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Synthesis of a Substituted Tetrahydropyrimidopyrimidine

Jack Lee Parsons

HOMOGENEOUS CATALYTIC HYDROGENATION OF ORGANIC COMPOUNDS USING RHODIUM-TRIARYLPHOSPHINE COMPLEXES

by

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INTRODUCTION

The purpose of this research was to study the homogeneous catalytic hydrogenation of α,β-unsaturated organic compounds containing a wide variety of reducible functional groups. The catalysts to be used were rhodium complexes of triarylphosphines. It was also desired to develop these catalytic systems into practical synthetic methods for the reduction of unsaturated compounds.

HISTORICAL REVIEW

Homogeneous catalytic hydrogenation of organic compounds was first reported in 1962 by Kwiatek and co-workers.[1] The catalyst used in this work was pentacyanohydridocobaltate(II), prepared and used *in situ* from an aqueous solution of potassium chloride, potassium cyanide and hydrogen gas. Using this catalyst, the carbon-carbon double bonds in several terminal olefins such as alkenes, α,β-unsaturated acids, and α,β-unsaturated esters were reduced at atmospheric pressure and room temperature. A disadvantage of this catalytic system is that its applicability is limited to water soluble compounds.

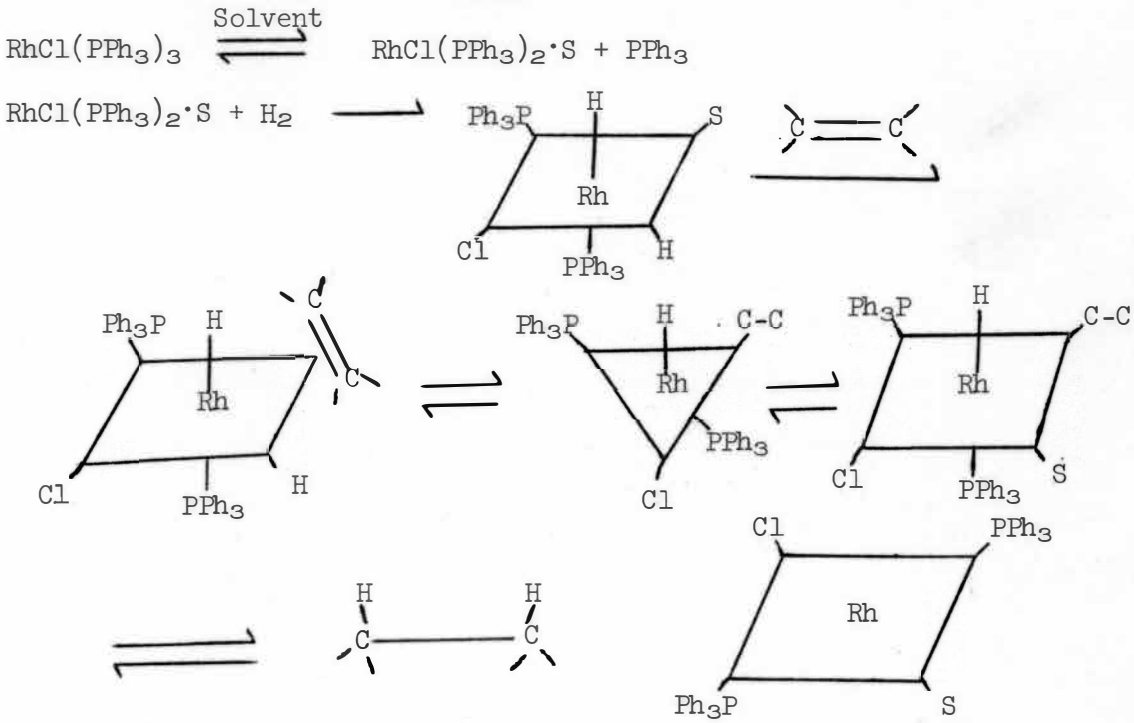
Wilkinson and co-workers[2] reported in 1965 that chlorotris(triphenylphosphine)rhodium(I) will homogeneously catalyze the hydrogenation of simple alkenes at room temperature and atmospheric pressure. In 1966, Wilkinson and co-workers,[3] using this catalyst, reported an extensive quantitative study on the rates of hydrogenation of hept-1-ene, cyclohexene, and hex-1-yne as a function of catalyst concentration, temperature, and pressure.

Chlorotris(triphenylphosphine)rhodium(I) has been used in the last three years to reduce simple α,β-unsaturated organic compounds. Birch and Walker[4] reported that this catalyst was used to reduce β-nitrostyrene to 2-phenylnitroethane; however the saturated nitro compound was not fully characterized. Wilkinson and co-workers[5] selectively reduced acrylamide and acrylonitrile to obtain the saturated amide and cyanide. Jardine and Wilkinson[6] attempted, with

very little success, the selective reductions of α,β-unsaturated aldehydes to saturated aldehydes. This complex has been used by Djerassi and Gutzwiller[7] to reduce some unsaturated keto steroids to the saturated keto steroids.

A mechanism by which chlorotris(triphenylphosphine)rhodium(I) activates molecular hydrogen has been proposed. Wilkinson and co-workers[3] and Collman[8] have postulated the activation process as follows: Chlorotris(triphenylphosphine)rhodium(I) dissociates in solution to give the solvated chlorobis(triphenylphosphine)rhodium(I) and triphenylphosphine. Molecular hydrogen reacts oxidatively with the dissociated complex to give a cis addition product. The olefinic bond of the substrate is bonded to the intermediate hydrido species at the coordination site previously occupied by the solvent molecule. The hydrogen atoms are transferred in a cis manner to the olefin. The reduced substrate is then replaced by a solvent molecule, and the catalyst is regenerated. Heck[9] pictures the hydrogen transfer step as going through a five coordinate bipyramidal rhodium(III) species. This entire process is outlined in Scheme(I).

SCHEME I



Rhodium(III) complexes have been used more sparingly as hydrogenation catalysts. Knowles and Sabacky[10] have used trichlorotris (methylpropylphenylphosphine)rhodium(III) to reduce atropic acid and itaconic acid under conditions of high temperature and pressure. Jardine and McQuillin[11] reported the reaction of trichlorotripyridylrhodium(III) with sodium borohydride using liquid amides as the solvent to obtain complexes of the following type py_2amide $RhCl_2(BH_4)$ which homogeneously catalyze the hydrogenation of simple alkenes. Trichlorotris(diethylsulfide)rhodium(III)[12] in liquid amides also furnishes a catalyst for the reduction of alkenes.

Horner and co-workers[13] have recently reported a study on catalytic hydrogenation of the isomeric pentenes using rhodium trichloride with trialkyl and triarylphosphines. The rates were determined as a function of ligand to metal ratio. It was found that

tertiary amines enhance the rate of reaction. Horner postulated the mechanism by which coordinatively saturated rhodium(III) complexes activate molecular hydrogen. The difference between this mechanism and the one Wilkinson proposed for rhodium(I) complexes, involved the addition of hydrogen to rhodium. Horner proposed that two molecules of hydrogen react to give the dihydrido solvated species and two molecules of hydrogen chloride. Thus, hydrogen is not oxidatively added to the rhodium but a substitution reaction occurs. This explains the enhancement of reduction by the addition of triethyl amine. Scheme II shows this process.

SCHEME II

$$RhCl_3 + 3PAr_3 \longrightarrow RhCl_3(PAr_3)_3$$

$$RhCl_3(PAr_3)_3 + H_2 + Solvent \longrightarrow RhHCl_2(PAr_3)_2 \cdot S + PAr_3 + HCl$$

$$RhHCl_2(PAr_3)_2 \cdot S + H_2 + NR_3 \longrightarrow RhH_2Cl(PAr_3)_2 + HCl \cdot NR_3$$

Other transition metal complexes besides cobalt and rhodium have been used to a lesser extent as homogeneous hydrogenation catalysts. Vaska[14] has used $IrCl(CO)(PPh_3)_2$, $IrH(CO)(PPh_3)_2$, and $OsHCl_2(CO)(PPh_3)_2$ as catalysts. These complexes have been used to homogeneously catalyze the hydrogenation of ethylene, propylene, and acetylene. However, it has been shown that these complexes are much less efficient catalysts than the rhodium complexes. Ruthenium-phosphine complexes were found to be active homogeneous hydrogenation catalysts. Hydridochlorotris(triphenylphosphine)ruthenium(II)[15] was found to be very selective for the reduction of alk-1-enes, however the general applicability of this catalyst is limited by

its selectivity for terminal olefins.

One additional transition metal complex that has received considerable attention is dichlorobis(triphenylphosphine)platinum(II). tin(II)chloride. Bailar and co-workers[16] have reported several studies in which this complex has been used to homogeneously catalyze the hydrogenation of polyenes to monoenes. This compound will not catalyze the reduction of a monoene, but has been used successfully to reduce long chain polyunsaturated acids to acids containing one carbon-carbon double bond.

EXPERIMENTAL

Experimental Procedure. All hydrogenations were performed in a Parr Model 4500 Medium Pressure Reaction Vessel. The solvents used for hydrogenations were deoxygenated by refluxing under a stream of argon for three hours and stored under argon. The solutions were transferred to the reaction vessel under argon and flushed with hydrogen five times.

