Synthesis of diastereomeric 1,2-disubstituted ferrocenes of high optical purity from racemic α-dimethylaminoalkylferrocenes

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A novel approach to the synthesis of optically active 1,2-bifunctional ferrocenes of high optical purity with any combination of absolute configurations of the chiral center and the chiral plane has been proposed. The method is based on asymmetric cyclopalladation of racemic α-dimethylaminoethylferrocene under the conditions of its kinetic resolution.

Key words: asymmetric cyclopalladation; kinetic resolution.

In recent years, optically active 1,2-bifunctional derivatives of ferrocene have acquired wide use in asymmetric catalysis either as catalysts themselves or as inductor ligands in metallocomplex catalysts. The enantioselective alkylation of carbonyl compounds with dialkylzinc in the presence of amino alcohols of the ferrocene series and the synthesis of enantiomeric binaphthyls catalyzed by nickel and palladium complexes incorporating optically active ferrocenes as ligands are examples of their successful application.[1]

The currently used optically active ferrocenes are mostly prepared from *N*,*N*-dimethyl-1-ferrocenylethylamine (**1**) and contain both a chiral center and a chiral plane. The practical use of these compounds in asymmetric synthesis became possible owing to the works of I. Ugi *et al.* This group developed a method for the resolution of compound **1** into enantiomers *via* diastereomeric tartrates[2] and found that lithiation of these enantiomers occurs with a high degree of diastereoselectivity yielding mostly either the R_cS_p- or S_cR_p-diastereomer* depending on the configuration of the starting amine.[3] Subsequent reactions with electrophiles and transformation of the amino group made it possible to prepare a wide array of optically active ferrocenes.

In the laboratory where the present work was carried out, a similar steric course was established for the cyclopalladation of the enantiomers of compound **1**, though this reaction is somewhat less selective.[4] The peculiarities of the reactivity of organopalladium compounds supplement the possibilities of lithium derivatives and enhance the usefulness of the starting amine as a source of optical activity in the ferrocene series.

However, though this method is in general use, it has some shortcomings. First of all, it is necessary to start from an enantiomeric amine, so that the preliminary resolution of the racemate into its antipodes, the conditions of which are specific for each particular amine, is a mandatory step. In addition, the problem of preparing the second diastereomer remains essentially unsolved, since the only pathway to it offered by Japanese chemists seems to be rather cumbersome.[5]

We developed an alternative approach to optically active ferrocenes starting from a prochiral amine based on asymmetric cyclopalladation of dimethylaminomethylferrocene. This technique affords optically active, chelate-type σ-palladium derivatives of the latter. The strategy used is the opposite of that applied by Ugi: first, a chiral plane with a particular configuration is formed. In the course of further transformations accompanied by the appearance of a new element of chirality, the chiral plane causes asymmetric induction (of a center, an axis, or a plane).

Results and Discussion

Asymmetric cyclopalladation of homochiral N,N-dimethyl-1-ferrocenylethylamine (1)

The asymmetric cyclopalladation of chiral *N*,*N*-dimethyl-1-ferrocenylalkylamines, which combines both of the above-mentioned approaches, seemed to be promising with regard to the development of a versatile method for preparing optically active ferrocenes that have both a chiral center and a chiral plane. In this connection, by looking at *N*,*N*-dimethyl-1-ferrocenylethylamine (**1**), we studied the overall effect exerted by an intramolecular chiral center and a chiral catalyst as asymmetric inductors in the creation of a chiral plane. A

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* Hereinafter, the subscripts denote the element of chirality to which the configuration given refers: c is the center, p is the plane.

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number of possible stereochemical consequences of their competition is believed to be of interest for preparative purposes.

It was found previously[4] that cyclopalladation of the enantiomers of compound **1** in the presence of sodium acetate occurs diastereoselectively to yield a product with a diastereomeric ratio of 85 : 15. The steric outcome of the reaction was determined by chemical correlation and then confirmed by X-ray diffraction analysis. The *R*-(+)-configuration of the starting amine leads predominantly to the chiral plane with the *S*-(−)-configuration, and *vice versa*, cyclopalladiation of the *S*-(−)-amine predominantly affords the diastereomer with the *R*-(+)-configuration of the chiral plane (Scheme 1).

