(3′-formyl-4′-hydroxyphenyl)-naphthalene, 1



Triaryl **1** undergoes fast rotation about the two aryl−aryl bonds at room temperature, which results in the interconversion of the enantiomeric *anti*-isomers via the thermodynamically less stable meso *syn*-intermediate. We realized that imine formation with amino alcohols disturbs this equilibrium and strongly favors

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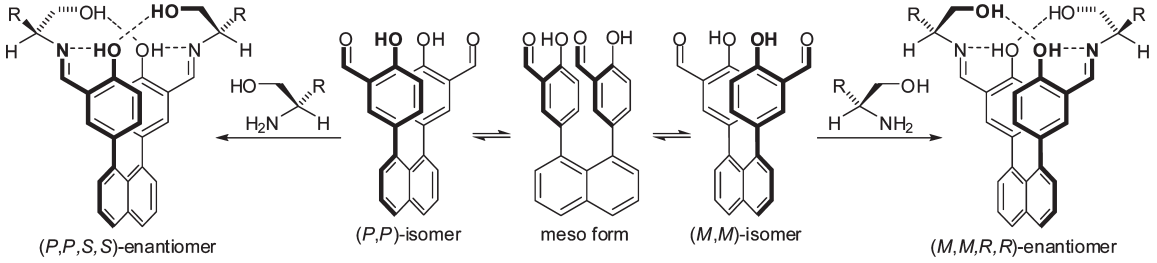
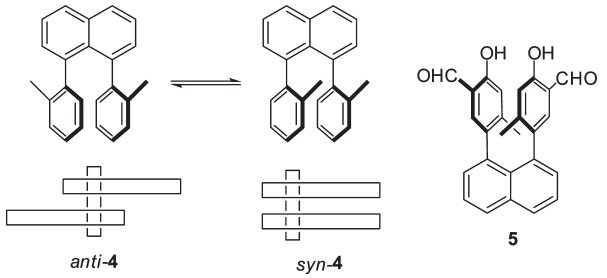
Scheme 2. Central-to-Axial Chirality Induction upon Diimine Formation with Stereodynamic Triaryl 1



Scheme 3. Structures of 4 Exhibiting *anti*-Parallel (*anti*-Isomer) and Parallel (*syn*-Isomer) 2-Methylphenyl Moieties and of 5



population of a single diastereomer that is stabilized by intramolecular hydrogen bonding (Scheme 2). The diimine formed displays strong Cotton effects at high wavelengths and NMR and crystallographic analysis showed that the central chirality of the amino alcohol substrate induces a rigid, axially chiral triaryl scaffold with perfect stereocontrol: Condensation of **1** and (*R*)-amino alcohols results in well-defined amplification of asymmetric induction and the triaryl was found to adopt an (*M*,*M*)-conformation. The opposite sense of chiral induction was observed with (*S*)-amino alcohols. We were able to demonstrate that the fast diimine formation, which is complete within 5 min, followed by in situ CD measurements allows time-efficient determination of the absolute configuration and the enantiomeric purity of the substrate used. Similar results were obtained with amino acids.[11]

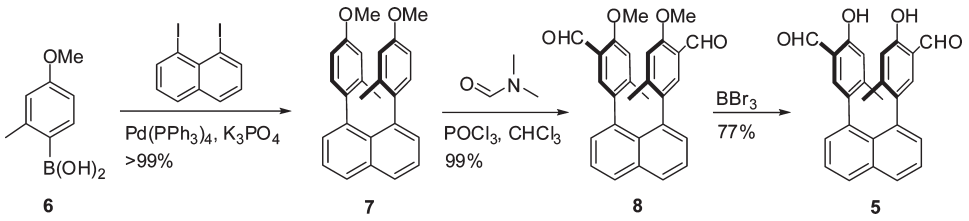
We envisioned that a less fluxional analogue of **1** would provide further insights into (a) the amplification of asymmetric induction and (b) the effect of the intramolecular hydrogen bonding on the conformational stability of the diimine derivatives and provide (c) an entry to the potential use of these compounds in enantioselective recognition and catalysis. Since Clough and Roberts estimated the energy barrier to *syn*/*anti*-diastereomerization of 1,8-bis(2-methylphenyl)naphthalene, **4**, as approximately 100 kJ/mol,[12] we expected that incorporation of methyl groups into the ortho-positions of **1** would produce conformational isomers that are stable to interconversion and separable at room temperature (Scheme 3). We therefore decided to prepare 1,8-bis(2′-methyl-4′-hydroxy-5′-formylphenyl)naphthalene, **5**, exhibiting moderate bulk adjacent to the chiral axes which should suffice to isolate and characterize the stereoisomers of this atropisomer and its diimine derivatives while racemization and diastereomerization reactions could be studied at elevated temperatures.

RESULTS AND DISCUSSION

We began the synthesis of **5** with Suzuki coupling of 1,8-diiodonaphthalene and commercially available 4-methoxy-2-methylphenylboronic acid, **6** (Scheme 4). Initially, we screened the effect of various catalysts, solvents, base, and temperature to identify suitable reaction conditions for the construction of the sterically congested scaffold of **5**. We were pleased to find that 1,8-bis(2′-methyl-4′-methoxyphenyl)naphthalene, **7**, can be obtained in quantitative amounts by using $Pd(PPh_3)_4$ as catalyst and K_3PO_4 as base in toluene. NMR analysis revealed that **7** was a 1:3 mixture of the *syn*- and *anti*-isomers. The Vilsmeier reaction with an excess of phosphorus oxychloride and dimethyl formamide then furnished 1,8-bis(2′-methyl-4′-methoxy-5′-formylphenyl)naphthalene, **8**, with 99% yield in approximately the same diastereomeric ratio. Finally, deprotection with boron tribromide gave **5** having a *syn*- and *anti*-isomer ratio of 1:4 in 77% yield.

The diastereomers of **8** were separated by column chromatography and the racemic *anti*-isomer was converted to *anti*-**5** and then to (*P*,*P*,*R*,*R*)-**9** and (*M*,*M*,*R*,*R*)-**9** by condensation with 2 equiv of (*R*)-2-amino-1-propanol. The diimine formation proceeds with quantitative yields and is completed at room temperature within 1 h. Chromatographic purification on silica gel then allowed isolation of the two diastereomeric products (Scheme 5). Heating of the diastereomeric mixture of **9** to establish thermodynamic equilibrium showed that the first eluted diimine corresponds to the more stable diastereomer, see below. The sense of amplification of asymmetric induction observed with the diimines of **1** and CD and crystallographic analysis of **5**

Scheme 4. Synthesis of 1,8-Bis(2′-methyl-4′-hydroxy-5′-formylphenyl)naphthalene, 5



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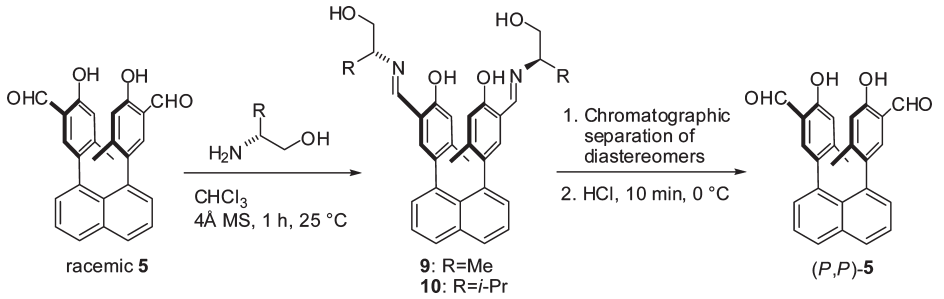
Scheme 5. Isolation of Enantiopure 5



