# Chiral Synthesis via Organoboranes. 46. An Efficient Preparation of Chiral Pyridino- and Thiopheno-18-crown-6 Ligands from Enantiomerically Pure $C_2$-Symmetric Pyridine- and Thiophenediols[1]

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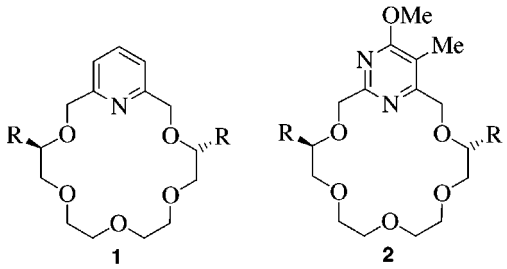
Asymmetric reduction of 2,6-diacylpyridines with *B*-chlorodiisopinocampheylborane provides the corresponding $C_2$-symmetric diols in very high de and ee. Asymmetric allylboration of 2,6-pyridinedicarboxaldehyde and 2,5-thiophenedicarboxaldehyde provides the corresponding bis-homoallylic alcohols in very high de and ee. These optically pure diols were converted to the disodium or dipotassium salts and treated with tetra(ethylene glycol) ditosylate to obtain the corresponding chiral pyridino and thiopheno-18-crown-6 ligands. However, the perfluoroalkyl diols failed to provide the macrocycles.

Attempts to understand the phenomena of molecular recognition occurring in chemical interactions involving enzymes, antibodies, antigens, stereoselective catalysts, etc. led to the rapid development of the area of synthetic host−guest chemistry.[3] Since the serendipitous discovery of dibenzo-18-crown-6 ether three decades ago,[4] systematic research by Pederson,[5] Cram,[6] Lehn,[7] Stoddart,[8] Bradshaw,[9] and others[10] has led to the rational synthesis of receptor molecules with the desired qualities. Pederson postulated a qualitative relationship between the stability of the complex and the ratio of the cation diameter to the ligand cavity diameter,[5] and subsequent research has revealed the importance of cation and ligand parameters. Pirkle's pioneering research involving chiral recognitions for enantiomer separations in chromatographic columns containing chiral macrocyclic ligands led to an empirical three-point rule,[11] which states that "*chiral recognition requires a minimum of three simultaneous interactions between the chiral crown ether and at least one of the enantiomers, with at least one of the interactions being stereochemically dependent.*"

The preparation and properties of chiral crown ethers have attracted considerable attention of analytical, biological, organic, material, and medicinal chemists recently.[12] The syntheses of chiral macrocycles for the selective recognition of enantiomers is an active area of research.[3c] Chiral pyridino- and pyrimidino-18-crown-6 ethers (**1** and **2**) are among them.[9]




The remarkable achievements of organic chemists over the past two decades in developing new chiral reagents and asymmetric synthetic methodologies[13] to prepare most types of organic molecules have made the synthesis of chiral receptor molecules relatively simple. We made our own contributions to the asymmetric synthetic program on the basis of the application of our chiral organoboranes to the synthesis of enantiomerically pure molecules.[14] Our approaches include asymmetric hydroboration, asymmetric reduction, asymmetric allyl- and

(1) (a) Presented at the 213th National Meeting of the American Chemical Society (#ORGN 15), Orlando, FL, August 25, 1996. (b) For a brief discussion of our initial results, see: Ramachandran, P. V.; Brown, H. C. In *Reductions in Organic Synthesis*; Abdel-Magid, A. F., Ed.; ACS Symposium Series 641; American Chemical Society: Washington, DC, 1996; Chapter 5.

