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Synthesis and absolute configuration of planar chiral ferrocenophanes by amide-directed *ortho*-lithiation

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ABSTRACT

trans-1,2-Diaminocyclohexane has been used as the backbone of the chiral macrocycles of amido- and amino-ferrocenophanes. Planar chirality was introduced via a self assembled amide-directed diastereoselective *ortho*-lithiation. Detailed NMR analysis revealed the (R_p)-configuration in the newly synthesised compounds.

1. Introduction

The possibility of some ferrocene derivatives possessing both central and planar chiralities provoked the discovery of a number of very active and selective ligands and catalysts,[1] which were successfully used in enantioselective homogeneous catalysis on both small and large (industrial) scales.[2] However, the low energy barrier for rotation of the cyclopentadienyl rings may be crucial to the application of these derivatives.[3]

An interesting and rapidly developing alternative are the ferrocenophanes, which are ferrocenes with a more rigid structure due to the presence of an intramolecular linkage between the two cyclopentadienyl rings (Fig. 1, I).[1,4] The concept of ferrocenophanes possessing chiral carbon bridges with coordinating centres, and their application in asymmetric catalysis, was initially introduced by Weissensteiner et al.[5] *ortho*-Diphenylphosphino-1′-dialkylamino[3]ferrocenophanes (Fig. 1, II) and their analogues have been successfully used as chiral ligands. Erker et al. further developed this chemistry by providing a broad variety of functionalised [3]ferrocenophane derivatives (Fig. 1, III) via an elegant Mannich type condensation reaction.[6] In both cases, the advantage of the central chirality of the carbon bridge promotes the introduction of planar chirality in the ferrocene, via an amine-directed *ortho*-lithiation.[7]

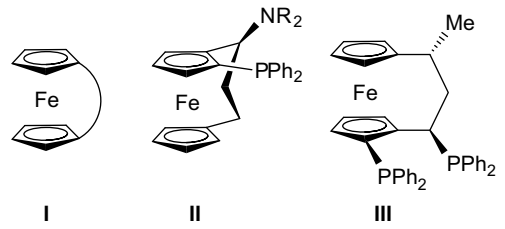

Figure 1. Ferrocenophanes.

Ferrocenophanes bearing heteroatoms in the chiral bridge are less investigated.[8] Hence, we decided to direct our efforts towards the synthesis of such chiral macrocycles and to apply them as chiral pockets in catalytic reactions. Herein, we report the synthesis of a chiral intramolecular amido- and amino-bridged ferrocenophanes with the introduction of planar chirality by amide-directed *ortho*-lithiation.[9,10] The latter, to the best of our knowledge, is the first example of a directed diastereoselective metallation of ferrocene caused by an amide function as a chiral auxiliary.

2. Results and discussion

Since the *trans*-1,2-diaminocyclohexane is the backbone of many useful chiral ligands,[11] we became interested in using it as a building block for the planned chiral linkage. The enantiomerically pure (*R*,*R*)- and (*S*,*S*)-1,2-diaminocyclohexane can be easily obtained from the inexpensive racemic mixture.[12] Coupling with 1,1′-ferrocenedicarbonyl chloride **1** in the presence of NEt_3 and catalytic amounts of DMAP led to the formation of the target ferrocenophane **2**, but in very low yield (4%). An experiment has also been performed with (*R*,*R*)-1,2-*N*,*N*′-(dimethyl)-diaminocyclohexane.[13] In this case, no desired product **3** was isolated (Scheme 1). Crucial for the creation of the macrocycle is the strong competition between the desired intramolecular reaction and the intermolecular reactions, which gives mixtures of oligomers.

