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# Fluoro- and Chloroferrocene: From 2- to 3-substituted Derivatives

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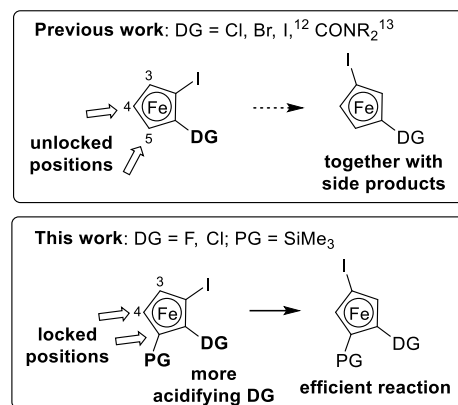
## Supporting Information

**ABSTRACT:** Ferrocene halogen ‘dance’ is deemed hardly controllable. Here, we describe the first efficient examples of this reaction. Conversion of 1-fluoro-2-iodo- (or 1-chloro-2-iodo-) to 1-fluoro-3-iodo- (or 1-chloro-3-iodo-) ferrocenes was ensured by suitably protecting the free 5 position.

Ferrocene is present in numerous scaffolds for applications such as catalysis, material sciences and medicinal chemistry.<sup>1</sup> However, despite a very rich history, transformation of mono-substituted ferrocenes is challenging when it comes to regioselectively introducing a function at C3. While deprotonation has been largely developed to introduce a substituent next to a directing group,<sup>2</sup> one can deplore the lack of an equally general method to access 1,3-disubstituted ferrocenes in spite of promising applications.<sup>3</sup> If building the ferrocene core is a way to obtain such structures,<sup>4</sup> ferrocene functionalization avoids the tedious synthesis of the required building blocks. Whereas direct electrophilic substitutions on mono-substituted ferrocenes are hardly made regioselective,<sup>5</sup> current stoichiometric and catalytic remote CH-functionalizations stay restricted to specific examples.<sup>6</sup> Alternative approaches take the central group (Cl,<sup>7</sup> Br<sup>8</sup> or sulfoxide<sup>9</sup>) away from 1,2,3-trisubstituted ferrocenes, but remain lengthy. Herein, we report a convenient alternative which relies on the halogen ‘dance’ (I > Br) known for benzene derivatives.<sup>10</sup>

Little is described on this ferrocene base-triggered reaction allowing 2-halogeno substituted compounds to be converted into the 3-halogeno derivatives. Since our early observation of the unintended formation of 1-bromo-3-iodoferrocene in the course of bromoferrocene deprotonation using LiTMP (TMP = 2,2,6,6-tetramethylpiperidino) in the presence of a zinc trap followed by iodolysis,<sup>11</sup> very few investigations have been made. In 2015, Wang, Weissensteiner and co-workers reported a study in which scrambling was noticed upon treatment of 1,2-dihalogenoferrocenes (1,2-diiodo-, 1,2-dibromo-, 1-bromo-2-iodo- and 1-chloro-2-iodo-) by LiTMP in THF (tetrahydrofuran) at -30 °C.<sup>12</sup> We recently showed that using *N,N*-

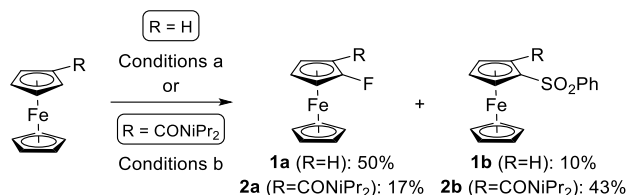
dialkyl 2-iodoferrocenecarboxamides, in which a fixed directing group (DG) is present, reduced the complexity in favour of a better controlled migration; however competitive deiodination and formation of diiodo derivatives were not discarded, at the origin of yield loss.<sup>13</sup> These results led us to believe (i) that the ferrocene substrates we used were not acidic enough to ensure the disappearance of LiTMP in the course of the reaction, and (ii) that it is necessary to block the free position next to the DG. As a consequence, we chose fluorine and chlorine as efficient short-range acidifying substituents to stabilize the produced ferrocenyllithiums,<sup>14</sup> and selected trimethylsilyl (a poor DG) as a protecting group for both the 5 and 4 positions (Fig. 1).



