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# Retention Stereochemistry in Ligand Coupling Reaction of Optically Active (1*R*)-Phenylethyl 2-Quinolyl (*R*)- and (*S*)-Sulfoxide with Methylmagnesium Bromide

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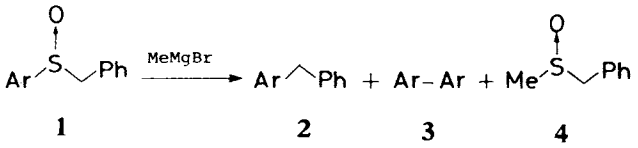
## ABSTRACT

*Reactions of* (+)-(1R)-*phenylethyl 2-quinolyl* (R)-*sulfoxide* **7a** *and* (−)-(1R)-*phenylethyl 2-quinolyl* (S)-*sulfoxide* **7b** *with methylmagnesium bromide were examined. The reaction gave* (R)-2-(1-*phenylethyl)quinoline* **9** *as a ligand-coupling product, and a mixture of methyl(1R)-phenylethyl* (R)- *and* (S)-*sulfoxide* **11a** *and* **11b** *as ligand exchange products. The other* (S) *stereoisomer at the 1-phenylethyl carbon center was not detected in the reaction products. That is, both the ligand coupling and ligand exchange reactions proceeded with retention of configuration at the asymmetric carbon center.*

## *INTRODUCTION*

Ligand coupling has received much attention as a novel concept to explain many reactions occurring at a hypervalent atom [1]. Particularly, in the reactions of $\sigma$-sulfuranes, hypervalent sulfur compounds, which have a three-center four-electron apical bond, the central sulfur atom tends to resume the lower valency of the octet by extruding a ligand that takes with it an electron pair. Of the three conceivable ways to expel such a ligand with an electron pair, that is, self-decomposition, ligand exchange, and ligand coupling, we have focussed our attention on the last reaction because the concerted coupling of two ligands, one an electron-withdrawing ligand existing at an apical position and the other an electron-donating or $\pi$ ligand present at an equatorial position, would result, in an appropriate case, in the retention of configuration of the two ligands.

A typical example is shown in Scheme 1, and the mechanistic view of the reaction process reported previously [2] is also described in Figure 1. The reaction of an aryl benzyl sulfoxide **1** with methylmagnesium bromide gives three types of products, **2**, **3**, and **4**. They are categorized into a ligand-coupling product, a dimer, and a ligand exchange product, respectively.




**1** **2** **3** **4**

**Scheme 1**

An important feature of the coupling is whether it proceeds by a concerted process. This was experimentally confirmed previously by the observation that a substrate having a chiral carbon bonded to the sulfoxide group reacted with an alkylmagnesium halide to give the coupling product **5** [3] or **6**[4] with retention of configuration, as shown in Scheme 2. Whereas in the earlier experiments the stereochemical studies were performed by the use

This article is dedicated to Professor E. Eliel on the occasion of his seventieth birthday.