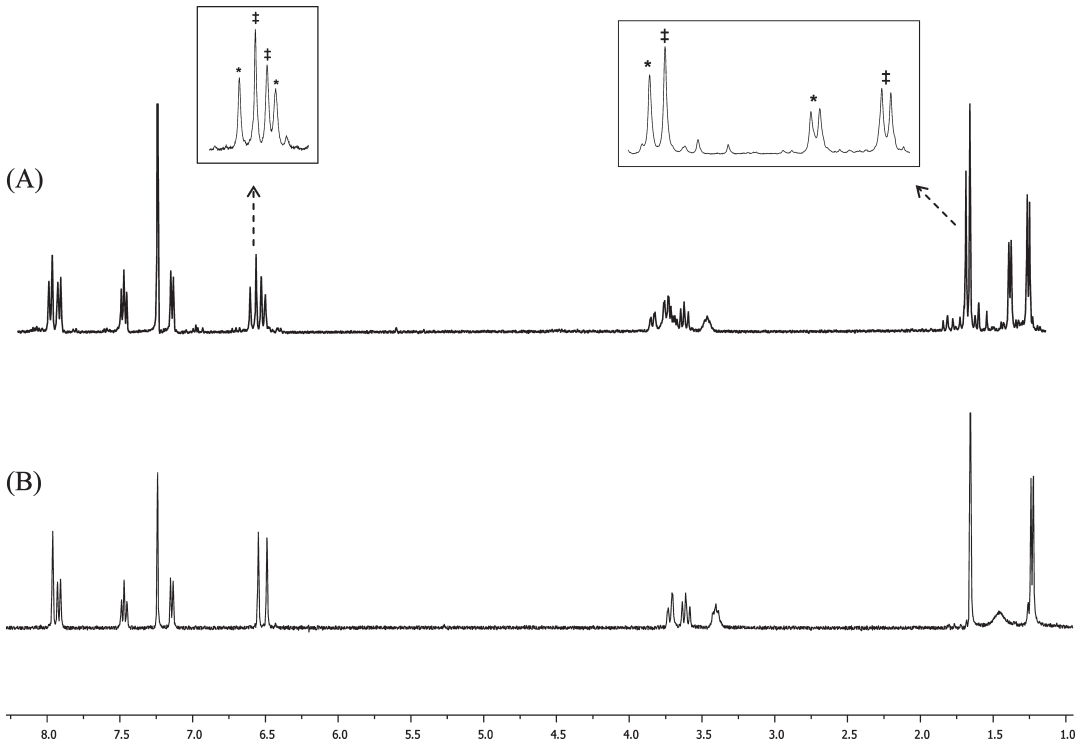


Figure 1. ^{1}H NMR spectra of diimine diastereomers obtained from racemic **5** and (*R*)-2-amino-1-propanol and quantitative conversion toward (*P*,*P*,*R*,*R*)-**9**: (A) 60 °C, 0 h, (B) 60.0 °C, 14 h; ∗, corresponds to (*M*,*M*,*R*,*R*)-**9**; ‡ corresponds to (*P*,*P*,*R*,*R*)-**9**.

and **9** suggest that (*P*,*P*,*R*,*R*)-**9** is the thermodynamically favored atropisomer. Hydrolysis of (*P*,*P*,*R*,*R*)-**9** with aqueous HCl at 0 °C afforded enantiopure (*P*,*P*)-**5** in 85% yield, with no trace of the *syn*-diastereomer based on NMR analysis. The enantiopurity of **5** was confirmed by derivatization to the corresponding (*P*,*P*,*R*,*R*)-diimine with (*R*)-2-amino-1-propanol and NMR analysis did not show any signals of the diastereomeric (*M*,*M*,*R*,*R*)-isomer.

On the basis of our experience with stereolabile **1**, which spontaneously adopts a single conformation upon diimine formation with enantiopure amino alcohols and the kinetic analysis of **4** by Clough and Roberts, we investigated the possibility to convert the atropisomeric mixture of **9** to a single isomer upon heating. Such an asymmetric transformation of the first kind would generate the thermodynamically favored diimine isomer and thus facilitate the formation of enantiopure **5** with a theoretical yield of 100% and without the need for an elaborate chromatographic separation of the equimolar mixture of (*M*,*M*,*R*,*R*)- and (*P*,*P*,*R*,*R*)-**9**. Several cases in which asymmetric transformation of the first kind was used to manipulate the diastereomeric ratio of axially chiral compounds have been reported. For example, Meyers et al. found that the stereochemical outcome of the diastereoselective oxazoline-mediated asymmetric Ullmann coupling of aryl bromides is significantly improved upon heating of the product mixture.[13] This transformation favors the formation of the desired (*P*)-atropisomer, a key intermediate for the total synthesis of permethylated tellimagrandin.[14] The same principle has been used for the deracemization of *o*-dihydroxylated biaryl ligands VANOL and VAPOL[15] and for the preparation of the aglycon of vancomycin.[16]

We realized that (*M*,*M*,*R*,*R*)- and (*P*,*P*,*R*,*R*)-**9**, formed from racemic **5** and (*R*)-2-amino-1-propanol at 25 °C, showed distinct NMR spectra, for example two doublets at 1.26 and 1.40 ppm corresponding to the imino alcohol methyl groups (Figure 1). We therefore used NMR analysis to monitor the atropisomerization process. Upon heating to 60.0 °C, the signals of the thermodynamically less favored diastereomer decreased in intensity and (*P*,*P*,*R*,*R*)-**9** with >98% de was obtained after 14 h.

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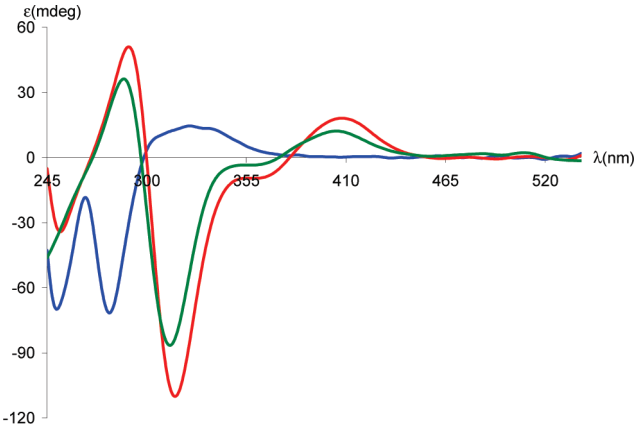


Figure 2. CD spectra of (*P*,*P*)-**5** (blue), (*P*,*P*,*R*,*R*)-**9** (red), and (*P*,*P*,*S*,*S*)-**9** (green) at 5.0×10^{-5} M in $CHCl_3$.

We previously reported that condensation of stereolabile **1** and (*R*)-2-amino-1-propanol exclusively generates the (*M*,*M*,*R*,*R*)-stereoisomer, which is the thermodynamically favored conformer due to stabilization by intramolecular hydrogen bonding and concomitant minimization of steric repulsion. Accordingly, diimine formation with (*S*)-2-amino-1-propanol gave the (*P*,*P*,*S*,*S*)-enantiomer, Scheme 2.[10] These results are in perfect agreement with the asymmetric transformation of a mixture of (*M*,*M*,*R*,*R*)- and (*P*,*P*,*R*,*R*)-**9** toward the latter diastereomer. In analogy to the amplification of asymmetric induction observed with **1**, the central chirality of the imino alcohol moiety in **9** controls the chiral amplification and induces the same sense of axial chirality.[17] Since the atropisomerization occurs with more than 99% de, it provides quantitative access to stereochemically pure **9** on the gram scale, which can then be hydrolyzed without concomitant isomerization to enantiopure **5**. Having developed a convenient procedure producing (*P*,*P*)-**5**, we were able to prepare (*P*,*P*,*R*,*R*)-**9** and (*P*,*P*,*S*,*S*)-**9**, the thermodynamically less stable diastereomer, via condensation with either enantiomer of 2-amino-1-propanol. Analyzing the CD spectra of the enantiomeric (*M*,*M*,*R*,*R*)-and (*P*,*P*,*S*,*S*)-diimines of **1**, we previously speculated that the Cotton effects are predominantly controlled by the sense of axial chirality while the chiral centers in the imino alcohol units were expected to have little or no effect on the chiroptical properties. Comparison of the CD spectra of (*P*,*P*)-**5**, (*P*,*P*,*R*,*R*)-**9**, and (*P*,*P*,*S*,*S*)-**9**, all exhibiting the same sense of axial chirality, now clearly shows that this assumption is correct (Figure 2). The three atropisomers exhibit a pronounced positive Cotton effect, and the incorporation of the diimino alcohol units results in a significant red shift. Importantly, the diastereomeric (*P*,*P*)-diimines of **9** show almost perfectly superimposable CD spectra, which underscores the overwhelming or possibly exclusive contribution of the relative orientation of the two cofacial salicylidenimine rings to the observed CD activity.[18]

Slow evaporation of a solution of enantiopure (*P*,*P*)-**5** in chloroform gave single crystals suitable for X-ray studies (Figure 3). As expected, crystallographic analysis shows that the two salicylaldehyde rings reside in almost perfectly perpendicular orientation relative to the naphthalene backbone, exhibiting a C_2-symmetric structure with a torsion angle of 5.32°. The splaying between the two phenyl rings was determined as 20.51°, which results in a centroidal phenyl-to-phenyl separation of 3.47 Å. On the basis of the enforced π-stacking of the proximate salicylaldehyde rings, the positive Cotton effect and

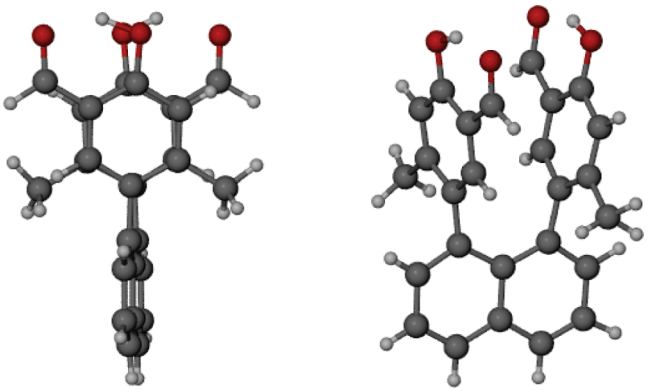
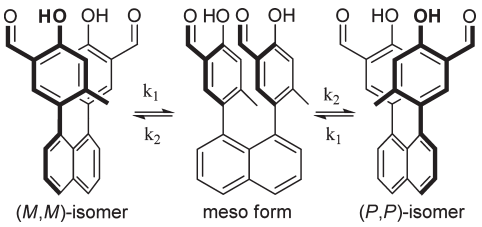


Figure 3. Different views of the crystal structure of (*P*,*P*)-**5**.

