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Article

The Synthesis of Tetrakis(*N,N*-Dimethylaminomethyl)ferrocene and its Bimetallic Nickel(II) Dichloride Complex: Key Precursors for Methoxycarbonylation Ligands

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Abstract

The family of *N,N*-dimethylaminomethylferrocenes is one of the most important in ferrocene chemistry. They serve as precursors for a range of anti-malaria and anti-tumour medicinal compounds in addition to being key precursors for ferrocene ligands in the Lucite alpha process. A brief discussion on the importance of, and the synthesis of *N,N*-dimethylaminomethyl-substituted ferrocenes preludes the synthesis of the new ligand 1,1′,2,2′-tetrakis-(*N,N*-dimethylaminomethyl)ferrocene. The crystal structure of this compound is reported and a comparison is made with its disubstituted analogue, 1,2-bis-*(N,N*-dimethylaminomethyl)ferrocene. The tetrahedral nickel dichloride complexes of both these ligands have been crystallographically characterised. Finally, a pointer to future research in the area is given which includes a discussion of a new method to extract ferrocenylmethylamines from mixtures using additives and a new synthetic avenue from substituted cyclopentadiene itself.

Keywords: ferrocene; amine; synthesis; crystal structure; anti-malaria; precursor

1. Introduction

Metallocenes have applications in a broad range of materials and medicinal science [1–12]. We have a longstanding interest in these compounds and have sought to facilitate the rapid synthesis of ferrocene derivatives. We have developed the synthesis of a range of tetra-substituted ferrocenes such as haloferrocenes [13,14], trimethylsilyferrocenes [15], lithioferrocenes [16], and phosphinoferrocenes [17]. One related subclass of compounds in the metallocene family is the class of ferrocenylalkylamines. We have a particular interest in this compound class because it is the one which led to the development and synthesis of literally thousands of ferrocene-based ligands. Refining this class of compounds still further, one compound stands out in importance partly due to its simplicity of structure and ease of synthesis. This is the commonly used precursor compound *N,N*-dimethylaminomethylferrocene, **1**, [18,19] (Figure 1) which was one of the original ferrocenylalkylamines, made in the pioneering days of ferrocene chemistry research. Its synthesis is a simple Friedel Crafts reaction using a phosphoric acid "catalyst" and bis-*N,N*-(dimethylamino)methane [18]. Simple substitution of this compound led to the family of chiral alkylamines developed by Ugi and co-workers [20] followed by others [21–27] which in turn led to the family of chiral phosphines [28,29]. As a commercial precursor it is relatively inexpensive and it may be used as a substitute for the more expensive chiral *α-N,N*-dimethylaminoethylferrocene, **2** in

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synthetic route development. In these compounds the fuctionalised nitrogen-containing group may also be changed readily. There are several anti-tumour and anti-malaria compounds which derive from compound **1** which have been under investigation for many years. The anti-malarial family of ferroquine compounds **4**, which are essentially ferrocene analogues of the anti-malaria drug chloroquine (CQ), stand out in their importance in medicinal chemistry [30–32]. Chloroquine (CQ) **5** (Figure 1) was used for the treatment of people infected by the *Plasmodium falciparum* (*Pf*) parasite that causes malaria; however, due to widespread use, strains of the parasite that are resistant to the drug have formed across the world [33]. Many researchers have worked on these and related compounds; however, the main research in the ferrocene area has been championed by research groups in France, primarily by Biot and coworkers [34–41]. Ferroquines and chloroquines were also among the earliest compounds examined in the fight against COVID19 [42,43].

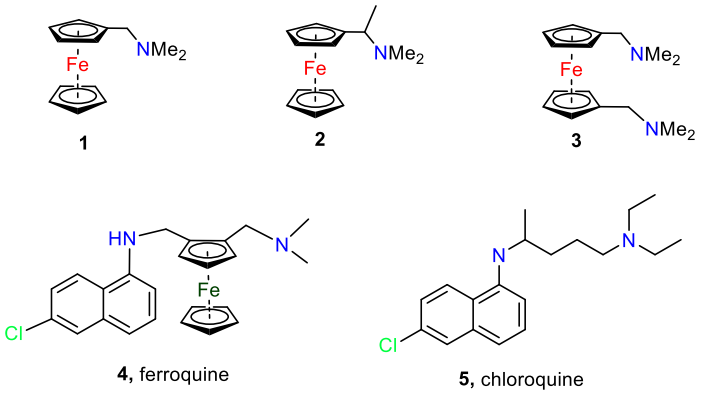

Figure 1. Key ferrocenylalkylamines **1-3** and a structural comparison with the anti-malaria compounds ferroquine **4** and chloroquine **5**.

We have used compound **1** in many applications, the most important of which is as a synthon on the route to ferrocene-based ligands used in the alpha process [44–46]. The related 1,1′-bis-(*N*,*N*-dimethylaminomethyl)ferrocene **3** (Figure 1) was reported by Glidewell and coworkers [47] and we have reported the synthesis of the related 1,2-bis-(*N*,*N*-dimethylaminomethyl)ferrocene **6** and 1,2,3-tris-(*N*,*N*-dimethylaminomethyl)ferrocenes **8** (Figure 2) [48,49]. Compound **6** is converted to its phosphine analogue *butphos* **14** which is the parent ligand in the ferrocene family of *alpha* ligands. The natural progression of the work is the preparation of 1,1′,2,2′-tetrakis-(*N*,*N*-dimethylaminomethyl)ferrocene **15** (Figure 2). The clean synthesis of this compound would be expected to be simple using lithiation methods, but product mixtures, which were extremely difficult to separate using conventional chromatography, were invariably formed. The newly developed methods are considered unsuitable because the quench reagent in the preparation of these methylamines is Eschenmosser's salt, which has a very low solubility in non-polar solvents; changing the solvent would lead to isomerisation. This compound was sought as a precursor to a range of compounds including the 1,1′,2,2′-{tetrakis-(*tert*-butyl-methyl)phosphino}ferrocene, which will be an excellent ligand for palladium-catalysed alkoxycarbonylation.

