POLYMERIC Pd CATALYSTS FOR THE REDUCTION OF ACETAMIDOCINNAMIC ACID AZLACTONE AND ITS SOLVOLYSIS PRODUCTS

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Pd complexes have been obtained from linear and cross-linked copolymers of R,S-, R-, *and* S-*1-(4-vinylphenyl)ethylamine (1) with styrene and divinylbenzene. Reduction of these compounds gave catalysts which were active in the reductive solvolysis of α-acetaminocinnamic acid azlactone (2) and hydrogenation of the solvolysis products α-acetamidocinnamic acid (ACA), its esters, and its 1-phenylethylamide. The catalysts showed no enantioselective properties in the reductive hydrolysis, but were more active than the catalyst obtained in the absence of the polymer (the "monomeric" analog). The use of polymeric catalysts has shown that, in reductive aminolysis, the chiral nucleophile plays the dominant part in determining the stereoselectivity of the reaction, rather than the chiral ligand of the catalytic complex. The polymer matrix stabilizes the low-valent state of the palladium in the complex. In the hydrogenation of ACA and its esters, the catalyst on the cross-linked polymer is much more active than its "monomeric" analog, but showed no enantioselectivity. Hydrogenation of acetamidocinnamic acid* R- *and* S-*1-phenylethylamides on a chiral Pd-polymer catalyst occurred with double asymmetric induction.*

Keywords: *Pd catalysts on chiral polymers, asymmetric reduction, azlactones, reductive aminolysis.*

We have previously reported that a catalyst for the enantioselective reductive aminolysis of unsaturated azlactones is the zerovalent complex of palladium with 1-phenylethylamine, stabilized by a coordinately bound substrate, acetamidocinnamic acid azlactone (2) [1-5]. This catalyst is, however, unstable under the reaction conditions, and it cannot be re-used. The aim of the present study was to synthesize a palladium catalyst on a polymeric aromatic carrier, and to examine the effects of the polymeric environment on the stereoselectivity of the reactions which it catalyzed. In addition to the known advantages of polymeric catalysts [6], the unstable zerovalent state of the palladium in the complex should be stabilized by the π-acceptor polymeric ligand [7]. Furthermore, transmission of the stabilizing effects of the substrate to the polymer ligand should extend the range of substrates for asymmetric hydrogenation using this catalytic system. Finally, by using a polymer, it might be possible to assess the contributions of the ligand and the nucleophile to the stereoselectivity of the reductive aminolysis of azlactones.

*Deceased.

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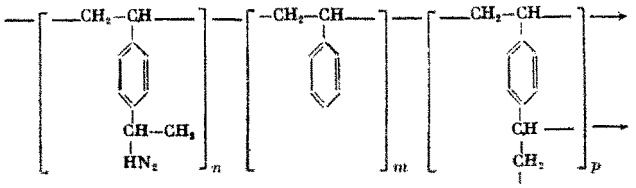
TABLE 1. Properties of Copolymers of 1-(4-Vinylphenyl)ethylamine, Styrene, and Divinylbenzene



Compound	Composition of polymer			Elemental analysis		
	n	*m*	*p*			
R,S-CP*	0.24	0.74	0.02	88.60	8.39	2.94
R,S-LP	0.26	0.74	0.00	88.32	8.31	3.20
R-CP†	0.25	0.73	0.02	87.18	7.90	3.14
S-LP‡	0.26	0.74	0.00	88.30	8.12	3.24

*R,S-CP and R,S-LP are the cross-linked and linear polymers respectively, obtained from R,S-1.

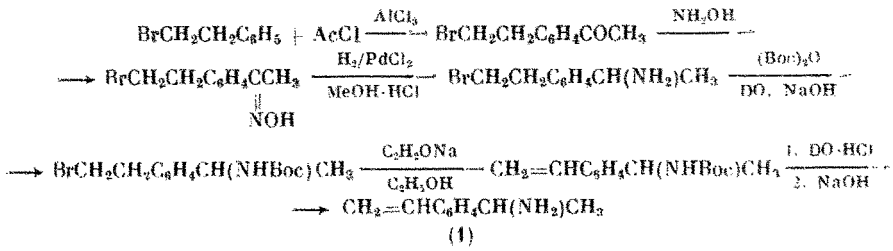
†R-CP is the cross-linked polymer obtained from R-1, optical purity $p = 89\%$.

‡S-LP is the linear polymer obtained from S-1, $p = 55\%$.

