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Synthesis of (*R*)-6-Methyltryptophan via Enantioselective Catalytic Hydrogenation

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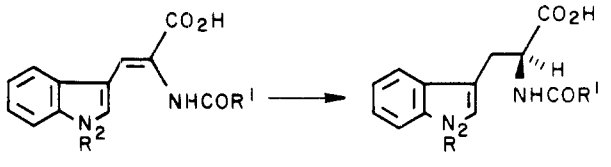
A novel synthesis of the potential sweetening agent (*R*)-6-methyltryptophan (**15**) via enantioselective catalytic hydrogenation is described. The methyl (*Z*)-α-(acylamino)indoleacrylates **8a–c** were obtained by reduction of the α-nitroindoleacrylate **6** with stannous chloride and subsequent acylation. Alternatively, decarboxylative condensation of the carboxaldehyde **12** with the ethyl half-ester of acetamidomalonic acid in acetic anhydride–pyridine furnished the ethyl ester **8d** in high yield. Basic hydrolysis of **8a** or **8d** produced the acrylic acid **9**. The asymmetric hydrogenations of these substrates with several chiral rhodium–phosphine complexes are discussed. An optimized process to convert **9** into **15** in 60% yield is presented. Catalytic hydrogenation with Rh-**16b** gave (*R*)-*N*-acetyl-6-methyltryptophan (**14e**) (82% ee) which was purified as its ammonium salt **14f** (>99.8% ee) and deacetylated to afford enantiomerically pure **15**.

The asymmetric catalytic hydrogenation of α-(acylamino)acrylic acids with chiral rhodium–phosphine complexes has opened a new pathway to optically active amino acids.[1] It has been successfully applied to indoleacrylic acids of type **1** affording **2** in excellent enantiomeric excess (ee).[2] The synthetic utility of this reaction



1a $R^1 = CH_3$, $R^2 = COCH_3$ — **2a,b,c**

b $R^1 = CH_3$, $R^2 = H$

c $R^1 = C_6H_5$, $R^2 = H$

for the preparation of enantiomerically pure tryptophans, however, does not depend only on the enantioselectivity of the hydrogenation step. A practical synthesis also requires an efficient preparation of the hydrogenation substrate, a hydrogenation process which uses rhodium efficiently (high substrate/catalyst ratio), a simple process to obtain pure enantiomer from the hydrogenation product, and a facile removal of the *N*-acyl group (R^1CO) under nonracemizing conditions. In this paper, we describe a synthesis of (*R*)-6-methyltryptophan (**15**), which satisfies all of these requirements. Our interest in this particular tryptophan was caused by its potential value as a nonnutritive sweetening agent.[3]

Results and Discussion

Our first approach to the potentially useful hydrogenation substrates **8a–c** and **9** is outlined in Scheme I.[4] 6-Methylindole (**5**), readily prepared from 2-nitro-1,4-dimethylbenzene (**3**) by the indole synthesis of Batcho and Leimgruber,[5] was reacted with methyl α-nitro-β-ethoxy-

(1) For reviews on enantioselective catalytic hydrogenations, see: D. Valentine Jr. and J. W. Scott, *Synthesis*, 329 (1978); J. W. Scott and D. Valentine Jr., *Science*, **184**, 943 (1974).

(2) (a) W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *Chem. Technol.*, **2**, 590 (1972); (b) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **97**, 2567 (1975); (c) P. Aviron-Violet, Ger. Offen. 2424543 (March 21, 1973); *Chem. Abstr.*, **82**, P171186 (1975).

(3) (a) E. C. Kornfeld, T. Suarez, R. Edie, D. R. Brannon, D. Fukuda, J. Sheneman, G. C. Todd, and M. Scondino, "Abstracts of Papers", 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974; MEDI 41; (b) E. C. Kornfield, J. M. Sheneman, and T. Suarez, German Offen. 1917844 (Nov 6, 1969); *Chem. Abstr.*, **72**, P30438 (1970).

(4) The corresponding *N*-benzoyl derivative was disfavored, since the conditions for acidic hydrolysis of the benzoylamino group are too harsh for the acid-sensitive 6-methylindole moiety, while alkaline hydrolysis leads to partial racemization.

(5) (a) A. D. Batcho and W. Leimgruber, German Offen. 2057840 (1971); *Chem. Abstr.*, **75**, 63605 (1971); (b) W. Leimgruber and A. D. Batcho, "Abstracts of Papers", 3rd International Congress of Heterocyclic Chemistry, Tohoku University, Sendai, Japan, Aug 1971, p 462.

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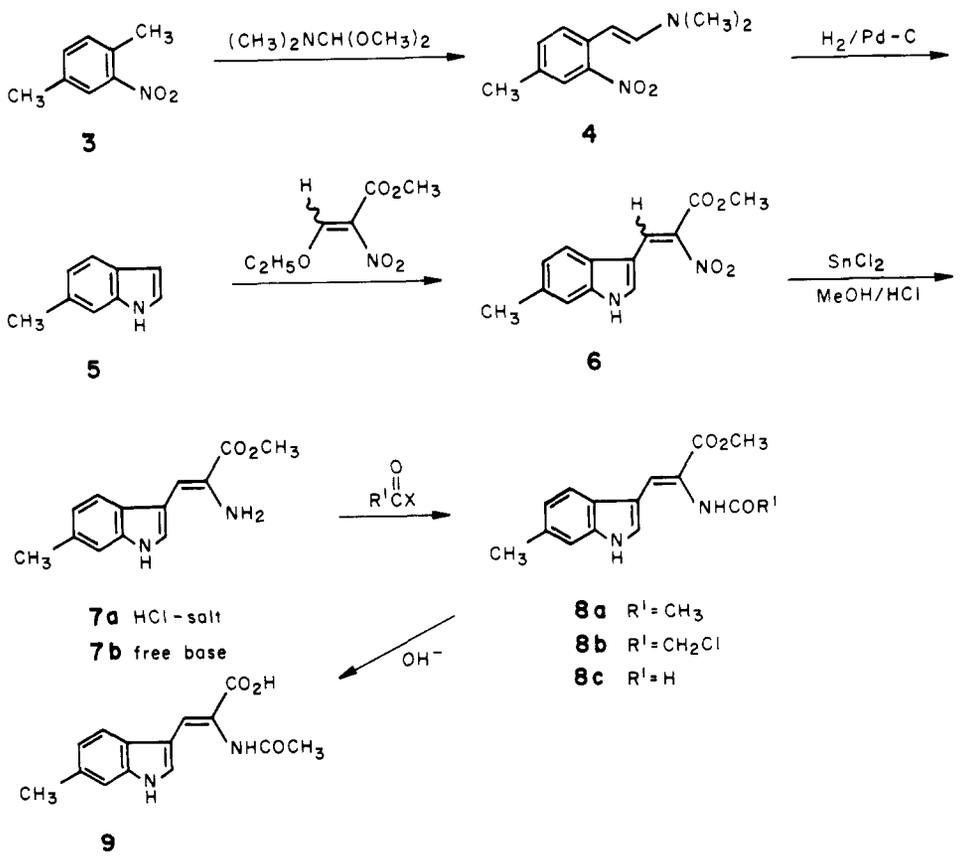
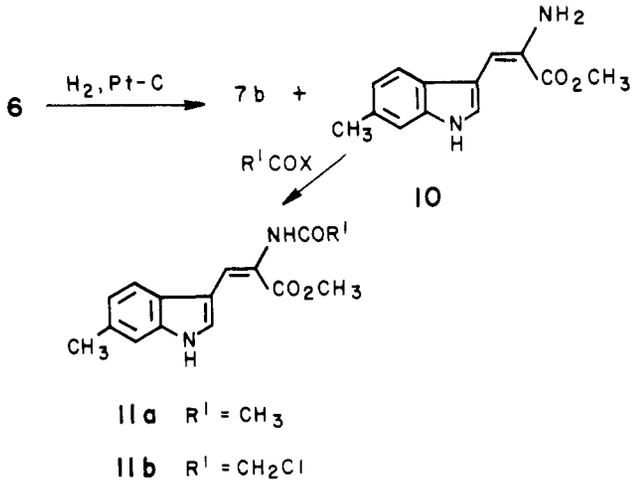
Scheme I