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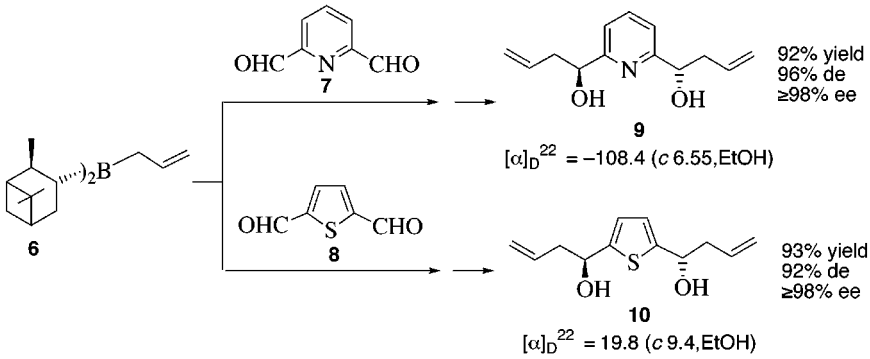
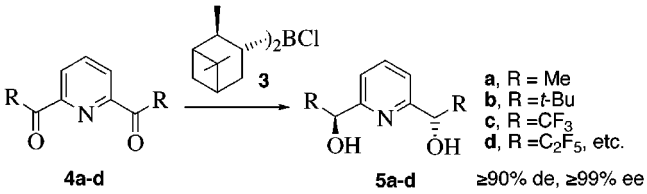
**Scheme 1**



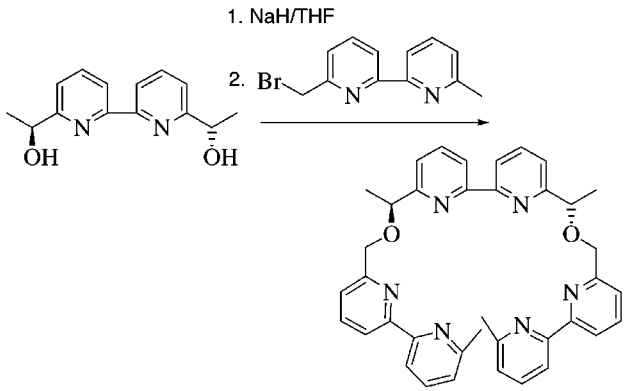

crotylboration, asymmetric enolboration, asymmetric ring-opening of epoxides, asymmetric homologation, etc.

Recently, we applied our asymmetric reduction procedure using *B*-chlorodiisopinocampheylborane (DIP-Chloride) (**3**)[15] to the reduction of diketones, including several 2,6-diacylpyridines (**4a**−**d**), and achieved the synthesis of the corresponding $C_2$-symmetric diols in very high diastereo- and enantiomeric excess (de and ee) (eq 1).[16]

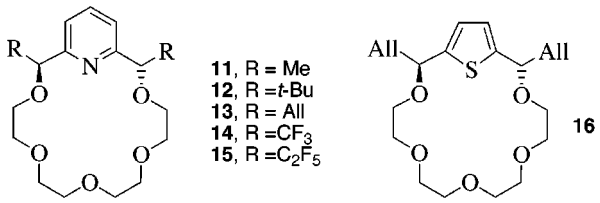



These pyridinediols (**5a**−**d**) have been examined as chiral tridentate ligands for catalytic asymmetric reactions.[17] We have since applied enantioselective allylboration with *B*-allyldiisopinocampheylborane[18] (**6**) to dicarboxaldehydes, including 2,6-pyridine- and 2,5-thiophenedicarboxaldehydes (**7** and **8**, respectively), for the preparation of $C_2$-symmetric bis-homoallylic diols **9** and **10**, respectively (Scheme 1).[19]

On the basis of a recent report by Lehn and co-workers on the synthesis of helical macrocycles from (+)-(*S*,*S*)-bipyridine-6,6′-diethanol and bromomethylbipyridine (eq 2),[20] we envisaged the synthesis of a series of chiral




pyridino- and thiopheno-crown ligands where the chirality arose from the pyridine and thiophenedimethanols. We succeeded in the synthesis of the crown ethers 2,16-dimethyl-, 2,16-di-*tert*-butyl-, and 2,16-diallyl-pyridino-18-crown-6 ligands (**11**−**13**) and 2,16-diallyl-thiopheno-18-crown-6 ligand (**16**). Our attempts to prepare the corresponding 2,16-ditrifluoromethyl- and 2,16-dipentafluoroethyl-pyridino-18-crown-6 ligands (**14** and **15**) have been unsuccessful thus far.