More successful was the condensation of 1,1′-ferrocene-dicarboxylic acid with *trans*-1,2-diamino-cyclohexane in the presence of *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI) and 1-hydroxy-benzotriazole hydrate (HOBT), which resulted in formation of the desired macrocyclic amide **2** in 21% yield. Subsequent deprotonation and alkylation of the amide provided the stable ferrocenophane **3** (Scheme 2).[14]

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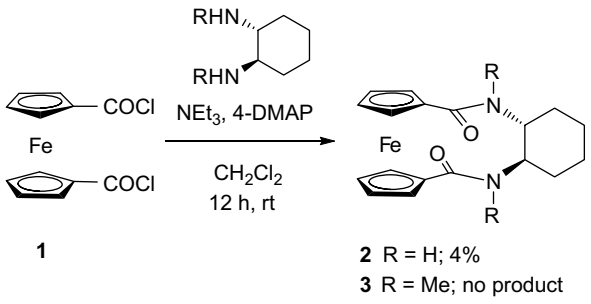
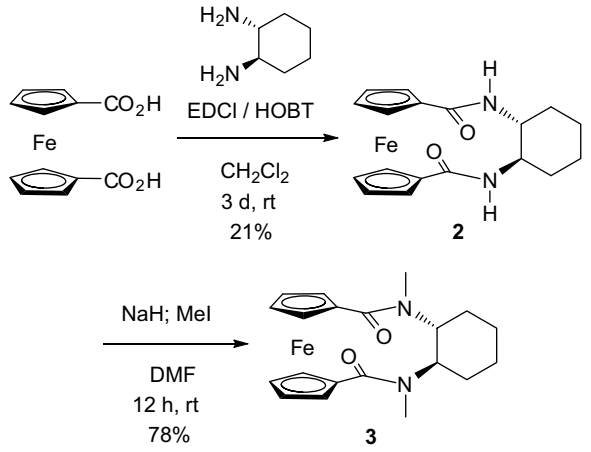
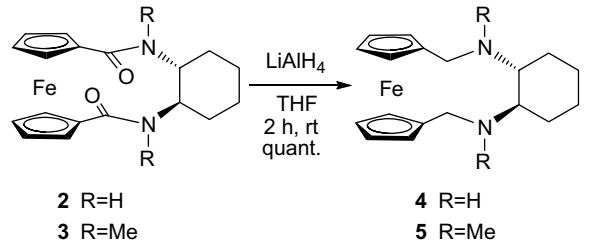


Scheme 1.



Scheme 2.

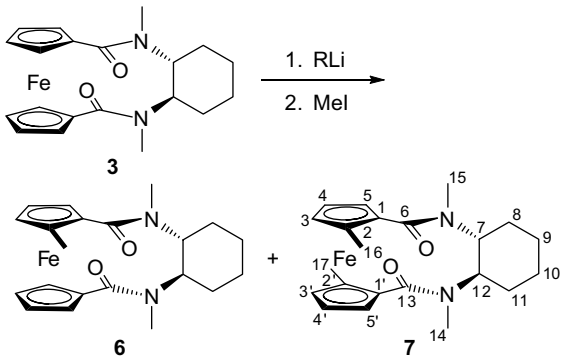
Both structures were further converted to the corresponding amines **4** and **5** by a hydride reduction (Scheme 3). Unfortunately, all our attempts to direct *ortho*-lithiation by the amino functions of the macrocycle failed. Furthermore, these amino ferrocenophanes are unstable, and are difficult to work with.



Scheme 3.

Considering that the amide groups direct *ortho*-metallation on phenyl rings,[9] we decided to take advantage of our amide bridge in order to direct the lithiation. Our attempts started with the lithium 2,2,6,6-tetramethylpiperidide (TMPLi).[15] After quenching with MeI as a testing electrophile, we isolated a mixture of mono- and di-substituted ferrocenophanes **6** and **7,** and the starting material **3** (Scheme 4). After separation over silica gel, both ferrocenophanes were obtained as predominant diastereomers (de >97.5% by NMR as compared to the corresponding ^{13}C sattelites). Products **6**[16] and **7**[17] have been obtained with a de >98.5% after subsequent purification on silica gel.

In order to optimise the conditions, we monitored the reaction pathway by varying three main factors: the lithiating reagent, its quantity and the duration of the lithiation. MeI was used as a test electrophile (Table 1).



Scheme 4.