TABLE 2. Polymeric Pd Catalysts

Cat	Polymer	Method of application	Reducing agent	Pd compound, mass %	N : Pd
Pd-1	R,S-CP	$PdCl_2$, 20°	H_2	21.8	1.3
Pd-2	»	»	$NaBH_4$	8.0	4.3
Pd-3	»	$PdCl_2$, 84°	H_2	23.0	1.25
Pd-4	»	$(\pi\text{-all-PdCl})_2$	H_2	19.8	1.5
Pd-5	R,S-LP	$PdCl_2$, 20°	H_2	16.6	2.0
Pd-6	R-CP	»	H_2	16.6	2.0
Pd-7	S-LP	»	$NaBH_4$	4.6	8.0
Pd-8	»	»	H_2	16.6	2.0

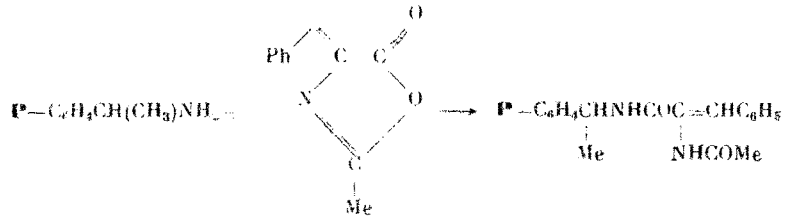
Synthesis of Polymeric Pd Catalysts. The polymer ligands chosen were copolymers of 1-(4-vinylphenyl)ethylamine (**1**) obtained as follows:



(1)

(where DO is dioxane). Cleavage of *R,S*-**1** was effected with *S*-(−)-malic and *R,R*-(+)-tartaric acids, as reported previously [8, 9]. It may be mentioned that the method of synthesis of **1** given in [8], requiring reduction of *p*-bromoethylacetophenone with $NaBH_3CN$ and dehydrobromination without protection for the amino group, afforded samples contaminated with the hydrochloride (**1**·HCl), which it was not possible to remove.

Radical copolymerization of racemic and optically active monomers with styrene gave the linear, soluble polymers (LP), while suspension polymerization with divinylbenzene afforded cross-linked, insoluble polymers (CP) (Table 1). These polymeric ligands were characterized by their elemental composition, IR spectra (free primary NH_2 group), and PMR spectra for the linear polymer (the proportion of units corresponded to the elemental composition), and titration data indicating almost total protonation of the amino groups. The availability of the amino groups for reactions was clearly shown by the kinetic data for the acylation of the amino polymers **1** (followed by UV).



Substrate	*R*, *S*-CP	*R*, *S*-LP	*R*, *S*-PEA [10]
$k \cdot 10^2$, liter/(mole·min)	10	12	14

Comparison of the second-order rate constants for the polymers and for PEA indicates that the reactivities of the amino groups in the polymer and monomer are comparable. When the reaction was complete, the polymers contained no free amino groups (by IR). Palladium was applied to the polymer by a method involving rupture of the bridge Pd–Cl bonds [11, 12], either from a suspension of $PdCl_2$ in dimethoxyethane (DME), or from a similar solution of bis(π-allylpalladium dichloride). The temperature of application was also varied. The resulting Pd(II) polymer complexes were reduced with hydrogen or, in some instances, $NaBH_4$. When soluble polymers were reacted with $PdCl_2$, the polymer chains underwent cross-linking, and the metal-polymer was precipitated. The hydrogenation catalysts (Cat) obtained are shown in Table 2. It will be seen that when the palladium was applied and reduced, it became firmly bound to the polymer, and did not pass into solution. Reduction of catalysts obtained from LP, carried out with stirring, resulted in liberation of the reduced metal-polymer solution on the walls of the glass reaction vessel in the form of a solid ring above the level of the solvent. The catalyst was retained in the reaction solution by adding finely chopped glass fiber, onto which the metal-polymer was precipitated.

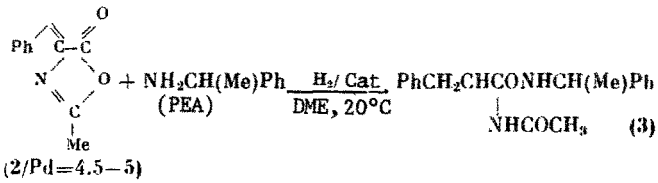
Catalyst Pd-6 was examined by RPES. The $3d_{5/2}$ spectrum of the Pd in a sample obtained by reacting *R*-SP with $PdCl_2$ in DME showed a single band, E_{fr} = 338.6 eV, showing that the $PdCl_2$ was fully bonded to the polymer (E_{fr} for $PdCl_2$ = 338.0 eV, and for $Pd(PEA)_2Cl_2$, 338.8 eV [3, 13]). When reduction was effected with hydrogen, in addition to the band at 338.6 eV, one appeared at 337.3 eV, the proportion of the reduced state being approximately 43%. It is difficult to establish the valence state of the Pd in the polymer, but its "monomeric" analog obtained by reducing a mixture (1:2) of $PdCl_2$ with PEA in chloroform has an E_{fr} value of 336.1 eV, rising to 337.8 eV on coordination with the highly conjugated molecule **2**. These findings, together with other information, showed that a zerovalent complex was formed, which was stabilized by the substrate [3-5]. Clearly, in this instance the aromatic polymer serves as the stabilizing agent. The catalysts were tested in the reductive solvolysis of **2**, and hydrogenation of its acyclic derivatives as in [1].