Scheme 6. Interconversion of the Stereoisomers of 5



the large CD amplitudes of (*P*,*P*)-**5** can be attributed to strong exciton coupling of the cofacial chromophores.

We then turned our attention to the kinetic analysis of **5** (Scheme 6). Interconversion of the stereoisomers of **5** requires one salicylaldehyde ring to rotate about the chiral naphthyl–phenyl axis. Accordingly, the edge of the rotating ring points toward the adjacent phenyl moiety in the transition state. In general, this process can proceed via two T-shaped transition states having the methyl group of the rotating phenyl ring either directed toward or away from the other phenyl ring.[19] The latter orientation is expected to afford significantly less steric hindrance and is therefore the favored interconversion pathway.

A solution of (*P*,*P*)-**5** in chloroform was stirred at 45.0 °C and small aliquots were taken at 1 h intervals and diluted to 5.0×10^{-5} M for CD analysis. After 10 h, the CD signals disappeared indicating complete racemization (Figure 4). The *syn*/*anti* ratio of **5** at 45.0 °C in chloroform at equilibrium was determined by ^{1}H NMR spectroscopy as 23.4:76.6. The observed ratio corresponds to a difference in Gibbs free energy of the *anti*- and *syn*-isomers, ΔG, of 1.3 kJ/mol according to the Boltzmann eq 1.[20]

$$2N_{syn}/N_{anti} = \exp(-\Delta G^{\circ}/RT) \qquad (1)$$

Figure 5 shows the decrease of the mole fraction of (*P*,*P*)-**5** as a function of time. The mathematical solution for the kinetics of consecutive, first-order, reversible reactions involving three species such as the *syn*/*anti*interconversion of **5** has been reported by Vriens.[21] Curve fit analysis with use of eq 2 allowed the determination of the rate constant for the *anti*- to *syn*-isomerization, k_1.

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

k_1 = rate constant of the *anti*- to *syn*-interconversion, K_1 = equilibrium constant for the formation of the *syn*-isomer, K_2 = equilibrium

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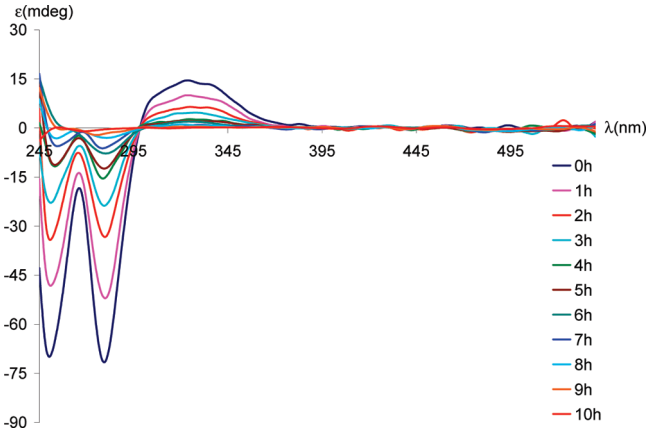


Figure 4. Decrease of the CD signal of (*P*,*P*)-**5** as a result of racemization in chloroform (6.95×10^{-4} M) at 45.0 °C. The CD spectra were collected at 25 °C at a concentration of 5.0×10^{-5} M in chloroform.

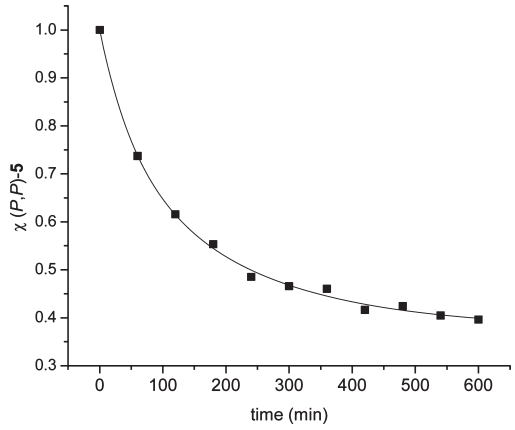


Figure 5. Change in the mole fraction of (*P*,*P*)-**5** upon heating to 45.0 °C. For conditions, see Figure 4.

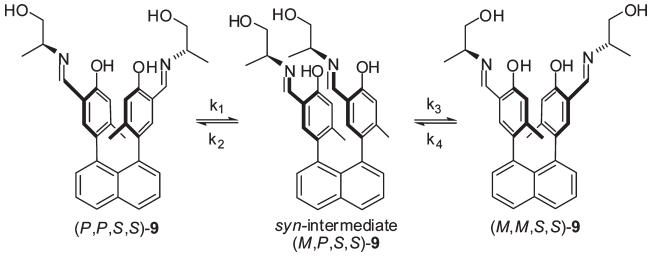
constant for the formation of either *anti*-isomer, α = ratio of forward rate constants (k_2/k_1) for the consecutive, reversible, first-order reactions, k_2 = rate constant for *syn*- to *anti*-interconversion, and C_1, C_2, D_1, D_2, and E_2 are constants.[22]

Having determined the *syn*/*anti*-ratio and thus the equilibrium constant for the isomerization of **5**, we were able to determine the rate constants for the reversible interconversion steps, k_1 and k_2, as 6.308×10^{-5} s^{-1} for the *anti* → *syn* and as 1.038×10^{-4} s^{-1} for the *syn* → *anti* interconversion, respectively. As expected, the observed isomerizations proved to obey first-order kinetics. With use of the Eyring equation, the Gibbs activation energy, $\Delta G^{\ddagger}$, for the atropisomerization of **5** was calculated as 103.7 (102.4) kJ/mol for the conversion of the *anti*-(*syn*-) to the *syn*-(*anti*-)isomer (see the SI).

The analysis of the atropisomerization of **9** is more complicated and involves four different rate constants (Scheme 7). Because CD analysis does not provide quantitative information about individual diastereomer concentrations we used NMR spectroscopy to monitor the conversion of (*P*,*P*,*S*,*S*)-**9**, which was prepared by condensation of (*P*,*P*)-**5** with 2 equiv of (*S*)-2-amino-1-propanol, to the thermodynamically stable atropisomer (*M*,*M*,*S*,*S*)-**9** via the intermediate (*M*,*P*,*S*,*S*)-isomer.

A solution of (*P*,*P*,*S*,*S*)-**9** in deuterated chloroform was heated to 58.0 °C and the isomerization was studied by integration of the

Scheme 7. Interconversion of the Atropisomers of 9



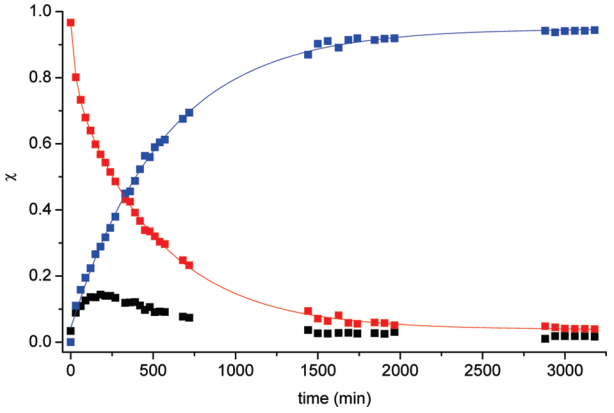


Figure 6. Analysis and curve fitting of the change in the mole fractions of (*P*,*P*,*S*,*S*)-**9** (red), (*M*,*P*,*S*,*S*)-**9** (black), and (*M*,*M*,*S*,*S*)-**9** (blue) upon heating of (*P*,*P*,*S*,*S*)-**9** to 58.0 °C in chloroform.