acrylate to give the crystalline α-nitroacrylate **6** as a 1:1 mixture of the *Z* and *E* isomers.[6a] Selective reduction of the nitro function with stannous chloride in anhydrous methanolic HCl at −20 °C[6b] gave the α-aminoacrylic ester hydrochloride **7a** which crystallized from the reaction mixture in high yield as a single isomer. The free base **7b**, prepared either in situ or after isolation, was then acylated with the appropriate agent to give **8a–c**; compound **9** was obtained by basic hydrolysis of **8a**. All of these compounds were isomerically pure by TLC and ^{1}H NMR analysis. The indicated *Z* configuration was established in the following way. Hydrogenation of **6** over platinum-on-carbon in ethyl acetate gave the α-aminoacrylic esters **7b** and **10** in about equal amounts. Acetylation of this mixture with acetic anhydride, followed by fractional crystallization, afforded a pure sample of the isomer **11a**. This compound was completely converted to **8a** with a catalytic amount of sodium methoxide. Examination of the ^{13}C NMR spectra of **8a** and **11a** showed that the long-range coupling between the β-hydrogen of the acrylic ester moiety and the carbonyl carbon of the ester function was smaller for **8a** (J = 3.5 Hz, H_β cis to C=O) than for **11a** (J = 10.5 Hz, H_β trans to C=O).[7] This allowed us to assign the *Z* configuration to **8a** and, by analogy, to the other substrates **8b**, **8c**, and **9**. Finally, an X-ray crystallographic analysis of the α-[(chloroacetyl)amino]acrylic ester **8b** confirmed that it was the *Z* isomer.



While the route presented in Scheme I is convenient to prepare a variety of α-(acylamino)indoleacrylic esters and acids, the overall yield and practicality of scale up are unsatisfactory. A more efficient synthesis of the *N*-acetyl compounds **8d** and **9** is summarized in Scheme II.

The carboxaldehyde **12**, obtained in 98% yield by a Vilsmeier formylation of **5**, is only one glycine molecule away from the acrylic acid **9**. Treatment of **12** with *N*-acetylglycine under the conditions of the Erlenmeyer azlactone synthesis gave a poor yield (≤30%) of the desired azlactone **13**.[8] Reaction with the ethyl half-ester of

(6) (a) The analogous reaction with indole was reported by N. I. Aboskalova, K. K. Babievskii, V. M. Belikov, V. V. Perekalin, and A. S. Polyanskaya, *J. Org. Chem. USSR (Engl. Transl.)*, **9**, 1082 (1973). (b) Babievskii et al. (K. K. Babievskii, V. M. Belikov, and E. V. Zaporo, *ibid.*, **9**, 1087 (1973)) have reported that catalytic hydrogenation of methyl α-nitro-β-(3-indolyl)acrylate with palladium goes simultaneously in two directions, reducing either the nitro group (34%) or the double bond (52%).

(7) (a) S. Braun, *Org. Magn. Reson.*, 11, 197 (1978); (b) E. P. Prokofev and E. I. Karpeiskaya, *Tetrahedron Lett.*, 737 (1979).

Scheme II

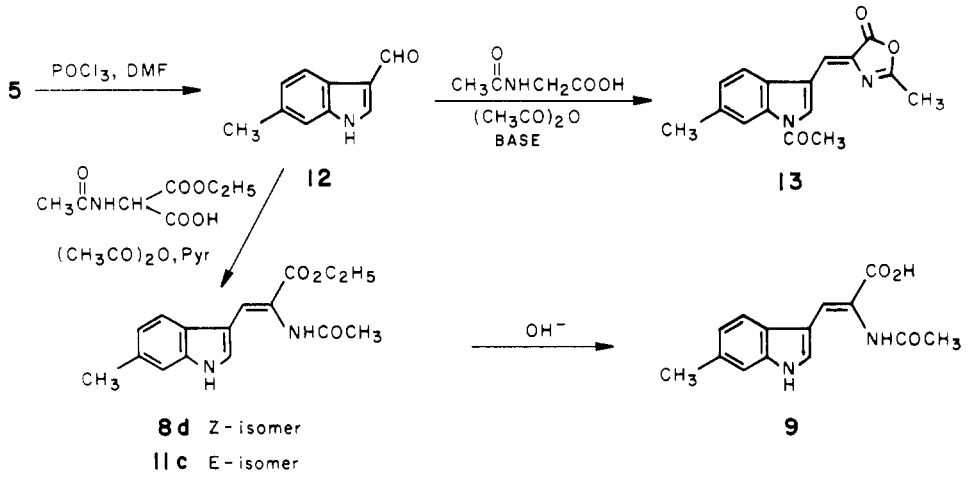
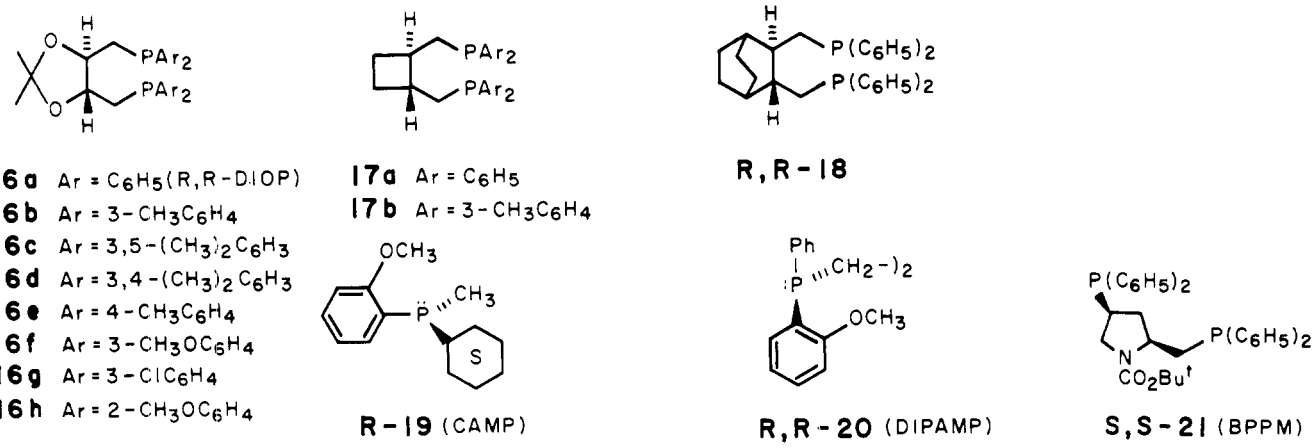


Chart I



acetamidomalonic acid[9] was more successful. Hellmann and Piechota[10] have reported that this compound undergoes a triethylamine-catalyzed decarboxylative aldol condensation with aromatic aldehydes to give the corresponding *N*-acetyl arylserine esters. They noted, however, that this reaction failed when the aldehyde was deactivated by electron-donating substituents. In particular, indole-3-carboxaldehyde was recovered quantitatively under their conditions. We have now found that the desired decarboxylative condensation does take place when the reaction is run in acetic anhydride–pyridine at room temperature. A 5:1 mixture of the isomeric α-acetamidoacrylic esters **8d** and **11c** was obtained in high yield. This isomer mixture was converted into the more stable *Z* isomer **8d** by treatment with sodium ethoxide. Spectral comparisons as well as sodium alkoxide promoted transesterification (**8d** → **8a** → **8d**) supported the structure assigned to **8d**. Basic hydrolysis of the **8d–11c** isomer mixture was also accompanied by isomerization and gave pure **9** in 75% yield from **12**.

