Highly Enantioselective Reaction of α-Lithio 2-Quinolyl Sulfide Using Chiral Bis(oxazoline)s: A New Synthesis of Enantioenriched Thiols

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The enantioselective reaction of α-lithio benzyl 2-quinolyl sulfide proceeds through a dynamic thermodynamic resolution pathway, giving the products with high stereoselectivity. The products afford chiral thiols without racemization upon removal of the quinolyl group.

Introduction

Asymmetric reactions of carbanions α to a heteroatom have been well studied in recent years.[1] We recently reported highly enantioselective reactions of the α-sulfenyl carbanions derived from benzyl phenyl sulfide and benzyl 2-pyridyl sulfide with electrophiles in the presence of chiral bis(oxazoline) ligands.[2] We demonstrated the stereochemical courses of these enantioselective reactions to be dynamic kinetic resolution and dynamic thermodynamic resolution, respectively. Chiral sulfides and chiral thiols have been used as chiral templates[3] or asymmetric catalysts,[4] and, therefore, it is important to develop the enantioselective synthesis of chiral thiols.[5] We now report the highly enantioselective reaction of α-lithio benzyl 2-quinolyl sulfide with electrophiles in the presence of bis(oxazoline)s as an external chiral ligand, which serves as an efficient method for the preparation of chiral thiols.

Results and Discussion

Enantioselective Reactions of α-Lithio Benzyl 2-Quinolyl Sulfide

Benzyl 2-quinolyl sulfide (**1**) was prepared by treatment of 2-quinolinethiol with benzyl bromide in the presence of 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU) in benzene at room temperature.[6] The enantioselective reaction of the α-sulfenyl carbanion of **1** with various carbonyl compounds in the presence of chiral bis(oxazoline)s[7] was examined under various conditions. The results are summarized in Table 1.

A cumene solution of benzyl 2-quinolyl sulfide (**1**) was treated with *n*BuLi (1.25 equiv.) at the temperature (T^1) shown in Table 1 for 10 min. The bis(oxazoline)-*i*Pr (**2a**) or -*t*Bu (**2b**) (1.3 equiv.) was then added. After stirring for 30 min, an electrophile (1.3 equiv.) was added. The reaction of Li-**1** with benzophenone using the bis(oxazoline)s **2a** and **2b** gave the product **3** in high yields with moderate to high enantioselectivities (entries 1−4). The reaction using the bis(oxazoline) **2a** showed a higher enantiomeric induction than that using the bis(oxazoline) **2b** (entries 1 vs. 3, and 2 vs. 4). The reaction of Li-**1** with acetone and cyclohexanone, which have acidic protons, gave the products **4** and **5**, respectively, in lower yields but with high stereoselectivity (entries 7 and 8). The reaction with other electrophiles such as paraformaldehyde, benzaldehyde, CO_2, and CH_3OTf gave the products **6**−**9**, respectively, with high stereoselectivity (entries 9−12). The stereochemistry of the products was determined after transformation to the thiols as discussed in the next section.

Preparation of Chiral Thiols

We examined deprotection of the quinolyl group according to the reported procedure.[8] The quinolyl sulfides **3**−**6**, **8**, and **9** were treated with $NaBH_3CN$ in acetic acid to give the chiral thiols **10**−**15** in high yields (Table 2). The optical purity of the thiols was analyzed by HPLC using Chiralpak AD, and the deprotection was found to proceed without loss of optical purity. The stereochemistry of the chiral thiols **13**,[9] **14**,[10] and **15**[11] was assigned to be *R*, *R*, and *S*, respectively, by comparison of the values of the specific rotation with the reported values. The stereochemistry of the thiols, in turn, determined the corresponding stereochemistry of the major products of the chiral sulfides **6**, **8**, and **9**. The stereochemical outcome in the electrophilic reactions of lithiated benzyl 2-quinolyl sulfide was thus found to be

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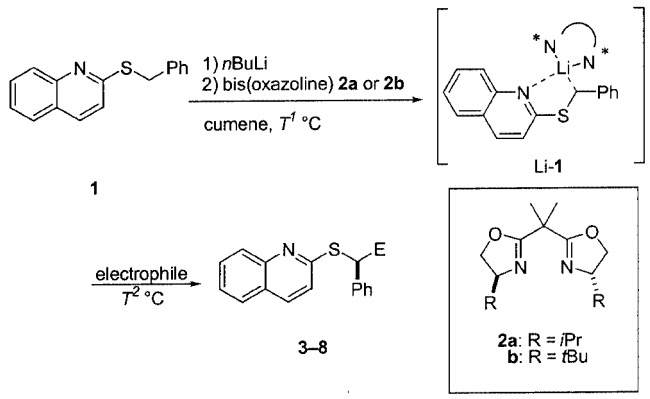
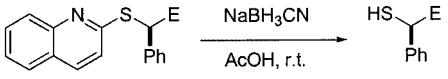
Table 1. Enantioselective reaction of the α-sulfenyl carbanion of benzyl 2-quinolyl sulfide **1**



