Asymmetric Hydroformylation Catalyzed by Homogeneous and Polymer-Supported Platinum Complexes Containing Chiral Phosphine Ligands

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Abstract: A complex of Pt(II) containing the chiral ligand (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine [(-)-BPPM] in the presence of stannous chloride catalyzed the hydroformylation of a variety of prochiral olefins. Although the branched/normal (*b*/*n*) ratios were low (~0.5), high ee's were achieved in the hydroformylation of styrene (70–80%), *p*-isobutylstyrene (80%), 2-vinylnaphthalene (77%), 2-ethenyl-6-methoxynaphthalene (81%), 4-(2-thienylcarbonyl)styrene (78%), vinyl acetate (82%), *N*-vinylphthalimide (73%), methyl methacrylate (60%), and norbornene (60%). When the hydroformylation of styrene, 2-ethenyl-6-methoxynaphthalene, and vinyl acetate with [(-)-BPPM]$PtCl_2/SnCl_2$ was carried out in the presence of triethyl orthoformate, enantiomerically pure acetals were obtained. The hydroformylation in the presence of ethyl orthoformate also could be carried out by using a catalyst containing the [(-)-BPPM]$PtCl_2/SnCl_2$ complex bound to 60-μm beads composed of cross-linked polystyrene.

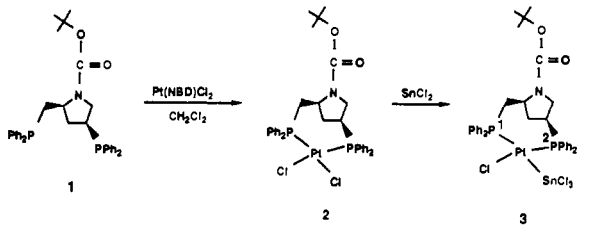
The stereospecific addition of dihydrogen and carbon monoxide to an olefin containing a prochiral center is an important goal in synthetic organic chemistry, since the process involves both carbon–carbon bond formation and the introduction of a synthetically useful functionality in the molecule. The significance of this asymmetric reaction is that there is the potential for the synthesis of a wide variety of chiral compounds.

There are a number of reports of asymmetric hydroformylations of olefins with chiral catalysts, particularly those involving rhodium complexed to optically active phosphine ligands.[1] Although platinum complexes generally give hydroformylation products with higher asymmetric induction than those of rhodium, the enantiomeric excesses achieved in these reactions with either rhodium or platinum catalysts are relatively low. For example, the hydroformylation of 1-butene in the presence of a platinum catalyst bearing the ligand 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane [(-)-DIOP] gave the corresponding aldehyde in 46.7% ee,[2] while a platinum catalyst containing the *chiraphos* ligand hydroformylated styrene in 45% ee.[3]

Catalytic asymmetric reactions have been carried out by utilizing transition-metal catalysts complexed to chiral phosphine ligands on polymer supports, the primary advantages being the ease of workup and the ability to recover and reuse both the transition metal and the optically active ligand.[4] Relatively few polymer-supported chiral catalysts have been synthesized, and most of these have been used for asymmetric hydrogenation. Hydroformylation reactions with optically active polymer-supported catalysts have afforded chiral aldehydes in moderate to low enantiomeric excess.[5]

The asymmetric hydroformylation of a variety of olefins with a platinum catalyst bearing the phosphine ligand 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP)—(DIOP)$PtCl_2/SnCl_2$—and the dibenzophosphazole analogue—(DBP-DIOP)$PtCl_2/SnCl_2$[5a]—as well as these catalysts bound to polymer supports has provided aldehydes in moderate enantiomeric excesses (35–65% ee from styrene). The highest enantiomeric excesses in hydroformylation reactions of styrene (~70–80% ee) have been achieved with a platinum catalyst containing the chiral ligand (2*S*,4*S*)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine—[(-)-BPPM]$PtCl_2/SnCl_2$—and its polymer-supported analogue.[6] Unlike the other chiral phosphines used in hydroformylation catalysts, BPPM does not have a C_2 axis of symmetry. In this paper, asymmetric hydroformylation of a variety of prochiral olefins with both homogeneous and polymer-bound [(-)-BPPM]$PtCl_2/SnCl_2$ under different conditions, some of which provide enantiomerically pure products, is described.

Scheme I



Results and Discussion

Homogeneous Hydroformylation. The reaction of (-)-BPPM (**1**)[6,7] with (norbornadiene)dichloroplatinum(II) gave [(-)-BPPM]$PtCl_2$ (**2**), which was used in the presence of stannous chloride dihydrate as a homogeneous catalyst precursor for hydroformylation (Scheme I). Alternatively, preformed [(-)-BPPM]$Pt(SnCl_3)Cl$ (**3**) was prepared by the reaction of **2** with stannous chloride.

Structure **3**, in which the tin ligand is trans to the phosphorus attached to the exo-methylene carbon (phosphorus 1), was assigned on the basis of the following ^{31}P NMR information. In the uncomplexed ligand (**1**) and the platinum complex (**2**), the chemical shifts of the phosphorus bound to the exo-methylene carbon are farther upfield (δ -20.5 and 4.6, 4.8, respectively) than those for the ring-attached phosphorus (δ -8.5 and 28.8, respectively).[7b] The two chemical shifts for the phosphorus bound to the exo-methylene phosphorus are due to the two amide conformations of the *t*-Boc group syn and anti. When the tin complex

