Sitting out the Halogen Dance. The Room Temperature Formation of the 2,2'-Dilithio-1,1'-dibromoferrocene.TMEDA complex: A Synthetic Route to Multiply-substituted Ferrocenes.

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ABSTRACT: The clean, room temperature, synthesis of 2,2'dilithio-1,1'-dibromoferrocene from 1,1'-dibromoferrocene is reported. On quenching this dilithium compound with electrophiles the synthesis of 2,2'-disubstituted-1,1'-dibromoferrocenes are facilitated. For example, quenching with 1,2-dibromohexafluoropropane as an electrophile precursor yields 1,1',2,2'-tetrabromoferrocene in high yield. The similar dilithiation reaction of the 1,1',2,2'-tetrabromoferrocene produces 3,3'-dilithio-1,1',2,2'-tetrabromoferrocene, which in turn furnishes 1,1',2,2',3,3'-hexabromoferrocene again in high yield. Essentially the bromines are added in pairs beginning with the readily available 1,1'-dibromoferrocene. All 2,2'-dihalogeno-1,1'-dibromoferrocenes have been obtained and characterised. The reaction sequence when continued in an iterative fashion should ultimately afford decabromoferrocene, however the highly brominated products such as octabromoferrocenes, nonabromoferrocene and decabromoferrocene are not isolated cleanly because of their poorer solubility as the synthetic method is optimised in non-polar solvents. Just as 1,1'-dibromoferrocene has played an important role in the broader synthesis of other ferrocenes it fully expected that 1,1',2,2'-tetrabromoferrocene and 1,1´,2,2´,3,3´-hexabromoferrrocene will play similar roles.

This paper represents the culmination of an idea that started 30 years ago. This idea encompasses two areas of research but principally it is about the ability to obtain any substitution pattern on ferrocene. The synthesis of ortho-lithiated halobenzenes and haloferrocenes is central to their substitution chemistry. Interwoven with this is the history of benzyne chemistry with the original halobenzene lithiation work of Roberts1 and Wittig², which of course is legendary. We have been interested in ortho-dehydrobenzene, i.e. benzyne chemistry for a considerable time, and the link to the possible existence of ferrocyne, its ferrocene analogue either as a transitory species or as a metal complexed species since the early investigations on organometallic benzyne chemistry.3 By analogy to benzyne chemistry, the simplest precursor compound is clearly the 1,2dibromoferrocene which was first prepared in 1994.⁴ At that time the first reaction attempted was the reaction of the ortholithiated bromoferrocene with a range of known benzyne-trapping compounds - unfortunately we were unable to obtain any

principal products from ferrocyne intermediates. Other authors have since noted similar results.5 In addition to the formation of ortho-lithiated bromoferrocene the dilithiation of 1,1'-dibromoferrocene was also examined and again no discernible ferrocyne derived products were observed. As part of this exercise, it was decided to prepare a larger quantity of the decomposition products without the addition of any ferrocyne trapping compound to see if we could identify any solely ferrocene derived products that may have arisen from a ferrocyne intermediate. This led to the discovery of a new synthetic route towards the broader objective of producing a simple general route to bromoferrocenes, which is outlined now. We recently reported the low yielding preparation and crystal structures of the 1,1´,2,2´-tetrabromo-ferrocene and -ruthenocene⁶ Earlier we also reported the stepwise synthesis of 1,2,3,4,5-pentabromoferrocene using the ortho-lithiation methodology, a synthetic strategy which has been used by many others since, figure 1.7 However it was clear that a better general synthesis of bromoferrocenes where both cp-rings are substituted, because of the problems of isomerisation in the existing synthetic routes, was required.



