Synthesis of Chiral Bis(phosphinite) Ligands with a Tetrahydrothiophene Backbone: Use in Asymmetric Hydrogenation

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A series of novel chiral nonracemic bis(phosphinites) derived from (*R*,*R*)-*trans*-2,5-tetrahydrothiophenedimethanol has been prepared. Reaction of these ligands, **6**, with $Rh(COD)_2X$ (COD = cyclooctadiene, X = $OS(O)_2CF_3$, SbF_6) yields rhodium complexes which have been tested in the asymmetric hydrogenation of methyl α-acetamidocinnamate, providing enantioselectivities of up to 55%. The racemic bis(diphenylphosphinite) ligand **6c** binds in an unusual tridentate mode, forming the thioether-bridged species $((\mathbf{6c})Rh)_2(OTf)_2$ (**7**). This was characterized by conventional spectroscopic methods and by single-crystal X-ray analysis.

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Introduction

The search for new chiral ligands is an ongoing process in the field of asymmetric synthesis.[1] Already more than 1000 chiral nonracemic bis(phosphines) have been synthesized; striking examples of their practical applications include the manufacture of L-Dopa[2] and L-menthol.[3] Despite the proven efficiency of catalysts derived from these ligands,[4] the possibility of discovering improved utility, activity, and selectivity by the design of new ligand classes has continued to stimulate research. Recently, bis(phosphinites)[4p,5] and mixed-donor ligands such as (P,O),[6] (P,N),[7] and (P,S)[8] com-

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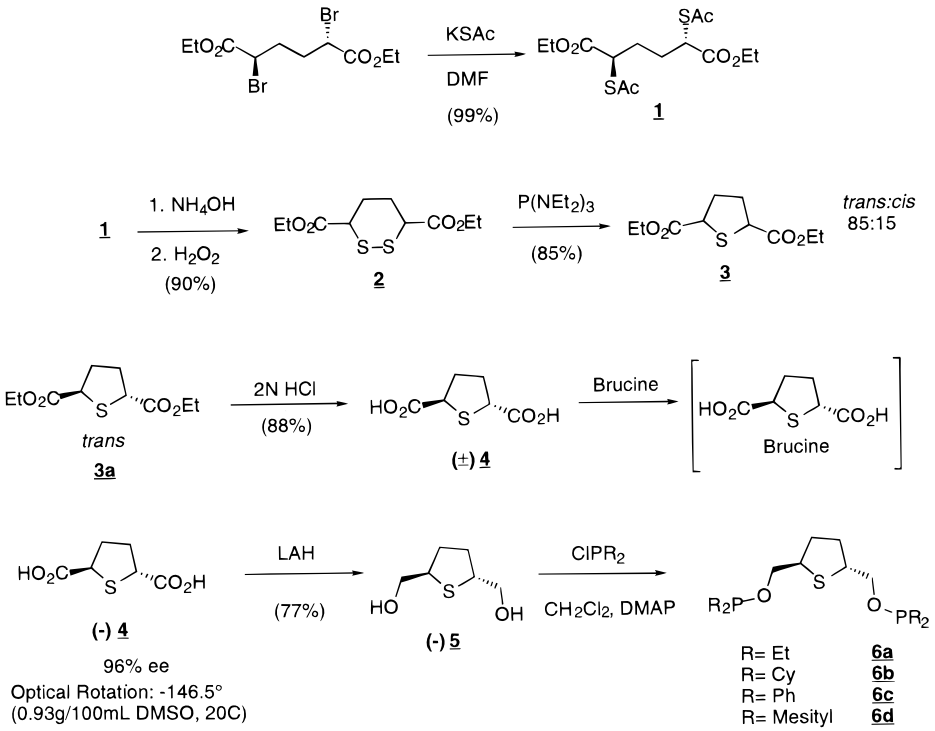
Scheme 1



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pounds have been of great interest and have proved advantageous in some cases. The last class is by far the least explored and has been used with limited success in catalysis. Examples include the carbonylation of methanol,[8m] the hydrogen transfer reduction of ketones (ee up to 20%),[8i,l] and the hydroformylation of styrene (ee up to 14%).[8i] Pregosin has recently reported the synthesis of chiral (P,S) ligands and their use in asymmetric allylic alkylation (ee up to 88%).[8a,c,d] A very recent article by Achiwa reported the use of chiral (P,S) ligands in asymmetric hydrosilylation of ketones (ee up to 57%).[8p] Herein, we report the synthesis of a new class of C_2-symmetric (P,S,P) ligands, their Rh(I) complexes, and their behavior in the asymmetric hydrogenation of methyl α-acetamidocinnamate. An unprecedented bonding mode is observed for one of the ligands which forms a novel bimolecular rhodium complex.

Results and Discussion

Synthesis of Ligands 6. Ligands **6** were synthesized as outlined in Scheme 1. The synthesis of the dicarboxylic acid intermediate **4** was adapted from a previously published procedure.[9] Reaction of diethyl *meso*-2,5-dibromoadipate with 2 equiv of potassium thioacetate in DMF proceeds cleanly to give the corresponding diethyl *meso*-2,5-bis(acetylthio)adipate (99%). The dithiol is then generated in situ by treating compound **1** with ammonium hydroxide and immediately oxidized to the disulfide **2** with hydrogen peroxide. Stoichiometric desulfurization is then carried out with tris(diethylamino)phosphine to yield the tetrahydrothiophene diester **3** as an 85:15 trans:cis mixture. The (±)-trans product is purified by chromatography and hydrolyzed to the corresponding dicarboxylic acid **4**. Resolution of the dicarboxylic acid is then carried out as described by Fredga[9] via the brucine salt (37% yield, 96% ee, $[\alpha]_D$-(DMSO, 0.93 g/100 mL at 20 °C) = −146.5 ± 0.8°).[10] Subsequent lithium aluminum hydride reduction yields the corresponding diol **5** in 77% yield.[11] Treatment of the diol with PR_2Cl in the presence of 4-(dimethylamino)pyridine gives the corresponding bis(phosphinites) **6a**−**d** in good yields (70−93%). Typical features of the ^{1}H NMR spectra include the two diastereotopic protons α to oxygen (multiplets at ca. 3.7 ppm) and the methine group α to sulfur (multiplet at ca. 3.5 ppm). The ^{31}P NMR chemical shifts are typical for dialkyl (140.5 ppm for **6a**, 149.0 ppm for **6b**) and diaryl phosphinites (114.9 ppm for **6c**, 123.1 ppm for **6d**).