Preliminary results of our success have been reported earlier.[1] Recently, Bradshaw and co-workers have reported the preparation and properties of three of the pyridinyl crown ethers (**11**−**13**) via a cumbersome resolution of racemic **5a**, **5b**, and **9**.[21] Our methodologies involve the asymmetric syntheses of the required diols. The details of our study follows.

## Results and Discussion

Either enantiomer of the necessary diols **5a**−**d** was obtained by the asymmetric reduction of the corresponding diketones with the enantiomers of **3**, as described by us earlier.[16] We obtained **5a** in 59% yield as a 90:10 mixture of the dl and meso components, which were separated as the bis-3,5-dinitrobenzoate via crystallization from chloroform. Enantiomerically pure **5b**, **5c**, and **5d** were obtained in 57%, 72%, and 75% yields, respectively.

During this study, we developed an improved procedure to prepare the diketone **4b**. Sharpless and Hawkins reported a 35% yield of racemic **5b** by treating the 2,6-dilithiopyridine with pivalaldehyde at −78 °C, with subsequent oxidation to **4b** in 80% yield.[22] Our experiences in the synthesis of several of these types of pyridyl ketones from the lithiopyridines suggested that the poor

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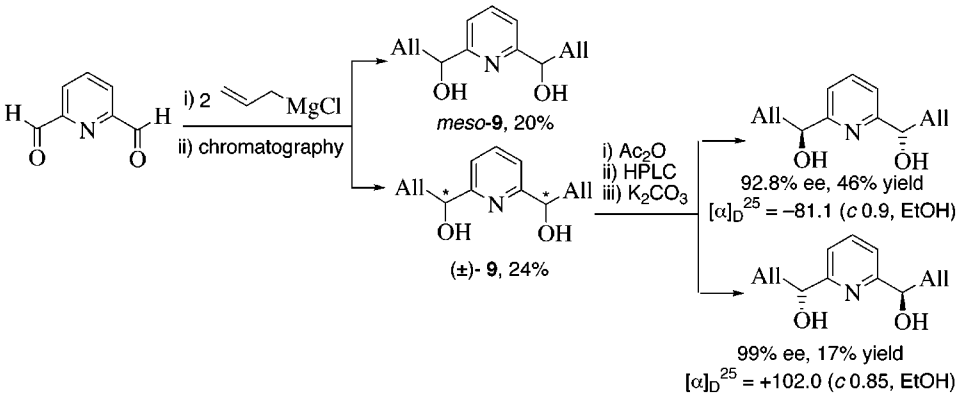
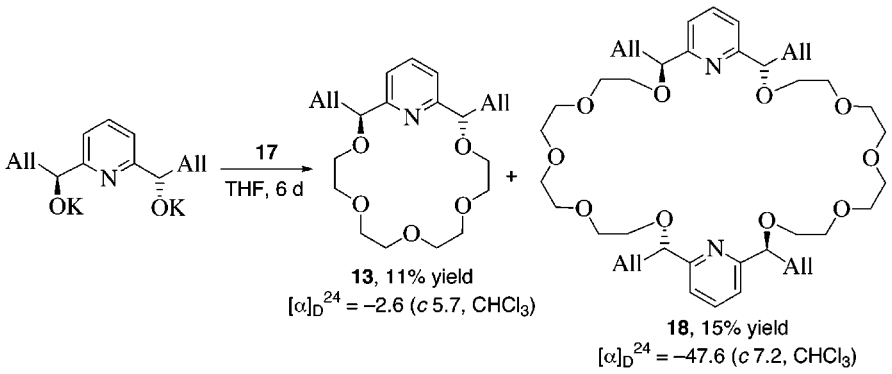
**Scheme 2**




**Scheme 3**

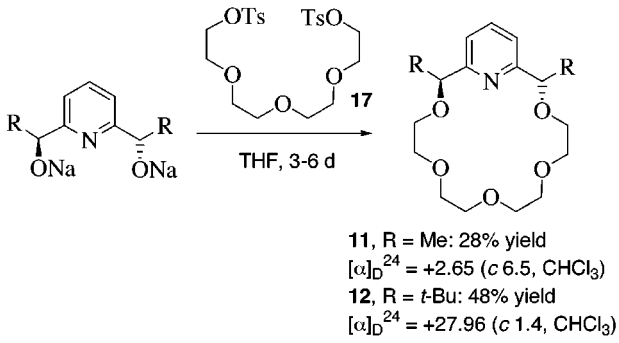



yield might be the result of the instability of the dilithio salt. Accordingly, we conducted the preparation at −100 °C and realized an 83% yield of racemic **5b**. Subsequent oxidation provided an 80% yield of the necessary diketone **4b**, as reported previously.[22]