Enantioselective hydrogenations of **8a–d** and **9** catalyzed by rhodium complexes of **16–21** (Chart I) were studied in methanol with the results summarized in Tables I and II.[11,12] The enantiomeric excess (ee) values given in the tables were obtained by hydrolysis of the crude hydro-

Table I. Catalytic Enantioselective Hydrogenation of (*Z*)-α-(Acylamino)-6-methylindole-3-acrylic Acid Derivatives with Rh-16b and Rh-20[a]

substrate	phosphine[b]	ee, %	confign	(*S*/*C*)/*h*[c]
8b	16b	72	*R*	0.03
8c	16b	67	*R*	0.006
8d	16b	70	*R*	1
9	16b	82	*R*	0.3
8a[d]	20	95	*S*	0.01
8c[e]	20	92	*S*	0.01
8d[f]	20	96	*S*	0.03
9[g]	20	91	*S*	0.06

[a] All reactions were carried out in purified CH_3OH at 23 °C and a 40-psi initial H_2 pressure at substrate/catalyst weight ratios of (100–3000):1 unless otherwise noted. The Rh^I precursor was $[RhCl(1,5\text{-}COD)]_2$ (1,5-COD = 1,5-cyclooctadiene). [b] See Chart I for structures. [c] Quotient of substrate/catalyst ratio (*S*/*C*) (weight basis) divided by the number of hours required to reach ca. 85% conversion, normalized to 1. An (*S*/*C*)/*h* ratio of unity corresponds to ca. 0.4 turnovers/s. These data were obtained on substrates of varying quality and solubility in the reaction medium and are very approximate. [d] At 55 °C. [e] At 50–55 °C and 100-psi H_2 pressure. [f] At 50 °C. [g] At 65 °C.

(8) Low yields in the condensation of indole-3-carboxaldehyde with *N*-acetylglycine were reported by: (a) G. W. Kirby and M. J. Varley, *J. Chem. Soc., Chem. Commun.*, 833 (1974); (b) K. N. F. Shaw, A. McMillan, A. G. Gudmundson, and M. D. Armstrong, *J. Org. Chem.*, **23**, 1171 (1958).

(9) H. Hellmann, K. Teichmann, and F. Lingens, *Chem. Ber.*, **91**, 2427 (1958).

(10) H. Hellmann and H. Piechota, *Justus Liebigs Ann. Chem.*, **631**, 175 (1960).

(11) (a) H. B. Kagan and T. P. Dang, *J. Am. Chem. Soc.*, **94**, 6429 (1972); (b) T.-P. Dang, J.-C. Poulin, and H. B. Kagan, *J. Organomet. Chem.*, **91**, 105 (1975); (c) D. Sinou and H. B. Kagan, *ibid.*, **114**, 325 (1976); (d) J.-C. Poulin, T.-P. Dang, and H. B. Kagan, *ibid.*, **84**, 87 (1975).

Table II. Catalytic Enantioselective Hydrogenation of 9 and 8d with Rh^I and Various Chiral Phosphines[a]

	substrate					
	9			8d		
phosphine	ee, %[b]	config	(S/C)/h[c]	ee, %[b]	config	(S/C)/h[c]
16a[d]	73.2	R	1	56.8	R	1
16b[e]	83	R	3	70.4	R	3
16c	86	R	2	70.8	R	1
16d	77.8	R	2	(57)	R	1
16e[f]	71.6	R	0.8			
16f	72.2	R	0.7	64.9	R	1
16g	53.6	R	0.008			
16h	26.7	S	0.002			
17a[g]	77.6	R	4	(46)	R	5
17b	53.4	R	3			
18[h]	85.6	R	3	72	R	2
19[i]	(67)[l]	S				
20[j]	91.2[m]	S	0.2	96.2[n]	S	0.008
21[k]	90	R	1	87	R	0.6

[a] See note a, Table I. [b] Values in parentheses are optical purities based on maximum rotations of $[\alpha]^{25}_D$ −27.2° (c 1, CH_3OH) for 14e and $[\alpha]^{25}_D$ −13.3° (c 1, CH_3OH) for 14d. Rotations are not reliable indicators of optical purity due to possible occlusion of solvent or other trace impurities. [c] See note c, Table I, and text. Reaction time using 16a defined as 1.0 for both 9 and 8d. [d] Reference 11a. [e] Reference 11b. [f] Reference 11c. [g] Reference 2c. [h] Reference 11b. [i] Reference 2a. [j] Reference 2b. [k] Reference 12. [l] At 50 °C. [m] At 65 °C. [n] At 50 °C.

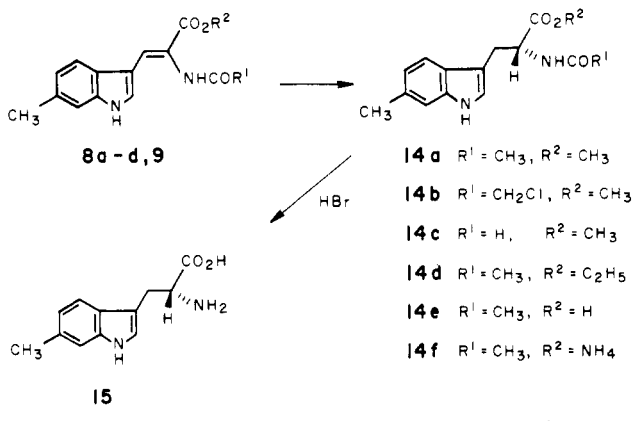
genation product 14 and treatment of the free amino acid with (S)-glutamic acid N-carboxyanhydride to give the diastereomeric dipeptides (S)-Glu-(R)-6-MeTrp and (S)-Glu-(S)-6-MeTrp, which were analytically separated by ion-exchange chromatography on an amino acid analyzer.

The preferred method for obtaining (R)-6-methyltryptophan (15) was hydrogenation of 9 catalyzed by Rh-16b or Rh-16c (see below). This hydrogenation was conveniently run at 23 °C and 3–7 atm of hydrogen by using a slurry of 9 with 5 mL/g of methanol containing as little as 0.03% catalyst by weight. The rate approached 1 turnover/s when purified solvents and reagents were used under anaerobic conditions. As the hydrogenation proceeded, the reaction mixture became homogeneous and eventually a solution of 14e was obtained. Evaporation of solvent gave crude 14e (100% yield, 82% ee) whose crystallization from aqueous ammonia gave the ammonium salt 14f (81% yield, >99.8% ee).[13] Heating of 14f with aqueous hydrobromic acid removed the N-acetyl group without racemization to give chemically and enantiomerically pure 15 in 60% yield from 9 (Scheme III).

The other substrate–phosphine combinations examined (Tables I and II) were judged less satisfactory for our purposes. Hydrogenations of 8b and 8c were too slow to allow use of high substrate/catalyst ratios. Hydrogenation of 8a was similar to that of 8d, but 8d was more readily obtained by our synthetic methods (Scheme II). Hydrogenation of 9 was more enantioselective than hydrogenation of 8d with all but one chiral phosphine tried. This one exception was the most enantioselective combination found: compound 8d as substrate and Rh-20 (DIPAMP) as catalyst. Hydrogenation of 8d was conveniently run as a slurry of 8d in 9:1 methanol–water from which the product 14d precipitated in high optical purity (>99.8% ee). Hydrolysis of 14d by heating with 2.5 M hydrochloric acid completed the synthesis of 15.

