Asymmetric Carbonylation of α-Methylbenzyl Bromide Catalyzed by Oxazaphospholane–Palladium Complexes under Phase-Transfer Conditions

Henri Arzoumanian,* Gérard Buono, M'Barek Choukrad, and Jean-François Petrignani

Institut de Pétroléochimie et de Synthèse Organique Industrielle et Ecole Supérieure de Chimie de Marseille, Université Aix-Marseille III, UA 126 du CNRS, 13397 Marseille Cedex 13, France

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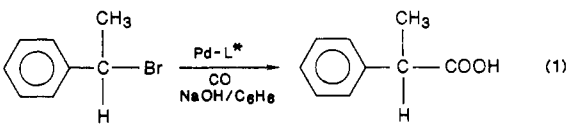
Carbonylation of α-methylbenzyl bromide using 5 N NaOH and CH_2Cl_2 at room temperature and 1 atm of pressure in the presence of bis(dibenzylideneacetone)palladium and a series of 2-substituted-3,1,2-oxazaphospholanes results in the formation of 2-phenylpropionic acid with various enantiomeric excesses. The reaction is shown to be a kinetic resolution process with a discriminative slow oxidative addition step. It is further shown that the reaction occurs at the liquid–liquid interphase, but the presence of a phase-transfer agent is necessary to attain enantiomeric discrimination. This is rationalized in terms of a second-order interaction involving hydrogen-bond formation between the nitrogen atom of the oxazaphospholane and a hydroxyl group attached to palladium prior to the oxidative addition to the substrate.

Introduction

The need of stereochemical control, especially in reactions involving carbon to carbon bond formation, is of great importance; this often requires mild conditions in order to attain high enantiomeric excesses.[1] It is also known that catalytic reactions under phase-transfer conditions achieve high selectivities under moderate conditions.[2] We have thus attempted to perform an asymmetric reaction using this technique. Previous attempts to do so have encountered little success with the use of chiral-transfer agents.[3] This report describes the first example of the use of a metal catalyst bearing chiral ligands under phase-transfer conditions leading to optically active products.

The model reaction chosen was the well-studied carbonylation of α-methylbenzyl bromide (1) catalyzed by palladium.[4,5]



(1)

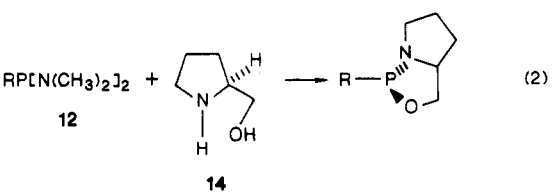
1 2

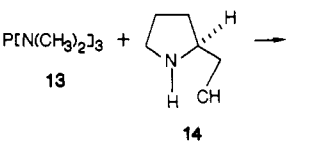
This enantioselective reaction could a priori proceed either by a kinetic resolution or by a true asymmetric induction via the intermediacy of a trigonal substrate ($PhCHCH_3^+$).

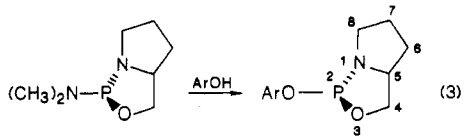
Results and Discussion

It has been shown that in the palladium-catalyzed carbonylation of benzyl halides the ligand attached to the metal has an important influence on the course of the reaction.[5] Since the use of dibenzylideneacetone (dba) as a ligand gives little or no carbonylation, we used the complex $Pd(dba)_2$ as a precursor and carried out the reaction by adding an excess of the chiral ligand to be tested, assuming that a ligand exchange with dba would occur.