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(2) Healg, P.; Consiglio, G.; Pino, P. *J. Organomet. Chem.* **1985**, *296*, 281.
(3) Consiglio, G.; Morandini, F.; Scalone, M.; Pino, P. *J. Organomet. Chem.* **1985**, *279*, 193.
(4) (a) Stille, J. K. *Pure Appl. Chem.* **1982**, *54*, 99 and references therein. (b) Stille, J. K.; Fritschel, S. J.; Takaishi, N.; Masuda, T.; Imai, H.; Bertelo, C. A. *Ann. N.Y. Acad. Sci.* **1980**, *333*, 35.
(5) (a) Parrinello, G.; Deschenaux, R.; Stille, J. K. *J. Org. Chem.* **1986**, *51*, 4189. (b) Stille, J. K. In *Catalysis of Organic Reactions*, Augustine, R. L., Ed.; Marcel Dekker: New York, 1985. (c) Stille, J. K. *J. Macromol. Sci., Chem.* **1984**, *A21*, 1689. (d) Consiglio, G.; Pino, P.; Flowers, L. I.; Pittman, C. U., Jr. *J. Chem. Soc., Chem. Commun.* **1983**, 612. (e) Pittman, C. U., Jr.; Kawabata, Y.; Flowers, L. I. *Ibid.* **1982**, 473. (f) Fritschel, S. J.; Ackerman, J. J. H.; Keyser, T.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 3152. (g) Bayer, E.; Schurig, V. CHEMTECH **1976**, 212. (h) Strukul, G.; Bonivento, M.; Graziani, M.; Cernia, E.; Palladino, N. *Inorg. Chim. Acta* **1975**, *12*, 15.
(6) Stille, J. K.; Parrinello, G. *J. Mol. Catal.* **1983**, *21*, 203.
(7) (a) Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954. (b) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728. (c) Achiwa, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265.

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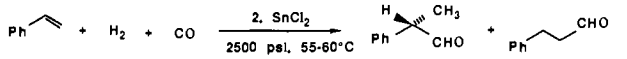
is formed, phosphorus 1 experiences the greatest chemical shift (δ 15.1) in comparison with phosphorus 2 (δ 27.4). In addition, $J(^{31}P-^{119}Sn)$ for phosphorus 1, trans to tin, is 375 Hz compared to phosphorus 2, 100 Hz.

Hydroformylation reactions with the homogeneous platinum catalysts were carried out under conventional conditions. Initially, hydroformylations were carried out on styrene in order to optimize the reaction conditions.

Styrene hydroformylation with [(−)-BPPM]$PtCl_2$ and added $SnCl_2$ to yield a mixture of 2- and 3-phenylpropanal has been carried out in benzene at different reaction pressures (1500–2650 psi), temperatures (50–95 °C), and times (2–15 h).[6] The ratio of 2-phenylpropanal to 3-phenylpropanal (branched to normal ratio, b/n) was constant (0.4–0.5), approximately the same ratio as had been obtained with the [(−)-DIOP]$PtCl_2/SnCl_2$ catalyst.[5e] The selectivity to aldehyde was high, less than 2% of ethylbenzene being obtained in each case. Branched aldehyde, 2-phenylpropanal, was obtained in relatively high enantiomeric excess,



particularly when the reaction times were short and the temperature was low, 78–80% ee being obtained at 56–57 °C after 2–4 h and low conversion.

The lower enantiomeric excesses obtained at longer reaction times are a result of product racemization under the reaction conditions. When a mixture of 2- and 3-phenylpropanal was stirred in the presence of the catalyst under the reaction conditions (2800 psi of a 1:1 H_2/CO mixture at 60 °C) for 60 h, the enantiomeric excess of the 2-phenylpropanal was reduced from 48% to 33.5%.

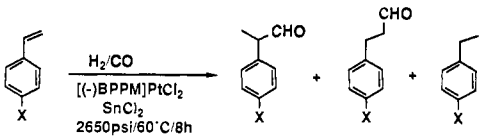
Varying the H_2/CO ratio (within the range 0.25–4) and the total pressure (between 600 and 4500 psi) only affected the reaction rate but did not influence the product distribution significantly. The enantiomeric excess changed only as a function of conversion. Addition of free ligand, (−)-BPPM, to the catalyst caused a dramatic decrease in reaction rate (2% conversion in 6 h); however, >96% ee was achieved. This high ee also could be obtained when the reaction was carried out at 25 °C for 20 h, but the conversion was only 5%. Under the same reaction conditions a 12% conversion was achieved after 6 days, but the ee decreased to 58%. Thus the extent of racemization is a function of the concentration of the chiral aldehyde in the reaction mixture, the temperature, and the reaction time. Hydroformylation of styrene in solvents other than benzene (1,2-dichlorobenzene, 1,2-dichloroethane, dichloromethane, THF, and ethanol) gave comparable b/n ratios, but somewhat slower rates and lower enantiomeric excesses.

Hydroformylation of substituted styrenes catalyzed by rhodium complexes shows a linear relationship both between the relative rates or b/n ratios and the Hammett σ-values.[8] When $Rh_2Cl_2(CO)_4$ was introduced as the hydroformylation catalyst, the b/n ratio was increased by (−) σ-substituents, but in the presence of triphenylphosphine the order was reversed, higher b/n ratios being obtained with (+) σ-substituents. Thus, although higher b/n ratios for styrenes containing electron-withdrawing para substituents were anticipated in hydroformylations with [(−)-BPPM]$PtCl_2/SnCl_2$, higher b/n ratios were observed with both electron-withdrawing and electron-donating substituents (Table I). In addition, slower rates were observed with para-substituted styrenes containing (+) and (−) σ-substituents as compared with styrene. With all substrates, the selectivity was high and the ee's were comparable, with the exception that the ee from *p*-nitrostyrene was significantly lower and that from *p*-acetylstyrene was significantly higher.

The hydroformylation reaction of vinyl aromatics lends itself to the synthesis of a number of optically active non-steroidal antiinflammatory agents, 2-arylpropionic acids.[9] Previous asymmetric syntheses of these acids required the use of stoichiometric amounts of chiral auxiliaries, which in most cases are not easily recovered.[10] A synthetic route to (*S*)-(+)-Ibuprofen (Scheme II) utilized a standard Friedel–Crafts acylation of isobutylbenzene to yield the corresponding acetophenone, followed by reduction to the alcohol and dehydration to the styrene derivative (**4**). Hydroformylation to the 2-arylpropanal (**5**) was achieved in 78% ee (b/n = 0.5); **5** can be readily transformed to (*S*)-Ibuprofen by oxidation.