Reductive Aminolysis. This reaction is a combination of saturation of the C=C double bond, and cleavage of the ring in **2** by the chiral amine. It has previously been shown that when the reaction is carried out in DME, both these reactions occur synchronously without any of the possible intermediates separating from solution. The amine plays a dual role, namely as the chiral ligand for the catalyst and as a chiral reactant [1]. It might be expected that the use of a polymeric catalyst would enable these functions to be separated, so that the contributions of asymmetric induction of the enantioselective catalyst and the chiral nucleophile could be separately assessed. The test results are shown in Table 3, in which the first-order rate constants in substrate **2** (k) and its ratio to the g-atoms of Pd present in unit volume of the reaction solution (k_0) are taken as a measure of the activity of the catalyst. Comparison of the various catalyst samples shows that the catalysts are formed differently in the cross-linked and linear polymers. In the first case, it is important that the nucleophile (PEA) be present during reduction of the Pd(II). Addition to the reaction mixture when reduction was complete resulted in a decrease in the reaction rate and stereoselectivity (Nos. 7 and 9). In the case of the linear polymer, however, maximum activity is achieved when the PEA is added following reduction of the Pd(II), the order of addition of the PEA having little effect on the stereoselectivity of the reaction (Nos. 10-13).

The most active catalysts were those obtained from LP (Pd-5, Pd-8). The activity of the CP catalysts was similar to that of catalysts obtained by reduction *in situ* from $PdCl_2$ and PEA (the "monomeric" analog). All the catalyst samples were similar in their stereoselectivity, being slightly inferior to the "monomeric" analog.

Study of the optically active catalysts (Pd-6, Pd-8) showed that an excess of the diastereoisomer (*RR* or *SS*) was largely independent of the chirality of the nucleophile. This shows that the enantioselective properties of the catalyst (should it possess any) are not manifested in this reaction. It proceeds under the steric control of the nucleophile. It may therefore be assumed that even in the case of the "monomeric" catalyst the principal contribution to the stereoselectivity of the reaction is made by the chiral reagent, apparently at the stage of protonation of the semihydrogenated intermediate [2].

TABLE 3. Reductive Aminolysis of Metal-Polymer Catalysts

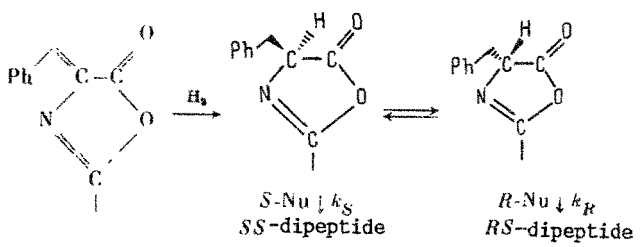


Comp. No.	Cat	Configuration of PEA	Order of addition of PEA*	$k \cdot 10^2$, min^{-1}	k_0, liter/(g-atom·min)	D.e.† 3, %
1	Pd-1	*S*	a	1.1	0.7	26 *SS*
2	Pd-2	*S*	a	1.0	0.8	28 *SS*
3	Pd-3	*S*	a	1.8	1.0	25 *SS*
4	Pd-4	*S*	a	1.7	1.2	30 *SS*
5	Pd-5	*S*	a	1.1	1.6	31 *SS*
6	Pd-5	*S*	b	2.3	3.2	32 *SS*
7	Pd-6	*R*	a	1.5	1.0	31 *RR*
8	Pd-6	*S*	a	1.0	0.8	27 *SS*
9	Pd-6	*R*	b	0.6	0.6	18 *RR*
10	Pd-8	*S*	b	3.8	5.4	28 *SS*
11	Pd-8	*R*	b	1.6	2.3	33 *RR*
12	Pd-8	*S*	a	1.6	2.3	30 *SS*
13	Pd-8	*R*	a	1.2	1.7	28 *RR*
14	$PdCl_2$+ PEA[14]	*S*	a	1.8	1.4	40 *SS*

*PEA added in an amount of 1.5 moles per mole of 2 either before (a) or after (b) reduction of the $PdCl_2$.

†D.e. is excess of the diastereoisomer.

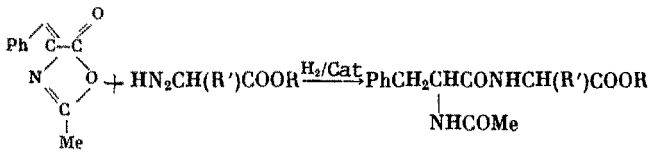
The results with other chiral nucleophiles (esters of α-amino acids) are shown in Table 4. Reductive aminolysis in the presence of esters of phenylalanine and valine is highly stereoselective as compared with PEA. However, relatively high values of the D.e. were obtained only in the presence of Et_3N. This effect has been reported previously in the catalytic activity of $PdCl_2$–amino acid ester systems [15]. The Et_3N functions by modifying the stepwise nature of the reaction (one of the single steps is changed to two steps with the intermediate formation of an azlactone), markedly accelerating racemization of the latter, and changing the aminolysis rate constant k_R/k_S [15, 16].



The similarities of the D.e. values obtained with the polymeric catalyst to those obtained with the catalytic system $PdCl_2$–*S*-PheOMe indicates that in the case of the polymeric catalyst the reaction is a two-step one proceeding via an intermediate, saturated azlactone. It is noteworthy than in order to obtain an active cross-linked catalyst, it must be reduced in the presence of a nucleophile, as in the case of PEA.