The allylboration of a series of dicarboxaldehydes, including 2,6-pyridinedicarboxaldehyde (**7**), with **6** was reported by us recently.[19] The reaction in THF at −100 °C provides the product diol (**9**) in 92% yield and 96% de. The dl portion was enantiomerically pure, separated from the meso (2%) over silica gel. Compared to this, the earlier procedure (Scheme 2)[21] using allylmagnesium bromide and **7** provided a mixture of the meso and dl components, separated by column chromatography in 20% and 24% yields, respectively. The dl component was then acetylated and resolved using a Regis−Pirkle column. The experimental procedure involves repeated injections of 20 $\mu$L each of the sample to obtain (−)-**9** in 46% yield and 92.8% ee, and (+)-**9** in 17% yield and 99% ee (Scheme 2).

2,6-Thiophenedicarboxaldehyde (**8**) was allylborated with **6** at −100 °C to obtain **10** in 93% yield and 92% de. Enantiomerically pure **10** was separated from the meso compound by crystallizing the bis-3,5-dinitrobenzoate from hexane/ethyl acetate, followed by hydrolysis (Scheme 1).

**Preparation of Aza-Crown Ethers.** The aza-crown ethers **11**−**13** were prepared using standard procedures.[23] The 2,6-pyridinedimethanols were converted to the corresponding disodium salt with NaH, followed by treatment with the ditosylate (**17**) of the tetra(ethylene glycol) to provide the chiral pyridino-18-crown-6 molecules in 11−48% yields. The reaction of the disodium salt of **5a** showed only one major product by TLC (eq 3).




We isolated 28% of **11** by column chromatography. Bradshaw et al. reported a 1.5% and 0.4% yield, respectively, of **11** and a dimeric compound, (*S*,*S*,*S*,*S*)-2,16,22,-36-tetramethyl-3,6,9,12,15,23,26,29,32,35-decaoxa-41,42-diazatricyclo[36.3.1.1$^{17,21}$]dotetraconta-1(41),17,19,21,37,39-hexaene, from the same reaction. We did not attempt to isolate any of the side products from the residue which may have contained the dimer. The reaction of the disodium salt of **5b** provided a 48% of the desired aza-crown ether **12** (eq 3).

A similar reaction with the dipotassium salt of the diallyl diol **9** with **17** showed two major and several minor products by TLC. We separated the major products by column chromatography, which revealed them to be the required pyridino-18-crown-6 **13** and the dimeric compound **18** (Scheme 3).

Our attempts to prepare the $CF_3$ and $C_2F_5$ analogues **14** and **15**, respectively, have not succeeded thus far. When we applied the same reaction procedure in eq 5 to

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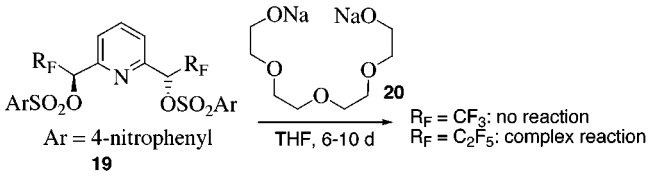
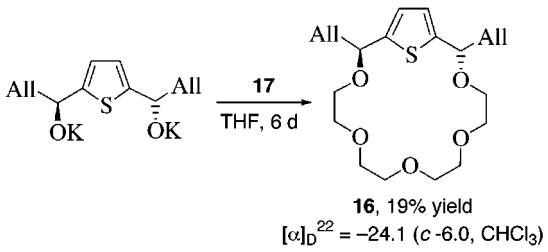
prepare **14**, the TLC of the reaction mixture revealed that no reaction had taken place. Indeed, we recovered 85% of the starting diol after workup. Conducting the reaction under varying conditions of temperature, time, and solvents was not fruitful. With an intention of facilitating the displacement, we attempted the coupling by preparing and utilizing the bis-*p*-nitrobenzenesulfonate of the tetra(ethylene glycol) but failed to achieve the coupling.

