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Controlling Axial Conformation in 2-Arylpyridines and 1-Arylisoquinolines: Application to the Asymmetric Synthesis of QUINAP by Dynamic Thermodynamic Resolution

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Abstract: Unlike related biphenyl compounds, 2-arylpyridines and 1-arylisoquinolines can be induced to adopt preferentially one of two axial conformations by the presence of a sulfinyl substituent adjacent to the Ar−Ar bond. In the case of more substituted biaryls, the compounds are atropisomeric, and thermodynamic selectivities of about 4:1 may be attained on heating. In the case of less hindered compounds, conformer ratios of up to 20:1 may be achieved. Preferred conformations are deduced by comparison of experimental CD spectra with those derived from theory. The conformational preferences induced by the sulfoxides may be exploited in the asymmetric synthesis of atropisomers, including the ligand QUINAP, by dynamic resolution under thermodynamic control.

Introduction

While stereoselective synthesis has traditionally aimed to control the configuration at new stereogenic centers, comparable control over the conformation of single bonds is now also a realizable aim.[1−3] The orientation of single bonds in extended, open chain compounds falls under the control of a combination of steric and electronic effects, and careful choice of substitution pattern can favor population of a small number, or even just one, of the many alternative conformers.[1] Conformational control in acyclic systems has allowed problems of remote stereochemical control to be addressed rationally.[4,5] In a related context, we have shown that single C−C, C−N, or C−O bonds linking two π-systems (such as those of aromatic amides, ethers, and ureas) may be orientated reliably by the appropriate positioning of nearby substituents.[2,6−8] Interactions between the dipoles associated with the two functional groups allow the conformation of atropisomeric and near-atropisomeric molecules to be controlled.[5,9] Such strategies have been used in the asymmetric synthesis (by dynamic resolution under thermodynamic control, or "dynamic thermodynamic resolution"[10]) of atropisomeric amides[11−13] and diaryl ethers.[14]

The most effective controlling groups have been those with the greatest associated dipoles,[6] with sulfoxides reigning supreme in applicability:[7,11,14] not only are the conformational

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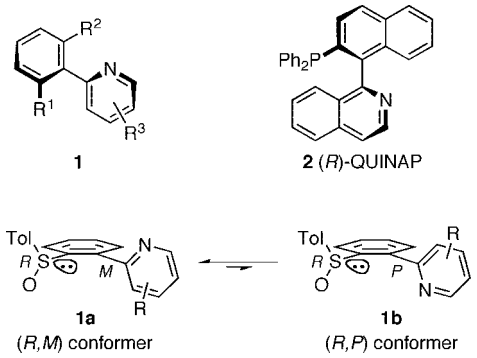
Scheme 1. 2-Arylpyridines and 1-Arylisoquinolines: Conformation and Conformational Preference.[a]



[a] *M* axial conformer is favoured as a result of interaction between axis and sulfoxide centre.

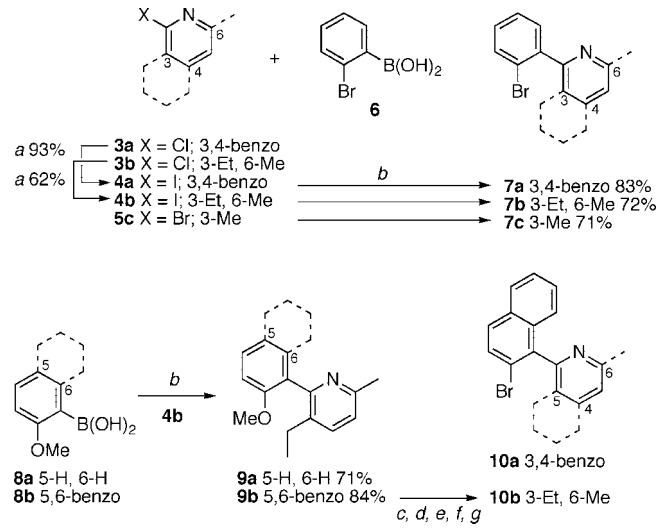
selectivities provided generally high, but they are also easy to introduce in enantiomerically pure form and easy to displace by a variety of substitution or oxidation methods. Unfortunately however, even with sulfoxides the level of control achievable in comparable biphenyl systems is only poor,[2] because of the weakness of the dipole associated with the Ar−Ar axis. This limitation has curtailed the extension of methods for conformational control to the synthesis of biaryl atropisomers, which of course form the majority of those atropisomers considered useful.

In this paper we show that conformational control is however achievable in an important subset of biaryl compounds, namely those based on the 2-arylpyridine structure **1** (Scheme 1), which includes the chiral monophosphine ligand QUINAP **2**.[15] We present spectroscopic evidence that a 2-sulfinyl group induces the arylpyridine (or arylisoquinoline) axis to adopt a favored conformation in solution, as shown in Scheme 1 for **1a** (with very high selectivity in some instances), and we show that the conformational control achievable in 1-arylisoquinolines may be applied synthetically in the first asymmetric (i.e., not relying on classical resolution) synthesis of QUINAP. [16]

Synthesis of 2-Arylpyridines and 1-Arylisoquinolines. 2′-Bromo-2-arylpyridines **7a-c** were made by palladium-catalyzed coupling of 2-bromophenylboronic acid **6** with 1-iodoisoquinoline **4a**, 2-iodopyridine **4b** or commercially available 2-bromopyridine **5c**. The former two were made from the corresponding chloropyridines **3** by TMS-promoted substitution of Cl by I.[17] (Scheme 2).

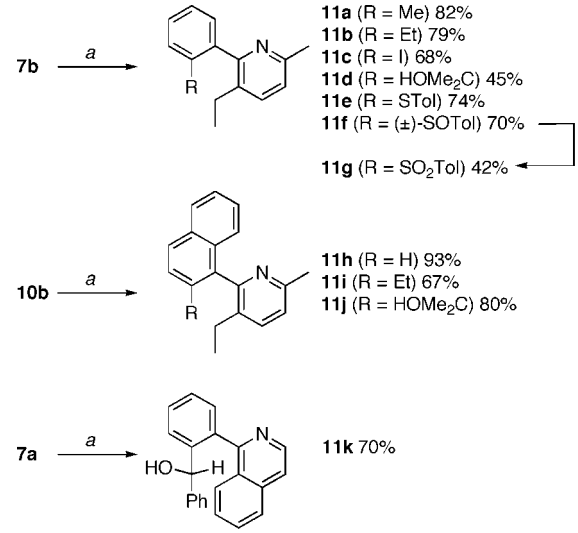
Iodopyridine was also coupled[16] with 2-methoxyarylboronic acids **8a** and **8b** to yield methoxyphenylpyridine **9a** and 1-naphthylpyridine **9b**. The methoxy substituent of **9b** was converted via a multistep sequence[18] to the bromo substituent of **10b**. **10a** was made by a variant of the method reported by Knochel.[19]

Scheme 2. Synthesis of Bromophenylpyridines[a]



[a] (*a*) $ClSiMe_3$, NaI, EtCN, Δ, 15 h; (*b*) $Pd(OAc)_2$, (0.03 equiv), PPh_3 (0.3 equiv), K_2CO_3, 1,2-diethoxyethane, Δ, 18 h; (*c*) BBr_3, $CHCl_3$, Δ, 16 h (99%); (*d*) Tf_2O, DMAP, CH_2Cl_2, 0−20 °C, 6 h (95%); (*e*) $Ph_2C{=}NH$, $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, THF, 65 °C, 15 h (46%); (*f*) NaOAc, $NH_2OH.HCl$, MeOH, 20 °C, 1.5 h (85%); (*g*) *t*-BuONO, $CuBr_2$, MeCN, 0−65 °C, 1 h (95%).

Scheme 3. Further Substituted 2-Arylpyridines[a]



[a] (*a*) 1. *n*-BuLi, THF, −78 °C 2. Electrophile (see Supporting Information). (*b*) *m*-CPBA, CH_2Cl_2.

For studies of barriers to rotation, a series of aryl pyridines were required: these were made by bromine−lithium exchange[20] from **7a, 7b** and **10b**, and quenching with a range of electrophiles, as detailed in Scheme 3. 2-Substituted phenylpyridines **11a-f** and 2-substituted naphthylpyridines **11 h-j** were obtained in this way; racemic sulfoxide **11f** was oxidized to sulfone **11g**. The hydroxy-substituted isoquinoline **11k** was obtained from **7a**.

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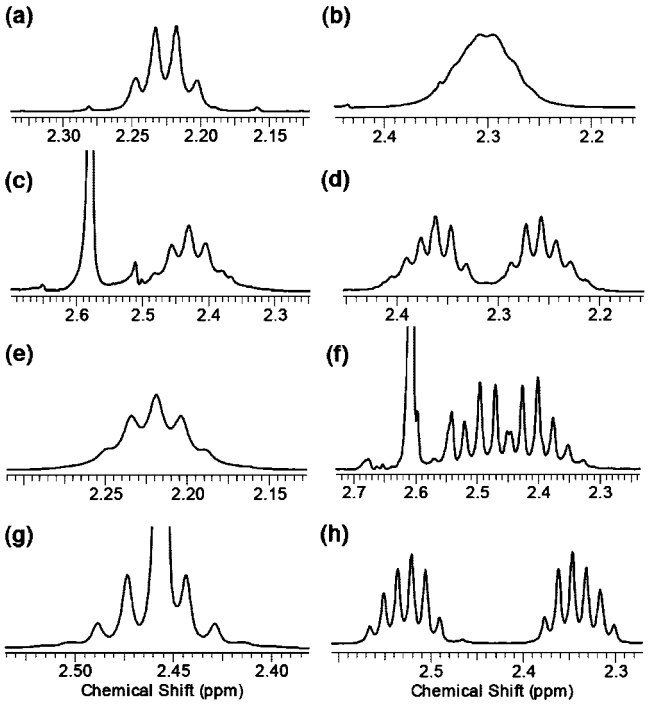

Figure 1. ^{1}H NMR ($CDCl_3$, 23 °C) CH_2Me peaks of arylpyridines 11. (a) **11a** (R = Me); (b) **11b** (R = Et); (c) **9a** (= **11**, R = OMe) (d) **11c** (R = I); (e) **7b** (= **11**, R = Br); (f) **11d** (R = CMe_2OH); (g) **11e** (R = STol); (h) **11g** (R = SO_2Tol).

Rotational Barriers in 2-Arylpyridines and 1-Arylisoquinolines. Multiply ortho substituted biphenyls were the first reported class of atropisomers,[21] and extensive empirical and theoretical data is available on barriers to rotation in biphenyl derivatives.[22] By contrast, barriers to rotation in arylpyridines have been reported for only a few compounds.[23]

The ^{1}H NMR spectra of ethyl substituted arylpyridines **7b**, **9a**, **11a**−**d**, **11g** and **11h,** each of which bears one other ortho substituent, show features characteristic of compounds exhibiting restricted bond rotation[24] (Figure 1). In some cases, the methylene group of the ethyl substituent appeared broadened to a greater or lesser degree, while in others it appeared as a fully resolved diastereotopic ABX_3 system, indicating chirality, and hence slow interconversion between enantiomeric conformers, on the NMR time scale. Slow rotation on the NMR time scale was also evident in the spectrum of **11k**, which displays two *diastereoisomeric* conformers in an approximately 1:1 ratio. **11k** appears as a single spot by TLC however, suggesting that the conformers interconvert too fast to be separable (see below).