Figure 1.: stepwise synthesis of bromoferrocenes.7

It is also worth noting at this point that many chiral ferrocenes may be obtained by haloferrocene metalation simply using a chiral ferrocene starting material instead of ferrocene itself.⁸ This also applies to the current work. The area and scope of halo-ferrocene synthesis has been reviewed recently,⁹ and there have been several papers on the so-called halogen dance (isomerisation in lithiohaloferrocenes) in ferrocenes.¹⁰ This halide dance can be a nuisance in synthesis if isomeric mixtures are formed. Poly-bromoferrocene synthesis¹¹ was pioneered by Winter and co-workers using organomercury intermediates, however the methodology is environmentally unsound, and the separation of products is difficult. While the lithiation of fluoro- and chloro-ferrocenes can be achieved easily they are not suitable precursors for developing synthetic routes because of their inherent stability hence the interest in substituent replaceable bromo- and iodo-ferrocenes.

Results and Discussion

The original plan was to investigate why "ferrocyne" was not trapped in the decomposition reactions of 2-lithio=1-bromoferrocene and 2,2'-dilithio-1,1'-dibromoferrocene with 1,3-diphenylbenzoisofuran. As part of the process, the dilithiation of 1,1'-dibromoferrocene was carried out using the ortho-lithiation method.12 Because we could find no evidence for the formation of ferrocyne, (only for traces of red ferrocene substituted benzoisofurans were observed), it was decided to examine the composition of the ferrocene containing by-products. As one part of the study it was decided to add TMEDA to possibly trap any lithiated species before quenching with DMF. The dilithiation reaction of 1,1'-dibromoferrocene was carried out at -70°C and the reaction mixture was warmed to room temperature before being reacted with dry DMF to trap out any reactive lithiated compounds left in the reaction mixture. It was anticipated that a complex mixture of products would be formed. In fact, the only products observed were the air sensitive dialdehydes 3^{13} fig. 2, which could be isolated in greater than 90% yield. This was a revelation because it meant that dilithio- compounds 2 as a TMEDA complex were stable at room temperature.



Figure 2.: Preparation of bromoferrocenylcarbaldehydes from 1,1'-dibromoferrocene.

This turns out to be a general observation for all the dilithium polybromoferrocenes involved in the broader synthesis of deca-bromoferrocene and is crucial to this work. Since hexane was used as reaction solvent in the test reactions, (a key point) we sought to find a different, more effective, bromine quench reagent as an alternative to the commonly used 1,1,2,2-tetrabromoethane, because we have known since the early 1980's that 1,1,2,2-tetrabromoethane is ineffective as a quench reagent in hexane in the presence of TMEDA with which it reacts. The other commonly used quench reagent 1,2-dibromotetrachloroethane was also ruled out simply because of poor its solubility in hexane. The reagent chosen was dibromohexafluoropropane (DBHFP), which is readily commercially available and is also reasonably inexpensive. Because we had no access to Schlenkware or specialised filtration equipment available to us a synthetic method had to be devised so undergraduate students could routinely use with normal lab apparatus. The result can be seen in the video-file (supplementary section). Essentially LiTMP is prepared in hexane at room temperature in the presence of TMEDA and this mixture is observed as a "semi-fluorescent" solution. The 1,1'-dibromoferrocene is added in the minimum volume of hexane for dissolution (generally 25mL per 1mmol)-the solution retains the apparent fluorescent appearance and takes on the orange ferrocene hue. After stirring for 20 minutes the reaction mixture is cooled to -70°C and the quenching reagent is added slowly. When the dilithiation is carried out using these new reaction conditions followed by quenching with DBHFP high yields of the 1,1',2,2'-tetrabromoferrocene are routinely obtained: the reaction has been carried out on scales ranging from 10-100mmol with yields ranging from 80 to 94% and has been repeated more than 40 times without problem -the only important consideration is that if the solvent/substrate volume ratios are

lowered a thick oil can be sometimes be formed rather than a precipitate (depends on scale) and when this happens the product purity is lowered. The 1,1',2,2'-tetrabromoferrocene is readily crystallised and is obtained as large yellow brown blocks or needles from either petrol or methanol. The extent of room temperature dilithiation is lessened in absence of TMEDA because some unreacted 1,1'-dibromoferrocene remains after 4hrs when DMF is used as the quench with the additional production of mono-aldehydes **4a** and **b**.¹³ A representation shown in figure 3 is a simplification of the complex structure of the dilithioferrocene.TMEDA complex.¹⁴ The stereochemistry of the product dialdehydes may be assigned as the NMR data for **3b** had been published previously.¹³



Figure 3: The influence of TMEDA on diastereomer formation. (simplified). The product isomer ratios obtained depend on the quench reagent effectiveness, the crystallisation process as well as the ratio of the lithium reagents themselves.