Analytical Procedure. Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. The nmr spectra were obtained with a Varian A-60 spectrometer. A Beckman IR-8 spectrophotometer was used to determine the ir spectra. All rotations were determined on a Standard Model D Keston Photoelectric Polarimetric Unit attached to a Beckman DU spectrophotometer.

Chemicals. Chlorotris(triphenylphosphine)rhodium(I), was prepared according to the procedure of Wilkinson and co-workers[3] and was obtained in 94% yield, mp 156-8°, Lit.mp 157-8°. α-Acetamido cinnamic acid was prepared according to the procedure of Herst and Shermin,[17] mp 189-91°, Lit.mp 191-2°. p-Nitro-β-nitrostyrene, mp 201-3°, Lit.mp 203°, 3,4-methylenedioxy-β-nitrostyrene, mp 156-9°, Lit.mp 159°, and 3-methoxy-4-benzyloxy-β-nitrostyrene, mp 120-2°, Lit.mp 122°, were prepared by reacting nitromethane with the corresponding substituted benzaldehyde according to the procedure of Lange and Hambourger.[18] Benzalacetophenone, mp 60-2°, Lit.mp 62°, and

3,4-diphenyl-3-buten-2-one, mp 53-5°, Lit.mp 55°, were prepared by the condensation of benzaldehyde with acetophenone and phenyl acetone respectively, following the procedure of Zimmerman and co-workers.[19] The remaining starting materials used were purchased as reagent grade. Their purity was checked by melting points, ir, and nmr spectroscopy.

The Hydrogenation of α,β-Unsaturated Acids

The general procedure followed is exemplified by the hydrogenation of 2,3-diphenylacrylic acid. Chlorotris(triphenylphosphine) rhodium(I) (0.40 g, 0.44 mmole) was added to a solution of 2,3-diphenylacrylic acid (2.0 g, 9.0 mmole) in 200 ml of benzene-ethanol (1:1) under argon. The resulting clear red solution was transferred under an argon atmosphere to the medium pressure reaction vessel. After flushing 5 times with hydrogen, the reaction mixture was stirred for 12 hr at 60° and a hydrogen gas pressure of 80 psi. The pressure was released and the solution evaporated to dryness under reduced pressure. The residue was mixed with 200 ml of 5% NaOH and filtered to remove the insoluble catalyst. The filtrate was acidified with dilute HCl and extracted 4 times with 50 ml of ethyl ether. After drying and evaporating the ether, 1.7 g (85%) of 2,3-diphenylpropionic acid, mp 77-9°, was obtained, Lit.[20] mp 85-7°; nmr ($CHCl_3$-d)δ 3.18(m,2,CH_2), 3.80(m,1,CH), 7.12(s,5,aromatics); ir ν_{max}^{Nujol}(cm^{-1}), 1700 (C=O) and 690, 755 (aromatic).

The hydrogenation procedure and method of isolation is similar for all of the α,β-unsaturated acids and only the reaction conditions, physical properties, and spectral data are given for the other acids reduced.

The hydrogenation of cinnamic acid. The reaction mixture was stirred for 7 hr at 60° under a hydrogen gas pressure of 100 psi. After isolation, 1.7 g (85%) mp 45-7°, Lit.[20] mp 48.5°, of hydrocinnamic acid was obtained; nmr(DMSO-d_6) δ 2.70(m,4,CH_2), 7.26(s,5,aromatics); ir ν_{max}^{Nujol}(cm^{-1}), 1700 (C=O) and 750, 700 (aromatic).

The hydrogenation of p-methylcinnamic acid. The reaction mixture was stirred for 12 hr at 60° and with a hydrogen gas pressure of 120 psi. p-Methyl-hydrocinnamic acid, 1.7 g (85%) was obtained from the reaction mixture, mp 102-4°, Lit.[20] mp 120°; nmr (DMSO-d_6) δ 2.26(s,3,CH_3), 2.67(m,4,CH_2), 7.09(s,4,aromatics); ir ν_{max}^{Nujol} (cm^{-1}), 1700 (C=O) and 850, (aromatic).

The hydrogenation of α-methylcinnamic acid. The conditions used for this reduction were a hydrogen gas pressure of 120 psi and 24 hr of stirring at 60°. After isolation, α-methylhydrocinnamic acid, 1.65 g (83%) was obtained; nmr($CHCl_3$-d) δ 1.18(m,3,CH_3), 2.80(m,2,CH_2), 3.50(m,1,CH), 7.21(s,5,aromatic); ir ν_{max}^{Nujol}(cm^{-1}), 1700 (C=O) and 700, 750 (aromatic).

The hydrogenation of itaconic acid. The reaction mixture was stirred for 12 hr at 60° under a hydrogen gas pressure of 100 psi. After isolation, α-methyl succinic acid, 1.8 g (90%) was obtained, mp 103-6°, Lit.[20] mp 110°; nmr (DMSO-d_6) δ 1.10(d,3,J=6.0,CH_3), 2.33(m,2,CH_2), 2.75(m,1,CH); ir ν_{max}^{Nujol}(cm^{-1}), 1690 (C=O).

The hydrogenation of citraconic acid. The reaction mixture was stirred for 6 hr at 60° under a hydrogen gas pressure of 100 psi. The product obtained, 1.8 g (90%) was a mixture of citraconic acid and α-methylsuccinic acid, mp 80-5°, Lit.[20] mp 110°; nmr(DMSO-d_6)

δ 1.13(d,2.4,J=6.0,CH_3 for saturated acid), 2.05(d,0.6,J=8.0,CH_3 for saturated acid), 2.50(m,2.4,CH_2 and CH for saturated acid), 5.89(s,0.2,olefin H); irν_{max}^{Nujol}(cm^{-1}), 1690 (C=O).

The hydrogenation of α-(acetamido) cinnamic acid. Chlorotris-(triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) and α-(acetamido) cinnamic acid (3.0 g, 0.015 mole) were dissolved in 200 ml of benzene-ethanol (1:1) under an argon atmosphere. The resulting clear red solution was transferred to the reaction vessel and after flushing with hydrogen, stirred for 12 hr at 60° under a hydrogen gas pressure of 100 psi. After completion, the solvent was removed by evaporation under reduced pressure and the residue mixed with 350 ml of water and stirred for 30 min. This mixture was filtered to remove the catalyst and the filtrate evaporated to dryness to give 2.4 g (80%) mp 142-5°, of N-acetyl-β-phenylalanine, Lit.[20] mp 145°, nmr(DMSO-d_6), δ 1.81(s,3,CH_3), 2.97(m,2,CH_2), 4.50(m,1,CH), 7.23(s,5,aromatics), 8.10(d,1,J=8.0,NH); irν_{max}^{Nujol}(cm^{-1}), 3300 (NH), 1710, 1620 (C=O), 740, 700 (aromatic).

The Preparation of α,β-Unsaturated Esters

Preparation of ethyl α-phenylcinnamate. α-Phenylcinnamic acid (8.0 g, 0.036 mole) and sulfuric acid (9.8 g, 0.10 mole) were dissolved in 300 ml of absolute ethanol and refluxed for 24 hr. The ethanol was removed by distillation and the remaining liquid added to 200 ml of ethyl ether. After removing the ether, the remaining liquid was vacuum distilled to yield 6.1 g (78%) of ethyl α-phenylcinnamate, bp 135-40° (2.0mm); nmr($CHCl_3$-d) δ 1.23(m,3,CH_3), 4.17(m,2,OCH_3),

7.13(m,5,aromatics), 7.35(m,5,aromatics), 7.82(s,1,olefinic H); ir ν_{max}^{Nujol}(cm^{-1}), 1700 (C=O), 760, 695 (aromatic).

Preparation of l-menthyl-α-phenylcinnamate. α-phenylcinnamic acid (10.0 g, 0.045 mole) and thionyl chloride(5.3 g, 0.045 mole) were dissolved in 100 ml of anhydrous benzene and refluxed for one hr. l-Menthol (7.0 g, 0.045 mole) and quinoline (7.0 g, 0.045 mole) were added and reflux was continued for an additional hr. After cooling to room temperature, the reaction mixture was filtered to remove the quinoline hydrogen chloride, followed by evaporation of the benzene. The remaining yellow oil was added to 100 ml of cold 10% NaOH and extracted 3 times with 50 ml portions of ethyl ether. The combined ether extracts were dried ($MgSO_4$) and the ether removed by evaporation. The resulting yellow oil was dissolved in 200 ml of ethanol-water (1:1). Crystals of l-menthyl-α-phenylcinnamate, 11.0 g (68%) mp 37-8° were obtained after cooling at 5° for 24 hr; nmr ($CHCl_3$-d) δ .93(m,9,menthyl CH_3), 1.30(m,6,menthyl CH_2), 3.62(m,3, menthyl CH), 7.20(m,10,aromatics), 7.80(s,1,olefinic H); ir ν_{max}^{neat} (cm^{-1}), 1700 (C=O), 760, 695 (aromatic).

