Pure & Appl. Chem., Vol. 55, No. 11, pp. 1837-1844, 1983.
Printed in Great Britain.

0033-4545/83 $3.00+0.00
Pergamon Press Ltd.

ASYMMETRIC CYCLOPALLADATION AS A TOOL OF ENANTIOSELECTIVE SYNTHESIS

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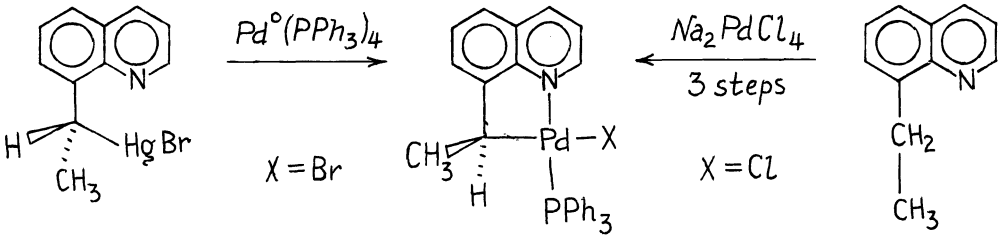
Abstract - Cyclopalladation of dimethylaminomethylferrocene and its analogues in the presence of the salts of optically active acids as nucleophilic catalysts affords the planar chiral organopalladium in a high chemical and enantiomeric yield. This has been used to induce the new chiral centre developed during the carbonylation in prochiral diols. The new entry to the enantiomeric glycerides is an example. Asymmetric cyclopalladation is a key step in the synthesis of the optically active analogues of natural prostanoids whose molecules contain the typical side chains and the ferrocene nucleus instead of cyclopentane.

INTRODUCTION

Cyclopalladation is the formation of a chelated metallocycle having the coordinative bond palladium - heteroatom (such as nitrogen or sulfur) in the course of the hydrogen replacement by the metal. This reaction has been discovered by Arthur C.Cope and co-workers for azoerenes (1) and benzylamines (2) and is now the most investigated case of cyclometalation (for reviews, see Ref. 3-5). The usual organic substrates of cyclopalladation are mostly arenes, so it is sp^2 carbon at which the substitution occurs.

With the classical planar arenes no chirality problem exists because the resulted metallocycles are inherently achiral. The situation is different, however, with aromatic metal π-complexes, like ferrocene, whose molecules will acquire the planar chirality as soon as two different substituents are introduced into the same ring. Before to study this interesting aspect more closely, one should still consider the cyclopalladation into alkyl group which may result in the development of a new chiral centre.

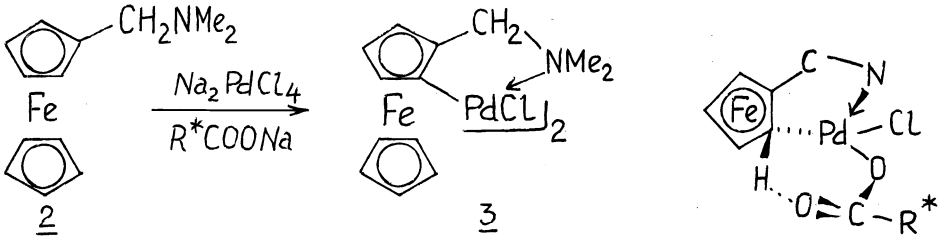
sp^3-Cyclopalladation has been at first found in 1970 for 8-methylquinoline (Ref. 6) and shortly after 8-ethylquinoline has been used with the special aim to get the chiral carbon bearing the transition metal. Crystallisation of a diastereomeric complex with (+)α-phenylethylamine followed by the exchange of the latter for triphenylphosphine afforded enantiomerically enriched σ-organopalladium 1, possibly, the first optically active organopalladium ever reported (Ref. 7). More recently, the same metallocycle was prepared in a different way (Ref. 8) as shown below.



Several further examples of sp^3-cyclopalladation were reported recently which are of some interest for the asymmetric sybthesis in future (Ref. 9 & 10). Up to now, no examples of asymmetric induction in the course of the formation of Pd-C(sp^3) bond were reported, including oxy-palladation of allyl amines and sulfides (see Note a).

