

REMARKS ON THE ASYMMETRIC LITHIATION

OF (S)-1-FERROCENYLMETHYL-2-METHYLPYPERIDINE AND RELATED SUBJECTS (1)

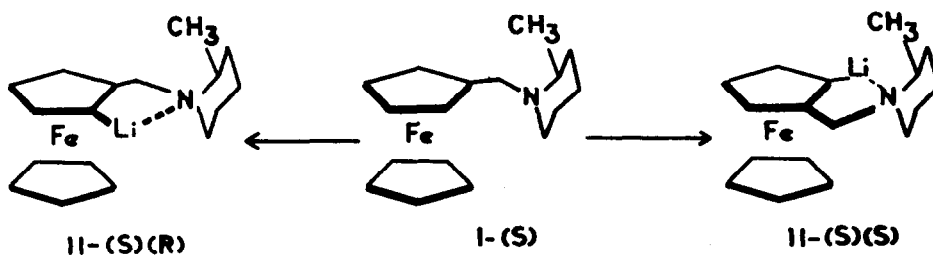
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Recently, the asymmetrically induced lithiation of I-(S) was claimed (2) to form II-(S)(S) (3) almost exclusively and no detectable amounts of II-(S)(R).

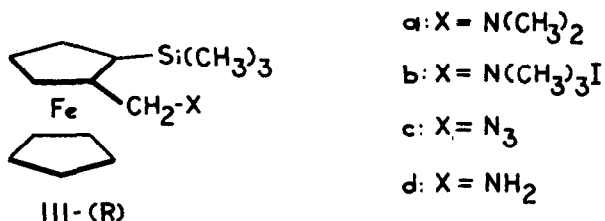


This was inferred from the observed optical rotations of various ferrocene derivatives, e. g. IV, which were obtained from II; the optical rotation observed for IV was $[\alpha]_D^{20} = +130^\circ$, $c = 0.25$, ethanol.

The reasons for such pronounced stereoselectivity (4) were not at all clear to the present authors.

In order to clarify this matter, the following sequence of reactions was carried out.

The readily accessible IIIa (5) was transformed into IIId, via intermediates IIIb and IIIc (4,6).

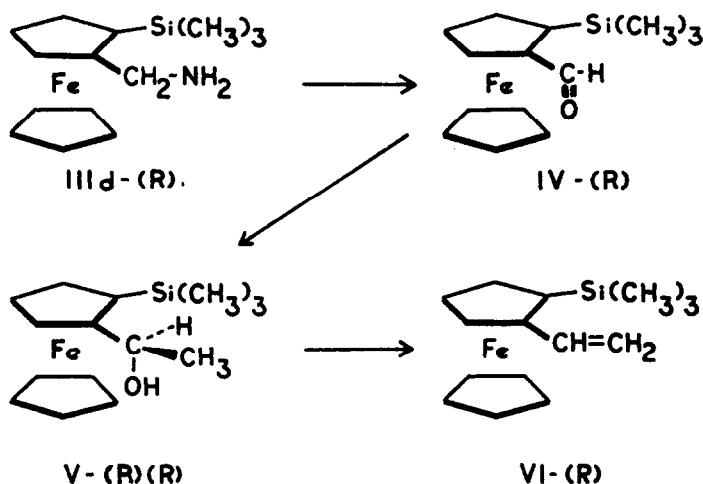


The resolution of III d with (R)-0,0'-di- α -naphthoyletartaric acid in methanol yields III d-(R) ($[\alpha]_D^{20} = -58.5^\circ$, $c = 2.2$, ethanol). The Sommelet oxidation (7) of III d-(R) yields IV-(R) (84%, mp: 91-92 $^\circ$; $[\alpha]_D^{20} = +194^\circ$, $c = 0.28$, ethanol; TLC: C₆H₆ R_f \approx 0.4).

The positive algebraic sign of the optical rotation of IV-(R) [vs. V-(R)] is opposite to what one would predict on the basis of Schlögl's rule (8). In fact, it is not to be expected that simple rules concerning observations of chirality are generally valid for these ferrocene derivatives, because most of the sp²-ligands on ferrocene are themselves axially chiral [e. g. the anti-aldehyde group in IV-(R)]. Simple rules on chirality are valid for group theoretical reasons (9) and are confined to chiral molecules with achiral molecular frameworks and achiral ligands.

Excess methylmagnesium iodide in ether and subsequent hydrolysis transforms IV-(R) stereospecifically into V-(R)(R) [90%; bp 0.01: 120-25 $^\circ$; TLC: C₆H₆ R_f \approx 0.3; $[\alpha]_D^{20} = -48.3^\circ$, $c = 0.54$, benzene; identical with a sample prepared in 85% yield from (R)(R)-2-trimethylsilyl-1-

α -dimethylaminoethyl-ferrocene (4) by treatment with methyl iodide and sodium hydroxide at 20° in



aqueous glyme (4,6)].

This confirms the assumption that methylmagnesium iodide attacks the indicated conformation of IV-(R) from the "top" side of the substituted cyclopentadienyl moiety of IV-(R).

The treatment of V-(R)(R) in benzene at 0° with phosgene and excess triethylamine, and subsequent refluxing (0.5 h) yields VI-(R) (78%, $[\alpha]_D^{20} = -885^\circ$, $c = 0.52$, acetone) which is found, by comparison with an authentic sample (4), to be optically pure. III-(R) and IV-(R) were, therefore, also optically pure.

Accordingly, compound IV which was synthesized by Aratani, Gonda and Nozaki (2) from I-(S) was only 67% optically pure, and hence the lithiation of I-(S) proceeds with considerably lower stereoselectivity than claimed.

References

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