Our initial intent was to convert the OH group into a good leaving group (OMs, OTs) and subsequently form a C−P bond using a phosphorus nucleophile. However, this leads to a mixture of nonidentifiable products presumably owing to the nucleophilicity of the sulfur. Degradation of these types of ring systems has been observed by Turos[12a] and Lautenschlaeger.[12b]

Generation of Rhodium Catalysts. The effectiveness of the ligands **6** was evaluated in a simple screen. The asymmetric hydrogenation of (*Z*)-α-(acylamino)-acrylates (enamides) is a standard test for new chiral P-based ligands. Typically, catalysts are generated in situ by mixing $Rh(COD)_2^+X^-$ (COD = cyclooctadiene, X = $OS(O)_2CF_3$, SbF_6, BF_4) and the ligand in a stoichiometric manner. However, we decided to preform the

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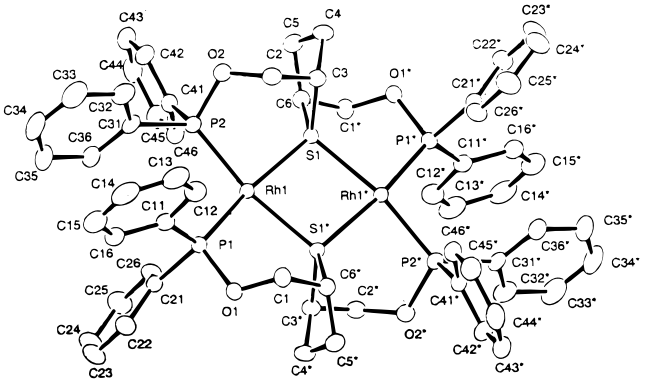
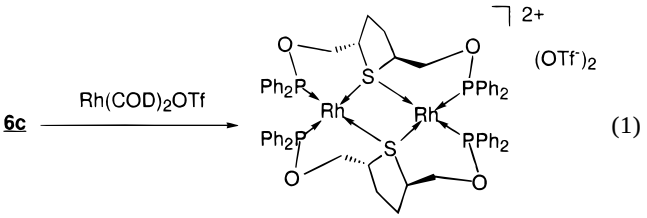


Figure 1. ORTEP drawing of $(\mathbf{6c})_2Rh_2(OTf)_2$ (**7**). Thermal ellipsoids are drawn at the 50% probability level. The counterion $CF_3SO_3^-$ and the hydrogen atoms have been omitted.

rhodium complexes and use them for our hydrogenation runs (see the Experimental Section for details). Results of these studies follow.

In the case of R = Ph, after days of slow recrystallization, we were able to isolate in good yield (73%) the product of the reaction of ligand **6c** (racemic) and $Rh(COD)_2OTf$ ($OTf = OS(O)_2CF_3$).

This unusual complex, **7**, was characterized by ^1H and ^{31}P NMR spectroscopy and X-ray crystallography. ^1H



(1)

7

and ^{31}P NMR spectroscopy indicates the presence of two isomers in a 37:63 ratio. We believe that these are isomers, on the basis of their close chemical shifts and coupling constants in both their ^1H and ^{31}P NMR spectra (see the Experimental Section for more details). We were able to obtain single crystals of one of these isomers[13] by slow recrystallization from THF/hexane at ambient temperature. An ORTEP diagram and labeling scheme are shown in Figure 1. Two additional informative views are shown in Figure 2.

Crystallographic data, collection parameters, and refinement parameters are listed in Table 1; selected interatomic distances and angles are summarized in Tables 2 and 3, respectively. The dinuclear structure of complex **7** results from the displacement of both cyclooctadienes and bridging of the tetrahydrothiophene ring between the two rhodium centers. It consists of discrete binuclear units possessing a center of symmetry at the midpoint of the Rh(1)−Rh(1)* vector, which imposes planarity upon the Rh_2S_2 moiety. Each Rh atom is four-coordinate, displaying square-planar geometry. There are a number of structures containing the Rh−S−Rh−S motif,[15] but to the best of our knowledge this is the only cationic Rh(I) structure possessing a neutral bridging sulfur. Most of the reported structures possess a Rh_2S_2 butterfly core with a thiolate bridge. The Rh−Rh distance, 3.641 Å, indicates that these two metals are not bound directly to each other (typically 2.6−2.8 Å in dinuclear Rh(II) complexes[15f,g]). This distance is long, closer to dinuclear Rh(III) analogues (3.5−3.6 Å)[15a−e] than to dinuclear Rh(I) analogues (2.9−3.4 Å).[15h−l] This might be attributed to a considerable buildup of cationic charge at both rhodium atoms as well as to the planar geometry of the core. This charge buildup could be the result of efficient back-donation from rhodium to sulfur and would result in a strong electrostatic repulsion between the two metal atoms. This also explains the large Rh−S−Rh angle (99.46 Å) closer to Rh(III) (85−100°) than Rh(I) analogues (75−80°). The average Rh−S distance (2.386 Å) is typical.[15]

It is also interesting to note, in light of the chiral amplification phenomenon,[16] that the dinuclear species consists of a combination of the *R*,*R* and *S*,*S* ligands and that many attempts at crystallizing a dinuclear species using an enantiomerically pure ligand failed. However, there does not seem to be any obvious steric reason for this pairwise coupling, and crystallization of the racemate might simply be due to crystal packing requirements. Upon exposure to hydrogen by vigorous bubbling of H_2 through a solution of complex **7** in CD_2Cl_2, no signal broadening or shift is observed in the ^1H NMR spectrum indicating a rather stable species. However, this compound is not inert and was able to readily catalyze the hydrogenation of methyl α-acetamidocinnamate under 60 psi of H_2.