In contrast, the reaction of the disodium salt of **5d** with the ditosylate or bis-*p*-nitrobenzenesulfonate of the tetra(ethylene glycol) at reflux for 10 days provided a complex mixture of eight to ten products (TLC). Column chromatography did not provide any of the required ether **15**. The structures of the different products are yet to be determined. We then attempted the coupling of the ditosylate of the perfluoroalkyl pyridinediols (**19**) and the disodium salt of the tetra(ethylene glycol) (**20**) (eq 4). This




also was in vain. We are continuing our efforts to synthesize **14** and **15**.

**Thio-Crown Ethers.** We encountered no difficulty in preparing the new thio-crown ether **16**. Thus, the reaction of the dipotassium salt of **10** with the ditosylate of the tetra(ethylene glycol) in THF at room temperature for 6 days and workup provided 19% of the product (eq 5). There were a number of side products from this




reaction that were not identified.

## Conclusions

In conclusion, we have successfully synthesized several pyridino- and thiopheno-18-crown-6 ligands in 11−48% yield. The possibility of synthesizing several types of enantiomerically pure diols via the asymmetric reduction of diketones with the enantiomers of $Ipc_2BCl$ and the asymmetric allylboration of dialdehydes with the enantiomers of $Ipc_2BAll$ has provided the opportunity to synthesize a variety of chiral crown ethers having substituents differing in their electronic and steric environments for application in host−guest chemistry. We believe that this aspect can be exploited in a systematic study of these chiral crown ethers for molecular recognition.

We are continuing our efforts to synthesize **14** and **15**. We are also synthesizing chiral crown ethers from the chiral diols **5a**−**d**, **9**, and **10** and oligodiols bearing chiral centers.

## Experimental Section

**General Methods**. All operations were carried out under an inert atmosphere. Techniques for handling air- and moisture-sensitive materials have been previously described.[24] The $^1H$, $^{11}B$, and $^{19}F$ NMR spectra were plotted on a Varian Gemini-300 spectrometer with a Nalorac-Quad probe. The optical rotations were measured using a Rudolph Autopol III polarimeter.

**Materials.** Anhydrous ethyl ether (EE) purchased from Mallinckrodt, Inc. was used as received. THF was distilled from sodium/benzophenone ketyl. DIP-Chloride, allylmagnesium bromide, 2,6-pyridinedicarboxaldehyde, 2,5-thiophenedicarboxaldehyde, tetra(ethylene glycol), potassium *tert*-butoxide, *p*-toluenesulfonyl chloride, and 4-nitrobenzenesulfonyl chloride were all obtained from the Aldrich Chemical Co. The diols **5a**−**e** were obtained via the asymmetric reduction of the corresponding diketones with **3**.[16] The diols **9** and **10** were obtained via the allylboration of the corresponding dicarboxaldehydes with **6**.[19] (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) was purchased from the Aldrich Chemical Co. and converted to the acid chloride using Mosher's procedure.[25]