Entry	Electrophile	Ligand	T^1	T^2	Product	Yield (%)	*ee* (%)[a]
1	Ph_2CO	**2a**	−50	−50	**3**	95	89
2	Ph_2CO	**2a**	−78	−78	**3**	79	77
3	Ph_2CO	**2b**	−50	−50	**3**	99	71
4	Ph_2CO	**2b**	−78	−78	**3**	77	50
5	Ph_2CO	**2a**	−50	−78	**3**	86	91
6[b]	Ph_2CO	**2a**	−78	−78	**3**	19	51
7	acetone	**2a**	−50	−50	**4**	40	80
8	cyclohexanone	**2a**	−50	−50	**5**	46	81
9	$(CH_2O)_n$	**2a**	−50	−50→0	**6**	35	82
10	benzaldehyde	**2a**	−50	−50	**7**	55[c]	*syn* 95 *anti* 93
11	CO_2	**2a**	−50	−50	**8**	54[d]	83
12	CH_3OTf	**2a**	−50	−50	**9**	85	78[e]

[a] The enantiomer excess was determined by HPLC analysis using Chiralcel OD-H or Chiralpak AD. [b] Ph_2CO (0.2 equiv.) was used. [c] *syn*:*anti* = 45:55. [d] Determined after conversion into the methyl ester. [e] Determined after conversion into the thiol.

Table 2. Conversion of the sulfides **3**−**6**, **8**, **9** into chiral thiols **10**−**15**



3–6.8.9 10–15

Entry	E	Sulfide (% *ee*)	Product	Yield (%)	*ee* (%)[a]
1	$C(OH)Ph_2$	**3** (89)	**10** (*R*)[b]	94	87
2	$C(OH)(CH_3)_2$	**4** (80)	**11** (*R*)[b]	81	80
3	$C(OH)C_5H_{10}$	**5** (81)	**12** (*R*)[b]	80	80
4	CH_2OH	**6** (82)	**13** (*R*)	80	82[c][d]
5	CO_2H	**8** (83)	**14** (*R*)	86	82[c,d]
6	CH_3	**9** (−)	**15** (*S*)	84	78[c,d]

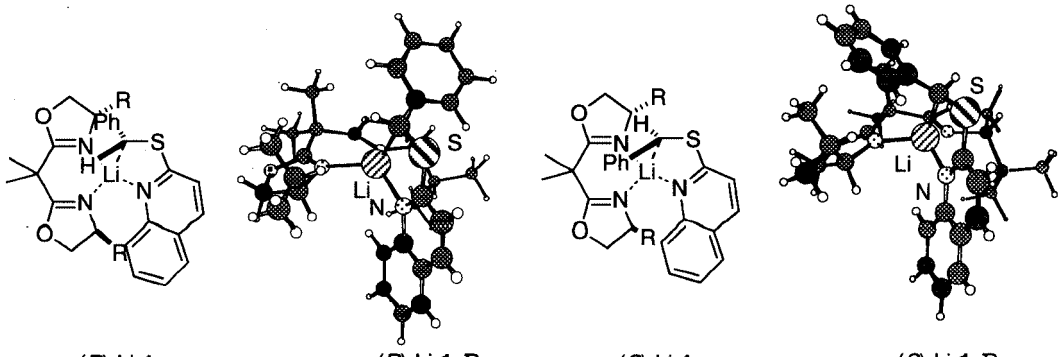
[a] Determined by the HPLC analysis using Chiralpak AD. [b] The absolute stereochemistry was deduced to be the same as that of **13**. [c] The absolute configuration was determined by comparison of the specific rotation with the reported value. [d] The enantiomer excess was determined by the specific rotation.

the same as that obtained in the reactions of lithiated benzyl 2-pyridyl sulfide.[2]