benzylic ^{1}H NMR signals of the three diastereomers (see the SI for details). Equilibrium was reached after 2 days, and the atropisomeric ratio was determined as 94.4:3.9:1.7 [(*M*,*M*,*S*,*S*):(*P*,*P*,*S*,*S*):(*M*,*P*,*S*,*S*)] (Figure 6). Accordingly, the thermodynamically favored (*M*,*M*,*S*,*S*)-atropisomer is more stable than the *syn*-intermediate by 11.2 kJ/mol while conversion of the latter to (*P*,*P*,*S*,*S*)-**9** is driven by only 2.4 kJ/mol. Comparison of the relative amounts of the two *anti*-isomers of **9** reveals a difference in Gibbs free energy of 8.8 kJ/mol. Crystallographic analysis of *syn*-**9** and (*P*,*P*,*R*,*R*)-**10** shows that these results can be explained by selective intramolecular hydrogen bonding and concomitant optimization of steric repulsion in (*M*,*M*,*S*,*S*)-**9**, vide infra. Following Vriens' mathematical treatment for two consecutive reversible reactions and curve fitting we then determined the individual rotational energy barriers (see the SI for details). The interconversion of (*P*,*P*,*S*,*S*)-**9** to the *syn*-diastereomer has a Gibbs activation energy, $\Delta G^{\ddagger}_{(P,P,S,S)\text{-}9 \rightarrow (P,M,S,S)\text{-}9}$, of 108.7 kJ/mol. The intermediate *syn*-isomer undergoes diastereomerization to the two *anti*-conformers and the corresponding activation energies were calculated as 106.3 ($\Delta G^{\ddagger}_{(M,P,S,S)\text{-}9 \rightarrow (P,P,S,S)\text{-}9}$) and 104.5 kJ/mol ($\Delta G^{\ddagger}_{(M,P,S,S)\text{-}9 \rightarrow (M,M,S,S)\text{-}9}$). As expected from the asymmetric transformation experiments discussed above, the energy barrier for the conversion of (*M*,*M*,*S*,*S*)-**9** to the *syn*-isomer, $\Delta G^{\ddagger}_{(M,M,S,S)\text{-}9 \rightarrow (M,P,S,S)\text{-}9}$, is significantly higher and was determined as 115.7 kJ/mol. To confirm these data, we analyzed the initial decay of (*P*,*P*,*S*,*S*)-**9** at low conversion (less than 2% completion), which can be approximately treated as an irreversible first-order reaction (see the Experimental Procedures section). We thus obtained a rotational energy barrier, $\Delta G^{\ddagger}_{(P,P,S,S)\text{-}9 \rightarrow (M,P,S,S)\text{-}9}$, of

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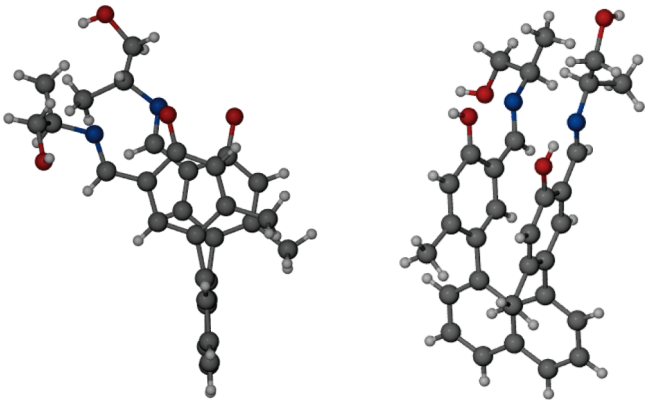

Figure 7. Single crystal structure of *syn*-**9**.

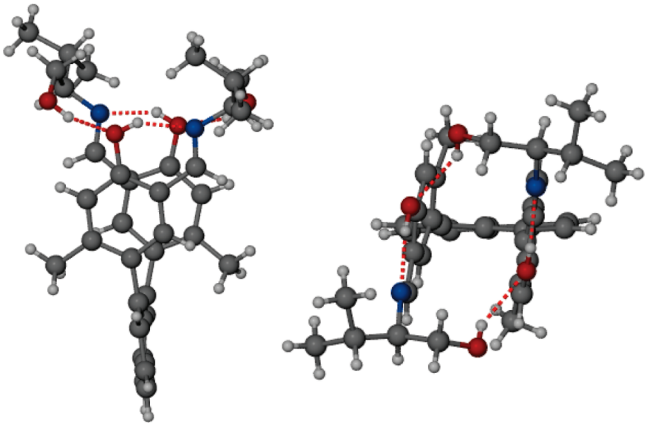

Figure 8. Different views of the crystal structure of (*P*,*P*,*R*,*R*)-**10** showing the hydrogen bonding motif.

109.2 kJ/mol, which is in very good agreement with the value determined by curve fitting.

Attempts to grow a single crystal of (*P*,*P*,*R*,*R*)- or (*M*,*M*,*S*,*S*)-**9** for crystallographic analysis were unsuccessful. But we were able to obtain a crystal structure of the *syn*-isomer (Figure 7). This atropisomer has a torsion angle of 18.33° and the splaying between the two phenyl rings is 21.09° corresponding to a centroidal phenyl-to-phenyl separation of 3.52 Å. The steric repulsion between the two salicylidenimine rings explains the low relative stability compared to the (*P*,*P*,*R*,*R*)- or the (*M*,*M*,*S*,*S*)-isomer.

To better understand the overwhelming thermodynamic stability of the (*P*,*P*,*R*,*R*)- and the (*M*,*M*,*S*,*S*)-configuration, we decided to prepare the corresponding diimine using (*R*)-2-amino-3-methyl-1-butanol (see the SI for details on the synthesis, CD analysis, etc.). Fortunately, a crystal of (*P*,*P*,*R*,*R*)-**10** was obtained by crystallization from a hexane solution (Figure 8). Crystallographic analysis revealed a torsion angle of 18.17° and splaying between the two phenyl rings was calculated as only 13.46° resulting in a centroidal phenyl-to-phenyl separation of 3.33 Å. The significantly reduced splaying compared to *syn*-**9** is quite remarkable and results from reduced steric repulsion between the imino alcohol units and additional hydrogen bonding between the alcohol groups and the phenol units in the opposite salicylidenimine ring. The arrangement of the two salicylidenimines in (*P*,*P*,*R*,*R*)-**10** allows formation of a total of four intramolecular hydrogen bonds (the phenol groups also undergo hydrogen bonding with the adjacent imines) while the steric bulk of the imino alcohol moieties is placed outside of this ring structure in the least crowded positions. The C═N···HOC$_{phenyl}$ and the C$_{aliph}$OH···OC$_{phenyl}$ hydrogen bond lengths are 1.861 and 2.178 Å, respectively.

In analogy to the results obtained with **9**, we observed quantitative asymmetric transformation of the first kind with **10**, which can be used to prepare either pure (*M*,*M*,*S*,*S*)- or (*P*,*P*,*R*,*R*)-atropisomers of these diimines. The kinetic and thermodynamic analyses of the unidirectional atropisomerization process of **9** and **10** discussed above and in the SI are in perfect agreement with the crystallographic data showing distinct stabilization of the (*P*,*P*,*R*,*R*)-isomer due to intramolecular hydrogen bonding and minimized steric repulsion between the imine moieties.

We also found that (*P*,*P*)-**5** can be used for the kinetic resolution of the enantiomers of 2-amino-1-propanol. Diimine formation of the enantiopure dialdehyde **5** and 4 equiv of the racemic substrate at room temperature followed by extraction after 5 h allowed recovery of the remaining amino alcohol in 47% yield. Chiral HPLC analysis showed that the (*S*)-amino alcohol was enriched to 54% ee, which proves the expected favored formation of (*P*,*P*,*R*,*R*)-**9** (see the Experimental Procedures section).

In conclusion, we have synthesized the first examples of axially chiral 1,8-bisphenolnaphthalenes that are stable to racemization at room temperature. The incorporation of two ortho-substituted phenol moieties into a rigid C_2-symmetric scaffold that is reminiscent of the successful BINOL motif has been of general interest due to potential applications in asymmetric catalysis and enantioselective sensing for a long time. Stereochemical analysis showed that the *anti*-stereoisomers of 1,8-bis(2′-methyl-4′-hydroxy-5′-formylphenyl)naphthalene, **5**, and its diimine analogues **9** and **10** are significantly more stable than the corresponding *syn*-isomer. Slow *syn*/*anti*-interconversion, obeying reversible first-order kinetics, of **5**, **9**, and **10** occurs at elevated temperatures and this provides a convenient entry toward enantiopure bisphenols that can be prepared on the gram scale via asymmetric transformation of the first kind. Spectroscopic NMR and CD analyses supported by crystallography of *syn*- and *anti*-1,8-bisphenolnaphthalenes showed that the incorporation of two imino alcohol units into the triaryl scaffold controls the outcome of the unidirectional atropisomerization with literally perfect stereocontrol, resulting from a unique intramolecular hydrogen bonding motif and concomitant reduction of steric repulsion. While the stereochemical bias of the atropisomers studied originates from the central chirality of the incorporated amino alcohol units, the chiroptical properties are solely determined by the sense of axial chirality. Chiral recognition studies using 1,8-bisphenolnaphthalenes as UV, CD, and fluorescence sensors are currently underway in our laboratories.