Variable temperature NMR experiments[24] allowed us to evaluate activation parameters for rotation about the arylpyridine bond of **7b**, **9a**, **11a**−**d**, **11g** and **11h**. Spectra were recorded on a Varian 500 MHz spectrometer equipped with a VT probe, with a temperature range of −90 to 150 °C, using d_8-toluene as the NMR solvent. For spectra close to the coalescence temperature T_c, the line shape of the ABX_3 system was simulated using the gNMR modeling package. Optimal fitting allowed a rate constant (k) for bond rotation to be estimated at each of temperatures. The values of k were used to construct an Eyring plot, from which values for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were obtained. Inserting the values for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ into the Gibbs free energy equation ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$) enabled the barrier to rotation ($\Delta G^{\ddagger}$) to be calculated at temperature T. Setting T to a standard temperature (298 K) allowed the barriers to rotation for the various arylpyridines to be compared. Calculating the half-life of racemisation ($t_{1/2}$) gave another point of reference, and these values are reported in Table 1.

Barriers to bond rotation of these 2,6′ disubstituted arylpyridines all fell within the range 57−68 kJ mol^{-1}, with a clear dependence of the barrier on steric bulk of the substituents. Importantly for the discussion below, at temperatures below 0 °C, all Ar-py bond rotations were slow on the NMR time scale (ie all spectra fell into the slow exchange regime below 0 °C).

Conformational Control by Sulfinyl Substituents 1: Equilibration of Atropisomers. Bromoisoquinoline **10a** and bromopyridine **10b** were treated under conditions analogous to those shown in Scheme 3 to give aryllithiums which, on addition of (1*S*,2*R*,5*S*,R_S)-(+)-menthyl toluenesulfinate **12**[25] returned pairs of diastereoisomeric sulfoxides (*R*,*M*)- and (*R*,*P*)-**13** and (*R*,*M*)- and (*R*,*P*)-**14** (Scheme 4) in enantiomerically pure form and in an approximately equimolar ratio: the diastereoisomeric atropisomers were separated by chromatography and isolated each in approximately 50% yield.[26]

Remarkably, the pairs of diastereoisomers exhibited a huge difference in their R_F values, and the identity of the more polar of the diastereoisomers of **13** was established by X-ray crystallography as (*R*,*P*) (Figure 2).[27] Although we were unable to obtain crystals of sufficient quality for X-ray analysis from either diastereoisomer of **14**, we assign their stereochemistry by analogy with the corresponding polar diastereoisomer of **13**.

Related isoquinolines have barriers to bond rotation in the region of 115 kJ mol^{-1} [23] corresponding to half-lives to epimerisation or racemisation in the order of months at ambient temperature but only minutes at 100 °C. We expected therefore that at raised temperatures, the two diastereoisomers of **13** and of **14** would interconvert, and that on attainment of equilibrium we would be able to quantify the difference in stability between the two diastereoisomers. Sulfoxide diastereoisomer (*R*,*P*)-**14** was dissolved in anhydrous d_6-toluene and heated at 90 ± 3 °C under a nitrogen atmosphere. A ^{1}H NMR spectrum of the solution was taken periodically to monitor the interconversion of the diastereoisomers (Figure 3a). Over a period of 24 h, (*R*,*P*)-**14** equilibrated to the thermodynamically more stable (*R*,*M*)-**14** diastereoisomer. A final equilibrated ratio of 10:1 in favor of (*R*,*M*)-**14** was attained by refluxing the solution for a number of hours. The mixture was purified by flash column chromatography to return (*R*,*M*)-**14** in 89% yield and (*R*,*P*)-**14** in 11% yield. The purified sulfoxide (*R*,*M*)-**14** was then likewise refluxed in toluene to promote equilibration of the diastereoisomers, which returned the previously observed equilibrium ratio

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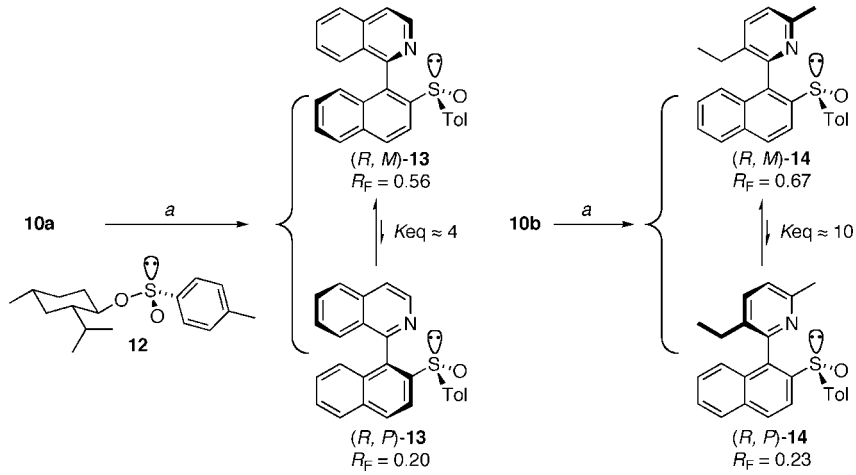
(26) Concurrently with our work, Knochel reported the use of sulfoxides for the synthesis of QUINAP by classical resolution; see ref 19.
(27) The X-day crystallographic data for *(R,P)*-**13** has been deposited with the Cambridge Crystallographic Database, deposition number 716802.

Table 1. Activation Parameters for a Series of Arylpyridines Bearing Two Ortho Substituents

Entry	Aryl Pyridine	R =	T_c/ °C[a]	$\Delta G^{\neq}$ / kJ mol^{-1} [b]	$t_{1/2}$ / s [c]
1	**11a**	2-Me	~ 0	58.0	0.003
2	**11b**	2-Et	~ 10	60.2	0.006
3	**9a**	2-OMe	~ 20	61.5	0.010
4	**11c**	2-I	~ 40	62.2	0.014
5	**11h**	2,3-Benzo	~ 30	63.0	0.020
6	**7b**	2-Br	~ 50	65.7	0.060
7	**11d**	2-C(CH$_3$)$_2$OH	~ 65	66.6	0.086
8	**11g**	2-SO$_2$Tol	~ 90	67.7	0.131

[a] Coalescence temperature. [b] $\Delta G^{\ddagger}$ calculated at 298 K. [c] Half-life for enantiomerization calculated at 298 K.

Scheme 4. Synthesis and Equilibration of Naphthylsulfoxides[a]



[a] (*a*) 1. *n*-BuLi, THF, −78 °C; 2. **12**. R_F values determined in 1:1 EtOAc: petroleum ether.

of 10:1 in favor of sulfoxide (*R*,*M*)-**14**. A kinetic analysis[28] of the evolution of the composition of a mixture of the atropisomers of **14** starting from pure (*R*,*P*)-**14** (Figure 4a) allowed us to establish that the half-life for attainment of equilibrium at 90 °C is 6 h, corresponding to barriers to epimerisation of 121 kJ mol^{-1} for (*R*,*P*)-**14** and 129 kJ mol^{-1} for (*R*,*M*)-**14**.

Treatment of (*R*,*P*)-**13** in the same way also led to equilibration (Figure 3b), though more slowly: the half-life for attainment of equilibrium was 37 h at 90 °C (Figure 4b), corresponding to barriers to epimerisation of 127 kJ mol^{-1} for (*R*,*P*)-**13** and 131 kJ mol^{-1} for (*R*,*M*)-**13**. The final equilibrium ratio of (*R*,*M*)-**13**:(*R*,*P*)-**13** was only 4:1, in contrast with the 10:1 ratio observed for **14**.

Direct comparisons of rates of bond rotation with the reported[23] related compound bearing a methoxy group in the place of the *p*-tolylsulfinyl substituent suggest that the sulfinyl group raises the barrier relative to the methoxy group by something in the region of 5−10 kJ mol^{-1}. For steric or electronic reasons, bond rotations in sulfinyl-substituted compounds are evidently slower than in the equivalent methoxy-substituted ones, a fact which has bearing on the discussion below.

Density functional calculations were performed on **13**. Starting from the crystal structure of *(R,P)*-**13** the geometry was fully optimized at the B3LYP/6−31G** level using the Gaussian suite of programs.[29] Figure 5a shows the structure obtained.

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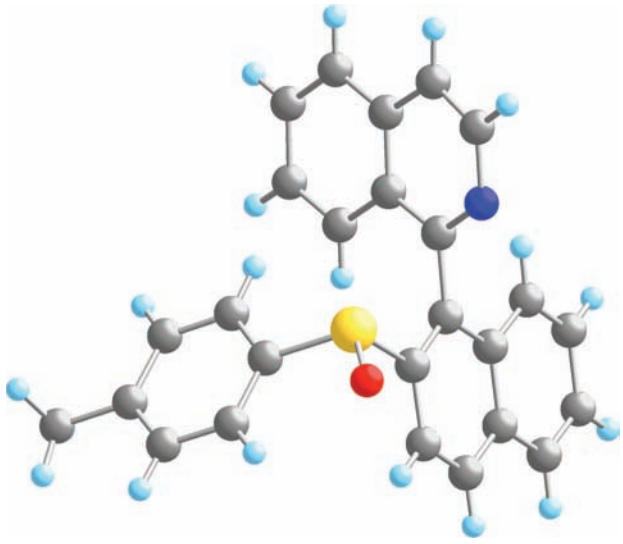


Figure 2. X-ray crystal structure of *(R,P)*-**13**.[27]

The dihedral angle between the arene C=N bond and the plane of the aryl ring carrying the S atom is calculated to be 71.6° (compared to 70.5° in the crystal structure). Following this, the *(R,M)*-**13** structure was obtained by rotating the same dihedral through 180° and fully reoptimizing. Figure 5b shows the structure obtained. The final value for this dihedral angle obtained for the minimized *(R,M)*-**13** structure is −80.8°. The *(R,M)*-**13** structure is calculated to be 11.9 kJ mol^{-1} lower in energy than the *(R,P)*-**13** structure. The addition of solvation in methanol, through the polarizable continuum model (PCM), lowers this difference to 7.0 kJ mol^{-1}. Reoptimization in methanol yielded a small further lowering to 5.6 kJ mol^{-1}, a value which would give rise to a ratio of 5.8:1 *(R,M)*-**13**: *(R,P)*-**13** at 110 °C (the observed value is 4:1).

The more polar diastereoisomer turns out to be the one in which the C−N and S−O dipoles appear to be aligned in rather more parallel fashion (Figures 1 and 5a) than in the less polar diastereoisomer, in which the dipoles are able to oppose one another (Figure 5b). In accordance with this observation, the dipole moments calculated for **13** are 5.26 D for *(R,P)*-**13** (the more polar diastereoisomer) and 3.94 D for *(R,M)*-**13** (the less polar diastereoisomer).