Preparation of atropic acid. Atrolactic acid[21] (30.0 g, 0.18 mole), phosphorous oxychloride (7.7 g, 0.05 mole), and p-toluene sulfonic acid (1.0 g, 5.7 mmole) were dissolved in 500 ml of anhydrous benzene. This reaction mixture was refluxed using a Dean Stark Trap for 12 hr during which time 2.7 g(0.15 mole) of water was collected. After cooling to room temperature, the benzene was evaporated under reduced pressure leaving an oily residue. This material was dissolved in 200 ml of water-ethanol (2:1) at 5° for 24 hr. After filtering and

drying, 15.0 g(55%) of crystalline atropic acid was obtained, mp 103-5°, Lit.[21] mp 106-7°; nmr ($CHCl_3$-d)δ 5.96(d,1,J=1.0,olefinic H cis to ring), 6.50(d,1,J=1.0,olefinic H cis to acid), 7.35(m,5,aromatics); ir ν_{max}^{Nujol}(cm^{-1}), 1700 (C=O), 1610, (C=C), 750, 700 (aromatic).

Preparation of l-menthyl atropate. Sodium atropate was prepared by titrating atropic acid (8.3 g, 0.056 mole) with 10% NaOH solution. The water was evaporated under reduced pressure and the salt was dried under vacuum for 24 hr. Phosphorous oxychloride (7.7 g, 0.050 mole) was added to a suspension of the sodium salt in 100 ml of anhydrous benzene. This reaction mixture was stirred for 10 min and then gently warmed over a steam bath for 30 min. l-Menthol (7.8 g, 0.050 mole) dissolved in 25 ml of pyridine was added dropwise with stirring. After addition was complete, heating on a steam bath was continued for 30 min. The benzene was evaporated under reduced pressure and the remaining yellow oil mixed with 150 ml of water. The oil separated after standing several hr and was collected, washed with 5% HCl solution, and dried ($MgSO_4$) in ethyl ether. The ether was evaporated under reduced pressure and l-menthyl atropate, 7.2 g(50%) was obtained; $[\alpha]_D^{25°}$ -63.5°(c,.73,EtOH); Lit.[22] $[\alpha]_D^{25°}$ -63.0°(c,EtOH).

The Hydrogenation of α,β-Unsaturated Esters

The hydrogenation of ethyl cinnamate. Ethyl cinnamate (6.0 g, 34 mmole) and chlorotris(triphenylphosphine)rhodium(I) (0.40 g, o.44 mmole) were dissolved in 200 ml of benzene under argon. After transferring to the reaction vessel and flushing with hydrogen, the reac-

tion mixture was stirred for 12 hr at 60° under a hydrogen gas pressure of 100 psi. The benzene was distilled at atmospheric pressure and the resulting oil vacuum distilled to yield ethyl hydrocinnamate, 5.6 g(93%), bp 60-5° (0.1mm); nmr ($CHCl_3$-d)δ 1.20(t,3,J=7.0,CH_3), 2.75(m,4,CH_2), 4.13(m,2,OCH_2), 7.21(s,5,aromatics); irν_{max}^{neat}(cm^{-1}), 1720 (C=O), 745, 690 (aromatic).

The hydrogenation of l-menthyl atropate. Chlorotris(triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) and l-menthylatropate (2.0 g, 7.0 mmole) were dissolved in 200 ml of benzene-ethanol (1:1) under argon. This reaction mixture was transferred to the reaction vessel and stirred for 12 hr at 50° under a hydrogen pressure of 80 psi. The benzene was removed by distillation and the residue mixed with 200 ml of petroleum ether (30-60°). After filtration to remove the catalyst, the filtrate was dried ($MgSO_4$) and the ether removed by evaporation under reduced pressure. l-Menthyl hydrotropate 1.4 g(70%) was obtained as a yellow oil; nmr ($CHCl_3$-d)δ .90(m,9,menthyl CH_3), 1.50(d,3,J=7.0,CH_3), 1.30(m,6,menthyl CH_2), 3.65(m,3,menthyl CH), 4.18(m,1,CH), 7.23(s,5,aromatics); irν_{max}^{neat}(cm^{-1}), 1680 (C=O), 770, 710 (aromatic).

Attempted hydrogenation of ethyl-α-phenylcinnamate. Chlorotris(triphenylphosphine)rhodium(I) (0.4 g, 0.44 mmole) and ethyl α-phenylcinnamate (3.0 g, 12 mmole) were dissolved in 200 ml of benzene under an argon atmosphere. This reaction mixture was transferred to the reaction vessel and stirred for 12 hr at 65° and a hydrogen gas pressure of 120 psi. The ester was isolated by vacuum distillation to give 2.2 g(74%) of a colorless oil bp 125° (0.1mm). The ir and

nmr spectra of this compound were identical with those of ethyl α-phenylcinnamate.

Attempted hydrogenation of l-menthyl α-phenylcinnamate. Chlorotris(triphenylphosphine)rhodium(I) (0.50 g, 0.52 mmole) and l-menthyl-α-phenylcinnamate (4.0 g, 13 mmole) were dissolved in 200 ml of benzene under an argon atmosphere. This reaction mixture was transferred to the reaction vessel and stirred for 12 hr at 65° under a hydrogen gas pressure of 100 psi. The benzene was removed from the reaction mixture by evaporation at reduced pressure. The oily residue was mixed with 150 ml of 10% NaOH solution and stirred at 80° for 2 hr to hydrolyze the ester. After cooling to room temperature, this alkaline solution was extracted 6 times with 50 ml portions of ethyl ether to remove the menthol and any remaining ester. The aqueous solution was acidified with 200 ml of 10% HCl, followed by filtration to give 3.6 g(90%) of white crystals, mp 170-2. The ir and nmr spectra of this material confirmed it to be α-phenyl cinnamic acid. This hydrogenation was attempted again, however, stirring for 36 hr at 70° and a hydrogen gas pressure of 400 psi and still no reduction occurred.

The Hydrogenation of α-β-Unsaturated Nitro Compounds

The Hydrogenation of p-nitro-β-nitrostyrene. Chlorotris(triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) was added to a solution of p-nitro-β-nitrostyrene (3.0 g, 16 mmole) dissolved in 300 ml of benzene-ethanol (1:1). The red solution was transferred under argon to the reaction vessel and stirred for 6 hr at 40° and a

hydrogen gas pressure of 50 psi. The solution was evaporated to dryness under reduced pressure. Ethyl ether was added to the resulting residue and filtered to remove the bulk of the catalyst. The filtrate was evaporated to dryness and the residue dissolved in 20 ml of hot ethanol. After crystallization, 1.8 g(60%) of 2(p-nitrophenyl) nitroethane, mp 92-4° was obtained. An analytical sample after four recrystallizations from benzene malted at 97-8°; nmr ($CHCl_3$-d) δ 3.42(t,2,J=7.0,benzyl CH_2), 4.75(t,2,J=7.0, CH_2), 7.80(m,4,aromatics); ir ν_{max}^{Nujol}(cm^{-1}), 1510 (NO_2), 825 (aromatic).

Anal. Calcd. for $C_8H_8N_2O_4$: C,48.98; H, 4.06; N, 14.28. Found: C, 48.99; H, 4.01; N, 14.09.

The hydrogenation of 3,4-methylenedioxy-β-nitrostyrene. 3,4-Methylenedioxy-β-nitrostyrene (2.5 g, 13 mmole) and chlorotris(triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) were dissolved in 300 ml of benzene. After transfer to the reaction vessel and flushing with hydrogen, stirring was continued for 9 hr at 60° under a hydrogen gas pressure of 60 psi. The oily residue remaining after evaporation of the benzene was mixed with 50 ml of ethyl ether and filtered. The filtrate was evaporated to dryness and this procedure repeated to give 2.1 g(81%) of 2(3,4-methylenedioxyphenyl)nitroethane, mp 51-4°. An analytical sample was prepared by three recrystallizations from ethanol, mp 53-4°; nmr ($CHCl_3$-d) δ 3.20(t,2,J=8.0,benzyl CH_2), 4.56(t,2,J=7.0, CH_2), 5.91(s,2,OCH_2), 6.69(m,3,aromatics); ir ν_{max}^{Nujol}(cm^{-1}), 1500 (NO_2) 820, 790 (aromatic).

Anal. Calcd. for $C_9H_9NO_4$: C,55.38; H, 4.65; N, 7.18. Found: C, 55.44; H, 4.60; N, 7.18.

The hydrogenation of 3-methoxy-4-benzyloxy-β-nitrostyrene.

The previous hydrogenation conditions and isolation procedure were used on a (3.0 g, 10 mmole) sample of 3-methoxy-4-benzyloxy-β-nitrostyrene. 2(3-Methoxy-4-benzyloxyphenyl) nitroethan 2.8 g(90%), mp 57-60° was obtained, from which an analytical sample was prepared by 3 recrystallizations from benzene, mp 63.0-3.5°; nmr ($CHCl_3$-d) δ 3.18(t,2,J=7.0,benzyl CH_2), 3.83(s,3,OCH_3), 4.50(t,2,J=7.0, CH_2) 5.08(s,2,OCH_2), 6.73(m,3,aromatics), 7.35(m,5,aromatics); ir ν_{max}^{Nujol} (cm^{-1}), 1510 (NO_2), 800, 745, 695 (aromatic).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.98; N, 4.88. Found: C, 66.78; H, 5.83; N, 4.84.