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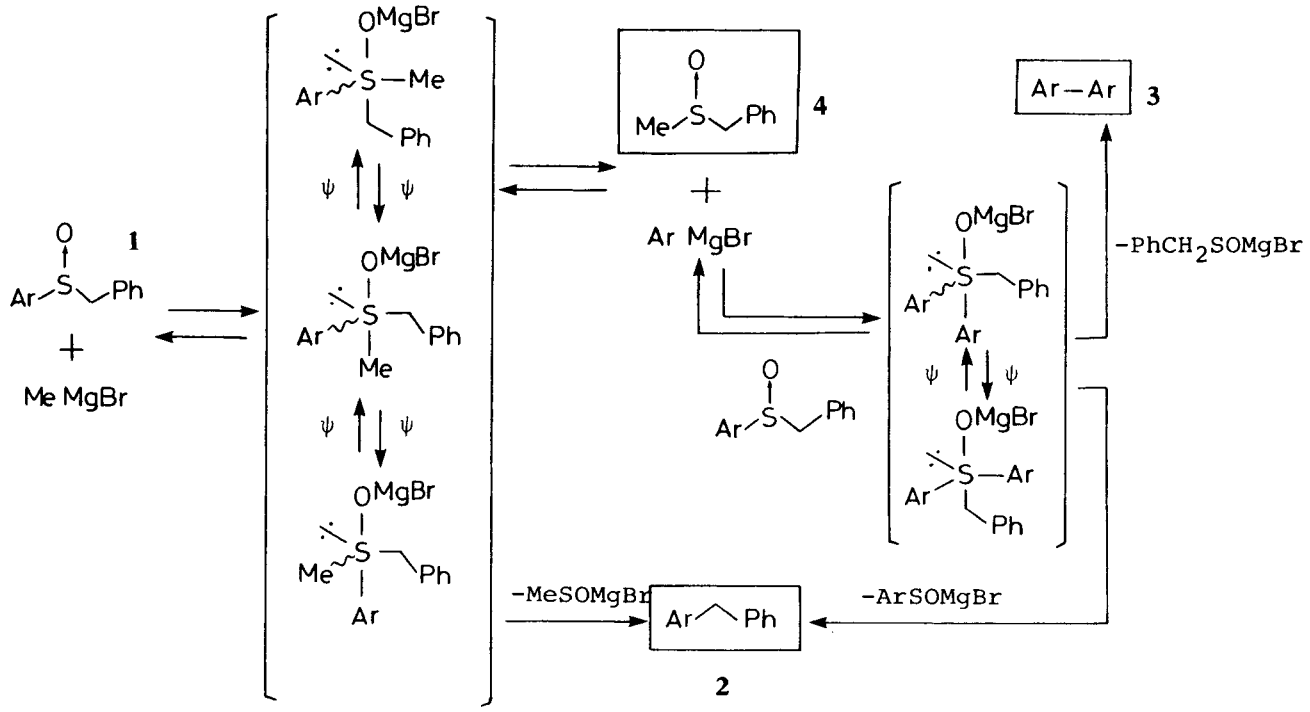
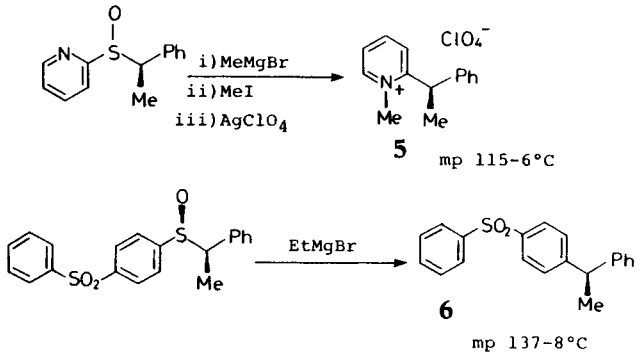


**Figure 1**

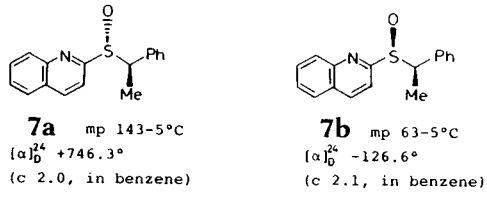


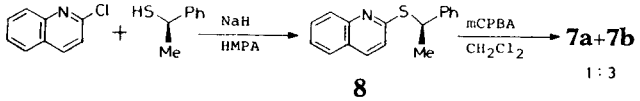
**Scheme 2**

of a single stereoisomer or a mixture of diastereomers, we now have examined the chemical behavior of the optically active diastereomers **7a** and **7b** having adjacent chiral carbon and sulfur atoms in the ligand coupling reaction, and we have obtained results that are similar but much clearer from a stereochemical viewpoint then found in the previous studies [3, 4]. We also found that the ligand exchange reaction proceeds with retention of configuration at the $\alpha$ carbon center but in an equilibrium giving a 3:1 mixture of diastereomers with respect to the sulfur stereocenter.

