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ASYMMETRIC CYCLOPALLADATION OF 1′-DIMETHYLAMINO-[3]FERROCENOPHANE: CENTRAL AND PLANAR CHIRALITY AND THE EFFECT OF CONFORMATIONAL RIGIDITY

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Summary

1′-Dimethylamino[3]ferrocenophane undergoes asymmetric cyclopalladation in the presence of the sodium salt of *N*-acetyl-D- or -L-leucine to give an optically active organopalladium derivative in nearly quantitative yield. Due to the restriction of the conformational mobility of the bridged molecule, the *S*-configuration of the chiral centre induces preferentially S_p planar chirality. An enantiomeric excess of 84.0% was achieved when 0.5 equivalent of Na_2PdCl_4 was used with the simultaneous kinetic resolution of amine, affording nearly 50% of enantiomeric purity.

Introduction

Cyclopalladation of enantiomeric (1-dimethylamino)ethylferrocene (I) has been shown to proceed with a high degree of asymmetric induction of planar chirality [1], albeit less than is the case for lithiation of I [2]. More recently, we succeeded in the enantioselective cyclopalladation of achiral dimethylaminomethylferrocene (II) in the presence of a salt of an optically active carboxylic acid [3]. This version of the reaction can be applied to the kinetic resolution of racemic I. Both I and II are conformationally labile molecules with completely free rotation around the C_α—C(Fc) bond. In this connection, we became interested in the behaviour of a related ferrocenophane derivative III (Fig. 2) whose molecule has a restricted conformational mobility due to the heteroannular bridge. Amine III is known as enantiomers from previous work [4,5].

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Results and discussion

We carried out under the conditions previously described [3] the cyclopalladation of (±)III using equimolar quantities of Na_2PdCl_4 and the sodium salt of *N*-acetyl-L-leucine at an initial pH of 7.3 (before adding III). The reaction proceeded smoothly to give in a nearly quantitative yield the expected organopalladium as the dimeric chloride IV, $[\alpha]_{578}$ +50.5° (CH_2Cl_2, *c* 1.4), acetylacetonate +47.3° (CH_3OH, *c* 0.24). Since the sign of optical rotation in the ferrocene series is determined by the absolute configuration of the chiral plane, and not the centre, the configuration $R_p(+)$ can be deduced for this product IV. This corresponds to the absolute configuration of the chiral plane, which has been previously observed [3] for the same configuration of the inducing amino acid during the cyclopalladation of achiral II. However, the enantiomeric purity of isolated IV and, therefore the extent of asymmetric induction were probably low judging from the value of $[\alpha]$. It is known that pure enantiomers of this cyclopalladated series exhibit $[\alpha]_{578}$ ca. 500—600° [3,6].

It might be expected that the conformational rigidity of molecule III could be the additional factor which controls the direction of attack. Unfavourable steric interaction with the inducing anion does not completely determine asymmetric induction. To check this supposition, we carried out the reaction under the conditions for kinetic separation on the chiral centre, that is, at the following ratio of the reagents: amine (±)III : Na_2PdCl_4 : *N*-acetyl-D-leucine-Na = 2 : 1 : 1. The result was as follows: The S_c (—)III enantiomer reacted preferentially to give the S_cS_p (—)IV diastereomer, $[\alpha]_{578}$ —280°, which indicated higher enantiomeric purity (compared to the experiment with the ratio 1 : 1 : 1) approximately by a factor 5.5. Unreacted amine III in excess turned out to be the $R_c(+)$ enantiomer, $[\alpha]_{578}$ +15.4° (EtOH, *c* 5.5), whose enantiomeric purity was about 50% based on the reported value of $[\alpha]_D$ —31° [4]. The S_c(—)III enantiomer prepared by $LiAlH_4$ reduction of the S_cS_p(—)IV diastereomer, $[\alpha]$ —280°, had $[\alpha]$ —14.42° (EtOH, *c* 1.15).

One can clearly see the difference between I, whose S_c(—) enantiomer affords the cyclopalladated S_cR_p(+) diastereomer, and the ferrocenophane amine III where S_p(—) chirality has been induced by the S_c chiral centre in the course of a similar process. This result can account for the different conformational behaviour of both amines, as illustrated in Figs. 1 and 2.

In the presence of an "S_p' inducer (which is here the D-leucine derivative), the most favourable transition state is formed from R_c-I to give the R_cS_p product. But for ferrocenophane III the similar required conformation of R_c-III is unfavourable owing to the strain imposed by the short three-membered bridge. This enantiomer can give rise to the R_cR_p-IV diastereomer but the rate of this process under the conditions used here is less than the rate of formation of S_cS_p-IV from S_c-III. On the contrary, the attained conformation of S_c-III favours the occurrence of S_p chirality (Fig. 2). This type of conformation is that which is less favourable for I (Fig. 1).