Optically active phosphines with either a chiral phosphorus atom or a chiral-bearing substituent are well-known; these mono- as well as bidentate systems such as the diop ligand or the recently reported chelating aminophosphine phosphinite have been used with success in asymmetric metal-catalyzed reactions.[6,7] Unfortunately, most of the ones tested gave poor optical yields in the carbonylation reaction of benzyl halides under phase-transfer conditions (entries 1–4, Table I). On the other hand, a simpler aminophosphine (entry 5, Table I) and a series of 2-substituted-3,1,2-oxazaphospholanes (entries 6–10, Table I) easily synthesized from arylbis- (**12**) or tris(dimethylamino)phosphines (**13**) and (*S*)-(+)-prolinol[8,9] (**14**) according to eq 2 and 3 gave significant enantiomeric excesses.







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(1) Bosnich B. *NATO ASI Ser. Ser., E* 1986, *No. 103.*
(2) Alper, H. *Fundam. Res. Homogeneous Catal.* **1984**, *4*, 79.
(3) D'Incan, E.; Viout, P.; Gallo, R. *Isr. J. Chem.* **1985**, *26*, 277.
(4) Cassar, C.; Foa, M.; Gardano, A. *J. Organomet. Chem.* **1976**, *121*, C55.
(5) Alper, H.; Hashem, K.; Heveling, J. *Organometallics* **1982**, *1*, 775.
(6) Kagan, H. B. In *Asymmetric Synthesis*; Morrison J. D., Ed.; Academic: New York, 1985; Vol. 5, p 17.
(7) Buono, G.; Siv, C.; Peiffer, G.; Triantaphylides, C.; Denis, P.; Mortreux, A.; Petit, F. *J. Org. Chem.* **1985**, *50*, 1781.
(8) Cros, P.; Buono, G.; Peiffer, G.; Denis, P.; Mortreux, A.; Petit, F. *Nouv. J. Chim.* **1987**, *11*, 573.
(9) Only one chiral diastereoisomer, (2*R*,5*S*)-2-(dimethylamino)-3,1,2-oxazaphosphabicyclo[3.3.0]octane (**8**) was formed in the exchange reaction between tris(dimethylamino)phosphine (**4**) and (*S*)-(+)prolinol (**5**). The stereochemistry was determined by ^{13}C NMR. Indeed, the magnitude of $^2J_{PC}$ in cyclic phosphines seems to be strongly controlled by the dihedral angle associating the lone-pair orbital (assuming substancial s character in the hybridization about PIII) and the β-carbon of the group attached to P. For example in the diastereoisomers of **10** coupling to the C_8 is quite different in the cis (**10**:) ($^2J_{PC}$ = 40 Hz) and trans (**10a**) ($^2J_{PC}$ = 0) forms.

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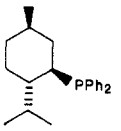
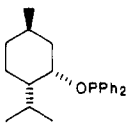
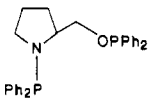
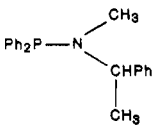
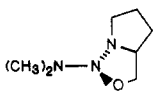
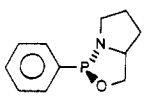
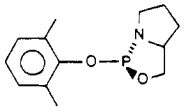
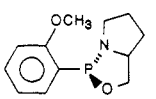
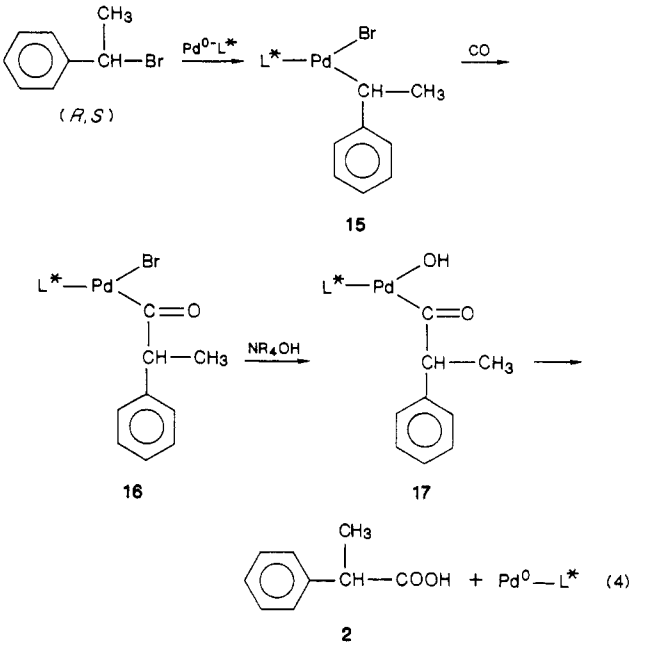
Table I. Carbonylation of α-Methylbenzyl Bromide Catalyzed by Pd–L* under Phase-Transfer Conditions[a]