Table 1
Directed *ortho*-lithiation of ferrocenophane **3** under different reaction conditions

Entry	Base	Equiv	Time (h)	Yield **6** (%)	Yield **7** (%)	Yield **3** (%)
1	TMPLi	1.5	2	14	2	80
2	TMPLi	2.3	2	29	18	37
3	TMPLi	2.3	6	37	22	39
4	TMPLi	2.3	9	16	—	58
5	TMPLi	4	6	30	2	62
6	TMPLi	6	6	23	—	44
7	TMPLi	10	6	15	—	32
8	*t*-BuLi	2.3	2	16	—	24
9	*s*-BuLi	2.3	2	7	—	6
10	*n*-BuLi	2.3	2	4	—	68

Both the reaction duration and the excess of the lithiating reagent were optimised. The optimal conversion was achieved with 2.3 equiv TMPLi for 6 h at −78 °C (entry 3). Varying the time period (entry 2 vs entry 3 vs entry 4) and the quantity of the lithiating reagent (entry 1 vs entry 2 and entry 3 vs entries 5–7) generally resulted in lower conversions. The yields dropped considerably with the decrease of the power of the lithiating reagent (entries 8–10). In the latter cases, no di-substituted product was isolated.

The absolute configuration of compound **6** was determined by detailed NMR analysis taking into account the known (*R*,*R*)-configuration of the starting 1,2-diaminocyclohexane (see Fig. 2). For determining the configuration of compound **6**, the most probable conformation of **3** is very important. Inspection of molecular models in combination with the observed NOE's revealed that the molecule of **3** is highly symmetric and rather rigid with carbonyl oxygen atoms pointing in opposite directions. This most probable

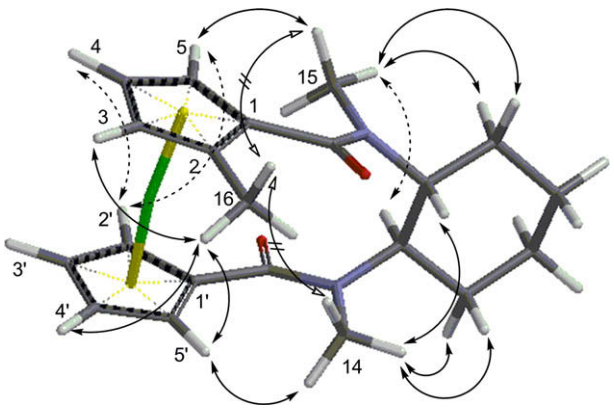
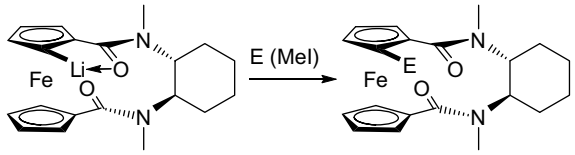


Figure 2. NOE's, important for the elucidation of the configuration of **6**.

conformation is fully consistent with the observed proton and carbon chemical shifts and with the strong NOE's between the N-Me-groups and H-5 and H-5′, respectively. We exclude, based on the NMR data, an alternative conformation for compound **3** with oxygens pointing in the same direction. Therefore, to determine the configuration of **6**, we had to distinguish between the two possible diastereoisomers, one with the *ortho*-attached Me-group on the side of the carbonyl oxygen and another with the Me-group on the side of the N-Me-group. Proton chemical shifts of the ferrocenyl protons indicated proximity of the H-2′ proton (5.13 ppm) from the mono-substituted Cp-ring to a carbonyl group, whereas all other ferrocenyl protons lack a closely spaced deshielding group. Thus, the Me-group within the 1,2-disubstituted Cp-ring occupies the *ortho*-position on the side of the carbonyl oxygen, which is also supported by the observed NOE's of CH_3-16 with H-3, H-4′ and H-5′. The latter, together with the observed proton proximities of H-2′ with H-4 and H-5, strongly supports the staggered conformation of the Cp-rings. Therefore, the configuration with respect to the chirality plane is (R_p) taking into account the known configuration within the 1,2-diamidocyclohexane moiety. Proof of this configuration also delivers the lack (less than 0.05%) of Overhauser enhancements between the CH_3-16 protons and both N-Me-groups (H-14 and H-15). Therefore, the alternative diastereoisomer with the CH_3-16 group on the side of the N-Me-group should be excluded. In a similar way, the observed NMR spectra and NOE's for the disubstituted compound **7** are consistent with the (R_p)-configuration.