By application of the general synthetic method, it is possible to prepare the other 2,2'-disubstituted dibromoferrocenes such as those shown in figure 4. All reactions furnish high product yields except in the case of the dibromodifluoroferrocene 5, where the yields are lower (ca 60%), which is a reflection on the efficiency of the quenching reagent (poorly soluble) rather than a problem with the initial lithiation reaction.



Figure 4: Related halogenoferrocenes prepared using the room temperature lithiation.

There are now three synthetic routes **A**, **B**. **C**, figure 5, by lithiation to the set of 2,2'-dihalogeno-1,1'-dibomoferrocenes, an example of which is shown for compounds **6**.



A: normal dilitiation and quench, B: dithiation by bromine exchange and quench and C: alpha-lithiation and quench.

Figure 5: Alterative synthetic methods to mixed 2,2'-dichloro-1,1'-bro-moferrocene, **6**.

Compounds **5-8** have been characterised by single crystal diffraction which will be the subject of a forthcoming paper. Compound **9** has only been obtained as an oil and its characterisation is based on NMR only, but it is also used in the preparation of compound **8** which provides unequivocal evidence for its structural formulation. The ferrocene ring

proton chemical shifts of the 2,2'-disubstituted-1,1'-dibromoferrocenes are summarised in Table 1.

Com- pound	H-2(ppm)	H-3 (ppm)	H-4(ppm)
5	4.41, 4.39	3.92, 3.95	4.23, 4.20
6	4.44*	4.17	4.44
7	4.46*	4.17	4.46
8	4.48*	4.17	4.42
9	4.40, 4.56	4.18, 4.11	3.92, 3.94

Table 1: Chemical shifts for the ferrocene protons in compounds **5-9**. (Numbering: H-2 in compound **5** are positions alpha to bromines, H-5 alpha to fluorines). *Both isomers have identical (overlapping at 400Mz) ¹H NMR spectra.

Continuing, the synthesis of 1,1',2,2',3,3'-hexabromoferrocene 10, was achieved using the general synthetic method. Several reactions using a range of solvent combinations and addition methods were attempted before a synthesis was optimised. The optimised synthesis uses a reverse addition method where the active lithiating mixture is added to the 1,1',2,2'-tetrabromoferrocene, 7, to counter its poorer solubility in hexane. Compound 10 is obtained as a bright pale yellow microcrystalline solid, again in yields greater than 90%. This compound is difficult to crystallise and hence completely purify as it tends to form microcrystalline powders from a range of solvents. Its proton NMR spectrum however is characteristic: a singlet at 4.46 ppm.⁶ It is also difficult to redissolve in the same solvent from which it powdered out although it is reasonably soluble in THF. Persistent trace by-products are 1,1',2,2',3,3',4-heptabromoferrocene, 15 and more highly brominated ferrocenes. Structural confirmation for 15 was obtained from an impure sample. A synthetic grid can be constructed to show all possible routes to the higher bromoferrocenes, figure 6.



Figure 6.: General synthetic route "plan" for bromoferrocenes. A: alphalithiation and quench; B: debromination by lithium-bromine exchange; C: debromination by lithium-bromine exchange with several possible isomeric products, D: single alpha-lithiation. (Compounds shown in red will require the use of different solvents for yield optimization)