The planar chirality makes the main contribution to the optical rotation of the products, such that the sign of optical rotation is determined by the configuration of the chiral plane and its magnitude depends primarily on the enantiomeric purity with respect to the plane. The maximum magnitudes of the specific rotation $[\alpha]_D$ for optically pure $R_c{}^*S_p{}^*$- and $R_c{}^*R_p{}^*$-diastereomers were found to be 479° and 587°, respectively.[4]

On the other hand, enantiomers of the planarly chiral palladium derivative of prochiral dimethylaminomethylferrocene with optical purity as high as 90 % may be prepared by cyclopalladation in a slightly alkaline medium in the presence of sodium salts of optically active *N*-acetylvaline or -leucine (see Scheme 1). The product with the *R*-(+)-configuration is formed in the presence of *S*-amino acid salts; the use of *R*-amino acids results in the chelated palladium σ-complex with the *S*-(−)-configuration of the chiral plane.[6]

The stereochemical outcome of the asymmetric cyclopalladation of homochiral compound **1** in the presence of an amino acid, whose inducing effect coincides in direction with the induction by the center, is more or less obvious: the diastereoselectivity should approach 100 %. When these effects are opposite, the steric course of the reaction is difficult to predict.

The results of a series of experiments on the asymmetric cyclopalladation of (*S*)-**1** (Na-salt of an optically active *N*-acetylamino acid, slightly alkaline medium) are listed in Table 1.

On the basis of the sign and the magnitude of optical rotation of reaction product **2** one may assign the absolute configuration of the chiral plane predominantly formed and determine the absolute configuration of the prevailing diastereomer.

Though all of the experiments were carried out with

Scheme 1

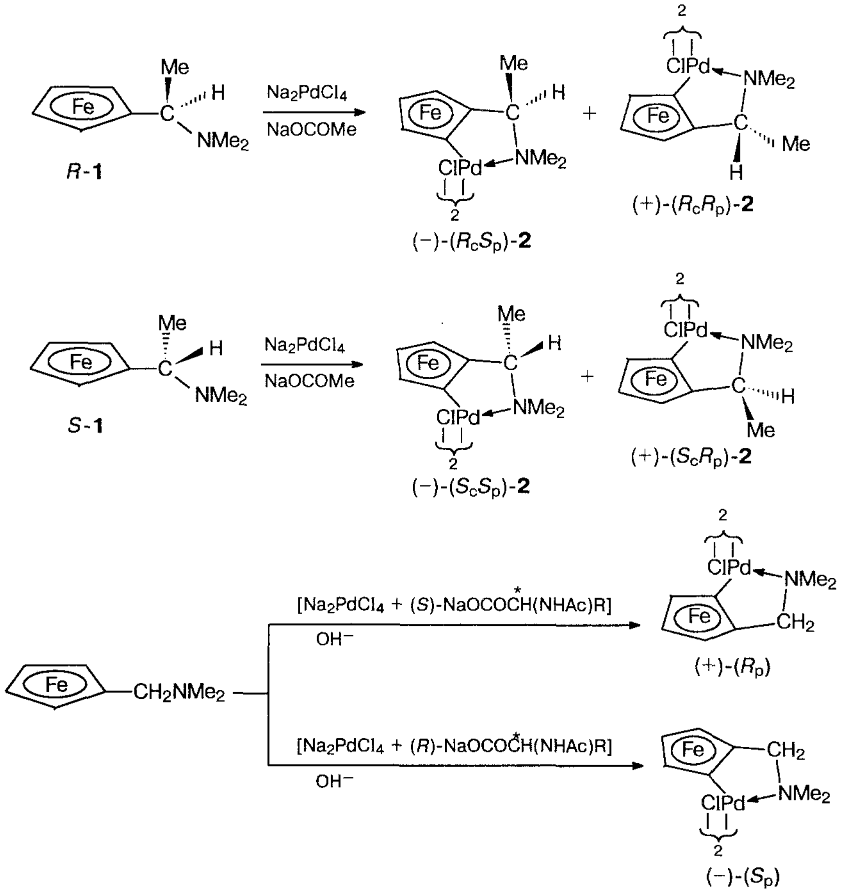


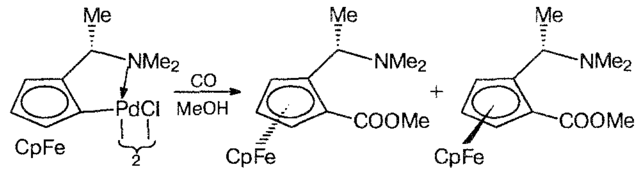
Table 1. Stereochemistry of the cyclopalladation of (*S*)-**1** as a function of the pH of the medium and the absolute configuration of the amino acid Na-salt used as the catalyst