(*S*)-(+)-2-(2-Naphthyl)propionic acid (**6**, Scheme II), which also exhibits antiinflammatory and analgesic activity,[11] was obtained by the hydroformylation of 2-vinylnaphthalene in 78% ee followed by separation of the 2-(2-naphthyl)propanal (**5**) and oxidation. The hydroformylation took place in 66% conversion after 18 h to yield the two propanals, 2- and 3-(2-naphthyl)-propanal, b/n = 0.53. Oxidation was carried out in 70% yield to give acid (**7**) of 77% optical purity. Asymmetric hydroformylation also was utilized as the key step in the synthesis of Naproxen. The palladium-catalyzed vinylation of 2-bromo-6-methoxynaphthalene with vinyltributylstannane gave 2-vinyl-6-methoxynaphthalene (**8**) in 83% yield.[12] Hydroformylation gave the corresponding aldehydes in 0.7 b/n ratio. The branched aldehyde (**9**), which was isolated by medium-pressure liquid chromatography, was oxidized to (*S*)-(+)-Naproxen (**10**), 82% ee, in 84% yield. Recrystallization from acetone/hexane gave a first crop of crystals in 100% ee.

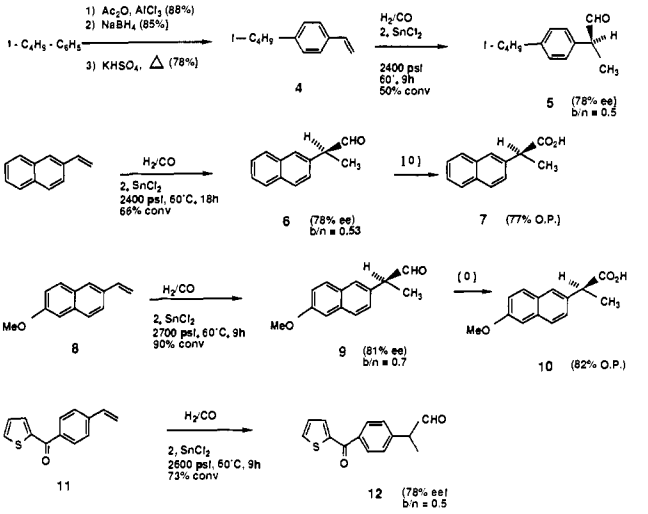
Table I. Asymmetric Hydroformylation of Para-Substituted Styrenes in the Presence of [(−)-BPPM]$PtCl_2/SnCl_2$[a]



X	conv, %	b/n[b]	ee,[c] %
OMe	65	0.60	73
Me	77	0.57	72
H	89	0.47	70
Br	49	0.53	75
Ac	47	0.87	85
NO_2	14	1.40	58

[a] Carried out in benzene with $SnCl_2/Pt$ = 2.5 and H_2/CO = 1 (2650 psi), 60 °C for 8 h; styrene/Pt = 800. [b] Branched/normal ratio. [c] Determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent.

Scheme II



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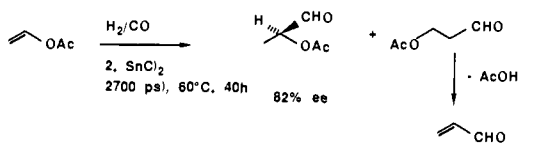
An analgesic with greater antiinflammatory and antipyretic activity than Naproxen is α-methyl-4-(2-thienylcarbonyl)-benzeneacetic acid, Suprofen.[13] This compound has been tested only as a racemic mixture, and any difference in the activity of the enantiomers is not known. Acylation of thiophene with *p*-bromobenzoyl chloride gave the corresponding ketone, which was converted to 4-(2-thienylcarbonyl)styrene (**11**) by the palladium-catalyzed reaction with vinyltributylstannane.[12] Hydroformylation of **11** to the 2- and 3-arylpropanals (b/n = 0.5) was achieved in 78% ee for the branched aldehyde (**12**, (+) enantiomer in excess), which can be converted to Suprofen by oxidation.

Hydroformylations of several other vinyl substrates were carried out. Vinyl acetate is a particularly interesting substrate, since it gives 2-acetoxypropanal, a precursor in the Strecker synthesis of threonine.[14] The product can be converted to 2-hydroxypropanal, a useful intermediate in the synthesis of steroids,[15] pheromones,[16] antibiotics,[17] and peptides.[18] Asymmetric hydroformylation of vinyl acetate has been achieved with Rh/DIOP or Rh/DBP-DIOP catalysts, but only in 24–32%[19] or 51% ee,[20] respectively. When [(−)-DBP-DIOP]$PtCl_2/SnCl_2$ was used as the catalyst, 2-acetoxypropanal was obtained in 60% ee.[5a]

Hydroformylation of vinyl acetate catalyzed by [(−)-BPPM]-$PtCl_2/SnCl_2$ gave 2-acetoxypropanal and large amounts of 3-acetoxypropanal in 70% conversion. The 3-acetoxypropanal partially decomposed to acetic acid and acrolein, which in turn was hydrogenated to propanal under the reaction conditions. GC analysis showed that 70% of the product was acrolein and propanal; 2-acetoxypropanal was obtained in 82% ee.



N-Vinylphthalimide undergoes hydroformylation (50% conversion in 5 days) in the presence of Rh[I]/(−)-DBP-DIOP to yield the branched product almost exclusively, but in low ee (~30%).[21] Use of the [(−)-DBP-DIOP]$Pt(SnCl_3)Cl$ catalyst allowed a faster reaction with a higher ee (70%), but low aldehyde selectivity (57%) was achieved.[5a]

The hydroformylation of *N*-vinylphthalimide in the presence of [(−)-BPPM]$PtCl_2/SnCl_2$ gave a 52% conversion to branched and normal aldehydes (b/n = 0.5) with relatively low aldehyde selectivity (85%). The (*R*)-(+)-branched isomer, obtained in 73% ee, was isolated by medium-pressure liquid chromatography and oxidized to the corresponding acid in 72% optical purity.

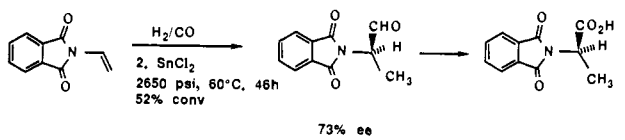
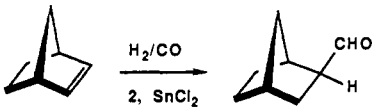


Table II. Hydroformylation of Methyl Methacrylate with [(−)-BPPM]$PtCl_2/SnCl_2$[a]

run	time, h	H_2/CO	conv, %	sel,[b] %	ee,[c] %
1	50	0.2	44	100	43
2	42	1	38	97	40
3	50	3	36	98	60
4	50	4	50	90	53
5	50	5	64	85	39

[a] $SnCl_2/Pt$ = 2.5; T = 60 °C; P = 2650 psi; olefin/Pt = 700. [b] Selectivity = aldehyde/total products. [c] Determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent. The (*R*)-(+) enantiomer was obtained in excess.