In hydrogenations of 9 catalyzed by Rh-16, it was found that meta-electron-releasing substituents on the phosphine aryl groups gave catalysts which generally effected faster and more enantioselective hydrogenations than catalysts

Scheme III



containing the parent DIOP 16a. A m-chloro substituent had the opposite effect. The effect of para substituents was less. All ortho-substituted phosphines gave poor catalysts. In agreement with similar work on other substrates, it was found in hydrogenations of 8a and 9 with Rh-16b and Rh-20 catalysts that hydrogenations were about 20 times faster when Rh-16b was used.[11d] Tables I and II include some very approximate rate data for other substrate–catalyst systems we have studied.

Experimental Section

General Procedures. Melting points were taken on a Thomas Hoover capillary melting point apparatus and are not corrected. Spectral measurements were taken by members of the physical chemistry department of Hoffmann-La Roche. ^1H NMR spectra were recorded on Varian A-60, HA-100, and XL-100 instruments in the continuous-wave mode. ^{13}C and ^{31}P NMR spectra were obtained on a Varian XL-100 spectrometer in the Fourier-transform mode at 25.2 and 40.5 MHz, respectively. The $^3J_{CH}$ values were determined from the proton-coupled ^{13}C spectra. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane for ^1H and ^{13}C nuclei and external phosphoric acid for ^{31}P nuclei. Infrared spectra were obtained on a Beckman IR-9 or Digilab FTS-14 spectrometer. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Mass spectra were obtained on a Jeolco OISG or CEC 21-110 instrument.

***trans*-β-(Dimethylamino)-4-methyl-2-nitrostyrene (4).** A stirred mixture of 675 g (4.46 mol) of 2-nitro-1,4-dimethylbenzene,

(12) K. Achiwa, *J. Am. Chem. Soc.*, 98, 8265 (1976).

(13) Optical purification of D- and L-6-chlorotryptophan by this method was recently reported by I. Chibata, S. Yamada, M. Yamamoto, and H. Sanematsu, Japanese Kokai 76 19 761 (Feb 17, 1976); *Chem. Abstr.*, 85, P47056 (1976).

736 g (6.17 mol) of *N,N*-dimethylformamide dimethyl acetal, and 3.0 L of *N,N*-dimethylformamide was heated under nitrogen for 37 h, while the pot temperature was raised gradually from 130 to 144 °C. The methanol formed during the reaction was continuously removed by distillation through a fractionating column. The deep red reaction mixture was concentrated in vacuo on a rotavap. The residual oil (924 g) was mixed with 640 mL of methanol and stirred at 0 °C overnight. The precipitate was filtered, washed with methanol (−70 °C), and dried to afford 760 g (83%) of **4**, mp 41.5–43.5 °C. The analytical sample was prepared by recrystallization from ether/pentane followed by evaporative distillation at 100 °C (0.1 mm): dark red crystals, mp 42.5–44 °C; IR ($CHCl_3$) 1630, 1615, 1520, 1340 cm^{-1}; NMR ($CDCl_3$) δ 2.26 (s, 3), 2.83 (s, 6), 5.78 (d, 1, J = 14 Hz), 6.85 (d, 1, J = 14 Hz), 7.12 (d, 1, J = 8 Hz), 7.32 (d, 1, J = 8 Hz), 7.62 (s, 1); mass spectrum m/e 206 (M^+).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.24; H, 6.87; N, 13.73.

6-Methylindole (5). A solution of 300 g (1.45 mol) of enamine **4** in 3 L of benzene was hydrogenated over 15 g of 5% palladium-on-carbon at 200 psi and room temperature for 5 h. The filtered solution was concentrated to half its volume and washed with 0.25 N HCl, aqueous $NaHCO_3$, and brine. The aqueous phases were reextracted with benzene, and the combined organic phases were dried (Na_2SO_4), concentrated, and distilled at 80–85 °C (0.05 mm), giving 157.9 g (83%) of a slightly yellow oil, which solidified upon standing: mp 29–30.5 °C (lit.[14] mp 28 °C); IR ($CHCl_3$) 3465 cm^{-1}; NMR ($CDCl_3$) δ 2.33 (s, 3), 6.34 (m, 1), 6.6–7.0 (m, 4), 7.43 (d, 1, J = 8 Hz); mass spectrum m/e 131 (M^+).

Anal. Calcd for C_9H_9N: C, 82.41; H, 6.91; N, 10.68. Found: C, 82.38; H, 6.81; N, 10.55.

Methyl α-Nitro-6-methylindole-3-acrylate (6). A mixture of 32.5 g (0.25 mol) of 6-methylindole (**5**) and 52.5 g (0.30 mol) of methyl α-nitro-β-ethoxyacrylate[15] was stored under nitrogen in a wide crystallizing dish for 20 h at room temperature. The reddish solid was triturated with ether/hexane (1:1), and the crystalline material was filtered, washed with ether, and dried to afford 44.5 g (69%) of **6**, mp 167–169 °C. The analytical sample was prepared by recrystallization from 1-butanol: orange crystals, mp 169–170 °C; IR ($CHCl_3$) 3350, 1725 cm^{-1}; NMR (Me_2SO-d_6) δ 2.42 (s, 3), 3.88 (s, 1.5), 3.96 (s, 1.5); mass spectrum m/e 260 (M^+).

Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.20; H, 4.40; N, 10.85.

Methyl (*Z*)-α-Amino-6-methylindole-3-acrylate (7b). To a stirred solution of 133.6 g (0.59 mol) of stannous chloride dihydrate and 47 g (1.29 mol) of HCl gas in 420 mL of methanol was added portionwise at −25 °C over 1 h 44.0 g (0.17 mol) of compound **6**. The slurry was stirred at −10 °C for 2.5 h. Ether (210 mL) and concentrated HCl (210 mL) were then added and the resulting slurry was stirred at 0 °C for 30 min. The precipitate was filtered, washed with methanol/9 N aqueous HCl (1:1, −20 °C) and ether, and dried in vacuo to give 39.7 g (88%) of the hydrochloride **7a**: mp 186–187 °C; NMR (Me_2SO-d_6) δ 2.40 (s, 3), 3.85 (s, 3), 7.02 (d, 1, J = 8 Hz), 7.34 (s, 1), 7.68 (d, 1, J = 8 Hz), 7.82 (s, 1), 8.36 (s, 1), 8.50 (br s, 3), 12.40 (br s, 1); mass spectrum m/e 230 (M^+, free base).

The hydrochloride **7a** was partitioned between aqueous $NaHCO_3$ and ethyl acetate, and the organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo, leaving 31.8 g (82%) of **7b**, mp 129–131 °C. A sample was recrystallized from methanol: light yellow crystals, mp 130–131.5 °C; IR ($CHCl_3$) 3470, 1700 cm^{-1}; NMR (Me_2SO-d_6) δ 2.40 (s, 3), 3.77 (s, 3), 4.57 (br s, 2), 6.70 (s, 1), 6.90 (d, 1, J = 8 Hz), 7.20 (s, 1), 7.55 (d, 1, J = 8 Hz), 7.70 (d, 1, J = 2 Hz), 11.3 (br s, 1); mass spectrum m/e 230 (M^+).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.60; H, 6.03; N, 12.11.