In the case of R = mesityl (ligand **6d**), the ^{31}P NMR and ^1H NMR spectra suggest that two isomers are formed in a 25:75 ratio (close chemical shifts and identical coupling patterns); both isomers possess one coordinated phosphorus (minor isomer, δ at 123.2 ppm, d, J_{Rh-P} = 150 Hz; major isomer, δ at 121.5 ppm, d, J_{Rh-P} = 149 Hz) and one uncoordinated phosphorus (minor isomer, δ at 128.1 ppm, s; major isomer, δ at 127.9 ppm, s). In the ^1H NMR spectrum, integration of the aromatic region versus the remainder of the spectrum indicates the presence of one coordinated cyclooc-

(13) We do not know if the crystal selected for the X-ray diffraction experiment is the major isomer. When the batch of crystals is dissolved (CD_2Cl_2, ambient temperature), a mixture of both isomers is obtained in a ca. 75:25 ratio. Information might be gained by dissolving the crystals at low temperature.

(14) CAChe Version 3.9; Oxford Molecular Group Inc., Oxford, U.K., 1996.

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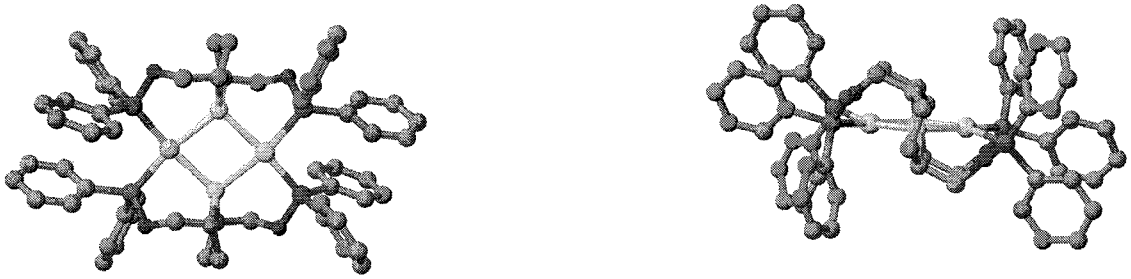


Figure 2. CAChe[14] drawings of $(\mathbf{6c})_2Rh_2(OTf)_2$ (**7**). The counterion $^-OS(O)_2CF_3$ and the hydrogen atoms have been omitted.

Table 1. Crystallographic Data, Collection Parameters, and Refinement Parameters for $(\mathbf{6c})_2Rh_2(OTf)_2$·THF (7)

mol formula	$C_{70}H_{76}Rh_2S_4P_4F_6O_{12}$
fw	1781.34
cryst dimens, mm	0.25 × 0.12 × 0.42
space group	$P2_1/n$
cell params	
a, Å	10.929(1)
b, Å	24.806(1)
c, Å	13.214(1)
β, deg	104.40(1)
V, Å^3	3469.9
Z	2
D_c, g/cm^3	1.609
temp (°C)	−114
radiation (λ (Å))	Mo Kα (0.7107)
monochromator	graphite
linear abs coeff, cm^{-1}	7.5
detector type	R-AXIS-II image plate
2θ limits, deg	$4.6 \le 2\theta \le 48.2$
no. of data frames	45
exposure time, min	15
oscillation range deg/frame	4
total no. of data collected	17 102
no. of unique rflns with $I \ge 3.0\sigma(I)$	4076
R	0.033
R_w	0.042
GOF	2.49
no. of params	442
max Δ/σ	0.01
largest resd density, e/Å^3	0.54

Table 2. Interatomic Distances (Å) for $(\mathbf{6c})_2Rh_2(OTf)_2$ (7)[a]

Rh(1)−S(1)	2.3905(7)	O(1)−C(1)	1.449(3)
Rh(1)−S(1)*	2.3810(7)	O(2)−C(2)	1.445(3)
Rh(1)−P(1)	2.2227(7)	C(1)−C(6)	1.522(4)
Rh(1)−P(2)	2.2203(7)	C(2)−C(3)	1.532(4)
S(1)−C(3)	1.852(3)	C(3)−C(4)	1.523(4)
S(1)−C(6)*	1.840(3)	C(4)−C(5)	1.532(4)
P(1)−O(1)	1.645(2)	C(5)−C(6)*	1.520(4)
P(2)−O(2)	1.630(2)		

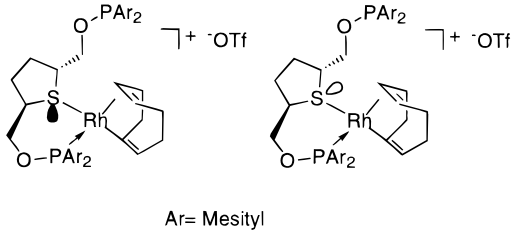
[a] Numbers in parentheses are the estimated standard deviations.

Table 3. Selected Bond Angles (deg) for $(\mathbf{6c})_2Rh_2(OTf)_2$ (7)[a]

S(1)−Rh(1)−S(1)*	80.54(3)	S(1)*−C(6)−C(5)*	106.3(2)
S(1)−Rh(1)−P(1)	167.43(3)	O(1)−C(1)−C(6)	111.4(2)
S(1)*−Rh(1)−P(1)	92.23(3)	O(2)−C(2)−C(3)	114.2(2)
S(1)−Rh(1)−P(2)	88.65(2)	C(2)−C(3)−C(4)	116.9(2)
Rh(1)*−S(1)−C(6)*	114.9(1)	P(1)−Rh(1)−P(2)	97.84(3)
C(3)−S(1)−C(6)*	95.4(1)	Rh(1)−S(1)−Rh(1)*	99.46(2)
Rh(1)−P(1)−O(1)	111.52(7)	Rh(1)−S(1)−C(3)	108.3(1)
Rh(1)−P(2)−(2)	110.36(7)	Rh(1)*−S(1)−C(3)	117.53(9)
P(1)−O(1)−C(1)	117.4(2)	Rh(1)−S(1)−C(6)*	122.34(9)
P(2)−O(2)−C(2)	120.0(2)	C(3)−C(4)−C(5)	109.2(2)
S(1)−C(3)−C(2)	109.9(2)	C(4)−C(5)−C(6)*	108.8(2)
S(1)−C(3)−C(4)	105.3(2)	C(1)−C(6)−C(5)*	116.0(2)
S(1)*−C(6)−C(1)	109.7(2)	S(1)*−Rh(1)−P(2)	168.78(3)

[a] Numbers in parentheses are the estimated standard deviations.