**Figure 1.** Strategy used to achieve efficient ferrocene halogen ‘dance’ reactions.

We first tested this designed halogen ‘dance’ reaction by using fluorine as DG. To access the required substrate, we initially studied the functionalization of fluoroferrocene (**1a**), itself prepared from ferrocene. NFSI (*N*-fluorobenzene-sulfonimide), which has a lower redox potential than *N*-fluoropyridinium triflate and Selectfluor, is a suitable fluorinating agent towards lithioferrocene;<sup>15</sup> optimization of the reaction (see ESI) allowed **1a** to be isolated in an average 50% yield at a scale up to 50 mmol. It is worth noting that the sulfone concomitantly formed when trapping with NFSI may become a real issue from sterically hindered ferrocenes such as the *N,N*-diisopropylcarboxamide (Scheme 1).

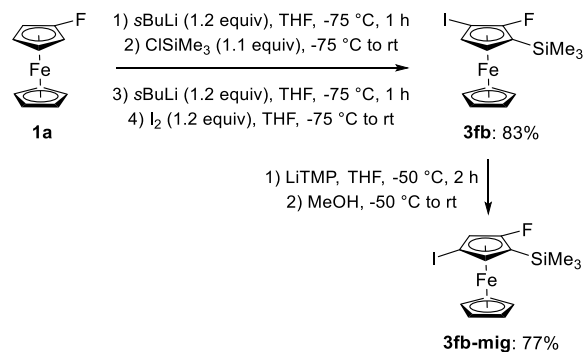
**Scheme 1. Expected and Unexpected Ferrocenes Formed by Deprotolithiation-NFSI Trapping.** Conditions a: 1) *t*BuLi (2 equiv), *t*BuOK (0.1 equiv), THF, -75 °C, 1 h; 2) NFSI, THF, -20 °C. Conditions b: 1) *s*BuLi (1.2 equiv), THF, -75 °C, 1 h; 2) NFSI, THF, -20 °C.



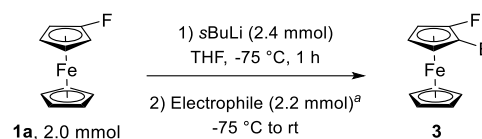
In their synthesis of pentafluoroferrocene from **1a** by iterative deprotometallation-fluorolysis, Sünkel and co-workers employed LiTMP.<sup>15a</sup> In order to achieve a strict monofunctionalization of **1a**, we rather turned to alkyllithiums. *sec*-Butyllithium proved superior to butyllithium and avoided the use of additives such as *N,N,N',N'*-tetramethylethylenediamine<sup>16</sup> or potassium *tert*-butoxide.<sup>17</sup> After 1 h contact time at -75 °C in THF, the 2-lithio derivative was quantitatively formed, as evidenced by subsequent deuteration (Table 1, entry 1). Its trapping by electrophiles afforded 1,2-dihalides **3b-e** (entries 2-5), silane **3f** (entry 6), phosphine **3g** (entry 7), sulfide **3h** (entry 8), alcohols **3i-m** (entries 9-13), aldehyde **3n** (entry 14), ketone **3o** (entry 15) and acid **3p** (entry 16) in high to excellent yields.

This effective fluoroferrocene functionalization can be pushed a step further with iterative deprotometallation-trapping sequences. Using *sec*-butyllithium and two different electrophiles, we managed to develop a one-pot access to **3fb**, *i.e.* the required substrate to attempt our designed halogen ‘dance’ (Scheme 2, top).