**Preparation of α,α′-Diallyl-2,5-thiophenedimethanol (10).** Allylmagnesium bromide (72.6 mL, 1.0 M, 72.6 mmol) was added dropwise to a well-stirred solution of (−)-**3** (24.45 g, 76.2 mmol) in EE (200 mL) at −78 °C. The mixture was then stirred for 0.5 h at −78 °C, allowed to warm to room temperature, and stirred for 4 h. The solvent was removed under aspirator vacuum, and the residue was extracted with pentane (3 × 150 mL), filtered through a Kramer filter,[24] and concentrated to afford $^d Ipc_2BAll$ (**6**) ($^{11}B$ NMR $\delta$ 79 ppm) in essentially quantitative yield. The above $^d Ipc_2BAll$ was dissolved in THF (100 mL) and cooled to −100 °C. A solution of 2,5-thiophenedicarboxaldehyde (4.06 g, 29.0 mmol) in anhydrous THF (50 mL) was added dropwise over 0.5 h, and the reaction mixture was stirred at −100 °C for 4 h when the reaction was complete ($^{11}B$ NMR shift from $\delta$ 79 to 52 ppm). Addition of methanol (1 mL) to this intermediate, followed by alkaline $H_2O_2$ oxidation, afforded a crude product which was chromatographed (ethyl acetate/hexane, 3:7 as eluent) to provide 6.04 g (93%) of **10**. Analysis of the bis-MTPA ester using $^{19}F$ NMR spectroscopy showed the diol to be of 92% de. The dl component revealed ≥98% ee. $^1H$ NMR ($CDCl_3$) $\delta$ (ppm): 2.32 (d, 2H), 2.57 (m, 4H), 4.88−4.95 (m, 2H), 5.14−5.23 (m, 4H), 5.75−5.90 (m, 2H), 6.82 (s, 2H). $^{13}C$ NMR ($CDCl_3$) $\delta$ (ppm): 43.66, 69.54, 118.81, 123.33, 133.88, 147.02. $[\alpha]^{24}_D$ = +19.87 (*c* 9.4, EtOH).

**Preparation of Tetra(ethylene glycol) Ditosylate.** Tetra(ethylene glycol) (6.66 g, 34.3 mmol) in 200 mL dry THF was added dropwise to a vigorously stirred suspension of NaH (2.64 g, 110 mmol) in dry THF (50 mL) at 0 °C. The reaction mixture was slowly warmed and refluxed for 4 h and then cooled to 0 °C, followed by the addition of tosyl chloride (16.38 g, 85.8 mmol) in dry THF (100 mL). The mixture was warmed to room temperature and stirred for 48 h. The solvent was removed, and the residue was treated cautiously with water and extracted with ethyl ether (3 × 100 mL). The organics were dried over anhydrous $MgSO_4$, concentrated, and purified by column chromatography (hexane/ethyl acetate, 8:2) to provide 16.40 g (96%) of the ditosylate as a colorless viscous oil. $^1H$ NMR ($CDCl_3$) $\delta$ (ppm): 2.43 (s, 6H), 3.50−3.60 (m, 8H), 3.68 (t, 4H), 4.15 (t, 4H), 7.33 (d, 4H), 7.79 (d, 4H).

**Synthesis of Enantiomerically Pure Dimethylpyridino Crown Ether.** (*R*,*R*)-α,α′-Dimethyl-2,6-pyridinedimethanol (1.07 g, 6.4 mmol) in THF (50 mL) was added dropwise to a vigorously stirred suspension of NaH (0.49 g, 20.4 mmol)

(24) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975; Reprinted edition, Vol. 1. Aldrich Chemical Co. Inc.: Milwaukee, WI, 1997; Chapter 9.

(25) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.***1969**, *34*, 2543. As a result of the limitations of the NMR technique, a maximum of ≥98% ee is assigned for the products, although none of the peaks corresponding to the enantiomer was observed.

in dry THF (15 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and warmed to reflux. After refluxing for 2 h, the reaction mixture was cooled to room temperature, followed by the dropwise addition of tetra(ethylene glycol) ditosylate (3.21 g, 6.4 mmol) in THF (100 mL). The mixture was then stirred at room temperature for 3 days, after which the solvent was removed under aspirator vacuum, and the residue was treated with water and extracted with ethyl ether (3 × 40 mL). The organics were dried over anhydrous $MgSO_4$, concentrated, and purified by column chromatography (silica gel; hexane/ethyl acetate, 8:2) to yield 0.59 g (28%) of the dimethylpyridino crown ether **11** as a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 1.50 (d, 6H), 3.35−3.75 (m, 16H), 4.69 (q, 2H), 7.37 (d, 2H), 7.72 (t, 1H). $[\alpha]^{24}_D = +2.65$ (*c* 6.5, $CHCl_3$).