Chart 1



tadiene. Broad signals corresponding to the olefinic protons of the coordinated cyclooctadiene can be found in the 5.7−5.0 ppm region. The bulky nature of the mesityl group prevents the formation of a bimetallic species such as **7**. Likely structures for the two isomers are shown in Chart 1 and are based on simple inversion at S and are consistent with the NMR results.

In the case of the more electron-rich R = cyclohexyl, integration of the olefinic region versus the remainder of the spectrum indicates the presence of one coordinated cyclooctadiene. The ^{31}P NMR spectrum is complex and suggests the presence of a rhodium complex bearing at least three phosphines. The spectrum consists of a doublet of triplets (17%, 166.0 ppm, J = 193 Hz, J = 34 Hz), three doublets in a ca. 1:1:1.5 ratio (46%, δ 153.3 br d, J = 149 Hz; δ 152.9, d, J = 147 Hz; δ 152.8, d, J = 147 Hz), and a very broad doublet of multiplets (37%, δ ca. 150, J is ca. 147 Hz). These NMR data cannot be easily interpreted, and it is clear that a complex mixture of compounds is formed and oligomeric species are likely.[17] The R = ethyl case (ligand **6a**) is similarly complicated. Again, patterns in the ^{31}P NMR spectrum are indicative of a rhodium species with at least three phosphorus ligands attached (ca. 30%, δ 158.1, ddd, J = 188 Hz, $2J$ = 40 Hz; δ 154.6, ddd, J = 147 Hz, $2J$ = 40 Hz). There are also three sets of doublets in a 3:5:2 ratio accounting for 30% of the integrated phosphine resonances (δ 151.9, J = 171 Hz; δ 150.0, J = 150 Hz; δ 149.9, J = 151 Hz). A broad ^{31}P NMR signal (600 Hz) accounting for ca. 40% of the integrated phosphine resonances is also observed. Integration in the ^{1}H NMR spectrum suggests that some of the species formed do not have a coordinated cyclooctadiene. In both the ethyl and cyclohexyl cases, the phosphorus atoms are all metal-bound (no singlets in the ^{31}P NMR spectra). As described above, the ^{1}H and ^{31}P NMR spectra of these catalysts are often complicated by dynamic processes

(17) When the temperature is lowered to −80 °C in an NMR tube, the broad peak sharpens to a multiplet. However, coupling constants could not be correlated with other peaks.

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Table 4. Asymmetric Hydrogenation of Methyl α-Acetamidocinnamate Using Ligands 6a−d, (*R,R*)-Me-DuPhos, and DPPE (Bis(diphenylphosphino)ethane)[a]

ligand	ee, % solvent MeOH	ee, % solvent THF
6a	19	6
6b	55	46
6c	19	25
6d	no reacn	
(*R,R*)-MeDuPhos[b]	97	97
DPPE[b]	0	0

[a] Reactions were carried out at 20−25 °C and 60 psi of H_2 overnight (100% conversion except when noted). Substrate solutions were 1.3 M with 2 mol % catalyst (see the Experimental Section for details). [b] Control experiments.

which presumably result from a combination of exchange between free and coordinated phosphorus, inversion at sulfur,[18] and the formation of bimetallic or oligomeric complexes.[19] The multitude and fluxional nature of these complexes make them difficult to fully characterize or isolate in pure form; therefore they were used without further purification.

Asymmetric Hydrogenation of Methyl α-Acetamidocinnamate. The rhodium complexes which were generated using the chiral nonracemic ligands were tested for asymmetric hydrogenation of methyl α-acetamidocinnamate. The results of this study are shown in Table 4. As can be seen, moderate enantioselectivities were achieved in these hydrogenation reactions. The enantiomeric excess is higher for the bulky and electron-rich ligand **6b** (55%). To our surprise, the "mesityl" ligand **6d** gave no conversion at all under our reaction conditions. This result might be attributed to the generation of a very sterically hindered rhodium complex. In addition, in all cases, the solvent does not appear to have a strong influence on the enantioselectivity, indicating its lack of participation in the enantioselective step.

The enantiomeric excesses (ee's) are moderate but are higher than in any other P,S ligand system used. Higher ee's have been obtained by Pregosin in the allylic alkylation reaction[8a,c,d] and by Achiwa in the hydrosilylation of ketones,[8p] but these processes are sufficiently different from the hydrogenation reaction for a comparison to be meaningful. With further modification of the phosphine substitution, higher ee's might be obtainable.

Conclusions

This paper describes the synthesis of novel phosphorus−sulfur type ligands and the discovery of an unusual mode of coordination of one of these ligands, forming a bimetallic rhodium species. We also have shown that these ligands could be used for enantioselective hydrogenation, and we are currently exploring their use in other asymmetric transformations.

(18) (a) Abel, E. W.; Farrow, G. W.; Orrell, K. G. *J. Chem. Soc., Dalton Trans.* **1976**, 1160. (b) Ascenso, J. R.; de Deus Carvalho, M.; Dias, A. R.; Romao, C. C.; Calhorda, M. J.; Veiros, L. F. *J. Organomet. Chem.* **1994**, *470*, 147. (c) Abel, E. W.; Long, N. J.; Orrell, K. G.; Osborne, A. G.; Sik, V. *J. Organomet. Chem.* **1990**, *394*, 455. (d) Yamazaki, S.; Ama, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 931.

(19) When it is arranged in a bidentate manner, the (P, Metal, S) ring will be in an unfavorable seven-membered conformation.