Reductive Hydrolysis of α-Acetamidocinnamic Acid Azlactone. Since, in reductive hydrolysis, the water functions as the nucleophile, it is difficult to see how an asymmetric effect could be expected, and in practice it is not seen. Reductive hydrolysis in the absence of polymer proceeds only to the half-way stage, whereupon the reaction ceases. In the presence of a metal-polymer catalyst, the reaction takes place rapidly to completion, and the catalyst may be re-used, albeit at a much-reduced rate for most catalyst samples. Table 5 shows the relevant data. The straight-line relationship of log *C* to *t* shows a break at 30-50% conversion, depending on the catalyst. The first-order rate constants *k* shown in this table correspond to the first region, except in the case of Pd-2, with which no such break was seen. The most active catalyst was Pd-3, and either of these two catalysts could be re-used with little reduction in reaction rates.

TABLE 4. Reductive Aminolysis of Acetamidocinnamic Acid Azlactone in the Presence of α-Amino acid Esters



(2/Pd=4.7. Et_3N added in amounts of 1 mole per mole of free aminoester)

Catalyst	Nucleophile			Et_3N	$k \cdot 10^2$, min^{-1}	k_0, liter/g-atom·min	E.d., %
	R′	R	configuration				
Pd-6	$PhCH_2$	Me	*R*	–	1.0	1.2	10 *SR*
Pd-6	$PhCH_2$	Me	*R*	+	1.2	1.4	51 *SR*
Pd-6	*i*-Pr	Me	*S*	–	0.6	0.7	4 *RS*
Pd-6	*i*-Pr	Me	*S*	+	1.4	0.9	57 *RS*
Pd-7	*i*-Pr	*t*-Bu	*S*	–	0.15	0.2	7 *RS*
Pd-6	*i*-Pr	*t*-Bu	*S*	+	0.5	0.6	53 *RS*
$PdCl_2$	$PhCH_2$	Me	*S*	–	3.8	2.9	18 *RS**
$PdCl_2$	$PhCH_2$	Me	*S*	+	2.6	2.0	47 *RS**

*[15].

TABLE 5. Reductive Hydrolysis

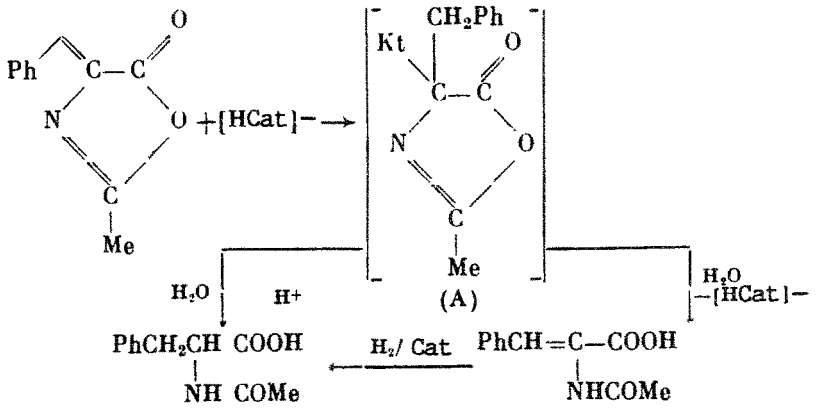
Catalyst	$k \cdot 10^2$, min^{-1}	k_0, liter/g-atom·min	τ, min	Conversion, %
Pd-1	4.4	2.8	120	100
Pd-2	1.7	1.4	120	100
Pd-3	8.5	5.0	136	92
Pd-4	1.8	1.5	180	100
Pd-6	3.7	2.8	350	82
Pd-8	2.5	3.5	220	78

TABLE 6. Changes in the Composition of the Reaction Mixture in the Reductive Hydrolysis of Acetamidocinnamic Acid Azlactone (Pd-1 catalyst)

τ, min	Composition of reaction mixture, %		
	AcPhe	ACA	2
12	30	48	22
30	44	56	–
60	52	48	–
120	66	34	–

The occurrence of a break in the kinetic plots indicates that the reaction changes in character with time. It has been found that, even in the earliest stages of the reaction, significant amounts of α-acetamidocinnamic acid (ACA) are present, which is then hydrogenated (Table 6), and using the cross-linked polymer the rate of hydrogenation of ACA in the absence of azlactone is much greater than the rate of hydrogenation of the latter.

It follows that on treatment with **2** a different catalyst is formed, probably by acylation of some of the polymer amino groups. It is noteworthy that ACA is formed only during hydrogenation, and not by the polymer or metal-polymer, as might appear at first sight. Over a period of 2 h, when reductive hydrolysis was 66% complete, in the absence of hydrogen but in the presence of polymer or metal-polymer in DME, **2** remains unchanged (according to IR and PMR). These observations suggest the following mechanism for reductive hydrolysis:



The azlactone reacts with the hydride form of the reduced catalyst [1, 2] to give the σ-alkyl intermediate (A), which then reacts in one of two ways: 1) by adding a proton and a water molecule to give the final product AcPhe, or 2) by adding a water molecule and losing the catalyst to give ACA, which is in turn hydrogenated in the presence of this catalyst.