## *RESULTS AND DISCUSSIONS*

Starting materials **7a** and **7b** were prepared in two steps from 2-chloroquinoline and (*S*)-1-phenylethylmercaptan [5], as shown in Scheme 3. The sodium salt of the optically pure mercaptan, prepared carefully with NaH in HMPA (hexamethyl phosphoric triamide) was treated with 2-chloroquinoline in the presence of tetrabutylammonium bromide to afford (*R*)-1-phenylethyl 2-quinolyl sulfide **8** in 78% yield. The resulting sulfide was oxidized with *m*CPBA (*m*-chloroperbenzoic acid) in chloroform at 0°C to give a diastereomeric mixture of sulfoxides **7a** and **7b** in the ratio of 1:3 in 98% yield. The isomers could not be separated by column chromatography. A minor sulfoxide was easily induced to crystallize from the mixture in a benzene and hexane (3:1) solution. Repeated recrystallizations (three times) from the same solvent system afforded

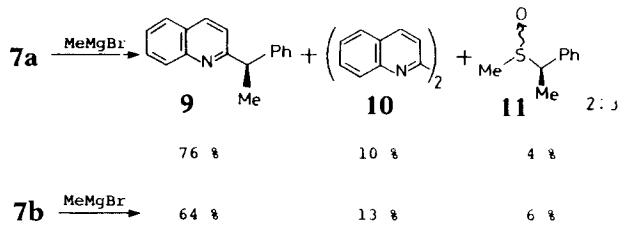




**Scheme 3**

an optically pure single sulfoxide, **7a**, possessing a consistent optical rotation $[\alpha]_D^{23}$ + 746 ± 3° (c 2.0, chloroform) and the melting point 143–145°C. The absolute configuration of **7a** was determined by single crystal X-ray diffraction analysis to have RcRs stereocenters [6]. The ORTEP view is shown in Figure 2. Subsequently, the major isomer **7b** remaining in the mother liquid after removal of the minor isomer **7a** was induced to crystallize from a benzene and hexane (3:1) solution. Repeated recrystallization of **7b** from the same solvent system gave a pure single diastereomer having a consistent optical rotation $[\alpha]_D^{23}$ − 126 ± 2° (c 2.1, in chloroform) and the melting point 63–65°C. Both isomers were subjected to the ligand coupling reaction.

The reaction of **7a** with methylmagnesium bromide in THF took place smoothly within 10 min at room temperature to give 2-(1-phenylethyl)-quinoline **9** in 76% yield (Scheme 4). The oily product **9** had the optical rotation $[\alpha]_D^{23}$ − 174°C (c 1.8, benzene); this value remained consistent in a range of ± 3° even after repeated purifications. On the other hand, the coupling product **9** obtained by the reaction of **7b** with methylmagnesium bromide showed $[\alpha]_D^{23}$ − 177 ± 3° (c 1.8, benzene). A 1:3 mixture of diastereomers, **7a** and **7b**, also underwent reaction with methylmagnesium bromide to give **9** in 85% yield, which had almost the same degree of optical rotation, $[\alpha]_D^{23}$ − 174° (c 1.8, benzene). These three experimental results indicate that the stereocenter on the sulfur atom does not have any influence on the stereochemistry of the reaction process. The product **9** was an oil, and hence the absolute configuration could not be directly determined by X-ray diffraction analysis, but, fortunately, treatment of **9** with $AgClO_4$ in acetonitrile gave a crystalline complex. The structure of this complex was elucidated by X-ray diffraction analysis, and its ORTEP structure is represented in Figure 3. The silver atom is coordinated in the complex with two quinoline nitrogen atoms. The structure clearly indicates that the asymmetric carbon center has the *R* configuration [6].




**Scheme 4**

Other reactions that occurred were a ligand exchange and dimer formation, which can be seen in Figure 1. The reaction products, 2,2′-biquinolyl **10** and methyl 1-phenylethyl sulfoxide **11** were obtained in 10% and 4% yields, respectively, in the reaction of **7a** with methymagnesium bromide. The ligand exchange product **11** having two chiral centers consisted of a 3:4 mixture of unseparable diastereomers, **11a** and **11b**. The diastereomeric ratio was determined by proton NMR in which a signal of the methylsulfinyl group in the minor isomer appeared at $\delta$ = 2.19 and that in the major isomer at $\delta$ = 2.31. The isomer ratios obtained by the re-