pH	Amino acid (configuration)	Yield of the product (%)	$[\alpha]_D^{20}$ (CH_2Cl_2) /deg	Absolute configuration of the prevailing diastereomer
7.45	*N*-Acetylvaline (*R*)	91.5	−229.9[a]	S_cS_p
7.62	The same (*R*)	76.2	−151.8[b]	S_cS_p
7.97	»» (*R*)	79.0	−255.2[a]	S_cS_p
7.62	»» (*S*)	69.0	+335.0[a]	S_cR_p
7.65	»» (*S*)	59.4	+380.0[a]	S_cR_p
7.66	*N*-Acetylleucine (*S*)	76.5	+495.0[c]	S_cR_p
7.85	The same (*S*)	55.0	+514.0[a]	S_cR_p
7.74	»» (*S*)	69.0	+482.0[d]	S_cR_p
7.80	»» (*R*)[e]	93.2	−209.0[d]	S_cS_p
7.50	»» [f]	86.0	+51.9[e]	S_cR_p

[a] The amine with $[\alpha]_D$ −13.7°. [b] The amine with $[\alpha]_D$ −14.6°. [c] The amine with $[\alpha]_D$ −13.6°. [d] The amine with $[\alpha]_D$ −13.3°. [e] *ee* 88.6 %. [f] Racemic.

the amine of the same absolute configuration, *S*, the sign of the optical rotation of the products varied depending on the configuration of the catalyst used in full agreement with the results obtained in the asymmetric cyclopalladation of prochiral dimethylaminomethylferrocene. The sign was positive when the *S*-configuration of the catalyst was used and negative when its *R*-configuration was used, which corresponds to the predominant formation of S_cR_p- or S_cS_p-diastereomers of **2**, respectively. Other features of this reaction, namely, the increase in the degree of asymmetric induction, as the pH increases (up to a definite value) and on going from *N*-acetylvaline to *N*-acetylleucine, have also been observed. It may be concluded from the results obtained that the catalyst plays the crucial role in the determination of the steric course of the cyclopalladation of homochiral **1** under the conditions of asymmetric catalysis. The magnitude of the optical rotation of compound **2** in which the inducing effects of the chiral center and the catalyst act in opposite directions, indicates that these effects compete, and, as indicated by the sign of optical rotation, the effect of the catalyst prevails. In this case, the S_cS_p-diastereomer of compound **2**, which corresponds to the minor product of lithiation, is predominantly formed. The apparent exception of some of the values of optical rotation (see, for example, line 2 in Table 1) is due to the fact that the enantiomeric purity of the starting *S*-**1** was not always 100 % and, therefore, the resulting diastereomers were not optically pure.

When induction by the center and induction by the catalyst act in the same direction, the diastereomeric and optical purity of the isolated product approached 100 %. To confirm this conclusion and to determine the diastereomeric compositions in other cases, we carried out carbonylation of some of the resulting palladium derivatives in methanol. The diastereomeric amino acid esters **3** formed were separated by chromatography on SiO_2. The results are presented in Table 2.



2 (S_cS_p+S_cR_p) **3** (S_cS_p) **3** (S_cR_p)

The replacement of palladium by an ester group occurs with the complete retention of the absolute configuration of the chiral plane. The relative priority of the substituents also is not changed. Therefore, the configuration of the chiral plane in the prevailing diastereomer of amino acid ester **3** results from the sign of the optical rotation of the starting dimer of compound **2**, and the opposite configuration is attributed to the chiral plane in the second diastereomer of compound **3**.

In a qualitative sense, the results of the carbonylation of dimers **2** are fully consistent with the analysis of their

Table 2. Carbonylation of palladium derivatives **2**, prepared from (*S*)-*N*,*N*-dimethylamino-1-ferrocenylethylamine **1**, in MeOH

The optical purity of the starting (*S*)-**1**	Cyclopalladation catalyst	$[\alpha]_D$ **2** /deg	The overall yield of amino acid esters (%)	The yield of S_cS_p diastereomer (%)	$[\alpha]_D$ S_cS_p /deg	The yield of S_cR_p diastereomer (%)	$[\alpha]_D$ S_cR_p /deg	The S_cS_p : S_cR_p diastereomeric ratio
100	(*R*)-*N*-Acetylvaline Na-salt	−151.8	36.5 (48 % starting amine)	24.1	−88.7	12.4	+47.2	1.94 : 1
93.7	(*R*)-*N*-Acetylleucine Na-salt	−209.0	55.0	35.4	−97.0	19.6	+25.3	1.8 : 1
100	Racemic *N*-acetylleucine Na-salt	+51.9	71.8	22.5	−88.8	49.3	+42.8	1 : 2.2
100	$NaOCOCH_3$	+326.0	—	—	—	—	—	1 : 5.7
93.7	(*S*)-*N*-Acetylleucine Na-salt	+482.0	87.6	—	—	87.6	+35.7	0 : 100

diastereomeric composition based on the sign of optical rotation. In fact, the dimer prepared when the inducing effects of the center and the catalyst acted in the same direction afforded only one diastereomer of **3**, in this case, the S_cR_p-diastereomer. On the other hand, the dimer resulting from the competition of the above-mentioned effects yielded a mixture of two diastereomers in which the other diastereomer with S_cS_p-configuration prevails.