**Scheme 2. Halogen ‘dance’ from a Fluoroferrocene Deriving from 1a.**



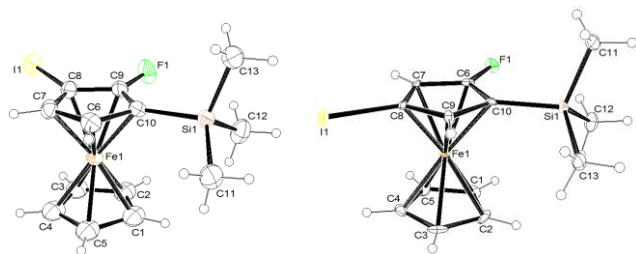
**Table 1. Scope of the Deprotolithiation-trapping Sequence on 1a.**



Entry	Electrophile (E)	Product	Yield <sup>b</sup> (%)
1	D <sub>2</sub> O (D)	<b>3a</b>	98 <sup>c</sup>
2	I <sub>2</sub> (I)	<b>3b</b>	96
3	CBr <sub>4</sub> (Br)	<b>3c</b>	92
4	C <sub>2</sub> Cl <sub>6</sub> (Cl)	<b>3d</b>	92
5	NFSI (F)	<b>3e</b>	72
6	ClSiMe <sub>3</sub> (SiMe <sub>3</sub> )	<b>3f</b>	96
7	CIPPh <sub>2</sub> (PPh <sub>2</sub> )	<b>3g</b>	16, 61 <sup>d</sup>
8	PhSSPh (SPh)	<b>3h</b>	97
9	Ph <sub>2</sub> CO (C(OH)Ph <sub>2</sub> )	<b>3i</b>	71
10		<b>3j</b>	72
11		<b>3k</b> ( <sup>l</sup> )	88 (72/28) <sup>e</sup>
12		<b>3l</b> ( <sup>l</sup> )	89 (56/44) <sup>e</sup>
13	<i>t</i> BuCHO (CH(OH) <i>t</i> Bu)	<b>3m</b> ( <sup>l</sup> )	99 (64/36) <sup>e</sup>
14	DMF (CHO)	<b>3n</b>	97
15		<b>3o</b>	60
16	CO <sub>2</sub> (CO <sub>2</sub> H)	<b>3p</b>	72 <sup>f</sup>

<sup>a</sup> Except for D<sub>2</sub>O and CO<sub>2</sub> which were used in excess. <sup>b</sup> After purification, as described in the ESI. <sup>c</sup> >95% D. <sup>d</sup> By reaction of the crude with BH<sub>3</sub>·THF, and subsequent regeneration of the free phosphine (see SI).<sup>18</sup> <sup>e</sup> Diastereoisomeric ratio (see ESI). <sup>f</sup> After acidic hydrolysis.

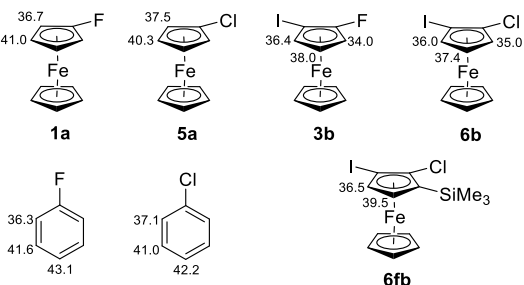
Whereas it took 14 h to achieve halogen ‘dance’ from *N,N*-diisopropyl 2-iodoferrocenecarboxamide,<sup>13</sup> the reaction from **3fb** only required 2 h, providing **3fb-mig** in 77% yield after methanolysis and purification (Scheme 2, bottom; Fig. 2). This better result might come from the higher acidity of **3fb** at the position next to the DG, leading to a more stable lithio product, and therefore to less LiTMP in the reaction mixture. As a consequence, the deiodinated product **3f**, probably formed by LiTMP-mediated iodine/lithium exchange,<sup>19</sup> was only identified in the crude as minor product (<10%). The trimethylsilyl group here perfectly played its role, avoiding competitive deprotonation at the origin of undesired products.



**Figure 2.** ORTEP diagrams (30% probability level) of silyl-protected 1-fluoro-2-iodo-ferrocene (**3fb**) before (left) and after (right) halogen migration.