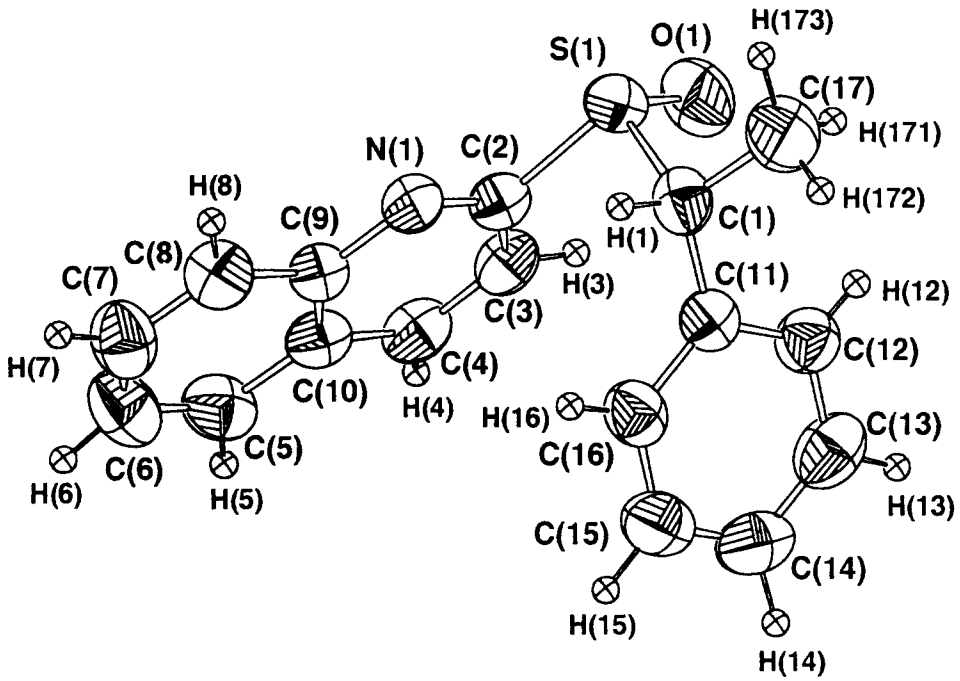



FIGURE 2 ORTEP view of 7a

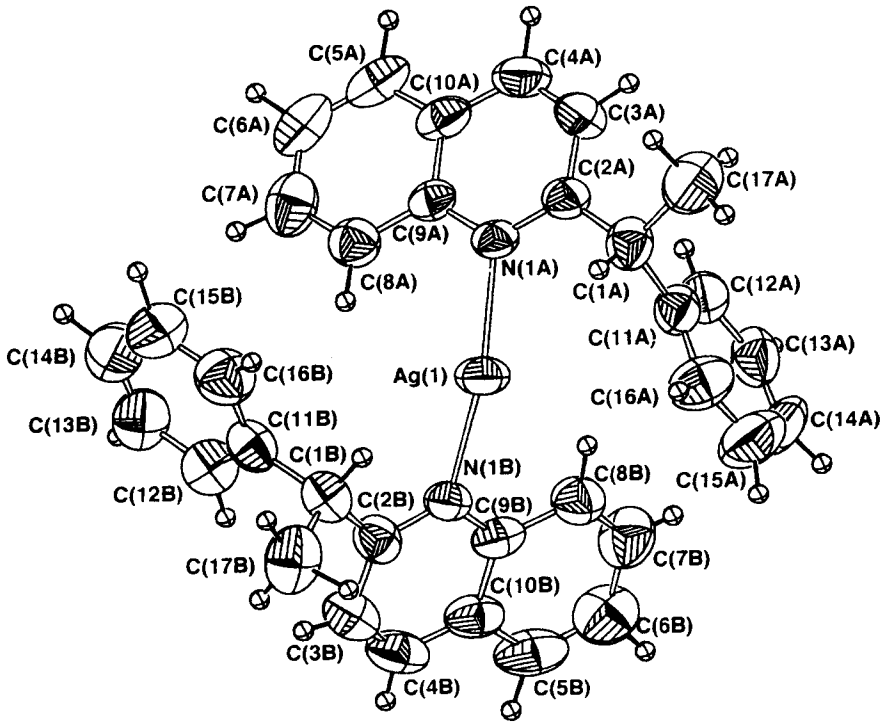


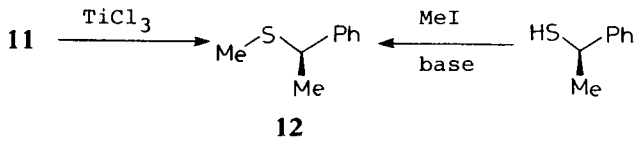

FIGURE 3 ORTEP drawing of a 2:1 crystalline complex of **9** and $AgClO_4$

action of **7b** or a mixture of **7a** and **7b** with methylmagnesium bromide were not much different. Reduction of the sulfoxide **11** to the sulfide was carried out with $TiCl_3$ in refluxing chloroform, and methyl 1-phenylethyl sulfide **12** [7] was obtained in 38% yield (Scheme 5). Its specific rotation was $[\alpha]_D^{23}$ + 133° (c 0.5, chloroform), the same rotation as that i.e., $[\alpha]_D^{23}$ + 135°(c 0.5, chloroform) of the optically pure sulfide obtained independently by methylation of optically pure (*R*)-1-phenylethylmercaptan with iodomethane. This result indicates that the sulfide **12** formed from **11** was a single enantiomer. This means that no racemization occurred at the asymmetric carbon center during the ligand exchange or the ligand coupling reactions. The sulfoxide **11** is present in an equilibrium mixture formed by further ligand exchange with an excess of methylmagnesium bromide present in the reaction mixture.

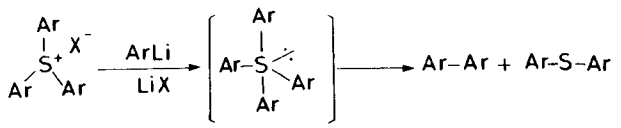