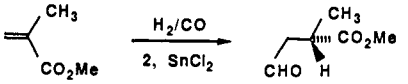
The hydroformylation of norbornene, which introduces three chiral centers, has been carried out with Rh/DIOP to yield exclusively the exo aldehyde, but in low optical yield (4%).[22] Higher ee's were achieved in the presence of [(−)-DIOP]$Pt(SnCl_3)Cl$ (29.2%)[23] and [(−)-DBP-DIOP]$Pt(SnCl_3)Cl$ (26%).[5a] Hydroformylation of norbornene with [(−)-BPPM]$PtCl_2/SnCl_2$ proceeded slowly in spite of the expected reactivity of the strained double bond. A higher ee (60%) could be obtained when the reaction was carried out at 30 °C, the (1*S*,2*S*,4*R*)-(+) enantiomer being obtained in excess. Racemization of the product aldehyde does not occur, since reaction at 30 °C for 7 or 20 h gave the same enantiomeric excess. The configuration of the aldehyde was established by its conversion to the corresponding acid[24] in 60.7% optical purity.



2700 psi	t	conv.	% ee
60°C	1h	23%	45
30°C	20h	84%	60

The hydroformylation of monosubstituted olefins with **2**/$SnCl_2$ has the disadvantage that the unwanted linear aldehyde is obtained in larger amounts than the desired branched aldehyde. However, when an unsymmetrically 1,1-disubstituted olefin is hydroformylated, the prevailing regioisomer obtained has a chiral center generated from carbon–hydrogen bond formation.

When methyl methacrylate was hydroformylated in the presence of **2**/$SnCl_2$, one aldehyde, the (*R*)-(+) enantiomer, was obtained in 60% ee. The enantiomeric excess increased with increasing the H_2/CO ratio to 3 (Table II). The importance of this reaction is derived from the usefulness of this chiral synthon and the fact that it is regioselective.



Hydroformylation in Triethyl Orthoformate. In the hydroformylation reactions of vinyl aromatics, racemization of the products takes place under the reaction conditions. Presumably racemization of the aldehydes also can take place in hydroformylations carried out with substrates other than vinyl aromatics, although this was not verified in all examples.

Racemization presumably could be avoided by removing the aldehyde as it is formed. This could be achieved, for example, either by utilizing a tubular reactor with a fixed bed (polymer-supported catalyst) to give relatively low conversion to aldehyde in each pass and recycling the olefin or by converting the aldehyde to a product that is less susceptible to racemization.

When the hydroformylation of styrene with **2**/$SnCl_2$ was carried out with triethyl orthoformate as the solvent, the reaction was considerably slower than that observed in benzene (60% conversion in 96 h), but the high selectivity to aldehyde (98.6%) and a 0.5

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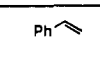
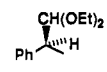
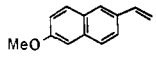
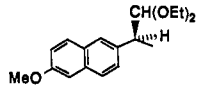
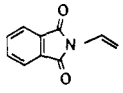
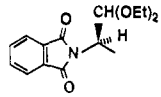
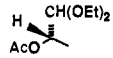
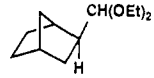
Table III. Hydroformylation with [(−)-BPPM]Pt($SnCl_3$)Cl in the Presence of Triethyl Orthoformate[a]

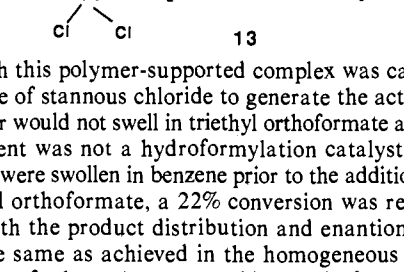
substrate	reaction time, h	product	conv, %	b/n[b]	ee,[c] %
	150 (6)		100 (52)	0.5 (0.45)	>96[d] (70)
	200 (9)		55 (90)	0.7 (0.7)	>96[d] (81)
	240 (46)		46 (52)	0.5 (0.5)	>96[d] (73)
	240 (40)		25 (70)	1.5[e] (0.43)	>98 (80)
	140 (20)[f]		100 (84)		60[d] (60)

[a] H_2/CO = 1; P = 2700 psi; T = 60 °C; substrate/Pt = 400. Numbers in parentheses are those values obtained when the hydroformylation was carried out in benzene to give the free aldehyde. [b] Branched/normal ratio. [c] Determined by ^1H NMR using Eu(hfc)$_3$ as chiral shift reagent. [d] Determined on both the acetal and the aldehyde obtained by hydrolysis. [e] Products of decomposition of the linear acetal were obtained, but the b/n ratio could not be determined. [f] T = 30 °C.

b/n ratio was observed. Within the limits of detection by ^1H NMR [Eu(hfc)$_3$] only one enantiomer was observed (>98% ee). Hydrolysis of the acetal to the corresponding aldehyde in acetone with pyridinium *p*-toluenesulfonate (PPTS) took place without racemization. Use of the preformed catalyst (**3**) gave a faster reaction (100% conversion in <150 h), giving the same product distribution and asymmetric induction.

Styrene also was hydroformylated with the polymer-supported analogue of **2**. Ligand **1** has been incorporated into a polystyrene resin by converting it to an acrylate. The monomer, (2*S*,4*S*)-*N*-acryloyl-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]-pyrrolidine, was synthesized by the deprotection of (−)-BPPM (**1**) with trifluoroacetic acid and subsequent acylation of the free amine with acryloyl chloride. This monomer was copolymerized with styrene and divinylbenzene by suspension polymerization to yield cross-linked beads, averaging 60 μm in diameter, containing 10 mol % of the phosphine monomer and 10 mol % divinylbenzene.[6] These beads swelled (2–3 times their original volume) in relatively nonpolar solvents such as benzene, tetrahydrofuran, and methylene chloride.