ASYMMETRIC CYCLOPALLADATION OF DIMETHYLAMINOALKYLFERROCENES

The cyclopalladation of dimethylaminomethylferrocene, 2, unlike dimethylbenzylamine, cannot be carried out under Cope's condition (Ref. 12), but this has been done in the presence of sodium acetate (Ref. 13). An interesting question arises concerning the role of the latter. It was assumed that carboxylate anion inserted into the ligand sphere of Pd atom wherefrom it promoted intramolecularly the rupture of C-H bond. If so, the usage of a chiral anion should result in the formation of the diastereomeric transition states, and there exists the potential for asymmetric induction. In fact, with the salts of optically active carboxylic acids as nucleophilic catalysts, the optically active organopalladium chloride 3 was obtained whose optical activity is solely due to planar chirality (Ref. 14).



2 3

The extent of asymmetric induction of planar chirality in this reaction appeared to be strongly pH dependent. With the best catalysts known at present (which are salts of N-acetyl aminoacids), both chemical and enantiomeric yields can attain nearly 90 per cent in the pH controlled reaction (Ref. 15) as shown in Fig. 1.

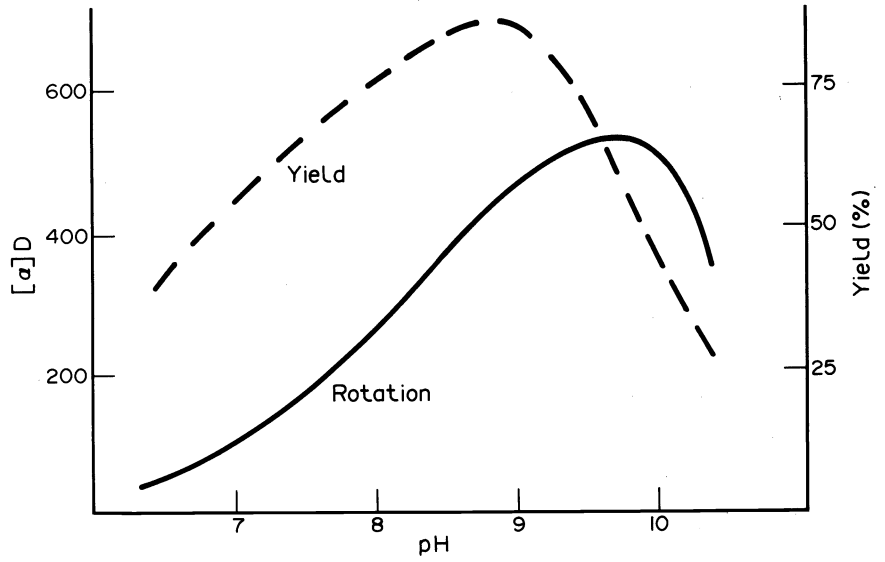
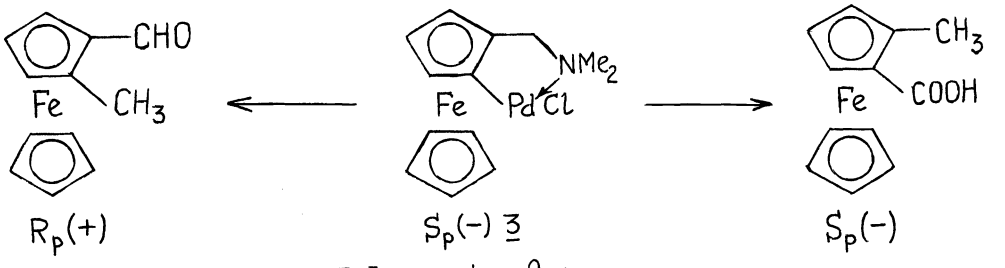


Fig. 1. pH dependence of the chemical yield (- - - -) and the optical rotation of 3 prepared in methanol-water (4:1) with Na salt of N-acetyl-S(+)valine as catalyst.

Note a. Cyclopalladation of tert.-butylmethallyl sulfide in methanol using $PdCl_2$ and Na salt of N-acetyl-S-valine gave in our hands only known (Ref. 11) racemic product.