entry	L*	chem yield,[b] %	% ee[c]	conf[d]
1	 **3**	14	3	*R*
2	 **4**	8	0	
3	(−)-diop **5**	0	0	
4	 **6**	3	0	
5	 **7**	25	17	*S*
6	 **8**	19	6	*R*
7	 **9**	12	2	*R*
8	 **10**	9 65[f]	64[e] 42	*R* *R*
9	 **11**	10	10	*S*

[a] Solvent, CH_2Cl_2/5 N NaOH; temp, 10 °C; reaction time, 12 h; CO pressure, 1 atm; [Pd]/[L*] = 1/6. [b] Yield of purified isolated 2-phenylpropionic acid. The only other identified product observed was 2-phenylethanol (~5% relative to the acid formed). No 2,3-diphenylbutane, ethylbenzene, styrene, or α-phenethyl-2-phenylpropionate were detected. [c] See Experimental Section for method of determination. [d] Configuration of the isolated acid in excess. [e] Measure of the rotatory power of the isolated remaining bromide in this case corresponded within experimental error to the enantiomeric enrichment of the acid (expected % ee remaining bromide 9%, found 13%). [f] Temp, 18 °C; reaction time, 4 h.

The results for a given set of experimental conditions are shown in Table I. These could in part be rationalized by the well-established catalytic carbonylation[4] (eq 4). They could not, however, indicate, a priori, the step in which the enantiomeric discrimination occurred. Carrying out a reaction at a higher CO pressure (5 atm) resulted in no increase in either chemical or optical yield, indicating that the oxidative addition (**1** to **15**) was the rate-determining step and, plausibly, also the stereochemical-determining step, although the latter does not always proceed from the former.



Kinetic resolution of racemic substrates by enantioselective catalytic reactions has often been used to obtain unreacted substrate with surprisingly high optical purity. Mathematical treatment and practical format have also been given, allowing easy prediction for such reactions.[10-12] Since it was more convenient for us to measure the percent enantiomeric excess of the acid product **2** rather than the starting bromide **1**, we adapted the mathematical treatment to obtain a plot of percent enantiomeric excess of product formed as a function of percent conversion. This format is given in Figure 1.[13]

In order to establish whether the reaction under study was truly a kinetic resolution process, we carried out a series of reactions with a given chiral ligand (**10**) and measured the optical purity of the isolated acid **2** at different percent conversion. The results are plotted in Figure 1 and fit well the calculated curves for K_A/K_B = 5.1 and 2.4, respectively, for a ratio of [Pd]/[L*] = 6 and 4. This strongly suggests that a kinetic resolution is indeed operative, implying a slow oxidative addition step.

Since in such a process it is possible to attain fairly high enantiomeric excesses (at low conversion), it was of interest to test the possibility to obtain at will an enrichment of either enantiomer by simply using two diasteroisomer ligands differing by the opposite chirality on the phosphorus atom. This was made possible by using ligand **10** since in the exchange reaction between the 2-(dimethylamino)-3,1,2-oxazaphospholane (**8**) and 2,5-dimethylphenol either diastereoisomer can be obtained, one being the

(10) Balavoine, G.; Moradpour, A.; Kagan, H. B. *J. Am. Chem. Soc.* **1974**, *96*, 5152.