Conformational Control by Sulfinyl Substituents 2: Equilibration of Conformers. Less sterically encumbered bromopyridines **7a**−**c** were converted to their sulfoxide derivatives **15a**−**c** in a similar way (Scheme 5) by halogen-lithium exchange and quench with (1*S*,2*R*,5*S*,R_S)-(+)-menthyl toluenesulfinate **12**.[25] On the basis of the barriers for rotation determined for related compounds (Table 1), the sulfoxide **15a** can be expected to have a barrier to Ar-py rotation lying somewhere between 61 kJ mol^{-1} (the value for methoxy-substituted **9a**) and 68 kJ mol^{-1} (the value for sulfone **11g**), with **15b** and **15c** being broadly similar. Sulfoxides **15** will thus not display atropisomerism at ambient temperature (for which barriers in excess of 90 kJ mol^{-1} are required)[30] but instead should consist of diastereoisomeric conformers which interconvert but nonetheless fall into the slow exchange régime by NMR.[24] As for **11k**, which is related to **15c** and also bears a chiral substituent, we expected to observe in their NMR spectra, if not at ambient temperature then (depending on the barrier to aryl-pyridine

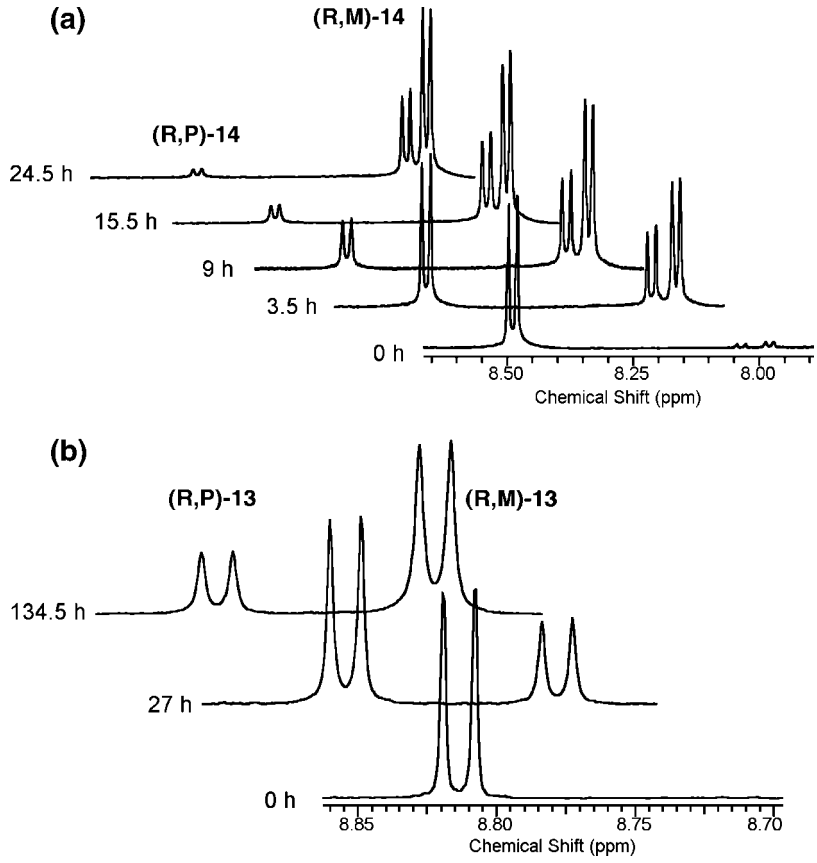


Figure 3. (a) Evolution with time of the ^{1}H NMR spectrum of a mixture of atropisomers of **14** at 90 °C in toluene (selected diagnostic peaks). (b) Evolution with time of the ^{1}H NMR spectrum of a mixture of atropisomers of **13** at 90 °C in toluene (selected diagnostic peaks).

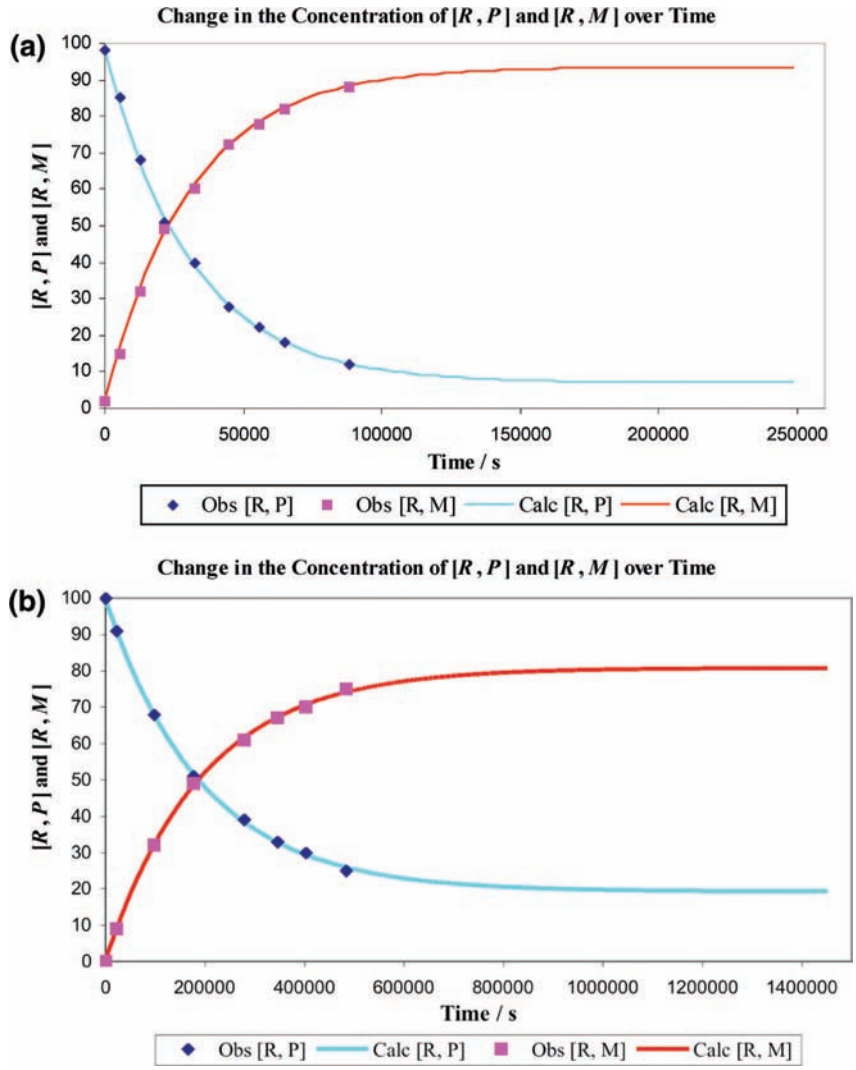


Figure 4. (a) Time course of the conversion of *(R,P)*-**14** to *(R,M)*-**14**. (b) Time course of the conversion of *(R,P)*-**13** to *(R,M)*-**13**.

rotation) certainly at temperatures below 0 °C (the lowest coalescence temperature observed arising from interconversion of the comparable *enantiomeric* conformers of **11**, Table 1) two sets of peaks arising from these diastereoisomeric conformers.

In the event, the ^{1}H NMR spectra of all three sulfoxides **15a**−**c** in various solvents and at various temperatures down to −50 °C displayed principally a single component (>90%) by NMR. We deduce therefore that one of the two conformers of **15a-c** is greatly favored over the other at equilibrium. Close inspection of each ^{1}H NMR spectrum revealed a minor set of peaks corresponding to 2−6% of the total which we assume represents the less populated conformer about the aryl-pyridine axis. On the basis that the (*R*,*M*)-atropisomers of **13** and **14** were more stable than their (*R*,*P*) atropisomers, we tentatively assign *(R,M)* stereochemistry to the major conformers of **15a**−**c** (Scheme 6).

An alternative explanation for the simplicity of the NMR spectra of **15a**−**c** could be that the conformers interconvert too rapidly to be distinguished by NMR (i.e., that the spectra in fact lie in the fast exchange régime, and that the minor sets of peaks are mere impurities). We discount this explanation for the reasons given above: most importantly, NMR spectra of **15** even at low temperature likewise showed essentially a single sharp set of peaks, while compounds **11** (Table 1) structurally similar to **15b** but without chiral substituents displayed diastereotopicity in their NMR spectra at temperatures even up to 90 °C, indicating that this family of ortho-disubstituted phenylpyridines is characterized by barriers to bond rotation easily high enough to allow identification of Ar-py conformers in solution at 25 °C.

In order to establish which of the two diastereoisomers was more stable, DFT (B3LYP/6−31G**)[29] calculations of the structure of **15b** in the gas phase were carried out. The X-ray crystal structure of (±)-**15b**[31] was used as a starting point: this was energy-minimized, and similar energy minimizations were carried out for structures resulting from successive 15° rotations about the biaryl axis of **15b**. The resulting energies are shown in Figure 6, which indicates that in the gas phase the (*R*,*M*) conformer of **15b** is more stable than the (*R*,*P*) conformer by some 9 kJ mol^{-1} (sufficient to favor the (*R*,*M*) conformer to the extent of 94:6, very close to the observed value). The calculated gas phase minimum energy conformation has a dihedral [N−C−C−C(SOAr)] angle of −68.9°, and the maxima

(30) Oki, M. *Top. Stereochem.* **1983**, *14*, 1.

(31) Clayden, J.; Fletcher, S. P.; Rowbottom, S. J. M.; Helliwell, M. Cambridge Crystallographic Database, deposition number 703502.

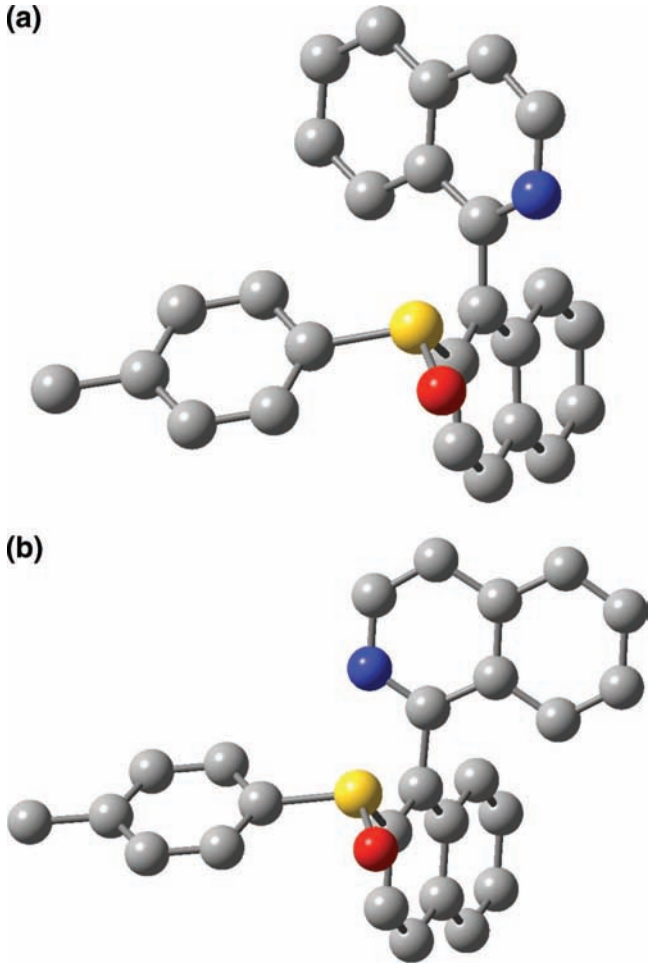


Figure 5. (a) Calculated structure of *(R,P)*-**13**. H atoms omitted for clarity. (b) Calculated structure of *(R,M)*-**13**. H atoms omitted for clarity.

on the potential energy surface arise when the rings are coplanar, and the calculated barrier of 23.4 kJ mol^{-1} for conversion of (*R*,*P*) to (*R*,*M*) suggests that they would equilibrate rapidly, becoming atropisomeric diastereoisomers only at low temperature.

