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New Chiral Benzothiazine Ligand and Its Use in the Synthesis of a Chiral Receptor

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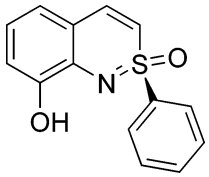
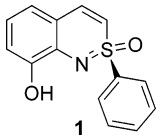


The development of chiral ligands to direct the course and stereoselectivity of many catalytic asymmetric reactions is an important area of interest for many research groups. As part of a program examining the chemistry of 2,1-benzothiazines, we have prepared a new chiral benzothiazine ligand. This ligand can be made in as few as three steps from commercially available starting materials. Presented herein is the synthesis of the ligand along with the synthesis of a chiral molecular receptor that potentially presages a new class of chiral molecular tweezers.

The preparation of ligands in an inexpensive, quick, and efficient manner is of considerable interest to both academic and industrial research. As frameworks for the development of both chiral catalysts and molecular receptors, chiral ligands that can be easily obtained can have a high impact. Our goal is to design a family of ligands based on the 2,1-benzothiazines, in particular, those that contain sulfoximine functionality as the source of chirality. We have reported some progress in this area, but in the context of both catalysis and receptor chemistry, much more needs to be done.[1]

The synthesis of sulfoximine-containing molecules in both racemic and nonracemic forms is a well-developed area where high yields and high reproducibility are noteworthy.[2] In addition to our work, the use of chiral sulfoximine-based ligands has been studied extensively by Bolm.[1b,3−6] In all cases, the ligands show moderate to excellent enantioselectivity in many asymmetric reactions. The variety of reactions containing sulfoximine-based ligands ranges from nickel-catalyzed asymmetric 1,4-additions to enones,[4] palladium-catalyzed C-allylation,[1a,5] vanadium-catalyzed sulfide oxidation,[6] copper-catalyzed Diels−Alder and hetero Diels−Alder reactions,[7] copper-catalyzed 1,4-additions,[8] copper-catalyzed Mukaiyama-type aldol reactions,[9] and iridium-catalyzed imine hydrogenation.[1b] The sulfoximine functional group continues to have promise as a convenient source of chirality that can be useful in catalytic reaction chemistry and stoichiometric chemistry[2] and shows promise in the development of materials for other applications.[10]

The intention of this work was to build a molecule that would serve as the foundation for a family of ligands generally applicable to both catalysis and molecular recognition. We chose **1** as our target, anticipating that the hydroxyl group would be a useful appendage for further functionalization.



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The synthesis of **1** could be achieved by a simple protection of the commercially available 2-bromo-3-hydroxybenzaldehyde under basic conditions to give the protected phenol **2** in 94% yield. Another route to **2** was recently reported in which the conversion of 3-methoxymethoxybenzaldehyde to **2** was achieved in 83% yield, via the Comins method[11] using a sequence of in situ protection/ortho-lithiation.[12] We next used our benzothiazine synthesis[2] to achieve the direct formation of benzothiazine **4** in 89% yield using enantiomerically pure sulfoximine **3**. An attempt to directly form **1** via the coupling of the commercially available phenol with sulfoximine **3** gave no evidence for the formation of **1**. The deprotection of **4** was achieved quantitatively by treatment with *i*-PrOH/HCl/THF (2:1:1)[13] to give benzothiazine **1** (Scheme 1). Upon vapor diffusion of hexane into an ethyl acetate solution containing **1**, crystals suitable for X-ray analysis were formed.[14]

We attempted to synthesize different P−N ligands by reacting **1** with a variety of P(III) reagents. Although in general it appeared that a reaction took place, the products appeared to be hydrolytically quite labile and attempted isolation or trapping

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(14) The X-ray crystal structure and its packing diagram of **1** are available in the Supporting Information.

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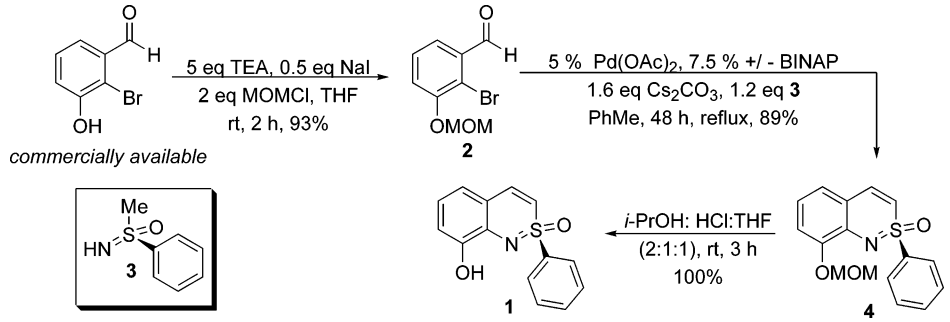
SCHEME 1