Reaction Pathway of α-Lithio Benzyl 2-Quinolyl Sulfide

The stereoselectivity in the reaction of α-lithio benzyl 2-quinolyl sulfide (Li-**1**) with electrophiles depends on the temperature of deprotonation (entries 1 vs. 3, and 2 vs. 4). The highest enantioselectivity (91% *ee*) was obtained in the reaction of a mixture of Li-**1** and **2a**, prepared at −50 °C, with Ph_2CO at −78 °C (entry 5). This enantiomeric excess value was basically the same as that obtained in the reaction performed at −50 °C (89% *ee*, entry 1). However, the enantioselectivity was lowered when deprotonation was carried out at −78 °C (Table 1, entries 2 and 4). These results indicate that the diastereomeric complexes derived from Li-**1** and the bis(oxazoline) **2** are configurationally stable at temperatures lower than −50 °C, at least on the time scale of the reaction with electrophiles, i.e., the diastereomeric complexes of Li-**1** with the bis(oxazoline) equilibrate at −50 °C. Thus, the enantioselective reaction of Li-**1** proceeds through a dynamic thermodynamic resolution pathway at −50 °C, and the enantiomer excess of the product reflects the ratio of the two diastereomeric complexes.[1b,12] In addition, the minor diastereomeric complex would have a lower activation energy and would therefore react with an electrophile more rapidly than the major complex, since the reaction with a substoichiometric amount of benzophenone resulted in a lower enantioselectivity than that obtained in the reaction with a stoichiometric amount of the electrophile (Table 1, entries 2 and 6).

The diastereomeric complexes of Li-**1** with **2a** and **2b** were estimated by the MO calculation using the MOPAC 93/PM3[13] method. The relative energies of the optimized structures showed that the (*R*)-Li-**1**-*i*Pr and -*t*Bu complexes



	(*R*)-Li-**1**	(*S*)-Li-**1**	
2a: R = *i*Pr	0	0.99	kcal/mol
2b: R = *t*Bu	0	0.83	

Figure 1. Optimized structures and energies of diastereomeric complexes of (*R*)- and (*S*)-Li-**1** with bis(oxazoline)-*i*Pr (**2a**) and -*t*Bu (**2b**) by MOPAC 93/PM3

were more stable than the respective (*S*)-Li-**1** complexes, as shown in Figure 1.

In each optimized structure, the quinolyl nitrogen is coordinated to the lithium ion together with the two nitrogens of the bis(oxazoline), giving the fully coordinated lithium complex. The reaction of carbanions with carbonyl compounds generally proceeds through coordination to the lithium ion to give the product with retention of the configuration of the carbanion.[14] Obviously, this is not the case here. The coordination of the nitrogen of the quinolyl group prevents the approach of an electrophile to the carbanion from the side of the lithium ion, while it allows the approach from the side opposite the carbanion-lithium bond. Thus, full coordination of the lithium ion allows not only methylating reagents such as CH_3OTf but also electrophiles such as carbonyl compounds or CO_2 to approach the back lobe of the carbon-lithium bond orbital giving the products with inversion of configuration.[15] This stereochemical pathway is in agreement with that in the reaction of lithiated benzyl 2-pyridyl sulfide,[2] as well as that in the reaction of chiral α-thiobenzyllithium derived from chiral thiocarbamates.[5a,16] In addition, all reactions of Li-**1** formed at −50 °C with various electrophiles gave the products **3**−**9** with degree of enantioselectivity (Table 1, entries 1, 9, 10, 11, and 12). All these results indicate that the reaction of Li-**1** with electrophiles proceeds through a dynamic thermodynamic resolution process.

Conclusion

In summary, we have demonstrated that the highly enantioselective reaction of α-lithio benzyl quinolyl sulfide in the presence of bis(oxazoline)s as the chiral ligand proceeds through a dynamic thermodynamic resolution pathway with inversion of configuration of the carbanion. Removal of the quinolyl group of the products provides an efficient method for the preparation of chiral thiols.