Circular Dichroism Studies of Conformation. Circular dichroism (CD) spectroscopy measures the difference in adsorption coefficients for left and right circularly polarized light and has become a valuable tool for determining the absolute configuration of chiral organic molecules.[32] The technique has been widely used to establish conformation in solution, and has found particular applicability in identifying the secondary structure of proteins[33] and the stereochemistry of biaryl systems.[34] CD spectroscopy's relative sensitivity to details in geometry and a molecule's electronic signature make it useful for elucidating molecular structures, and we set out to use the technique to provide independent empirical evidence of the favored conformation of sulfoxides **15** in solution.

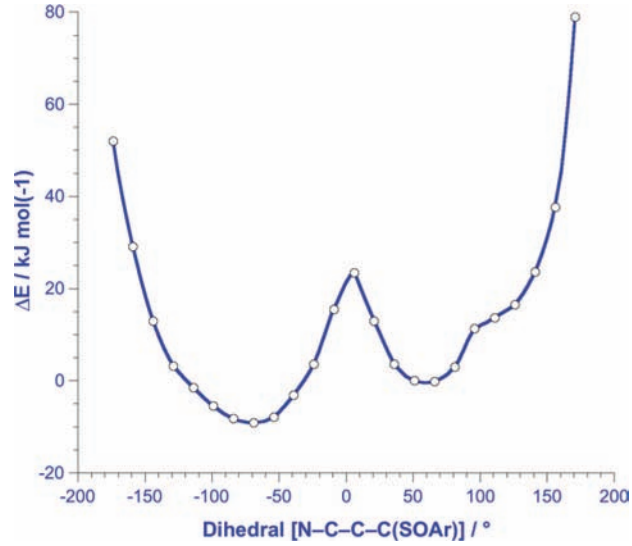


Figure 6. Fully optimized potential energy scan (B3LYP/6−31G**) along the dihedral [N−C−C−C(SOAr)] coordinate of **15b**.

To provide reference samples, and validate the method, we recorded CD spectra of (*R*,*M*)- and (*R*,*P*)-**13** (which have proven stereochemistry) in methanol (Figure 7) and in dichloroethane. The spectra of (*R*,*P*)-**13** were essentially the same in both solvents, while those of (*R*,*M*)-**13** showed a red shift in the less polar solvent.

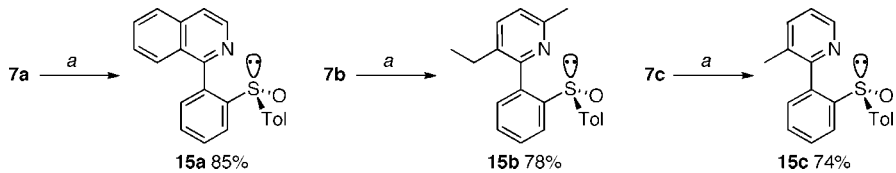
The differences between the spectra of (*R*,*M*)- and (*R*,*P*)-**13** can be ascribed to the opposite axial stereochemistry of these compounds, and we acquired the CD spectrum of **15b** (Figure 8) in the hope of establishing its conformation by correlation with either (*R*,*M*)- or (*R*,*P*)-**13.**

It was clear that conformational assignment was not possible by simple visual inspection and that more sophisticated theoretical treatments would be required.[35] Following reports in which details of molecular geometry have been elucidated by combining CD spectroscopy and theoretical analysis[36] ECD spectra of **13** were calculated using time-dependent density functional theory. The first 60 states were sought. The B3LYP functional was used with the Def2-TZVP basis set (available from the Turbomole library[37]) and the B3LYP/6−31G** geometries previously obtained.

The calculated CD spectra were compared to the results of those obtained experimentally (Figure 9a, b). Gratifyingly, the subtle difference between the CD spectra of the two isomers in the 200−220 nm range were correctly predicted by the gas phase calculations, although calculations at this level failed to reproduce the region between 270−320 nm with accuracy.

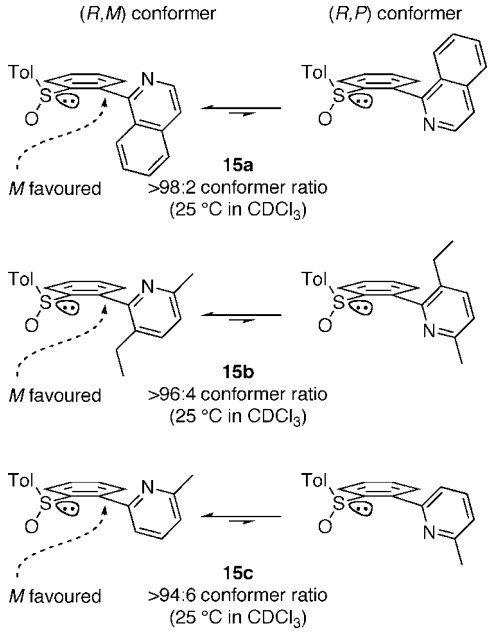
The same method was then applied to the major and minor conformers calculated for **15b**. The calculated CD spectra for *(R,M)*- and *(R,P)*-**15b** were compared with the experimental spectrum (Figure 10), and—especially when the region from

Scheme 5. Incorporation of a Sulfinyl Group into the Arylpyridines[a]



[a] (*a*) 1. *n*-BuLi (1.5 equiv), THF, −78 °C, 1 min; 2. (1*S*,2*R*,5*S*,R_S)-(+)-menthyl toluenesulfinate **12** (2.5 equiv), THF, −78 °C, 3 h; 3. MeOH, −78 to +20 °C.

Scheme 6. Conformational Preference in Sulfoxides 15a−c



270−320 nm, in which the calculation previous performed poorly, is ignored—a closer match is obtained between the observed spectrum (Figure 8) and that of *(R,M)*-**15b** (green line) than that of *(R,P)*-**15b** (brown line). We therefore conclude that **15b** adopts, in solution, a preferred *M* axial conformation, again to allow the dipole repulsion between the aryl C−N and the sulfoxide S−O bonds to be minimized.

Changing Rates of Bond Rotation by Protonation and Methylation. If the conformational preference is indeed a result of dipole interactions, then modification of the pyridine nitrogen ought to have two effects. First, it will modify the electronic nature of the system, changing the thermodynamic ratio of conformers. Second, it will alter the steric hindrance incurred on rotation about the Ar-py bond, leading to different kinetics for interconversion of the diastereoisomeric conformers.[38] We envisaged that protonation, one of the simplest methods for controlling molecular devices with an external stimulus,[39] would increase the barrier of rotation and slow rotation to a degree that we could quantify the barrier to interconversion.

The effect of protonation on the barrier to rotation of an arylpyridine was investigated with sulfoxide (*R*,*P*)-**13**, which, unprotonated, isomerizes over a period of hours upon heating at >90 °C. (*R*,*P*)-**13** was treated with 10 equiv TFA and heated in refluxing cumene at ca. 150 °C for 8 h. A 1:1 ratio of the diastereoisomers of **13** was recovered. The other diastereoisomer (*R*,*M*)-**13** remained unchanged, with no trace of (*R*,*P*)-**13**, after spending 2 days in refluxing cumene (ca. 150 °C) in the presence of 10 equiv TFA, or in acidified (TFA or 30% HCl) refluxing *n*-butanol that was heated to reflux (ca. 115 °C). The half-life for approach to equilibrium of unprotonated **13** at 150 °C can be estimated to be of the order of minutes, indicating that protonation raises the barrier to bond rotation in these compounds.

Protonation of (±)-**15b** in an NMR tube with 10 equiv of TFA in $CDCl_3$ showed broadened peaks characteristic of a compound exhibiting restricted bond rotation at room temperature. At temperatures below 0 °C, two clear sets of peaks, presumably arising from diastereoisomeric conformers **15b**H^+ (Scheme 7) were evident in a 2:1 ratio. Protonation of **15a** and **15c** similarly led to broadening of the ^{1}H NMR spectra at room temperature, with two sets of peaks being evident at temperatures below 0 °C. Barriers to rotation about the arylpyridinium bond in both the forward and reverse direction were determined by the method described above for **11**: **15aH**$^+$ exhibits a barrier for conversion of the major to the minor conformer of 63.6 kJ mol^{-1} and from the minor to the major of 62.6 kJ mol^{-1}. The corresponding values for **15bH**$^+$ are 63.0 kJ mol^{-1} and 62.7 kJ mol^{-1}. The corresponding values for **15cH**$^+$ are 57.6 kJ mol^{-1} and 55.9 kJ mol^{-1}. Corresponding estimated half-lives for equilibration at room temperature are of the order of 10^{-3} s.

Methylation of **15b** with MeOTf gave two atropisomeric diastereoisomers in a ratio dependent on conditions. These isomers were stable to interconversion: no change in the ratios was observed at 110 °C for 3 h in *n*-butanol (Scheme 8). When **15b** was dissolved in CH_2Cl_2 at −78 °C and MeOTf was added, a 3:1 ratio of diastereoisomers was obtained. Freezing a solution of **15b** in $CDCl_3$ in an NMR tube followed by addition of MeOTf to the sample and following the reaction by NMR while slowly warming produced a 7:1 ratio in favor of the same diastereomer that did not vary over time.