The NMR experiments prove that the methyl group is attached on the side of the oxygen of the neighbouring amide functionality (Fig. 2). Hence, the electron pair of this oxygen coordinates to the Li atom, and facilitates the proton abstraction at the *ortho*-position with diastereoselection based on the steric repulsion between the cyclohexane ring bearing the central chirality and the ferrocene nucleus (Scheme 5). This opens up the possibility for further development of the chiral amide functions as *ortho*-directing groups for the diastereoselective *ortho*-metallation of ferrocene derivatives.



Scheme 5.

3. Conclusion

In conclusion, we have accomplished the synthesis of new amido- and amino-bridged ferrocenophanes bearing *trans*-1,2-diaminocyclohexane as the backbone of their cycles. The central chirality of the latter is responsible for the introduction of planar chirality within the ferrocene core via amide-directed *ortho*-lithiation. The obtained planar chiral-lithiated ferrocenophanes can be easily elaborated further to a series of new ligands by proper selection of electrophiles. The amide-directed *ortho*-metallation, itself, has the potential to become a practical method for the introduction of planar chirality into the ferrocene framework. Research along these lines is currently underway, and will be reported in due lines.

Acknowledgements

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14. The structures of the new compounds were established by NMR experiments and mass spectra. The unambiguous assignment of the ^{1}H and ^{13}C NMR spectra has been made on the basis of the gradient-enhanced versions of COSY, HSQC, NOESY and 1D selective NOE experiments (Bruker pulse library programme: cosygpmfqf, hsqcedetgpsisp2.2, hmbcgplpndqf, noesygpphzs and selnogp). Analytical data for **3** (red crystal): $[\alpha]_D = +128.4$ (c 0.43, $CHCl_3$); mp: 239 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.37 (m, 2H, H-9ax, H-10ax), 1.70 (m, 2H, H-8ax, H-11ax) 1.78 (m, 2H, H-8eq, H-11eq), 1.86 (m, 2H, H-9eq, H-10eq), 3.10 (s, 6H, H-14, H-15), 4.16 (dt, 2H, J = 1.2, 2.6 Hz, H-3, H-3′), 4.52 (dt, 2H, J = 1.6, 2.6 Hz, H-4, H-4′), 4.74 (m, 2H, H-7, H-12), 4.86 (dd, 2H, J = 1.3, 2.6 Hz, H-5, H-5′), 5.26 (dd, 2H, J = 1.5, 2.6 Hz, H-2, H-2′); ^{13}C NMR (62.5 MHz, CD_2Cl_2) δ 25.42 (2C, C-9, C-10), 29.40 (2C, C-8, C-11), 32.98 (2C, C-14, C-15), 52.74 (2C, C-7, C-12), 69.72 (2C, C-3, C-3′), 73.69 (4C, C-4, C-4′, C-5, C-5′), 76.66 (2C, C-2, C-2′), 77.34 (2C, C-1, C-1′), 171.73 (2C, C-6, C-13); MS (EI) m/z: 380 (M^+ 100); Anal. Calcd for $C_{20}H_{24}FeN_2O_2$: C, 63.17; H, 6.36. Found: C, 62.89; H, 6.22.
15. Procedure for the *ortho*-lithiation of **3**: A dried flask was loaded under an Ar atmosphere with 2,2,6,6-tetramethylpiperidine (0.078 ml, 0.46 mmol) and toluene (3 ml). To the stirred solution was added dropwise at −20 °C *n*BuLi (1.6 M in hexane, 0.29 ml, 0.46 mmol). The mixture was stirred for 30 min at −20 °C and cooled to −78 °C. A solution of ferrocenophane **3** (0.076 g, 0.2 mmol) in toluene (10 ml) was added dropwise, and the reaction mixture was stirred at −78 °C for 6 h. MeI (0.06 ml, 1 mmol) was added in one portion and the mixture was left to reach rt on its own accord. It was then quenched with satd aq NH_4Cl, extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated under reduced pressure. Purification was done with flash column chromatography (silica, EtOAc/hexane = 1:1) to afford 0.018 g (22%) of ferrocenophane **7** and 0.029 g (37%) of ferrocenophane **6**, and 0.030 g (39%) of the starting material **3**.
16. Analytical data for **6** (orange solid): $[\alpha]_D = +0.7$ (c 1.03, $CHCl_3$); mp: 198 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.37 (m, 1H, H-9ax), 1.39 (m, 1H, H-10ax), 1.72 (m, 2H, H-8ax, H-11ax), 1.82 (m, 1H, H-11eq), 1.83 (m, 1H, H-8eq), 1.88 (m, 1H, H-10eq), 1.89 (m, 1H, H-9eq), 2.39 (s, 3H, H-16), 3.11 (s, 3H, H-15), 3.15 (s, 3H, H-14), 4.04 (dd, 1H, J = 2.6, 1.5 Hz, H-3), 4.15 (dt, 1H, J = 1.2, 2.6 Hz, H-3′), 4.45 (t, 1H, J = 2.6 Hz, H-4), 4.51 (dt, 1H, J = 1.6, 2.6 Hz, H-4′), 4.57 (dt, 1H, J = 2.7, 1.3 Hz, H-5′), 4.69 (dd, 1H, J = 1.5, 2.7 Hz, H-5), 4.76 (m, 1H, H-12), 4.79 (m, 1H, H-7), 5.13 (dt, 1H, J = 2.6, 1.5 Hz, H-2′); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 14.84 (C-16), 25.31 (C-10), 25.44 (C-9), 29.36 (C-11), 29.42 (C-8), 33.56 (C-14), 33.90 (C-15), 52.23 (C-12), 52.90 (C-7), 70.00 (C-3′), 71.41 (C-4), 72.74 (C-3), 73.94 (C-1),