The quantitative data require a special comment. In particular, they imply that the yield of amino acid esters depends on the diastereomeric composition of the starting palladium derivative. When the dimer was obtained with competing stereodirecting effects of the catalyst and the center, the yield was lower (see lines 1 and 2 in Table 2) and seemed to be insufficient to draw any conclusions about the stereochemistry of the reaction. The parent amine was formed as a by-product. The reason for its formation is probably the different stabilities of the diastereomeric σ-palladium complexes under the conditions of carbonylation, which do not exclude protolysis of the carbon—palladium bond (protic solvent, formation of HCl) or dissimilar possibilities for the formation of a carbon—carbon bond. However, the deviation of the ratio between the diastereomeric amino acid esters **3** from the initial diastereomeric composition of the cyclopalladation product may only occur in favor of the S_cR_p-diastereomer of **3**, which is apparently more stable under the experimental conditions used (see lines 3 and 5, Table 2). In fact, judging by the sign and the magnitude of optical rotation of the starting palladium-containing dimer, the proportion of the S_cR_p-diastereomer increases as the R_p-inducing effect of the catalyst becomes more pronounced (see Table 2). Simultaneously, the overall yield of amino acid esters steadily increases.

Two more experimentally observed facts should also be emphasized.

The first of these is the decrease in the optical rotation of the S_cR_p-diastereomer of **3** prepared from the product of the cyclopalladation of enantiomerically impure amine **1** (see lines 2 and 5 in Table 2). The sharpest decrease occurs in the case when the starting palladium dimer is prepared under the conditions of competing inductors [(*S*)-center → (*R*)-plane, (*R*)-catalyst → (*S*)-plane]. This may be rationalized by taking into account the fact that the inducing effects of the center and of the catalyst during cyclopalladation of (*R*)-**1**, which is an admixture in the starting (*S*)-**1**, on the contrary, coincide, so that it yields only the R_cS_p-diastereomer of dimer **2**. The relative proportion of this diastereomer in the expected enantiomeric S_cR_p-**2** increases, since under the given conditions the latter is a minor reaction product. Consequently, the optical rotation of the S_cR_p-diastereomer of the amino acid ester formed in the carbonylation dramatically decreases.

On the other hand, the optical purity of the S_cS_p-diastereomer of **3** formed from the corresponding S_cS_p-**2** must be close to 100 %. In fact, to obtain any noticeable amount of the R_cR_p-diastereomer of **2** under the conditions of cyclopalladation, which are so unfavorable for its formation, (*S*)-**1** must contain a considerable amount of the (*R*)-enantiomer, since both an (*R*)-chiral center and an (*R*)-catalyst induce the appearance of an (*S*)-chiral plane.

To avoid possible errors, the maximum specific rotation values for amino acid esters **3** should be determined only from experiments that involve optically pure amine **1**. Based on the data obtained in the present work, $[\alpha]_{D_{max}}$ values were taken to be 93±4° and 45±2° for the R^*R^*- and R^*S^*-diastereomers of **3**, respectively.

The second observation is that the steric courses of the reactions catalyzed by achiral NaOCOMe and by the Na-salt of chiral *N*-acetylleucine in the racemic form are different.

When the Na-salt of racemic *N*-acetylleucine is used in cyclopalladation (see Table 2), two parallel reactions, each of them involving catalysts with opposite absolute configurations, may be considered. The resulting ratio of diastereomers of **2** and of the carbonylation products should correspond to the sum of the effects found for each of the enantiomers of the catalyst in separate runs. This can be calculated from the data obtained in the experiments with the (*R*)- and (*S*)-catalysts:

$$0.5 \cdot S_cR_p + 0.5(0.64\ S_cS_p + 0.36\ S_cR_p) = \\ = 0.68\ S_cR_p : 0.32 S_cS_p.$$

This is very close to the experimentally found value: $0.69 S_cR_p : 0.31 S_cS_p$.

These results make it possible to consider the asymmetric cyclopalladation of racemic compound **1**.