The results may be summarized in the following manner: (1) Whether the starting sulfoxide, **7a**, **7b**, or even a mixture of the two stereoisomers is used, intermediate $\sigma$-sulfuranes of three structures (initially **A** or **B** is formed and later, **C**) are all in equilibrium and eventually give the same coupling product, as shown in Figure 4, and (2) the configuration of the asymmetric carbon center is perfectly retained throughout, and this is a strong indication that the ligand coupling proceeds in a concerted manner.

It was previously shown that the high reactivity of the $\sigma$-sulfurane derived from reaction of an aryl benzyl sulfoxide with an alkyl Grignard reagent provided new types of carbon–carbon bond formation. These results as well as the current ones prompted us to examine the possible formation and reaction of a $\sigma$-sulfurane derived from a sulfoxonium salt. In fact, it is known that a triarylsufonium salt reacts with an aryllithium to give a diaryl and a diaryl sulfide [8]. This reaction could have taken place within a $\sigma$-sulfurane intermediate, generated as shown in Scheme 6.

In order to prepare a sulfonium salt **13**, **7** was first treated with triethyloxonium tetrafluoroborate in methylene chloride, and then the successive addition of methylmagnesium bromide in either methylene chloride or THF (after replacement of the methylene chloride) gave methyl 2-quinolyl sulfide **14a** in 41% yield and 2,2′-biquinolyl disulfide




Scheme 5




Scheme 6

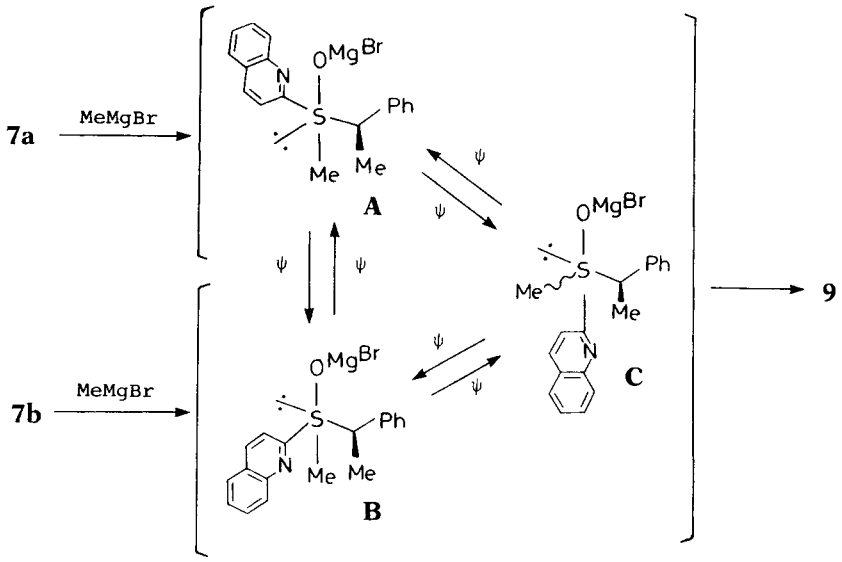
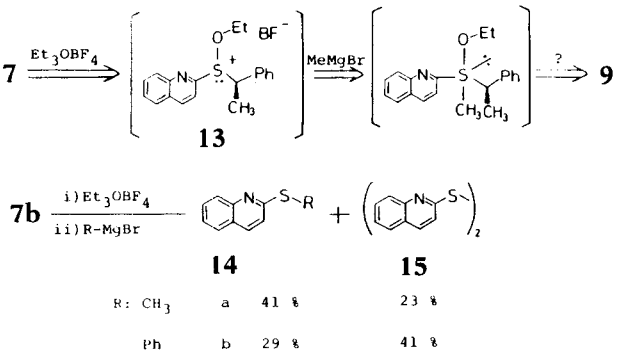