Experimental Section

General Information. All metal complexes were manipulated under an atmosphere of dry, oxygen-free nitrogen within a Vacuum Atmospheres drybox, on a high-vacuum line, or on a standard Schlenk line. Methylene chloride was distilled in an N_2 atmosphere from phosphorus pentoxide prior to use. Tetrahydrofuran (THF), toluene, diethyl ether, and hexane were distilled under an N_2 atmosphere from sodium/benzophenone. Methanol was distilled from $Mg(OMe)_2$. ^1H and ^{13}C NMR spectra were recorded on either a General Electric 300, Bruker 500, or Varian 500 spectrometer. Chemical shifts were reported by reference to protonated residues of solvents. ^{13}C and ^{31}P NMR chemical shifts are positive downfield (and negative upfield) from external Me_4Si and 85% H_3PO_4, respectively. Elemental analyses were performed by Oneida Research Services, Inc. Hydrogen (99.9995%) gas was purchased from Matheson and used as received. *n*-Butyllithium (1.6 M in hexanes) was purchased from Aldrich. Methyl α-acetamidocinnamate was prepared either by standard Erlenmeyer procedures[20] or by the method of Schmidt et al.[21] Gas chromatographic analyses were performed using a Hewlett-Packard Model HP 5890 GC. A 10 m × 0.53 mm HP-5 (cross-linked 5% phenyl methyl silicone, HP) column was used to follow the progress of the reactions in the synthesis of **2**, **3**, and **5**. A 30 m × 0.25 mm γ-Dex 120 (fused silica capillary, Supelco) column was used to determine enantiomeric excesses in the synthesis of chiral nonracemic **5**. A 25 m × 0.25 mm Chiralsil-L-Val column (chiral fused silica, Chrompack) was used to determine enantiomeric excesses in the asymmetric hydrogenation of methyl α-acetamidocinnamate.

Synthesis of *meso*-Diethyl 2,5-Bis(acetylthio)adipate (1). A 500-mL round-bottomed flask was charged with 60.0 g of potassium thioacetate (0.53 mol) in 120 mL of DMF. The flask was cooled to 0 °C under N_2, and 95 g (0.26 mol) of diethyl *meso*-2,5-dibromoadipate was added in portions. The reaction mixture was held at ambient temperature for 1 h, poured into 400 mL of water, and filtered. The solids were washed several times with water and dried in vacuo to afford 91.5 g (99%) of product, which can be recrystallized from acetone/hexane.

^1H NMR ($CDCl_3$, 23 °C, 300 MHz): δ 4.16 (q, 4H, $J = 7$ Hz, OCH_2CH_3), CH signal under quartet, 2.34 (s, 6H, $C(O)CH_3$), 2.00 (m, 2H, CH_2), 1.79 (m, 2H, CH_2), 1.25 (t, 6H, $J = 7$ Hz, OCH_2CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 23 °C, 75 MHz): δ 193.7 (s, C(O)), 171.1 (s, C(O)), 62.0 (s, CH_2), 45.6 (s, CH), 30.4 (s, CH_3), 29.4 (s, CH_2), 14.2 (s, CH_3). Anal. Found (calcd): C, 47.98 (47.93); H, 6.31 (6.33).

Synthesis of *cis*-Diethyl 1,2-Dithiane-3,6-dicarboxylate (2). A 1 L three-neck round-bottomed flask was charged with 94.2 g (0.27 mol) of compound **1** in 270 mL of EtOH. Then 82 mL of concentrated ammonium hydroxide was added dropwise under nitrogen. The slurry turned into a clear solution. Following the reaction by GC (HP-5) indicates that within 20 min formation of the dithiol was complete. At this point the solution was cooled to 0 °C and neutralized with concentrated HCl. Then 55 mL of 30% H_2O_2 was added dropwise. Gas chromatographic analysis of a sample indicates that the reaction is almost complete in 15 min. The solution was stirred overnight at ambient temperature. EtOH was then removed in vacuo and the product extracted with 3 × 200 mL of CH_2Cl_2. The combined organic layers were washed with 2 × 200 mL of H_2O and dried over $MgSO_4$. After filtration and removal of the solvent, 64.2 g (90%) of product was obtained. It can be purified by chromatography, but the crude product can also be used without purification for the next reaction.

^1H NMR ($CDCl_3$, 23 °C, 300 MHz): δ 4.17 (q, 4H, $J = 7$ Hz, OCH_2CH_3), 3.60 (br m, 2H, CH), 2.46 (m, 2H, CH_2), 2.12 (m, 2H, CH_2), 1.24 (t, $J = 7$ Hz, 6H, OCH_2CH_3). $^{13}C\{^1H\}$ NMR

(20) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159.

(21) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487.

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($CDCl_3$, 23 °C, 75 MHz): δ 170.2 (s, C(O)), 61.8 (s, CH_2), 45.6 (br s, CH), 27.7 (s, CH_2), 14.2 (s, CH_3). Anal. Found (calcd): C, 45.70 (45.43); H, 6.00 (6.10).

Synthesis of *cis*- and *trans*-Diethyl Tetrahydrothiophene-2,5-dicarboxylate (3). A 500 mL round-bottomed flask was charged with 66.3 g (0.25 mol) of compound **2** in 65 mL of toluene, and 61.0 g (0.25 mol) of hexaethylphosphorus triamide was added via syringe over 2 h. The mixture was then stirred at ambient temperature for 12 h, and the solvent was removed in vacuo. The residue was passed through a first silica gel column to remove most of $(Et_2N)_3P{=}S$ and then through a second column to purify the product. *trans*/*cis* = 85/15 (by ^{1}H NMR). A solvent mixture gradient was used (5−15% ethyl acetate/95−85% hexane) to separate the cis from the trans product (the trans product elutes faster than the cis product). The yield of the pure product is 43.8 g (75%).

NMR data of the cis diester **3a**: ^{1}H NMR ($CDCl_3$, 23 °C, 300 MHz) δ 4.06 (q, 4H, J = 7 Hz, OCH_2CH_3), 3.87 (dd, 2H, ^2J = 5 Hz, CH), 2.41 (m, 2H, CH_2), 2.06 (m, 2H, CH_2), 1.17 (t, J = 7 Hz, 6H, OCH_2CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 23 °C, 75 MHz) δ 172.08 (s, C(O)), 61.3 (s, CH_2), 48.9 (s, CH), 32.9 (s, CH_2), 14.0 (s, CH_3).