As examples, compound **13** may be obtained by removal of one bromine by lithium exchange followed by reaction with water or methanol and compounds **14** and **15** are accessible using routes **C** and **D**, from compounds **7** or **10** and **10** or **11** respectively, figure 7. Many attempts were made to synthesis 1,1',2,2',3,3',4,4'-octabromoferrocene **11**, using the general reaction conditions however the poor solubility of the compound **10** in non-polar solvents makes this difficult. This is also true for the remaining two brominated ferrocenes **12** and **16**. Thus unambiguous characterisation of octa- and nona-bromoferrocenes, **11** and **16** has not been achieved although these are present in the reaction products as observed by mass spectrometry, (see Supporting Information). Decabromoferrocene, **12**, was originally prepared by Winter and co-workers using organomercury chemistry¹¹ and is postulated that this should be best prepared directly from hexabromoferrocene by double *ortho*-lithiation in THF. Additional NMR trial reactions have been carried out to show that 1,1',2,2'-tetrabromoferrocene is a useful general reaction precursor for alpha-dilithiation: for example 2,2',3,3'-tetrabromo-1,1'-di-iodoferrocene, **17**, 2,2',3,3'-tetrabromo-1,1'-bis-(tri-n-butylstannyl)ferrocene, **18**, 3,3'-dichloro-1,1',2,2'-tetrabromoferrocene, **20**, figure 7, may be prepared.



Figure 7: products observed from trial alpha dilithiation reactions of 1,1',2,2'-tetrabromoferocene.

In these reactions multiple lithiation may occur with the formation of more highly substituted products therefore controlling stoichiometry is more important. The general synthetic method is also suitable for the synthesis of 1,1',2,2'-tetrabromoruthenocene⁶ and 1,1',2,2',3,3'-hexabromoruthenocene both of which have been obtained in excellent yields. This work makes the synthesis of literally hundreds of ferrocenes possible using bromoferrocenes as starting materials and circumvents the problems associated with the isomerisation of lithiobromoferrocenes (halogen dance¹⁰).

CONCLUSIONS and COMMENTS

A general synthetic regime has been developed for the controlled high yielding synthesis of multiply substituted bromoferrocenes and bromoruthenocenes. The bromine substituents allow the further synthesis of a range of substituted ferrocenes and ruthenocenes by bromide exchange. Other brominated quenching reagents may be used and indeed we have tried others which work reasonably well but with lower yields. The synthesis of mixed halogenoferrocenes is also possible. Preliminary experiments with ortho-lithiation of 1,1'-di-iodoferrocene have shown that lower temperatures and or shorter reaction times must be used- these results will be the subject of a forthcoming paper. Further work to determine isomer ratios of mixed halide ferrocenes products under specific reaction conditions is required and the methodology to separate these. The synthetic tools are now available to prepare all the possible bromoferrocenes isomers and we extend an invitation to other research groups to collaborate with us on this. Extension of the synthetic method to include other metallocene compounds and some arenes is also possible.

Supporting Information, this contains experimental details and NMR spectra of compounds reported here including

spectra of crude materials as obtained using the reported synthetic technique. Spectral details of several other compounds such as ferrocenophanes are also included. A video showing the preparation of 2,2'-dilithio-1,1'dibromoferrocene in progress is also available. This is available free of charge on the ACS Publications website.