EXPERIMENTAL PROCEDURES

All reagents and solvents were used without further purification. Reactions were carried out under nitrogen atmosphere and under anhydrous conditions. 1,8-Diiodonaphthalene was prepared from 1,8-diaminonaphthalene as described in the literature.[23] Products were purified by flash chromatography on SiO_2 (particle size 0.032−0.063 mm). NMR spectra were obtained at 400 (^{1}H NMR) and 100 MHz (^{13}C NMR), using $CDCl_3$ as solvent. Chemical shifts are reported in ppm relative to TMS. For CD analysis, samples were diluted to 5.0×10^{-5} M with anhydrous chloroform and the instrument was purged with nitrogen for 20 min. Spectra were collected between 245 and 540 nm at 25.0 °C with a

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standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a bandwidth of 1 nm, a scanning speed of 500 nm s^{-1}, and a response of 0.5 s using a quartz cuvette (1 cm path length). The data were adjusted by baseline correction and binomial smoothing.

1,8-Bis(2′-methyl-4′-methoxyphenyl)naphthalene (7). A solution of 1,8-diiodonaphthalene (1.70 g, 4.5 mmol), 2-methyl-4-methoxyphenylboronic acid, **2** (2.20 g, 13.4 mmol), $Pd(PPh_3)_4$ (0.78 g, 0.67 mmol), and K_3PO_4, (4.30 g, 20.1 mmol) in 50 mL of toluene was stirred at 100 °C for 18 h. The resulting mixture was allowed to come to room temperature, quenched with water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2:hexanes 2:3) afforded 1.65 g (4.5 mmol, >99%) of off-white crystals containing *syn*- and *anti*-isomers of **7** in a ratio of 1:3.

^{1}H NMR: δ 1.76 (s, 4.6H), 1.83 (s, 1.4H), 3.69 (s, 4.4H), 3.71 (s, 1.4H), 6.28−6.39 (m, 4H), 6.66 (d, J = 8.2 Hz, 0.5H), 6.87 (d, J = 8.2 Hz, 1.5H), 7.16 (d, J = 6.8 Hz, 2H), 7.46 (dd, J = 7.2, 7.8 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H). ^{13}C NMR: δ 20.9, 21.0, 55.1, 55.2, 109.9, 110.3, 114.3, 114.4, 124.8, 125.0, 128.5, 129.0, 130.2, 130.4, 131.0, 131.6, 132.3, 134.8, 134.9, 135.2, 135.4, 136.5, 136.9, 139.5, 157.6, 158.1. Anal. Calcd for $C_{26}H_{24}O_2$: C, 84.75; H, 6.57. Found: C, 84.74; H, 6.61.

1,8-Bis(2′-methyl-4′-methoxy-5′-formylphenyl)naphthalene (8). Phosphorus oxychloride (2.9 mL, 31.2 mmol) and dimethyl formamide (2.4 mL, 31.2 mmol) were stirred in 10 mL of chloroform at room temperature for 1 h. Then, **7** (0.60 g, 1.6 mmol) was added and the mixture was refluxed at 90 °C for 48 h. It was then cooled to 0 °C, carefully quenched with water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2:EtOAc 25:1) afforded 0.69 g (1.6 mmol, 99%) of *syn*/*anti*-**8** as a white powder. The diastereomers of **8** can be separated by using flash chromatography with gradient elution starting with dichloromethane to collect the *anti*-isomer (73%), then increasing the polarity to DCM:EtOAc 15:1 to recover the *syn*-diastereomer (27%).

^{1}H NMR *anti*-**8**: δ 1.81 (s, 6H), 3.80 (s, 6H), 6.35 (s, 2H), 7.15 (d, J = 7.0 Hz, 2H), 7.38 (s, 2H), 7.50 (dd, J = 7.0, 8.2 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 10.28 (s, 2H). ^{13}C NMR: δ 21.5, 55.5, 112.1, 121.6, 125.2, 127.8, 129.2, 130.1, 130.2, 134.8, 135.4, 137.4, 146.2, 160.3, 189.0. ^{1}H NMR *syn*-**8**: δ 1.90 (s, 6H), 3.85 (s, 6H), 6.42 (s, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.15 (s, 2H), 7.49 (dd, J = 7.0, 8.2 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 10.17 (s, 2H). ^{13}C NMR: δ 21.6, 55.6, 112.0, 122.0, 125.0, 129.0, 130.3, 131.3, 131.8, 135.2, 137.5, 144.1, 159.5, 188.7. Anal. Calcd for $C_{28}H_{24}O_4$: C, 79.22; H, 5.70. Found: C, 78.99; H, 5.72.

1,8-Bis(2′-methyl-4′-hydroxy-5′-formylphenyl)naphthalene (5). To a solution of 1,8-bis(2′-methyl-4′-methoxy-5′-formylphenyl)naphthalene, **8** (0.78 g, 1.9 mmol), in 35 mL of anhydrous CH_2Cl_2 at 0 °C was added BBr_3 (11.8 mL, 11.8 mmol) dropwise and the mixture was stirred for 6 h. The reaction was carefully quenched with isopropyl alcohol followed by addition of water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2:hexanes 20:1) afforded 0.58 g of **5** (1.5 mmol, 77%) as a white solid. The *anti*/*syn*-ratio was determined as 20:1 by ^{1}H NMR spectroscopy. Enantiopure *anti*-**5** was obtained via formation of **9** or **10** as described below and hydrolysis or by asymmetric transformation of the first kind and subsequent hydrolysis (see the SI).

^{1}H NMR (*P*,*P*)-**5**: δ 1.85 (s, 6H), 6.40 (s, 2H), 7.08 (s, 2H), 7.20 (d, J = 7.1 Hz, 2H), 7.54 (dd, J = 7.0, 7.1 Hz, 2H), 7.99 (d, J = 7.0 Hz, 2H), 9.66 (s, 2H), 10.73 (s, 2H). ^{13}C NMR: δ 21.7, 117.5, 118.0, 125.3, 125.4, 129.4, 129.5, 130.6, 132.9, 135.0, 136.9, 146.5, 160.5, 195.1. Anal. Calcd for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09. Found: C, 78.69; H, 5.42.

Diimine (9). To racemic **5** (67.0 mg, 0.17 mmol) dissolved in 8 mL of $CHCl_3$ over molecular sieves (4 Å, beads, 8−12 mesh) was added 2 equiv of (*R*)-2-amino-1-propanol (25.4 mg, 0.34 mmol) and the mixture was allowed to stir for 1 h at room temperature. The mixture was then extracted with water, dried over $MgSO_4$, and concentrated in vacuo. Chromatographic purification with EtOAc:EtOH (99.5:0.5) as the mobile phase allowed the isolation of the two diastereomeric products (*P*,*P*,*R*,*R*)-**9** and (*M*,*M*,*R*,*R*)-**9** as yellow solids in quantitative yield.

^{1}H NMR (*P*,*P*,*R*,*R*)-**9**: δ 1.26 (d, J = 6.4 Hz, 6H), 1.67 (s, 6H), 3.43 (t, J = 6.4 Hz, 2H), 3.62 (m, 2H), 3.72 (dd, J = 2.0, 12.0 Hz, 2H), 6.50 (s, 2H), 6.56 (s, 2H), 7.16 (d, J = 7.0 Hz, 2H), 7.49 (dd, J = 7.0, 8.0 Hz, 2H), 7.95 (m, 4H). ^{13}C NMR: δ 17.8, 20.8, 66.8, 67.2, 114.9, 117.8, 125.1, 129.0, 129.8, 130.8, 131.2, 133.4, 134.8, 138.0, 141.9, 161.8, 164.3. Anal. Calcd for $C_{32}H_{34}N_2O_4$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.05; H, 6.98; N, 5.14.

Hydrolysis of (*P*,*P*,*R*,*R*)-9 to (*P*,*P*)-5. Pure (*P*,*P*,*R*,*R*)-**9** (43.2 mg, 0.08 mmol) was dissolved in 5 mL of 1 M NaOH, and 1 mL of aqueous HCl (12.1 M) was added dropwise at 0 °C. The mixture was allowed to stir for 10 min. The resulting suspension was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2) afforded enantiopure (*P*,*P*)-**5** (28.5 mg, 0.07 mmol) in 85% yield, with no sign of the *syn*-diastereomer based on NMR analysis. The enantiopurity of **5** was confirmed by derivatization to the corresponding diimine, using (*R*)-2-amino-1-propanol. The NMR spectrum of the condensation product showed the presence of a single diastereomer.

Diimine (*P*,*P*,*R*,*R*)-10. To racemic **5** (200 mg, 0.51 mmol) dissolved in 15 mL of $CHCl_3$ over molecular sieves (4 Å, beads, 8−12 mesh) was added 2 equiv of (*R*)-2-amino-3-methyl-1-butanol (104 mg, 1.02 mmol) and the mixture was allowed to stir at 70 °C for 16 h. Upon completion of the asymmetric transformation, the mixture was cooled to room temperature, extracted with water, dried over $MgSO_4$, and concentrated in vacuo. Chromatographic purification with CH_2Cl_2:EtOAc (1:1) as the mobile phase gave (*P*,*P*,*R*,*R*)-**10** (285 mg, 0.50 mmol) in 99.8% yield.