Absolute configuration and enantiomeric purity of 3 were determined by way of the independent chemical correlations (Ref. 15) with two ferrocenes for which they had been established previously by Schlögl (Ref. 16).



$[A]_D$ 679 ± 13° (CH_2Cl_2)

The maximum optical rotation calculated therefrom were later confirmad when the straightforward resolution of 3 via the diastereomeric complex with L-proline was carried out (Ref. 17).

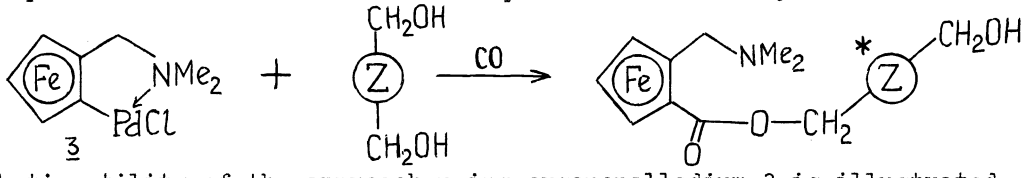
CYCLOPALLADATION OF CHIRAL FERROCENYL AMINES

Analogues of 2 substituted at α-carbon are chiral, and in the course of the reaction, they undergo the asymmetric selection on chiral centre as well as the induction of planar chirality. The considerable diastereoselectivity occurs when the initial amine is enantiomeric. Comparison with lithiation and the study of conformational factor on the [3]ferrocenophane derivative were performed (Ref. 18-20).

It is noteworthy that the observable asymmetric induction of ca. 1 per cent was found during the cyclopalladation of enantiomeric α-d$_1$-2 in the presence of sodium acetate which caused by the difference between deuterium and protium (Ref. 21). The sense of the planar chirality induced suggests the larger size of the latter.

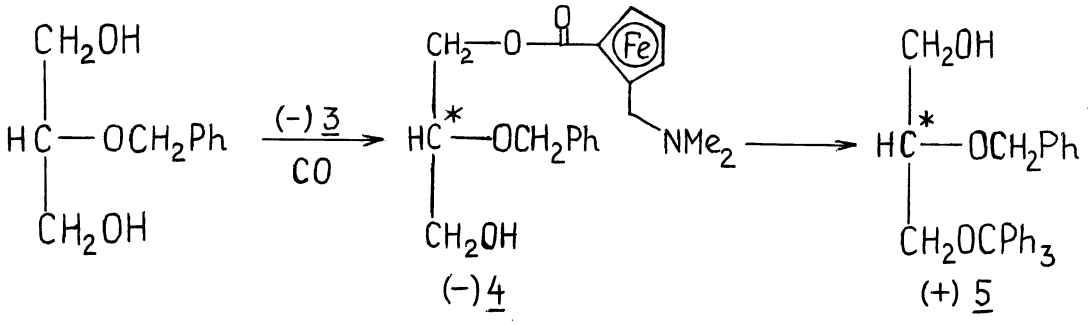
ENANTIOMERIC 3 AS INDUCTOR OF CENTRAL CHIRALITY

The high reactivity of C-Pd bond permits to use 3 for various syntheses among which of special interest is the carbonylation in the presence of alcohols to give esters. When another reagent is a prochiral diol, the new chiral centre will be developed in the formed mono-ester. Due to the considerable steric requirement of the molecule 3 a significant difference between diastereomeric transition states can be expected that may result in unequal amounts of opposite configurations (Ref. 15). One can note that the differentiation between two enantiotopic groups with the simultaneous development of a new chiral centre is quite usual for enzymatic reactions.



Synthetic utility of the approach using organopalladium 3 is illustrated by the asyymmetric synthesis in the glycerides series. Optically active 3 underwent carbonylation at 1 atm in the presence of 2 eq. of 2-O-benzylglycerol. Ferrocenylacyl mono-derivative 4 was obtained in a high yield as a 65:35 mixture of two diastereomers according to PMR spectrum.

Tritylation followed by alkaline hydrolysis gave a derivative 5 whose optical activity is solely due to the newly created centre C-2, the extent of asymmetric induction being about 30 per cent. Optically active glycerides can be obtained from 5 using conventional procedures.