74.70 (C-4′), 75.81 (C-5), 76.36 (C-2′), 77.38 (C-5′), 77.51 (C-1′), 93.51 (C-2), 172.57 (C-13), 173.33 (C-6); MS (EI) *m*/*z*: 394 (M^+ 100); Anal. Calcd for $C_{21}H_{26}FeN_2O_2$: C, 63.97; H, 6.65. Found: C, 63.59; H, 6.93.

17. Analytical data for **7** (red solid): $[\alpha]_D = -10.5$ (*c* 0.14, $CHCl_3$); mp: 185 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 1.36 (m, 2H, H-9ax, H-10ax), 1.72 (m, 2H, H-8ax, H-11ax), 1.86 (m, 2H, H-8eq, H-11eq), 1.88 (m, 2H, H-9eq, H-10eq), 2.32 (s, 6H, H-16, H-17), 3.12 (s, 6H, H-14, H-15), 4.04 (t, 2H, *J* = 1.8 Hz, H-3, H-3′), 4.35 (t, 2H, *J* = 2.5 Hz, H-4, H-4′), 4.46 (dd, 2H, *J* = 1.5, 2.5 Hz, H-5, H-5′), 4.79 (m, 2H, H-7, H-12); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 14.69 (2C, C-16, C-17), 25.81 (2C, C-9, C-10), 29.81 (2C, C-8, C-11), 34.45 (2C, C-14, C-15), 52.85 (2C, C-7, C-12), 72.86 (2C, C-4, C-4′), 73.38 (2C, C-3, C-3′), 74.95 (2C, C-1, C-1′), 79.11 (2C, C-5, C-5′), 93.17 (2C, C-2, C-2′), 174.11 (2C, C-6, C-13); MS (EI) *m*/*z*: 408 (M^+ 100); Anal. Calcd for $C_{22}H_{28}FeN_2O_2$: C, 64.71; H, 6.91. Found: C, 65.08; H, 7.13.