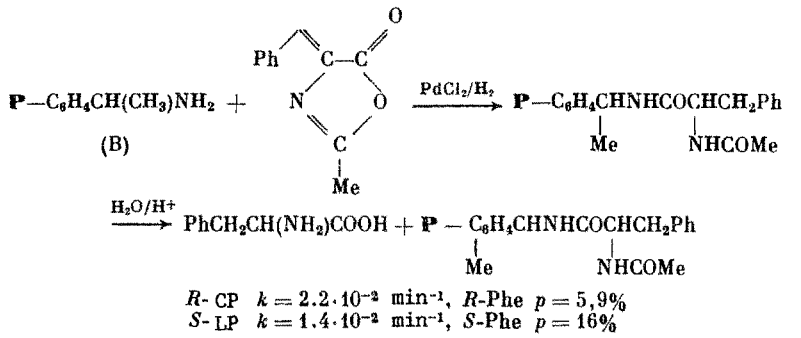
Hydrogenation of Acetamidocinnamic Acid and Its Methyl Ester. The hydrogenation of ACA and its methyl ester takes place readily in the presence of the above-mentioned catalysts, but without any appreciable enantioselectivity. The results are shown in Table 7. The rate of hydrogenation in the presence of catalysts on cross-linked polymers (Pd-1, Pd-3, Pd-6) is greater than that on catalysts with linear polymers (Pd-5, Pd-8). It is noteworthy that the catalyst may be used for the hydrogenation of new portions of substrate with little loss of activity, although when the catalyst is isolated from the reaction mixture in the presence of air, it is deactivated.

As is apparent from Table 7, the activity of the catalysts on cross-linked polymers is comparable with that of palladium black, obtained by reducing $PdCl_2$ in the absence of polymer. It may be that with cross-linked polymers, clusters of metallic palladium are formed, which are retained in the nodes of the polymer structure. However, examination of the catalyst Pd-6 by XPS (see above) showed that, under our conditions, reduction proceeded only to the half-way stage, and to a state which did not correspond to metallic Pd [more likely, Pd(0) complexed with the polymeric amine]. Of course, in order to assess the effect of the polymer ligand on the activity of the catalyst, it was necessary to compare the polymeric catalyst with one obtained by reducing $PdCl_2$ in the presence of PEA. This comparison showed that the activity of the cross-linked metal-polymers was some twenty times greater than that of the "monomeric" catalyst, although in the absence of the stabilizing effect of the polymer (and/or) **2**, we obtained metallic palladium with surface-adsorbed amine.

Hydrogenation of Chiral Precursors of Amino Acids. In spite of the absence of appreciable enantioselective properties in these catalysts, it could be that double asymmetric induction might be detected in the hydrogenation of chiral products of the aminolysis of **2**. The results of hydrogenation of ACA *S*- and *R*-α-phenylethylamides are shown in Table 8. In the hydrogenation of unsaturated amides, the polymeric catalysts were much less active than the "monomeric" analog, and the linear polymer was inferior to the cross-linked compound. In the latter case, both enantiomers of the substrate were hydrogenated at essentially the same rate, but the diastereoselective effect was greater in the hydrogenation of the *S*-amide, which is evidence for double asymmetric induction, even if only to a small extent. This effect was not seen with the linear polymer, perhaps as a result of its low optical purity. It is noteworthy that addition of PEA to polymeric catalysts reduces their activity and stereoselectivity, unlike the "monomeric" analog.

In the hydrogenation of dehydrodipeptides (Table 9), it was found that the enantiomers were hydrogenated at quite different rates, but evidence for double asymmetric induction was difficult to obtain as a result of the low absolute values of the D.e.

Chiral Polymers as Reactants in Reductive Aminolysis. When reductive aminolysis was carried out with polymers, functioning both as ligands and as reactants, polymeric amides were obtained, as shown by IR and by subsequent acid hydrolysis to give phenylalanine.



Bearing in mind that the optical purity of *S*-LP is 55%, and assuming a straight-line relationship between the optical yield in the reaction and the optical purity of the reactant, it may be concluded that the optical yield in the reaction with *S*-LP is 29%. This is close to the value obtained for reductive aminolysis with PEA (Table 3). With the cross-linked polymer there is considerable decrease in stereoselectivity. When the reaction was carried out in two stages (preparation of the saturated azlactone in the presence of the $PdCl_2-Et_3N$ system, followed by aminolysis with the solid-phase chiral reactant B) gave *R*-Phe with $p = 4\%$.

Hence, polymeric carriers to a large extent stabilize the low-valent state of the palladium in these catalysts. A chiral polymeric catalyst shows the double asymmetric induction effect in the hydrogenation of *R*- and *S*-1-phenylethylamides of acetamidocinnamic acid. The use of chiral polymeric catalysts has shown that in the reductive aminolysis of azlactones by chiral amines the chiral nucleophile makes an important contribution to the stereoselectivity of the reaction.

EXPERIMENTAL

PMR spectra were obtained on a Bruker WP-250 spectrometer (δ, ppm), IR spectra on a Perkin-Elmer M-577 spectrophotometer, UV spectra on a Specord M-40 spectrophotometer, and XPS on a Kratos ES-200B spectrometer. The optical rotation was measured with an AI EPO photoelectronic polarimeter, and GLC analyses were carried out on a Biokhrom-1 chromatograph, FID on a glass capillary column with N-cocosanoyl-S-valine *tert*-butylamide as the chiral phase [17].