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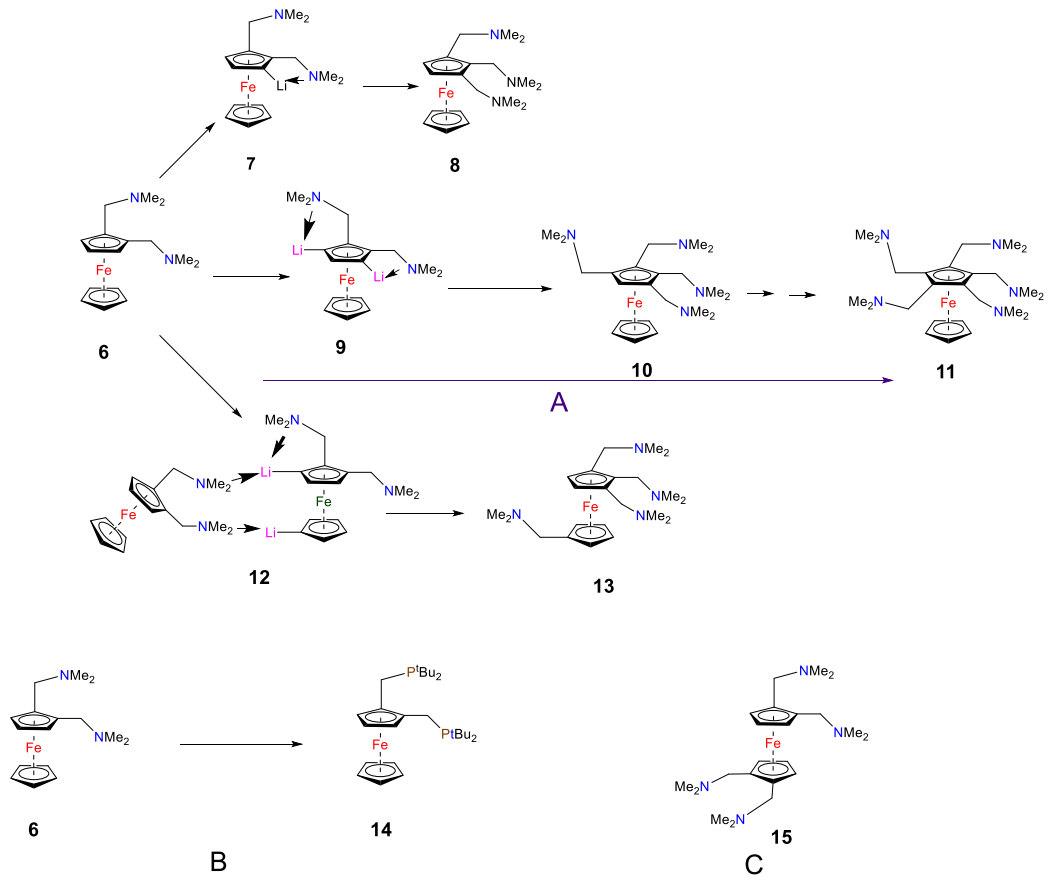

Figure 2. A: schematic of the lithiation of compound **6** to compound **11** showing problems with the synthetic route as the formation of lithium adducts such as **12** can result in the formation of **13**, **B:** formation of *butphos*, **14**, from compound **6**, and **C:** the target compound **15** for this work.

The lithiation of *N,N*-dimethylaminoalkylferrocenes has been studied extensively because of its importance to ligand chemistry [50–52]. It is a simple synthesis in that it is one of the first studied directed lithiations of ferrocene compounds. Mechanistically it is possible the lithiation can take place on the alpha carbon before the lithium is transferred to the alpha position on the ferrocene ring or more likely directly on the ring, like that of *N,N*-dimethylbenzylamine (Figure 3). We should also be aware that Eschenmoser's salt, being a quasi-alkyl halide, can quaternize the amine or take part in more complex reactions as we have observed previously; see structure in Figure 3. At the outset it is important to recognise that there are several inherent problems in the use of lithiation methodology for the preparation of multiply substituted ferrocenes containing a directing group: the first problem is that of *over-* or poly-lithiation i.e., preparation of mixtures of more highly substituted products are formed which may be difficult to separate. For example, in the lithiation of compound **6,** additional lithiated compounds such as **9** and **12** can form. A second problem is that the products become more air-sensitive due to iron oxidation as the degree of substitution increases.

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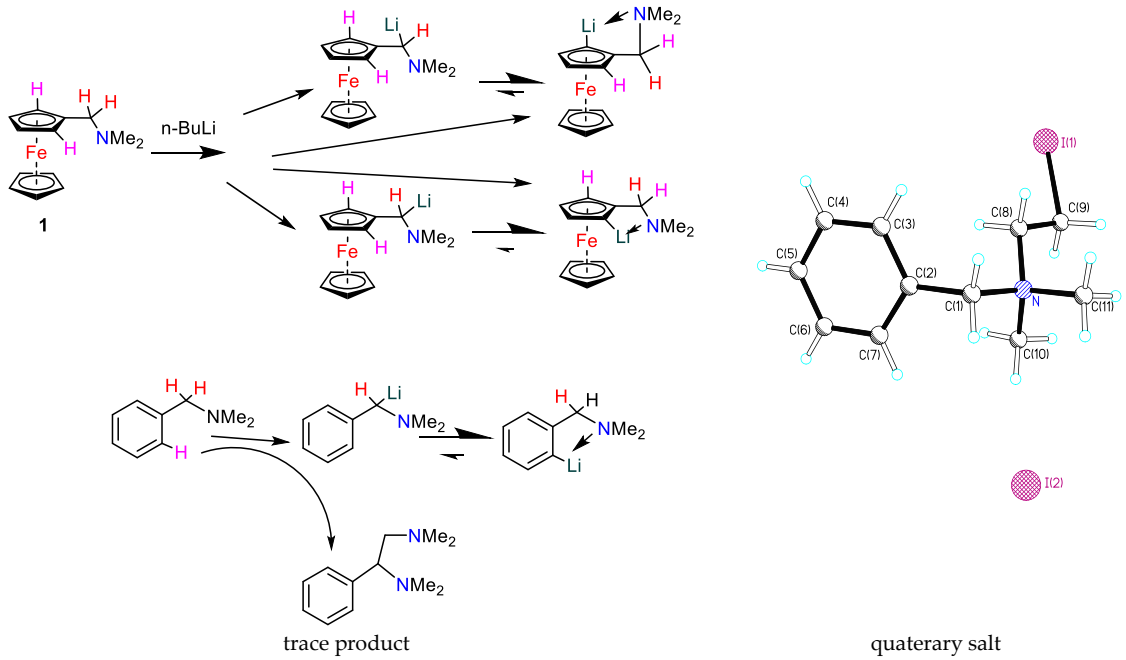

Figure 3. On the mechanism of lithiation of ferrocene and benzene methylamines. In the left section the lithiation of *N,N*-dimethylaminomethylferrocene indicates that the Cp-ring protons and the methylene protons may be exchanged with lithium directly or indirectly, ultimately leading to the lithioferrocenes. In the lower left the analogous benzylamine may also be alpha lithiated in the normal fashion or the Eschenmoser's reagent can act as an alkyl iodide to give the quaternary salt as shown by the crystal structure on the right-hand side.

Finally, the products may be oils at room temperature, making purification very difficult, although it may be possible to crystallise, if not separate, their ammonium salts reasonably easily. These ferrocenyl-alkylamines tend to elute when using column chromatography as overlapping diffuse bands, even on a basic alumina support, making compound separation difficult, if not impossible. Given that we have spent an inordinate time attempting the synthesis of pure ferrocenylmethylamines, it was felt that finding a simple synthetic solution to the problem would be a good objective. The target compound was set as compound **15,** Figure 2, as it was felt that once the synthesis was achieved the method could be easily generalised to other multiply substituted derivatives.