Methyl (*Z*)-α-Acetamido-6-methylindole-3-acrylate (8a). To 38.5 g (0.14 mol) of **7a** and 165 mL of acetic anhydride was added slowly with ice bath cooling 13.2 g (0.16 mol) of pyridine. The mixture was stirred at 20 °C for 45 min; then 80 mL of water was added at 20 °C over 30 min and stirring was continued for 90 min. An additional 370 mL of water was added. After 1 h the precipitate was collected by filtration, washed with water, and dried to afford 33 g (84%) of **8a**, mp 180–182 °C. A sample was recrystallized from methanol: light yellow crystals, mp 182–183 °C; ^1H NMR (Me_2SO-d_6) δ 2.09 (s, 3), 2.40 (s, 3), 3.72 (s, 3), 6.96 (d, 1, J = 8 Hz), 7.27 (s, 1), 7.62 (d, 1, J = 8 Hz), 7.69 (s, 1), 7.81 (d, 1, J = 2 Hz), 9.30 (br s, 1), 11.58 (br s, 1); ^{13}C NMR (Me_2SO-d_6) δ 21.2, 22.6, 51.6 (3 q, 3, 6-CH_3, $COCH_3$, OCH_3), 111.7, 117.4, 121.8, 126.2, 128.1 (5 d, 5), 108.7, 120.3, 124.7, 131.2, 135.9 (5 s, 5), 165.5 (m, 1, $COOCH_3$), 168.8 (m, 1, CONH); mass spectrum m/e 272 (M^+); UV max (2-PrOH) 342 nm (ε 21 300).

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.20; H, 5.91; N, 10.38.

Methyl (*Z*)-α-[(Chloroacetyl)amino]-6-methylindole-3-acrylate (8b). A mixture of 9.20 g of **7b**, 120 mL of tetrahydrofuran, and 15.2 g of chloroacetic anhydride was stirred at room temperature for 3 h. Petroleum ether (240 mL) was added. The precipitate was filtered, washed with petroleum ether/chloroform (1:1), and dried to afford 11.9 g (97%) of **8b**, mp 200–201 °C. A sample was recrystallized from acetone: off-white crystals, mp 201–202 °C; NMR (Me_2SO-d_6) δ 2.41 (s, 3), 3.73 (s, 3), 4.32 (s, 2), 6.98 (d, 1, J = 8 Hz), 7.26 (s, 1), 7.63 (d, 1, J = 8 Hz), 7.75 (s, 1), 7.83 (d, 1, J = 2 Hz), 9.63 (br s, 1), 11.68 (br s, 1); mass spectrum m/e 306 (M^+); UV max (2-PrOH) 346 nm (ε 20 750).

Anal. Calcd for $C_{15}H_{15}N_2O_3Cl$: C, 58.74; H, 4.93; N, 9.13; Cl, 11.56. Found: C, 58.94; H, 5.07; N, 9.45; Cl, 11.28.

Methyl (*Z*)-α-Formamido-6-methylindole-3-acrylate (8c). A mixture of 20.0 g of **7b**, 280 mL of tetrahydrofuran, and 15 mL of formic acetic anhydride was stirred at room temperature for 2.5 h. The precipitate was collected by filtration and washed with ethyl acetate. A second crop was obtained by diluting the filtrate with ethyl acetate/hexane. The combined crops were recrystallized from acetonitrile to yield 18.4 g (82%) of **8c** as light beige crystals, mp 195–196 °C. The NMR (Me_2SO-d_6) indicated a 2:1 mixture of rotamers of RNHCHO: cis, δ 8.24 (br s), 9.36 (br s); trans, δ 7.96 (d, J = 12 Hz), 9.06 (d, J = 12 Hz). UV max (2-PrOH) 346 nm (ε 21 600)).

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.10; H, 5.58; N, 10.84.

Methyl (*E*)-α-Acetamido-6-methylindole-3-acrylate (11a). A mixture of 4.0 g of **6** and 0.4 g of 10% platinum-on-carbon in 100 mL of ethyl acetate was hydrogenated at room temperature and atmospheric pressure. The hydrogenation ceased after uptake of 3 equiv of hydrogen (3 h). The filtered solution was concentrated in vacuo to give 3.8 g of a dark yellow oil: NMR (Me_2SO-d_6) δ 3.70, 3.76 (2 s, 3), 4.50 (br, 2), 6.35, 6.70 (2 s, 1), 10.9, 11.3 (2 br s, 1); after the Me_2SO-d_6 solution was heated at 115 °C for 10 min, the NMR spectrum was identical with that of compound **7b**. The crude hydrogenation product was dissolved in 30 mL of acetic anhydride and stirred for 20 min. The resulting suspension was diluted with 60 mL of ether, and the precipitate was collected, washed with ether, and dried to give 1.38 g (33%) of **11a**, mp 197–199.5 °C. The analytical sample was prepared by recrystallization from methanol: yellow crystals, mp 202–203 °C; ^1H NMR (Me_2SO-d_6) δ 2.00 (s, 3), 2.40 (s, 3), 3.70 (s, 3), 6.93 (d, 1, J = 8 Hz), 7.00 (s, 1), 7.24 (s, 1), 7.47 (d, 1, J = 8 Hz), 7.85 (d, 1, J = 2 Hz), 9.67 (br s, 1), 11.30 (br s, 1); ^{13}C NMR (Me_2SO-d_6) δ 21.2, 22.4, 51.4 (3 q, 3, 6-CH_3, $COCH_3$, OCH_3), 111.5, 117.2, 119.7, 121.3, 126.0 (5 d, 5), 108.0, 121.7, 125.7, 130.1, 135.9 (5 s, 5), 165.3 (m, 1, $COOCH_3$), 168.2 (m, 1, CONH); mass spectrum m/e 272 (M^+); UV max (2-PrOH) 346 nm (ε 14 200).

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.44; H, 5.98; N, 10.39.

Conversion of 11a to 8a. A mixture of 174 mg of **11a** and 5 mL of 0.02 M sodium methoxide in methanol was heated at reflux for 3.5 h. Complete conversion of the *E* isomer **11a** to the *Z* isomer **8a** was verified by TLC analysis (silica gel, EtOAc). Workup of the reaction mixture gave 160 mg of yellow crystals, mp 173–178 °C, identical with those of the previously prepared **8a**.

Methyl (*E*)-α-[(Chloroacetyl)amino]-6-methylindole-3-acrylate (11b). One gram of **6** was catalytically hydrogenated as described above. The 1:1 mixture of **7b** and **10** was treated for 20 min at room temperature with 2.5 g of chloroacetic anhydride in 8 mL of tetrahydrofuran. The precipitate was collected, washed with tetrahydrofuran, and dried to give 0.33 g of **11b**, mp

(14) H. N. Rydon, *J. Chem. Soc.*, 705 (1948).
(15) M. J. Kamelot, *J. Org. Chem.*, **24**, 714 (1959).

199 °C. The analytical sample was prepared by recrystallization from acetone: yellow crystals, mp 200 °C; NMR (Me_2SO-d_6) δ 2.43 (s, 3), 3.73 (s, 3), 4.17 (s, 2), 6.96 (d, 1, J = 8 Hz), 7.24 (s, 1), 7.29 (s, 1), 7.49 (d, 1, J = 8 Hz), 8.05 (d, 1, J = 2 Hz), 9.78 (br s, 1), 11.36 (br s, 1); mass spectrum m/e 306 (M^+); UV max (2-PrOH) 355 nm (ε 15 000).

Anal. Calcd for $C_{15}H_{15}N_2O_3Cl$: C, 58.74; H, 4.93; N, 9.13; Cl, 11.56. Found: C, 58.87; H, 4.90; N, 9.14; Cl, 11.54.

6-Methylindole-3-carboxaldehyde (12). A solution of 156 g (1.19 mol) of 6-methylindole (**5**) in 160 mL of *N,N*-dimethylformamide was added at 5–10 °C over 1 h to a mixture of 217 g (1.42 mol) of phosphorus oxychloride and 630 mL of *N,N*-dimethylformamide. The orange solution was stirred at room temperature for 1 h. Ice (1.2 kg) was added, followed by a solution of 840 g (13 mol) of potassium hydroxide in 2 L of water. The mixture was heated at 93 °C for 30 min and then stored at room temperature overnight. The precipitate was collected, washed with water, and dried to afford 186.5 g (98%) of **12**, mp 183–186 °C. The analytical sample was prepared by recrystallization from ethanol: white crystals, mp 184.5–186.5 °C (lit.[16] mp 190–192 °C); NMR (Me_2SO-d_6) δ 2.43 (s, 3), 7.11 (d, 1, J = 8 Hz), 7.41 (s, 1), 8.07 (d, 1, J = 8 Hz), 8.22 (s, 1), 9.97 (s, 1).