(11) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Masonori, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(12) Chen, C. S.; Fujimoto, Y.; Girdankas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

(13) The graph was computer-generated from the equation K_A/K_B = ln [1 − c(1 + ee)]/ln [1 − c(1 − ee)], where K_A and K_B are the relative rates of each enantiomer, c is the fraction of the racemic mixture consumed, and ee is the percent enantiomeric excess of product divided by 100. The equation was simply derived from the one given in ref 12 by equating ee(product) = ((1 − c)/c)ee (remaining substrate). It is analogous to the equation given in ref. 13 for biochemical kinetic resolution.

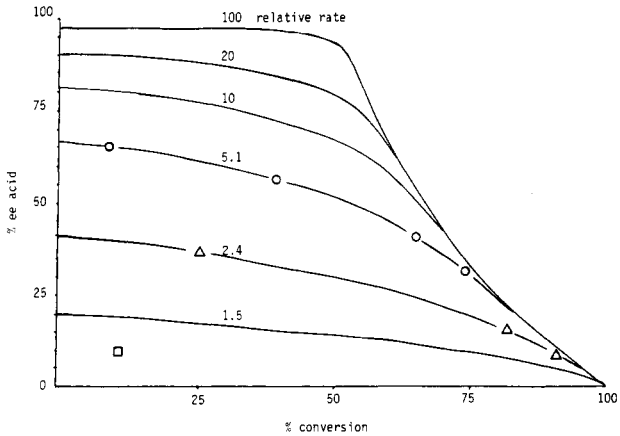
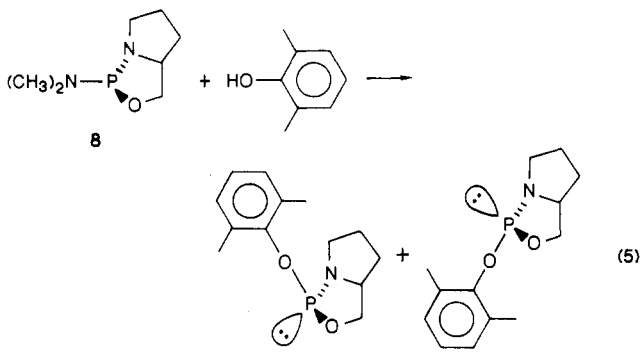


Figure 1. Plot of enantiomeric excess of product as function of the percent of starting substrate consumed. Experimental points correspond to **2** obtained at 25 °C with $Pd(dba)_2/10 = 1/6$ (○) and 1/4 (△) and in the absence of transfer agent (□).

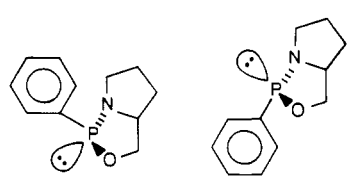
kinetic product **10a** and the other being the thermodynamic one **10b**.



(5)

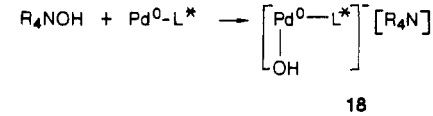
The ratio, dependent on the reaction temperature and reaction time, was easily monitored by ^{31}P NMR spectroscopy. After 4 h at 100 °C in toluene the ratio **10a/10b** was 80/20; after 12 h at reflux temperature it was 64/36. After evaporation of the solvent and heating the crude product for 1 h at 100–110 °C, under nitrogen, mainly the thermodynamic product (**10a/10b** = 10/90) was obtained. When the carbonylation reaction was carried out in the presence of a mixture of **10a** and **10b** (80/20), it resulted in the formation of the acid with an enantiomeric excess of 64% (entry 8, Table I), whereas when the same reaction was repeated in the presence of mainly the thermodynamic diastereoisomer (**10a/10b** = 10/90), almost no enantiomeric excess was observed. This might, a priori, indicate that the enantiomeric discrimination must occur only through coordination on the nitrogen side of the ligand. This is corroborated with the result obtained with 2-phenyl-3,1,2-oxazaphospholane (entry 7, Table I).

