1,1´,2,2´-Tetralithioferrocene and 1,1´,2,2´,3,3´-Hexalithioferrocene: Useful Additions to Ferrocene Precursor Compounds.

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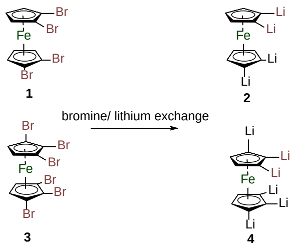
Ferrocene; lithioferrocene; synthesis; organometallic; lithiation.

ABSTRACT: The direct synthesis of 1,1´,2,2´-tetralithioferrocene from 1,1´,2,2´-tetrabromoferrocene is reported. In addition, the related 1,1´,2,2´,3,3´-hexalithioferrocene is also described, prepared directly from 1,1´,2,2´,3,3´-*hexa*-bromoferrocene. These lithioferrocenes may be isolated as orange red (tetralithio-) and red (hexalithio-) powders, respectively. When these are prepared in situ and reacted with chlorotrimethylsilane, the corresponding tetrakis-1,1´,2,2´-tetrakis(trimethylsilyl)ferrocene and 1,1´,2,2´,3,3´-hexakis(trimethylsilyl)ferrocene are obtained as red and crimson crystalline solids respectively. The single crystal structures of 1,1´,2,2´-*tetrakis*(trimethylsilyl)ferrocene, **11**, and 1,1´,2,2´,3,3´-*hexakis*(trimethylsilyl)ferrocene, **12**, have been determined and are described.

Introduction

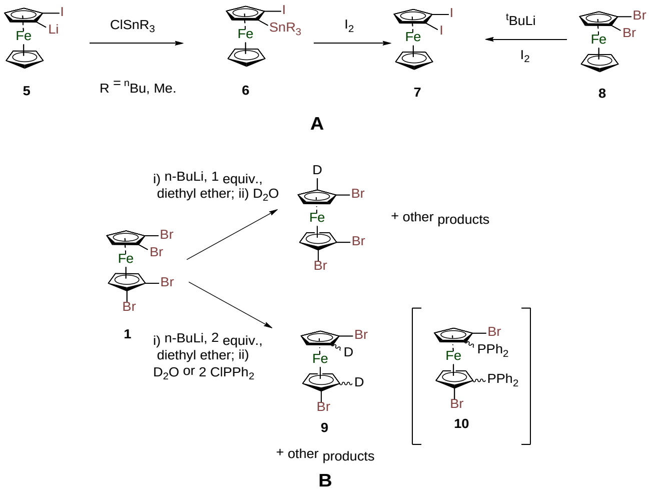
Metallated ferrocenes are an important family of compounds because of their general synthetic utility.[1] One subgroup of these compounds is the lithiated ferrocenes.[2] The mechanism of the lithiation has been examined.[3] Arguably the most synthetically useful compound has been the 1,1´-dilithioferrocene.TMEDA complex,[4] which is used in the preparation of a wide range of disubstituted ferrocenes, prominent among these being the well-used ligand dppf,[5] 1,1´-ferrocenedicarboxylic acid,[6] ferrocene-1,1´-dicarbaldehyde,[7] and 1,1´-dibromoferrocene.[8] The latter compound, in turn, serves as a precursor to pure 1,1´-dilithioferrocene.[9] We have developed the synthesis of *ortho*-lithiated derivatives[10] of the bromoferrocene and 1,1´-dibromoferrocene and this work has been augmented in several recent papers from other research groups, and this has turned into an active area of ferrocene synthesis.[11] Our focus was always to develop a high yielding syntheses of any ferrocene by simple methods[12], and in this context we have recently reported the characterisation of 1,1´,2,2´-*tetra*-bromoferrocene and related bromoferrocenes.[13] This area of research is topical with many recent references in the area on the halide mediated lithiation reaction and the isomerisation - “halogen dance” of the intermediates.[14] Clearly by analogy with both 1,2-dibromoferrocene and 1,1´-bromoferrocene these compounds should serve as versatile precursors towards many substituted ferrocenes, e.g. Scheme 1. This paper is the first of many applications carried out on the preparation of highly lithiated ferrocenes. This work complements that of Mulvey et al. [15] on metallated ferrocenes.