(-) 4 (+) 5

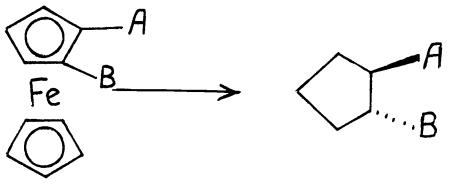
Interestingly enough, carbonylation of 3 in the presence of the related 2-isopropylpropanediol-1,3 did not exhibit any asymmetric induction. This fact is likely to suggest the important role of the oxygen atom at C-2 whose interaction with palladium in transition state may probably fix the conformation in which enantiotopic CH_2OH groups can be distinguished.

Carbonylation of 3 in the excess of racemic glycerol 1,2-acetonide led to asymmetric selection on C-2 of ca. 3 per cent.

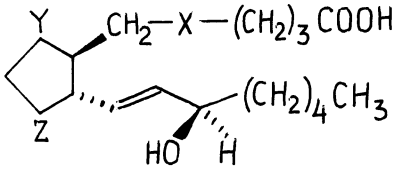
This reaction can be considered as a mild method for acylation under the neutral conditions which seems to have good prospects for the areas where the selective acylation is required, e.g. in carbohydrates.

FERROCENE ROUTE TO ENANTIOMERIC ANALOGUES OF PROSTAGLANDINES

All π-cyclopentadienyl complexes, including ferrocenes, have five-membered carbocycles and therefore can be regarded as structural precursors of cyclopentanes. At least two methods for the decomplexation of C_5 ring were reported, namely, the treatment with lithium in amines (Ref. 22), and catalytic hydrogenation (Ref. 23). On the other hand, owing to some features of the ferrocene chemistry, some side chains can be constructed in simpler ways than for cyclopentane. Hence the main idea was to build the ferrocene molecule substituted in an appropriate way and then to remove CpFe moiety in order to get a specifically substituted cyclopentane. It should be emphasized that the planar chirality in di- and more substituted homoannular ferrocenes will turn to the central chirality with two or more centres. This makes it possible to go from chiral ferrocenes to chiral cyclopentanes with the preservation of optical activity, as shown here.



Among polysubstituted cyclopentanes, of great importance are prostanoids, or prostaglandines, which possess strong and diverse biological activity. The structural elements characteristic of many prostaglandines are represented by a following general formula



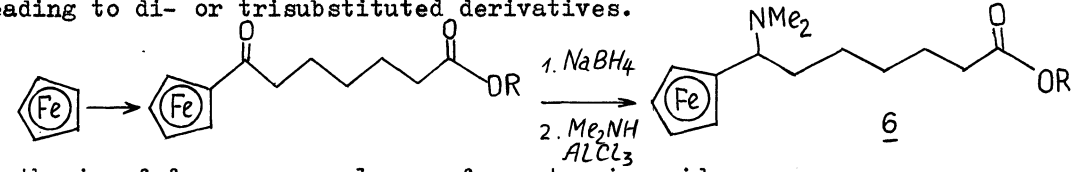
X = $-CH_2CH_2-$ or *cis* $-HC=CH-$

Two long side chains of different length occupy the neighbouring positions in the five-membered ring. The allyl alcohol unit can be easily obtained from vinyl ketone which readily accessible from chelated organopalladiums (Ref. 24). Asymmetric cyclopalladation has to ensure the optical activity in ferrocene analogues due to planar chirality. Either enantiomer can be easily prepared with the inductors of opposite absolute configurations. The third group can be introduced in ferrocene using repeated cyclopalladation in the simple, non-asymmetric variant (with sodium acetate).

Thus, there were all necessary prerequisites for the preparation of different "ferrocene prostaglandines" as either of enantiomers. They are of some interest as the possible intermediates in chemical synthesis of real prostaglandines. Besides, they can exhibit some biological activity themselves since they probably will undergo decomplexation in vivo, and, consequently, can serve as the source of prostaglandines in organism. At least one ferrocene derivative, (o-carboxybenzoyl)ferrocene (Ref. 25), trade name "ferrocerone", is used in medicine for the treatment of some diseases caused by the iron deficiency. In this connection, one should mention that a recent study (Ref. 26) revealed a considerable activity of one prostaglandine analogue based on a benzene framework instead of cyclopentane.