The important difference between I and III is in the diminished rate of the formation of the R_cS_p isomer for the latter. Roughly, the rates of the formation for all four diastereomers of IV in the presence of an S_p inducer can be

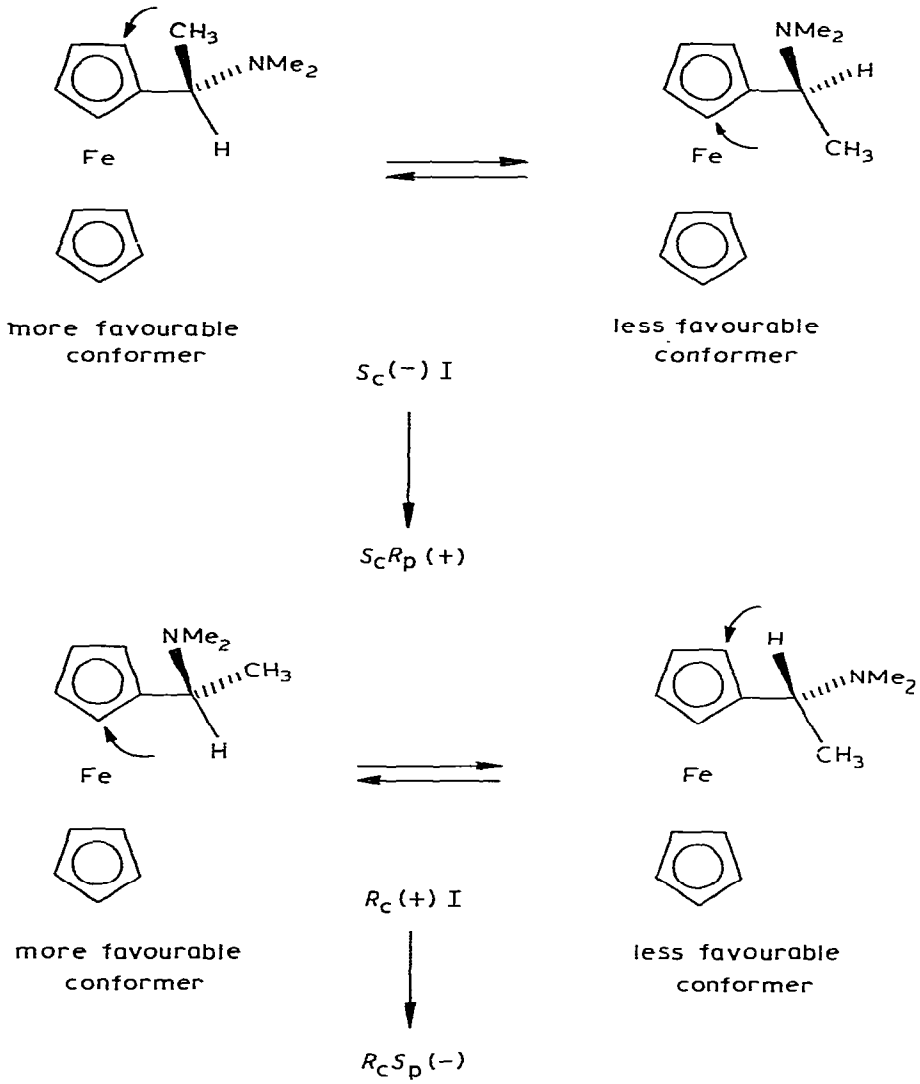

Fig. 1.

estimated as follows:

$S_cS_p > R_cR_p > R_cS_p \sim S_cR_p$ for III,

cf.:

$S_cS_p > R_cS_p \gg R_cR_p > S_cR_p$ for I.

In other words, S_p inducer fails to induce preferential S_p chirality in the course of the cyclopalladation of R_c-III. This suggests that the sense of the planar chirality arising is strongly affected by the configuration of the chiral centre in III. In fact, cyclopalladation of R_c(+)III catalyzed by sodium acetate yielded R_cR_p(+)IV with high rotation, $[\alpha]_{578}$ +250°, and acetylacetonate $[\alpha]_{578}$ +189° (CH_2Cl_2).