Experimental Section

General Remarks: All reactions were performed in oven- and flame-dried glassware under a positive pressure of argon. Air- and moisture-sensitive reagents and solvents were transferred with a syringe or cannula, and were introduced into the reaction vessels through a rubber septum. Cumene was distilled from calcium hydride under nitrogen. *n*BuLi was purchased from Mitsuwa Chemical Co,. Ltd. and was titrated by Kofron's method[17] prior to use. All of the reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica-gel plate (60f-254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid or *p*-anisaldehyde in ethanol/heat. Column chromatography was carried out on a column packed with Fuji Silysia silica gel BW-200. ^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra for solutions in $CDCl_3$ were recorded on a Varian Gemini-200. Chemical shifts (δ) are expressed in ppm downfield from internal tetramethylsilane or $CHCl_3$. Infrared spectra were recorded on a JASCO FT/IR-200 spectrometer. Mass spectra (eV) were recorded on a Hitachi M-2000 spectrometer. Microanalyses were performed with a Perkin−Elmer 2400 analyser. Optical rotations were measured on a HORIBA SEPA-300 operating at λ = 589 nm. HPLC analyses were performed on a JASCO TRI ROTOR IV using 4.6 × 250 mm COSMOSIL, Chiralpak AD and Chiralcel OD-H packed column.

Preparation of Benzyl 2-Quinolyl Sulfide (1): DBU (610 μL, 4.08 mmol) was added at room temperature to a solution of 2-quinolinethiol (650 mg, 4.04 mmol) in benzene (12 mL), and the solution was stirred for 30 min. Benzyl bromide (0.49 mL, 4.08 mmol) was then added and the solution was stirred for 210 min. The reaction mixture was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 80:20) to afford **1** (950 mg, 94%). R_f = 0.78 (hexane/ethyl acetate = 80:20). ^{1}H NMR: δ = 4.64 (s, 2 H), 7.17−8.05 (m, 11 H). ^{13}C NMR: δ =

33.9, 120.7, 125.3, 126.0, 127.0, 127.6, 128.0, 128.3, 129.1, 135.4, 138.4, 148.2, 158.8. IR (neat): $\tilde{\nu}$ = 3070, 1620, 1590, 1420, 1300, 1140, 940, 820, 780 cm^{-1}. EIMS: *m*/*z* (%) = 251 (98) [M^+], 218 (100), 174 (50); 129 (80). $C_{16}H_{13}NS$ (251.3): calcd. C 76.46, H 5.21, N 5.57; found C 76.37, H 5.22, N 5.31.

Enantioselective Reaction of Lithiated Benzyl 2-Quinolyl Sulfide with Electrophiles in the Presence of 2a. (*R*)-1,1,2-Triphenyl-2-(2-quinolylthio)-1-ethanol (3): *n*BuLi (1.42 mol L^{-1} solution in hexane, 120 μL, 0.170 mmol) was added at −78 °C to a solution of **1** (23 mg, 0.092 mmol) in cumene (0.5 mL), and the solution was stirred for 10 min. A solution of **2a** (48 mg, 0.179 mmol) in cumene (0.5 mL) was then added, and the reaction mixture was warmed to −50 °C. After stirring for 1 h, a solution of benzophenone (34.5 mg, 0.187 mmol) in cumene (0.5 mL) was added, and the reaction mixture was stirred for an additional hour at −50 °C. Saturated aqueous NH_4Cl was then added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave a residue which was purified by column chromatography (silica gel, hexane/ethyl acetate = 98:2) to afford **3** (38 mg, 95%). $[\alpha]_D^{20}$ = +12.6 (*c* = 0.62, $CHCl_3$). R_f = 0.42 (hexane/ethyl acetate = 80:20). ^1H NMR: δ = 4.79 (s, 1 H), 6.37 (s, 1 H), 7.00−8.20 (m, 21 H). ^{13}C NMR: δ = 57.9, 81.4, 121.5, 125.5, 126.3, 126.5, 126.8, 127.4, 127.8, 128.4, 129.7, 130.3, 135.6, 139.6, 145.0, 146.7, 147.6, 157.4. IR (neat): $\tilde{\nu}$ = 3500, 3040, 1590, 1490, 1300, 1140, 910, 730 cm^{-1}. EIMS: *m*/*z* (%) = 433 (15) [M^+], 251 (100), 128 (52). $C_{29}H_{23}NOS$ (433.6): calcd. C 80.34, H 5.35, N 3.23; found C 80.55, H 5.21, N 3.23. HPLC (Daicel Chiralpak AD, Hexane/*i*PrOH (80:20), 1.0 mL/min) t_R = 22.3 (*S*) and 37.4 (*R*) min (89% *ee*).