Enantioselective Synthesis of Biaryl Atropisomers by Dynamic Resolution under Thermodynamic Control. The control exerted over the atropisomeric axis of sulfoxides **13** and **14** can in principle be translated into a method for asymmetric synthesis of atropisomers by dynamic resolution under thermodynamic control, provided the sulfoxide "auxiliary" can be removed in a useful manner. We have previously used a similar strategy for the synthesis of atropisomeric amides[11,13] and ethers.[14] The simplest method for removal of the sulfoxide center is oxidation to a sulfone, and indeed either enantiomer of the sulfones **16** and **18** were formed on treatment of either diastereoisomer of the sulfoxides **13** and **14** with *m*-CPBA. However, even with a deficit of oxidant it proved impossible

(32) Berova, N.; Di Bari, L.; Pescitelli, G. *Chem. Soc. Rev.* **2007**, *36*, 914–931.
(33) (a) Holzwarth, G.; Doty, P. *J. Am. Chem. Soc.* **1965**, *87*, 218. (b) Greenfield, N.; Fasman, G. D. *Biochemistry* **1969**, *8*, 4108–4116. (c) Greenfield, N. J. *Anal. Biochem.* **1996**, *235*, 1–81.
(34) (a) Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, *30*, 1671–1682. (b) Bari, B. D.; Pescitelli, G.; Salvadori, P. *J. Am. Chem. Soc.* **1999**, *121*, 7998–8004. (c) Gawroñski, J.; Grycz, P.; Kwit, M.; Rychlewska, U. *Chem.−Eur. J.* **2002**, *8*, 4210–4215. (d) Tartaglia, S.; Padula, D.; Scafato, P.; Chiummiento, L.; Rosini, C. *J. Org. Chem.* **2008**, *73*, 4865–4873, and references therein.
(35) (a) Diedrich, C.; Grimme, S. *J. Phys. Chem. A.* **2003**, *107*, 2524–2539. (b) Mori, T.; Inoue, Y.; Grimme, S. *J. Phys. Chem. A.* **2007**, *111*, 4222–4234.
(36) For examples, see: (a) Bringmann, G.; Gulder, T. A. M.; Reichert, M; Gulder, T. *Chirality* **2008**, *20*, 628–642. (b) Furche, F; Ahlrichs, R.; Wachsmann, C.; Weber, E.; Sobanski, A.; Vögtle, F.; Grimme, S. *J. Am. Chem. Soc.* **2000**, *122*, 1717–1724. (c) Kondru, R. K.; Wipf, P.; Beratan, D. N. *J. Am. Chem. Soc.* **1998**, *120*, 2204–2205. (d) Gawronski, J. K.; Kwit, M.; Boyd, D. R.; Sharma, N. D.; Malone, J. F.; Drake, A. F. *J. Am. Chem. Soc.* **2005**, *127*, 4308–4319. (e) Bringmann, G.; Maksimenka, K.; Mutanyatta-Comar, J.; Knauer, M.; Bruhn, T. *Tetrahedron* **2007**, *63*, 9810–9824. (f) Schlingmann, G.; Taniguchi, T.; He, H.; Bigelis, R.; Yang, H. Y.; Koehn, F. E.; Carter, G. T.; Berova, N. *J. Nat. Prod.* **2007**, *70*, 1180–1187. (g) Bracher, F.; Eisenreich, W. J.; Mühlbacher, J.; Dreyer, M.; Bringmann, G. *J. Org. Chem.* **2004**, *69*, 8602–8608. (h) Mori, T.; Grimme, S.; Inoue, Y. *J. Org. Chem.* **2007**, *72*, 6998–7010. (I) Mori, T.; Inoue, Y.; Grimme, S. *J. Phys. Chem. A.* **2007**, *111*, 7955–8006.
(37) http://www.ipc.uni-karlsruhe.de/tch/tch1/TBL/tbl.html
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(39) Feringa, B. L. *Molecular Switches*; Wiley-VCH: Weinheim, 1995.

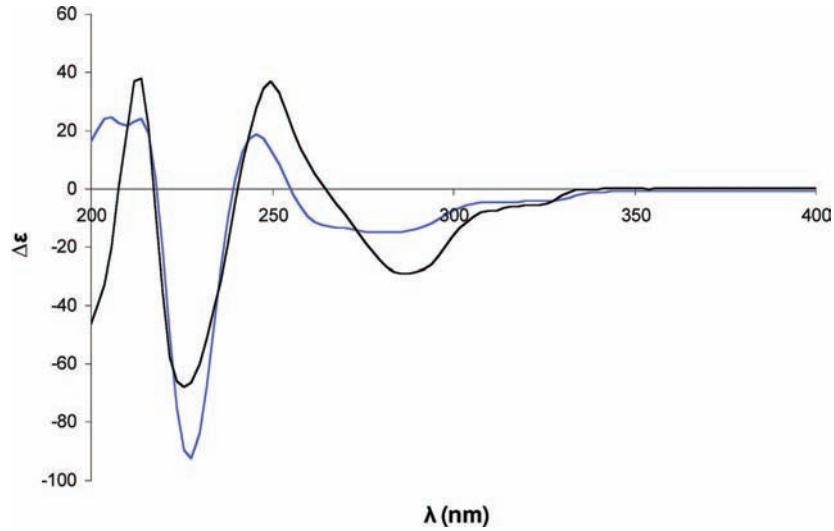


Figure 7. CD spectra of (*R,M*)-**13** (black) and (*R,P*)-**13** (blue) in MeOH.

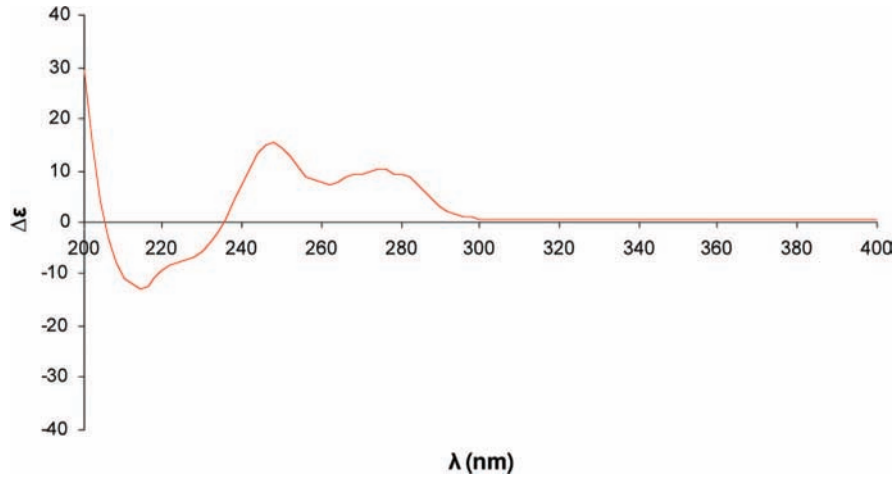


Figure 8. CD spectrum of **15b** in MeOH.

to prevent partial concomitant oxidation of the pyridine or quinoline nitrogen to the N-oxide (Scheme 9). Nonetheless, the sulfones were formed with 99:1 e.r., and as expected, the enantiomeric pairs of sulfones and their N-oxide counterparts displayed equal and opposite optical rotations.

QUINAP **2** is a chiral monophosphine ligand which has been used widely in asymmetric hydroboration, diboration, allylic alkylation, cycloadditions and hydrogenations.[15] Despite the amount of research focusing on QUINAP and related P,N biaryl ligands by numerous research groups, their asymmetric synthesis has been, with the exception of PINAP,[40] problematic. Published synthetic routes[16,19] to enantiomerically pure QUINAP involve classical resolution either of the ligand itself or of a precursor, using for example fractional crystallization of diastereomeric Pd complexes or preparative HPLC on a chiral nonracemic stationary phase.[41] During the work we describe in this paper, Knochel et al. published[19] an asymmetric synthesis of QUINAP using chromatographic separation of diastereoisomeric sulfoxides **13** in the key resolution step, which allows the synthesis of both enantiomers of QUINAP from **10a** after sulfoxide-metal exchange and quenching with a phosphorus electrophile.

Our results show that equilibration of sulfoxides **13** prior to sulfoxide-lithium exchange allows the desired diastereoisomer to be obtained in significantly greater than 50% yield. Application of the principle described in this paper converts a synthesis based on classical resolution into a truly asymmetric synthesis of QUINAP by dynamic resolution under thermodynamic control. We have previously employed sulfoxides for both purposes: we showed that sulfoxide-containing intermediates could be used in the classical resolution of binaphthyls[13] or in the dynamic resolution of atropisomeric amides or ethers.[11,13,14]

Accordingly we took the crude reaction mixture containing the unseparated diastereoisomeric sulfoxides **13** from the synthesis shown in Scheme 4 and heated them in cumene to 120 °C for 2 h. Under these conditions, equilibration gave a 4:1 mixture of diastereoisomers (^{1}H NMR spectroscopy or HPLC) from which (*R,M*)-**13** could be isolated in 77% yield after column chromatography (Scheme 10). Knochel and coworkers coverted (*R,M*)-**13** to (*R*)-QUINAP in two steps and 60% yield.[19] Thus the total yield of this sulfoxide intermediate

(40) Knöpfel, T. E.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971–5973.

(41) For the asymmetric synthesis of aryl-pyridines using a sulfinyl group to induce asymmetry under kinetic control, see ref 23. For other methods, see: (a) Kakiuchi, F.; Le Gendre, P.; Yamada, A.; Ohtaki, H.; Murai, S. *Tetrahedron Asymmetry* **2000**, *11*, 2647. (b) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem.* **2004**, *116*, 3795–3797.

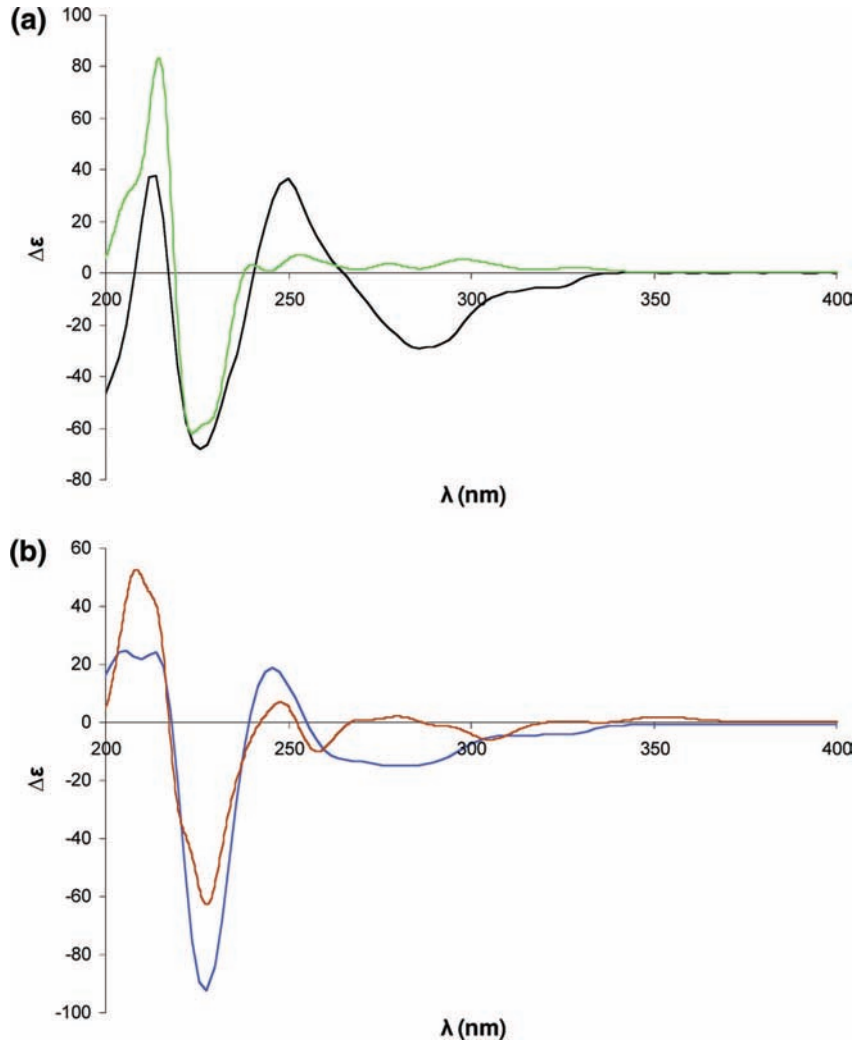


Figure 9. (a) CD spectrum of (*R*,*M*)-**13** in MeOH (black) and that calculated for (*R*,*M*)-**13** (green). (b) CD spectrum of (*R*,*P*)-**13** in MeOH (blue) and that calculated for (*R*,*P*)-**13** (brown)