**Figure 4**

**15** in 23% yield. When phenylmagnesium bromide was employed, the reaction gave **14b** and **15** in 29 and 41% yields, respectively (Scheme 7). No desired coupling product **9** was found in either of the reactions. However, when the reaction was stopped at the stage before the addition of the Grignard reagent, **15** was obtained in 88% yield. A method to prepare a sulfonium salt from the sulfoxide using TMSOTf (trimethylsilyl methanesulfonate) and a Grignard reagent found in the literature [9] was also examined but gave a similar result. In these experiments, the formation of sulfonium salt **13** is in doubt. Even if it had been formed, the salt might have been unstable and decomposed to the disulfide **15**. It is well known that a disulfide reacts with a Grignard reagent to afford a sulfide.




**Scheme 7**

## *EXPERIMENTAL*

Melting points were determined on a Yanako micromelting point apparatus and were uncorrected. Infrared (IR) spectra were taken on a JASCO IRA-1 spectrometer. Mass spectra (MS) were obtained by a JEOL-JMS 303 HF spectrometer at 70 eV using a direct inlet system. Only significant peaks are described here for IR and MS. $^1$H and $^{13}$C NMR spectra were measured on a JEOL GXS spectrometer (400 HMz for $^1$H and 100 MHz for $^{13}$C) and a Varian Gemini-300 (300 MHz for $^1$H and 75 MHz for $^{13}$C). Tetramethylsilane (0 ppm) for $^1$H and chloroform (77.0 ppm) for $^{13}$C were used as a standard. Silica gel (Merck 7347, 70-230 mesh) was used for column chromatography and precoated silica gel plate (Merck 5715, $60F_{254}$) was used for thin-layer chromatography. Methylmagnesium bromide in THF solution was purchased from Kanto Chemical Co Ltd. All reactions were carried out under an argon atomosphere. Tetrahydrofuran (THF), benzene, and ether for reactions were dried over sodium benzophenone ketyl, and methylene chloride was dried over phosphorus pentoxide. The solvent was freshly distilled just before use.

### (R)-*1-Phenylethyl 2-Quinolyl Sulfide*, 8

To a mixture of (*R*)-(+)-1-phenylethylmercaptan [5] (1.26 g, 9.15 mmole), 2-chloroquinoline (1.88 g, 11.0 mmole)) in HMPA (25 mL) was added NaH (590 mg, 14.8 mmole, 60% in mineral oil) in several portions at room temperature. The mixture was stirred overnight, poured into ice water (30 mL), and extracted with ether (50 mL × 3). The combined extracts were washed with water (3 mL) and brine (3 mL) and drived over $MgSO_4$. Solvent was removed by evaporation and the residue was purified by silica gel column chromatography, elution being effected with 1–2% ethyl acetate in hexane to give **8** as an oil, 2.2 g in 78% yield. $[\alpha]_D^{23}$ + 591° (c 2.06, benzene). *Rf* = 0.56 (hex-

ane). $^1$H NMR ($CDCl_3$) $\delta$ 7.93 (1H, d, $J$ = 8.4 Hz), 7.84 (1H, d, $J$ = 8.8 Hz), 7.69 (1H, dd, $J$ = 8.1, 1.1 Hz), 7.65 (1H, ddd, $J$ = 8.4, 7.0, and 1.1 Hz), 7.53 (2H, d, $J$ = 7.7), 7.41 (1H, ddd, $J$ = 8.1, 7.0, and 1.1 Hz), 7.31 (2H, t, $J$ = 7.7 Hz), 7.21 (1H, d, $J$ = 8.8 Hz), 5.41 (1H, q, $J$ = 7.1 Hz), 1.83 (3H, d, $J$ = 7.1 Hz). MS *m/e*) (rel. intensity) 265 (100, $M^+$), 232 (36), 188 (18), 161 (47), 128 (20), 105 (68). Anal. Calcd. for $C_{17}H_{15}NS$: C, 76.94; H, 5.70; N, 5.28. Found: C, 77.04; H, 5.57; N, 5.35.