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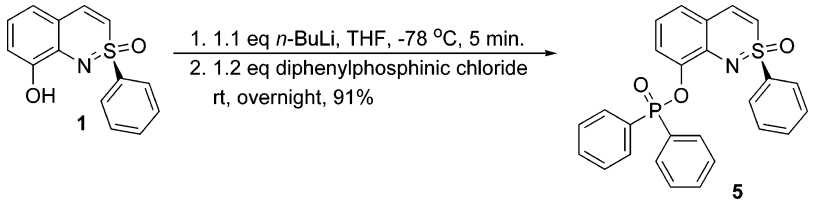
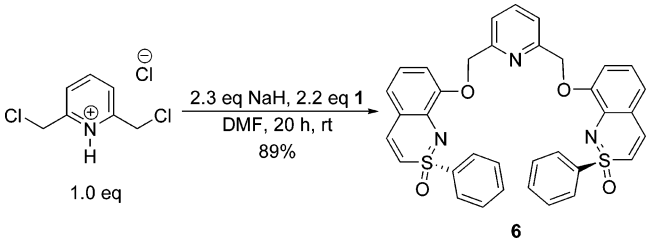


SCHEME 3



with metals was ultimately unsuccessful. However, the functionalization of **1** with a P(V) reagent was quite straightforward. For example, reaction of **1** with diphenylphosphinic chloride gave phosphinic ester **5** in 91% yield as shown in Scheme 2. This compound was stable and easy to isolate and purify and was structurally characterized by both spectral and X-ray analysis.

We subsequently became interested in building systems that could serve as metal binders and possibly assemble into larger chiral arrays, such as helices.[15] We thus reacted enantiomerically pure **1** with 2,6-bis(chloromethyl)pyridinium chloride[16] in the presence of NaH in DMF, obtaining ligand **6** in 89% yield after chromatography, as shown in Scheme 3. To test the metal binding abilities of this ligand, we mixed it with a number of metal salts, particularly with the aim of obtaining a crystalline material that could be characterized by X-ray analysis. Of the metal salts chosen for this study,[17] most formed noncrystalline insoluble precipitates or oils; only the cadmium iodide complex **7** afforded X-ray quality crystals. Attempts to obtain a crystalline sample of the free ligand or a simple (e.g., protonated) derivative were unsuccessful.

We were somewhat disappointed that complex **7** formed with **6** functioning as a tridentate ligand using only a single benzothiazine for binding.[15b] The metal was unable to bind to both sulfoximine nitrogens but rather bound to the ether in two five-membered ring chelates with the pyridine-N and sulfoximine-N as shown in the X-ray structure (see Supporting Information, Figure 1). This result gave new insight to the possibilities of the ligand and some insight as to the reason the molecules were having trouble packing in the crystal lattice. Using both sulfoximines as ligands is sterically disfavored, regardless of the metal. It is likely that the unbound benzothiazine in structures such as **7** makes packing into a crystal lattice difficult, hence the small number of crystalline materials obtained. Therefore, if we remove the unbound benzothiazine, it might be replaced with another group, such as a flat aromatic ring, to produce materials of higher crystallinity that could function as chiral molecular tweezers. We are investigating this idea.

The chiral scaffold embodied in **1** can be potentially modified in many ways, including hydroxyl functionalization and carbanion formation and alkylation, among others. This should make it highly suitable for the generation of large numbers of related chiral ligands for use in both asymmetric synthesis and the generation of chiral species for molecular recognition and supramolecular chemistry. In addition, fundamental insight into the chemistry of these hetereocycles and the sulfoximine functional group will result from such studies. Further work in this area is in progress, and results will be reported in due course.