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REFERENCES

- 1. Robert, J.D.; Simmons, Jr., H.E.; Carlsmith, L. A.; Wheaton, V. Rearrangement in the Reaction of Chlorobenzene-1-C14 with Potassium Amide. *J. Am. Chem. Soc.*, **1953**, *75*, 3290-1.
- (a) Wittig, G.; Pohmer, L., Intermediäre Bildung von Dehydrobenzol (Cyclohexa-dienin). *Angew. Chem.*, **1955**, *67*, 348-348.
 (b) Wittig, G. Phenyl-lithium, der Schlüssel zu einer neuen Chemie metallorganischer Verbindungen. Naturwissenschaften, **1942**, *30*, 696-703.
- (a) Cullen, W.R.; Rettig, S.J.; Zheng, T.C. Ferrocyne and ferrodicyne. Preparation and structures of Os₃(CO)₅[µ-3-(C₅H₃)Fe(C₅H₅)][µ-3-P(C₅H₄)Fe(C₅H₅)], Os₃(H)₂(CO)₈(PPriso2C₅H₂)Fe(C₅H₂PPr-iso₂)Os₃(H)₂(CO)₈, and Os₃(CO)₉[µ-3-C₆H₄][µ-3-P(C₅H₄)Fe(C₅H₅)] *Organometallics*, **1992**, *11*, 928-935. (b) Cullen, W.R.; Chacon, S.T.; Bruce, M.I.; Einstein, F.W.B.; Jones, T. Preparation and structure of Ru₃(CO)₇(µ-3-η²-C₆H₄)(µ-PPhFc)₂ *Organometallics*, **1988**, *7*, 2273-2278.
- 4. Butler, I.R.; Drew, M.G.B. 1,2-Dibromoferrocenes: synthesis and structure. *Inorg. Chem. Commun.*, **1999**, *2*, 234-237.
- (a) Chen. L.S; Chen, G.C.; Tamborski, C. The synthesis and reactins of ortho bromophenyllithium. *J. Organometal. Chem.* **1980**, *193*, 283-293. (b) Werner, G.; Butenschön, H. Improved Syntheses of 1,2-Disubstituted Ferrocenes. *Eur. J. Inorg. Chem.*, **2017**, 378-387.
- Butler, I.R.; Beaumont, M.; Bruce, M.I.; Zaittseva, N.N.; Iggo, J.A.; Robertson, C.; Horton, P.N.; Coles, S.J. Synthesis and Structures of 1,1',2-Tribromoferrocene, 1,1',2,2'-Tetrabromoferrocene, 1,1',2,2'-Tetrabromoruthenocene: Expanding the Range of Precursors for the Metallocene Chemist's Toolkit. *Aust. J. Chem.* 2021, 74, 204-210.
- 7. (a)Butler, I.R. The conversion of 1,1'-dibromoferrocene to 1,2dibromoferrocene: The ferrocene-chemist's dream reaction. Inorg. Chem. Commun. 2008, 11, 15-19. (b) Sünkel, K.; Bernhartzeder, S. Coordination chemistry of perhalogenated cyclopentadienes and alkynes. Part 30. New high-yield syntheses of monochloroferrocene and 1,2,3,4,5pentachloroferrocene. Molecular structures of 1,2dichloroferrocene and 1,2,3-trichloroferrocene. J. Organometal Chem., 2012, 716, 146-149. (c) Sünkel, K.; Bernhartzeder, S. Coordination chemistry of perhalogenated cyclopentadienes and alkynes. XXVIII. new high-yield synthesis of monobromoferrocene and simplified procedure for the synthesis of pentabromoferrocene. Molecular structures of 1,2,3-tribromoferrocene and 1,2,3,4,5-pentabromoferrocene. J. Organometal Chem., 2011, 696, 1536-15440. (d) Tazi, M.; Erb,

W.; Roisnel, R.; Dorcet, V.; Mongin, F.; Low, P. From ferrocene to fluorine-containing penta-substituted derivatives and all points in-between; or, how to increase the available chemical space. *Org. Bio-mol. Chem.*, **2019**, *17*, 9352-9359. (e)Sünkel, K.; Weigand, S.; Hoffmann, A.; Blomeyer, S.; Reuter, C.G.; Vishnevskiy, Y.V.; Mitzel, N.W. Synthesis and Characterization of 1,2,3,4,5-Pentafluoroferrocene. *J. Am. Chem. Soc.*, **2015**, *137*, 126-129.