Asymmetric cyclopalladation of racemic N,N-dimethyl-1-ferrocenylethylamine under conditions of kinetic resolution

Based on the postulate that the enantiomers of **1** react independently of one another and taking into account the results of their asymmetric cyclopalladation in the presence of the same catalyst, one would expect that under similar conditions racemic **1** would afford only three of the four possible diastereomers. For example, when the (*S*)-configuration of the catalyst is used, the S_cR_p-, R_cR_p-, and R_cS_p-diastereomers of compound **2** are the major reaction products (listed in order of decreasing proportions). Thus, the optical purity of the R_cR_p-product should approach 100 %; a satisfactory chemical yield of this compound is also possible. It should be once again emphasized that the stereochemistry of this diastereomer corresponds to that of the minor product of the lithiation of *R*-**1**, whose maximum possible yield is no more than 4 %.

The two other diastereomers comprise an enantiomeric pair. However, since their amounts are not equal, we are dealing with one diastereomer of some optical

Table 3. Asymmetric cyclopalladation of racemic *N*,*N*-dimethylamino-1-ferrocenylethylamine (**1**) under the conditions of its kinetic resolution

pH of the medium	The AC* of the catalyst	The yield of the initially isolated **2** (%)	The $[\alpha]_D$ of the initially isolated **2** (CH_2Cl_2)/deg	The yield of **2** isolated from the filtrate (%)	The $[\alpha]_D$ of **2** isolated from the filtrate /deg	The yield of the amine recovered (CH_2Cl_2) (%)	The AC* of the amine recovered	The *ee* of the amine recovered (%)
7.70	*S*	50	+468.8	34	+290	45.8	*R*	10
7.75	*S*	50	+461.2	24	+320.7	45.5	*R*	10
7.76	*S*	43	+477**	26	312	56	*R*	10
7.95	*R*	55	−383.8	5	−357.6	58.4	*S*	6
8.00	*S*	75	+424.6	18	+161	47.7	*R*	—

* AC, absolute configuration. ** After separation of the precipitate, which did not dissolve in the CH_2Cl_2—C_6H_6 mixture.

purity. Obviously, this diastereomer must become dominant in the mixture of products of the asymmetric cyclopalladation of racemic **1**. At an equimolar ratio between the reactants, its optical purity may be about 50 %, judging on the data obtained for homochiral **1**.

If 0.5 eqv. of the palladating reagent and the catalyst used in the reaction, *i.e.*, if the conditions for the kinetic resolution of **1** are realized, the optical purity of this diastereomer may also be substantially increased.

Table 3 presents the results of the asymmetric cyclopalladation of racemic **1** at a Na_2PdCl_4 : catalyst : amine ratio of 1 : 1 : 2. The Na-salt of optically active *N*-acetylleucine, which is the most efficient inductor in asymmetric cyclopalladation, was used as the catalyst in all of the experiments.

The direction and degree of the asymmetric induction were determined, as before, from the magnitude and the sign of the specific optical rotation of the reaction products.

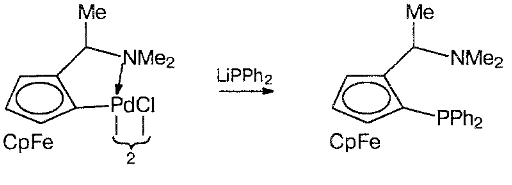
As can be seen from Table 3, during cyclopalladation of racemic **1** under the conditions of asymmetric catalysis by the Na-salt of (*S*)- or (*R*)-*N*-acetylleucine, an (*R*)- or (*S*)-chiral plane, respectively, is predominantly formed. Simultaneously, partial resolution of the starting amine occurs. As might be expected, in the presence of the inductor of the (*R*)-chiral plane, the *S*-enantiomer of **1** reacts in preference, and the recovered compound **1** is enriched in the *R*-enantiomer. When the catalyst of the opposite configuration is used, the reverse situation is observed.

However, the enantiomeric purity of the recovered **1** is rather low, 6—10 %. In other words, both enantiomers are involved in the reaction, though there is undoubtedly a certain difference between the reaction rates.

Based on the magnitude of the optical rotation of the product, the optimal pH value lies in the range 7.7—7.75 and the yield of the Pd derivative precipitating from the reaction mixture is up to 50 %. Although a further increase in pH results in an increase in the amount of the isolated dimer, it is accompanied by a decrease in its optical rotation. This is in agreement with the previous finding that the curve of the dependence of asymmetric induction on the pH of the medium passes through a maximum, which, however, does not coincide with the point where the decrease in the chemical yield begins.[6] The optical rotation of the additional product that is obtained by treatment of the filtrate is substantially lower.