^{1}H NMR (*P*,*P*,*R*,*R*)-**10**: δ 0.96 (d, J = 6.8 Hz, 12H), 1.64 (s, 6H), 1.91 (m, 2H), 3.05 (m, 2H), 3.68 (t, J = 10.5 Hz, 2H), 3.87 (m, 2H), 6.50 (s, 2H), 6.59 (s, 2H), 7.16 (d, J = 7.0 Hz, 2H), 7.50 (dd, J = 7.0, 8.0 Hz, 2H), 7.94 (m, 4H). ^{13}C NMR: δ 18.6, 20.0, 20.8, 29.9, 64.2, 114.7, 118.1, 125.2, 128.9, 129.7, 130.9, 131.1, 133.2, 134.7, 138.1, 142.3, 163.0, 165.0. Anal. Calcd for $C_{36}H_{42}N_2O_4$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.18; H, 7.28; N, 4.87.

The hydrolysis of (*P*,*P*,*R*,*R*)-**10** to (*P*,*P*)-**5** was conducted as described above with (*P*,*P*,*R*,*R*)-**9** and gave enantiopure (*P*,*P*)-**5** in 80% yield.

Deracemization of 5 via Asymmetric Transformation of the First Kind with 9. Racemic **5** (10.14 mg, 0.026 mmol) was dissolved in 1.0 mL of $CDCl_3$. Molecular sieves (4 Å, beads, 8−12 mesh) were added and the mixture was stirred with 2 equiv of (*R*)-2-amino-1-propanol (3.84 mg, 0.051 mmol) for 1 h at 25 °C. After the diimine formation was complete, ^{1}H NMR analysis indicated the presence of two diastereomers—evidenced for example by the two doublets at 1.26 and 1.40 ppm (Figure 1). Upon heating to 58.0 °C, the signals of the thermodynamically less favored diastereomer decreased in intensity. In agreement with the amplification of asymmetric induction observed upon diimine formation of 1,8-bis(3′-formyl-4′-hydroxyphenyl)naphthalene with (*R*)-2-amino-1-propanol, it is assumed that the central chirality of amino alcohol controls the stereoselective outcome of this atropisomerization process. The mixture is almost entirely converted to the more stable diastereomer after 14 h (Figure 1).

Pure (*P*,*P*,*R*,*R*)-**9** (43.2 mg, 0.08 mmol) was dissolved in 5 mL of 1 M NaOH, and 1 mL of aqueous HCl (12.1 M) was added dropwise at 0 °C. The mixture was allowed to stir for 10 min. The resulting suspension was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2) afforded enantiopure (*P*,*P*)-**5** (28.5 mg, 0.07 mmol) in 85% yield, with no sign of the *syn*-diastereomer based on NMR analysis. The enantiopurity of **5** was confirmed by derivatization to the corresponding diimine, using (*R*)-2-amino-1-propanol. The NMR

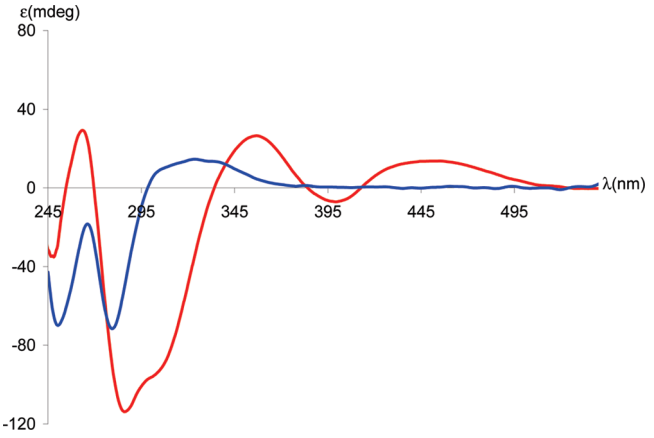


Figure 9. CD spectra of (*P*,*P*)-**5** (blue) and (*P*,*P*,*R*,*R*)-**10** (red) at 5.0×10^{-5} M in $CHCl_3$.

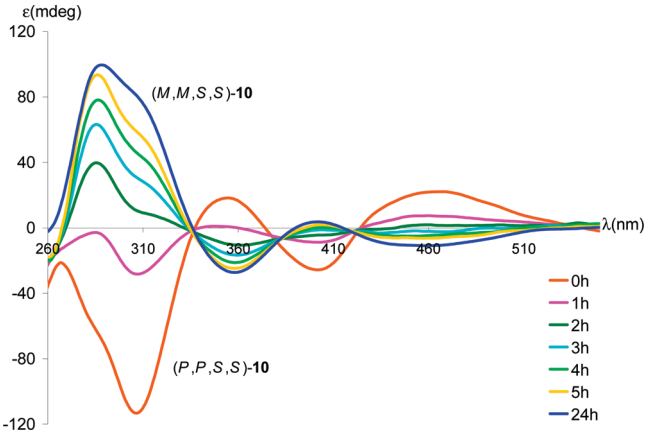


Figure 10. Change in the CD signal of (*P*,*P*,*S*,*S*)-**10** as a result of diastereomerization at 50.0 °C. The CD spectra were collected at 25.0 °C with a concentration of 5.0×10^{-5} M in $CHCl_3$.

spectrum of the condensation product showed the presence of a single diastereomer.

Deracemization of 5 via Asymmetric Transformation of the First Kind with 10. The diimine (*P*,*P*,*R*,*R*)-**10** was prepared in quantitative yields from racemic **5** and (*R*)-2-amino-3-methyl-1-butanol, using the same asymmetric transformation protocol as described above for **9**. The hydrolysis of (*P*,*P*,*R*,*R*)-**10** to (*P*,*P*)-**5** was conducted as described above with (*P*,*P*,*R*,*R*)-**9** and gave enantiopure (*P*,*P*)-**5** in 80% yield. The CD spectra of (*P*,*P*,*R*,*R*)-**10** and (*P*,*P*)-**5** are shown in Figure 9.

The unidirectional atropisomerization of (*P*,*P*,*S*,*S*)-**10** to (*M*,*M*,*S*,*S*)-**10** was monitored by CD spectroscopy and is in perfect agreement with the results obtained with **9**. Enantiopure (*P*,*P*)-**5** (10.14 mg, 0.026 mmol) was dissolved in 1.0 mL of $CDCl_3$. Molecular sieves (4 Å, beads, 8−12 mesh) were added and the mixture was stirred with 2 equiv of (*S*)-2-amino-3-methyl-1-butanol (5.52 mg, 0.051 mmol) for 1 h at 25.0 °C. The mixture was then heated to 50.0 °C. Aliquots were taken at 1 h intervals and diluted to 5.0×10^{-5} M with anhydrous $CHCl_3$ for CD analysis. After 24 h, the CD signal indicated almost complete diasteriomerization (Figure 10).

Determination of the Initial Rate Constant for the Isomerization of (*P*,*P*,*S*,*S*)-9. Enantiopure (*P*,*P*)-**5** (10.14 mg, 0.026 mmol) was dissolved in 1.0 mL of $CDCl_3$. Molecular sieves (4 Å, beads, 8−12 mesh) were added and the mixture was stirred with 2 equiv of (*S*)-2-amino-1-propanol (3.84 mg, 0.051 mmol) for 1 h at 25 °C. The mixture was then heated to 58.0 °C and ^{1}H NMR spectra were collected at short intervals to follow the decay of (*P*,*P*,*S*,*S*)-**9** (same signals as (*M*,*M*,*R*,*R*)-**9**, Figure 1) before the appearance of any (*M*,*M*,*S*,*S*)-**9** (same signals as (*P*,*P*,*R*,*R*)-**9**, Figure 1). By plotting the mole fraction of (*P*,*P*,*S*,*S*)-**9** versus time, the initial rate of the reaction can be obtained from the slope of the fitted line (Figure 11). Curve fitting to $y = A1x + B$ was performed with OriginPro 8.1, with A1 = −0.00245 and *B* = 0.8634, A2 = 0.351, with R^2 = 0.9929. The initial rate constant denoted k_1 was determined as 4.083×10^{-5} s^{-1}, $\Delta G^{\ddagger}_{(P,P,S,S)\text{-}9 \rightarrow (P,M,S,S)\text{-}9}$ = 109.2 kJ/mol.

Determination of the Rate Constants for the Isomerization of 9[20]. As described above, enantiopure (*P*,*P*)-**5** (10.12 mg, 0.026 mmol) was dissolved in 1.0 mL of $CDCl_3$, treated with 2 equiv of (*S*)-2-amino-1-propanol (3.84 mg, 0.051 mmol) for 1 h at 25 °C, and then heated to 58.0 °C. ^{1}H NMR spectra were collected at different intervals to monitor the change in the intensity of the resolved methyl signals of (*P*,*P*,*S*,*S*)-**9** (1.69 ppm), (*M*,*P*,*S*,*S*)-**9** (1.81 ppm), and (*M*,*M*,*S*,*S*)-**9** (1.66 ppm) until equilibrium was reached.

$$(P,P,S,S)\text{-}\mathbf{9} \underset{k_2}{\overset{k_1}{\rightleftarrows}} (P,M,S,S)\text{-}\mathbf{9} \underset{k_4}{\overset{k_3}{\rightleftarrows}} (M,M,S,S)\text{-}\mathbf{9}$$

The relative amounts of the three stereoisomers at equilibrium were determined as 94.4:3.9:1.7 [(*M*,*M*,*S*,*S*):(*P*,*P*,*S*,*S*):(*M*,*P*,*S*,*S*)] in $CDCl_3$ at 58.0 °C. The individual rate constants were then calculated as described in the SI.