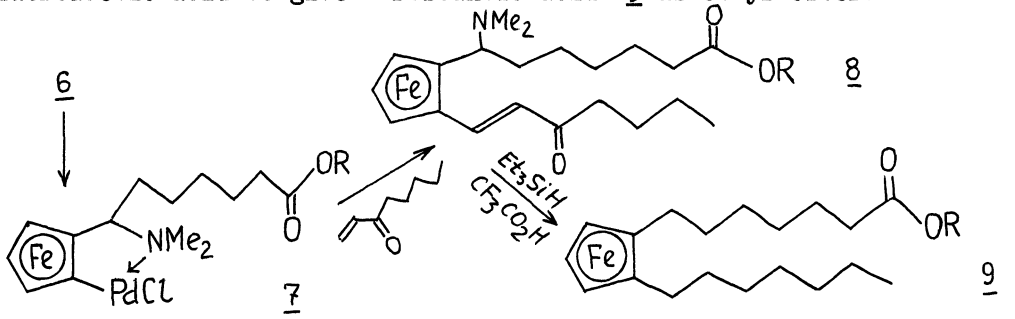
General synthetic design

According to the chosen synthetic plan, the shorter 7-carbon chain with a terminal ester group was introduced into ferrocene ring from the very beginning, and amine 6 was a key compound for all further reactions leading to di- or trisubstituted derivatives.

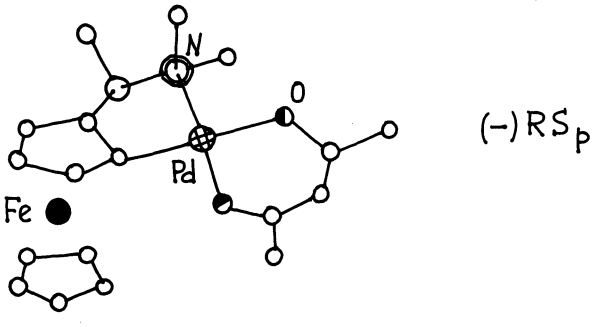


Synthesis of ferrocene analogue of prostanoic acid

Amine 6 was subjected to cyclopalladation in the presence of Na salt of N-acetyl-D-leucine to afford preferentially S_p(-) enantiomer of organopalladium 7. This was further reacted with pentylvinylketone at room temperature or below in order to avoid accompanying elimination of amino group with the formation of double bond. The unsaturated ketone 8 now possesses two long chains. It was totally reduced with triethylsilane in trifluoroacetic acid to give "Prostanoic acid" 9 as ethyl ester.

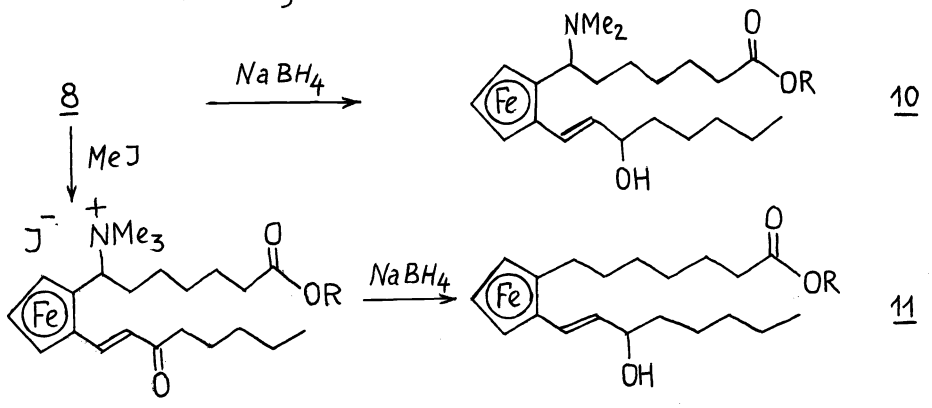


Absolute configuration of chiral plane can be assigned for all molecules here since it is determined by the configuration of inductor and exactly the same for 3 and 7 as was confirmed by CD spectra. The correlation between the sign of optical rotation and the absolute configuration of chiral plane was established directly, using X-ray method, for α-CH_3-3 (Ref. 27).