2. Results

Initially it was thought that the synthesis should be reasonably routine (Figure 4) as it combines both the previously reported synthetic methods. However, the problems mentioned in the introduction have played a part in the delayed reporting of this synthetic method. Part of the problem is ensuring that the intermediate compounds are pure. Based on the deceptively simple synthetic route shown in Figure 4, we had attempted the synthesis many times, over many years, but the recurrent problem of the difficult final purification of mixtures obtained by over/under-lithiation thwarted the publication of the results. Typically, mixtures of products were obtained which were similar to those that also plagued the attempted synthesis of 1,2,3,4-tetrakis(*N,N*-dimethylaminomethyl)ferrocene **10** and 1,2,3,4,5-(pentakis-*N*,N-dimethylaminomethyl)ferrocene **11**.

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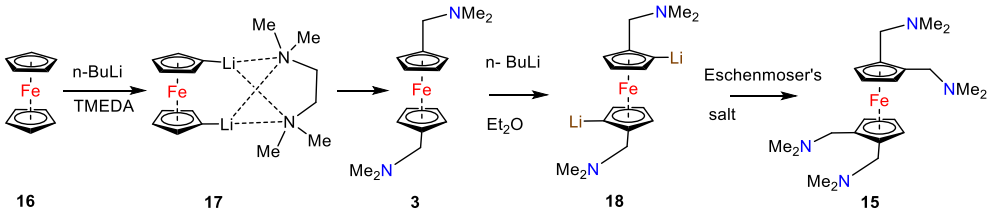

Figure 4. Synthetic route to target compound **15**.

The problem is that all the amino groups may act as lithium directors as well as coordinating groups just as TMEDA does (Figure 4), so both cyclopentadienyl rings may be multiply lithiated. As an example, in the preparation of compound **4** from **3** many different lithiations may take place dictated by kinetics, including the formation of bimolecular intermediates such as **12**. There is direct evidence for this type of intermediate as Sp-3 as shown by Strohmann and co-workers [55,56], who proved that a dimeric complex is present during the asymmetric lithiation of **3** in pentane using iso-propyllithium as the lithiating reagent (Figure 5, reproduced with permission).

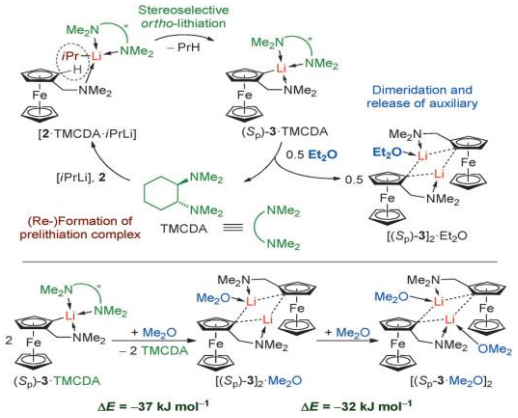

Figure 5. Reproduced in full, with thanks, with permission from "Stereoselective ortho-Lithiation of a Ferrocene Derivative, Strohmann *et al.* [55], *Angewandte Chemie*. Original Caption: Postulated catalytic cycle for the stereoselective ortho-lithiation involving dimerization of the lithiated substrate [(Sp)-3] to the etherate [(Sp)-3]2·Et2O under release of the chiral auxiliary TMCDA. Below: Computed energies for ligand exchange/dimerization processes of (Sp)-3 under release of TMCDA [M052X/6-31+G(d)].

When the synthesis is carried out according to the synthetic route shown in Figure 4, compound **15** is the major product (46% based on integration); however, many by-products in which both rings were substituted are clearly present and, not surprisingly, these are almost impossible to separate on any meaningful scale using standard column chromatographic techniques.

This can be seen in a typical NMR spectrum of the product mixture which is shown in Figure 6. In the top left of Figure 6(a) the *N*-methyl region of the spectrum may be used as a diagnostic where there are several singlets. When compounds **3** or **6** are used as precursors we know such complications result in the formation of a range of mixed products. After considering all these problems it was possible to develop a high-yielding synthesis of compound **15**. The answer, which came about after numerous methodological adaptations, was simply to control the lithiation and use hexane or hexanes as the solvent with only a small quantity of diethyl ether added: the lithiation takes place slowly because of the solvent change but has the effect of precipitating the bright yellow di-lithium adduct **18** which may then be effectively quenched (Figure 4). Here again the di-lithium product is likely to be much more complicated than is depicted in the figure, but from a practical perspective this representation serves the purpose. Compound **15** is a solid at room temperature and may be crystallised, although traces of the starting material and trisubstituted compound tend to co-crystallise. Its NMR spectrum is essentially as anticipated with the typical ferrocene doublet and triplet resonances at 3.88 and 4.04 ppm respectively and is shown in Figure 6b (left). For reference a sample of a typical preparation in diethyl ether is

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shown for comparison. In the latter preparation there are 6 -NMe_2 singlets which essential equates to 3 products, one of which is compound **15**. The other products are isomers of tris-methylamines and *tetrakis*-methylamines such as **13**. We will briefly discuss what chemical modifications may be carried out on mixtures in a later section. However, because in the new synthesis the target compound **15** is formed essentially pure, the crystallization is now an easy process. Its crystal structure is shown in Figure 7 in which the nitrogen atoms lie above the cyclopentadienyl rings which are essentially fully staggered.