This polymer, containing the chiral phosphine ligand, was converted to the platinum catalysts (**13**) by reaction with bis(benzonitrile)dichloroplatinum(II). The hydroformylation of



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styrene with this polymer-supported complex was carried out in the presence of stannous chloride to generate the active catalyst. The polymer would not swell in triethyl orthoformate and therefore in this solvent was not a hydroformylation catalyst. However, if the beads were swollen in benzene prior to the addition of styrene and triethyl orthoformate, a 22% conversion was realized after 10 days, with the product distribution and enantiomeric excess (>98%) the same as achieved in the homogeneous case.

A number of other substrates could be hydroformylated in the presence of triethyl orthoformate (Table III). The numbers in parentheses in each column, for comparison, are the reaction times, conversions, b/n ratios, and ee's of the free aldehyde obtained when the reaction was carried out in benzene.

In triethyl orthoformate, most of the reaction rates are at least an order of magnitude slower, but the branched to normal ratios are the same. In all reactions, except for that with norbornene, enantiomerically pure products were obtained. Since the aldehyde obtained from norbornene is not racemized in benzene under the reaction conditions, a higher enantiomeric excess would not be expected by running the reaction in ethyl orthoformate. Thus it is possible to obtain enantiomerically pure aldehydes by the hydroformylation of certain olefins in the presence of **2** ([(−)-BPPM]$PtCl_2/SnCl_2$) or **3** ([(−)-BPPM]Pt($SnCl_3$)Cl).

Experimental Section

All reactions involving the synthesis of phosphinated compounds were performed under an inert atmosphere of nitrogen or argon. Manipulations involving phosphines in solution were carried out in a glovebag or by Schlenk techniques.

The ^1H NMR spectra were obtained on an IBM WP-270 spectrometer (270 MHz) or on a Nicolet NT-360 spectrometer (360 MHz), with tetramethylsilane as the internal standard. The ^{13}C NMR spectra were obtained on an IBM WP-200 spectrometer (50.3 MHz) or an IBM WP-270 spectrometer (67.9 MHz), with tetramethylsilane (δ 0.00) or chloroform (δ 77.00) as the internal standard. The ^{31}P NMR spectra were obtained on an IBM WP-200 spectrometer (81 MHz) or a Nicolet NT-150 spectrometer (60.7 MHz), with 85% phosphoric acid (δ 0.00) as the external reference. Unless otherwise stated, the spectra were obtained in deuteriochloroform. Optical rotations were measured on an Autopol III automatic polarimeter.

All melting points are uncorrected. Gas chromatographic analyses were carried out on a Varian Model 3700 using 10% OV-101 Chromosorb W-HP, 80/100 (2 m × $^1/_8$ in.), with a thermal conductivity detector or a DB1 Durabond fused-silica capillary column (30-m length × 0.25-mm i.d.) with a flame ionization detector and helium as the carrier gas. The chromatograph was interfaced with a Varian Chromatographic Data System III C for determining relative peak areas by electronic integration.

Synthesis gas (1:1 H_2/CO) was purchased as a custom mixture from SCP Inc. and was used as received. Styrene, vinyl acetate, and methyl methacrylate were purchased from Aldrich, freshly distilled, and stabilized with *p*-methoxyphenol before use as hydroformylation substrates. Norbornene and 2-vinylnaphthalene were purchased from Aldrich and purified by sublimation before use. *N*-Vinylphthalimide was purchased from Monomer-Polymer and Dajac Laboratories Inc. and used as received. The NMR chiral shift reagents Eu(hfc)$_3$ and Eu(tfc)$_3$ were purchased from Aldrich. The para-substituted styrenes 2-vinyl-6-methoxynaphthalene and 4-(2-thienylcarbonyl)styrene were synthesized following a reported procedure.[12]

(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine [(−)-BPPM] (1). This ligand was synthesized as reported,[7] giving a product with mp 103–105 °C (lit.[7] mp 103.5–105 °C); ^{31}P NMR ($CDCl_3$) δ −8.5 (s, 1 P), −20.5 (s, 1 P).

[(−)-BPPM]$PtCl_2$ (2). A deoxygenated solution of 300 mg (0.542 mmol) of (−)-BPPM (**1**) in 5 mL of dichloromethane was added to a refluxing solution of 109 mg (0.304 mmol) of (norbornadiene)dichloroplatinum(II) in 10 mL of dichloromethane. The solution was heated to reflux for 1 h under argon. Half the volume of the solvent was evaporated and the product was precipitated with diethyl ether, filtered, washed with diethyl ether, and dried under reduced pressure to give 232 mg (93.0%) of **2** as a white powder: mp 180–220 °C (dec); ^{31}P NMR ($CDCl_3$) $\delta(P_2)$ 28.8 [d, $^2J(P_2,P_1)$ = 16 Hz], $\delta(P_{1A})$ 4.6 [d, $^2J(P_1, P_2)$ = 16 Hz], $\delta(P_{1B})$ 4.4 [d, $^2J(P_1, P_2)$ = 16 Hz], [$^1J(Pt, P_2)$ = 3573 Hz, $^1J(Pt, P_{1A})$ = 3511 Hz, $^1J(Pt, P_{1B})$ = 3478 Hz]. P_2 is the phosphorus of the

secondary phosphino group and P_1 is the phosphorus of the primary phosphino group. The two peaks P_{1A} and P_{1B} result from the two conformations of the *t*-Boc group at room temperature.