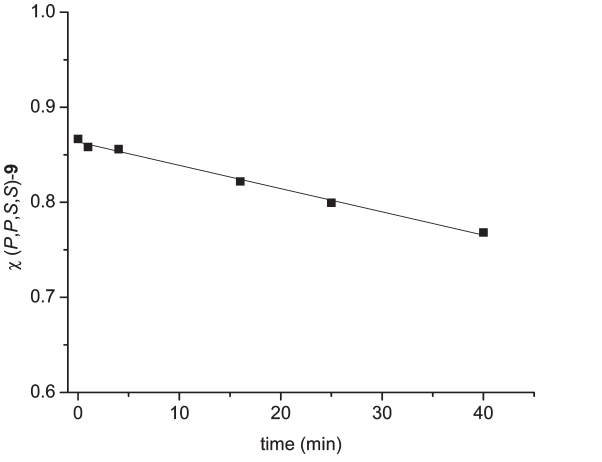
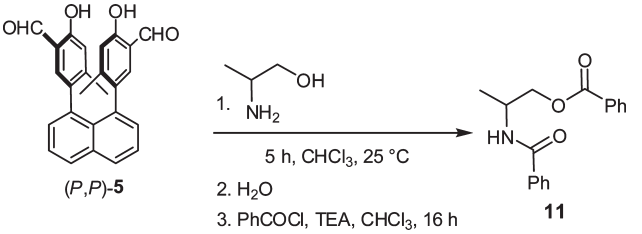


Figure 11. Plot of the mole fraction of (*P*,*P*,*S*,*S*)-**9** versus time (min).

Scheme 8. Kinetic Resolution of 2-Amino-1-propanol with (*P*,*P*)-5



Kinetic Resolution. Enantiopure (*P*,*P*)-**5** (15.89 mg, 0.040 mmol) was dissolved in 1.0 mL of anhydrous $CHCl_3$ (Scheme 8). Molecular sieves (4 Å, beads, 8−12 mesh) were added and the mixture was stirred with 4 equiv of racemic 2-amino-1-propanol (12.04 mg, 0.160 mmol) for 5 h at 25 °C. The mixture was then extracted with water, and the aqueous layer was freeze-dried to recover the unreacted amino alcohol. The crude material (6.02 mg, 0.080 mmol) was dissolved in 1.5 mL of chloroform and treated with benzoyl chloride (117.8 mg, 0.801 mmol) in the presence of triethylamine (162.2 mg, 1.60 mmol). The mixture was

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allowed to stir for 16 h, then quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2:EtOAc 9:1) afforded **11** (22.0 mg, 0.074 mmol) as a colorless oil in 93%. The ee was determined as 54% by HPLC on Chiralpak AD, using hexanes:ethanol (90:10) as the mobile phase. As expected, formation of (*P*,*P*,*R*,*R*)-**9** is favored and comparison of the HPLC chromatogram with separately prepared enantiopure samples of **11** proved that 77% of the unreacted amino alcohol had (*S*)-configuration.

Crystallization and X-ray Diffraction. Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Data were integrated and corrected with the Apex 2 program. The structures were solved by direct methods and refined with full-matrix least-squares analysis, using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameters.

A crystal of enantiopure (*P*,*P*)-**5** was obtained by slow evaporation of a solution of 5.0 mg of (*P*,*P*)-**5** in 3 mL of $CHCl_3$. Crystal structure data for (*P*,*P*)-**5**: formula $C_{26}H_{20}O_4$, M = 396.43, crystal dimensions 0.15 × 0.10 × 0.05 mm^3, tetragonal, space group $P4_3$, a = 11.7955(17) Å, b = 11.7955(17) Å, c = 28.4769(40) Å, V = 3962.10 Å^3, Z = 1, ρ_{calcd} = 1.3290 g cm^{-3}. Selected distances and angles: phenyl−phenyl (centroid to centroid), 3.470 Å; splaying angle between salicylidenimine planes, 20.51°; and torsion angle, 5.32°.

The slow evaporation of a solution of 5.0 mg of **5** and 2 equiv of (*R*)-2-amino-1-propanol in 3 mL of $CHCl_3$ afforded single crystals of *syn*-**9**. Crystal structure data for *syn*-**9**: formula $C_{32}H_{34}N_2O_4$, M = 510.62, crystal dimensions 0.120 × 0.10 × 0.07 mm^3, monoclinic, space group $P2_1/c$, a = 22.3400(21) Å, b = 6.8469(6) Å, c = 17.6753(16) Å, β = 100.956(1), V = 2654.33 Å^3, Z = 4, ρ_{calcd} = 1.2726 g cm^{-3}. Selected distances and angles: phenyl−phenyl (centroid to centroid), 3.518 Å; splaying angle between salicylidenimine planes, 21.09°; and torsion angle, 18.33°.

A crystal of (*P*,*P*,*R*,*R*)-**10** was obtained by crystallization of 100.0 mg of (*P*,*P*,*R*,*R*)-**10** from 15 mL of hexanes. Crystal structure data for (*P*,*P*,*R*,*R*)-**10**: formula $C_{32}H_{34}N_2O_4$, M = 566.73, crystal dimensions 0.10 × 0.10 × 0.05 mm^3, orthorhombic, space group $P2_1$, a = 10.8469(44) Å, b = 21.3655(86) Å, c = 13.6440(55) Å, V = 3161.99 Å^3, Z = 2, ρ_{calcd} = 1.1903 g cm^{-3}. Selected distances and angles: C═N···HOC$_{phenyl}$ hydrogen bond length, 1.861 Å; C$_{aliph}$OH···OC$_{phenyl}$ hydrogen bond length, 2.178 Å; phenyl−phenyl (centroid to centroid), 3.326 Å; splaying angle between salicylidenimine planes, 13.46°; and torsion angle, 18.17°.

■ ASSOCIATED CONTENT

Supporting Information. Details of calculations of the isomerization rate constants, thermal ellipsoid plots of the X-ray structures, and CD and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cw27@georgetown.edu.

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■ REFERENCES

(1) Wolf, C., Ed. *Dynamic Stereochemistry of Chiral Compounds*; RSC: Cambridge, UK, 2008.

(2) (a) Qiao, X.; Padula, M. A.; Ho, D. M.; Vogelaar, N. J.; Schutt, C. E.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 741–745. (b) Reetz, M. T.; Neugebauer, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 179–181. (c) Ueki, M.; Matsumoto, Y.; Jodry, J. J.; Mikami, K. *Synlett* **2001**, 1889–1892. (d) Dominguez, Z.; Dang, H.; Strouse, M. J.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 7719–7727. (e) Charbonniere, L. J.; Ziessel, R.; Montalti, M.; Prodi, L.; Zaccheroni, N.; Boehme, C.; Wipff, G. *J. Am. Chem. Soc.* **2002**, *124*, 7779–7788. (f) Wong, K.-T.; Chien, Y.-Y.; Chen, R.-T.; Wang, C.-F.; Lin, Y.-T.; Chiang, H.-H.; Hsieh, P.-Y.; Wu, C.-C.; Chou, C. H.; Su, Y. O.; Lee, G.-H.; Peng, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 11576–11577. (g) Rathore, R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832–14833. (h) Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15–32. (i) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3212. (j) Aikawa, K.; Mikami, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5455–5458. (k) Aikawa, K.; Mikami, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5458–5461. (l) Clayden, J.; Lund, A.; Vallverdu, L.; Helliwell, M. *Nature* **2004**, *431*, 966–971. (m) Reetz, M. T.; Li, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 2959–2962. (n) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427. (o) Mikami, K.; Kakuno, H.; Aikawa, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7257–7260. (p) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269–279. (q) Bringmann, G.; Scharl, H.; Maksimenka, K.; Radacki, K.; Braunschweig, H.; Wich, P.; Schmuck, C. *Eur. J. Org. Chem.* **2006**, 4349–4361. (r) Obrien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6877–6880. (s) Etxebarria, J.; Degenbeck, H.; Felten, A.-S.; Serres, S.; Nieto, N.; Vidal-Ferran, A. *J. Org. Chem.* **2009**, *74*, 8794–8797.