The Hydrogenation of α,β-Unsaturated Ketones

The hydrogenation of benzalacetophenone. Chlorotris(triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) was added to a solution of benzalacetophenone (3.0 g, 13 mmole) dissolved in 300 ml of benzene under argon. The resulting clear red solution was transferred to the reaction vessel and stirred for 10 hr at 50° and a hydrogen gas pressure of 100 psi. After completion, the benzene was evaporated under reduced pressure and the residue mixed with 300 ml of petroleum ether (30-60°). The solution was filtered to remove the insoluble catalyst and the filtrate dried ($MgSO_4$) and evaporated to yield 2.4 g(80%) of 4-phenyl-2-butanone, mp 64-6°, Lit.[20] mp 62°; nmr ($CHCl_3$-d) δ 3.14(m,4 CH_2), 7.50(m,10,aromatics); ir ν_{max}^{Nujol}(cm^{-1}), 1680 (C=O), 740, 700, 690 (aromatic).

Attempted hydrogenation of 3,4-diphenyl-3-buten-2-one. Chlorotris(triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) and 3,4-diphenyl-3-buten-2-one (4.4 g, 20 mmole) were dissolved in 200 ml of benzene under an argon atmosphere. The red solution was transferred to the reaction vessel and stirred for 12 hr at 60° under a hydrogen gas pressure of 100 psi. After completion, the remaining oily residue was vacuum distilled at 120-5° (0.1mm) to give 3.1 g(75%) of unreacted 3,4-diphenyl-3-buten-2-one, mp 52-4°; nmr ($CHCl_3$-d)δ 2.28(s,3,CH_3), 7.20(m,10,aromatics), 7.65(s,1,olefinic H); ir ν_{max}^{Nujol}(cm^{-1}), 1660 (C=O), 1620 (C=C), 755, 720, 690 (aromatic).

The Hydrogenation of α,β-Unsaturated Nitriles

The hydrogenation of cinnamonitrile. Chlorotris(triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) and cinnamonitrile (5.0 g, 0.039 mole) were dissolved in 200 ml of benzene under an argon atmosphere. The clear red solution was transferred to the reaction vessel and stirred for 12 hr at 60° and a hydrogen gas pressure of 80 psi. The benzene was distilled using a Vigreaux column and the remaining oil vacuum distilled to yield 4.3 g(86%), bp 65° (0.1mm), of hydrocinnamonitrile; nmr ($CHCl_3$-d)δ 2.75(m,4, CH_2), 7.24(s,5,aromatics); ir ν_{max}^{neat}(cm^{-1}), 2250 (C≡N), 750, 700 (aromatic).

Attempted hydrogenation of 2,3-diphenylacrylonitrile. Chlorotris(triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) and 2,3-diphenylacrylonitrile (3.0 g, 15 mmole) were dissolved in 200 ml of benzene under an argon atmosphere and transferred to the reaction vessel. The reaction mixture was stirred for 12 hr at 60° under a

hydrogen gas pressure of 100 psi. The benzene was then evaporated under reduced pressure. The oily residue was mixed with 600 ml ethyl ether-petroleum ether (1:2). The solution was filtered to remove the catalyst and the filtrate evaporated to dryness to yield 2.7 g(90%) of 2,3-diphenylacrylonitrile, mp 65-75°, Lit.[20] mp 88°; nmr ($CHCl_3$-d)δ 7.40(m,10,aromatics); irν_{max}^{Nujol}(cm^{-1}), 2210 (C=N), 760, 745, 690 (aromatic).

The Hydrogenation of α,β-Unsaturated Aldehydes

The hydrogenation of cinnamaldehyde. Cinnamaldehyde (4.0 g, 0.030 mole) and chlorotris(triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) were dissolved in 200 ml of absolute ethanol under an argon atmosphere. Because of the catalyst's decreased solubility in ethanol, the time required to dissolve the catalyst was one hr. The resulting clear red solution was transferred to the reaction vessel and stirred for 7 hr at 60° and a hydrogen gas pressure of 80 psi. The benzene was distilled from the reaction mixture with a Vigreaux Column. The remaining liquid was vacuum distilled to yield 3.7 g (90%) of a mixture of hydrocinnamaldehyde and ethyl benzene, bp 60-70° (0.1mm); nmr ($CHCl_3$-d)δ 1.20(t,1.2,J=3.5, CH_3), 2.80(m,2.4, CH_2 in aldehyde), 3.62(m,.8, CH_2 in ethyl benzene), 7.26(s,5,aromatics), 9.82 (s,.6,aldehyde H); irν_{max}^{neat}(cm^{-1}), 1690 (C=O), 750, 690 (aromatic).

The hydrogenation of o-nitrocinnamaldehyde. o-nitrocinnamaldehyde (4.0 g, 24 mmole) and chlorotris(triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) were dissolved in 250 ml of ethanol under an argon atmosphere. The resulting clear red solution was transferred under

argon to the reaction vessel and, after flushing with hydrogen, stirred for 24 hr at 60° under a hydrogen gas pressure of 100 psi. The benzene was then distilled to leave a thick oil. This material was vacuum distilled to yield 2.8 g(70%) of a mixture of o-nitrohydrocinnamaldehyde and o-nitro-ethyl benzene; bp 190-210° (1.1mm); nmr ($CHCl_3$-d) δ 1.25(t,1.2,J=3.5, CH_3), 2.70(m,2.4, CH_2 in aldehyde), 3.60(m,.8, CH_2 in ethyl benzene), 6.88(m,5,aromatics), 9.72(s,.6, aldehyde H); ir ν_{max}^{neat} (cm^{-1}), 1720 (C=O) 1510 (NO_2), 800 (aromatic).

Attempted hydrogenations of p-dimethylamino cinnamaldehyde and α-methyl cinnamaldehyde. The aldehyde, 0.024 mole, and chlorotris (triphenylphosphine)rhodium(I) (0.40 g, 0.44 mmole) were dissolved in 250 ml of ethanol. The resulting solution was transferred to the reaction vessel and stirred for 12 hr at 60° under a hydrogen pressure of 100 psi. After completion, the reaction mixture was distilled to remove the benzene. However, a thick very dark colored oil remained. Vacuum distillation and solvent extraction failed to separate a characterizable component.

Preparation of 4-biphenylyl-2-naphthyl phenylphosphine. 4-Biphenylyl magnesium bromide and 2-naphthyl magnesium bromide were prepared in the usual manner from the aromatic bromide and magnesium turnings. However, tetrahydrofuran was found to be a better solvent than was ethyl ether.

Dichlorophenylphosphine used in this preparation was vacuum distilled before use and stored under nitrogen.

4-Biphenylyl magnesium bromide (89.9 g, 0.35 mole) and 2-naphthyl magnesium bromide (80.9 g, 0.35 mole) were dissolved in 1.2 l of

anhydrous tetrahydrofuran in a three neck 3 l round bottom flask equipped with a mechanical stirrer, a 500 ml dropping funnel, and a gas dispersion tube. This solution was cooled to 0°C and flushed with nitrogen during the course of the reaction. Dichlorophenylphosphine (62.6 g, 0.35 mole), dissolved in 300 ml of anhydrous ethyl ether, was placed in the dropping funnel and added dropwise to the mixed Grignard reagents with vigorous stirring. After the addition was completed in 2 hr, the reaction mixture was stirred at room temperature for 30 min. A distillation apparatus was attached to the reaction flask and 1.0 l of solvent removed. Following this, 300 ml of water was cautiously added and stirring was continued for 30 min. Ethyl ether, 600 ml, was added and mixed thoroughly with the reaction mixture, followed by removal of the ether layer. A second ether extraction was performed. The combined ether extracts were dried ($MgSO_4$) and evaporated to yield an oily residue. This crude material was triturated in succession with 300 ml of water, ethanol, and n-keptane to yield 50.0 g(37%) of a pale yellow solid mp 152-72°. After three recrystallizations from benzene, 20.0 g(15%) of 4-biphenylyl-1-naphthylphenylphosphine, mp 190-1°, Lit.[23] mp 191-2°, was obtained. This material showed one spot on a tlc chromatogram using Silica Gel as the carrier and n-heptane-benzene (1:1) as the developing solvent; nmr ($CHCl_3$-d) 7.40(m,aromatics); ir $\nu_{max}^{Nujol}(cm^{-1})$, 830, 800, 760, 755, 740, 690 (aromatic).

Partial resolution of 4-biphenylyl-1-naphthylphenylphosphine.

The resolving agent, d-camphor-10-sulfonic acid, was purified by recrystallizing three times from glacial acetic acid which had

previously been distilled from potassium permanganate and phosphorous pentoxide. The crystals obtained were pulverized and air dried for 12 hr, mp 194-5°, Lit.[20] mp 195°. The following specific rotations were observed, $[\alpha]_{578}^{25°}$ + 23.3°, $[\alpha]_{546}^{25°}$ + 28.6°, $[\alpha]_{476}^{25°}$ + 81.5° (c, 6.60, H_2O), Lit.[24] $[\alpha]_{436}^{25°}$ + 78.7 (c, 6.62, H_2O). The triaryl phosphine used in this resolution was recrystallized three times from benzene, mp 190-1°.