(*R*)-2-Methyl-1-phenyl-1-(2-quinolylthio)-2-propanol (4): The reaction was carried out as described in the preparation of **3** but with **1** (32 mg, 0.127 mmol), *n*BuLi (1.50 mol L^{-1} solution in hexane, 98 μL, 0.146 mmol), **2a** (34.5 mg, 0.129 mmol) and acetone (0.012 mL, 0.155 mmol). Usual workup gave the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 98:2) to afford **4** (15.7 mg, 40%). $[\alpha]_D^{20}$ = −403.0 (*c* = 0.22, $CHCl_3$). R_f = 0.31 (hexane/ethyl acetate = 80:20). ^1H NMR: δ = 1.34 (s, 3 H), 1.42 (s, 3 H), 5.16 (s, 1 H), 5.27 (s, 1 H), 7.20−8.00 (m, 11 H). ^{13}C NMR: δ = 26.3, 29.8, 61.1, 73.6, 121.2, 125.7, 126.1, 127.3, 127.5, 127.6, 128.3, 129.2, 130.0, 135.8, 140.1, 147.5, 159.6. IR (neat): $\tilde{\nu}$ = 3376, 3059, 2971, 1614, 1593, 1419, 1376, 1294, 944, 700 cm^{-1}. EIMS: *m*/*z* (%) = 309 (0.4) [M^+], 251 (100), 128 (16), 91 (7), 59 (6). $C_{19}H_{19}NOS$ (309.4): calcd. C 73.74, H 6.20, N 4.52; found C 73.45, H 6.48, N 4.54. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH (95:5), 0.50 mL/min) t_R = 30.1 (*R*) and 33.9 (*S*) min (80% *ee*).

(*R*)-1-[1-Phenyl-1-(2-quinolylthio)methyl]-1-cyclohexanol (5): The reaction was carried out as described in the preparation of **3** but with **1** (41 mg, 0.165 mmol), *n*BuLi (1.5 mol L^{-1} solution in hexane, 130 μL, 1.95 mmol), **2a** (54 mg, 0.200 mmol) and cyclohexanone (0.022 mL, 0.216 mmol). Usual workup gave the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 99:1) to afford **5** (27 mg, 46%). $[\alpha]_D^{20}$ = −387.0 (*c* = 0.20, $CHCl_3$, 81% *ee*); R_f = 0.41 (hexane/ethyl acetate = 80:20). ^1H NMR: δ = 1.42−2.00 (m, 10 H), 3.85 (br, 1 H), 5.36 (s, 1 H), 7.18−8.00 (m, 11 H). ^{13}C NMR: δ = 21.8, 25.6, 37.2, 60.2, 73.9, 121.2, 125.5, 127.2, 127.6, 127.8, 127.9, 128.1, 129.5, 129.8, 135.6, 140.0, 147.6, 159.3. IR (neat): $\tilde{\nu}$ = 3377, 3060, 2929, 2240, 1614, 1593, 1449, 1376, 1294, 1138, 1089, 944, 863, 700 cm^{-1}. EIMS: *m*/*z* (%) = 349 (0.2) [M^+], 251 (100), 128.0 (11), 91 (8). $C_{22}H_{23}NOS$ (349.5): calcd. C 75.60, H 6.65, N 4.01; found C 75.46, H 6.94, N 3.86. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH (95:5), 0.50 mL/min) t_R = 16.0 (*S*) and 17.4 (*R*) min (79% *ee*).

(*R*)-2-Phenyl-2-(2-quinolylthio)-1-ethanol (6): *n*BuLi (1.54 mol L^{-1} solution in hexane, 65 μL, 0.100 mmol) was added to a solution of **1** (20.5 mg, 0.082 mmol) in cumene (0.5 mL) at −78 °C, and the solution was stirred for 10 min. A solution of **2a** (27 mg, 0.102 mmol) in cumene (0.5 mL) was then added, and the reaction mixture was warmed to −50 °C. After stirring for 1 h, a solution of paraformaldehyde (12 mg, 0.408 mmol) in cumene (1.0 mL) was added, and the reaction mixture was warmed to 0 °C and stirred for an additional 3 h. Usual workup gave the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 90:10) to afford **6** (8.0 mg, 35%). $[\alpha]_D^{20}$ = −180.0 (*c* = 0.20, $CHCl_3$, 82% *ee*). R_f = 0.21 (hexane/ethyl acetate = 80:20). ^1H NMR: δ = 2.18 (s, 1 H), 4.27 (d, *J* = 7.3 Hz, 1 H), 4.28 (d, *J* = 6.1 Hz, 1 H), 5.26 (dd, *J* = 6.1, 7.3 Hz, 1 H), 7.20−7.80 (m, 10 H), 7.90−8.00 (m, 1 H). ^{13}C NMR: δ = 52.5, 62.0, 120.9, 125.9, 126.5, 127.7, 128.0, 129.0, 129.5, 130.2, 136.4, 136.5. IR (neat): $\tilde{\nu}$ = 3300, 3080, 2920, 1600, 1500, 1140, 1090, 910, 730 cm^{-1}. EIMS: *m*/*z* (%) = 281 (5) [M^+], 264 (50), 250 (100). $C_{17}H_{15}NOS$ (281.4): calcd. C 72.57, H 5.37, N 4.98; found C 72.67, H 5.17, N 5.09. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH (95:5), 0.50 mL/min) t_R = 45.3 (*R*) and 51.2 (*S*) min (82% *ee*).