Anal. Calcd for $C_{10}H_9NO$: C, 75.46; H, 5.70; N, 8.80. Found: C, 75.38; H, 5.87; N, 8.88.

Ethyl (*Z*)-α-Acetamido-6-methylindole-3-acrylate (8d). To a mixture of 100 g (0.63 mol) of carboxaldehyde **12**, 119 g (0.63 mol) of ethyl acetamidomalonate,[9] and 500 mL of pyridine was added at 15 °C over 15 min 175 mL of acetic anhydride. The yellow solution was stirred at room temperature for 3 h. An additional 36 g (0.19 mol) of ethyl acetamidomalonate was added and stirring was continued for 22 h. Ice (1 kg) was added, and the mixture was stirred for 2 h and then diluted with 2 L of water. The precipitate was collected, washed with water, and dried to afford 162 g (90%) of a yellow crystalline material, mp 156–159 °C, which consisted of a 5:1 mixture of the *Z* and *E* isomers. The product was dissolved in 640 mL of refluxing ethanol. A small amount of water was removed by adding 100 mL of benzene and distilling off 200 mL of solvent. Sodium ethoxide (20 mL of a 2 M solution in ethanol) was added. The solution was refluxed for 2 h, neutralized with acetic acid, and chilled overnight. The precipitate was collected, washed with ethanol (–70 °C), and dried to give 118.2 g (66%) of **8d**, mp 172.5–174 °C. A second crop of 17.0 g (9%) of **8d**, mp 171–173 °C, was obtained by concentrating the mother liquor. The analytical sample was prepared by recrystallization from ethanol: light yellow crystals, mp 174.5–176.5 °C; NMR (Me_2SO-d_6) δ 1.27 (*t*, 3, J = 7 Hz), 2.07 (s, 3), 2.43 (s, 3), 4.17 (q, 2, J = 7 Hz), 6.97 (d, 1, J = 8 Hz), 7.25 (s, 1), 7.62 (d, 1, J = 8 Hz), 7.65 (s, 1), 7.80 (s, 1), 9.00 (br s, 1), 11.30 (br s, 1); mass spectrum m/e 286 (M^+); UV max (2-PrOH) 342 nm (ε 21 050).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.13; H, 6.31; N, 9.77.

(*Z*)-α-Acetamido-6-methylindole-3-acrylic Acid Monohydrate (9). Carboxaldehyde **12** (143.3 g, 0.90 mol) was treated as described above with 221.3 g (1.17 mol) of ethyl acetamidomalonate, 700 mL of pyridine, and 250 mL of acetic anhydride to give 223 g of crude product **8d** (*Z*/*E* ratio 5:1). This material was heated with 100 g of sodium hydroxide in 600 mL of methanol and 600 mL of water at 70 °C for 20 min. Ice (400 g) was added, followed by 250 mL of 12 N HCl. The precipitate was collected, washed with water, and dried. The beige solid (204 g, mp 217 °C) was dissolved in 1.4 L of methanol and 250 mL of *N,N*-dimethylformamide. Water (600 mL) was slowly added while reflux was maintained. The cooled mixture was filtered, and the cake was washed with methanol/water (1:1) and dried [50 °C (0.2 mm)] to afford 187.5 g (75%) of **9** as yellow crystals, mp 229 °C dec. A sample was recrystallized from methanol/*N,N*-dimethylformamide/water: yellow crystals, mp 231 °C dec; IR (KBr) 3300, 3260, 1665, 1627, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 2.05 (s, 3), 2.41 (s, 3), 6.96 (d, 1, J = 8 Hz), 7.23 (s, 1), 7.57 (d, 1, J = 8 Hz), 7.64 (s, 1), 7.71 (d, 1, J = 2 Hz), 9.12 (br s, 1), 11.47 (br s, 1). A small broad absorption observed at δ 1.72 collapsed with the $NHCOCH_3$ peak at δ 2.05 to a single sharp peak on heating to 90 °C and reappeared upon cooling. This band was attributed to a rotamer of the $NHCOCH_3$ group: mass spectrum m/e 258 (M^+); UV max (2-PrOH) 333 nm (ε 17 000).

Anal. Calcd for $C_{14}H_{14}N_2O_3 \cdot H_2O$: C, 60.86; H, 5.84; N, 10.14; H_2O, 6.52. Found: C, 61.00; H, 6.01; N, 10.19; H_2O, 6.34.

In a similar manner, compound **8a** (obtained from compound **6**) was saponified to give the acrylic acid **9**, identical in all respects (UV, IR, NMR, TLC) with the above-prepared material.

Ammonium Salt of (*R*)-*N*-Acetyl-6-methyltryptophan (14f). Rigorous exclusion of oxygen is essential for successful catalytic hydrogenation at high substrate/catalyst ratios. The operations below were carried out under an inert atmosphere. Methanol was purified by hydrogenation over Raney nickel.[17] A 5-gal magnetically stirred autoclave was charged with 400 g (1.45 mol) of (*Z*)-α-acetamido-6-methylindole-3-acrylic acid monohydrate (**9**) and 2.8 L of methanol. A catalyst solution was prepared separately from 92.8 mg of (4*R*,5*R*)-*trans*-4,5-bis-[[bis(3-methylphenyl)phosphino]methyl]-2,2-dimethyl-1,3-dioxolane (**16b**)[11b] and 41.2 mg of μ,μ′-dichloro-bis(η⁴-1,5-cyclooctadiene)rhodium(I)[18] in 100 mL of methanol. The catalyst solution was introduced into the autoclave to give a substrate/catalyst ratio of 3000:1 by weight. The resultant slurry was stirred at 25 °C under 100 psi of hydrogen for 20 h. A sample was removed and analyzed by TLC to indicate complete hydrogenation. The methanol was evaporated, the residue was dissolved in 2.2 L of 3% aqueous NH_3 at 82 °C, and the filtered solution was refrigerated overnight. The precipitate was collected, washed with ethanol (–70 °C), and dried to afford 286.4 g (71%) of **14f** as off-white crystals: mp 215 °C dec; ee >99.8%; $[\alpha]^{25}_D$ –29.1° (*c* 1, H_2O); IR (KBr) 3390, 3305, 2850, 1637, 1580 cm^{-1}; NMR (D_2O) δ 2.24 (s, 3), 2.74 (s, 3), 3.47 (dd, 1, J = 8, 14 Hz), 3.72 (dd, 1, J = 5, 14 Hz), 4.91 (dd, 1, J = 8, 5 Hz), 7.34 (d, 1, J = 8 Hz), 7.50 (s, 1), 7.56 (s, 1), 7.90 (d, 1, J = 8 Hz); UV max (EtOH) 277 (ε 5250), 283 (5510), 294 (4800) nm.

Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.64; H, 6.91; N, 15.15. Found: C, 60.66 H, 6.81; N, 15.03.

A second crop of **14f** was obtained as follows. The mother liquor was acidified with 320 mL of 12 N HCl; the precipitated acid was then collected and dissolved in 650 mL of 3% aqueous NH_3 at 75 °C. After the mixture was seeded (0.3 g of **14f**), it was stirred for 16 h and filtered to afford 41.5 g (10%) of off-white crystals: mp 214 °C dec; ee >99.8%; $[\alpha]^{25}_D$ –29.2° (*c* 1, H_2O).