Indeed, this ligand, which results from the exchange of phenylbis(dimethylamino)phosphine (**12**) and L-prolinol (**14**), could also give two possible diastereoisomers, **9a** and **9b**.



However, when the exchange reaction was monitored by ^{31}P NMR, the ratio of **9a/9b**, which was 90/10 after 15% conversion, was almost totally transformed into the thermodynamic product **9b** at the end of the reaction. The ligand thus used in the carbonylation reaction was the latter (entry 7, Table I), giving a low enantiomeric excess.

One more point remained to be cleared up: was the reaction a real phase transfer process or a reaction occurring at the liquid–liquid interface. This was checked by choosing one set of conditions (e.g. entry 8, Table I) corresponding to one experiment and repeating it in the absence of transfer agent. The result obtained showed that the acid product **2** was formed with a comparable chemical yield (10% vs 9%), indicating, as previously reported,[5] that the reaction occurred at the interface.[14] However, it was totally unexpected to observe that the absence of transfer agent inhibited almost totally the asymmetric induction (see Figure 1). This implies strongly that in cases in which enantiomeric discrimination occurs the transfer agent interacts with the catalyst before the oxidative addition (slow step).[17] Since the most plausible role of the ammonium cation is to transfer a hydroxyl moiety into the organic phase, one could envisage the hydroxylation of the zerovalent palladium complex to give a new ionic species stabilized by the onium cation **18** onto which the oxidative addition would occur.



(6)

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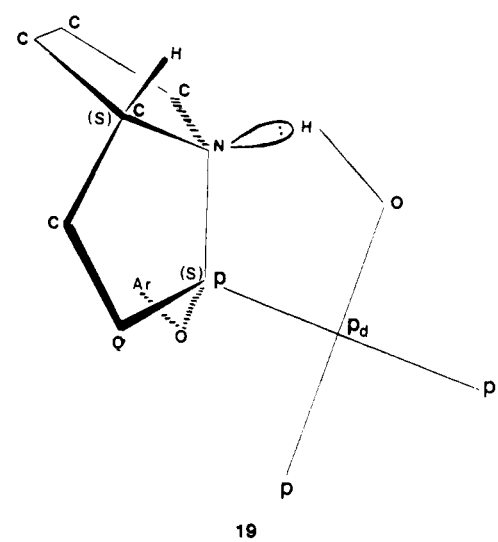
Although somewhat speculative, such a zerovalent palladium anion has previously been proposed to explain different selectivities in the carbonylation of benzyl halides.[5] The asymmetric induction can then be rationalized in terms of hydrogen-bond formation between the hydroxyl group and the nitrogen atom of the ligand, creating a second-order interaction on the ligand **19**, thus giving a new insight into the way the enantiomeric discrimination might occur.[18]



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(14) An interfacial mechanism in phase-transfer-catalyzed reactions was first proposed by Makosza[15] in 1975 and has recently been reviewed by Rabinovitz.[16]

(15) Makosza, M. *Pure Appl. Chem.* **1975**, *43*, 439.

(16) Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 960.

(17) It appears also that in the presence of a phase-transfer agent a "classical" extraction[16] mechanism rather than an interfacial one is operative.

(18) This is analogous to the second-order interaction proposed by Bosnich on the asymmetric hydrogenation.[19]

(19) Bosnich, B.; Fryzuk, M. D. *Top. Stereochem.* **1981**, *12*, 119.

This is also in agreement with the observation mentioned that within a pair of diastereoisomers (e.g. **10a**,b), only the one having free access to the nitrogen atom was able to achieve such a discrimination. It seems, therefore, that it is based on the possibility of forming a Pd–OH–N linkage rather than a preferential coordination mode.