(3) (a) Casarini, D.; Lunazzi, L.; Macciantelli, D. *Tetrahedron Lett.* **1984**, *25*, 3641–3642. (b) Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1988**, *53*, 182–185. (c) Casarini, D.; Foresti, E.; Lunazzi, L.; Macciantelli, D. *J. Am. Chem. Soc.* **1988**, *110*, 4527–4532. (d) Casarini, D.; Davalli, S.; Lunazzi, L. *J. Org. Chem.* **1989**, *54*, 4616–4619. (e) Villani, C.; Pirkle, W. H. *Tetrahedron: Asymmetry* **1995**, *6*, 27–30. (f) Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **1997**, *62*, 3315–3323. (g) Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **1998**, *63*, 4746–4754. (h) Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **1998**, *63*, 4991–4995. (i) Casarini, D.; Mazzanti, A.; Alvarez, A. M. *J. Org. Chem.* **2000**, *65*, 3200–3206. (j) Bragg, R. A.; Clayden, J.; Morris, G. A.; Pink, J. H. *Chem.—Eur. J.* **2002**, *8*, 1279–1289. (k) Dell'Erba, C.; Gasparrini, F.; Grilli, S.; Lunazzi, L.; Mazzanti, A.; Novi, M.; Pierini, M.; Tavani, C.; Villani, C. *J. Org. Chem.* **2002**, *67*, 1663–1668. (l) Wolf, C.; Pranatharthiharan, L.; Ramagosa, R. B. *Tetrahedron Lett.* **2002**, *43*, 8563–8567. (m) Sabater, L.; Guillot, R.; Aukauloo, A. *Tetrahedron Lett.* **2005**, *46*, 2923–2926. (n) Sabater, L.; Lachaud, F.; Hureau, C.; Aukauloo, A. *Tetrahedron Lett.* **2006**, *47*, 569–571. (o) Carreno, M. C.; Gonzalez-Lopez, M.; Latorre, A.; Urbano, A. *J. Org. Chem.* **2006**, *71*, 4956–4964. (p) Ghosn, M. W.; Wolf, C. *J. Org. Chem.* **2010**, *75*, 6653–6659. (q) Basheer, M. C.; Oka, Y.; Mathews, M.; Tamaoki, N. *Chem.—Eur. J.* **2010**, *16*, 3489–3496.

(4) (a) Fields, D. L.; Regan, T. H. *J. Org. Chem.* **1971**, *36*, 2986–2990. (b) Fields, D. L.; Regan, T. H. *J. Org. Chem.* **1971**, *36*, 2991–2995. (c) Fields, D. L.; Regan, T. H. *J. Org. Chem.* **1971**, *36*, 2995–3001.

(5) (a) House, H. O.; Magin, R. W.; Thompson, H. W. *J. Org. Chem.* **1963**, *28*, 2403–2406. (b) House, H. O.; Bashe, R. W. *J. Org. Chem.* **1965**, *30*, 2942–2947. (c) House, H. O.; Bashe, R. W. *J. Org. Chem.* **1967**, *32*, 784–791. (d) House, H. O.; Campbell, W. J.; Gall, M. *J. Org. Chem.* **1970**, *35*, 1815–1819. (e) House, H. O.; Koepsell, D. G.; Campbell, W. J. *J. Org. Chem.* **1972**, *37*, 1003–1011. (f) Cozzi, F.; Cinquini, M.; Annunziata, R.; Dwyer, T.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 5729–5733. (g) Cozzi, F.; Cinquini, M.; Annunziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330–5331. (h) Cozzi, F.; Siegel, J. S. *Pure Appl. Chem.* **1995**, *67*, 683–689. (i) Cozzi, F.; Ponzini, F.; Annunziata, R.; Cinquini, M.; Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1019–1020. (j) Pieters, G.; Terrasson, V.; Gaucher, A.; Prim, D.; Marrot, J. *Eur. J. Org. Chem.* **2010**, 5800–5806.

(6) (a) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *Tetrahedron* **1996**, *52*, 8703–8706. (b) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *J. Org. Chem.* **1996**, *61*, 7018–7021. (c) Maier, N. M.; Zoltewicz, J. A. *Tetrahedron* **1997**, *53*, 465–468. (d) Zoltewicz, J. A.;

Maier, N. M.; Fabian, W. M. F. *J. Org. Chem.* **1997**, *62*, 2763–2766. (e) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *J. Org. Chem.* **1997**, *62*, 3215–3219. (f) Zoltewicz, J. A.; Maier, N. M.; Lavieri, S.; Ghiviriga, I.; Abboud, K. A. *Tetrahedron* **1997**, *53*, 5379–5388. (g) Ernst, L.; Sakhaii, P. *Magn. Reson. Chem.* **2000**, *38*, 559–565. (h) Lavieri, S.; Zoltewicz, J. A. *J. Org. Chem.* **2001**, *66*, 7227–7230.

(7) (a) Pritchard, R. G.; Steele, M.; Watkinson, M.; Whiting, A. *Tetrahedron Lett.* **2000**, *41*, 6915–6918. (b) Cross, W.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loerting, T.; Nasser, R.; Pritchard, R. G.; Steele, M.; Watkinson, M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 459–467. (c) Steele, M.; Watkinson, M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 588–598. (d) Thirsk, C.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loerting, T.; Nasser, R.; Pritchard, R. G.; Steele, M.; Warren, J. E.; Whiting, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1510–1519.

(8) (a) Wolf, C.; Ghebramariam, B. T. *Tetrahedron: Asymmetry* **2002**, *13*, 1153–1156. (b) Wolf, C.; Tumambac, G. E. *J. Phys. Chem. A* **2003**, *107*, 815–817. (c) Tumambac, G. E.; Wolf, C. *J. Org. Chem.* **2004**, *69*, 2048–2055. (d) Tumambac, G. E.; Mei, X.; Wolf, C. *Eur. J. Org. Chem.* **2004**, 3850–3856. (e) Wolf, C. *Chem. Soc. Rev.* **2005**, *34*, 595–608. (f) Tumambac, G. E.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 2930–2938. (g) Wolf, C.; Xu, H. *Tetrahedron Lett.* **2007**, *48*, 6886–6889.

(9) (a) Mei, X.; Wolf, C. *Chem. Commun.* **2004**, 2078–2079. (b) Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2004**, *126*, 14736–14737. (c) Tumambac, G. E.; Wolf, C. *Org. Lett.* **2005**, *7*, 4045–4048. (d) Mei, X.; Martin, R. M.; Wolf, C. *J. Org. Chem.* **2006**, *71*, 2854–2861. (e) Liu, S.; Pestano, J. P. C.; Wolf, C. *J. Org. Chem.* **2008**, *73*, 4267–4270. (f) Mei, X.; Wolf, C. *Tetrahedron Lett.* **2006**, *47*, 7901–7904. (g) Wolf, C.; Liu, S.; Reinhardt, B. C. *Chem. Commun.* **2006**, 4242–4244. (h) Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13326–13327.

(10) (a) Watkinson, M.; Whiting, A.; McAuliffe, C. A. *J. Chem. Soc., Chem. Commun.* **1994**, 2141. (b) Ghosn, M. W.; Wolf, C. *J. Am. Chem. Soc.* **2009**, *131*, 16360–16361.

(11) Ghosn, M. W.; Wolf, C. *Tetrahedron* **2010**, *66*, 3989–3994.

(12) Clough, R. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 1018–1020.

(13) (a) Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 3061–3062. (b) Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 3259–3262. (c) Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1999**, *121*, 2762–2769.

(14) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577–2580.

(15) (a) Zhang, Y.; Yeung, S.-M.; Wu, H.; Heller, D. P.; Wu, C.; Wulff, W. D. *Org. Lett.* **2003**, *5*, 1813–1816. (b) Yu, S.; Rabalakos, C.; Mitchell, W. D.; Wulff, W. D. *Org. Lett.* **2005**, *7*, 367–369.

(16) (a) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700–2704. (b) Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2704–2708. (c) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 3226–3227. (d) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004–10011.

(17) Please note that the (*M*,*M*)-scaffold in **1** corresponds to the (*P*,*P*)-conformation in **5** and **9** because the presence of the *o*-methyl groups in the latter results in a change in the CIP priorities.

(18) It is noteworthy that the CD amplitudes of the less stable (*P*,*P*,*S*,*S*)-**9** diastereomer are slightly diminished compared to (*P*,*P*,*R*,*R*)-**9**. This is probably due to noticeable atropisomerization of (*P*,*P*,*S*,*S*)-**9** to its (*M*,*M*,*S*,*S*)-diastereomer, i.e. it is likely that the CD spectra obtained with (*P*,*P*,*S*,*S*)-**9** and (*P*,*P*,*R*,*R*)-**9** only differ because the former was not perfectly diastereomerically pure.

(19) Wolf, C., Ed. *Dynamic Stereochemistry of Chiral Compounds*; RSC: Cambridge, UK, 2008; p 89.

(20) The factor 2 in eq 1 accounts for the two enantiomeric *anti*-isomers of **5**.

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

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

(23) House, H. O.; Koepsella, D. G.; Campbel, W. J. *J. Org. Chem.* **1972**, *37*, 1003–1011.