Tetrahedron Letters No. 31, pp 2947 - 2950, 1973. Pergamon Press. Printed in Great Britain.

ASYMMETRIC INDUCTION, TIME AND SOLVENT DEPENDENCE IN THE METALLATION OF FERROCENYLALKYL ETHERS

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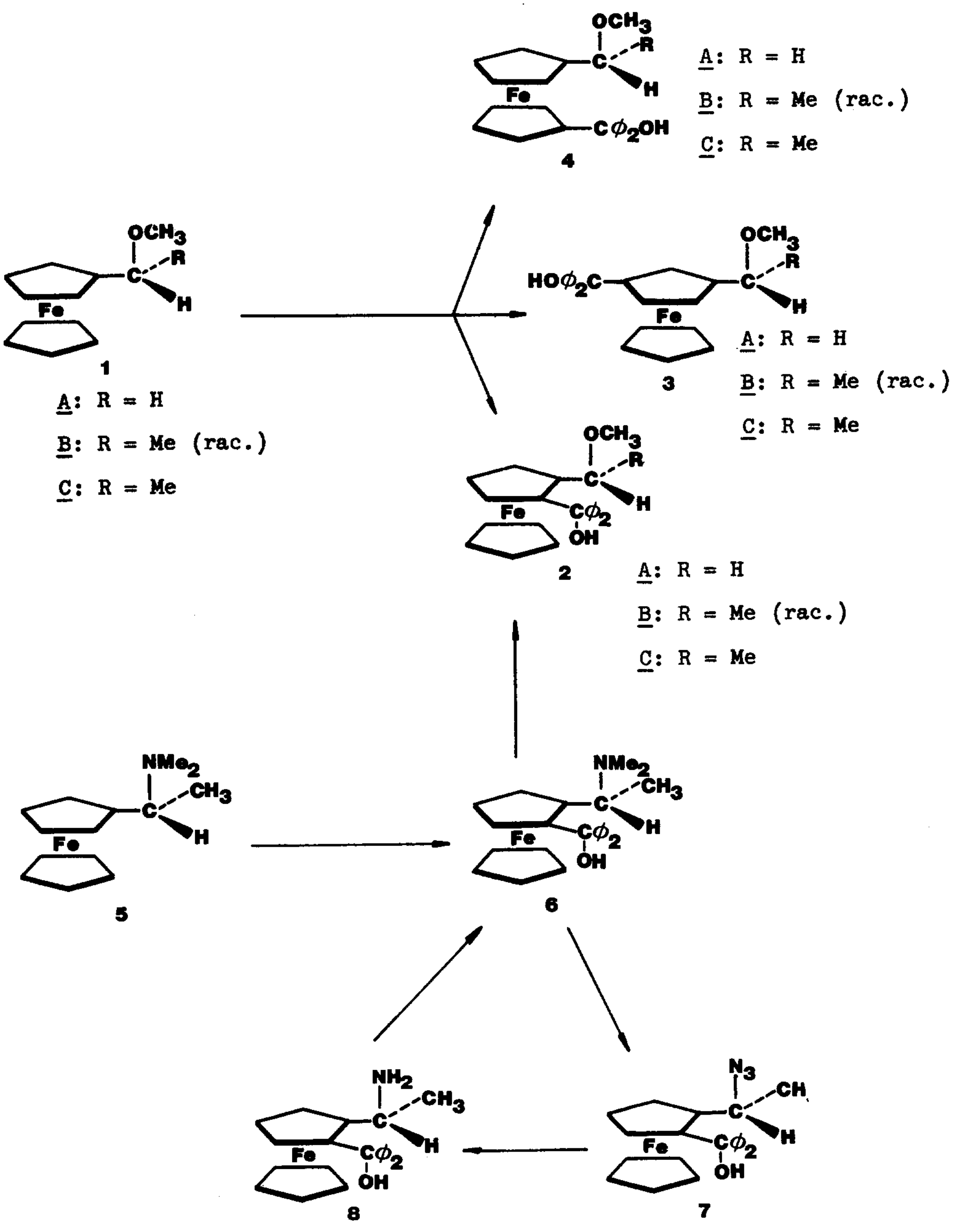
(Received in USA 12 March 1973; received in UK for publication 25 June 1973)

Our interest in asymmetrically induced ortho directed metallations of ferrocenylalkyl amine derivatives[2] led us to examine the metallation behavior of ferrocenylalkyl ethers, particularly as regards the oxygen atom's ability to coordinate and direct a metallating agent. Considerable work has been directed to this question recently, in both the benzene and ferrocene systems.[3] The use of ferrocene in such a study has the advantage that metallation at one of the ortho positions can be distinguished from metallation at the other if the molecule contains a chiral element.[2] A further difference is that heteroannular metallation is possible with ferrocene.

In early metallation studies on ferrocenylmethoxymethane (1A), Slocum and coworkers isolated 2A derived from the ortho metallated intermediate and later showed the presence of the heteroannular product 4A.[3b-d] We have further examined this reaction and have essentially verified these results: metallation of 1A with n-butyllithium (ether, 5 h, ambient temperature) followed by condensation with benzophenone (chromatography: alumina, benzene) afforded the 1,2-product 2A (38%, mp 109-110°, R_f 0.68 PhH)[3c] and the heteroannular product 4A (40%, mp 102-103°, found: C, 72.86; H, 5.95; R_f 0.35 PhH).