Scheme 1: Possible direct route to 1,1´,2,2´-tetralithioferrocene, **2**, and 1,1´,2,2´,3,3´-hexalithioferrocene, **4**, by lithium bromine exchange reactions.

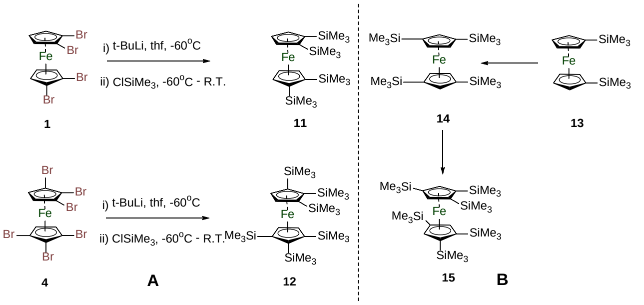
Results and Discussion

The reaction of 1,2-dibromoferrocene with butyllithium has been used previously by us in the preparation of a series of phosphanes[16] but we had experienced some problems when trying to remove two bromine atoms concurrently, so we anticipated problems with the attempted simultaneous removal of four bromine atoms to give the *tetra*-lithium compound. Merieter and co-workers experienced similar problems in the preparation of 1,2-diidoferrocene from 1,2-dibromoferrocene and they used the 2-trimethylstannyl compound **6**, R = Me, as an intermediate in its synthesis.[17] However recently it has been reported that the reaction of 1,2-dibromoferrocene with *tert*-butylithium gives yield of 1,2-di-iodoferrocene in excellent yields, Scheme 2A.[18] In an initial test reaction using deuterium labelling (using a D_2O quench) it was possible to show, using ^1H NMR spectroscopy, that the reaction of 1,1′,2,2′-tetrabromoferrocene **1,** at low temperature, with one equivalent of n-butyllithium gave the mono-deuterated derivative and with 2 equivalents gave predominantly the 2,2′-dideuterated compound, **9**. Similarly, again in a test reaction, the previously known 2,2′-bis-diphenylphosphino-1,1′-dibromoferrocenes, **10**, could be obtained on reaction of **1** with 2 equivalents of butyllithium followed by quenching with chlorodiphenylphosphine, Scheme 2B.



Scheme 2. **A**: Synthetic routes to 1,2-diiodoferrocene, **9**. **B**: Test lithiations using n-BuLi quenching D_2O or chlorodiphenylphosphine, main products only shown.

By analogy, the dilithiation of 1,2-dibromobenzene has been investigated in considerable detail by Bettinger and Fildhaus.[19] In their work, it was shown that 1,2-dilithiobenzene was not an intermediate in the conversion of 1,2-dibromobenzene to 1,2-bis(trimethylsilyl)benzene using *tert*-BuLi as the lithiation reagent. The 1,2-disubstituted derivatives could only be obtained where the quench reagent could coexist with lithium compounds at low temperatures. However, in one regard given our recent synthetic experience we do not expect ferrocene chemistry to exactly parallel benzene chemistry as we know ferrocyne formation does not occur under these conditions- this has been verified recently.[18] Indeed, we have been trying unsuccessfully to form ferrocyne for many years ever since the first preparation of 1,2-dibromoferrocene.[20] These fears were unfounded as the reaction of 1,1′,2,2′-tetrabromoferrocene with an excess of *tert*-butyllithium in THF at between -50°C and -60°C followed by quenching resulted in the formation of the tetrasilyl compound **11** (Figure 1) in yields up to 90%.



