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The conversion of 1,1'-dibromoferrocene to 1,2-dibromoferrocene: The ferrocene-chemist's dream reaction

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Abstract

The conversion of 1,1'-dibromoferrocene to a range of 2-substituted bromoferrocenes is described. The products are useful in the preparation of a wide number of 1,2-disubstituted ferrocenes. This includes the preparation of 1,2-dibromoferrocene and 2-(diisopropylphosphino)bromoferrocene in what is a clean and simple synthesis. The synthesis may be carried out on a large scale and for the first time produces multigram quantities of these important precursor compounds. In addition the synthetic procedure may be modified to produce a new family of ferrocene-based tris-phosphine ligands such as bis(2-diphenylphosphino-ferrocenyl)phenylphosphine.

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The substitution chemistry of ferrocene has been extensively explored since its discovery in 1951 and there are now a myriad of applications which use ferrocene as a key component. These range from its use in ligand chemistry [1], sensor chemistry [2], electrochemistry [3], medicine [4] to the many applications in material science [5]. It is now possible to prepare a range of ferrocene compounds essentially at will using what is very facile chemistry.

The research in our group has been aimed at the synthesis of key ferrocene compounds using very simple synthetic methodology. For example we reported the effective large scale synthesis of 1,1'-diiodoferrocene [6], the synthesis of a range of phosphine ligands [7], oligopyridines [8], all of which have been subsumed into the large research portfolios of the ever expanding number of ferrocene research chemists.

The rapid synthesis of 1,1'-disubstituted ferrocene is relatively very easy now including the preparation of heterodisubstituted ferrocene compounds. The synthesis of 1,2-

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disubstituted ferrocenes is more difficult normally requiring the initial introduction of a directing group which facilitates substitution into the 2-position. More often than not the directing group is necessarily retained, although in some recent work particularly that of Kagan and coworkers [9], it is possible to replace the directing group to produce a range of asymmetrically substituted ferrocenes. It has been a universal goal of ferrocene chemistry to obtain 1,2-disubstituted ferrocenes in a simple and effective manner for many years. We have long recognised this fact and have sought to obtain 2-bromo-substituted ferrocenes, which would be ideal synthons, in a straightforward manner. The reason this compound is key is because it unlocks the potential to obtain both chiral and achiral ferrocenes such as the 1,2-diamines, diphosphines, diacids, dialdehydes, dithiols, and dihydroxy compounds - in short, a myriad of important compounds could be obtained rapidly. Although we have already reported its preparation [10] the synthesis we used, which makes use in part of Kagan's methodology, is a little long-winded. We therefore have continued our impetus to prepare this and related strategic compounds efficiently. This paper reports a new definitive synthesis.

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Lithioferrocenes are an important class of compounds in their own right, the most common of which monolithioferrocene and 1.1'-dithioferrocene have been prepared and structurally characterised [11]. They allow the synthesis of a broad range of substituted ferrocenes by simply using an electrophillic quench. A few other lithioferrocenes have also been reported the most notable being decalithioferrocene [12] and 1,3,1',3'-tetralithioferrocene as an amine adduct reported by Mulvey and coworkers [13]. These compounds however do have some problems when they are quenched, as incomplete substitution is commonly encountered [14]. In our previous research the ortho-lithiation of 1,1'-dibromoferrocene was reported [15]: this opened up the possibility of the synthesis of a new range of ferrocenylphosphines, Scheme 1b. Prior to that we had also reported the preparation of a range of 1'-(diarylphosphino)bromoferrocenes, Scheme 1a [16].

The simple idea behind this current research was to combine these two pieces of research into one: to take 1.1'-dibromoferrocene, 1, which is readily available on the multigram scale [17] and this monolithiate by lithium-halogen exchange, as was done in the previous research, and then to isomerise the product according to the principle that the ortho-lithiated isomer should be favoured in an equilibration according to the second arm of our research. To test this idea 1'-lithio-bromoferrocene was prepared in THF at low temperature. As is normal this compound precipitated from solution. 2,2,6,6-Tetramethylpiperidine was then added to generate the ortho-lithiating agent in situ. The solution was then allowed to warm slowly to the point when all the precipitate had redissolved. The solution was then recooled and the lithiated species were quenched with chlorodiphenylphosphine. The product mixture was then worked up as normal. A mixture of two isomeric products **3a** and **6a** was formed in the ratio 60:40 (Scheme 2).





Scheme 2.

Whilst the outcome was not as hoped for it was encouraging to see that the basic principle actually worked, in that some 1.2-disubstituted product had actually formed. In the second experiment the reaction mixture was allowed to warm to -30 °C to facilitate the equilibration of the isomers, and the temperature was held at -30 °C for 3 h before the reaction mixture was guenched. In this case essentially only one product was crystallised from the solution, that of the 1,2-isomer, **6a**. The characteristic ${}^{31}P$ NMR resonance was observed at -20.11 ppm which is slightly shifted from the positions of monophosphine substituted resonances (-16.5 to -18.0 ppm, typically).Encouraged, the experiment was repeated with chlorodiiso propylphosphine as the quenching reagent and again only one product crystallised, which was the 1,2-isomer, **6b**, which was isolated as a crystalline semi-waxy solid. Again the phosphorus resonance of this compound (ca. -2.9 ppm) is shifted by approximately 2 ppm in comparison with compounds where the cylclopentadienyl ring is mono substituted with a di-isopropylphosphine group. This compound is easily transformed into the known compound 7 [18] following a further lithiation and quenching strategy, Scheme 3.