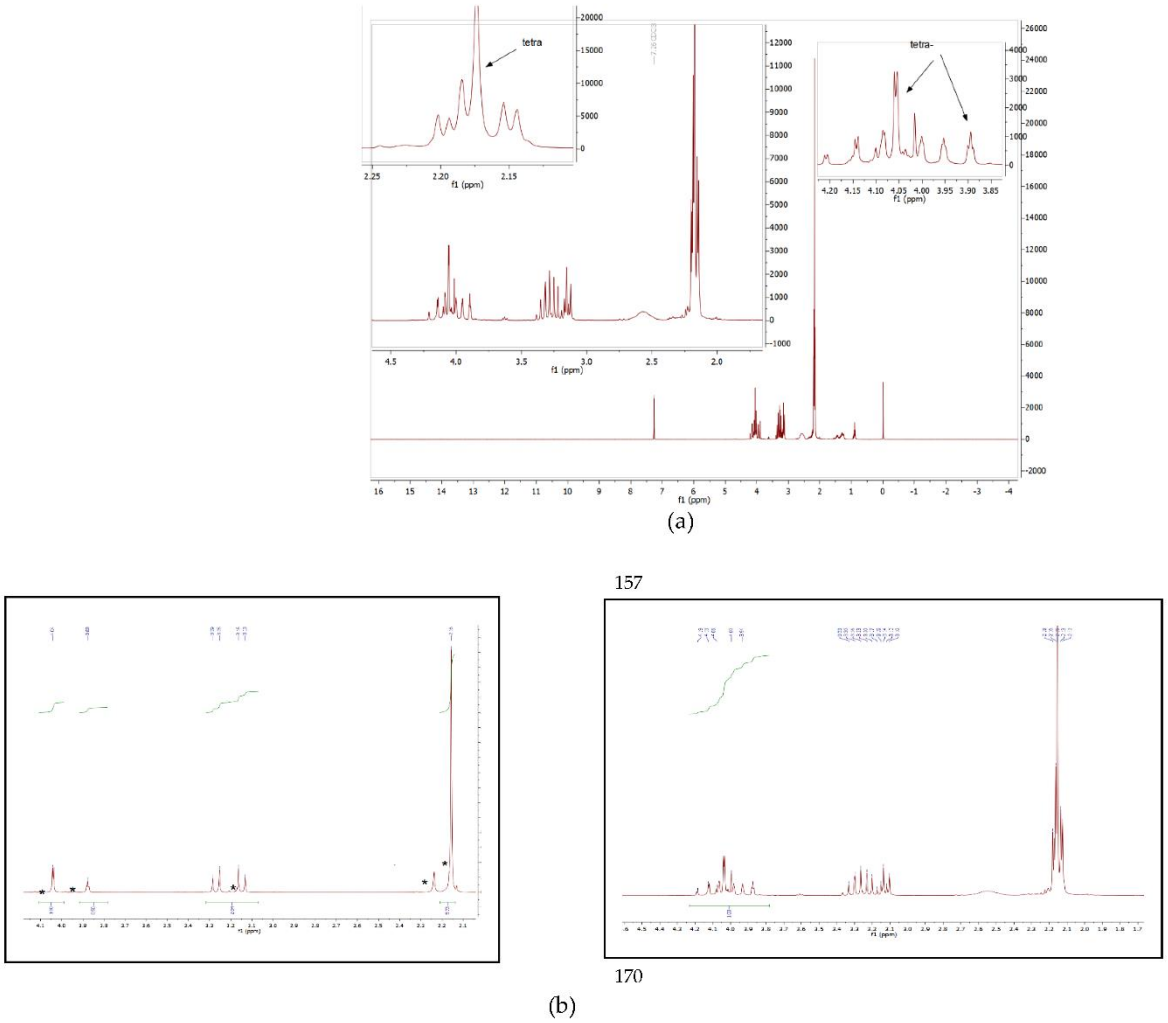
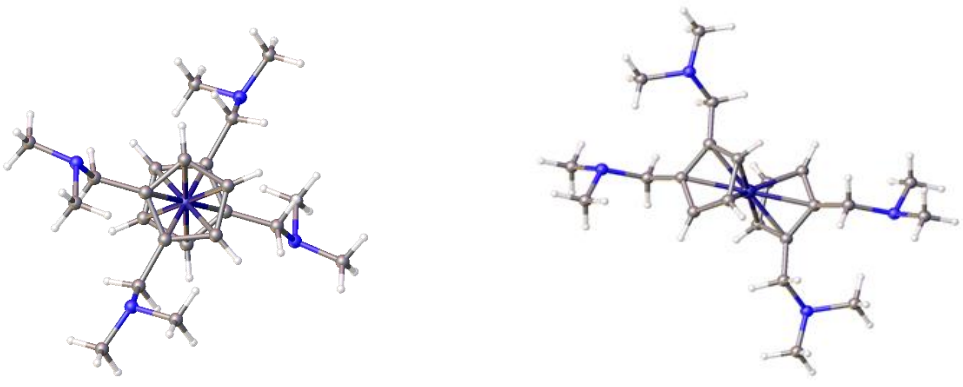


Figure 6. ^{1}H NMR spectrum of **a**: *tetrakis*-*N*,*N*-dimethylaminomethylferrocene when prepared in ether compared with **b:** left, preparation in hexane; right, the analogous ether preparation on the same scale.



(**a**) (**b**)

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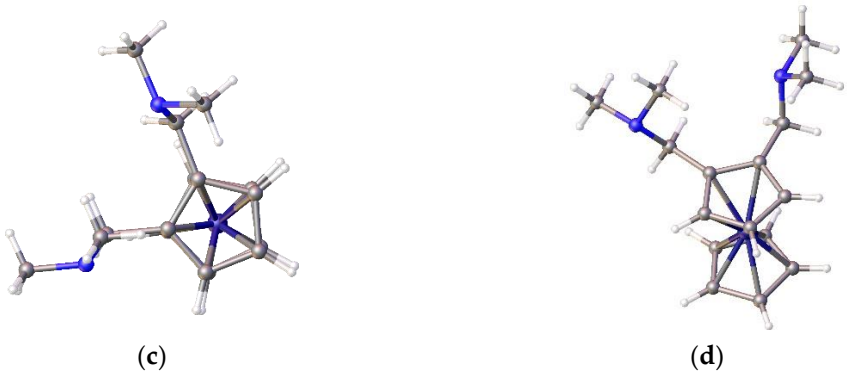

(**c**) (**d**)

Figure 7. (a) Top and **(b)** side views of 1,1′,2,2′-tetrakis(*N*,*N*-dimethylaminomethyl)ferrocene **15**, together with top **(c)** and **(d)** side views of the structure of 1,2-bis-(*N*,*N*-dimethylaminomethyl)ferrocene **6,** shown for comparison [44].

The present synthetic method is effective essentially because the di-lithium salt precipitates from solution, therefore isomerisation cannot take place. The use of these conditions will thus allow access to the range of all poly-substituted methylaminomethylferrocenes. There is no adverse steric crowding. In turn this should open the door to the facile synthesis of corresponding phosphines derivatives of these poly-dimethylaminoferrocenes. In the interim, it was decided to prepare the nickel complex of compound **15,** rather than the palladium derivative because the synthesis should be relatively more straightforward i.e. avoiding ortho-metalation (previously we have observed ortho-metallation of **6** with palladium [44]; see Figure **8**).

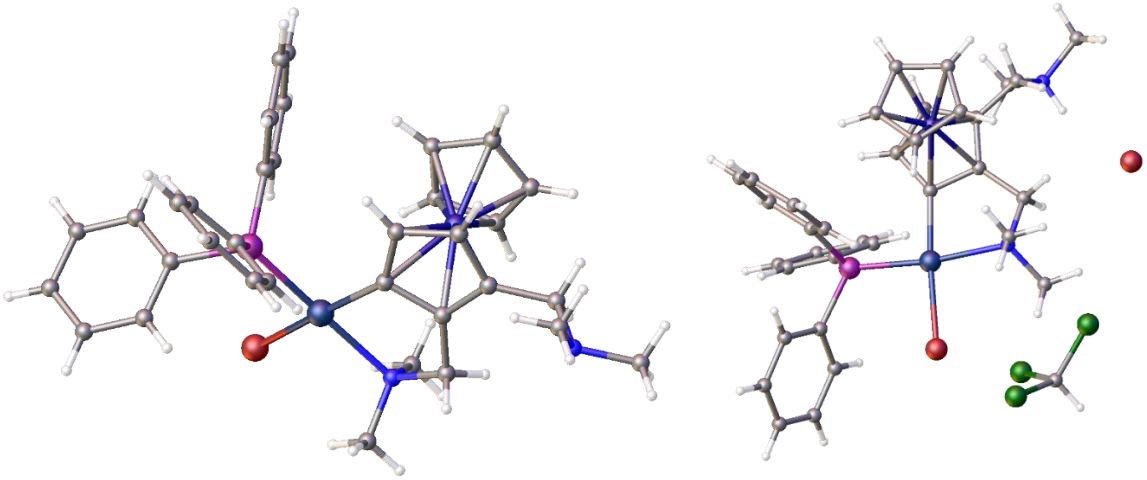

Figure 8. An example is where *ortho*-metalation occurs on reaction with palladium in preference to bidentate ligation. Crystal structure of the *ortho*-metallated palladium salt complex of compound **6,** which was trapped as a triphenylphosphine derivative **[44].**