Reactants. $PdCl_2$, pure, *S*-α-phenylethylamine $[\alpha]_D^{20} -39°$, *R*-α-phenylethylamine $[\alpha]_D^{20} +38.5°$. Acetamidocinnamic acid azlactone **2**, mp 150°C (from acetone), acetamidocinnamic acid, mp 192°C, methyl acetamidocinnamate (obtained as in [18]), mp 123-124°C (from methanol + benzene). Acetamidocinnamic acid *S*- and *R*-phenylethylamides were obtained as in [19], mp 195-197°C (from absolute alcohol), $[\alpha]_D$ +43° and −36° (*c* 1.4, EtOH), respectively. Methyl esters of the *S*- and *R*-methyl esters of phenylalanine hydrochlorides, $[\alpha]_D$ −4.6 and +4.5° (*c* 5, H_2O), respectively. Hydrochlorides of the tert-butyl esters of *S*-valine and *S*-phenylalanine, $[\alpha]_D$ +20.7 and −41.6° (*c* 2, EtOH), respectively.

4-(β-Bromoethyl)acetophenone (4) was obtained as in [20], but using dichloromethane in place of CS_2, and reducing the reaction temperature to −10°C, yield 80-85%, bp 115-120°C (0.1 mm), n_D^{20} 1.5740.

4-(β-Bromoethyl)acetophenone Oxime (5). Anhydrous AcONa (3.7 g, 0.045 mole) and hydroxylamine hydrochloride (3.15 g, 0.045 mole) were boiled in 100 ml of absolute ethanol for 2 h, cooled, and the NaCl filtered off. To the filtrate was added 3.75 g (0.016 mole) of **4**, and the mixture kept for 24 h. It was then treated with 150 ml of water, and the solid filtered off, washed with cold alcohol and with water, and dried to give 4 g (96%) of product, mp 111-112°C (from alcohol). PMR spectrum ($CDCl_3$), 2.3 s (3H, CH_3), 3.15 t (2H, CH_2 arom.), 3.60 t (2H, CH_2Br), 7.10-7.80 (4H, arom.), 9.5 s (1H, OH).

1-(4-β-Bromoethylphenyl)ethylamine Hydrochloride (6). In a hydrogenation vessel were placed 0.29 g of $PdCl_2$ and 100 ml of 1 *N* HCl in absolute methanol, reduced with hydrogen, and 6.45 g of **5** in 80 ml of 1*N* HCl in methanol added. When uptake of hydrogen had ceased (~9 h), the catalyst was filtered off and washed with methanol, and the combined filtrates were evaporated under reduced pressure and the residue washed with ether to give 92% of product, mp 162-169°C (from chloroform−ether).

Boc-1-(4-β-Bromoethylphenyl)ethylamine (7) was obtained as described in [21]. To a solution of 2.76 g (12.7 mmoles) of Boc pyrocarbonate in 20 ml of dioxane was added 3.35 g (12.7 mmoles) of **6** and 17 ml of 1*N* NaOH, the mixture stirred for 3 h, and the solid filtered off, washed with a mixture of dioxane and water, and dried to give 90% of product, mp 119-122°C. PMR spectrum (DMSO-d_6) 1.28 CH_3CH + 1.36 CH_3C (12H), 3.10 t (2H, CH_2 arom.), 3.70 t (2H, CH_2Br), 4.57 q (1H, CH), 7.22 (4H, arom.).

TABLE 7. Hydrogenation of Acetamidocinnamic Acid and Its Methyl Ester in the Presence of Pd-Polymer Catalysts

Catalyst	AcΔPhe				AcΔPheOMe			
	τ, min	conversion, %	$k \cdot 10^2$, min^{-1}	k_0, liter/g-atom·min	τ, min	conversion, %	$k \cdot 10^2$, min^{-1}	k_0, liter/g-atom·min
Pd-1	12[a]	–	43	46	–	–	–	–
	100	100	16	17				
Pd-3	–	–	–	–	15[a]	100	42	26
					40	100	26	16
Pd-6	40	100	27	29	13	100	33	35
Pd-5	60	100	4	4.1	60	97	4	5.5
Pd-8	66[b]	74	2	2.8	67[b]	78	2	2.8
	170	100	–	–	150	100	–	–
$PdCl_2$	40	100	44	31				
$PdCl_2$+ PEA 1 : 2.3	53[b]	78	2	1.4				
	300	100						
$PdCl_2$+ PEA 1 : 6.7	320	100	1	1.4				

[a]Hydrogenation of two successive portions of substrate.
[b]Samples withdrawn at the times shown.