[(−)-BPPM]Pt($SnCl_3$)Cl (3). A deoxygenated solution of 200 mg (0.244 mmol) of **2** in 20 mL of dichloromethane was added to a stirred suspension of 92 mg (0.48 mmol) of anhydrous stannous chloride in 15 mL of dichloromethane. The mixture was stirred at room temperature for 7 h under argon. The suspension was filtered to eliminate the excess stannous chloride. The solution was concentrated to 5 mL, and 15 mL of deoxygenated hexane was added. The precipitate (215 mg, 87.0%) was filtered, washed with hexane, and dried under reduced pressure: mp 280 °C (dec); ^{31}P NMR ($CH_2Cl_2/CDCl_3$) $\delta(P_2)$ 27.4 [$J(^{31}P-^{31}P)$ = 40.8 Hz, $J(^{31}P-^{119}Sn)$ = 78 Hz, $J(^{31}P-^{195}Pt)$ = 4443 Hz], $\delta(P_1)$ 15.1 [$J(^{31}P-^{31}P)$ = 41.3 Hz, $J(^{31}P-^{119}Sn)$ = 373 Hz, $J(^{31}P-^{195}Pt)$ = 3415 Hz]. Anal. Calcd for $C_{34}H_{37}Cl_4NO_2P_2PtSn$: C, 40.43; H, 3.90. Found: C, 40.33; H, 4.09.

Polystyrene-Supported Catalyst 13. A solution of 39.9 mg of bis(benzonitrile)dichloroplatinum(II)[25] in dichloromethane was added to 200 mg of 60-μm cross-linked beads[6] obtained from the copolymerization of (2*S*,4*S*)-*N*-acryloyl-4-(diphenylphosphino)-2-[(diphenylphosphino)-methyl]pyrrolidine[7] with styrene and divinylbenzene, and the mixture was stirred under argon for 8 h (ratio of P_2:Pt = 1.7). The mixture was filtered in a Schlenk tube, dried under reduced pressure, and stored under argon.

Homogeneous Hydroformylations. A 125-mL Parr Monel bomb was charged with 0.02 mmol of platinum catalyst and 0.04 mmol of stannous chloride dihydrate. The bomb was brought into an argon-filled glovebag and charged with 8.7 mmol of olefinic substrate dissolved in 3 mL of benzene. The bomb was sealed, pressurized and vented three times with the synthesis gas mixture (1:1 H_2/CO), and then pressurized (usually to 2400 psi at room temperature) and heated with stirring in an oil bath at 60 °C. At the end of the reaction, the bomb was quenched in a dry ice bath, the pressure was vented, and the solvent was removed by distillation. The product mixture was vacuum transferred or flash chromatographed from the catalyst and analyzed by GLC or by ^{1}H NMR to determine the conversion and the product composition. The ee's were determined with an accuracy of ±3% by ^{1}H NMR using Eu(hfc)$_3$ or Eu(tfc)$_3$ chiral shift reagents.

Typical Experiment for the Determination of Enantiomeric Excess. Approximately 0.1 mL of the reaction mixture containing 2-phenylpropanal was diluted with deuteriochloroform and placed in an NMR tube. Eu(hfc)$_3$ was added in small portions until a neat splitting of the peak of the formyl proton (doublet at 9.6 ppm) was observed in the ^{1}H NMR spectrum. The integration of the two peaks [14.46 ppm for the (*S*)-(+) and 14.34 ppm for the (*R*)-(−) enantiomer] was used to calculate the enantiomeric excess according to the equation % ee = $[|S-R|/(S+R)] \times 100$.

Hydroformylations with Polymer-Supported Catalyst 13. The procedure for hydroformylation utilizing the heterogeneous catalysts was the same as that followed in the homogeneous hydroformylation, except that at the end of the reaction, the bomb was opened in a glovebag and the catalyst was recovered by filtration.

***p*-Isobutylacetophenone.** A solution of 58.6 mL (0.375 mol) of isobutylbenzene and 36.3 mL (0.375 mol) of acetic anhydride was added dropwise over 4 h to a stirred suspension of 110 g (0.825 mol) of aluminum trichloride in 300 mL of dichloromethane kept at 0 °C. After the addition was complete, the mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature. The mixture was then poured into 100 mL of concentrated hydrochloric acid in 400 mL of crushed ice, extracted with dichloromethane, and washed with 2 N sodium hydroxide solution and brine. The solution was dried over magnesium sulfate, and removal of the solvent under reduced pressure gave a light brown liquid. Distillation of this liquid afforded 57.7 g (88% yield) of the colorless product: bp 94–100 °C at 1.5 mm; ^{1}H NMR δ 7.3 (d, *J* = 8.1 Hz, 2 H), 7.1 (d, *J* = 8.1 Hz, 2 H), 2.6 (s, 3 H), 2.5 (d, *J* = 7.2 Hz, 2 H), 1.8 (m, 1 H), 0.9 (d, *J* = 6.4 Hz, 6 H).

(*p*-Isobutylphenyl)methylcarbinol. A solution of 4.80 g (0.027 mol) of *p*-isobutylacetophenone in 50 mL of ethanol was added over a 10-min period to a stirred solution of 1.30 g (0.035 mol) of sodium borohydride in 10 mL of water at room temperature. After stirring for an additional 20 min, a concentrated solution of sodium hydroxide was added and the mixture was boiled for 5 min to destroy the excess of sodium borohydride and hydrolyze the borate ester formed. The mixture was then poured over ice, extracted with diethyl ether, washed with 2 N aqueous sodium hydroxide, 2 N aqueous hydrochloric acid, and brine, and dried over magnesium sulfate. Removal of the solvent gave an oil, which was distilled to obtain 58.4 g (85.3% yield) of the pure product: bp 100 °C at 0.75 mm; ^{1}H NMR δ 7.3 (d, *J* = 8.1 Hz, 2 H), 7.1 (d, *J* = 8.1 Hz, 2 H), 4.7 (q, 6.0 Hz, 1 H), 2.8 (s, 1 H, disappeared by shaking with D_2O), 2.5 (d, *J* = 7.2 Hz, 2 H), 1.8 (m, 1 H), 1.5 (d, *J* = 6.0 Hz, 3 H), 0.9 (d, *J* = 6.4 Hz, 6 H).