Scheme 3: Synthesis of *tetra*- and *hexa*-trimethylsilylferrocenes. **A**: 1,1′,2,2′- and 1,1′,2,2′,3,3′-isomers, this work; **B**: 1,1′,3,3′- and 1,1′,2,2′,4,4′-isomers.[21-23]

The isolation of the product proved to be trivial with no problems with air sensitivity. The ^1H NMR spectrum of compound **11** provided conclusive verification with the characteristic doublet and triplet patterns as observed for **1** except the doublet is upfield of the triplet in this case which is similar to the NMR spectrum of 1,1′,2,2′-tetrakis-(tri-*n*-butylstannyl)ferrocene. The new synthetic method provides a new isomer (Scheme 3A) in comparison to the 1,1′,3,3′-isomer **14**, which had been previously been prepared by Okuda and co-workers,[21-23] Scheme 3B. The reaction of 1,1′,2,2′,3,3′-hexabromoferrocene with tert-butyllithium at temperatures below -50°C in THF gave the corresponding hexalithioferrocene in *situ* and when reacted with chlorotrimethylsilane gave the 1,1′,2,2′,3,3′-hexasilyferrocene (Figure 2) as a deep red oil initially which crystallised from methanol as red needles in an isolated yield of ca. 90%. In the residual deep red oil, which remained after crystallisation, traces of heptakis- to decakis-trimethylsilylferrocenes were identified by mass spectroscopy. Their presence was due to lithiation and substitution of the trace poly bromides present in the starting material. Again the 1,1′,2,2′,4,4′-isomer of compound **12** i.e. compound **15** (Scheme 3B) has been prepared previously by Okuda and co-workers as this is the substitution pattern obtained during normal stepwise addition of trimethylsilyl- groups by dilithiation or from pre-substituted cyclopentadienes.[22] Thus the 1,1′,2,2′,3,3′-substitution pattern represents a new isomer which may be useful in solubilising further derived compounds such as in the preparation of silylated dppf′s.[24] The ^1H NMR spectrum at room temperature of compound **12** shows the expected ferrocene singlet and two trimethyl resonances in the 1:2 ratio. The low temperature synthesis obviously required external cooling, therefore, we decided to examine the preparation of the pure *tetra*- and *hexa*-lithioferrocenes by controlled metathesis.

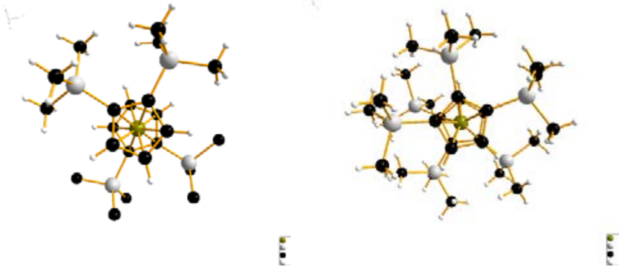


Figure 1: top views of 1,1′,2,2′-tetrakis(trimethylsilyl)ferrocene, **11**, and 1,1′,2,2′,3,3′-hexakis(trimethylsilyl)ferrocene, **12**.

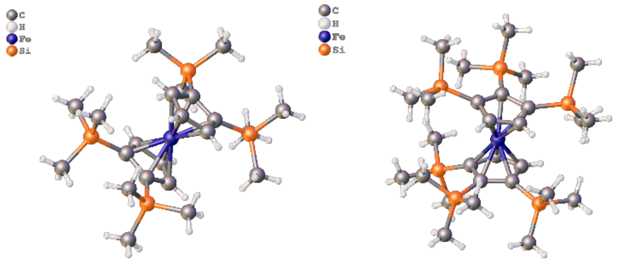


Figure 2: side views of 1,1′,2,2′-tetrakis(trimethylsilyl)ferrocene, **11**, and 1,1′,2,2′,3,3′-hexakis(trimethylsilyl)ferrocene, **12**.