1,2-Diphenyl-2-(2-quinolylthio)-1-ethanol (7): The reaction was carried out as described in the preparation of **3** but with **1** (77 mg, 0.306 mmol), *n*BuLi (1.50 mol L^{-1} solution in hexane, 0.24 mL, 0.360 mmol), **2a** (100 mg, 0.375 mmol) and benzaldehyde (40 μL, 0.393 mmol). Usual workup gave the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 98:2) to afford a diastereomeric mixture of **7** (61 mg, 55%). The *syn*:*anti* ratio was determined to be 45:55 by ^1H NMR spectroscopy. R_f = 0.30 (hexane/ethyl acetate = 80:20). ^1H NMR: δ = 5.10−5.30 [br, 1H (*syn*)], 5.43 [d, *J* = 3.8 Hz, 1 H, (*anti*)], 5.50−5.70 [br, 1 H, (*anti*)], 5.62 [d, *J* = 3.8 Hz, 1 H, (*syn*)], 7.00−8.10 (m, 16 H). ^{13}C NMR: δ = 56.6 (*anti*), 59.0 (*syn*), 77.3 (*anti*), 80.0 (*syn*), 121.2, 121.3, 125.7, 126.8, 127.4, 127.7, 127.9, 128.5, 128.2, 129.2, 130.1, 136.0, 136.3, 137.6, 138.5, 140.5, 140.3, 147.6, 159.1. IR (neat): $\tilde{\nu}$ = 3340, 3129, 2927, 2364, 1719, 1592, 1453, 1294, 1138, 1090, 819 cm^{-1}. EIMS: *m*/*z* (%) = 357 (20), 338 (10), 251 (100), 161 (20), 128 (70). $C_{23}H_{19}NOS$ (357.5): calcd. C 77.28, H 5.36, N 3.92; found C 77.01, H 5.48, N 4.06. HPLC (Daicel Chiralcel OD-H, hexane/*i*PrOH (95:5), 0.50 mL/min) t_R = 25.1 (1*S*,2*R*) and 32.4 (1*R*,2*S*) min (93% *ee*) for the *anti* isomer, and 37.6 (1*R*,2*R*) and 42.9 (1*S*,2*S*) min (95% *ee*) for the *syn* isomer.

(*R*)-Phenyl(2-quinolylthio)acetic Acid (8): *n*BuLi (1.50 mol L^{-1} solution in hexane, 230 μL, 0.345 mmol) was added to a solution of **1** (75 mg, 0.30 mmol) in cumene (1.0 mL) at −78 °C, and the solution was stirred for 10 min. A solution of **2a** (98 mg, 0.367 mmol) in cumene (0.5 mL) was then added, and the reaction mixture was warmed to −50 °C. After stirring the mixture for 1 h, CO_2 gas was bubbled through it for 1 h at −50 °C. The solution was quenched with aqueous HCl (1 mol L^{-1}) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 70:30) to give **8** (48 mg, 54%). The enantiomeric excess was determined by HPLC analysis after conversion into its methyl ester. $[\alpha]_D^{21}$ = −84.9 (*c* = 0.25, $CHCl_3$, 83% *ee*). ^1H NMR: δ = 5.38 (s, 1 H), 7.28−8.15 (m, 11 H), 10.2−10.8 (br, 1 H). ^{13}C NMR: δ = 41.0, 120.9, 126.1, 126.8, 128.0, 128.3, 128.8, 129.0, 131.1, 134.4, 137.6, 146.3, 159.3, 171.3. IR (neat): $\tilde{\nu}$ = 3422,

2926, 2367, 1719, 1655, 1591, 1493, 1420, 1138, 818 cm^{-1}. EIMS: *m/z* (%) =; 295 (0.1) [M^+], 249 (30), 233.3 (72), 205 (100), 105 (84). $C_{17}H_{13}NO_2S$ (295.4): calcd. C 69.13, H 4.44, N 4.74; found C 69.00, H 4.54, N 4.77.