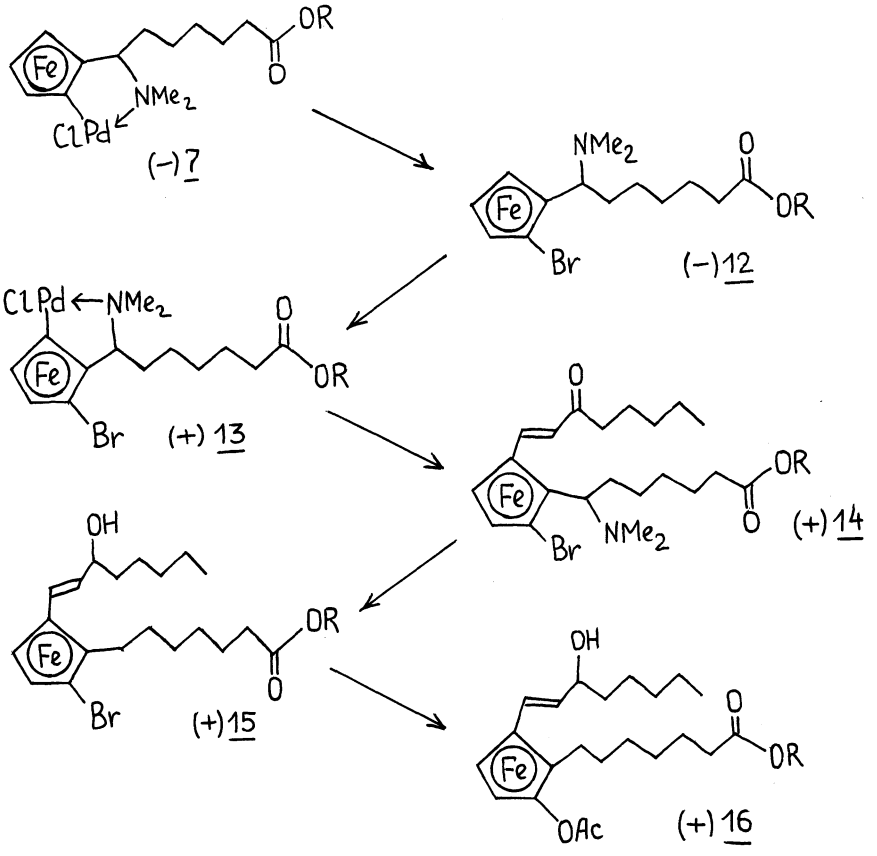


Synthesis of di- and trisubstituted analogues

Triethylsilane in CF_3COOH is a rather strong reducing agent (Ref. 28). But when ketone 8 was reduced by $NaBH_4$ in ethanol, the aminoalcohol 10 having the allyl alcohol moiety was obtained. Unexpected behaviour was observed when 8 in the form of methiodide was reacted with $NaBH_4$. Amino group was replaced by a hydrogen atom to give allyl alcohol 11. Normally C-N bond is not cleaved by borohydride. This unusual behaviour is no doubt due to the high ability of ferrocene system to stabilize a positive charge on α-carbon which becomes to be susceptible to the nucleophilic attack. The same process takes place, evidently, during the total reduction of protonated amine 8 in CF_3COOH.



However, native prostaglandines, as a rule, have a third substituent, namely, an oxygen function adjacent to a 7-carbon side chain. Our synthesis has been carried out by the following sequence of reactions shown on the Scheme.



SCHEME

The convenient precursor for oxygen function in ferrocenes is halogen atom which can be later exchanged for acyloxy group. Optically active organopalladium 7 was brominated to 12 which was exposed to the second cyclopalladation, now with sodium acetate as promotor, because the sense of the planar chirality had been already determined during the first, asymmetric cyclopalladation, and only one adjacent position is now unoccupied. The product 13 was, in its turn, reacted to pentylvinylketone to give 14 with the admixture of (-)8 as a result of partial debromination. Trisubstituted 14 was purified by thin-layer chromatography. The amino group having now served twice its purpose, it was removed with $NaBH_4$ reduction. Exchange of bromine in 15 for acetoxy group according to a [4]published procedure (Ref. 29) completed the synthesis of optically active ferrocene analogue of 11-desoxy-PGF_1, 16.