- A. Zirakzadeh, A. Herlein, M. A. Gross, K. Mereiter, Y. Wang, W. Weissensteiner. Halide-Mediated Ortho-Deprotonation Reactions Applied to the Synthesis of 1,2- and 1,3-Disubstituted Ferrocene Derivatives. Organometallics, 2015, 34, 3820-3832.
- (a) Erb, W.; Mongin, F. Twofold Ferrocene C-H Lithiations For One-Step Difunctionalizations. *Synthesis*, **2019**, *51*, 146-160 (b)Butenschön, H. Haloferrocenes: Syntheses and Selected Reactions. *Synthesis*, **2018**, *50*, 3787.
- For representative examples see (a) Tazi, M.; Erb, W.; Halauko, Y. S.; Ivashkevich, O.A.; Matulis, V. E.; Roisnel, T.; Dorcet, V.; Mongin, F. From 2- to 3-Substituted Ferrocene Carboxamides or How to Apply Halogen "Dance" to the Ferrocene Series. *Organometallics*, **2017**, *36*, 4770-4778. (b)Butler, I.R.; Drew, M.G.B.; Greenwell, C.H; Lewis, E.; Plath, M.; Mussig, S.; Szewczyk, J. 1,3-Bisdiphenylphosphinoferrocenes: the unexpected 2,5,dilithiation of dibromoferrocene towards a new area of ferrocene-ligand chemistry. *Inorg.. Chem, Commun.* **1999**, *2*, 576-580.
- 11. (a) Han, Y.-H.; Heeg, M.-J.; Winter, C.H. Permercuration of Ferrocenes and Ruthenocenes. New Approaches to Complexes Bearing Perhalogenated Cyclopentadienyl Ligands. Organometallics, 1994, 13, 3009-19. (b) Kur, S.A.; Winter, C.H. Permercuration of substituted ferrocenes: assessment of the degree of mercuration. J. Organomet. Chem. 1996, 512, 39-44 (c) Federman, N.; Borges, A.D.L.; Campos, P. De A.; Miller, J. Mercury (II) Trichloroacetate. Part II. Formation and Use as a Versatile Reagent in Ferrocene Chemistry. Synth. React. Inorg. Met.-Org, Chem., 1997, 27, 1543-1551. (d) Rupf, S.M.; Schrçder, G.; Sievers, R.; Malischewski, M. Tenfold Metalation of Ferrocene: Synthesis, Structures, and Metallophilic Interactions in FeC10(HgX) Chem. Eur. J. 2021, 27, 5125-5129. (e) Boev, V.I. (title not available on-line) Dombrovskii, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. T., 1977, 20, 1789-93.
- (a) Butler, I.R.; Drew, M.G.B.; Greenwell, C.H.; Lewis, E.; Plath, M.; Mussig, S.; Szewczyk, J. 1,3-Bisdiphenylphosphinoferrocenes: the unexpected 2,5-dilithiation of dibromoferrocene towards a new area of ferrocene-ligand chemistry. *Inorg. Chem. Commun.* **1999**, 2, 576-580. (b) I. R. Butler, The Simple Synthesis of Ferrocene Ligands from a Practitioner's Perspective. *Eur. J. Inorg. Chem.* **2012**, 4387-4406.
- 13. Locke, A. J.; Pickett, T.E., Richards, C. J. Diastereoselective Synthesis of Enantiopure C 2-Symmetric Dihaloferrocenes. *Synlett.*, **2001**, 141-143.
- 14. Butler, I.R.; Cullen, W.R.; Ni, J-j. The structure of the 3:2 adduct of 1,1'-dilithioferrocene with tetramethylethylenediamine. *Organometallics*, **1985**, *4*, 2196-2201.
- (a) Dayaker, G.; Sreeshailam, A.; Chevallier, F.; Roisnel, T.; 15. Krishna, P.R.; Mongin, F. Deprotonative metallation of ferrocenes using mixed lithium-zinc and lithium-cadmium combinations. Chem. Commun., 2010, 46, 2862-2864. (b) Zirakzadeh, A.; Herlein, A.; Groß, M.A.; Mereiter, K.; Wang, Y.; Weissensteiner, W. Halide-Mediated Ortho-Deprotonation Reactions Applied to the Synthesis of 1,2- and 1,3-Disubstituted Ferrocene Derivatives Organometallics, 2015, 34, 3820-3832. (c) Tazi, M.; Hedidi, M.; Erb, W.; Halauko, Y.S.; Ivashkevich, O.A.; Matulis, V.E.; Roisnel, T.; V Dorcet, V.; Bentabed-Ababsa, G.; Mongin, F. Fluoro- and Chloroferrocene: From 2- to 3-Substituted Derivatives. Organometallics, 2018, 37, 14, 2207-2211. (d) Erb, W.; Roisnel, T. Asymmetric synthesis of hetero-1,2,3,4,5-pentasubstituted ferrocenes. Chem. Commun., 2019, 55,9132-9135.

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