***p*-Isobutylstyrene (4).** A mixture of 20.0 g (0.112 mol) of *p*-(isobutylphenyl)methylcarbinol, 0.6 g of fused potassium bisulfate, and 10 mg of *p*-methoxyphenol was heated at 200 °C and the product–water azeotrope was distilled out (0.5 mm). The wet product was dried over magnesium sulfate. Removal of the solvent and fractional distillation afforded 14 g (78% yield) of product: bp 60 °C at 0.5 mm; ^{1}H NMR δ 7.3 (d, *J* = 8.1 Hz, 2 H), 7.1 (d, *J* = 8.1 Hz, 2 H), 6.7 (dd, *J* = 17.9, 10.9 Hz, 1 H), 5.6 (d, *J* = 17.9 Hz, 1 H), 5.2 (d, *J* = 10.9 Hz, 1 H), 2.4 (d, *J* = 7.2 Hz, 2 H), 1.8 (m, 1 H), 0.9 (d, *J* = 6.4 Hz, 6 H). This spectrum was consistent with the published data.[26]

Hydroformylation of *p*-Isobutylstyrene (4). A mixture of 3.00 g (18.7 mmol) of *p*-isobutylstyrene, 26.2 mg (0.032 mmol) of [(−)-BPPM]$PtCl_2$, 18.0 mg (0.080 mmol) of $SnCl_2 \cdot 2H_2O$, and a few crystals of *p*-methoxyphenol in 5 mL of benzene was placed into a 125-mL Parr Monel bomb. The bomb was pressurized with H_2/CO to 2400 psi and heated to 60 °C for 9 h. The reaction mixture was analyzed by GC to determine the conversion (50%), aldehyde selectivity (98%), and *b*/*n* ratio (0.5). ^{1}H NMR of the mixture with the chiral shift reagent Eu(hfc)$_2$ determined that the branched aldehyde was obtained in 78% ee. The (*S*)-(+) enantiomer was obtained in excess.

(*S*)-(+)-2-(2-Naphthyl)propanal (6). A mixture of 3.50 g (22.7 mmol) of 2-vinylnaphthalene, 72.0 mg (0.088 mmol) of [(−)-BPPM]-$PtCl_2$, 49.3 mg of $SnCl_2 \cdot 2H_2O$, and a few crystals of *p*-methoxyphenol in 15 mL of benzene was placed into a 125-mL Parr Monel bomb. The bomb was pressurized with H_2/CO to 2400 psi and heated to 60 °C for 18 h. The reaction gave 100% conversion to the corresponding branched and normal aldehydes (*b*/*n* = 0.5 by ^{1}H NMR). The mixture was submitted to medium-pressure chromatography (silica, benzene) and afforded 0.90 g (22%) of the branched aldehyde (**6**): mp 136 °C (lit.[27] mp 134–135 °C); ^{1}H NMR δ 9.7 (d, *J* = 4.1 Hz, 1 H), 7.7–7.2 (m, 7 H), 3.7 (dq, *J* = 6.3, 4.1 Hz, 1 H), 1.2 (d, *J* = 6.3 Hz, 3 H). ^{1}H NMR of **6** in the presence of Eu(hfc)$_3$ determined that the aldehyde was obtained in 78% ee.

(*S*)-(+)-2-(2-Naphthyl)propionic Acid (7). To a stirred mixture of 350 mg (1.90 mmol) of **6** and 350 mg of magnesium sulfate in 50 mL of acetone was added 331 mg (2.10 mmol) of potassium permanganate over 2 h. The mixture was stirred at room temperature for an additional 30 min. The solvent was evaporated under reduced pressure and the solid residue was treated with 3 × 50 mL of hot water and filtered. The cold aqueous solution was washed with chloroform, then acidified with hydrochloric acid to pH 2, and extracted with chloroform. The organic layer was dried over magnesium sulfate. Removal of the solvent under reduced pressure gave 230 mg (60.5%) of the product (**7**) as white crystals: mp 143 °C (lit.[28] mp 139.4–141 °C); $[\alpha]^{24}_D$ + 51° (*c* 2.5, $CHCl_3$); 77% OP (based on $[\alpha]^{25}_D$ + 66.4° reported for the pure (*S*) enantiomer[28]).

(*S*)-2-(6-Methoxy-2-naphthyl)propanal (9). A deoxygenated solution of 1.0 g (5.4 mmol) of 2-ethenyl-6-methoxynaphthalene (**8**)[12] in 15 mL of benzene was charged into a 125-mL Parr Monel bomb with 16 mg (0.02 mmol) of [(−)-BPPM]$PtCl_2$ (**2**) and 11 mg (0.05 mmol) of stannous chloride dihydrate. The bomb was sealed, pressurized to 2700 psi, and heated with stirring to 60 °C for 9 h. At the end of the reaction the bomb was quenched in a dry ice bath, the pressure was vented, and the mixture was eluted with benzene through an MPLC apparatus to afford 350 mg (30.1%) of the branched aldehyde: mp 145 °C; 81% ee (determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent); ^{1}H NMR δ 9.7 (d, *J* = 4.1 Hz, 1 H), 7.7–7.1 (m, 6 H), 3.9 (s, 3 H), 3.7 (dq, *J* = 6.3, 4.1 Hz, 1 H), 1.6 (d, *J* = 6.3 Hz, 3 H). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.50; H, 6.54. Found: C, 78.38; H, 6.59.

(*S*)-(+)-2-(6-Methoxy-2-naphthyl)propionic Acid (Naproxen) (10). A suspension containing 250 mg (1.17 mmol) of (*S*)-2-(6-methoxy-2-naphthyl)propanal (**9**) and 280 mg (1.13 mmol) of magnesium sulfate in 50 mL of acetone was treated with a solution of 269 mg (1.70 mmol) of potassium permanganate in 10 mL of acetone added dropwise over 1 h. The solvent was then removed and the residue was extracted with hot water and filtered. The cold aqueous solution was washed with chloroform and then acidified with HCl to pH 2 to obtain a white precipitate, which was filtered, washed with water, and dried under reduced pressure to yield 200 mg (74.3%) of product: mp 154 °C (lit.[11] mp 152–154 °C); $[\alpha]^{24}_D$ +54.1° (*c* 1, $CHCl_3$); 82% OP (based on $[\alpha]_D$ +66° reported for the pure enantiomer[11]). The product was recrystallized for acetone/

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hexane to afford a first crop of crystals with $[\alpha]^{24}_D$ +65.8° (*c* 1, $CHCl_3$) (100% OP). A second crop of crystals was recovered from the mother liquors ($[\alpha]^{24}_D$ +52.4°; 80% OP).