(*R*)-6-Methyltryptophan (15). A mixture of 40.0 g (0.144 mol) of **14f**, 77.5 mL (0.69 mol) of 48% aqueous hydrobromic acid, and 320 mL of water was heated to reflux for 5 h. The solution was brought to pH 5 with aqueous sodium hydroxide, and the suspension was chilled in an ice bath. The precipitate was collected, washed with water, and dried to give 27.5 g of light tan powder. A second crop of 2.55 g was obtained by concentrating the mother liquor. The two crops were dissolved in 210 mL of 0.7 N NaOH and the amino acid was again precipitated by adding 15 mL of acetic acid; it was collected by filtration, washed with water, and dried to afford 28.6 g (91%) of **15** as white crystals: mp 276 °C dec; ee >99.8%.

Analytically pure **15** was obtained by stirring the amino acid in 450 mL of glacial acetic acid at 20 °C; the acetic acid salt was collected by filtration and stirred with 100 mL of water at 20 °C. The slurry was filtered, and the cake was washed with water and dried at 90 °C (1 mm) to afford 20.5 g (65%) of white crystals: mp 278 °C dec; ee >99.8%; $[\alpha]^{25}_D$ +40.5° (*c* 0.3, CH_3OH); IR (KBr) 3395, 1665, 1597 cm^{-1}; NMR (Me_2SO-d_6/TFA) δ 2.37 (s, 3), 3.21 (br d, 2), 4.05 (br s, 1), 6.80 (d, 1, J = 8 Hz), 7.11 (br s, 2), 7.40 (d, 1, J = 8 Hz), 8.22 (br s, 3); UV max (EtOH) 275 (ε 5650), 282 (5800), 292 (4900) nm.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.99; H, 6.76; N, 13.07.

Workup of the mother liquors afforded a second crop of 2.93 g (9%) of pure **15**: mp 278 °C dec; ee >99.8%.

Chiral Phosphines. The following chiral phosphines were prepared as described in the references cited. Their ^{31}P NMR data are included for comparison: **16a**,[11a] δ –23.5 ($CDCl_3$); **16b**,[11b] δ –23.7 ($CDCl_3$); **17a**,[2c] δ –21.7 ($CDCl_3$); **18**,[11c] δ –20.9 (C_6D_6); **21**,[12]

(16) B. Heath-Brown and F. P. Philipott, *J. Chem. Soc.*, 7165 (1965).

(17) W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *Adv. Chem. Ser.*, **No. 132**, 274 (1974).

(18) J. Chatt and L. Venanzi, *J. Chem. Soc.*, 4735 (1957).

δ −9.53 (v br), −23.45 (br) (C_6D_6).

Phosphine **16a** was also obtained from Strem Chemical Co. Phosphines **19** and **20** were generous gifts from Dr. W. S. Knowles (Monsanto Chemical Co.), supplied to us as their rhodium cyclooctadiene tetrafluoroborate complexes. New analogues of **16** and **17** were prepared by appropriate modification of the literature syntheses.

16c. (−)-(4*R*,5*R*)-*trans*-4,5-Bis[(tosyloxy)methyl]-2,2-dimethyl-1,3-dioxolane[11a] was condensed with lithium bis(3,5-dimethylphenyl)phosphide in tetrahydrofuran, and **16c** was isolated by column chromatography on silica gel (benzene eluent): thick oil; $[\alpha]^{25}_D$ +1.91° (*c* 1, benzene); IR ($CHCl_3$) 2990, 2925, 1598, 1583, 1176, 1090, 1038 cm^{-1}; mass spectrum *m/e* 610 (M^+), 595, 369, 241 (base peak), 105; ^1H NMR ($CDCl_3$) δ 1.37 (s, 6), 2.26 (s over m, ca. 30), 3.85 (m, 2), 6.9–7.2 (m, 12); ^{31}P NMR ($CDCl_3$) δ −23.87 (s).

Anal. Calcd for $C_{39}H_{48}O_2P_2$: C, 76.70; H, 7.92; P, 10.14. Found: C, 76.71; H, 7.71; P, 9.87, 9.90.

Lithium bis(3,5-dimethylphenyl)phosphide was generated from *n*-butyllithium and bis(3,5-dimethylphenyl)phosphine, obtained from tris(3,5-dimethylphenyl)phosphine (**22**) by cleavage with lithium in tetrahydrofuran, hydrolysis, and fractional distillation to remove *m*-xylene. The secondary phosphine had a boiling point of 120–145 °C (0.01 mm) (Kugelrohr) and was not further characterized. Phosphine **22** was prepared from 5-bromo-*m*-xylene (Pfaltz and Bauer, Inc.) by the method of Willans:[19] mp 160–162 °C; IR (KBr) 1598, 1582, 850, 845, 695 cm^{-1}; mass spectrum *m/e* 346 (M^+), 331, 241, 239, 225, 209, 136; ^1H NMR ($CDCl_3$) δ 2.21, 6.89, 6.96.

Anal. Calcd for $C_{24}H_{27}P$: C, 82.94; H, 7.83; P, 9.23. Found: C, 83.21; H, 7.79; P, 8.86, 9.00.

16d. This compound was prepared from tris(3,4-dimethylphenyl)phosphine (**23**) analogously to **16c**. **16d**: thick oil; $[\alpha]^{25}_D$ +7.39° (*c* 1.1, benzene); IR ($CHCl_3$) 3000, 2980, 2935, 2920, 1490, 1450, 1380, 1220, 1095, 1035, 885, 815 cm^{-1}; mass spectrum *m/e* 610 (M^+), 595, 505, 369, 241; ^1H NMR ($CDCl_3$) δ 1.33 (s, 6), 2.18 (br s, 24), 2.30 (m, 4), 3.85 (m, 2), 7.0–7.4 (m, 2).

Anal. Calcd for $C_{39}H_{48}O_2P_2$: C, 76.70; H, 7.92; P, 10.14. Found: C, 76.50; H, 8.10; P, 9.07, 9.29.

Lithium bis(3,4-dimethylphenyl)phosphide was generated from *n*-butyllithium and bis(3,4-dimethylphenyl)phosphine, obtained from tris(3,4-dimethylphenyl)phosphine (**23**) by cleavage with lithium in ethylamine/tetrahydrofuran at ca. −65 °C, protonation (NH_4Cl), and distillation (Kugelrohr). The secondary phosphine had a boiling point of 110–130 °C (0.02 mm) and crystallized upon brief storage in the freezer. It was used within 24 h without further characterization. Tertiary phosphine **23** was prepared from phosphorus trichloride and the Grignard reagent from 4-chloro-*o*-xylene: mp 85–86 °C; IR (KBr) 3000, 2980, 2935, 2920, 1600, 1490, 1450, 1380, 1090, 820 cm^{-1}; mass spectrum *m/e* 346 (M^+), 331, 315, 241, 239, 136; ^1H NMR (C_6D_6) δ 1.90 (br s, 18), 6.8–7.5 (m, 9).

Anal. Calcd for $C_{24}H_{27}P$: C, 83.21; H, 7.86; P, 8.94. Found: C, 83.36; H, 7.66; P, 9.20, 9.17.