Camphor-10-sulfonic acid (2.23 g, 10 mmole) was refluxed in 215 ml of thiophene free benzene for 2 hr using a Dean-Stark Trap, followed by cooling to room temperature. 4-Biphenylyl-1-naphthylphenylphosphine, (7.76 g, 20 mmole) dissolved in 110 ml of hot anhydrous benzene and cooled to room temperature, was added to the camphor-10-sulfonic acid solution and stirred at room temperature for 2 hr. This solution was allowed to stand for 48 hr at 10-15°, followed by filtration to yield 3.5 g(55%) of α-hydroxymethyl, 4-biphenylyl-1-naphthylphenylphosphonium camphor-10-sulfonate, mp 108-10°, Lit.[23] mp 111-2°; $[\alpha]_{578}^{25°}$ + 18.7 (c, 3.20, CH_2Cl_2), Lit.[23] $[\alpha]_{578}^{25°}$ + 19.0 (c, 3.86, CH_2Cl_2). The camphor-10-sulfonate salt was released in the following manner. The salt (2.30 g, 3.5 mmole), dissolved in 25 ml of methylene chloride, was added to a solution of triethylamine (0.36 g, 3.6 mmole) dissolved in 15 ml of benzene. This mixture was shaken in a separatory funnel for 5 min. A sodium acetate solution (0.30 g, 3.60 mmole) in 40 ml of water, was added to the mixture and again shaken for 5 min. The methylene chloride layer was removed and the water layer extracted 3 times with 25 ml portions of methylene chloride. The methylene chloride extracts were

combined, dried (Na_2SO_4), and evaporated to yield the free phosphine. This material was washed with ethanol to remove traces of the camphor-10-sulfonate salt or camphor-10-sulfonic acid. The yield was 1.17 g(90%) of partially resolved 4-biphenylyl-1-naphthylphenylphosphine, mp 189-91°, Lit.[23] mp 194°; $[\alpha]_{578}^{25°}$ + 2.7, $[\alpha]_{546}^{25°}$ + 3.5°, $[\alpha]_{436}^{25°}$ + 9.3° (c, 2.4, CH_2Cl_2); Lit.[24] $[\alpha]_{578}^{25°}$ + 6.1°, $[\alpha]_{546}^{25°}$ + 7.4°, $[\alpha]_{436}^{25°}$ +18.2° (c, 2.08. CH_2Cl_2). The ir and nmr spectra of this triarylphosphine showed no trace of camphor-10-sulfonic acid or the camphor-10-sulfonate salt.

Preparation of trichlorotris (4-biphenylyl-1-naphthylphenylphosphine)rhodium(III). Rhodium trichloride trihydrate (0.28 g, 1.0 mmole) dissolved in 75 ml of deoxygenated hot absolute ethanol was added to a suspension of racemic 4-biphenylyl-1-naphthylphenylphosphine (1.20 g, 3.0 mmole) in 175 ml of hot absolute ethanol under an argon atmosphere. This reaction mixture was refluxed for 20 min. The reaction mixture, after cooling to room temperature, was filtered to yield 1.00 g(73%), mp 180-6° of a brown powder. This material was purified by dissolving in warm ethanol and reprecipating with n-heptane three times, mp 186°.

Anal. Calcd for C_{84} H_{63} Cl_3 P_3 Rh: C, 73.39; H, 4.62; Cl, 7.74; P, 6.76. Found: C, 72.95; H, 4.53; Cl, 7.62; P, 6.57.

Preparation of the above rhodium complex using optically active 4-biphenylyl-1-naphthylphenylphosphine. The same preparation was used as above except the reaction mixture was stirred for 15 min. at 50°. The complex was obtained in 70% yield, mp 186°.

Hydrogenation of α-β-Unsaturated Acids
Using Trichlorotris(4-biphenylyl-1-naphthylphenyl-
phosphine)rhodium III

The reaction conditions and isolation procedures were similar for all reductions and will be exemplified by the hydrogenation of itaconic acid. Itaconic acid (2.0 g, 16 mmole) and trichlorotris (4-biphenylyl-1-naphthylphenylphosphine)rhodium(III) (0.50 g, 0.41 mmole) were dissolved in 200 ml of benzene-ethanol (1:1) under an argon atmosphere. The resulting dark red solution was transferred to the reaction vessel and flushed with hydrogen gas 5 times. The reaction mixture was stirred for 12 hr at 60° under a hydrogen gas pressure of 100 psi. After completion, the solvent was evaporated under reduced pressure to yield a solid residue. This material was mixed with 100 ml of 10% NaOH solution and filtered. The filtrate was concentrated to 50 ml, acidified with HCl, and extracted 6 times with 50 ml portions of ethyl ether. The ether extracts were combined, dried ($MgSO_4$) and evaporated to yield 1.6 g(80%) of α-methyl succinic acid, mp 98-102°.

Attempted asymmetric reduction of α-acetamido cinnamic acid. The catalyst used in this reduction was trichlorotris(4-biphenylyl-1-naphthylphenylphosphine)rhodium(III) prepared with the optically active phosphine.

The catalyst (0.30 g, 0.22 mmole) and α-acetamidocinnamic acid (3.0 g, 15 mmole) were dissolved in 220 ml of benzene-ethanol (1:1). This clear dark red solution was transferred to the reaction vessel and, after flushing with hydrogen gas, stirred for 12 hr at 50° under a hydrogen gas pressure of 100 psi. After completion, the

solvent was evaporated to 25 ml under reduced pressure and a temperature not to exceed 35°. Upon standing at 5° for 24 hr, 1.5 g(50%) of crystalline N-acetyl-β-phenylalanine, mp 138-42°, were obtained. The specific rotation, $[\alpha]_D^{25°}$ 0.0°(C, 4.0, MeOH, 1, 1.0 dm) confirms that no asymmetric reduction occurred.

Attempted asymmetric reduction of atropic acid.

Procedure A

Atropic acid (1.3 g, 8.80 mmole) and the optically active catalyst (0.20 g, 0.15 mmole) were dissolved in 200 ml of benzene-ethanol (1:1) under an argon atmosphere. This reaction mixture was transferred to the reaction vessel and, after flushing with hydrogen gas, stirred for 30 hr at 60° under a hydrogen gas pressure of 100 psi. After completion, the solvent was removed under reduced pressure and the residue treated with 50 ml of cold 5% NaOH solution. This alkaline solution was filtered and the filtrate acidified with 60 ml of cold HCl solution. The mixture was extracted 6 times with 50 ml portions of ethyl ether. After drying ($NaSO_4$), the ether extracts were evaporated to dryness to yield 1.2 g(90%) of hydrotropic acid, $[\alpha]_D^{25°}$ 0.0°(C, 4.00, EtOH, 1, 1.0 dm); nmr ($CHCl_3$-d) δ 1.50(d,3,J=7.0, CH_3), 3.78(m,1,CH), 7.40(s,5,aromatics); ir ν_{max}^{neat} (cm^{-1}), 1710 (C=O), 760, 695 (aromatic).

Procedure B

The catalyst was prepared in situ. Optically active 4-biphenylyl-1-naphthylphenylphosphine (0.21 g, 0.54 mmole) was suspended in 100 ml of absolute ethanol under an argon atmosphere. Rhodium trichloride trihydrate (50.0 mg, 0.18 mmole) was added to the mixture. The

reaction mixture was heated to 40° under argon and stirred for 10 min. After cooling to room temperature, 100 ml of benzene was added to give a clear red solution. Atropic acid (1.48 g, 10.0 mmole) was dissolved in the reaction mixture. The resulting solution was stirred in the reaction vessel for 10 hr at 50° under a hydrogen gas pressure of 80 psi. The hydratropic acid was isolated in the same manner as above and 1.2 g(80%) was obtained $[\alpha]_D^{25°}$ 0.0°(C, 4.00, EtOH, 1, 1.0 dm).

Procedure C

Atropic acid (1.48 g, 10.0 mmole) and triethylamine (54 mg, 0.54 mmole) were dissolved in a solution of the catalyst prepared in situ as described above. This reaction mixture was stirred for 8 hr at 50° under a hydrogen gas pressure of 80 spi. The hydratropic acid was isolated as above to yield 1.3 g(87%) $[\alpha]_D^{25°}$ 0.0°(C, 4.00, EtOH, 1, 1.0 dm).

Procedure D

The same experiment was performed as in Procedure C except that three moles of α-D-phenethylamine per mole of catalyst were used instead of triethylamine. This also gave hydratropic acid, 1.2 g (80%), $[\alpha]_D^{25°}$ 0.0°(C, 4.00, EtOH, 1, 1.0 dm).

Preparation of l-N-acetyl-β-phenylalanine. l-β-Phenylalanine (5.00 g, 30.0 mmole) was stirred for 20 min with 20 ml of water. Acetic anhydride (6.20 g, 0.062 mole) was added to this suspension and stirred for 20 min. The reaction mixture was filtered to yeild 1.0 g of unreacted l-β-phenylalanine, mp 270-2°, Lit.[20] mp 272°. After cooling the filtrate at 5° for 24 hr, 2.8 g(45%) of l-N-acetyl-β-

phenylalanine was obtained, mp 170-1°, Lit.[25] mp 172°; $[\alpha]_D^{25°}$ + 40.3° (c, 3.20, MeOH), Lit.[25] $[\alpha]_D^{25°}$ + 40.5° (c, 3.20, MeOH).