TABLE 8. Hydrogenation of Acetamidocinnamic Acid α-Phenylethylamides

$$PhCH{=}C(NHCOMe)CONHCH(Me)Ph \xrightarrow[DME]{H_2/Cat} PhCH_2CH(NHCOMe)CONHCH(Me)Ph$$

(Substrate /Pd=4–5, C_0=0.04 *M*, reaction complete after 4–5 h)

Catalyst	PEA/Pd	Configuration		$k \cdot 10^2$, min^{-1}	k_0, liter/(g-atom·min)	D.e., %
		PEA	substrate			
Pd-6	–	–	*S*	2.6	3.4	45 *RS*
	–	–	*R*	2.5	3.1	31 *SR*
	1.7	*R*	*S*	0.5	0.6	12 *RS*
	1.7	*S*	*S*	0.3	0.4	20 *RS*
	1.7	*R*	*R*	0.7	0.9	19 *SR*
	1.7	*S*	*R*	0.3	0.4	21 *SR*
Pd-8	–	–	*R*	0.6	0.8	32 *SR*
	–	–	*S*	0.9	1.3	30 *RS*
	6.6	*S*	*S*	0.4	0.6	13 *RS*
	2.6	*S*	*R*	0.5	0.7	13 *SR*
$PdCl_2$ [1]	–	–	*S*	7.7	6.4	20 *RS*
	7.5	*S*	*S*	7.7	6.4	40 *RS*
	7.5	*R*	*S*	1.9	1.6	12 *RS*

TABLE 9. Hydrogenation of the Methyl Ester of Acetyldehydrophenylalanylphenylalanine

$$PhCH{=}C(NHCOMe)CONHCH(CH_2Ph)COOMe \xrightarrow[DME]{H_2/Cat} AcPhePheOMe$$

(Substrate /Pd=4)

Catalyst	Configuration of substrate	τ, min	Conversion, %	$k \cdot 10^2$, min^{-1}	k_0, liter/(g-atom·min)	D.e, %
Pd-6	*S*	150	100	5.5	6.6	16 *RS*
	R	360	100	1.5	2.0	5 *SR*
Pd-8	*S*	300	90	0.4	0.6	10 *RS*
	R	300	100	1.1	1.6	6 *SR*

Boc-1-(4-Vinylphenyl)ethylamine (8). To a solution of 1 g of sodium in 100 ml of absolute ethanol was added 4.75 g of **7**, the mixture boiled under argon for 30 min, cooled, and poured into 140 ml of water and ice, to which had been added 70 ml of ether. The ether layer was separated, the aqueous layer extracted with ether (3 × 70 ml), and the combined extracts

dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 90% of product, mp 94-98°C. PMR spectrum (DMSO-d_6), 1.30 d (3H, CH_3CH), 1.37 s (9H, CH_3C), 4.60 m (1H, CH), 5.18-6.7 (3H, AMX spectrum, vinyl, δ_A 5.21, δ_M 5.78, δ_X 6.70), 7.22-7.45 (4H, arom.).

***R,S*-1-(4-Vinylphenyl)ethylamine Hydrochloride (1·HCl).** A solution of 3.8 g of **8** in 4*N* HCl in dry dioxane was kept for 2.5 h, then the solvent was removed, and the residue dried *in vacuo* over KOH, and washed with ether to give 93% of product, mp 181-185°C. PMR spectrum (DMSO-d_6), 1.50 d (3H, CH_3CH), 4.35 q (1H, CH), 5.25-6.80 (3H, AMX spectrum, vinyl, δ_A 5.28, δ_M 5.87, δ_X 6.72), 7.5 (4H, arom.), 8.7 (3H, NH_3^+).

***R,S*-1-(4-Vinylphenyl)ethylamine (1).** To an aqueous solution of 18 g of **1**·HCl was added 100 ml of ethyl acetate, the mixture cooled with ice, and 50% NaOH solution added to pH 10. The ether layer was separated, and the aqueous layer extracted with ethyl acetate (3 × 100 ml). The combined extracts were dried over $MgSO_4$, the solvent removed under reduced pressure, and the residue distilled at 0.01 mm, temperature 56°C, to give 65% of product. PMR spectrum ($CDCl_3$), 1.38 d (3H, CH_3CH), 1.60 (2H, NH_2), 4.1 q (1H, CH), 5.22-6.80 (3H, AMX spectrum, vinyl, δ_A 5.22, δ_M 5.72, δ_X 6.71), 7.28-7.42 (4H, arom.).

***R*-1-(4-Vinylphenyl)ethylamine (*R*-1).** Resolution of **1** (9 g) was carried out with *S*-(−)malic acid [8, 9], to give 2.4 g of *R*-**1**, $[\alpha]_D$ = +31.8° (*C* 1, $CHCl_3$), p = 88% (cf. [9]: $[\alpha]_D$ = +36.2°).

***S*-1-(4-Vinylphenyl)ethylamine (*S*-1).** Obtained from **1** malate after removal of *R*-**1** malate. The free base was obtained and fractionated to give 6 g of **1**, which was resolved with *R,R*-(+)-tartaric acid [8] to give 1.85 g of *S*-**1**, $[\alpha]_D$ = −19.9°, p = 55%.

The cross-linked copolymers *R,S*-CP and *R*-CP were obtained by radical polymerization in suspension [22]. In a special reactor [6] were placed 2.09 g of **1**, 4 g of styrene, 0.28 g of divinylbenzene, 9 ml of toluene, and 90 ml of deaerated water containing 0.9 g of polyvinylpyrrolidone and 0.2 g of Triton-100, and the mixture stirred under nitrogen at a linear velocity of 42-45 m/min, then 0.095 g of azobisisobutyronitrile (AIBN) was added and the mixture heated for 26 h at 70°C. The resulting polymer was washed with water, acetone, and methanol, and dried under reduced pressure to give a yield of 70% (Table 1).