In conclusion, asymmetric reaction has been shown to be feasible under phase-transfer conditions. In the present study, it was shown that the palladium-catalyzed asymmetric carbonylation of α-methylbenzyl bromide is a kinetic resolution process. It was further shown that in the biphasic system, in the absence of a phase-transfer agent, the reductive elimination step (**16** → **2**) occurs most probably at the interface without asymmetric induction, whereas in the presence of such a transfer agent a new active species (**19**) is formed prior to the enantiomeric discriminative oxidative addition step.

Experimental Section

General Data. Unless otherwise noted, all material were obtained from commercial suppliers and used without further purification. All solvents were thoroughly degassed prior to use. Toluene, benzene, tetrahydrofuran, and diethyl ether were distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane and chloroform were dried over molecular sieves and used without further purification. NMR spectra were recorded on a Bruker AC-100 spectrometer from C_6D_6 solutions. The chemical shifts (ppm) were determined relative to $(CH_3)_4Si$ (^{13}C, ^1H) and 85% H_3PO_4(^{31}P). IR spectra were recorded on a Nicolet MX5 spectrometer. Gas chromatographic analyses were done by using a SE30 packed column (4 mm diameter, 3 m long) and *n*-decane as an internal standard. Thin-layer chromatography was performed on silica gel plate (purchased from Merck). The aminophosphines $PhP[N(CH_3)_2]_2$ and $P[N(CH_3)_2]_3$ were prepared according to a classical method.[20] Compound **3** was synthesized according to Morrison.[21] Compound **4** was prepared from L-menthol and chlorodiphenylphosphine in the presence of triethylamine (^{31}P, 109.6 ppm). Compounds **6**, **7**, and **9** were prepared by the procedure described in ref 22 and compounds **8** and **10** by the procedure described in ref 8.

Carbonylation of α-Methylbenzyl Bromide. In a typical experiment, to a well-deoxygenated 5 N NaOH solution (14 mL) was added 8 mL of CH_2Cl_2 containing 0.011 g (0.03 mmol) of hexadecyltrimethylammonium bromide (CTAB). To the mixture, placed under an atmosphere of CO, was added a green solution prepared by reacting 0.060 g (0.104 mmol) of bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) and 0.624 mmol of the desired chiral ligand (e.g. 0.157 g of **10**) in 10 mL of CH_2Cl_2 at room temperature for 15 min. To the two-phase system thus obtained was then slowly added through a dropping funnel 0.524 g (2.93 mmol) of α-methylbenzyl bromide (**1**) in 2 mL of CH_2Cl_2. The mixture was thoroughly stirred while CO was bubbled in for the desired length of time, after which the organic phase was separated and washed twice with water and all the combined aqueous phases acidified to pH 2 with HCl. The acid product was extracted with diethyl ether (3 × 20 mL) and evaporated to give a yellow oil that was further purified by preparative thin-layer chromatography (Silica, *n*-hexane/diethyl ether, 70/30 as eluent) to yield pure acid (e.g. 1.9 g, 46% yield).

Preparation of Bis(dimethylamino)(*o*-methoxyphenyl)phosphine[23] (20). Phosphorous trichloride (30.5 g, 0.22 mol) was added at room temperature with mechanical stirring to 72.3 g (0.44 mol) of tris(dimethylamino)phosphine. A vigorous exothermic reaction occurred with evolution of white fumes. The mixture was heated to 100 °C for 20 min, and the resulting solution was cooled to room temperature and diluted with approximatively 800 mL of dry diethyl ether. To the resulting solution cooled to −78 °C was slowly added over a period of 2 h a 500-mL tetrahydrofuran solution containing 130.8 g (0.7 mol) of *o*-methoxyphenyl bromide. The reaction mixture was allowed to reach slowly room temperature, and stirring was continued overnight. It was then hydrolyzed by pouring it over a period of 5 min into a vigorously stirred deoxygenated ice-cold aqueous solution (1300 mL) containing 214 g (0.75 mol) of ethylenediaminetetraacetic acid (EDTA) and 123 g (3 mol) of sodium hydroxide. After several minutes, the organic fraction was decanted and the aqueous portion extracted with an additional 400 mL of diethyl ether. The combined organic solutions were concentrated at 25 °C (40 mm) to give an oil as a crude product. Distillation yielded 90 g (40% yield) of **20** as a yellow liquid: bp 98 °C (1 mm); n^{20}_D 1.5535; ^{13}C NMR (C_6D_6) δ 41.76 ($N(CH_3)_2$, $^2J_{PC}$ = 18.4 Hz), 55.33 (OCH_3), 110.5, 120.9, 132.6, 133.0 (aromatic); ^{31}P NMR (C_6D_6) δ 96.7.