NMR data of the trans diester **3b**: ^{1}H NMR ($CDCl_3$, 23 °C, 300 MHz) δ 4.06 (q, 4H, J = 7 Hz, OCH_2CH_3), 3.91 (m, 2H, ^2J = 5 Hz, CH), 2.4−2.1 (2 sets of m, 4H, CH_2), 1.17 (t, J = 7 Hz, 6H, OCH_2CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 23 °C, 75 MHz) δ 172.7 (s, C(O)), 61.3 (s, CH_2), 48.4 (s, CH), 32.7 (s, CH_2), 14.0 (s, CH_3). Anal. Found (calcd): C, 51.35 (51.71); H, 6.90 (6.94).

Synthesis and Resolution of (*R*,*R*)-Tetrahydrothiophene-2,5-dicarboxylic Acid (4). The *trans*-2,5-diethyl ester **3b** (16.0 g, 0.069 mol) was treated with 107 mL of 2 N HCl in a 250 mL round-bottomed flask fitted with a Dean−Stark trap and a condenser. The mixture was brought to reflux and the reaction followed by GC (HP-5). The ethanol generated was removed on a regular basis. Once the reaction was complete, the product was extracted with 4 × 100 mL of ethyl acetate. The combined organic layers were washed with brine and dried over magnesium sulfate. After filtration and removal of the solvent 10.8 g (88%) of a white solid is obtained.

The resolution was carried out by adding an equimolar amount of brucine dihydrate to the diacid. Multiple recrystallization from water gave a final yield of 1.6 g (15%) of the enantiomerically pure product: $[\alpha]_D$(20 °C, 1 g/100 mL of DMSO) = −186.4 ± 2.0°, 97.8% ee. This operation was repeated on another batch of *trans*-dicarboxylic acid, and a 37% yield was obtained with a 96% ee ($[\alpha]_D$(20 °C, 0.93 g/100 mL of DMSO) = −146.5 ± 0.8°). This latter batch was used to carry out the synthesis of the chiral ligands. The recrystallization was followed by both optical rotation of the diacid and GC of the corresponding diester. A typical workup procedure is as follows. A sample (223 mg) of diacid/brucine salt was taken up in 3 mL of EtOAc and 1 mL of 4% H_2SO_4. The organic layer was separated and the aqueous layer washed with 3 × 3 mL of EtOAc. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo from the filtrate. A yield of 62 mg is obtained. Half the diacid was dissolved in 0.1 N HCl and submitted for optical rotation measurement. The other half was treated with AG 50W-X8 hydrogen form (acidic resin) in MeOH overnight (100 mg for 1.0 g of resin) to yield the corresponding diester, which can be analyzed by GC (γ-Dex).

^{1}H NMR (DMSO-d_6, 23 °C, 300 MHz): δ 3.99 (br m, 2H, CH), 4.0−2.7 (br s, 2H, CO_2H), 2.3−1.8 (br m, 4H, CH_2). ^{13}C-{^{1}H} NMR (DMSO-d_6, 23 °C, 75 MHz): δ 173.7 (s, C(O)), 48.1 (s, CH), 32.4 (s, CH_2). Anal. Found (calcd): C, 40.62 (40.90); H, 4.54 (4.58).

Synthesis of *trans*-2,5-Tetrahydrothiophenedimethanol (5). A 250 mL round-bottomed flask fitted with a condenser and a 125 mL addition funnel was charged with 3.96 g (0.10 mol) of lithium aluminum hydride (LAH; powder, 95%) and 80 mL of THF. The addition funnel was filled with a solution of the diacid **4** (4.0 g, 0.02 mol) in THF (40 mL). The LAH suspension was cooled to 0 °C, and the diacid solution was added dropwise. Once the addition was complete, the mixture was warmed to ambient temperature and then brought to reflux temperature, where it was kept for 3 h. It was then quenched sequentially with 6.8 mL of H_2O, 3.2 mL of 1 N NaOH, and 10 mL of H_2O. It was once again brought to reflux temperature and kept there for 1 h. The reaction mixture was then filtered and the solids were washed with 4 × 25 mL of THF. The solvent was then removed in vacuo from the filtrate and the resulting oil sublimed under high vacuum. A yield of 2.60 g (77%) was obtained. When enantiomerically pure, the alcohol is a waxy solid. As a racemate, it is a very viscous oil.

^{1}H NMR ($CDCl_3$, 23 °C, 300 MHz): δ 3.58 (m, 6H, C*H* and CH_2OH), 2.48 (br t, J = 6 Hz, 2H, CH_2OH), 2.07 (m, 2H, CH_2), 1.87 (m, 2H, CH_2). ^{13}C{^{1}H} NMR ($CDCl_3$, 23 °C, 75 MHz): δ 65.7 (s, CH_2), 51.6 (s, CH), 32.5 (s, CH_2). Anal. Found (calcd): C, 48.61 (48.62); H, 8.16 (8.16).

Synthesis of *trans*-2,5-Tetrahydrothiophenebis(diethyl phosphinite) (6a). A vial was charged with 187 mg of 4-(dimethylamino)pyridine (DMAP; 1.53 mmol) dissolved in 2.5 mL of toluene. Then 173 mg (1.39 mmol) of chlorodiethylphosphine in 2.5 mL of toluene was added. To this solution was added dropwise a solution of the diol **5** (103 mg, 0.69 mmol) in 5 mL of CH_2Cl_2. It was stirred at ambient temperature for 18 h; the solvent was then removed in vacuo. The residue was taken up in hexane, the solution was filtered, and the solvent was removed in vacuo from the filtrate to give a colorless oil. This was further purified by sublimation. The yield is 180 mg (80%).

^{1}H NMR (C_6D_6, 23 °C, 300 MHz): δ 3.63 (ddd, J = 9 Hz, J = 7 Hz, J = 2 Hz, 4H, CH_2OP), 3.49 (br m, 2H, C*H*S), 1.9−1.6 (br m, 4H, CH_2 tetrahydrothiophene ring), 1.6−1.4 (m, 2H, PCH_2), 1.4−1.2 (m, 2H, PCH_2), 1.06 (m, 6H, PCH_2CH_3). ^{31}P NMR: δ 140.5. ^{13}C{^{1}H} NMR (C_6D_6, 23 °C, 75 MHz): δ 74.1 (d, J_{P-C} = 17 Hz, CH_2O), 49.3 (d, J_{P-C} = 7 Hz, CHS), 31.8 (s, CH_2 of tetrahydrothiophene ring), 25.5 (d, J_{P-C} = 11 Hz, CH_2-CH_3), 25.3 (d, J_{P-C} = 11 Hz, CH_2CH_3), 8.1 (d, J_{P-C} = 7 Hz, CH_2CH_3), 8.0 (d, J_{P-C} = 6 Hz, CH_2CH_3). Anal. Found (calcd): C, 51.56 (51.84); H, 9.21 (9.32).