The reduction of samples of dimer **2** with $[\alpha]_D$ +468.8° and +461.2° by $LiAlH_4$ affords (*S*)-**1** with optical purities of 28 and 26 %, respectively, *i.e.*, the (*S*)- and (*R*)-enantiomers of the starting **1** react in ratios of 64 : 36 and 63 : 37, respectively.

To determine the diastereomeric composition and the optical purity of compound **2** obtained by asymmetric cyclopalladation of racemic **1** we carried out the carbonylation of dimers with $[\alpha]_D$ +477° and +312° in methanol. In addition, samples of the Pd derivative with $[\alpha]_D$ −383.8° and +483.5° were converted to known aminophosphines, whose maximum optical rotations, $[\alpha]_{D_{max}}$, have been determined previously[7] by reacting them with $LiPPh_2$.



2 **4**

The results are given in Table 4. They confirm the validity of the preliminary analysis of the steric course of the asymmetric cyclopalladation of racemic **1**. In fact, the reaction yields only three of the four possible diastereomers. Experimentally, the reaction products appear as two different diastereomers. As follows from the magnitude of the optical rotation of the diastereomeric products of the carbonylation and phosphorylation of these dimers, one of them is optically pure, and the optical purity of the other depends on the pH at which cyclopalladation of the racemic **1** was carried out.

At a definite pH value under the conditions of the kinetic resolution of the starting amine **1**, the second diastereomer is also formed with high optical purity (up to 84 %). The validity of the determination of the diastereomeric composition and the optical purity of the

Table 4. Carbonylation and phosphorylation of palladium derivatives **2**, prepared from racemic *N,N*-dimethylamino-1-ferrocenylethylamine, under the conditions of its kinetic resolution

$[\alpha]_D$ **2** (CH_2Cl_2) /deg	Reactant	Product	Yield (%)	Diastereomeric ratio	$[\alpha]_D$* of the prevailing diastereomer (AC, *ee* (%))	$[\alpha]_D$* of the minor diastereomer (AC, *ee* (%))
+477	CO	Amino acid ester	81	70.3 : 29.7	+37.7 (*c* 3.6) (S_cR_p, 87.6)	+96.4 (*c* 1.5) (R_cR_p, 100)
+312	CO	Amino acid ester	57.9**	52.4 : 47.6	+85.9 (*c* 3.9) (R_cR_p, 92.3)	+33.2 (*c* 3.5) (S_cR_p, 77.2)
−383.8 (pH 7.95)	$LiPPh_2$	Amino-phosphine	43	68.3 : 31.7	−258.3 (*c* 0.7) (R_cS_p, 66)	−364*** (*c* 0.6) (S_cS_p, 100)
+483.5 (pH 7.85)	$LiPPh_2$	Amino-phosphine	66.4	82.3 : 17.7	+367*** (*c* 0.5—0.7) (S_cR_p, 82)	+367*** (*c* 0.6) (R_cR_p, 100)

* $[\alpha]_D$ was measured in EtOH. ** Considerable amounts (up to 38 %) of (*R*)-amine with *ee* 34—50 % in various runs were isolated. *** $[\alpha]_D$ was measured in $CHCl_3$.

diastereomers was confirmed for a specimen of the Pd derivative with $[\alpha]_D$ +477°. The optical purity of the chiral center in this dimer was calculated from the diastereomeric ratio and optical purity of amino acid esters **3** obtained from this specimen (see Table 4):

$$70.3 \cdot 84\ \% - 29.7 \cdot 100\ \% = 29.35\ \%.$$

This value is close to the enantiomeric purity of (*S*)-**1** prepared by $LiAlH_4$ reduction of the Pd dimer with $[\alpha]_D$ +468.8°, which amounted to 28 %.

It is noteworthy that amino acid esters **3** isolated after carbonylation of dimers greatly differing in optical rotation (+477° and +312°) differ little in optical purity, but are formed in substantially different yields. The former of these dimers, the major cyclopalladation product, affords **3** in a good yield, whereas from the latter, obtained from the filtrate, a substantial amount of the starting amine **1** is produced, apart from amino acid ester **3**. It is not improbable that excess **1**, together with the Pd-containing dimer, precipitates as hydrochloride, as the filtrate evaporates, since, being a strong base, it requires a strongly alkaline medium to be isolated in the free state. Another explanation is that amine **1** may open the dimer bridge to give a fairly soluble, but unstable, monomeric complex.