(*S*)-1-Phenyl-1-(2-quinolylthio)ethane (9): The reaction was carried out as described in the preparation of **3** but with **1** (50 mg, 0.199 mmol), *n*BuLi (1.55 mol L^{-1} solution in hexane, 190 μL, 0.295 mmol), **2a** (82 mg, 0.309 mmol) and methyl triflate (15 μL, 0.133 mmol). Usual workup gave the crude product which was purified by column chromatography (silica gel, hexane/ethyl acetate = 99:1) to afford a mixture of the product **9** and the sulfide **1**. R_f = 0.71 (hexane/ethyl acetate = 80:20). ^1H NMR: δ = 1.83 (d, *J* = 7.1 Hz, 3 H), 5.41 (q, *J* = 7.1 Hz, 1 H), 7.00−8.05 (m, 11 H). ^{13}C NMR: δ = 22.3, 43.0, 121.0, 125.2, 127.1, 127.5, 128.1, 128.4, 129.5, 135.3. IR (neat): ṽ = 3395, 3060, 2925, 1592, 1494, 1373, 1265, 1137, 942 cm^{-1}. EIMS: *m/z* (%) = 265 (78) [M^+], 128 (26), 105 (100). $C_{17}H_{15}NS$ (265.4): calcd. C 76.94, H 5.70, N 5.28; found C 76.95, H 5.98, N 4.99.

General Procedure for Preparation of Chiral Thiols. (*R*)-1,1,2-Triphenyl-2-sulfanyl-1-ethanol (10): $NaBH_3CN$ (22 mg, 0.349 mmol) was added to a solution of **3** (31 mg, 0.072 mmol) in acetic acid (1.4 mL) at −78 °C, and the solution was stirred for 1 h. Water (1.0 mL) was then added, and the reaction mixture was stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 97:3) to give **10** (21 mg, 94%). $[\alpha]_D^{20}$ = +70.8 (*c* = 0.91, $CHCl_3$, 87% *ee*). R_f = 0.54 (hexane/ethyl acetate = 80:20). ^1H NMR: δ = 2.01 (d, *J* = 3.6 Hz, 1 H), 3.84 (s, 1 H), 5.26 (d, *J* = 3.6 Hz, 1 H), 6.95−7.50 (m, 13 H), 7.65−7.85 (m, 2 H). ^{13}C NMR: δ = 57.9, 81.4, 121.5, 125.5, 126.3, 126.5, 126.8, 127.4, 127.8, 128.4, 129.7, 130.3, 135.6, 139.6, 145.0, 146.7, 147.6, 157.4. IR (KBr) 3500, 3020, 1600, 1490, 1450, 1340, 1160, 1060, 980, 760 cm^{-1}. EIMS: *m/z* (%) = 306 (52) [M^+], 273 (100), 91 (62). $C_{20}H_{18}OS$ (306.4): calcd. C 78.40, H 5.92; found C 78.42, H 5.90.

(*R*)-2-Methyl-1-phenyl-1-sulfanyl-2-propanol (11): The reaction was carried out as described in the preparation of **10** but with **4** (44 mg, 0.142 mmol) and $NaBH_3CN$ (44 mg, 0.698 mmol). Usual workup gave the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 96:4) to afford **11** (22 mg, 81%). $[\alpha]_D^{20}$ = −105.3 (*c* = 0.08, $CHCl_3$, 80% *ee*); R_f = 0.18 (hexane/ethyl acetate = 80:20). ^1H NMR: δ = 1.21 (s, 3 H), 1.31 (s, 3 H), 2.01 (d, *J* = 6.8 Hz, 1 H), 2.22 (br, 1 H), 4.05 (d, *J* = 6.8 Hz, 1 H), 7.22−7.50 (m, 5 H). ^{13}C NMR: δ = 26.1, 28.3, 55.9, 72.6, 127.5, 128.2, 128.6, 129.1. IR (neat): ṽ = 3425, 3060, 1712, 1600, 1494, 1262, 1153, 1077, 957, 890 cm^{-1}. EIMS: *m/z* (%) = 182 (7) [M^+], 149 (100), 132 (59), 59 (30). $C_{10}H_{14}OS$ (182.3): calcd. C 65.88, H 7.74; found C 66.18, H 7.48. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH (97:3), 1.0 mL/min) t_R = 22.1 (*S*) and 26.3 (*R*) min (80% *ee*).