Attempted racemization of l-N-acetyl-β-phenylalanine. Racemic trichlorotris (4-biphenylyl-1-naphthylphenylphosphine)rhodium III (0.20 g, 0.12 mmole) and l-N-acetyl-β-phenylalanine (1.50 g, 7.3 mmole) were dissolved in 200 ml of benzene-ethanol (1:1) under an argon atmosphere. This clear solution was transferred to the reaction vessel and, after flushing with hydrogen gas, stirred for 24 hr at 60° and a hydrogen gas pressure of 120 psi. The solvent was evaporated under reduced pressure. The residue was mixed with 150 ml of water and filtered to remove the catalyst. The filtrate was concentrated to 15 ml, from which 1.2 g(80%) of crystalline l-N-acetyl-β-phenylalanine were obtained, $[\alpha]_D^{25°}$ + 38.0° (c, 3.20, MeOH).

Partial reduction of atropic acid using racemic catalyst. Atropic acid (1.00 g, 6.7 mmole) and trichlorotris (4-biphenylyl-1-naphthylphenylphosphine)rhodium(III) (0.10 g, 0.072 mmole) were dissolved in 200 ml of benzene-ethanol (1:1) under an argon atmosphere. The clear red solution was transferred to the reaction vessel and flushed with hydrogen gas 5 times. The reaction mixture was stirred for 2 hr, 15 min under a hydrogen gas pressure of 100 psi, during which time the temperature reached 50°. After completion, the solution was flushed with air immediately to remove the hydrogen gas in solution. The solvent was removed by evaporation under reduced pressure. The residue was treated with 50 ml of 5% NaOH solution, filtered and re-acidified with 10% HCl solution. This acidic solution was extracted 6 times with 25 ml portions of ethyl ether.

After combining and drying ($MgSO_4$) the ether extracts, the ether was evaporated under reduced pressure to give 0.87 g(87%) of a mixture of atropic and hydratropic acid; nmr ($CHCl_3$-d) δ 1.50(d,.75, J=7.0,CH_3) 3.65(m,.25,CH), 5.94(d,.75,J=1.0,olefinic H cis to ring), 6.50(d,.75,J=1.0,olefinic H cis to acid), 7.35(m,5,aromatics).

Partial reduction of atropic acid using optically active catalyst. This experiment, being a comparison of the rate of hydrogenation, was performed under the same conditions as used above. The catalyst used was trichlorotris (4-biphenylyl-1-naphthylphenylphosphine)rhodium(III), prepared from the optically active triarylphosphine. It gave 0.90 g(90%) of a mixture of atropic and hydratropic acid; nmr ($CHCl_3$-d) δ 1.52(d,.60,J=7.0,CH_3), 3.65(m,.20, CH), 5.95(d,.80,J=1.0,olefinic H cis to ring), 6.50(d,.80,J=1.0, olefinic H cis to acid), 7.35(m,5,aromatics).

DISCUSSION
PART I

Homogeneous Calalytic Hydrogenation of α,β-Unsaturated Compounds Using Chlorotris(triphenylphosphine)rhodium(I).

An investigation of the scope and limitations of chlorotris(triphenylphosphine)rhodium(I) as the catalyst for the homogeneous hydrogenenation of unsaturated compounds in organic syntheses has been performed. α,β-Unsaturated acids, esters, ketones, nitriles, aldehydes, and nitro compounds were selectively reduced at the carbon-carbon double bond with this catalyst. The compounds selected for this study cover a broad spectrum of substitution and steric hinderance on the olefinic bond.

The catalytic hydrogenations were performed in benzene-ethanol solutions in which oxygen and nitrogen were removed. The substrate to catalyst ratios were varied from thirty:one to fifty:one. A reduction was assumed to be quantitative when the nmr spectrum did not detect a trace of the characteristic olefinic hydrogens and when the protons on the newly formed methylene group or groups integrated properly.

Several trans-α,β-unsaturated carboxylic acids were selectively hydrogenated under mild conditions consisting of a hydrogen gas pressure of 60 to 100 psi, a reaction temperature of 60 degrees, and a reaction time of 8 to 12 hr. In most cases, the product recovery was in excess of 85 percent and the reduction was quantitative (Table I). The terminal olefin, itaconic acid was quantitatively

reduced using a hydrogen gas pressure of 100 psi and a reaction time of 12 hr, however, the isomeric internal olefin, citraconic acid, was hydrogenated under similar conditions in only 80 percent yield. The disubstituted olefins, cinnamic and p-methylcinnamic acid were reduced with ease.

In the case of the trisubstituted unsaturated acids, a pronounced difference was observed. α-Phenylcinnamic acid and α-(acetamido) cinnamic acid were reduced quantitatively under the conditions given above. α-Methyl cinnamic acid was only partially hydrogenated under these conditions, and a reaction time of 36 hr was required for complete reduction. This difference in rate cannot be attributed to steric effects since the phenyl and acetyl groups offer greater steric interference than the methyl group. This difference may be explained in terms of the availability of the electrons in the double bond. The literature[16] has suggested that electron deficient carbon-carbon double bonds are reduced with greater ease than are electron rich double bonds. Using inductive effect arguments, the methyl group will enhance the electron density on the bond, whereas the phenyl and acetyl groups will decrease the electronic density, in agreement with the observed rates.

TABLE I

Hydrogenation of α,β-Unsaturated Carboxylic Acids

Reactant	Product	Yield (%)	Reduction (%)
itaconic acid	α-methyl succinic acid	92	100
citraconic acid	α-methyl succinic acid and citraconic acid	90	80
cinnamic acid	hydrocinnamic acid	85	100
p-methylcinnamic acid	p-methyl hydro-cinnamic acid	90	100
α-phenyl-cinnamic acid	2,3-diphenyl propionic acid	85	100
α-(acetamido) cinnamic acid	N-acetyl-β-phenylalanine	80	100
α-methyl-cinnamic acid	α-methyl-hydro-cinnamic acid	83	100

The attempted homogeneous catalytic hydrogenations of several α,β-unsaturated esters have been performed (Table II). The use of this complex to homogeneously catalyze the hydrogenation of these unsaturated esters is good provided the carbon-carbon double bond is not highly substituted. Ethyl cinnamate was quantitatively hydrogenated to give ethyl hydrocinnamate. This reduction might be expected since the ethyl ester differs only slightly in steric and electronic effects from cinnamic acid. An ester containing a large alkyl group, the menthyl ester of the terminal olefin, atropic acid, is also quantitatively reduced. However, neither ethyl α-phenylcinnamate nor l-menthyl α-phenylcinnamate could be reduced using the hydrogenation conditions used for the other esters. Attempts were made using a hydrogen gas pressure of 400 psi and still no reduction occurred. Since the corresponding acids were reduced, steric effects cannot explain the inability of these esters to reduce.

Wilkinson and co-workers[5] have found that the tri and tetrasubstituted alkenes, l-methyl-cyclohexene, 2,3-dimethylbut-2-ene and 3-ethylpent-2-ene were not hydrogenated using chlorotris(triphenylphosphine)rhodium(I). These results correspond to our results for the highly substituted esters, but do not correspond to the successful hydrogenations of the trisubstituted acids. Since carboxylic acids are known to coordinate with rhodium,[26] it could be postulated that a rhodium-carboxylate complex formed in the reaction sequence is enhancing the reduction to overcome the steric interference seen in other olefins.

TABLE II

Hydrogenation of α,β-Unsaturated Carboxylic Esters

Reactant	Product	Yield (%)	Reduction (%)
ethyl cinnamate	ethyl hydrocinnamate	93	100
l-menthyl atropate	l-menthyl hydrotropate	70	100
ethyl α-phenyl cinnamate	ethyl α-phenyl cinnamate	74	0
l-menthyl-α-phenyl cinnamate	l-menthyl-α-phenyl cinnamate	90	0

This reaction series was extended to α,β-unsaturated nitro compounds which were hydrogenated in benzene-ethanol solutions under mild conditions. The β-nitrostyrene derivatives were selectively hydrogenated at the carbon-carbon double bond while leaving the nitro group intact (Table III). No trace of the amino group was observed in the ir and nmr spectra. The elemental analysis of these compounds were correct for the saturated nitro compound, indicating complete reduction. The significance of this result is the fact that the commonly used catalysts to reduce carbon-carbon double bonds such as platinum, palladium and nickel also reduces the nitro group to the amine. Thus, this homogeneous catalytic system which does not touch the nitro group, offers a convenient method to hydrogenate unsaturated nitro compounds to saturated nitro compounds.