Metallation of (±)-1-ferrocenyl-1-methoxyethane, 1B,[4] on the other hand, is even less regiospecific, leading (after condensation with benzophenone) to the products of random metallation: 2B,3B,4B in ratios which are both time and solvent dependent. In ether, hexane or tetrahydrofuran, metallation proceeds slowly



4

A: R = H

B: R = Me (rac.)

C: R = Me

1

A: R = H

B: R = Me (rac.)

C: R = Me

3

A: R = H

B: R = Me (rac.)

C: R = Me

2

A: R = H

B: R = Me (rac.)

C: R = Me

5

6

7

8

reaching a maximum of metallated products at 5-10 h elapsed time, after which time decomposition (presumably ether cleavage) sets in. The stability of the metallated ether in these solvents decreases in the order: ether > hexane > THF. At 5 h elapsed time, the reaction compositions[5] are (*solvent*: **1B**:**2B**:**3B**:**4B**): *ether*: 26:31:12:32; *hexane*: 43:8:6:43; and *THF*: 68:8:8:16. Metallation of **1B** (5 g)[6] or *R*-(+)-**1C** (5 g)[2,6] with *n*-butyllithium for *ca.* 6 h, followed by condensation with excess benzophenone, then chromatography (alumina, benzene) led (besides residual starting material) to the following products: **2B** (2.7g, mp 97.5°, nmr (60 MHz, $CDCl_3$): 7.22 ppm (m, 10H, C_6H_5); 5.82 (s, 1H, -OH); 4.20, 3.55 (s, m, 9H, ferrocene and methine); 3.12 (s, 3H, OMe) and 0.93 (d, 3H, J = 6.4 Hz, Me)); **3B** (1.03g, mp 158-160°, nmr: 7.23 (m, 10H, C_6H_5) 6.70 (s, 1H, -OH); 4.37 and 3.43-3.93 (s, m, 9H, ferrocene and methine); 2.97 (s, 3H, OMe); and 1.30 (d, 3H, J = 6.2 Hz, Me)); and **4B** (2.75g, mp 96-97°, nmr: 7.27 (m, 10H, C_6H_5); 4.93 (s, 1H, -OH); 4.22 and 3.97 (m, m, 9H, ferrocene and methine); 3.48 (s, 3H, OMe) and 1.36 (d, 3H, J = 6.2 Hz, Me)); **2C** (3.67g, mp 98-100°, calculated for $C_{26}H_{26}FeO_2$: C, 73.25; H, 6.15; found: C, 73.07; H, 6.16. $[\alpha]_D^{25}$ -6.6°, c = 1, ethanol); **3C** (1.3g, mp 158-159°, found: C, 73.45; H, 6.25; $[\alpha]_D^{25}$ 7.55°, c = 2.3, chloroform); and **4C** (2.18g, mp 102-104°, found: C, 73.30; H, 6.14; $[\alpha]_D^{25}$ -8.78°, c = 2, chloroform). In order to assess the degree of asymmetric induction leading to **2C**, optically pure **2C** was prepared as follows. Optically pure *R*-(+)-1-*N*,*N*-dimethylamino-1-ferrocenylethane (**5**)[6] was converted to (*R*,*S*)-1-*N*,*N*-dimethylamino-1-(2-diphenylhydroxymethyl)ferrocenylethane (**6**) by treatment with *n*-butyllithium followed by benzophenone. Aminoalcohol **6** was converted with methyl iodide and potassium carbonate to the methiodide salt which was converted *in situ* by methanol (solvent) to give optically pure **2C** (70%, mp 114-115° found:C, 73.51; H, 6.26; $[\alpha]_D^{25}$ -59.4°, c = 1, ethanol).

The optical purity and absolute configuration of **2C** are known if the $R\text{-}NMe_3I$ to R-OMe conversion occurs *via* a retentive S_N1 reaction as expected.[4] The possibility that the bulky diphenylhydroxymethyl group interferes with this reaction was ruled out by performing the cycle **6** → **7** → **8** → **6**. Treatment of aminoalcohol **6** ($[\alpha]_D^{25}$ -191.6°, c = 1, ethanol)[6] with methyl iodide in the presence of sodium azide (acetone solution) gave hydroxyazide (**7**) (74%, mp 162-163°, calc'd for $C_{24}H_{23}FeN_3O$: found: C, 67.72; H, 5.27; ir($CHCl_3$) $-N_3$ = 2130 cm^{-1}; $[\alpha]_D^{25}$ 2.5°, c = 1.5, ethanol). Reduction of 7 with $K_2[Sn(OH)_4]$[7] gives aminoalcohol 8 (76%, mp 159-160°, calc'd for $C_{24}H_{25}FeNO$; found: C, 72.38; H, 6.09; $[\alpha]_D^{25}$ -157.0°, c = 1.5, ethanol). The primary amine is then methylated[6] to give 6 identical with starting material ($[\alpha]_D^{25}$ -188.3°, c = 1, ethanol). Since the cycle involves only one reaction at carbon, it must proceed with retention and its course is apparently uninfluenced by the ortho group.

A comparison of the rotations observed for samples of 2C (-6.6°) obtained directly from 1C and 2C (-59.4°) obtained by the sequence 5 → 6 → 2C indicates that the net asymmetric induction where oxygen is the heteroatom (1C) is only about 10% of that observed for the nitrogen case (5).[8] Both the reduced asymmetric induction in 1C and the randomness of metallation of 1A-C are clear indications that oxygen does not chelate and direct the metallating agent nearly as effectively as nitrogen does.

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