Experimental Section

2-Bromo-3-(methoxymethoxy)benzaldehyde (2). 2-Bromo-3-hydroxybenzaldehyde (1.0 g, 4.97 mmol) was dissolved in THF (10 mL) along with triethylamine (3.4 mL, 24.8 mmol), NaI (0.372 g, 2.48 mmol) and a stirbar, resulting in a dark orange solution which was then flushed with dry N_2 gas. MOMCl (0.751 mL, 9.94 mmol) was added dropwise resulting in the formation of a precipitate. The reaction was allowed to stir further until TLC showed completion (1 h) (R_f = 0.72 in 50% EtOAc/hexanes; short UV dark spot). The reaction was taken up in water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated

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(17) A table listing the metal salts examined can be found in Table 1 of the Supporting Information.

in vacuo. Purification by flash chromatography, 25% EtOAc/hexanes, yielded **2** (1.13 g, 93%) as a yellow-orange semisolid. Spectral data corresponded to that reported in the literature.[12]

(*R*)-8-(Methoxymethoxy)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (4). Compound **2** (1.00 g, 4.08 mmol), $Pd(OAc)_2$ (45% Pd, 0.046 g, 0.204 mmol), *rac*-BINAP (0.191 g, 0.306 mmol), *R*-methylphenyl sulfoximine **3** (0.759 g, 4.89 mmol), and Cs_2CO_3 (2.12 g, 6.51 mmol) in toluene (80 mL) were combined in a flask which was flushed with dry N_2 for several minutes. A reflux condenser and a N_2 balloon were added, and the mixture was stirred at reflux temperature (120 °C) for 48 h. The solution was then cooled to room temperature, diluted with dichloromethane, filtered through a plug of Celite, and concentrated in vacuo. The dark brown semisolid was purified by flash chromatography (40% EtOAc/hexanes, R_f = 0.60 in 50% EtOAc/hexanes) to afford **4** (1.17 g, 89%) as a yellow-orange semisolid. ^{1}H NMR: (300 MHz, $CDCl_3$) δ 3.53 (s, 3H), 5.33 (q, J = 5.6 Hz, 2H), 6.38 (d, J = 9.8 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 7.07 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.34 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.50−7.62 (m, 3H), 7.63 (d, J = 9.8 Hz, 1H), 7.89 (d, J = 7.2 Hz, 1H). ^{13}C NMR: (300 MHz, $CDCl_3$) δ 56.1, 95.5, 110.4, 117.1, 118.4, 119.7, 123.4, 128.8, 129.1, 133.2, 136.4, 138.5, 141.6, 149.6. IR (NaCl, cm^{-1}) 3020, 1605, 1547, 1434, 1284, 1250, 1153, 1104, 1044, 992, 669. HRMS calcd for $C_{16}H_{15}NO_3SNa$ $[M + Na]^+$, 324.0664; found, 324.0661.

(*R*)-8-(Hydroxy)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (1). Compound **4** (2.43 g, 8.06 mmol) was added to a solution of 2-propanol (32.1 mL, 419 mmol), HCl (12.1 N, 16.6 mL, 201 mmol), and THF (17.05 mL, 209 mmol). The mixture was stirred at room temperature until completion was observed by TLC (3 h). The mixture was diluted with water (20 mL) and extracted by ether (3 × 20 mL). The comibined organic layers were washed with 5% (w/w) $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The remaining yellow-orange solid afforded 2.06 g of phenol **1** which was pure by NMR and TLC (R_f = 0.68 in 50% EtOAc/hexanes; brown/orange long UV spot) in >99% yield. Mp 146−147 °C. The solid can be purified by flash chromatography in 50% EtOAc/hexanes. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 6.37 (d, J = 9.7 Hz, 1H), 6.7 (s, 1H), 6.95 (d, J = 4.7 Hz, 2H), 7.10 (p, J = 4.6 Hz, 1H), 7.54−7.67 (m, 3H), 7.67 (d, J = 9.7 Hz, 1H), 7.88 (d, J = 6.8 Hz, 1H). ^{13}C NMR: (250 MHz, $CDCl_3$) δ 110.2, 114.9, 115.7, 120.2, 120.4, 128.8, 129.1, 133.2, 133.6, 138.7, 141.3, 148.5. IR (NaCl, cm^{-1}) 3460, 3022, 1620, 1592, 1550, 1440, 1278, 1223, 1244, 1206, 1190, 1101, 992, 792, 729, 588, 426. HRMS calcd for $C_{14}H_{11}NO_2SNa$ $[M + Na]^+$, 280.0402; found, 280.0399.