### (*1*R)-*Phenylethyl 2-Quinolyl* (R)-*Sulfoxide*, **7a** *and* (*1*R)-*Phenylethyl 2-Quinolyl* (S)-*Sulfoxide*, **7b**

To an ice-cooled solution of (*R*)-1-phenylethyl 2-quinolyl sulfide (2.20 g, 7.11 mmole) was added *m*-chloroperbenzoic acid (1.42 g, 7.11 mmole, 85%) in chloroform (30 mL) during half an hour. The mixture was stirred for an additional hour at room temperature and the reaction was then quenced with 5% sodium thiosulfate solution (20 mL). The aqueous layer was extracted with chloroform (30 mL × 2). All of the chloroform extracts were combined, washed with 5% sodium bicarbonate (5 mL × 2), and brine (8 mL) and dried over anhydrous $MgSO_4$. Solvent was removed by evaporation and the crude product was chromatographed on silica gel and eluted with 5% ethyl acetate in benzene to give a 1:3 mixture of diastereomers, 2.30 g, in 98% yield. The mixture was induced to crystalize from benzene:hexane (3:1) and the solid recrystallized twice from the same solvent system to give pure **7a**, 390 mg, mp 143–5°C; $[\alpha]_D^{23}$ +746° (c 2.0, chloroform). $Rf$ = 0.33 (20% ethyl acetate in benzene). $^1$H NMR ($CDCl_3$) $\delta$ 8.14 (1H, d, $J$ = 9.1 Hz), 8.04 (1H, d, $J$ = 8.8 Hz), 7.84–7.80 (2H, m), 7.63 (1H, m), 7.29 (1H, d, $J$ = 8.4 Hz), 7.12 (1H, m), 7.02 (2H, m), 6.80 (2H, m), 4.33 (1H, q, $J$ = 7.3 Hz), 1.91 (3H, d, $J$ = 7.3 Hz). Anal Calcd. for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.47; H, 5.37; N, 4.87. The other isomer **7b** was induced to crystallize from benzene:hexane (1:3) and then recrystallized three times from the mother liquor, to give 1.22 g as a pure material. mp 63–65°C, $[\alpha]_D^{23}$ −126°C (c 2.1, chloroform). $Rf$ = 0.33 (20% ethyl acetate in benzene). $^1$H NMR ($CDCl_3$) $\delta$ 8.30 (1H, d, $J$ = 8.4 Hz), 8.11 (1H, d, $J$ = 8.8 Hz), 7.89 (1H, dd, $J$ = 8.1 and 0.7 Hz), 7.85 (1H, d, $J$ = 8.4 Hz), 7.81 (1H, ddd, $J$ = 8.4, 7.0, and 1.1 Hz), 7.64 (1H, ddd, $J$ = 8.1, 7.0 and 1.1 Hz), 7.31 (5H,s), 4.40 (1H, q, $J$ = 7.3 Hz), 1.50 (3H, d, $J$ = 7.3 Hz). Anal Calcd. for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.72; H, 5.29; N, 4.90.