The optical purity of the R_cS_p-diastereomer of amino phosphine **4** corresponds to the optical rotation of the starting dimer **2** (−383.8° and +483.5°). However, the ratios between the diastereomers are considerably different (the absolute configuration is of no significance, since the reactivities of enantiomers of **1** must be identical). This result is probably due to the fact that these dimers have been prepared at somewhat different pH, *i.e.*, it implies that there is an optimal pH of the medium, when the difference between the reactivities of the enantiomers of **1** and the induction during asymmetric cyclopalladation are maximum.

However, the role of pH remains obscure. It is only evident that the σ-palladium derivative is formed *via* a number of transition states, always involving a carboxylate anion, because without this anion, cyclopalladation in the ferrocene series does not occur at all. However, only in one or a few of these transition states, does the carboxylate anion occupy a position that favors preferential attack at one of the diastereomeric reaction centers and depends on the pH of the medium.

Thus, the formation of a chiral plane during the asymmetric cyclopalladation of racemic **1** under conditions of kinetic resolution occurs diastereoselectively, and the product isolated is a mixture of two diastereomers with high optical purities.

The chelated σ-complexes of palladium are used as intermediates for the functionalization of molecules of various natures, including ferrocene. Replacement of the palladium atom in the product after chromatographic separation, which usually presents no special problems, makes it possible to prepare optically active derivatives in the α-dimethylaminoethylferrocene series with a high degree of optical purity and any combination of absolute configurations of the center and the plane.

An advantage of the above-described reaction as a novel approach to optically active ferrocenes that simultaneously possess central and planar chirality is, first, that the starting amine is racemic, *i.e.*, no preliminary resolution into enantiomers is needed, and, second, that the product is highly reactive, stable, has unlimited storage life, and may be used for synthesis as required. In addition, the preliminary data available indicate that this method is also applicable to other α-*N,N*-dimethylaminoalkylferrocenes.

Experimental

***N,N*-Dimethyl-1-ferrocenylethylamine (1)** was prepared and resolved into *S*(−)- and *R*(+)-enantiomers according to the method of Ugi,[2] $[\alpha]_D$ −14.4° and $[\alpha]_D$ +14.4° (*c* 2.7, EtOH). ^1H NMR (CCl_4), δ: 1.34 (d, 3 H, CMe); 1.97 (s, 6 H, NMe_2); 3.49 (q, 1 H, CH); 4.03 (s, 9 H, $C_5H_5FeC_5H_4$).

Asymmetric cyclopalladation of (*S*)-*N*,*N*-dimethyl-1-ferrocenylethylamine 1 at a stoichiometric ratio between the reactants. Standard procedure. The reaction between *N*,*N*-dimethyl-1-ferrocenylethylamine (1.18 g, 4.59 mmol, $[\alpha]_D$ −13.6°, *ee* 94.4 %), *N*-acetyl-L-leucine (0.791 g, 4.59 mmol) as the catalyst, and Na_2PdCl_4 (1.30 g, 4.59 mmol) carried out at pH 7.66 according to the procedure reported for cyclopalladation of dimethylaminomethylferrocene,[6] gave 1.40 g (76 %) of compound **2**, $[\alpha]_D$ +495°. The ^1H NMR spectrum of this compound entirely corresponded to the literature data.[8]

A set of experiments in which the pH of the medium and the catalyst were varied was carried out in a similar way.

Asymmetric cyclopalladation of racemic *N*,*N*-dimethyl-1-ferrocenylethylamine 1 under the conditions of its kinetic resolution. A solution of $NaPdCl_3$ (4.52 g, 19 mmol) in MeOH (150 mL) was mixed with a solution of *N*-acetyl-1-leucine (3.26 g, 19 mmol) and NaOH (0.76 g, 19 mmol) in water (50 mL), the pH of the mixture was adjusted to 7.76, and a solution of racemic **1** (9.8 g, 38 mmol) in MeOH (50 mL) was added. The mixture was stirred for ~24 h, and the precipitate was filtered off and dried *in vacuo* to give 3.25 g (43 %) of compound **2**, $[\alpha]_D$ +477° (*c* 0.5, CH_2Cl_2). After evaporation of the MeOH the filtrate was alkalized to pH 9—10 and extracted with benzene. The extract was dried with $MgSO_4$ and concentrated. The residue was diluted with hexane, the precipitate was thoroughly triturated, and the mixture was left for ~24 h in a refrigerator. The precipitate was filtered off and dried to give 2.0 g (26 %) of compound **2**, $[\alpha]_D$ +311.5° (*c* 0.5, CH_2Cl_2). The hexane solution was chromatographed on SiO_2 using a hexane—Et_3N mixture (5 : 1) as the eluent to afford 5.49 g (56 %) of recovered **1**, $[\alpha]_D$ +1.4° (*c* 4.43, EtOH), *ee* 10 %.