The straight-chain copolymers *R,S*-LP and *S*-LP were obtained in a sealed ampul containing **1**, styrene, toluene, and AIBN as initiator, at 70°C. The copolymer was precipitated with methanol, and dried by lyophilization from a benzene solution (see Table 1).

Preparation of Catalysts. Pd-1. The polymer *R,S*-CP (0.5 g) was shaken vigorously with 0.15 g of $PdCl_2$, then 25 ml of DME was added and the mixture stirred for 15-20 h and filtered. The resulting Pd(II) [MP-Pd(II)] complex was air-dried, and reduced *in situ* with hydrogen (see below). Pd-6 was obtained similarly, from *R*-CP.

Pd-2. M*p*-Pd(II) was treated with 1*N* HCl for 24 h, then washed with water and dried to give a polymer containing 8% of $PdCl_2$ which was not reduced by hydrogen. Reduction was effected with $NaBH_4$.

Pd-3. *R,S*-CP (1 g) and $PdCl_2$ (0.3 g) were boiled for 24 h in 50 ml of DME, filtered, air-dried, and reduced *in situ* with hydrogen.

Pd-4. To a solution of 0.16 g of (π-all-$PdCl_2$) in 25 ml of DME was added 0.5 g of *R,S*-CP. The mixture was stirred for 24 h, filtered, washed until the washings were colorless, and air-dried. The polymer contained 75% of the (π-all-$PdCl_2$) used in the reaction. Comparisons of the IR spectra of the polymer, the metal-polymer, and (π-all-$PdCl_2$) in KBr disks indicated the formation of a polymer complex with cleavage of the Pd−Cl bonds in the bis(π-allylpalladium chloride) [ν_{Pd-Cl} in the metal-polymer was 276 cm^{-1}, whereas in (π-all-$PdCl_2$) it was 256 cm^{-1}]. Reduction *in situ* was effected with hydrogen.

Pd-5. *R,S*-LP (50 mg) and $PdCl_2$ (10 mg) and a small amount of glass fiber were stirred in 5 ml of DME for 1 h, then reduced *in situ* with hydrogen. Catalyst Pd-8 was obtained similarly, from *S*-LP.

Pd-7 was obtained as for Pd-6, and contained 4.6% of $PdCl_2$. It was reduced with $NaBH_4$.

Reductive Aminolysis. a. In a hydrogenation vessel were placed 100 mg of MP-Pd(II), and 5 ml of DME, and left to swell for 0.5-1 h, then 0.1 ml of PEA was added, the system flushed out with hydrogen, and stirring commenced. When reduction was complete (the color of the catalyst changed from yellow-brown to gray-black over 15-30 min), a solution of 0.1 g of **2** and 2.5 ml of DME were added to the reactor contents. The rate of the reaction was shown by the rate of uptake of hydrogen. When the reaction was complete, the catalyst was filtered off, and the filtrate passed through a column of DOWEX 50 × 8 in the H^+ form, and evaporated to dryness. The product was analyzed by PMR in $CDCl_3$ or CD_3OD.

b. MP-P(II) was reduced in DME as described above, then treated successively with **2** and PEA.

c. When the reaction was carried out with amino acid esters, prior to reduction the amino acid ester hydrochloride and triethylamine were added in ratios of (1:1) or (1:2), and when reduction was complete, **2** was added (ratio of **2**:amino ester = 1:1). The reaction product was warmed up as above.

Solid-Phase Reductive Aminolysis. *R*-CP (0.4 g, 0.87 mg-equiv) and 19 mg of $PdCl_2$ were stirred in 10 ml of DME for 20 h, then reduced with hydrogen, 80 mg (0.43 mmole) of **2** in 4 ml of DME and 0.4 ml of water added, and hydrogenation continued for 6 h, to give 0.45 g of polymeric amide (by IR), the solution containing only traces of AcPhe. The polymeric amide was hydrolyzed as follows. A mixture of the amide (0.23 g) and 6*N* HCl (10 ml) was maintained at 150°C under argon for 7 h, then the polymer was filtered off, washed with HCl, and the hydrolyzate evaporated to dryness and kept *in vacuo* over KOH, to give 34.6 mg of Phe·HCl (80% yield calculated on **2**). Enantiomeric excess was determined by GLC as TFAPheOiPr. The reaction with *S*-LP was carried out similarly, with the addition of glass fiber but without the addition of water.

Reductive Hydrolysis. In a hydrogenation vessel were placed 100 mg of MP-P(II) and 5 ml of DME, reduction carried out with hydrogen, and **2** added in 2.5 ml of DME and 0.5 ml of water. When the reaction was complete, the catalyst was filtered off, and the filtrate evaporated and analyzed by PMR. When Pd-6 of Pd-8 were used, the AcPhe obtained was converted into AcPheOMe, and analyzed by enantiomeric GLC [17].

The kinetic data were treated by an equation which was first order in respect of substrate. The errors in determinations of rate constants were 15-20 rel. %.

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