The absolute configurations of planar chiral fragments which contribute mostly into the magnitude of optical rotation are opposite for (-)13, (-)14, (-)15, (-)16 - S_p, and for (+)7, (+)8, (+)11, (+)12 - R_p. This difference is in accordance with the CD spectra shown on Fig. 2. All these compounds exhibited three Cotton effects in the region 300-500 nm, the signs being correlated with the absolute configuration.

The strategical principles outlined above allow some variations in tactical pathways, the key step being invariably asymmetric cyclopalladation. In particular, it seems to be possible to introduce a triple bond in the shorter chain, then, on the later stage, to liberate ferrocenol hydroxyl and to carry out the intramolecular oxymercuration to close exomethylene-tetrahydrofurane ring which is characteristic of prostacycline.

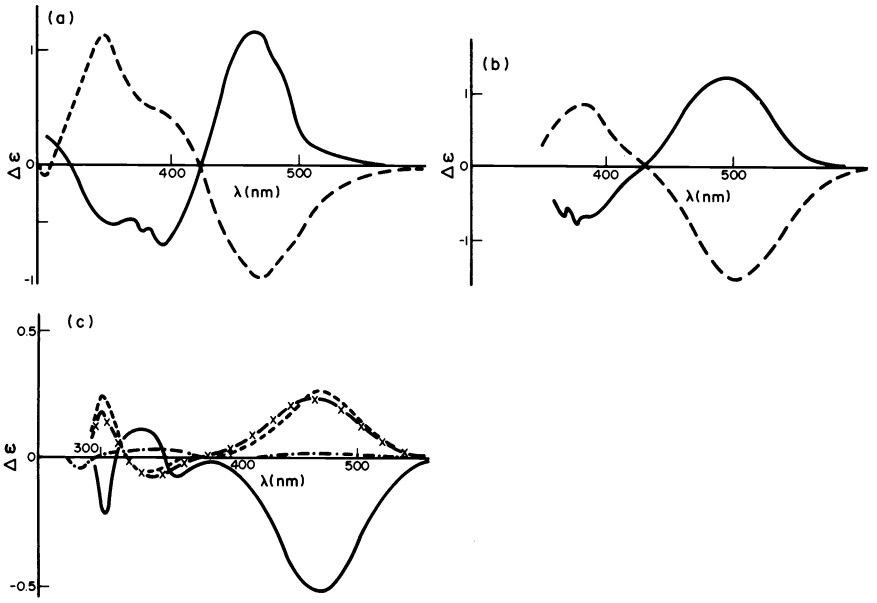


Fig. 2 CD spectra of some optically active di- and tri-substituted ferrocene analogues of prostaglandines measured at concentrations ca. 0.001 M/l in CH_2Cl_2 (2, a) and in EtOH (2, b, c):

(a) organopalladiums (-)7 (- - -) and (+)13 (———) ;
(b) vinylketones (-)8 (- - -) and (+)14 (———) ;
(c) bromide (-)12 (-.-.-.-), and allyl alcohols (-)11 (- - -), (+)15 (———), (+)16 (-x-x-x-).

It should be emphasized that enantiomeric purities about chiral plane are the same for all these compounds.

CONCLUSION

The asymmetric version of cyclopalladation in ferrocene series has been found, and the facile synthesis of either enantiomer of planar chiral organopalladium 3 and its analogues of a high enantiomeric purity has been elaborated. The utility of these reactive intermediates for enantioselective synthesis of organic molecules has been demonstrated in two ways. Firstly, the asymmetric induction of a new chiral centre by chiral plane has been observed with the enantioselective synthesis of glycerides as a result. Secondly, with ferrocene regarded as a latent form of cyclopentane, some analogues of prostaglandines based on the ferrocene framework have been synthesized. Further aspects of asymmetric cyclopalladation, yet unexplored, are believed to be of more use for the synthesis of enantiomeric organic molecules.

ACKNOWLEDGMENT

This work could not have been done without the efforts of those co-workers whose names appear in the references, especially, the brilliant work of Dr. L.L.Troitskaya is to be noted. The author wishes to express his thanks to Prof. O.A.Reutov for different kinds of help during the fulfilment of this work.

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