TABLE III

Hydrogenation of α,β-Unsaturated Nitro Compounds

Reactant	Product	Yield (%)	Reduction (%)
p-nitro-β-nitrostyrene	2(p-nitrophenyl) nitroethane	60	100
3,4-methylendioxy B-nitrostyrene	2(3,4-methylenedioxy phenyl) nitro ethane	84	100
3-methoxy-4-benzyloxy-β nitrostyrene	2(3-methoxy-4-benzyloxyphenyl) nitroethane	90	100

The homogeneous catalytic hydrogenation of α,β-unsaturated ketones and nitriles was attempted with limited success (Table IV). Benzalacetophenone was quantitatively reduced. However, the more highly substituted 3,4-diphenyl-3-buten-2-one failed to undergo reduction in benzene-ethanol solution. Cinnamonitrile was completely hydrogenated to hydrocinnamonitrile, but again the trisubstituted 2,3-diphenyl acrylonitrile did not reduce.

The inability of 3,4-diphenyl-3-buten-2-one and 2,3-diphenyl acrylonitrile to undergo reduction cannot be explained by steric interaction or the electronic charge density on the double bond, because of its similarity to α-phenylcinnamic acid. These results fit the pattern shown by the trisubstituted esters and olefins.[5] The failure of these highly substituted ketones and nitriles to reduce lends more support to the postulation that highly substituted acids are reduced because of some interaction associated with the carboxylic acid function.

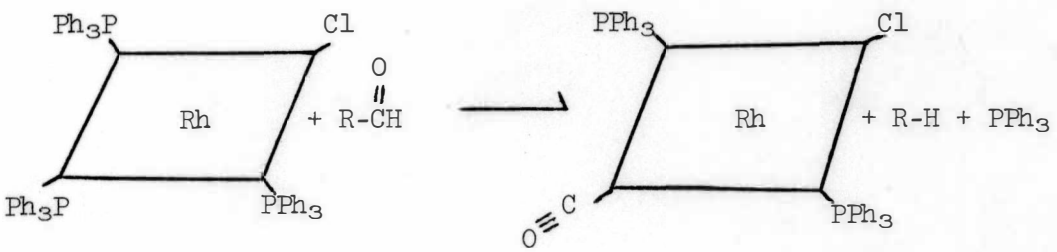
TABLE IV

Homogeneous Catalytic Hydrogenation
of α,β-Unsaturated Ketones and Nitriles

Reactant	Product	Yield (%)	Reduction (%)
benzalacetophenone	4-phenyl-2-butanone	80	100
3,4-diphenyl-3-buten-2-one	3,4-diphenyl-3-buten-2-one	85	0
cinnamonitrile	hydrocinnamonitrile	86	100
2,3-diphenyl acrylonitrile	2,3-diphenyl acrylonitrile	85	0

The homogeneous catalytic hydrogenations of α,β-unsaturated aldehydes offers special problems. Jardine and Wilkinson[6] were unsuccessful in attempts to selectively hydrogenate simple unsaturated aldehydes. They observed the formation of a yellow precipitate during the course of hydrogenation. This material was determined to be chlorocarbonylbis(triphenylphosphine)rhodium(I), resulting from a decarbonylation reaction with the aldehyde. Thus, the catalytic system is destroyed (Scheme III).

SCHEME III



We have found that cinnamaldehyde, when treated with chlorotris(triphenylphosphine)rhodium(I) in benzene-ethanol solutions in a hydrogen atmosphere is decarbonylated and reduced to ethyl benzene. Chlorocarbonylbis(triphenylphosphine)rhodium(I) is also formed. However, the saturated aldehyde, hydrocinnamaldehyde, was obtained in 60 percent yield when absolute ethanol was used as the solvent. The remaining 40 percent was ethyl benzene. o-Nitrocinnamaldehyde was similarly selectively reduced in 60 percent yield. However, from the attempted hydrogenation of α-methylcinnamaldehyde and p-(dimethylamino)-cinnamaldehyde, decomposition occurred and no characterizable products were obtained. Due to the side reaction

involved this catalytic hydrogenation procedure is not of great value as a synthetic tool (Table V).

TABLE V

Homogeneous Catalytic Hydrogenation of
α,β-Unsaturated Aldehydes

Reactant	Product	Yield (%)	Reduction (%)
cinnamaldehyde	hydrocinnamaldehyde and ethyl benzene	90	60 hydrocinnaldehyde 40 ethyl benzene
o-nitrocinnamaldehyde	o-nitrohydrocinnamaldehyde and o-nitroethylbenzene	70	60 o-nitrohydrocinnamaldehyde 40 o-nitroethylbenzene
α-methylcinnamaldehyde	non characterizable		
p-dimethylaminocinnamaldehyde	non characterizable		

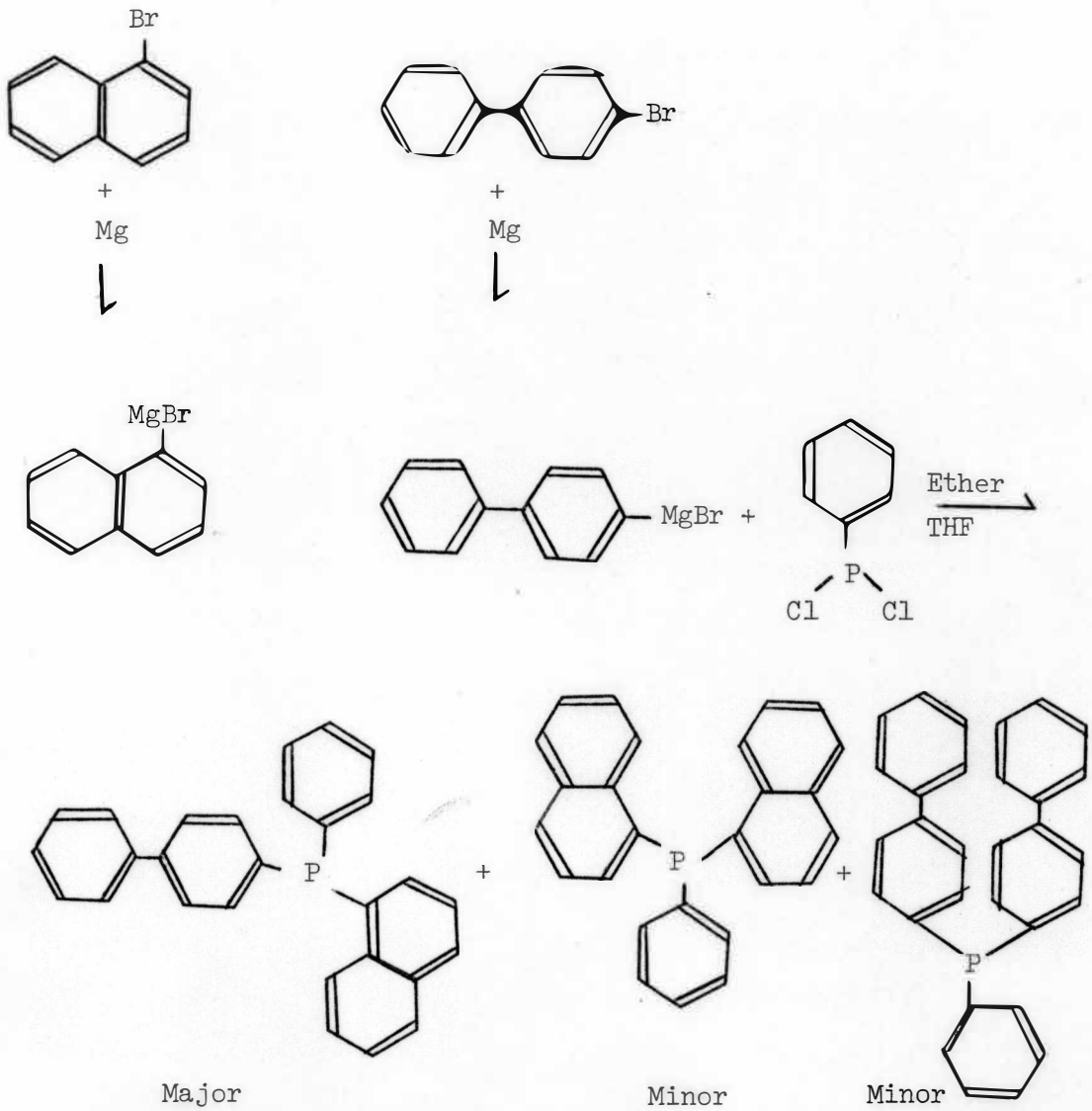
PART II

The Synthesis and Homogeneous Catalytic Properties of a New Rhodium Complex, Trichlorotris(4-biphenylyl-1-naphthylphenyl-phosphine)rhodium(III).

Trichlorotris(4-biphenyl-1-naphthylphenyl-phosphine)rhodium(III) has been prepared, characterized, and utilized in the homogeneous catalytic hydrogenation of several α,β-unsaturated acids.

The physical properties of 4-biphenylyl-1-naphthylphenylphosphine are reported in the literature,[23] but the exact method of preparation is unpublished. We used a mixed Gringard reagent to synthesize this compound (Scheme IV). Dichlorophenylphosphine was reacted with a mixture of 1-naphthyl magnesium bromide and 4-biphenylyl magnesium bromide to form triarylphosphines. The desired compound could be separated from bis (1-naphthyl) phenylphosphine and bis (4-biphenylyl) phenylphosphine by fractional recrystallization from benzene. This was confirmed through ir and nmr spectroscopy, tlc chromatrograms and melting points.