The easiest general synthetic method to tetra-substituted products is simply to add an ether solution of 1,1′,2,2′- tetrabromoferrocene or 1,1′,2,2′,3,3′-hexabromoferrocene to a solution containing a slight excess (4.4 mol equiv. or 8 equivalents respectively) of t-BuLi in diethyl ether at low temperatures (-30^{o}C) which produces a characteristic cherry coloured solution. This may be reacted with a quench reagent. When the room temperature *tetra*-lithiation reaction was attempted in diethyl ether using n-BuLi it led to the formation of a mixed "lithioferrocene" precipitate, which is unwanted in this case. The precipitate, when quenched with chlorotrimethylsilane gave a mixture of silyated ferrocenes. Although the lithiation proceeded smoothly at room temperature when THF was used as a solvent again product mixtures were obtained. This may be due to the isomerisation relating to the "halogen dance" or more likely coupling reactions. Finally, hexane was used as a solvent and a little diethyl ether was added to it. This method was based on the one we used (unpublished) in 1992 to obtain pure 1,1′-dilithioferrocene and to prepare the dicyclopentadienyltitanium-bridged ferrocene. In this case the reaction mixture is simply left to stir for more than 1 hour- the *tetra*-lithioferrocene precipitates as a red/orange powder from solution. It may be filtered off and used as a solid reagent. In a test reaction *hexa*-lithioferrocene was obtained in the same manner as a deep red powder. The mechanism of these lithiations is open to debate. As mentioned earlier, in the study on the lithiation of 1,2-dibromobenzene 1,2-dilithiobenzene was not obtained in the presence of *tert*-butylithium.[19] In the present case, it is more likely that *tetra*-lithioferrocene is obtained slowly after the initial rapid dilithiation. We anticipate that all lithioferrocenes including *deca*-lithioferrocene will become readily available once the isolation procedures for the octa- to decabromoferrocenes are improved. This may be relatively easy to achieve as the deca mercury compound has already been used as a source of decalithioruthenocene.[25] In addition the method should be applicable to the preparation of all isomeric lithio-metallocenes derived from recently published halo metallocenes.[13] We continue with this objective.

General Experimental: Reaction solvents were dried using a commercial solvent drying instrument while all other solvents including NMR solvents were reagent grade and were used as received. All reagents (butyllithiums, chlorotrimethylsilanes, silica and alumina were commercial samples and were used as received. Bromoferrocene precursors were all available in house and were dried on a high vacuum line prior to use. NMR experiments were performed on a Bruker Avance instrument operating at 400MHz for ^{1}H and 100Mz for ^{13}C. Reactions were carried out under a dry nitrogen atmosphere and workups were carried out under normal laboratory conditions.

Preparation of 1,1′,2,2′-tetrakis(trimethylsilyl)ferrocene, 11.
A solution of 1,1′,2,2′-tetrabromoferrocene (2.6g, 5 mmol), in thf, (100ml) maintained between -60 and -70^{o}C using an external cooling bath was treated with tert-butyllithium solution in pentane (14 ml of a 1.7 mol., 23.5mmol) whereupon the solution darkens to a red colour. The solution was stirred for 30 minutes before chlorotrimethylsilane (3ml) was added by syringe. The solution was warmed slowly to room temperature- the solution undergoes several colour changes on warming before developing a deep orange colour. The solution was further warmed to 40^{O}C briefly with a warm air gun before it was hydrolysed with an aqueous solution of potassium carbonate. Sodium chloride (to facilitate solvent separation) was added followed by diethyl ether 50ml. The organic layer was separated and dried over magnesium sulfate before it was filtered, and the solvent removed on a rotary evaporator to yield an orange solution. Following a rapid flash column chromatography on silica gel of this oil with diethyl ether on silica the orange solution was obtained and again the solvent was removed to yield an oil. Dissolution in methanol and diethyl ether followed by slow removal of the ether (partial vac.) until the mixture was slightly turbid. The solution was cooled slowly to -20^{o}C. From the cooled orange solution bright orange needle-shaped crystals rapidly formed. (2.2g, 90%).

1,1′,2,2′-Tetrakis(trimethylsilyl)ferrocene. $C_{22}H_{42}FeSi_4$: ^{1}H NMR (CDCl$_3$): 0.26 (s, 36H), 4.28(d, 4H, J= 2.0Hz), 4.44 (t, J = 2.0Hz, 2H). ^{13}C NMR: 1.57, 72.80, 76.23. 79.40. Mass spectrum: isotopic pattern, 472-479, observed parent ion: 474.1715, (theoretical, 474.1714). m. p. = 116-118^{o}C.