As a model for the co-ordination chemistry for the alpha process (the industrial synthesis of methyl methacrylate) it might be hoped that this would be square planar rather than tetrahedral. The nickel dichloride complex of the ligand **15** was prepared by reaction with [Ni(DME)Cl_2] and this is shown in Figure **9** together with the structure of the previously known nickel complex of ligand **6**. The solvated violet nickel complex was very easy to prepare at ambient temperature and was structurally characterised. The coordination chemistry around the nickel was tetrahedral as could be predicted from the colour alone. Interestingly the top view shows the nickel dichloride units located opposite each other and the cyclopentadienyl rings are staggered. The conformation of the metalacyclic rings in all 3 complexes are almost identical

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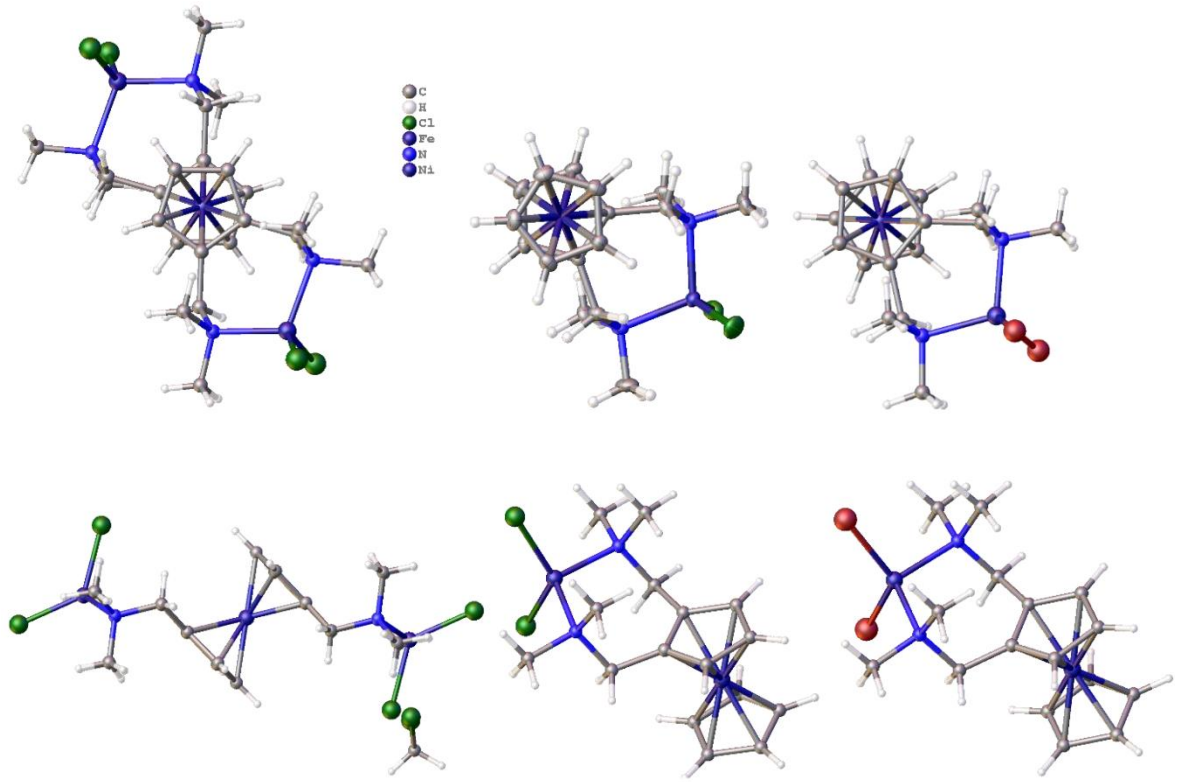

Figure 9. Comparison of the crystal structures of **(a)** the *bis*-(nickel dichloride) complex of compound **15** together with the crystal structures of the **(b)** nickel dichloride and **(c)** nickel dibromides of compound **6**.

This means that the catalysts which derive from these complexes should have similar activities or better activities. There is no adverse steric crowding.

2.2. Additional Information and Future Pointers.

As discussed earlier, when mixtures of *N,N*-dimethylaminomethylferrocenes are formed, compound separation using column chromatography is rarely successful; however, it is possible to obtain lower yields of individual compounds using chemical additives to derivatise the amines and hence crystallise the products. Firstly, quaternisation using methyl iodide has long been the long standard method used in extracting salts of ferrocenylmethylamines. This is not discussed in detail here as it has been successfully used for over 40 years or so and the product methiodides are easily crystallised from solution. In the case of compound **3** the mono methiodide readily crystallises from solution. For reference the crystal structure of a typical methylated salt is shown in the Supplementary Information. The second method is to use HBr to prepare the related hydrobromide salt but, rather than using HBr directly which can be messy, we have developed the technique of adding tetrabromoethane to an ether solution of the mixed amines. This has the effect of slowly adding HBr from the decomposing tetrabromoethane which normally results in a crystalline product. The *in situ* NMR reaction monitoring of the parent dimethylaminomethyl ferrocene and 1,1,2,2-tetrabromoethane in deuterochloroform indicated that the substituted aminoferrocene resonances are shifted progressively downfield during the reaction, indicating that the formation of a new product involved a rapid equilibrium (see Figure **10A**), rather than growth of new resonances into the spectrum, which would indicate the formation of new compounds. The resonances of the dimethylaminomethyl ferrocene did not shift in deuterochloroform in the absence of 1,1,2,2-tetrabromoethane, showing this was not a reaction of the amine with chloroform. This data was consistent with the formation of the protonated amine through deprotonation of 1,1,2,2-tetrabromoethane to give the *N,N*-(dimethylammonium)methylferrocenyl bromide salt.