16f. Bis(3-methoxyphenyl)phosphine oxide (**24**) was prepared from di-*n*-butyl phosphite (Aldrich) and 3 equiv of the Grignard reagent from *m*-bromoanisole in tetrahydrofuran.[20] Chromatography of the crude product on silica gel, with benzene and 19:1 benzene/ether as eluents, removed anisole and intermediate polarity byproducts in early fractions. Elution with methanol and removal of low boiling contaminants [70 °C, (0.06 mm), 1 h] left a thick oil containing **24** and another major component, probably $(m\text{-anisyl})_2P(O)Me$.[21] [$^1H$ NMR ($CDCl_3$) of mixture, δ 1.46 (d, 3, J_{PH} = 14 Hz, PCH_3), 3.73, 3.75 (2s, 6, OCH_3), 6.95–7.8 (m, 8, aromatics), 7.95 (d, 1, J_{PH} = 481 Hz, P(O)H); ^{31}P NMR ($CDCl_3$) δ 21.46 (s, 1), 33.91 (s, 5.5)]. Crude **24** was converted to bis(3-methoxyphenyl)phosphine by using $HSiCl_3$ in refluxing benzene.[22] The crude secondary phosphine was treated with 1 equiv of *n*-butyllithium in THF at −70 °C. Condensation of lithium bis(3-methoxyphenyl)phosphide with **24** gave, after silica gel chromatography, **16f** as a thick oil: $[\alpha]^{25}_D$ −10.40° (*c* 1, benzene); IR ($CHCl_3$) 1283, 1245, 693 cm^{-1}; mass spectrum *m/e* 618 (M^+), 603, 511, 373, 315, 245; ^1H NMR ($CDCl_3$) δ 1.36 (s, 6), 2.35 (m, 4), 3.73 (s, 12), 3.88 (m, 2), 6.8–7.3 (m, 16); ^{31}P NMR ($CDCl_3$) δ −21.52.

Anal. Calcd for $C_{35}H_{40}O_6P_2$: C, 67.95; H, 6.52; P, 10.01. Found: C, 68.12; H, 6.54; P, 9.76.

16g. The preparation was similar to that of **16f**. The intermediate bis(3-chlorophenyl)phosphine oxide was distilled [bp 160–180 °C (0.02 mm) (Kugelrohr)] before use, but the corresponding phosphine (**Caution**! Stench) was used without purification or spectral characterization. **16g** was purified by chromatography on silica gel, using benzene as eluent: thick oil containing a trace of residual benzene; $[\alpha]^{25}_D$ −4.52° (*c* 1, benzene); IR ($CHCl_3$) 1115, 1092, 1075, 1040, 690 cm^{-1}; mass spectrum *m/e* 634 (M^+), 619, 523, 381, 253; ^1H NMR ($CDCl_3$) δ 1.34 (s, 6), 2.30 (br d, 4), 3.80 (m, 2), 7.35 (m, 16); ^{31}P NMR ($CDCl_3$) δ −21.45.

Anal. Calcd for $C_{31}H_{28}Cl_4O_2P_2$: C, 58.51; H, 4.44; Cl, 22.29, P, 9.74. Found: C, 59.71; H, 4.82; Cl, 22.04; P, 9.24, 9.34.

16h. Bis(2-methoxyphenyl)phosphine oxide was prepared as described for the analogues above and crystallized from benzene: mp 132–136 °C (lit.[19] mp 135–136 °C); ^{31}P NMR ($CDCl_3$) δ 8.13. Reduction with $HSiCl_3$ in benzene at reflux afforded a colorless solid [mp 95–105 °C; ^{31}P NMR ($CDCl_3$) δ 8.23, −24.91], presumed to be a mixture of the desired bis(2-methoxyphenyl)phosphine[23] and unreduced (or regenerated) phosphine oxide. The crude product was used directly for the preparation of **16h** as described for the analogues above. The product was isolated by chromatography, followed by recrystallization from acetone to give **16h**: mp 147.5–150 °C; $[\alpha]^{25}_D$ −12.53° (*c* 1, benzene); IR (KBr) 1270, 1240, 1125, 760 cm^{-1}; mass spectrum *m/e* 618 (M^+), 603, 511, 373, 315, 245; ^1H NMR ($CDCl_3$) δ 1.31 (s, 6), 2.3–2.7 (m, 4), 3.69, 3.72 (2 s, 12, OCH_3, splitting assigned to nonequivalent rotamers), 3.99 (m, 2), 6.7–7.4 (m, 16); ^{31}P NMR ($CDCl_3$) δ −40.37 (br s).

Anal. Calcd for $C_{35}H_{40}O_6P_2$: C, 67.95; H, 6.52; P, 10.01. Found: C, 67.80; H, 6.56; P, 9.89, 9.94.

17b. This was prepared from sodium bis(3-methylphenyl)phosphide[24] and (1*R*,2*R*)-(−)-*trans*-1,2-bis[(tosyloxy)methyl]-cyclobutane[2c] [$[\alpha]^{25}_D$ −30.26° (*c* 1, MeOH)] in liquid ammonia–tetrahydrofuran. Purification by chromatography on silica gel afforded **17b**: thick oil; $[\alpha]^{25}_D$ −12.16° (*c* 1, benzene); IR ($CHCl_3$) 1593, 1577, 1478, 700 cm^{-1}; mass spectrum *m/e* 508 (M^+), 426, 417, 295, 213, 91; ^1H NMR ($CDCl_3$) δ 1.3–2.5 (m, ca. 11, phenyl CH_3, CH_2, CH), 2.32 (s), 7.15 (m, ca. 8, aromatic); ^{31}P NMR ($CDCl_3$) δ −22.07.

Anal. Calcd for $C_{34}H_{38}P_2$: C, 80.29; H, 7.53; P, 12.18. Found: C, 80.37; H, 7.39; P, 12.05, 12.00.

Registry No. **3**, 89-58-7; **4**, 66920-60-3; **5**, 3420-02-8; (*E*)-**6**, 71359-86-9; (*Z*)-**6**, 71360-05-9; **7a**, 71359-87-0; **7b**, 71359-88-1; **8a**, 71359-89-2; **8b**, 71359-90-5; **8c**, 71359-91-6; **8d**, 71359-92-7; **9**, 69203-27-6; **10**, 71359-93-8; **11a**, 71359-94-9; **11b**, 71359-95-0; **11c**, 71359-92-7; **12**, 4771-49-7; **14e**, 66920-63-6; **14f**, 66920-64-7; **15**, 33468-34-7; **16c**, 71359-96-1; **16d**, 71359-97-2; **16f**, 71359-98-3; **16g**, 71382-04-2; **16h**, 71359-99-4; **17b**, 71360-00-4; **22**, 69227-47-0; **23**, 69227-46-9; **24**, 71360-01-5; methyl α-nitro-β-ethoxyacrylate, 17648-26-9; acetic anhydride, 108-24-7; formic acetic anhydride, 2258-42-6; *N*,*N*-dimethylformamide, 68-12-2; ethyl acetamidomalonate, 54681-67-3; (−)-(4*S*-5*S*)-*trans*-4,5-bis(tosyloxymethyl)-2,2-dimethyl-1,3-dioxolane, 37002-45-2; lithium bis(3,5-dimethylphenyl)phosphide, 71360-02-6; bis(3-chlorophenyl)phosphine oxide, 71360-03-7; bis(2-methoxyphenyl)phosphine oxide, 71360-04-8; sodium bis(3-methylphenyl)-phosphide, 68998-33-4; (−)-(1*R*,2*R*)-*trans*-1,2-bis[tosyloxymethyl]-cyclobutane, 55641-14-0; *N*,*N*-dimethylformamide dimethyl acetal, 4637-24-5; bis(3,5-dimethylphenyl)phosphine, 71360-06-0; lithium bis(3,4-dimethylphenyl)phosphide, 71360-07-1; bis(3,4-dimethylphenyl)phosphine, 71360-08-2.

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(23) Fritzsche et al. (H. Fritzsche, U. Hasserodt, and F. Korte, German Patent 1 223 838 (1966); *Chem. Abstr.*, 65, P18619*d* (1965)) report a melting point of 138 °C, which should be treated with suspicion in view of the melting point of the corresponding phosphine oxide (mp 135–136 °C).

(24) Generated by the method of S. O. Grim and R. C. Barth, *J. Organomet. Chem.*, 94, 327 (1975).