In the previous work we had prepared the triphosphine ligand **8** [19], and it was anticipated that it should be possible to obtain the related isomeric ligand **9** also using this new synthetic strategy thus the *ortho*-lithiation reaction was again carried out where the product solution was quenched with 0.5 equiv. of dichlorophenylphosphine (Fig. 1).

The only difference in the nature of the product trisphosphine is the complication which arises from the chiral nature of the substituents which should lead to the formation of two isomeric products. Following column chromatography of the reaction mixture two isomeric products were indeed obtained. In the ferrocene region of the proton NMR one isomer exhibited seven resonances whereas the other exhibited 14 resonances, thus these may be tentatively assigned to the *meso* isomers and (*RR*)- and (*SS*)-mixtures respectively, Scheme 4.



Fig. 1. Isomeric ferrocenyltriphosphines.





A fraction from the *meso* isomers was converted to the tris-phosphine 9 to verify the synthetic protocol. This was achieved simply by treating a dry sample of compound **10c/d** with a slight excess of *n*-butyllithium in THF and quenching with chlorodiphenylphosphine. The spectral data of the product, 9c, d, are in accord with the formulation (³¹P: $\delta = -23.97$ (d, J = 64.5 Hz) (2P), -30.93 (t, J = 64.5 Hz) (1P)). These ligands represent the first in what should be an interesting ligand family, Scheme 5.

With all the evidence now in hand it was decided to attempt the preparation of 1,2-dibromoferrocene. The lithium salt was prepared once again *in situ* and the reaction mixture was quenched with dibromotetrafluoroethane to give the 1,2-dibromoferrocene product as expected, which was isolated from the solution as either a yellow powder or as dark brown nuggets in over 85% yield, Scheme 6. The product was spectroscopically identical to a pure sample from our laboratory.

Basic experimental procedures for these preparations are given elsewhere [20]. The isomerisation reaction should in theory be catalytic in terms of the tetramethylpiperidine added according to Scheme 7, therefore an attempt was made to carry out the reaction under catalytic conditions by only adding 0.1 mol equiv. of N,N'-2,2,6,6-tetramethylpiperidine to the reaction solution when it was run on a 20 mmol scale. However on warming to -30 °C most of the precipitated lithium salt had not dissolved, therefore



this idea was abandoned on purely practical grounds at least for the present time. This will be reinvestigated at a later date where a solubilising agent (other tertiary amine) or simply larger solvent to reagent ratios may be required. Indeed it may well be that no "catalyst" is required under the proper experimental regime.

Overall the original objective has worked effectively where we now have access to multigram quantities of 1,2dibromoferrocene. It is also possible to obtain 2-(bromo)iodoferrocene, Scheme 8, cleanly by following the same experimental method, quenching with diiodotetrafluoroethane [21]. The proton NMR of this compound is definitive and with all three protons on the substituted ring clearly delineated, it is directly comparable with the ferrocene part of the spectrum of 1',2-dibromo(iodoferrocene) of which we have authentic samples. This compound should be useful in the desymmetrisation of the ferrocenes as iodoferrocenes are more readily coupled particularly with alkynes in comparison with bromoferrocenes [22]. It should be noted that we have carried out a similar chemistry with 1,1'-diiodoferrocene and in general the results are similar although it has been known for a considerable period that 1,1'-diiodoferrocenes are more prone to the formation of ferrocene dimers by coupling of the lithio species with unreacted iodoferrocene when 1,1'-diiodoferrocene is mono-lithiated with n-butyllithium. 1,1'-Diiodoferrocene however may be *ortho*-lithiated in the same manner as 1,1'-dibromoferrocene. The results of these investigations will be communicated in future work [23].

In addition we have already carried out some dilithiation and quenching reactions to obtain, in one step, a number of symmetrically 1,2-disubstituted products. Here a broad range of substituted products should be easily obtained such as dihydroxy- dithio-, bis-phosphines etc. The only reservation in this case is where the quench is not clean, for example initial attempts to obtain 1,2-diaminoferrocene quenching 1,2-dilithioferrocene generated *in situ* with *O*benzylhydroxylamine gave only traces of the desired product; therefore, the method of Arnold [24] starting with



Scheme 8.

1,2-dibromoferrocene or 2-aminobromoferrocene is recommended for such a preparation (clearly there are safety implications here and a cautious approach is advised). These reactions are being carried out in collaboration with others as there is clearly much to explore. Our immediate goal will be to make the isomerisation asymmetric and here we invite a collaborative approach from interested parties. To summarise, a new simple and effective synthesis of 1,2disubstituted ferrocene compounds has been established which opens a door to the preparation of a broad range of ferrocenes both new and old.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.inoche.2007. 09.020.

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