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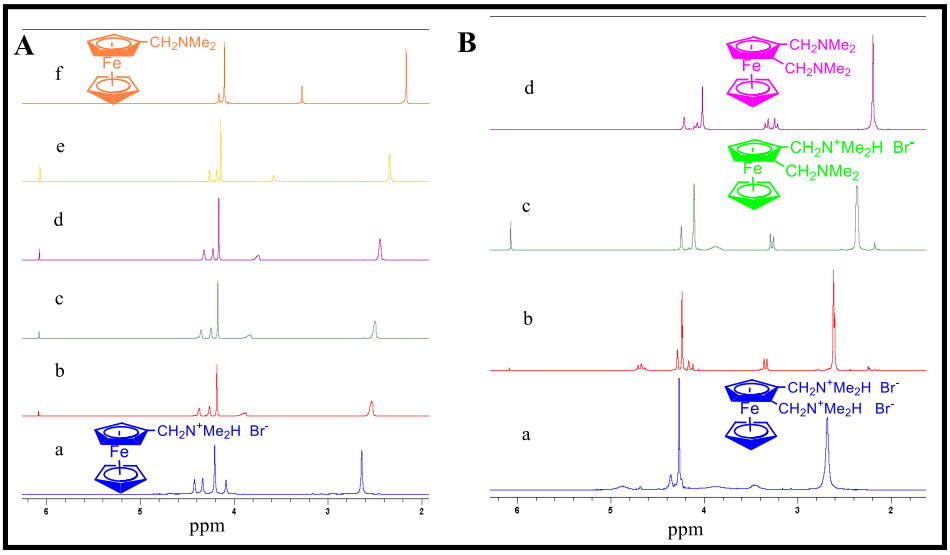

Figure 10. A: *In situ* NMR reaction monitoring in deuterochloroform indicates the formation of the dimethylmethyl(ferrocenyl)ammonium bromide salt. The resonances are shifted and some resonances become broader, as a result of exchange in the sample that is too fast on the NMR timescale. **Figure 10B**: (a) 1,2-bis amine **6** in $CHCl_3$ (no TBE); (b) 60 minutes after addition of TBE; (c) 120 minutes after addition of TBE; (d) *Ex situ* prepared 1,2-bis amine HBr crystals dissolved in $CHCl_3$. All spectra referenced to the shift of tetramethylsilane (TMS) (δ = 0 ppm).

A similar result is shown for compound **6** which forms the mono HBr salt rapidly, which subsequently changes to the less soluble bis HBr salt (Figure 10B). Both these results have been confirmed by crystallography. The most interesting feature of the structures is that in the mono-protonated salt of compound **6** (green in Figure 10) the proton sits between both pendant methylamine arms. The simplified methodology is universal: a solution of the appropriate amine (200mg) in diethyl ether (10 mL) was allowed to stand with an excess (0.5mL) of 1,1,2,2-tetrabromoethane for 4-5 days in the case of the ferrocenylethylamines. The crystals formed are removed by filtration and are washed with ether. To obtain crystals for structural work the crystals can be re-dissolved in the minimum quantity of dichloromethane or chloroform and then layered with petroleum ether (bp 40-60). Slow diffusion results in the formation of crystals suitable for diffraction experiments. To complete this discussion, the last method we have used to extract ferrocenylmethylamines is to add borane as its THF complex, which binds to the nitrogen to form the adduct(s) which may be crystallised. The borane adduct(s) are again easily crystallised and therefore structurally characterised.

As discussed in the introduction the next step in this work would be the preparation of the phosphine ligands which derive from these alkyl amines and their testing as ligands in the industrial methoxycarbonylation process. As we are no longer in the position to carry out this work in our own laboratories, we welcome on-line collaborations/interactions and we would be delighted to help other research groups. We have interesting preliminary data which we can share. At the time this work was carried out a concurrent project on the preparation of 1,2-diphosphinoalkylferrocenes was running in our laboratory, which has been published [17]. Both projects come together where mixed amine phosphine complexes are prepared such as the one shown below.

This work involves common precursor compounds, generally 1,2-dithioferrocenes or 1,2-di-substituted cyclopentadienes, which are key precursors in the synthesis of metallocenes, but themselves are rare. Related to the 1,2-*bis*-(*N*,*N*-dimethylaminomethyl)ferrocenes, discussed here, are the corresponding 1,2-bis-(disubstitutedphosphino)ferrocenes, as both have common precursors; see Figure **11** for ligand comparisons. Additional crystallographic data are given in the Supplementary Information. In this context, we, and many others, have been particularly interested in ferrocenylphosphines which can be synthesised from ferrocene itself or from the appropriately

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substituted cyclopentadiene. In the former synthetic method ferrocenylphosphines have been primarily prepared from the reaction of chlorophosphines with ferrocenyllithiums, but the latter synthetic method uses preformed cyclopentadiene salts. We can report that we have been able to isolate the naked 1,2-diphenylphosphinocyclopentadiene as its nickel dichloride complex, where clearly iron has been removed leaving a substituted cyclopentadiene, i.e. the decomposition of the ferrocene had occurred on complexation. This occurred during our complexation studies in strong magnetic fields [57], but without further evidence we cannot be sure the magnetic field played a role. What is evident, however, is the isolation of a crystalline sample of the nickel dichloride complex of *bis*-1,2-(diphenylphosphino)cyclopentadiene **19**. The structure of this complex is shown in Figure **12**. It is essentially a mixture of two conformers/resonance forms. Essentially this means that the metal-complexed substituted cyclopentadienes themselves may be isolated and used to build the corresponding metallocene complexes. This is an interesting future research challenge, which we hope others will now take forward.

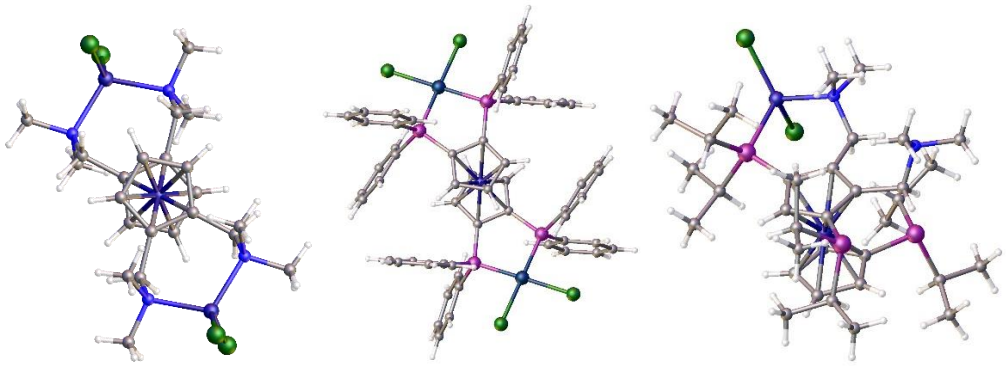

Figure 11. left, $NiCl_2$ complex of compound **15**, tetrahedral; middle, $NiCl_2$ complex of 1,1′,2,2′-tetraphenylphosphinoferrocene, square planar [57]; right, $NiCl_2$ complex of a mixed 1,2-dimethylaminomethyl-ferrocenyltriphosphine complex, tetrahedral, showing binding between the amine and one phosphine group.