Preparation of 1,1′,2,2′,3,3′-hexakis(trimethylsilyl)ferrocene, 12.
The reaction was carried out in an identical manner to the preceding synthesis using 1,1′,2,2′,3,3′-hexabromoferrocene* (ca. 98%), (3.3g, 5.0 mmol) but using 8 equivalents (excess) of t-BuLi (16 mL of 2.5 M sol.) and 8 equivalents of chlorotrimethylsilane, (4.32g, 40mmol). The workup was identical. The product is obtained as a deep red oil which crystallised from a mixture of methanol and diethyl ether (-20^{o}C) as deep red crystals, (2.8g, 87%).

*small quantities of more highly brominated ferrocenes are present in the sample.

$C_{28}H_{58}FeSi_6$ ^{1}H NMR (CDCl$_3$): 0.27 (s, 36H), 0.35 (s, 18H) 4.44 (s, 4H). ^{13}C NMR: 3.37, 3.77, 80.61, 81.44 (quat), 84.24. Mass spec., $C_{28}H_{58}FeSi_6$: m/z, observed (theoretical): 618.2505(618.2515). m. p. = 147-149^{o}C.

General Methods for the Preparation of Tetra-lithio- and hexalithioferrocene, in situ.
A solution of either 1,1′,2,2′-tetrabromoferrocene or 1,1′,2,2′,3,3′-hexabromoferrocene* (5 mmol) in diethyl ether (30 ml) is added to a stirred solution of t-BuLi (25 mmol or 35 mmol respectively) in diethyl ether (100ml), maintained at -30^{o}C. A characteristic cherry color develops.

The solution is stirred for 5 minutes before it is cooled and quenched with an appropriate reagent, (25mmol).
*may only be partially dissolved.

Room Temperature reactions

Note: All solid lithioferrocenes are pyrophoric. The isolation methods have not been optimised and we have only used t-BuLi and n-BuLi in our trial reactions. The poor solubility of 1,1´,2,2´,3,3´-hexabromoferrocene in non-polar solvents makes scale-up difficult. A study to optimize these isolation conditions using all alkyllithium reagents will be undertaken in the next work.

General Example

A solution of 1,1´,2,2´-tetrabromoferrocene (1.3g, 2.6mmol) in hexane (50 ml) is stirred at room temperature and a five-fold excess of n-BuLi in hexanes (5.2 ml of a 2.5M sol.) is added. Diethyl ether (5 ml) is then added, and the solution is stirred for > 1 hr. Throughout the time gradual precipitation occurs until a pink-red precipitate is obtained. This was filtered off using a sinter filter and the precipitate was washed with hexane and the solid was dried under vacuum. This solid may be quenched with a suitable quenching reagent to give tetra-substituted ferrocenes.
A similar reaction of 1,1´,2,2´,3,3´-hexabromoferrocene with a seven-fold excess of n-butyl lithium results in the formation of a deep red precipitate.

Additional Information

The solid powders isolated may be redissolved in thf and used directly. These compounds may be crystallized if left at low temperature from thf-diethyl ether mixtures thus obtaining their structures should be straightforward. It is recommended that both t-BuLi and n-BuLi are trialed in using this methodology, The key point is that the reactions only proceed effectively when a little ether is added.