Hydroformylation of 4-(2-Thienylcarbonyl)styrene (11). A deoxygenated mixture of 1.00 g (4.67 mmol) of 4-(2-thienylcarbonyl)styrene,[12] 7.70 mg (0.009 mmol) of [(−)-BPPM]$PtCl_2$, 5.30 mg (0.023 mmol) of stannous chloride dihydrate, and a few crystals of *p*-methoxyphenol in 7 mL of benzene was placed into a 125-mL Parr Monel bomb. The bomb was pressurized with H_2/CO to 2600 psi and heated to 60 °C for 9 h. The reaction mixture was analyzed by ^1H NMR to determine the conversion (73%), aldehyde selectivity (98%), and *b*/*n* ratio (0.5). ^1H NMR of the mixture with the chiral shift reagent $Eu(hfc)_3$ determined that the branched aldehyde was obtained in 78% ee. The (*S*)-(+) enantiomer was obtained in excess.

Hydroformylation of Vinyl Acetate. A deoxygenated mixture of 1.00 mL (0.934 g, 10.6 mmol) of vinyl acetate, 10.9 mg (0.013 mmol) of [(−)-BPPM]$PtCl_2$, and 7.50 mg (0.033 mmol) of stannous chloride dihydrate in 3 mL of benzene was placed into a 125-mL Parr Monel bomb. The bomb was pressurized with 1:1 H_2/CO to 2700 psi and heated to 60 °C for 40 h. The reaction mixture was analyzed by GC to determine the conversion (75%), the amount of volatile aldehydes (70%), and the *b*/*n* ratio (0.5). The mixture was washed with sodium bicarbonate saturated solution and dried over magnesium sulfate. ^1H NMR in the presence of the chiral shift reagent $Eu(tfc)_3$ determined that the branched aldehyde was obtained in 76% ee. The (*S*)-(+) enantiomer was obtained in excess.

(*R*)-(+)-2-*N*-Phthalimidopropanal. This compound was obtained in 25% yield by the hydroformylation of *N*-vinylphthalimide in the presence of [(−)-BPPM]$PtCl_2/SnCl_2$. The reaction yielded the branched and the linear aldehydes in 0.5 *b*/*n* ratio. The branched aldehyde was isolated by MPLC (1:1 hexane/ethyl acetate): mp 105–107 °C (lit.[21] mp 112–113 °C); 73% ee (determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent).

(*R*)-(+)-*N*-Phthalylalanine. This compound was obtained by oxidation of (*R*)-(+)-2-*N*-phthalimidopropanal following a reported procedure:[21] mp 148 °C (lit.[21] mp 150–151 °C); $[\alpha]^{24}_D$ +17.6° (*c* 8, EtOH); 72% OP (based on $[\alpha]^{25}_D$ +24.5° reported for the pure enantiomer[21]).

Hydroformylation of Norbornene. A deoxygenated mixture of 1.00 g (10.6 mmol) of norbornene, 10.9 mg (0.013 mmol) of [(−)-BPPM]$PtCl_2$, 7.50 mg (0.033 mmol) of stannous chloride, and a few crystals of *p*-methoxyphenol in 3 mL of benzene was placed into a 125-mL Parr Monel bomb. The bomb was pressurized with 1:1 H_2/CO to 2700 psi and heated to 30 °C for 20 h. The reaction mixture was analyzed by GC to determine the conversion (84%) and the aldehyde selectivity (98.7%). ^1H NMR of the mixture in the presence of $Eu(hfc)_3$ determined that the aldehyde was obtained in 60% ee. This mixture was dissolved in 50 mL of acetone containing 1.5 g of magnesium sulfate, and 1.6 mg of potassium permanganate was added over 1 h with stirring at room temperature. The solvent was removed under reduced pressure and the black solid was extracted with hot water and filtered. The solution was allowed to cool to room temperature and washed with chloroform. The aqueous layer was acidified to pH 2 with concentrated hydrochloric acid and extracted with chloroform. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure to afford a white solid. Recrystallization from water afforded white crystals: mp 57–58 °C (lit.[24] mp 58–58.5 °C); $[\alpha]^{24}_D$ +6.5° (*c* 2.45, EtOH) [lit.[24]-$[\alpha]^{25}_D$ +10.7° (*c* 2.4, EtOH)]; 60.7% OP. Comparison of these physical data with those reported in the literature[24] established that the exo-(1*S*,2*S*,4*R*)-(+) enantiomer was obtained in excess.

Hydroformylation of Methyl Methacrylate. A deoxygenated mixture of 1.00 mL (0.936 g, 9.30 mmol) of methyl methacrylate, 10.9 mg (0.013 mmol) of [(−)-BPPM]$PtCl_2$, and 7.50 mg (0.033 mmol) of stannous chloride dihydrate in 3 mL of benzene was placed into a Parr Monel bomb. The bomb was pressurized with 3:1 H_2/CO to 2600 psi and heated to 60 °C for 50 h. The reaction mixture was analyzed by GC to determine the conversion (36%) and aldehyde selectivity (98%). The product, methyl β-formylisobutyrate was identified by comparison of the ^1H NMR data to those reported.[29] ^1H NMR in the presence of $Eu(hfc)_3$ determined that the product was obtained in 60% ee. The (*S*)-(+) enantiomer was obtained in excess.

General Procedure for Hydroformylation in the Presence of Triethyl Orthoformate. This procedure was identical with that for hydroformylation described above except that triethyl orthoformate is used as the solvent (or cosolvent in the case of substrates which are insoluble in triethyl orthoformate). At the end of the reaction, the solvent was removed by vacuum distillation and the resulting mixture was analyzed by GC or ^1H NMR to determine the conversion and the product composition. The ee's were determined directly on the acetal (or on the aldehyde obtained by hydrolysis) by ^1H NMR using $Eu(hfc)_3$ chiral shift reagent.

General Procedure for the Hydrolysis of the Chiral Acetals. The mixture obtained from the reaction described above was dissolved in acetone, and a few crystals of pyridinium *p*-toluenesulfonate were added. The solution was heated at reflux for 5 h. The solvent was removed under reduced pressure and the product was distilled or flash chromatographed (silica, chloroform).

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(29) Flowers, L. I. Ph.D. Dissertation, University of Alabama, 1983. *Diss. Abstr., Int. B.* **1984**, *44*, 2426.