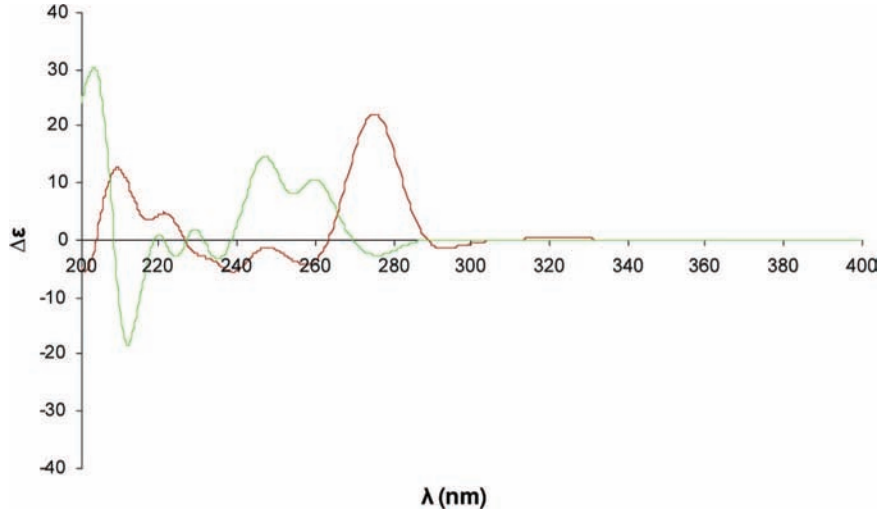
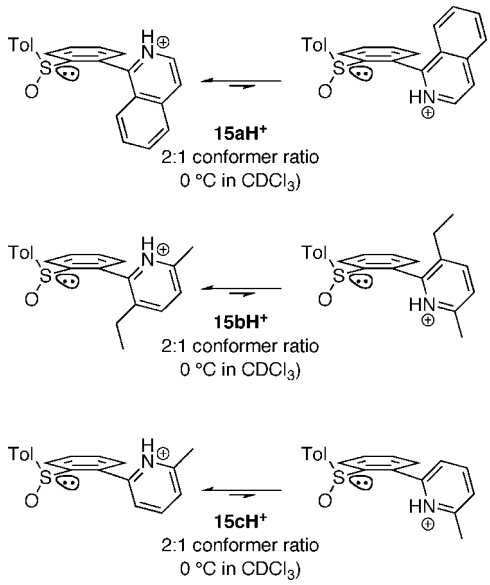


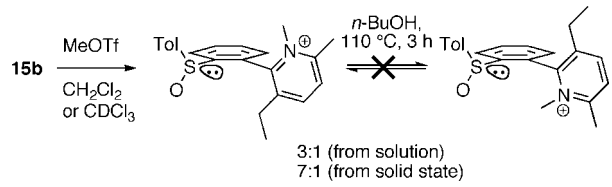
Figure 10. Calculated CD spectra for *(R,M)*-**15b** (green) and *(R,P)*-**15b** (brown).

in the synthesis of QUINAP obtained from **10a** may be increased from 47% to 77% by employing a single simple equilibration step,[42] a strategy which amounts to a dynamic resolution under thermodynamic control, or (in the terminology of Beak) a dynamic thermodynamic resolution.[10] It is however unfortunate that of all of the thermodynamic ratios we have determined, the 4:1 equilibrium ratio of **13** gives rise to much lower yields than would the 10:1 ratio of **14** or the >20:1 ratios of **15**. These

Scheme 7. Conformers of Arylpyridiniums



Scheme 8. *N*-Methylpyridinium Species

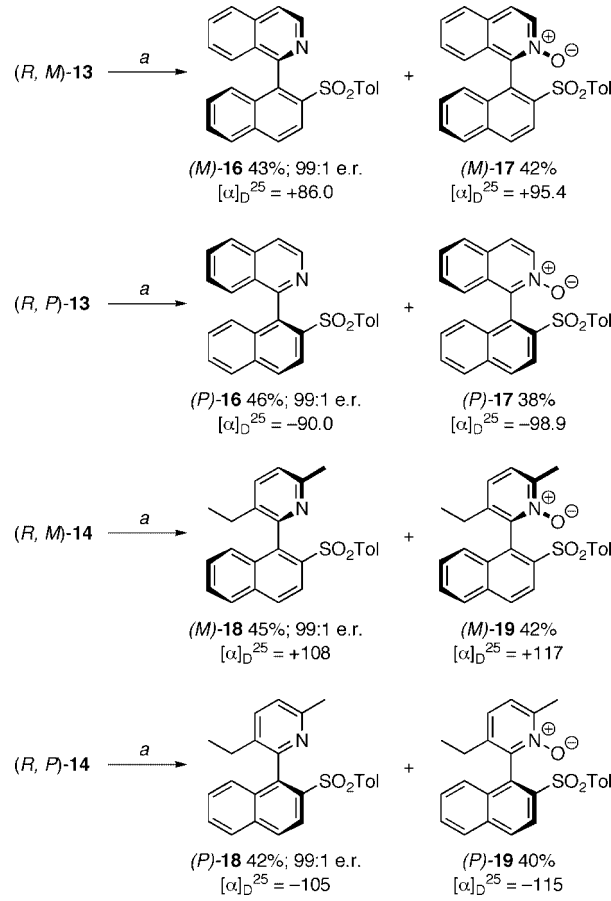


latter compounds may themselves be of value in the asymmetric synthesis of alternative P,N ligands by much more efficient dynamic thermodynamic resolution methods.

Conclusion

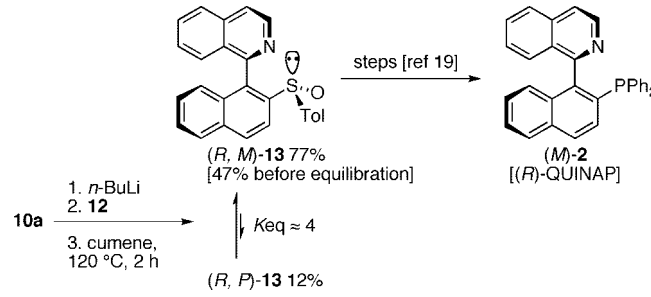
While an adjacent sulfoxide substituent provides only a weak influence over an aryl-aryl axis joining two benzenoid rings,[2] we have shown that its ability to orientate a similar axis in substituted or ring-fused 2-phenylpyridyls is much greater. Thermodynamic selectivities for one of the two diastereoisomeric conformers or atropisomers range from 4:1 to >20:1. In the case of the less hindered pairs of conformers of 2-phenylpyridyls bearing only two ortho substituents (which interconvert with half-lives in the region of 10^{-2} s at 298 K) the favored orientation was deduced by a combination of modeling and circular dichroism studies. For the more hindered pairs of atropisomers of 2-(1-naphthyl)pyridines bearing three substituents ortho to the restricted axis (which interconvert with half-lives in the region of hours at 90 °C) the stereochemistry of the favored atropisomer was established by X-ray crystallography and used to validate the circular dichroism spectroscopy results. The enantiomerically pure diastereoisomers of the atropisomeric sulfoxides could be converted to atropisomeric sulfones without loss of axial stereochemistry. Equilibration between diastereoisomeric atropisomers of a sulfoxide intermediate in the synthesis of QUINAP permits the asymmetric synthesis of this ligand avoiding a classical resolution.

Scheme 9. Enantiomerically Pure Atropisomeric Sulfones from Diastereoisomerically Pure Sulfoxides[a]



[a] Conditions: (*a*) *m*-CPBA, 0 °C, 10 min.

Scheme 10. Synthesis of (*R*)-QUINAP by Dynamic Thermodynamic Resolution



Experimental Section

General experimental details are given in the Supporting Information.

(*R*,*P*)-1-(2-(Phenylsulfinyl)naphthalen-1-yl)isoquinoline, (*R*,*P*)-13. *n*-BuLi (0.55 mL, 2.5 M in hexane, 1.36 mmol) was injected over one minute via syringe to a stirred and cooled (−78 °C) solution of isoquinoline **10a** (0.306 g, 0.92 mmol) in dry THF (15 mL). Stirring and cooling was continued for 30 min before this solution was added over 5 min via cannula to a stirred and cooled (−78 °C) solution of **12** (0.35 g, 1.2 mmol) in dry THF (15 mL). The cooling bath was allowed to slowly warm to RT overnight, then recooled to (−78 °C) before 2 M NaOH (10 mL) was added to the reaction mixture. The reaction mixture was warmed to RT,

(42) It is in fact possible to re-isolate and recycle (by further equilibration) the minor, less stable diastereoisomer of **13** in low yield (ca 12%) after this equilibration: yields are limited by the instability of 13 on silica. Higher yields were obtained by Knochel *et al.* (ref 19) employing Florisil, but our equilibration method is particularly suitable for use on large scale, where the expense of Florisil becomes prohibitive.

partitioned between water (5 mL) and CH_2Cl_2 (10 mL), and the aqueous phase extracted twice with CH_2Cl_2. The combined organic material was washed with brine, concentrated, taken up in cumene (10 mL) and heated at 120 °C. After 2 h the solvent was removed by rotary evaporator. Flash chromatography of the residue over silica gel, first using EtOAc−petrol mixtures (1:4, then 1:1), then EtOAc, and then MeOH−EtOAc mixture (1:9 then 1:4), gave the title sulfoxide (*R,P*)-**13** (0.174 g, 77%) as a white powder, mp 156−158 °C (from CH_2Cl_2-hexane) (lit. 148−150 °C);[19] R_f(EtOAc−hexane 1:1) 0.20; $[\alpha]_D^{29} = +178.7$ (c. 0.0008, $CHCl_3$); HPLC ((*R,R*)-*β*-Gem 1; flow rate, 1 mL/min; hexane−IPA, 92:8) retention times of the enantiomers (R_S,*P*) 142.9 min, (S_S,*M*) 161.0 min, *er* (R_S):(S_S) 99:1. Other spectroscopic details were identical with those published.[19]

(*R,M*)−1-(2-(Phenylsulfinyl)naphthalen-1-yl)isoquinoline, (*R,M*)-13. (*R,*M)-**13** was also obtained (0.026 g, 12%) as a clear oil; R_f (EtOAc−hexane 1:1) 0.56; $[\alpha]_D$ +203.8 (c. 0.0032, $CHCl_3$), HPLC (*R,R*)-*β*-Gem 1; flow rate, 1 mL/min; hexane:IPA, 92:8) retention times of the enantiomers (R_S,*M*) 50.1 min, (S_S,*P*) 57.9 min, *er* (R_S):(S_S) 99:1. Other spectroscopic details were identical with those published.[19]