**Synthesis of Enantiomerically Pure Di-*tert*-butylpyridino Crown Ether.** This reaction was carried out according to the above procedure using (*R,R*)-α,α′-di-*tert*-butyl-2,6-pyridinedimethanol (1.26 g, 5.0 mmol), NaH (0.38 g, 16.0 mmol), and tetra(ethylene glycol) ditosylate (3.01 g, 6.0 mmol). The mixture was stirred at room temperature for 6 days, the solvent was removed under aspirator vacuum, and the residue was treated with water and extracted with ethyl ether (3 × 40 mL). The organics were dried over anhydrous $MgSO_4$, concentrated, and purified by column chromatography (silica gel; hexane/ethyl acetate, 8:2) to provide 0.98 g (48%) of the di-*tert*-butyl pyridino crown ether **12** as a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ (ppm): (0.92 (s, 18H), 3.39−3.78 (m, 16H), 4.20 (s, 2H), 7.12 (d, 2H), 7.58 (t, 1H). $[\alpha]^{24}_D = +27.96$ (*c* 1.37, $CHCl_3$).

**Synthesis of Enantiomerically Pure Diallylpyridino Crown Ether.** Enantiomerically pure (*S,S*)-α,α′-diallyl-2,6-pyridinedimethanol (1.55 g, 7.1 mmol) in THF (30 mL) was added to a solution of *t*-BuOK (1.74 g, 15.5 mmol) in THF (10 mL) and stirred for 12 h. Tetra(ethylene glycol) ditosylate (3.56 g, 7.1 mmol) in THF (40 mL) was then added, and the resulting mixture was stirred at room temperature for 6 days. The solvent was removed under aspirator vacumm, and the residue was treated with water and extracted with ethyl ether (3 × 40 mL). The organics were dried over anhydrous $MgSO_4$ and concentrated, and the residue was purified by column chromatography (silica gel; hexane/ethyl acetate, 8:2) to provide 0.29 g (11%) of the diallylpyridino crown ether monomer **13** as a pale yellow oil and 0.40 g (15%) of the dimer crown ether **18** as a pale yellow oil. **13.** $^1$H NMR ($CDCl_3$) $\delta$ (ppm): (2.46−2.63 (m, 4H), 3.30−3.85 (m, 16H), 4.50−4.63 (m, 2H), 4.89−5.10 (m, 4H), 5.67−5.90 (m, 2H), 7.31 (d, 2H), 7.68 (t, 1H). $[\alpha]^{24}_D = -2.58$ (*c* 5.7, $CHCl_3$). **18.** $^1$H NMR ($CDCl_3$) $\delta$ (ppm): (2.48−2.75 (m, 8H), 3.40−3.80 (m, 32H), 4.50−4.65 (m, 4H), 4.90−5.12 (m, 8H), 5.62−5.89 (m, 4H), 7.15 (d, 4H), 7.58 (t, 2H). $[\alpha]^{24}_D = -47.64$ (*c* 7.2, $CHCl_3$).

**Synthesis of Enantiomerically Pure Diallylthiopheno Crown Ether (16).** Enantiomerically pure (*S,S*)-α,α′-diallyl-2,6-thiophenedimethanol (0.73 g, 3.26 mmol) in THF (20 mL) was added to a solution of *t*-BuOK (0.80 g, 7.17 mmol) in THF (5 mL) and stirred for 12 h. Tetra(ethylene glycol) ditosylate (1.64 g, 3.26 mmol) in THF (20 mL) was then added, and the resulting mixture was stirred at room temperature for 6 days. The solvent was removed under aspirator vacuum, and the residue was treated with water and extracted with ethyl ether (3 × 25 mL). The organics were dried over anhydrous $MgSO_4$ and concentrated, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 8:2) to provide 0.15 g of the starting diol and 0.24 g (19%) of the diallylthiopheno crown ether **16** as a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 2.50−2.75 (m, 4H), 3.50−3.70 (m, 16H), 4.54−4.60 (t, 2H), 5.03−5.13 (m, 4H), 5.75−5.90 (m, 2H), 6.80 (s, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 41.25, 67.76, 70.45, 70.68, 77.32, 117.21, 123.81, 134.48, 145.35. Anal. Calcd for $C_{20}H_{30}O_5S$: C, 62.80; H, 7.91; S, 8.38. Found: C, 63.19; H, 8.16; S, 8.31. $[\alpha]^{22}_D = -24.11$ (*c* 6.0, $CHCl_3$).

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra of compounds **10** and **16** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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