SCHEME IV



A three to one molar ratio of 4-biphenylyl-1-naphthylphenylphosphine to rhodium trichloride was reacted in deoxygenated absolute ethanol to obtain a brown powder which was insoluble in ethanol and water. This material, after purification and elemental analysis was confirmed to be the octahedral rhodium(III) complex, trichlorotris (4-biphenylyl-1-naphthylphenylphosphine)rhodium(III). This new complex is soluble in non-polar solvents in dilute concentrations.

The rhodium(I)-phosphine complex developed by Wilkinson and co-

workers[3] was prepared in ethanol by reacting a six molar excess of triphenylphosphine with rhodium trichloride. Triphenylphosphine oxide was determined to be present at the completion of this reaction. Thus it was postulated that the initially formed octahedral rhodium(III) complex was reduced by the excess triphenylphosphine to give dichlorotriphenylphosphine. This compound can react with hydroxy solvents to form the phosphine oxide.

An attempt was made to prepare chlorotris(4-biphenylyl-1-naphthylphenylphosphine)rhodium(I) using the same procedure. However the octahedral rhodium(III) complex was obtained. We postulate that the greater steric hindrance of this triarylphosphine prohibits it from attacking the chloride ligands on the initially formed rhodium complex.

The homogeneous catalytic activity of this new complex has been studied for the reduction of α,β-unsaturated acids (Table VI). All of these compounds were reduced quantitatively using mild reaction conditions of 50 to 100 psi of hydrogen gas and temperatures ranging from 40 to 60 degrees. The selection of acids included ones containing terminal, disubtituted, and trisubtituted carbon-carbon double bonds.

The only other rhodium(III)-phosphine complex reported as a homogeneous hydrogenation catalyst, trichlorotris(methylpropylphenyl)-rhodium(III)[10], was limited to the reduction of easily reducible terminal double bonds in two unsaturated carboxylic acids. The conditions necessary for reduction were rather severe, at temperatures of 60 to 80 degrees and pressures of 300 to 400 psi. Our complex was used to

TABLE VI

The Homogeneous Catalytic Hydrogenation of α,β-Unsaturated Carboxylic Acids Using Trichlorotris(4-Biphenylyl-1-Napthylphenylphosphine)-Rhodium(III)

Reactant	Product	Yield (%)	Reduction (%)
atropic acid	hydratropic acid	90	100
itaconic acid	α-methylsuccinic acid	70	100
cinnamic acid	hydrocinnamic acid	85	100
p-methyl-cinnamic acid	p-methylhydro-cinnamic acid	80	100
α-(acetamido) cinnamic acid	N-acetyl-β-phenylalanine	75	100

reduce the same acids and even more highly substituted unsaturated carboxylic acids at temperatures of 60 degrees and pressures of 60 to 100 psi of hydrogen gas. The steric bulk of the triarylphosphine would be greater than that of methylpropylphenylphosphine. However it could be postulated that the decreased bascity[23] of the triaryl-phosphine would permit greater dissociation from the complex than with the alkyl-arylphosphine.

PART III

The Attempted Asymmetric Reduction of α-(Acetamido)Cinnamic Acid and Atropic Acid.

The asymmetric catalytic hydrogenation of α-(acetamido)cinnamic acid and atropic acid using trichlorotris(4-biphenylyl-1-naphthylphenylphosphine)rhodium(III) prepared from partially resolved 4-biphenylyl-1-naphthylphenylphosphine was attempted. The partial resolution of the triarylphosphine, the preparation of the optically active catalyst, and the various modifications used in these reductions are discussed. The failure to obtain asymmetric synthesis is discussed in light of the data obtained.

The resolution of the trisubstituted phosphine was attempted according to the procedure used by Wittig.[23] The careful duplication of his procedure failed to separate the enantiomers. Employing a procedure described in correspondence from Prof. Wittig, partial resolution was obtained through the hydroxymethylphosphonium salt of optically active camphor-10-sulfonic acid. According to the values given for the rotations by Wittig,[23] the compound was 50 percent optically pure.

The catalyst used in this work was prepared by reacting a three to one molar ratio of optically active phosphine to rhodium trichloride in absolute ethanol. This preparation is similar to that used for the racemic catalyst except that the maximum temperature of the reaction was 40 degrees. The specific rotation of this complex was not determined because of its intense absorption in the visible region.

α-(Acetamido) cinnamic acid was catalytically hydrogenated using the catalyst prepared from the optically active phosphine. A substrate to catalyst ratio of twenty-five to one was employed. The isolation procedure was performed in the absence of base so that racemization could not occur. The N-acetyl phenylalanine obtained from this reaction was determined to have a specific rotation of zero degrees.

Several attempted asymmetric hydrogenations were performed on atropic acid. In all of these attempts, the catalyst was prepared and used in situ at a substrate to catalyst ratio of thirty to one. Atropic acid was hydrogenated in a benzene-ethanol solution under mild conditions. The isolation of hydratropic acid was performed under conditions which would minimize racemization, however, no asymmetric hydrogenation occurred. This reaction was repeated using triethylamine in the reaction mixture in an amine to catalyst ratio of three to one.

Finally, this experiment was performed using α-phenythylamine in the same amine to catalyst ratio. The specific rotation of the reduced hydratropic acid was zero in both cases. This optically active amine was used because we felt this added asymmetric environment could induce asymmetric reduction.

Two examples of asymmetric reduction using homogeneous catalysts prepared from optically active ligands are reported in the literature. Knowles and Sabacky used trichlorotris(methylpropylphenylphosphine)-rhodium(III),[10] prepared from 70 percent optically pure methylprophyphenylphosphine, to hydrogenate atropic acid. They used a three molar excess of triethylamine and obtained hydratropic acid 15 per-

cent optically pure. Jardine and McQuillin[11] used the complex obtained from the reduction of trichlorotripyridylrhodium with sodium borohydride in N-L-phenylethylformamide to hydrogenate methyl 3-phenylbut-2-enoate. The saturated ester obtained was 50 percent optically pure. Thus, the failure of our catalyst to direct asymmetric hydrogenation was puzzling.

It was possible that our catalyst was acting as a dehydrogenation catalyst and thus racemizing the initially formed asymmetric carbon atom. As a test of this hypothesis, optically active N-acetyl -D-phenylalanine was prepared and stirred in the presence of the catalytic system under the same conditions used for the hydrogenations. The recovered N-acetyl-phenylalanine showed a decrease in optical purity of only three percent. This decrease is not of significant magnitude to demonstrate racemization by the catalytic system.

Since the catalyst used in this work was not prepared from optically pure triarylphosphine, it was possible that there could be a difference in the rate of catalysis between the catalyst containing the d-phosphine and the one containing the l-phosphine. In light of this possibility, the following experiment was performed. Atropic acid was only partially reduced under very carefully controlled conditions using racemic catalyst. A second sample was partially reduced under the same conditions using the catalyst prepared from the optically active phosphine. The analysis of these two mixtures of atropc and hydratropic acid by nmr spectroscopy, indicated that the reaction mixture was approximately 25 percent hydratropic acid in both cases.

One question remaining in this attempted asymmetric hydrogenation is the optical purity of the triarylphosphine ligand. Wittig[23] suggests that his resolution may not be complete. Although a repeat of this resolution gave an optical purity of 50 percent based on Wittigs rotations, the absolute purity could not be ascertained.

It would be of interest to attempt to determine the optical purity. One possible method would involve nmr spectroscopy. It has been demonstrated[27] that protons alpha to diastereomeric centers show different chemical shifts. If an organic halide such as optically pure d or l methyl-α-bromophenylacetate were reacted with the partially resolved phosphine to form the diastereomeric quaternary phosphonium salts, the alpha hydrogen in each diastereomer could show a separate resonance peak in the nmr spectrum. Provided the difference in chemical shifts of the diastereomeric protons was of sufficient magnitude to permit a separate integration of each, the percentage of each diastereomer could be calculated directly.

CONCLUSION

Chlorotris(triphenylphosphine)rhodium(I) has been further developed as a homogeneous hydrogenation catalyst. The use of this complex for catalytic hydrogenations has been examined through extensive series of α,β-unsaturated organic compounds. This catalyst has been found to selectively catalyze the hydrogenation of carbon-carbon double bonds in the presence of easily reducible functional groups such as ketones, aldehydes, and nitro groups. Many highly substituted carbon-carbon double bonds were quantitatively reduced under mild conditions. A survey of unsaturated compounds not reducible using this catalyst has also been discussed.

Trichlorotris(4-biphenylyl-1-naphthylphenylphosphine)rhodium (III) has been synthesized, characterized, and developed as a homogeneous hydrogenation catalyst. The data collected confirm that this new catalyst is more efficient for the reduction of α,β-unsaturated acids than previous rhodium(III)-phosphine complexes. This work marks the first time a coordinatively saturated rhodium (III)-phosphine complex has been used to catalyze the hydrogenation of highly substituted unsaturated compounds.

Attempts were undertaken to asymmetrically reduce α,β-unsaturated acids using the above catalyst prepared from optically active 4-biphenylyl-1-naphthylphenylphosphine. The attempts were made on atropic acid and α-(acetamido) cinnamic acid under various conditions. All experiments attempted failed to achieve asymmetric reduction. These results were further examined in light of additional data collected.

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