X-ray Crystallography

For samples compound **11**, (**IRB_4SiFc)** and **12**, (**IRB_6SiFc)**, a suitable crystal was selected and mounted on a MITIGEN holder in oil on a Rigaku FRE+ (45.0 kV, 55.0 mA) diffractometer with an AFC12 goniometer equipped with either VHF Varimax confocal mirrors (70µm focus) and HyPix 6000 detector (**IRB_6SiFc, 12**) or HF Varimax confocal mirrors (100µm focus) and HG Saturn 724+ detector (**IRB_4SiFc, 11**). The crystals were kept at T = 100(2) K during data collection. Data were measured using profile data from ω-scans using MoK$_\alpha$ radiation. Cell determination, data collection, data reduction, cell refinement and absorption correction were carried out using CrystalisPro[26]. Using Olex2,[27] the structures were solved with the ShelXT[28] structure solution program and the models were refined with version 2014/7 of ShelXL[29] using Least Squares minimisation. All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.
Crystal Data for **IRB_4SiFc, 11:** $C_{22}H_{42}FeSi_4$, M_r = 474.76, monoclinic, $P2_1/c$ (No. 14), a = 12.8277(7) Å, b = 17.3411(8) Å, c = 30.2297(17) Å, β = 99.703(5)°, $\alpha = \gamma$ = 90°, V = 6628.3(6) Å^3, T = 100(2) K, Z = 10, Z' = 2.5, μ(MoK$_\alpha$) = 0.756 mm^{-1}, 24631 reflections measured, 24631 unique which were used in all calculations. The final wR_2 was 0.2276 (all data) and R_1 was 0.0883 (I > 2(I)).
Crystal Data for **IRB_6SiFc, 12:** $C_{28}H_{58}FeSi_6$, M_r = 619.13, monoclinic, $P2_1/n$ (No. 14), a = 12.8946(5) Å, b = 15.8866(6) Å, c = 17.7606(10) Å, β = 92.752(4)°, $\alpha = \gamma$ = 90°, V = 3634.1(3) Å^3, T = 100(2) K, Z = 4, Z' = 1, μ(MoK$_\alpha$) = 0.628 mm^{-1}, 40950 reflections measured, 8314 unique (R_{int} = 0.0907) which were used in all calculations. The final wR_2 was 0.1870 (all data) and R_1 was 0.0671 (I > 2(I)).
CCDC2025341 and 2025342 contains supplementary X-ray crystallographic data for **IRB_4SiFc** and **IRB_6SiFc** respectively. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/structures/, or from the Cambridge Crystallographic Data.

Conclusions

1,1´,2,2´-tetralithioferrocene and 1,1´,2,2´,3,3´-hexalithioferrocenes have been prepared and converted to the corresponding tetrakis- and hexakis-(trimethylsilyl)ferrocenes. These were obtained in high yields and this work will facilitate the synthesis of many more ferrocene derivatives. We see no reason why this work could not be extended to the lithiation of all bromo- (and iodo) - ferrocenes and -ruthenocenes, which we and others have recently described, including the synthesis of deca-trimethylsilylferrocene. It is noted that the synthesis of tetra-substituted triethylsilyl-derivative was also attempted but the product was found to be difficult to crystallise - it was obtained as an impure orange oil. The authors actively encourage interested research groups to work with us in collaborative work developing this chemistry by contacting the corresponding author.

The Supporting Information is available free of charge at (insert URL)

Supporting Information (47 pages) contains NMR spectra, mass spectrometric data and additional crystallographic data for compounds **11** and **12**.

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"The authors declare no competing financial interests."

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ABBREVIATIONS

THF: tetrahydrofuran; tert: tertiary TMEDA: N,N,N′,N′-tetramethylethylenediamine; n-BuLi and t-BuLi: normal and tertiary butyllithium; dppf: 1,1′-bis-(diphenylphosphino)ferrocene.

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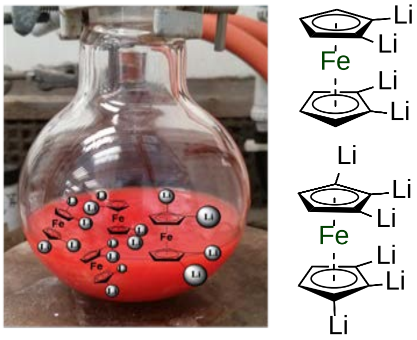

Synopsis: The formations of 1,1′,2,2′-tetralithioferrocene and 1,1′,2,2′,3,3′-hexalithioferrocene, from the corresponding 1,1′,2,2′-tetrabromoferrocene and 1,1′,2.2′,3.3′-hexabromoferrocene, respectively, in a controlled manner, are described. The new isomers of 1,1′,2,2′-tetrakis(trimethylsilyl)ferrocene and 1,1′,2,2′,3,3′-hexakis(trimethylsilyl)ferrocene which result from the reaction of these lithium compounds with chlorotrimethylsilane confirm the regiochemistry. This isomer pattern represents a valuable addition to the preparation of more highly substituted ferrocene derivatives.