(*R,P*)-2-(2-(*p*-Tolylsulfinyl)naphthalen-1-yl)-3-ethyl-6-methylpyridine, (*R,P*)-14. In the same way, but without equilibration, pyridine **10b** gave the title sulfoxide (*R,P*)-**14** (0.165 g, 47%) as a waxy white solid, mp 73−75 °C (from CH_2Cl_2-hexane); R_f (EtOAc−hexane 1:1) 0.23; ν_{max}(film/cm^{-1}) 1620, 1582, 1558, 1497 (Ar) and 1035 (S═O); δ_H(500 MHz; $CDCl_3$) 8.31 (1H, d, *J* 8.9, Ar−H), 8.12 (1H, d, *J* 8.9, Ar−H), 7.92 (1H, d, *J* 8.2, Ar−H), 7.53 (1H, t, *J* 7.6, Ar−H), 7.47 (1H, d, *J* 7.9, Ar−H), 7.40 (1H, t, *J* 7.9, Ar−H), 7.29 (1H, d, *J* 7.9, Ar−H), 7.27 (1H, d, *J* 7.6, Ar−H), 7.11 (2H, d, *J* 8.2, Ar−H), 7.08 (2H, d, *J* 8.2, Ar−H), 2.67 (3H, s, Pyr-CH_3), 2.31 (3H, s, Ar−CH_3), 1.72 (1H, qd, *J* 15.2, and 7.6, CH_AH$_B$), 1.23 (1H, qd, *J* 15.2, and 7.6, CH$_A$$H_B$) and 0.74 (3H, t, *J* 7.6, CH_2CH_3); δ_C(126 MHz; $CDCl_3$) 156.0, 152.5, 141.7, 141.5, 140.8, 137.0, 135.9, 135.4, 135.2, 131.3, 129.5, 128.4, 127.4, 127.0, 126.3, 125.9, 125.1, 124.1, 123.3, 120.1, 24.1, 23.5, 21.3 and 12.5; *m/z* (ES+) 386 (100%, M^+) and 408 (60, M + Na); (Found M^+, 386.1568. $C_{25}H_{24}NOS$ requires *M*, 386.1573); $[\alpha]_D^{29} = +166.7$ (c. 0.00234, $CHCl_3$); HPLC (Column, (*R,R*)-Whelk 01; flow rate, 1 mL/min; solvent system, hexane−IPA, 90:10) retention times of the enantiomers (R_S,*P*) 39.9 min, (S_S,*M*) 42.6 min, *er* (R_S):(S_S) 99:1.

(*R,M*)-2-(2-(*p*-Tolylsulfinyl)napthalen-1-yl)-3-ethyl-6-methylpyridine, (*R,M*)-14. (*R,M*)-**14** was also obtained (0.165 g, 47%) as a clear oil; R_f (EtOAc−hexane 1:1) 0.67; ν_{max}(film/cm^{-1}) 1620, 1582, 1558, 1497 (Ar) and 1035 (S═O); δ_H(500 MHz; $CDCl_3$) 8.00 (1H, d, *J* 8.6, Ar−H), 7.94 (1H, d, *J* 8.9, Ar−H), 7.88 (1H, d, *J* 8.2, Ar−H), 7.71 (1H, d, *J* 6.9, Ar−H), 7.57−7.52 (3H, m, Ar−H), 7.43 (1H, ddd, *J* 8.2, 7.0 and 1.3, Ar−H), 7.32 (1H, dd, *J* 8.6 and 1.0, Ar−H), 7.28 (1H, d, *J* 7.9, Ar−H), 7.19 (2H, d, *J* 7.9, Ar−H), 2.54 (3H, s, Pyr-CH_3), 2.49 (1H, qd, *J* 15.1, and 7.6, CH_AH$_B$), 2.42 (1H, qd, *J* 15.1, and 7.6, CH$_A$$H_B$), 2.33 (3H, s, Ar−$CH_3$) and 1.09 (3H, t, *J* 7.6, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 153.3, 141.9, 141.7, 140.7, 137.4, 136.7, 135.9, 134.7, 131.5, 130.2, 129.6, 128.3, 127.8, 127.3, 126.4, 125.1, 123.2, 120.3, 24.9, 24.0, 21.3 and 14.4; *m/z* (ES+) 386 (100%, M^+) and 408 (60, M + Na); (Found M^+, 386.1568. $C_{25}H_{24}NOS$ requires *M*, 386.1573); $[\alpha]_D^{29} = +192.6$ (c. 0.0059, $CHCl_3$); HPLC (Column, (*R,R*)-Whelk 01; flow rate, 1 mL/min; solvent system, hexane−IPA, 90:10) retention times of the enantiomers (R_S,*M*) 12.2 min, (S_S,*P*) 17.3 min, *er* (R_S):(S_S) 99:1.

(*R,M*)-1-(2-(*p*-Tolylsulfinyl)phenyl)isoquinoline, 15a. In the same way, pyridine **7b** gave the title isoquinoline **15a** (0.9 g, 85%) as white prisms, mp 110−111 °C (from CH_2Cl_2); R_f(EtOAc) 0.50; ν_{max}(film/cm^{-1}) 1621, 1582, 1556, 1495 (Ar) and 1034 (S═O); δ_H(500 MHz; $CDCl_3$) 8.58 (1H, d, *J* 5.7, Ar−H), 8.25 (1H, d, *J* 7.9, Ar−H), 7.85 (1H, d, *J* 8.6, Ar−H), 7.74−7.70 (2H, m, Ar−H), 7.66 (1H, t, *J* 7.3, Ar−H), 7.58 (1H, t, *J* 7.6, Ar−H), 7.54 (1H, d, *J* 8.6, Ar−H), 7.45 (1H, d, *J* 7.6, Ar−H), 7.40 (1H, t, *J* 7.6, Ar−H), 7.12 (2H, d, *J* 8.2, Ar−H), 6.89 (2H, d, *J* 7.9, Ar−H) and 2.16 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 157.4, 146.1, 141.9, 141.6, 141.0, 137.3, 136.4, 130.4, 130.2, 130.1, 129.7, 129.3, 127.4, 127.2, 126.8, 126.7, 125.6, 125.1, 120.9 and 21.1; *m/z* 344 (100%, M^+) and 328 (10, M − O); (Found: M^+, 344.1106. $C_{22}H_{18}NOS$ requires *M*, 344.1104); $[\alpha]_D^{29} = +64$ (c. 0.00175, $CHCl_3$); HPLC (Column, (*R,R*)-*β*-Gem 1; flow rate, 1 mL/min; solvent system, hexanes−IPA, 92:8) retention times of the enantiomers (R_S) 88.4 min, (S_S) 96.5 min, *er* (R_S):(S_S) 99:1.

(*R,M*)-2-(2-(*p*-Tolylsulfinyl)phenyl)-3-ethyl-6-methylpyridine, 15b. In the same way, pyridine **7b** gave the title sulfoxide **15b** (0.19 g, 78%) as a white solid, mp 102−104 °C (from CH_2Cl_2); R_f (EtOAc−hexane, 1:1) 0.32; ν_{max}(film/cm^{-1}) 1592, 1567, 1492 (Ar) and 1032 (S═O); δ_H(500 MHz; $CDCl_3$) 8.13 (1H, dd, *J* 7.9 and 1.0, Ar−H), 7.60 (1H, td, *J* 7.3 and 1.3, Ar−H), 7.50 (1H, td, *J* 7.6 and 1.3, Ar−H), 7.49 (1H, d, *J* 8.2, Ar−H), 7.28 (1H, dd, *J* 7.3, and 1.0, Ar−H), 7.20 (2H, d, *J* 8.2, Ar−H), 7.14 (1H, d, *J* 7.9, Ar−H), 7.09 (2H, d, *J* 8.2, Ar−H), 2.46 (3H, s, Pyr-CH_3), 2.43 (1H, qd, *J* 15.2 and 7.6, CH_AH$_B$), 2.31 (3H, s, Ar−CH_3), 2.26 (1H, qd, *J* 15.2 and 7.6, CH$_A$$H_B$) and 1.03 (3H, t, *J* 7.6, CH_2CH_3); δ_C($CDCl_3$) 155.3, 154.6, 144.8, 142.3, 141.5, 138.9, 137.1, 135.0, 130.8, 129.8, 129.7, 129.4, 126.2, 124.8, 123.3, 25.1, 24.1, 21.6 and 14.7; *m/z* 336 (100%, M^+); (Found: M^+, 336.1420. $C_{21}H_{21}NOS$ requires *M*, 336.1417) (Found: C, 75.2; H, 6.6; N, 3.9. $C_{21}H_{21}NOS$ requires C, 75.2; H, 6.3; N, 4.2%). $[\alpha]_D^{29} = +171.3$ (c. 0.00174, $CHCl_3$); HPLC (Column, (*R,R*)-Whelk 01; flow rate, 1 mL/min; solvent system, hexane−IPA, 90:10) retention times of the enantiomers (R_S) 59.5 min, (S_S) 64.9 min, *er* (R_S):(S_S) 99:1.

(*R,M*)-2-(2-(*p*-Tolylsulfinyl)phenyl)-3-methylpyridine, 15c. In the same way, pyridine **7b** gave the title sulfoxide **15c** (0.21 g, 74%) as a white powder, mp 112−114 °C (from CH_2Cl_2); R_f (EtOAc) 0.41; ν_{max}(film/cm^{-1}) 1571 (Ar) and 1043 (S═O); δ_H(300 MHz; $CDCl_3$) 8.50 (1H, dd, *J* 4.8 and 0.9, Ar−H), 8.17 (1H, dd, *J* 7.8 and 0.9, Ar−H), 7.63 (1H, td, *J* 7.5 and 1.2, Ar−H), 7.56−7.50 (2H, m, *J* Ar−H), 7.32 (1H, dd, *J* 6.3 and 1.2, Ar−H), 7.30−7.21 (3H, m, Ar−H), 7.11 (1H, d, *J* 8.1, Ar−H), 2.33 (3H, s, Pyr-CH_3) and 2.04 (3H, s, Ar−CH_3); δ_C(75 MHz; $CDCl_3$) 156.0, 146.8, 145.1, 141.5, 138.8, 138.6, 132.6, 130.8, 129.8, 129.7, 129.6, 125.9, 125.0, 123.4, 21.6 and 19.4; *m/z* 308 (100%, M^+) and 168 (10, M − SOtolyl); (Found: M^+, 308.1110. $C_{19}H_{17}NOS$ requires *M*, 308.1104) (Found: C, 73.8; H, 5.7; N, 4.4. $C_{19}H_{17}NOS$ requires C, 74.2; H, 5.6; N, 4.6%). $[\alpha]_D^{29} = +86.6$ (c. 0.00298, $CHCl_3$); HPLC (Column, (*R,R*)-Whelk 01; flow rate, 1 mL/min; solvent system, hexane:IPA, 90:10) retention times of the enantiomers (R_S) 53.9 min, (S_S) 59.5 min, *er* (R_S):(S_S) 99:1.