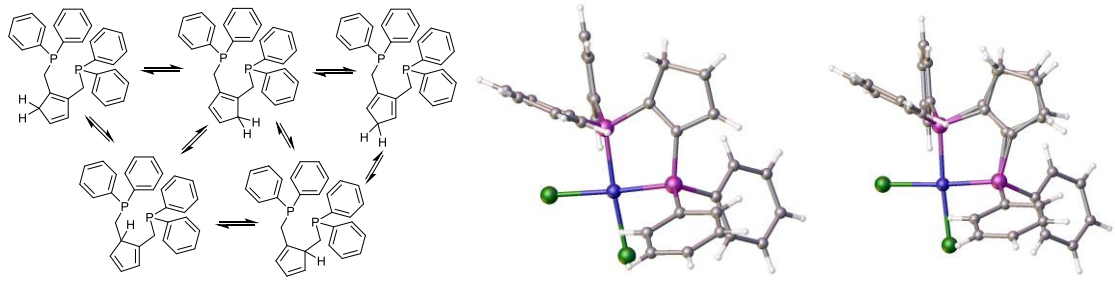

Figure 12. The crystal structure of the complex $[(1,2\text{-}C_5H_3(PPh_2)_2NiCl_2]$ **19′;**, middle, single conformer; right, both disordered conformers.

Finally, we note that an alternative precursor compound 1,1′-dibromo-[2,2′-bis-(*N*,*N*-dimethylaminomethyl)]-ferrocene **20** is now available in our laboratories since the present work was carried out and may be a convenient reagent which may be used as a mixture of diastereomers. Further details of these compounds are available in the Supporting Information.

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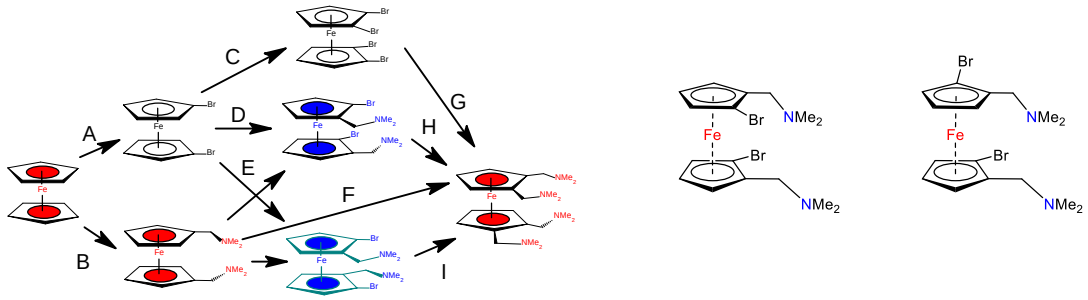

20 a, b

Figure 13. the synthetic routes to the tetramethylamine **15:** red , this paper; blue, route via dibromoferrocenes, **20**a,b, which are possible to use.

3. Materials and Methods

3.1. Synthetic Work

Experimental Section

3.2. 1,2-Bis-(N,N-Dimethylaminomethyl)ferrocene (6) [44,45]

N,N-dimethylaminomethylferrocene **1** (24.3 g, 100 mmol) was added to a solution of hexane (100 ml) and dry ether (200 ml) in a 3-necked round-bottom flask equipped with a stopper, septum, nitrogen bubbler and magnetic stirrer. *N*-Butyllithium (40 ml of a 2.5 molar solution) was added by syringe and the reaction mixture was stirred overnight. The reaction vessel was cooled in an acetone/liquid nitrogen bath to below -50°C, before quenching with Eschenmoser's salt (18.5 g, 100mmol). Without removal from the bath, the mixture was allowed to warm slowly to room temperature. The solution/slurry was then diluted with 200 ml water and the aqueous and organic layers separated and the organic layer was washed with 3x100 ml water. The organic solution was dried over $MgSO_4$, the solvent removed, and the product dried under high vacuum to yield the product as a dark red oil. The oil was then crystallized in petrol (-20°C) to give 27.3g, 91% product. ^{1}H NMR ($CDCl_3$) δ = 4.21 (d, 2H), 4.08 (t, 1H), 4.02 (s, 5H), 3.38 (dd, 4H), 2.20 (s, 12H). ^{13}C NMR - DEPTQ ($CDCl_3$), δ, 45.47 (N-CH3), 57.56 (-CH2-), 68.14 (cp), 68.61 (cp), 69.39 (cp), 70.52 (cp); MS: 300.07 [M]+, 287.24 [M-CH_3]+., 255.22 [M-N(Me)$_2$]+., 240.27 [M-N(Me)$_2$,-CH_3]+. N.B this compound, like ferrocene, is easy to sublime under high vacuum conditions and is obtained as a highly crystalline compound [44,45].

1,1′-Bis-(*N,N*-dimethylaminomethyl)-ferrocene **5. (**Prepared from 1,1′-dilithioferrocene).

This compound is ideally obtained from a pure solid sample of 1,1′-dilithioferrocene.TMEDA which, when powdered, is a pale orange colour. This is suspended in an ether/hexane 50/50 mixture and reacted with Eschenmoser's salt in the general manner. We normally prepared bulk samples of the dithium salt and stored them in a large Schlenk tube. However, for researchers without such Schlenkware, simply dilthiating ferrocene in the presence of TMEDA in hexane will give a satisfactory source of this compound. Under these conditions, on quenching the product is likely to contain some ferrocene and some monoamine product. The ferrocene is easy to remove by extracing the amine products into an aqueous solution of 10% phosphoric acid and then discarding the organic layer containing ferrocene. After fresh ether is added the aqueous amine salt solution can then be back-extracted into ether carefully with 10% aqueous sodium carbonate before the ether solution is separated and dried over magnesium sulfate

H NMR: 2.15 (s, 12H), 3.25(s, 4H), 4.05 (dd, 4H), 4.07 (dd, 4H). ^{13}C 44.86 (N<u>C</u>H$_3$), 59.30 (<u>C</u>H$_2$)), [68.76 (s) 70.73 (s) subs. Cp] 83.54 (*ipso*-Cp).

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3.3. 1,2,1′,2′ -Tetrakis(N,N-Dimethylaminomethyl)ferrocene 15. (Original Method)

Note: Since Escenmoser's salt is essentially insoluble in hexane any quench requires the use of diethyl ether or even thf as a solvent; however, the lithiation must be carried out in predominantly hexane to avoid the formation of isomers.