As shown by the calculated  $pK_a$  values in THF,<sup>20</sup> chloro and fluoroferrocene have similar CH acidities (see Fig. 3, top left). In order to synthesize **6fb** and test the halogen ‘dance’ on this chloro analogue of **3fb**, we started from chloroferrocene<sup>21</sup> (**5a**) and carried out two deprotonation-trapping sequences. If butyllithium<sup>22a,b,7,22c</sup> and LiTMP<sup>21,12,22c</sup> can be used to deprotonate **5a**, we chose the more reactive *sec*-butyllithium to efficiently access **6f** and **6fb**. Under the conditions used for fluoride **3fb**, chloride **6fb** was isomerized to afford **6fb-mig** in high yield (Scheme 3, left & bottom).

In order to evaluate the need of a protecting group, 1-chloro-2-iodoferrocene (**6b**) was similarly prepared and treated by the lithium amide. Under the conditions used for silyl-protected **6fb** (Scheme 3, bottom; Fig. 3, bottom right), 1-chloro-3-iodoferrocene (**6b-mig**) was identified, but in a low 23% conversion (Scheme 3, right). Although further studies are required, this result might come from competitive deprotonation next to the chlorine substituent. Indeed, **6b** show similar  $pK_a$  values at its positions next to Cl and I (while **3b** appears as an even less appropriate substrate; Fig. 3, top right).



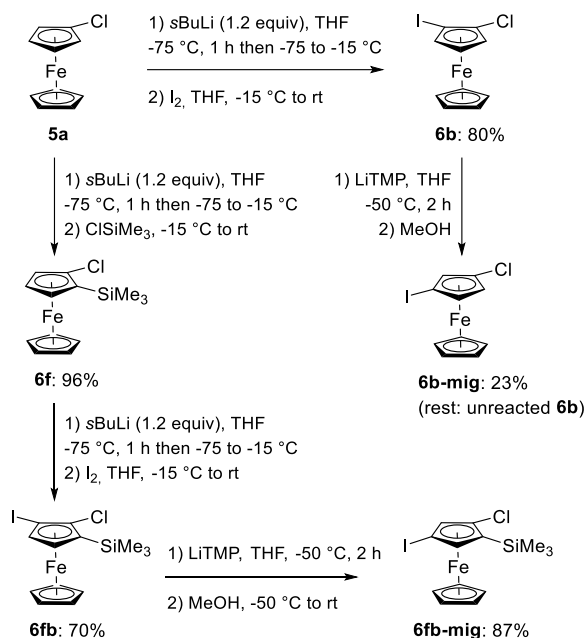
**Figure 3.** Calculated  $pK_a$  values in THF for the halogenoferrocenes **1a**, **5a**, **3b**, **6b** and **6fb**, fluorobenzene and chlorobenzene.

This study also evidenced remarkably stable 2-halogenoferrocenyllithiums when compared to their 2-halogenophenyl analogues. In particular, 1-chloro-2-lithioferrocene is quite stable at  $-15$  °C whereas chlorobenzene has to be deprotonated at about  $-100$  °C to avoid benzyne formation.<sup>23</sup> On the basis of the calculated  $pK_a$  values for both 2-halogenoferrocenes and benzenes (see Fig. 3, left), one might suggest that the unstability of 2-halogenoferrocenyllithiums is not at the origin of ferrocene formation.<sup>22a,24</sup>

Thus, efficient methods were developed from fluoro- and chloroferrocene to access 2- and 3-substituted derivatives, allowing original ferrocene-based halogenated compounds to be built. As fluorinated aromatic compounds are present in numerous pharmaceuticals and agrochemicals (in which fluo-

rine substituent improves both membrane permeability and metabolic stability),<sup>25</sup> it is of interest to build ferrocene analogues of such scaffolds in the search for derivatives with improved activity. Further studies on the chemistry of fluoroferrocene derivatives and their use in halogen ‘dance’ reactions with interception of the rearranged lithioferrocenes by various electrophiles towards tetrasubstituted derivatives are ongoing and will be reported in due course.

### Scheme 3. Halogen ‘dance’ from chloroferrocenes.



## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.XXX.

Experimental procedures, compounds analyses, X-ray crystallographic details, NMR spectra (PDF) Crystallographic data (CIF)

### Accession Codes

CCDC 1841221-1841234. The crystallographic data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Notes

The authors declare no competing financial interest.

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