General Method for Sulfoxide Oxidation. 3-Chloroperbenzoic acid (1.4 mmol, 1.4 equiv) dissolved in dichloromethane (2 mL) was added dropwise to a stirred solution of the sulfoxide/sulfide (1.0 mmol, 1 equiv) dissolved in dichloromethane (2 mL) at 0 °C. After 10 min the reaction had gone to completion. The mixture was then diluted with dichloromethane (10 mL) and methanol (1 mL) and washed with sodium hydroxide solution (2M, 2 × 10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2; EtOAc−hexane 1:1, then 1:0) to give the product.

(*P*)-1-(2-Tosylnaphthalen-1-yl)isoquinoline, (*P*)-16. By this method, sulfoxide (*R,P*)-**16** gave the title sulfone (*P*)-**16** (0.03 g, 46%) as a white powder, mp 211−213 °C (from CH_2Cl_2); R_f (EtOAc−hexane 1:1) 0.62; ν_{max}(film/cm^{-1}) 1621, 1558, 1541, 1507 (Ar) and 1318, 1152 (SO_2); δ_H(500 MHz; $CDCl_3$) 8.58 (1H, d, *J* 5.7, Ar−H), 8.34 (1H, d, *J* 8.9, Ar−H), 8.13 (1H, d, *J* 8.8, Ar−H), 7.98−7.91 (2H, m, Ar−H), 7.82 (1H, d, *J* 5.7, Ar−H), 7.68 (1H, ddd, *J* 7.9, 6.6 and 1.0, Ar−H), 7.57 (1H, ddd, *J* 7.9, 6.6 and 1.0, Ar−H), 7.48−7.45 (2H, m, Ar−H), 7.34 (1H, ddd, *J* 8.2, 7.0 and 1.0, Ar−H), 7.29 (1H, ddd, *J* 8.2, 6.6 and 1.0, Ar−H), 7.25 (1H, d, *J* 8.6, Ar−H), 7.13−7.10 (2H, m, Ar−H) and 6.94 (1H, d, *J* 8.5, Ar−H); δ_C(75 MHz; $CDCl_3$) 157.1, 143.7, 141.7, 138.6, 137.6, 135.6, 135.1, 132.8, 131.5, 130.2, 129.8, 129.5, 129.3, 128.7, 128.0,

127.9, 127.6, 127.5, 127.4, 127.3, 126.7, 124.4, 121.0 and 21.5; *m/z* (ES$^+$) 410 (100%, M$^+$); (Found M$^+$, 409.1131. $C_{26}H_{19}NO_2S$ requires *M*, 409.1136); $[\alpha]_D$ − 90 (c. 0.003, $CHCl_3$); HPLC (Column, (*R,R*)-*β*-Gem 1; flow rate, 1 mL/min; solvent system, hexane:IPA, 92:8) retention times of the enantiomers (*P*) 50.9 min, (*M*) 45.8 min, *er* (*P*):(*M*) 99:1.

(*P*)-1-(2-Tosylnaphthalen-1-yl)isoquinoline N-oxide, (*P*)-17. (*P*)-17 was also obtained (0.026 g, 39%) as clear oil, R_f (EtOAc-MeOH 7:3) 0.76; ν_{max}(film/cm^{-1}) 1621, 1558, 1541, 1505 (Ar), 1267 (N−O) and 1156 (SO_2); δ_H(500 MHz; $CDCl_3$) 8.30 (1H, d, *J* 7.3, Ar−H), 8.12 (1H, d, *J* 8.8, Ar−H), 8.10 (1H, d, *J* 8.8, Ar−H), 7.97 (1H, d, *J* 8.2, Ar−H), 7.88 (1H, d, *J* 8.2, Ar−H), 7.84 (1H, d, *J* 7.0, Ar−H), 7.76 (2H, d, *J* 8.2, Ar−H), 7.62 (1H, ddd, *J* 7.9, 6.9 and 1.0, Ar−H), 7.54 (1H, ddd, *J* 8.2, 7.0 and 1.0, Ar−H), 7.41 (1H, ddd, *J* 8.5, 7.0 and 1.3, Ar−H), 7.31 (1H, ddd, *J* 8.5, 7.0 and 1.3, Ar−H), 7.16 (2H, d, *J* 7.9, Ar−H), 7.15 (1H, d, *J* 8.5, Ar−H), 6.84 (1H, d, *J* 8.2, Ar−H) and 2.35 (3H, s, Ar−CH_3); δ_C(126 MHz; $CDCl_3$) 144.2, 138.5, 138.3, 138.0, 137.1, 135.2, 131.3, 130.9, 130.8, 129.7, 129.5, 129.3, 129.2, 128.6, 128.5, 128.3, 128.2, 128.1, 126.8, 126.0, 124.9, 124.8, 124.3 and 21.6; *m/z* (ES+) 426 (20%, M$^+$) and 448 (100, M + Na); (Found M$^+$, 426.1150. $C_{26}H_{20}NO_3S$ requires *M*, 426.1158); $[\alpha]_D$ − 98.9 (c. 0.0018, $CHCl_3$).

(*M*)-1-(2-Tosylnaphthalen-1-yl)isoquinoline (*M*)-16. In the same way, sulfoxide (*M*)-**13** gave the title sulfone (*M*)-**16** (0.049 g, 43%) as white powder. ^{1}H NMR matched that of (*P*)-**16**, $[\alpha]_D$ + 86 (c. 0.0023, $CHCl_3$); HPLC (Column, (*R,R*)-*β*-Gem 1; flow rate, 1 mL/min; solvent system, hexane−IPA, 92:8) retention times of the enantiomers (*P*) 50.9 min, (*M*) 45.8 min, *er* (*P*):(*M*) 1:99.

(*M*)-17. (*M*)-**17** was also obtained (0.050 g, 42%) as clear oil. H NMR matched that reported for (*P*)-**17** $[\alpha]_D$ + 95.4 (c. 0.0027, $CHCl_3$).

(*P*)-3-Ethyl-6-methyl-2-(2-tosylnaphthalen-1-yl)pyridine (*P*)-18. In the same way, (*P*)-**14** gave the title sulfone (*P*)-**18** (0.037 g, 42%) as clear oil, R_f (EtOAc-hexane 1:1) 0.60; ν_{max}(film/cm^{-1}) 1590, 1569, 1513 (Ar) and 1316, 1155 (SO_2); δ_H(500 MHz; $CDCl_3$) 8.34 (1H, d, *J* 8.9, Ar−H), 8.04 (1H, d, *J* 8.8, Ar−H), 7.91 (1H, d, *J* 8.2, Ar−H), 7.67 (1H, d, *J* 7.9, Ar−H), 7.57 (1H, t, *J* 7.6, Ar−H), 7.44 (2H, d, *J* 8.2, Ar−H), 7.38 (1H, t, *J* 7.3, Ar−H), 7.23 (1H, d, *J* 7.9, Ar−H), 7.16 (2H, d, *J* 8.2, Ar−H), 7.13 (1H, d, *J* 8.6, Ar−H), 2.50 (1H, qd, *J* 15.2, and 7.6, CH_AH$_B$), 2.36 (3H, s, Pyr-CH_3), 2.21 (1H, qd, *J* 15.2, and 7.6, CH$_A$$H_B$), 2.18 (3H, s, Ar−$CH_3$) and 1.04 (3H, t, *J* 7.6, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 156.0, 152.3, 141.5, 140.1, 139.3, 137.4, 135.5, 134.7, 133.7, 129.1, 128.3, 128.1, 127.7, 127.1, 126.9, 126.4, 126.3, 123.3, 122.0, 23.8, 21.5, 20.5 and 12.6; *m/z* (ES+) 402 (100%, M$^+$); (Found M$^+$, 402.1514. $C_{25}H_{24}NO_2S$ requires *M*, 402.1522); $[\alpha]_D$ − 105 (c. 0.003, $CHCl_3$); HPLC (Column, (*R,R*)-Whelk 01; flow rate, 1 mL/min; solvent system, hexane−IPA, 90:10) retention times of the enantiomers (*P*) 27.3 min, (*M*) 31.8 min, *er* (*P*):(*M*) 99:1.

(*P*)-3-Ethyl-6-methyl-2-(2-tosylnaphthalen-1-yl)pyridine N-oxide, (*P*)-19. (*P*)-**19** was also obtained (0.037 g, 40%) as clear oil, R_f (EtOAc-hexane 1:1) 0.10; ν_{max}(film/cm^{-1}) 1591, 1569, 1507 (Ar), 1265 (N−O) and 1156 (SO_2); δ_H(500 MHz; $CDCl_3$) 8.14 (1H, d, *J* 8.8, Ar−H), 8.04 (1H, d, *J* 8.9, Ar−H), 7.91 (1H, d, *J* 8.2, Ar−H), 7.71 (2H, d, *J* 8.2, Ar−H), 7.59 (1H, t, *J* 7.3, Ar−H), 7.45 (1H, t, *J* 7.9, Ar−H), 7.33 (1H, d, *J* 7.9, Ar−H), 7.26−7.22 (2H, m, Ar−H), 7.18 (2H, d, *J* 8.5, Ar−H), 2.38 (3H, s, Pyr-CH_3), 2.36 (1H, qd, *J* 15.2, and 7.6, CH_AH$_B$), 2.34 (3H, s, Ar−CH_3), 2.08 (1H, dq, *J* 15.2, and 7.6, CH$_A$$H_B$) and 1.01 (3H, t, *J* 7.9, CH_2CH_3); δ_C(126 MHz; $CDCl_3$) 146.1, 143.9, 143.8, 141.2, 137.7, 136.9, 135.2, 131.8, 131.3, 130.0, 129.3, 128.9, 128.4, 128.2, 128.1, 125.6, 125.5, 124.5, 123.8, 25.3, 21.6, 17.5 and 13.5; *m/z* (ES+) 418 (40%, M$^+$) and 440 (100, M + Na); (Found M$^+$, 418.1464. $C_{25}H_{24}NO_3S$ requires *M*, 418.1471); $[\alpha]_D$ −115 (c. 0.0022, $CHCl_3$).

(*M*)-3-Ethyl-6-methyl-2-(2-tosylnaphthalen-1-yl)pyridine, (*M*)-17. In the same way, (*M*)-**14** gave the title sulfone (*M*)-**18** (0.062 g, 45%) as clear oil. ^{1}H NMR matched that reported for (*P*)-**18**. $[\alpha]_D$ +108 (c. 0.0004, $CHCl_3$); HPLC (Column, (*R,R*)-Whelk 01; flow rate, 1 mL/min; solvent system, hexane−IPA, 90:10) retention times of the enantiomers (*P*) 27.3 min, (*M*) 31.8 min, *er* (*P*):(*M*) 1:99.

(*M*)-3-Ethyl-6-methyl-2-(2-tosylnaphthalen-1-yl)pyridine N-oxide, (*M*)-19. (*M*)-**19** was also obtained (0.069 g, 42%) as clear oil. ^{1}H NMR matched that of (*P*)-**19**. $[\alpha]_D$ + 117.7 (c. 0.0026, $CHCl_3$).

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Supporting Information Available: Details of experimental procedures for the synthesis of **7**−**11**; methods for determination of barriers to rotation; X-ray crystallographic data for *(R,P)*-**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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