Synthesis of *trans*-2,5-Tetrahydrothiophenebis(dicyclohexyl phosphinite) (6b). A vial was charged with 198 mg of DMAP (1.62 mmol) dissolved in 2.5 mL of toluene. Then 342 mg (1.47 mmol) of chlorodicyclohexylphosphine in 2.5 mL of toluene was added. This solution was added dropwise to a solution of diol **5** (109 mg, 0.74 mmol) in 5 mL of CH_2Cl_2. This mixture was stirred at ambient temperature for 18 h; the solvent was then removed in vacuo. The residue was taken up in hexane, the solution was filtered, and the solvent was removed in vacuo from the filtrate to give 278 mg of a colorless oil (70%).

^{1}H NMR (C_6D_6, 23 °C, 300 MHz): δ 3.74 (dd, ^2J = 8 Hz, 4H, CH_2OP), 3.57 (br m, 2H, C*H*S), 2.20−1.00 (br m integrated for 48H, CH_2). ^{31}P NMR: δ 149.0. ^{13}C{^{1}H} NMR (C_6D_6, 23 °C, 75 MHz): δ 76.7 (d, J_{P-C} = 20 Hz, CH_2O), 49.3 (d, J_{P-C} = 8 Hz, CHS), 38.46 (d, J_{P-C} = 18 Hz, CH of Cy), 38.43 (d, J_{P-C} = 18 Hz, CH of Cy), 32.0 (s, CH_2 of tetrahydrothiophene ring), 30.0−25.0 (many doublets accounting for CH_2's of Cy). Anal. Found (calcd): C, 66.68 (66.63); H, 9.80 (10.07).

Synthesis of *trans*-2,5-Tetrahydrothiophenebis(diphenyl phosphinite) (6c). A 100-mL round-bottomed flask was charged with 296 mg of DMAP (2.42 mmol) dissolved in 20 mL of toluene. Then 486 mg (2.20 mmol) of chlorodiphenylphosphine in 20 mL of toluene was added. This was followed by dropwise addition of 163 mg (1.10 mmol) of diol **5** dissolved in 10 mL of CH_2Cl_2. Upon addition a white precipitate forms immediately. After the mixture was stirred at ambient temperature for 24 h, the solvent was removed in vacuo. The residue was then taken up in toluene, the solution was filtered,

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and the solvent was removed in vacuo from the filtrate to give 528 mg of a colorless oil (93%).

^{1}H NMR (C_6D_6, 23 °C, 300 MHz): δ 7.60 (m, 8H, Ar), 7.12 (m, 12H, Ar), 3.72 (m, 4H, CH_2OP), 3.44 (brm, 2H, CHS), 1.55 (m, 4H, CH_2). ^{31}P NMR: δ 114.9. ^{13}C{^{1}H} NMR (C_6D_6, 23 °C, 75 MHz): δ 142.9 (d, J_{P-C} = 19H, quaternary C), 130.78 (d, J_{P-C} = 22 Hz, Ar C−H), 130.73 (d, J_{P-C} = 22 Hz, Ar C−H), 129.5 (s, Ar C−H), 128.6 (d, J_{P-C} = 6 Hz, Ar C−H), 73.7 (d, J_{P-C} = 19 Hz, CH_2O), 49.1 (d, J_{P-C} = 8 Hz, CHS), 31.9 (s, CH_2). Anal. Found (calcd): C, 69.46 (69.75); H, 5.71 (5.85).

Synthesis of *trans*-2,5-Tetrahydrothiophenebis(dimesityl phosphinite) (6d). A vial was charged with 236 mg of DMAP (1.93 mmol) dissolved in 2.5 mL of toluene. Then 535 mg (1.76 mmol) of chlorodimesitylphosphine in 2.5 mL of toluene was added. To this solution was added dropwise a solution of diol **5** (130 mg, 0.88 mmol) in 5 mL of CH_2Cl_2. This mixture was stirred at ambient temperature for 18 h; the solvent was then removed in vacuo. The residue was then taken up in hexane (40 mL), the solution was filtered, and the solvent was removed in vacuo from the filtrate. Traces of DMAP can be removed by sublimation under high vacuum. The yield was 521 mg (87%).

^{1}H NMR (C_6D_6, 23 °C, 300 MHz): δ 6.68 (d, J = 2.5 Hz, 4H, Ar), 3.66 (m, 4H, CH_2OP), 3.31 (brm, 2H, CHS), 2.44 (s, 12H, CH_3), 2.07 (s, 6H, CH_3), 1.6−1.3 (br m, 4H, CH_2 tetrahydrothiophene ring). ^{31}P NMR: δ 123.1. ^{13}C NMR (C_6D_6, 23 °C, 75 MHz): δ 141.4 (d, J = 11 Hz, quaternary C), 141.3 (d, J = 11 Hz, quaternary C), 138.6 (s, quaternary C), 138.5 (s, quaternary C), 135.3 (s, quaternary C), 135.1 (s, quaternary C), 130.3 (d, J_{C-H} = 150 Hz, C−H Ar), 128.3 (d, J_{C-H} = 158 Hz, C−H Ar), 74.1 (dt, J_{P-C} = 25 Hz, J_{C-H} = 145 Hz, CH_2O), 49.2 (d, J_{P-C} = 9 Hz, J_{C-H} = 142 Hz, CHS), 32.1 (t, J_{C-H} = 129 Hz, CH_2 of tetrahydrothiophene ring), 22.47 (q, J_{C-H} = 127 Hz, CH_3), 22.44 (q, J_{C-H} = 127 Hz, CH_3), 22.36 (q, J_{C-H} = 127 Hz, CH_3), 22.33 (q, J_{C-H} = 127 Hz, CH_3), 20.9 (q, J = 126 Hz, $2CH_3$). Anal. Found (calcd): C, 73.39 (73.65); H, 8.04 (7.95).