(*R*)-8-(*P*-oxa-*P*-Diphenyl)-2-*S*-oxa-2-*S*-phenyl-2,1-benzothiazine (5). A flask was charged with benzothiazine **1** (0.0587 g, 0.228 mmol) and flushed with dry argon. THF (1.5 mL) was added, and the solution was cooled to −78 °C. *n*-BuLi (2.20 M in hexanes, 0.114 mL, 0.250 mmol) was added dropwise, affording a dark brown solution. This solution was stirred further for 5 min at −78 °C, and then diphenylphosphinic chloride (0.522 mL, 0.273 mmol) was added. The reaction was warmed to room temperature and stirred overnight. MeOH (2 mL) was added, and the solvent was removed in vacuo to afford a yellow oil. Flash chromatographic purification (50% EtOAc/hexanes, then EtOAc; R_f = 0.23 in 50% EtOAc/hexanes) gave **5** (0.0953 g, 91%) as a yellow semisolid. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 6.37 (d, J = 9.8 Hz, 1H), 6.86 (t, J = 7.9 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 7.30−7.50 (m, 5H), 7.54−7.65 (m, 4H), 7.71 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 6.6 Hz, 2H), 8.02 (d, J = 7.5 Hz, 2H), 8.07 (d, J = 7.3 Hz, 2H). ^{13}C NMR: (250 MHz, $CDCl_3$) δ 110.6, 117.5, 119.5, 123.9, 123.9, 125.9, 128.0, 128.2, 128.5, 128.7, 129.0, 129.8, 130.5, 131.9, 132.0, 132.1, 132.8, 133.3, 138.3, 138.3, 141.6, 143.3.^{31}P NMR (250 MHz, $CDCl_3$): δ 32.1. IR (NaCl, cm^{-1}) 3064, 2998, 2927, 2361, 2340, 1609, 1592, 1545, 1444, 1440, 1289, 1131, 1104, 1037, 994, 877, 748, 695, 666.

(*R*,*R*)-2,6-Bis(dimethyl-8-*O*-2-(*S*)-oxa-2-*S*-phenyl-2,1-benzothiazine)pyridine (6). Benzothiazine **1** (0.106 g, 0.414 mmol) in DMF (10 mL) was treated with NaH (60% in mineral oil, 0.026 g, 0.6587 mmol) at 0 °C, resulting in a dark red solution. After 5 min, the 2,6-bis(chloromethyl)pyridinium chloride (0.040 g, 0.188 mmol) was added as a solid. The reaction was allowed to warm to room temperature and was stirred until completion by TLC (20 h) (R_f = 0.15 in 50% EtOAc/hexanes). The reaction was quenched with water (5 mL) and extracted by dichloromethane (3 × 5 mL). The organic extracts were washed with water (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The remaining crude oil was purified by flash chromatography in (50% EtOAc/hexanes; 80% EtOAc/hexanes) to afford **6** (0.073 g, 89%) as an off-white solid. Mp 123−124 °C. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 5.42 (s, 4 H), 6.35 (d, J = 9.8 Hz, 2H), 6.6 (t, J = 7.6 Hz, 2H), 6.95 (d, J = 7.6 Hz, 4H), 7.47−7.66 (m, 11H), 7.89 (d, J = 6.6 Hz, 4H). ^{13}C NMR: (250 MHz, $CDCl_3$) δ 71.6, 110.3, 115.3, 117.0, 119.6, 120.0, 122.3, 128.8, 129.05, 133.2, 136.1, 137.6, 138.5, 141.7, 150.8, 157.0. IR (NaCl, cm^{-1}) 3015, 1605, 1546, 1464, 1449, 1432, 1284, 1256, 1223, 1206, 1105, 1090, 993, 792, 729, 426. HRMS calcd for $C_{35}H_{27}N_3O_4S_2Na$ $[M + Na]^+$, 640.1335; found, 680.1362.

Cd Complex (7). Compound **6** (0.0244 g, 0.00394 mmol) was dissolved in dichloromethane (1 mL) and added to a flask containing CdI_2 (0.0217 g, 0.00592 mmol) in methanol (1 mL) and a stirbar. After flushing with dry N_2, the solution was heated to reflux (40 °C) for 3 h and then cooled to room temperature. The flask was capped and allowed to stand for 48 h during which off-white spikes formed. The crystals were filtered to afford **7** (0.0354 g, 84%) as an off-white solid. Mp 191.5−192.5 °C. The structure was established by X-ray crystal analysis.

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Supporting Information Available: Copies of ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, HRMS, and IR for all new compounds as well as X-ray structure data for the benzothiazine **1**, phosphine oxide **5**, and cadmium metal complex **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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