Carbonylation of palladium derivatives 2 prepared from *N*,*N*-dimethyl-1-ferrocenylethylamine 1. Standard procedure. A flow of CO was passed for 2 h through a solution of compound **2** (0.4 g, 1 mmol, $[\alpha]_D$ +477°) in a 5 : 1 C_6H_6—MeOH mixture (20 mL), and the mixture was left overnight. The precipitate was filtered off, the solvent was evaporated, the residue was treated with 10 % aqueous Na_2CO_3, the product was extracted with benzene, and the extract was dried with $MgSO_4$. Chromatography on SiO_2 with hexane—Et_3N (5 : 1) as the eluent afforded the first diastereomer of compound **3**, yield 0.07 g (24.2 %), $[\alpha]_D$ +96.4° (*c* 1.4, EtOH); further elution with C_6H_6—Et_3N (5 : 1) gave the second diastereomer of **3**, yield 0.18 g (57.2 %), $[\alpha]_D$ +37.7° (*c* 3.6, EtOH). ^1H NMR (C_6D_6), δ: diastereomer I: 1.40 (d, 3 H, COOMe); 2.41 (s, 6 H, NMe_2); 3.6 (s, 3 H, $FcCH\underline{Me}$); 4.17 (s, 5 H, C_5H_5); 4.14 (m, 1 H, C_5H_3); 4.38 (m, 1 H, C_5H_3); 4.54 (m, 1 H, C_5H_3); 4.89 (m, 1 H, $Fc\underline{CH}Me$); diastereomer II: 1.49 (d, 3 H, COOMe); 2.22 (s, 6 H, NMe_2); 3.59 (s, 3 H, $FcCH\underline{Me}$); 4.04 (s, 5 H, C_5H_5); 4.10 (m, 1 H, C_5H_3); 4.17 (m, 1 H, C_5H_3); 4.85 (m, 2 H, $C_5\underline{H}_3C\underline{H}$).

Reduction of palladium derivatives 2 prepared from *N*,*N*-dimethyl-1-ferrocenylethylamine 1. Standard procedure. A suspension of $LiAlH_4$ (0.01 g, 0.26 mmol) in abs. ether (15 mL) was added to a suspension of compound **2** (0.1 g, 0.25 mmol, $[\alpha]_D$ +468.6°) in abs. ether (15 mL), and the mixture was stirred for 30 min. The reaction mixture was treated with 10 % aqueous Na_2CO_3 at 0 °C. The organic layer was separated, dried with $MgSO_4$, and chromatographed on SiO_2 with hexane—Et_3N (5 : 1) as the eluent to give 0.05 g (81 %) of compound **1**, $[\alpha]_D$ −4.0° (*c* 1.5, EtOH).

2-(1-Dimethylaminoethyl)-1-diphenylphosphinoferrocene 4. A suspension of compound **2** (0.5 g, 1.3 mmol, $[\alpha]_D$ −383.8°) and PPh_3 (0.7 g, 2.7 mmol) in abs. THF (10 mL) was added to a solution of Ph_2PLi prepared from PPh_3 (0.7 g, 2.7 mmol) and lithium (0.1 g, 14.3 mg-at.) in abs. THF (20 mL) under Ar, and the mixture was left overnight. The precipitate was filtered off, and the filtrate was concentrated, dried with $MgSO_4$, and chromatographed on SiO_2. Elution with a hexane—Et_3N (5 : 1) mixture successively afforded diastereomers of compound **4**. The first diastereomer: yield 0.1543 g (28 %), $[\alpha]_D$ −258° (*c* 0.7, EtOH); the second diastereomer: yield 0.0716 g (13 %), $[\alpha]_D$ −364° (*c* 0.6, EtOH). ^1H NMR ($CDCl_3$), δ: diastereomer I: 1.27 (d, 3 H, *J* = 7.3 Hz, $CH\underline{Me}$); 1.77 (s, 6 H, NMe_2); 3.94 (s, 5 H, C_5H_5); 3.84—4.39 (m, 4 H, C_5H_3CH); 7.16—7.64 (m, 10 H, Ph); diastereomer II: 1.38 (d, 3 H, *J* = 7 Hz, $CH\underline{Me}$); 2.15 (s, 6 H, NMe_2); 4.00 (s, 5 H, C_5H_5); 3.63—4.37 (m, 4 H, C_5H_3CH); 7.20—7.57 (m, 10 H, Ph).

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