1,1′-bis-(*N,N*-dimethylaminomethyl)-ferrocene **5** (2.65 g, , 8.83 mmol) [47] was added to a solution of hexane (100 ml) in a 3-necked round-bottom flask equipped with a stopper, septum, nitrogen bubbler and magnetic stirrer. *N*-Butyllithium (8 ml, 20 mmol) was added by syringe. A few mL of diethyl ether (ca 5 mL) is added and the reaction is stirred for 24h. This should result in the formation of a bright yellow precipitate of the dilithium salt. If there is no obvious change to the initial solution colour, add a few more mL of diether ether and again stir until the yellow precipitae forms. It may be necessary to repeat the addition of ether up to 3 times. Diethyl ether (10ml) was added and the solution was stirred for a further 1h. The solution was then diluted with 100 ml water and the phases were separated. The organic layer was washed with 3x100 ml water and then dried over $MgSO_4$. After the removal of volatiles the product was dried under high vacuum to yield the product as a dark red oil (86.1% yield). This oil was recrystallized from hexane* to give the pure product. ^{1}H NMR ($CDCl_3$) δ, 4.07 (d, 4H), 3.91 (t, 2H), 3.30 (d, 4H), 3.17 (d, 4H), 2.19 (s, 24H). ^{13}C NMR - DEPTQ ($CDCl_3$) δ, 45.27 (N-CH_3), 56.90 (-CH_2-), 69.04 (cp), 71.85 (cp); 84.15 *(ipso*-Cp). MS: 414.03 [M]+, 383.14 [M-$(CH_3)_2$]+, 369.19 [M-N$(Me)_2$]+,268.32 [M-(($CH_2N(Me)_2)_2$-$(Me)_2$). (*the product crystallises at room temperature from a few ml of hexane if left to stand for 24h; if crystallization does not begin, the vessel may be cooled to -20^{0}C to facilitate crystallization, but the product may contain trace impurities.)

3.4. Preparation of Nickel Complex of 1,2,1′,2′-Tetra-(N,N-Dimethylaminomethyl)ferrocene

In dichloromethane (20 ml) nickel(dimethoxyethane) dichloride (1.0 g) was treated with 1,2,1′,2′-tetra-(*N,N*-dimethylaminomethyl)ferrocene **9** (1.0 g, excess). The mixture was rapidly agitated and then left to settle. Over the course of 24-48 hours, a violet colour developed. A layer of diethyl ether (20 ml) was added on top, taking care that the layers do not mix initially and the layers were allowed to diffuse over 5 days. The product was filtered to give deep violet crystals which were separated form the powdered material residue in approx. 80% yield based on the ligand. (To obtain a quantitive yield, stir the mixture for 2 weeks and then filter off the solid product which can be extracted with dichloromethane and dried to give the product, which in this case contains microcrystals).

3.5. Alternative Synthetic Method for Compound 15

The second method used to form lithio-ferrocenylmethylamines is the exchange reaction of brominated ferrocenes. As we were working on the direct lithiation outlined in part 1 we were also examining the formation of brominated ferrocenylmethylamines for use as precursors in our work as well as the range of bromoferrocenes we had previously developed. We also were able to use 1,1′-dibromo-2,2′-bis-(*N,N*-dimethylaminomethyl)ferrocene, which may be made either by dilithiation of 1,1′-bis-(*N,N*-dimethylaminomethyl)ferrocene (quenched with dibromohexafluoropropane) or from dilithiated 1,1′-dibromoferrocene [57] quenched with Eschenmoser's salt. Note that

1,1′-dibromo-2,2′-bis-(*N,N*-dimethylaminomethyl)ferrocene was used as a mixture of diastereomers.

Thus the compounds **3**, **6** and **15** may be additionally obtained from analytically pure samples of the coresponding bromine analogues, i.e., 1,1′-dibromoferrocene, 1,2-dibromoferrocene, and 1,1′,2,2′-tetrabromoferrocene by complete halogen exchange with t-butyllithium (slight stoichiometric excess with respect to the number of bromines in starting material) at -30^{o}C in a 50/50 hexane/ether mixture followed by the addition of a slight stoichiometric excess of Eschenmoser's salt and warming to room temperature and holding at room temperature for 4-5 hr. Workup involves quenching with a dilute sodium bicarbonate solution, ether extraction and drying with $MgSO_4$. The yields range between 85 and 95%.

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4. Conclusions

In general, the synthesis of multiply substituted ferrocenylmethylamines is complicated by the fact that the precursor compounds themselves are normally also ferrocenylmethylamines, with methylated amine groups which themselves function as lithium directing groups. We conclude that it is better not to add additional reagents such as TMEDA unless the precursor is ferrocene itself, i.e not an amine precursor. The solvent of choice is hexane because the product lithiated salts themselves will precipitate in a pure form, although a small amount of ether is generally required to provide the solubility necessary to drive the reaction.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Part A: Figures and crystal structural data for 9 compounds and Part B: NMR spectra of the products including lithiation studies. Structure of compound **15**, 1,1′,2,2′-*tetrakis*-(*N*,*N*-dimethylaminomethyl)ferrocene. Date Code: 2016ncs0380; $C_{22}H_{38}FeN_4$. CCDC No 2481501. Structure of compound **6**, (lit) 1,2-*bis*-(*N*,*N*-dimethylaminomethyl)ferrocene. Date Code: 02src144; $C_{16}H_{24}FeN_2$. CCDC No 236435 Structure of Tetrachloro-dinickel complex of compound **15**, (dichloromethane solvate), Date Code: 2016ncs0370; $C_{24}H_{42}C_{18}FeN_4Ni_2$. CCDC No 2481502. Structure of Dichloro-nickel complex of compound **6**, Structure Code: ssf1245; $C_{16}H_{24}Cl_2FeN_2Ni$. CCDC No 2121223. Structure of Dibromo-nickel complex of compound **6**, Structure Code: ssf1244; $C_{16}H_{24}Br_2FeN_2Ni$ CCDC No 1966126. Structure of methiodide salt of compound **6**: Structure Code: 02src283**;** $C_{17}H_{27}FeIN_2$ CCDC No 2481503. Structure of Dichloro-nickel complex of the bis-(trimethylsilyl)- compound **6**, Structure Code ssf0791; $C_{52}H_{52}Br_2FeN_2NiSi_2{\cdot}CH_2Cl_2$ CCDC No 1965846. Structure of the [***N,P***]-Dichloro-nickel complex of 1,2-*bis*-(*N*,*N*-dimethylaminomethyl-*tris*-3,5-1′-tris-diisopropylphosphino)ferrocene. Structure Code sse1098; $C_{34}H_{39}BrFeN_2PPd^{+}{\cdot}Br^{-}.CHCl_3$. CCDC No 1965610. Structure of the $NiCl_2$ complex of 1,2-Cp(PPh_2), compound **19**, $C_{29}H_{24}Cl_2NiP_2$, CCDC No. Total number of Crystallographic Tables 75.

Author Contributions: P.N.H.: Crystallographic analysis, crystal data handling, and data deposition. W.C.: Crystallographic analysis, director of synchrotron crystallographic facilities. S.J.C.: Director of laboratory-based National Crystallographic Services and project overseer. I.R.B.: Conceptualization, methodology, synthetic work, writing, review and editing. S.E.: synthetic work, literature research and paper drafting. L.M. manuscript proofing project supervision. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Please refer to suggested Data Availability Statements in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics. You might choose to exclude this statement if the study did not report any data.

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