Preparation of (2*R*,5*S*)-2-(*o*-Methoxyphenyl)-3,1,2-oxazaphospholane (11). A mixture of 8.43 g (0.084 mol) of (*S*)-(+)-prolinol[24] and 18.98 g (0.084 mol) of **20** in 100 mL of toluene was heated to reflux temperature. The reaction was monitored by both titration of evolved dimethylamine and ^{31}P NMR. Removal of solvent under vacuum followed by distillation of the oily residue gave 13 g (70% yield) of[11] as a viscous liquid: bp 110–115 °C (0.05 mm); n^{22}_D 1.5509, $[\alpha]^{25}_D$ +138,4° (*c* 1, CH_2Cl_2); ^{31}P NMR (C_6D_6) δ 144.1 (major stereoisomer, 2*R*,5*S*, 98%); ^{13}C NMR (C_6D_6) δ 72.8 (C_4, $^2J_{PC}$ = 11.1 Hz), 62.8 (C_5, $^2J_{PC}$ = 4.8 Hz), 32.01 (C_6), 26.54 (C_7, $^3J_{PC}$ 4.1 Hz), 52.8 (C_8, $^2J_{PC}$ = 31.5 Hz), 162 ($^2J_{PC}$ = 15.4 Hz), 110.8, 120.3, 130.2 ($^1J_{PC}$ = 40.2 Hz), 130.46 ($^2J_{PC}$ = 3.3 Hz), 131 (aromatics), 55.3 (OCH_3). Anal. Calcd for $C_{12}H_{16}NO_2P$: C, 65.0; H, 7.2; N, 6.8. Found: C, 64.6; H, 7.0; N, 6.3.

Enantiomeric Excess Determination. This was done either by measuring the rotatory power, based on known specific rotation $[\alpha]^{27}_D$ −77.0° (*c* 2.38, chloroform) for the (−)-(*R*)-hydratropic acid,[25] or by the method developed by König[26] that consists of converting the acid into an amide followed by gas chromatographic separation of the two enantiomers on a chiral phase packed column. As a typical example, 0.030 g (0.2 mmol) of 2-phenylpropionic acid was heated in a sealed capped vial at 100 °C for 1 h with 0.260 g (3 mmol) of isopropyl isocyanate. The yellow solution was then placed under a stream of nitrogen at room temperature to evaporate the excess isocyanate, and the residue was diluted with 2 mL of CH_2Cl_2 before the gas chromatographic analysis on a 50-m column packed with Chrompack XE60 (*S*)-valine-(*S*)-phenylethylamide. When the acid obtained in one given reaction was analyzed by both methods, the values of enantiomeric excess measured were within 5%.

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Registry No. **1**, 585-71-7; **2**, 492-37-5; **3**, 43077-31-2; **4**, 60189-32-4; **5**, 32305-98-9; **6**, 110904-80-8; **7**, 52364-43-9; **8**, 110904-81-9; **9**, 111002-64-3; **10**, 110904-82-0; **11**, 110904-83-1; **13**, 1608-26-0; **20**, 110904-84-2; $Pd(dba)_2$, 32005-36-0; *o*-methoxyphenyl bromide, 578-57-4; (*S*)-(+)-prolinol, 23356-96-9.

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