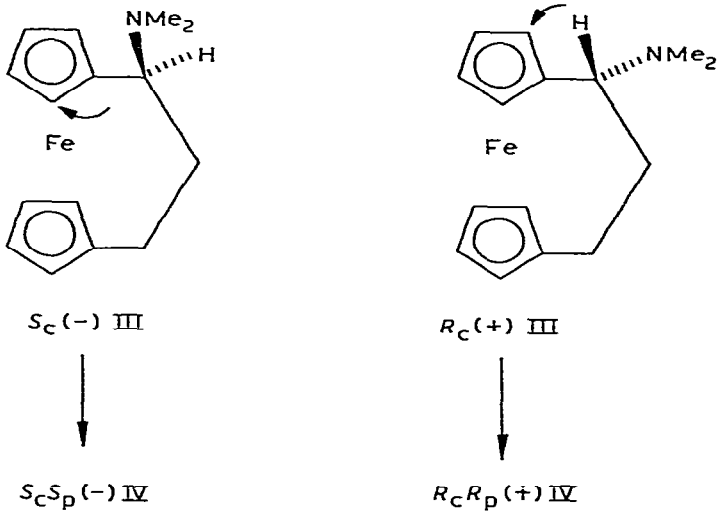

Fig. 2.

To summarize, the following relations between optical rotations of III and IV were observed without any chiral reagents:

III		IV
R_c, +15.4°	$\xrightarrow[NaOCOCH_3]{Na_2PdCl_4}$	R_cR_p, +250°
S_c, −14.42°	$\xleftarrow[LiAlH_4]{}$	S_cS_p, −280°

The extent of the asymmetric induction of planar chirality by a chiral centre can be calculated as being as high as 84%, provided that the $LiAlH_4$ reduction proceeds with no loss of central chirality (which seems probable). This value is to be compared with 70% as determined for the labile amine I [1].

The final conclusion is that the low extent of asymmetric induction in the cyclopalladation of racemic III by 1 equivalent of Na_2PdCl_4 in the presence of an asymmetric catalyst results from the low conformational mobility of III and thus reflects the importance of the conformational control in this type of reaction.

Experimental

All optical rotations were measured using a Perkin-Elmer 241 polarimeter, in CH_2Cl_2 at 578 nm when unspecified.

Asymmetric cyclopalladation of (±)III

To a solution of Na_2PdCl_4 (0.3 g, 1 mmol), *N*-acetyl-L-leucine (0.175 g, 1 mmol) and NaOH (0.05 g, 1.25 mmol) in 75% aqueous CH_3OH (20 ml), the pH being adjusted to 7.32, were added 0.270 g (1 mmol) of the amine (±)III in 5 ml of CH_3OH. The reaction mixture was stirred for several hours, and the solid

filtered and dried in vacuo. 0.4 g of dimer IV (ca. 100%) was obtained, [α] +50.5°. Found: C, 43.43; H, 4.57. Calcd. for $C_{15}H_{18}ClFeNPd$: C, 43.94; H, 4.42%.

Kinetic resolution of (±)III

To the same quantities of reagents as above, except that with *N*-acetyl-D-leucine instead of the L-enantiomer, at pH 7.4 was added 0.54 g (2 mmol) of racemic III in 5 ml of CH_3OH. After stirring for 3 days the precipitated dimer IV (0.4 g, ca. 100%) was separated, [α] −280°. The aqueous filtrate, after the evaporation of methanol, was extracted with ether. The ether solution was dried, concentrated and placed on a short SiO_2 column. Elution with benzene/triethylamine (5/1 v/v) afforded 0.240 g (88%) of starting amine III, [α] +15.4° (EtOH, *c* 3.7).

Reduction of dimer (−)IV obtained by kinetic resolution of III

To 0.1 g of $LiAlH_4$ suspended in THF (5 ml) was added a suspension of (−)IV (0.1 g, prepared in the preceding experiment) in THF (5 ml). After stirring for 3 h, the mixture was treated with water, aqueous Na_2CO_3 and extracted with ether. After the usual chromatographic work-up as above, 0.048 g (73%) of (−)III was obtained, [α] −14.42° (EtOH, *c* 1.15).

Cyclopalladation of (+)III catalyzed by NaOAc

To a solution of Na_2PdCl_4 (0.21 g, 0.7 mmol) and $NaOAc \cdot 2H_2O$ (0.15 g, 0.11 mmol) in aqueous CH_3OH was added a methanolic solution of 0.185 g (0.7 mmol) (+)III ([α] +15.4°). After stirring for 1 h the mixture was diluted with water and extracted with CH_2Cl_2, from which 0.140 g (46%) of (+)IV was obtained; chloride: [α] +250°, acetylacetonate: [α] +189°.

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