(*R*)-1-(1-Phenyl-1-sulfanyl)methyl-1-cyclohexanol (12): The reaction was carried out as described in the preparation of **10** but with **5** (57 mg, 0.163 mmol) and $NaBH_3CN$ (88 mg, 0.876 mmol). Usual workup gave the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 98:2) to afford **12** (28.5 mg, 80%). $[\alpha]_D^{20}$ = −60.3 (*c* = 0.20, $CHCl_3$, 80% *ee*). R_f = 0.47 (hexane/ethyl acetate = 80:20). ^1H NMR: δ = 1.08−1.95 (m, 10 H), 1.90 (d, *J* = 6.6 Hz, 1 H), 2.01 (s, 1 H), 4.00 (d, *J* = 6.6 Hz, 1 H), 7.22−7.50 (m, 5 H). ^{13}C NMR: δ = 21.8, 25.4, 36.4, 55.4, 72.7, 127.4, 128.2, 128.7, 141.1. IR (neat): ṽ = 3475, 3060, 2930, 2856, 1701, 1601, 1491, 1374, 1287, 1153, 1058, 978 cm^{-1}. EIMS: *m/z* (%) = 222 (4) [M^+], 189 (100), 171 (63), 99 (44), 91 (32). $C_{13}H_{18}OS$ (222.3): calcd. C 70.22, H 8.16; found C 70.09, H 8.29. HPLC (Daicel Chiralpak AD, hexane/*i*PrOH (95:5), 0.5 mL/min) t_R = 18.7 (*R*) and 37.5 (*S*) min (80% *ee*).

(*R*)-2-Phenyl-2-sulfanyl-1-ethanol (13): The reaction was carried out as described in the preparation of **10** but with **7** (8 mg, 0.028 mmol) and $NaBH_3CN$ (9 mg, 0.142 mmol). Usual workup gave the crude product, which was purified by column chromatography (silica gel, hexane) to afford **13** (3.5 mg, 80%). $[\alpha]_D^{20}$ = −73.0 (*c* = 0.12, $CHCl_3$, 82% *ee*) {ref.[9] $[\alpha]_D^{20}$ = +90 (*c* = 0.022, $CHCl_3$, (*S*)-isomer)}. ^1H NMR: δ = 2.00 (s, 1 H), 2.25 (s, 1 H), 3.60−3.80 (m, 1 H), 3.90−4.00 (m, 1 H), 4.10 (ddd, *J* = 6.4, 6.4, 7.8 Hz, 1 H), 7.15−7.45 (m, 5 H).

(*R*)-2-Phenyl-2-sulfanylacetic acid (14): The reaction was carried out as described in the preparation of **10** but with **8** (50.3 mg, 0.170 mmol) and $NaBH_3CN$ (53.5 mg, 0.851 mmol). Usual workup gave the crude product, which was purified by column chromatography (silica gel, hexane) to afford **14** (24.6 mg, 86%). $[\alpha]_D^{20}$ = −109 (*c* = 0.15, 95% EtOH, 82% *ee*) {ref.[10] $[\alpha]_D^{20}$ = −132.4 (95% EtOH, (*R*)-isomer)}. ^1H NMR: δ = 2.60 (d, *J* = 7.8 Hz, 1 H), 4.66 (d, *J* = 7.8 Hz, 1 H), 7.20−7.40 (m, 5 H), 11.5 (s, 1 H).

(*S*)-1-Phenylethanethiol (15): The reaction was carried out as described in the preparation of **10** except but with **9** (25 mg, 0.094 mmol) and $NaBH_3CN$ (30 mg, 0.477 mmol). Usual workup gave the crude product, which was purified by column chromatography (silica gel, hexane) to afford **15** (10 mg, 78%). $[\alpha]_D^{20}$ = −74.5 (*c* = 0.12, Et_2O) {ref.[11] $[\alpha]_D^{20}$ = +91.8 (*c* = 6.06, Et_2O (*R*)-isomer)}. R_f = 0.47 (hexane/ethyl acetate = 80:20). ^1H NMR: δ = 1.67 (d, *J* = 6.9 Hz, 3 H), 1.99 (d, *J* = 5.2 Hz, 1 H), 4.23 (dq, *J* = 5.2, 6.9 Hz, 1 H), 7.18−7.50 (m, 5 H). IR (neat): ṽ = 3584, 3061, 1602, 1492, 1260, 1092, 910, 803, 760 cm^{-1}.

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