### *Reaction of* **7a** *and* **7b** *with Methylmagnesium Bromide*

Methylmagnesium bromide (1.2 mmole, 0.92 M THF solution, 1.3 mL) was added dropwise to **7a** (281 mg, 1 mmole) in THF (15 mL) during 5 min at room temperature under an argon atomosphere. After the reaction mixture had been stirred for 15 min, the reaction was quenched with water (3 mL), and the mixture was extracted with ethyl acetate (300 mL). The extract was washed with water (2 mL × 3) and brine (5 mL) and dried over anhydrous $MgSO_4$. Solvent was removed by evaporation, and the residual oil was purified by column chromatography on silica gel. The coupling product **9** (177 mg) was obtained in 76% yield (5% ether in hexane being used as an elution solvent for the chromatography). $Rf$ = 0.50 (10% ether in hexane). $[\alpha]_D^{23}$ +174° (c 1.8, benzene). $^1$H NMR ($CDCl_3$) $\delta$ 8.11 (1H, dd, $J$ = 8.4 and 0.7 Hz), 7.99 (1H, d, $J$ = 8.4 Hz), 7.74 (1H, dd, $J$ = 8.1 and 1.1 Hz), 7.69 (1H, ddd, $J$ = 8.4, 7.0 and 0.7 Hz), 7.48 (1H, ddd, $J$ = 8.1, 7.0, and 1.1 Hz), 7.35–7.34 (2H, m), 7.31–7.25 (2H, m), 7.22–7.17 (2H, m), 4.50 (1H, q, $J$ = 7.0 Hz), 1.80 (3H, d, $J$ = 7.0 Hz). Anal Calcd. for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.41; H, 6.50; N, 6.27. 2,2′-Biquinolyl **10** was obtained in 10% yield (20% ether in hexane as an eluent for the chromatography); mp 192–195°C. $R$ = 0.42 (20% ether in hexane). $^1$H NMR ($CDCl_3$) $\delta$ 8.85 (2H, d, $J$ = 8.4 Hz), 8.34 (2H, d, $J$ = 8.8 Hz), 8.24 (2H, d, $J$ = 8.4 Hz), 7.89 (2H, dd, $J$ = 8.1 and 0.7 Hz), 7.76 (2H, ddd, $J$ = 8.4, 7.0 and 0.7 Hz), 7.58 (2H, dd, $J$ = 8.1 and 7.0 Hz). Ligand exchange product **11** was obtained as a diastereomeric mixture in 4% yield (5% methanol in chloroform being used as an eluent for the chromatography). $Rf$ = 0.44 (5% methanol in chloroform). $^1$H NMR ($CDCl_3$) $\delta$ 7.40–7.25 (5H, m), 3.86 (3/7H, q, $J$ = 7.3 Hz), 3.76 (4/7H, q, $J$ = 7.3 Hz), 2.30 (12/7H, s), 2.19 (9/7H, s), 1.75 (12/7H, d, $J$ = 7.3 Hz), 1.73 (9/7H, d, $J$ = 7.3 Hz). The reaction of **7b** with methylmagnesium bromide was carried out in the same manner as described for **7a** and gave **9**, **10**, and **11** in 65, 13 and 6% yields, respectively.

### (*R*)-*Methyl 1-Phenylethyl Sulfide*, **12**

A mixture of (*R*)-(+)-1-phenylethane-2-thiol (200 mg, 1.44 mmole), iodomethane (0.4 mL, 912 mg, 6.42 mmole) and tetrabutylammonium bromide (174 mg, 0.54 mmole) in benzne (4 mL) and aq. sodium hydroxide (0.9 mL, 1 N solution) was vigorously stirred for 30 min at room temperature. The mixture was extracted with ether (30 mL) and washed with water (3 mL × 3) and brine (5 mL). The extract was dried over anhydrous $MgSO_4$, the solvent evaporated, and the residue purified by column chromatography on silica gel with elution by hexane to give **12** (182 mg) as an oil in 82% yield. $Rf$ = 0.42 (hexane). $[\alpha]_D^{23}$ + 135° (c 1.5, chloroform), $^1$H NMR ($CDCl_3$) $\delta$ 7.34–7.21 (5H, m), 3.85 (1H, q, $J$ = 7.3 Hz), 1.90 (3H, s), 1.58 (3H, d, $J$ = 7.3 Hz).

### *Reduction of* **11**

A diastereomeric sulfoxide **11** (58 mg, 0.34 mmole) dissolved in a mixture of chloroform (2 mL) and methanol (4 mL) was added to 20% aq. $TiCl_3$ solution (1.6 mL, approximately 2.06 mmole) and heated under reflux for 2 h. The mixture was extracted with chloroform (100 mL) and washed with water (3 mL × 4), sodium thiosulfate (2 mL), and brine (4 mL). The extract was dried over anhydrous $MgSO_4$, the solvent evaporated, and the residue purified by column chromatography on silica gel. Elution with hexane gave the sulfide **12** (25 mg) in 48% yield. $[\alpha]_D^{23}$ + 133.0° (c 0.5, chloroform).

### *ACKNOWLEDGMENT*

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