Typical Procedure for the Generation of Rhodium Catalysts. A vial was charged with the ligand (0.15 mmol) in ca. 7 mL of THF. This solution was added dropwise to a suspension of $Rh(COD)_2SbF_6$ (0.15 mmol) in 3 mL of THF ($Rh(COD)_2OTf$ can be used as well). Upon addition the suspension turns clear orange. After the mixture was stirred overnight (18 h) at ambient temperature, the solvent was removed in vacuo. The residue was triturated with hexane until a solid was obtained. The solid was isolated by filtration, washed with hexane, and dried in vacuo. Yields ranged from 85% to 93%. These complexes were used as obtained for catalysis. NMR spectra were often complicated by the presence of a mixture of isomers and fluxional processes which may be associated with dechelation, sulfur inversion, and possible formation of oligomeric species (broad signals). No attempts were made to elucidate the details of these processes or to fully assign the signals (see Results and Discussion for details). The synthesis and spectroscopic analysis of complex **7** are described below.

Typical Procedure for the Hydrogenation Runs. Hydrogenation reactions were carried out using 2 mol % catalyst (2.6×10^{-2} M in THF or MeOH) and a 1.3 M solution of substrate, PhC(H)C(CO_2Me)(NHAc), in MeOH or THF. The reaction vessel was placed at 60 psi of H_2 and the mixture stirred at ambient temperature for 16 h. Conversion analysis was achieved by ^{1}H NMR spectroscopy, and analysis of the enantiomeric excess was done by GC (Chirasil-Val-L). Rhodium catalysts were not soluble in MeOH and were added as a slurry when this solvent was used. The substrate was not soluble in THF and was added as a slurry when used. Results are given in Table 4.

Synthesis of the Rhodium Complex 7. A vial was charged with 292 mg (0.57 mmol) of ligand **6c** in ca. 10 mL of THF. This solution was added dropwise to a suspension of 264 mg of $Rh(COD)_2OTf$ (0.56 mmol) in 5 mL of THF. Upon addition the solution turns clear orange. After the mixture was stirred overnight (18 h) at ambient temperature, the solvent was removed in vacuo. The residue was triturated with hexane until a solid was obtained. It was isolated by filtration, washed with hexane, and dried in vacuo. This solid was recrystallized over several days from THF/hexane at ambient temperature. A total yield of 158 mg (73%) is obtained. ^{31}P NMR indicates the presence of two isomers in a 37:63 ratio. Several crystallizations indicate that the minor isomer crystallizes first and the filtrate is consistently enriched in the "major isomer".

^{1}H NMR (CD_2Cl_2, 23 °C, 300 MHz): δ 8.5−6.5 (m, aromatics), 6.12 (br t, major isomer, J = 12 Hz), 5.82 (br t, J = 12 Hz, minor isomer), 4.5−4.0 (m), 2.0−1.0 (m). ^{31}P NMR: δ 136.3 (d, J_{Rh-P} = 184 Hz, major isomer), 135.7 (d, J_{Rh-P} = 184 Hz, minor isomer). Key ^{13}C NMR features of the two isomers: isomer 1 (63%) δ 150−115 (aromatic carbons), 76.7 (t, J_{C-H} = 148 Hz, CH_2), 57.7 (d, J_{C-H} = 146 Hz, CH), 33.6 (t, J_{C-H} = 139 Hz); isomer 2 (37%) δ 150−115 (aromatic carbons), 75.3 (t, J_{C-H} = 150 Hz, CH_2), 56.6 (d, J_{C-H} = 148 Hz, CH), 33.8 (t, J_{C-H} = 139 Hz). Anal. Found (calcd): C, 48.61 (48.45); H, 4.29 (3.93).

X-ray Structural Analysis of the Rhodium Complex 7. A single golden crystal of **7** (irregular block, ca. 0.25 × 0.12 × 0.42 mm) was grown by diffusion from THF/hexane at ambient temperature. The crystal is monoclinic ($P2_1/n$, No. 14) with the following cell dimensions (μ(Mo Kα) = 7.50 cm^{-1}): a = 10.929(1) Å, b = 24.806(1) Å, c = 13.214(1) Å, β = 104.40-(1)°; V = 3469.9 Å^3, Z = 2; fw 1781.34 ($C_{70}H_{76}Rh_2S_4P_4F_6O_{12}$); calculated density 1.609 g/cm^3.

Data were collected at −114 °C on a Rigaku RU 300 diffractometer with an R-AXIS image plate area detector. (Mo Kα radiation; anode power 55 kV × 200 mA; crystal to plate distance 85.0 mm; 105u pixel raster; number of frames 45; oscillation range 4.0°/frame; exposure 15.0 min/frame; box sum integration). A total of 17 102 data were collected ($4.6° \leq 2\theta \leq 48.2°$; maximum h, k, l 11, 28, 15; no absorption correction, 4591 duplicates; 1.7% R(merge); 4076 unique reflections with $I \geq 3.0\sigma(I)$). Because test data sets have shown I sigma's from R-AXIS software to be unrealistically small, a value of 5.0 was added to all $\sigma(I)$'s.

The structure was solved by direct methods (SHELXS); the refinement was carried out by full-matrix least squares on F (H atoms fixed, all other anisotropic). The scattering factors were taken from ref 22, including anomalous terms for Rh, S, P (biweight $\propto [\sigma^2(I)+0.0009I^2]^{-1/2}$; excluded 10).[22] There were 442 parameters, and the data-to-parameter ratio was 9.20; final R = 0.033 (R_w = 0.042). The error of fit is 2.49 with a maximum Δ/σ = 0.01. Because the refinement for a few hydrogens gave thermal parameters larger than desired (15.1), all of the hydrogens have been idealized close to their previously refined positions. The largest residual density is 0.54 e/Å^3 near C64.

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Supporting Information Available: X-ray data for **7**, including tables of fractional coordinates and isotropic thermal parameters, anisotropic thermal parameters, interatomic distances, intramolecular angles, intramolecular nonbonding distances, intermolecular distances, and two ORTEP diagrams of **7** (7 pages). Ordering information is given on any current masthead page.

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(22) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. 4.