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ChemComm

Christophe Pichon, Barbara Odell and John M. Brown*

Dyson Perrins Laboratory, Department of Chemistry, University of Oxford, South Parks Road, Oxford, UK OX1 3OY. E-mail: john.brown@chem.ox.ac.uk

Received (in Cambridge, UK) 13th November 2003, Accepted 9th January 2004 First published as an Advance Article on the web 10th February 2004

Ferrocenyl sulfides afford meta-lithiation products with up to 94% regioselectivity on reaction with s-BuLi; the resulting 1,3-disubstituted ferrocenes can then be reacted with a variety of electrophiles.

In a recent communication, we reported a route to a ferrocene-based pincer ligand and a simple hydridorhodium complex derived from it.¹ The synthesis involved a multistep preparation of the diol $\mathbf{1}$, which could be phosphinated directly with t-Bu₂PH in AcOH to give the desired diphosphine 2. In turn, this was readily converted into the desired Rh complex 3 (Scheme 1). Production of planar asymmetric analogues for catalytic dehydrogenation was then the goal and an improved route to 1,3-disubstituted ferrocenes became a priority.2

In initial experiments, a sulfoxide group was employed as the template, with the intention of employing two sequential directed ortho-metallations to introduce two different flanking side-chains, followed by removal of the sulfoxide.3 The first step in the sequence is well precedented,⁴ whilst the rest requires novel chemistry and proved more challenging. This led us to examine the directing properties of different S-ferrocenyl compounds in metallation and, in particular, introducing the second ring functionality by lithiation of a ferrocenyl sulfide and electrophilic trapping of the intermediate. Simple model ferrocenyl sulfides 4a-c were easily prepared from ferrocenyllithium and the corresponding disulfide5 or, alternatively, via the corresponding sulfoxide (Scheme 2).6 Although the preparation of FcLi is normally undertaken following Kagan's procedure, we discovered that the reaction of ferrocene with s-BuLi in THF at 0 °C is a simple clean route to ferrocenyllithium.

As part of the survey of directing effects in sequential metallations necessary for us to achieve our stated objective, the products were subjected to various lithiation procedures. Initial experiments involved comparison between s-BuLi and t-BuLi as base in THF solution, trapping the lithiated species from 4a with DMF. With t-BuLi, there were three products, which were



10.1039/b314641c Scheme 2 Method A: s-BuLi, 0 °C, 5 h, then R-SS-R. Method B: (i) s-BuLi, 0 °C, 5 h, then *p*-TolSO₂*i*Pr (R = *p*-Tol) or *t*-BuSO–S–*t*-Bu (R = *t*-Bu); (ii) Me₂SiCl₂, Zn, 0 °C, 10 min, acetone.

separated by silica chromatography and identified by NMR spectroscopy.† The key was provided by NOEs between neighbouring ferrocenyl protons and ferrocenyl substituents, e.g. H (CHO group) and ortho-H (-S-p-Tol group), respectively.

The expected 1,2-disubstituted product 5 was the minor component, accompanied by the 1,1'-isomer 6 and the 1,3-isomer 7, the last being the dominant product.⁷ With s-BuLi, the reaction was far more selective in favour of compound 7. No evidence for products arising from phenyl metallation was obtained, consistent with the higher intrinsic acidity of ferrocene over benzene.⁸

Through further experiments, it was established that each of these three products could dominate, depending on the reaction conditions. In order to promote formation of the 1,2-lithiated species, the Schlosser superbase was needed.⁹ The 1,1'-isomer was best formed under conditions of thermodynamic control (Table 1). With s-BuLi, the same regiochemical course was observed with the other ferrocenyl sulfides 4b and 4c.

The availability of a simple route to meta-lithiated ferrocenes encouraged us to examine the reaction of the s-BuLi-generated intermediate with a range of electrophiles. Trapping with D₂O gave product 8 that was 85% deuterated, and the ²H NMR spectrum of a sample quenched at 75% metallation established the distribution shown in Fig. 1.

In general, yields of 50–65% were obtained (Scheme 3), with the remainder being largely recovered starting material. The regioisomeric bias towards formation of the 1,3-isomer was consistently in the range 90–93%, with the nature of the electrophile exerting little influence. A range of 1,3-disubstituted ferrocenes was obtained in this way, in 95-98+% purity.

In order to demonstrate the synthetic application of this sequence, the primary alcohol 9a was converted into its tertbutyldimethylsilyl (TBDMS) ether 12. Oxidation of the sulfide to sulfoxide 13 was followed by reaction with *t*-BuLi,¹⁰ trapping with DMF, as before, to give 14 and NaBH₄ reduction to the

Table 1	Conditions	for	regioselective	metallation	of	4	a
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Conditions	5	6	7	$ au^{a}\left(\% ight)$
<i>i</i> -Pr ₂ NLi, RT, 13 h				3
<i>n</i> -BuLi, RT, 13 h	_	_	_	17
s-BuLi, 0 °C, 7 h	2	4	94	84
<i>t</i> -BuLi, 0 °C, 7 h	13	32	55	68
<i>s</i> -BuLi, 0 °C, 7 h, then 30° C, 48 h	3	85	12	83
s-BuLi, t-BuOK, -78 °C, 7 h	65	10	25	75
a Conversion (0/)				





Fig. 1 ²H NMR spectrum of deuterated 4a in C₆H₆ at 81.3 MHz.



Scheme 3 *Meta*-lithiation of 4a: (a) *s*-BuLi, THF, 0 °C, 7 h; (b) the electrophile used is listed in brackets before the isolated yield.



Scheme 4 (a) TBDMS–Cl, DBU (98%); (b) MCPBA (94%); (c) *t*-BuLi (2.5 eq.), -78 °C, then DMF (91%); (d) NaBH₄ (97%).

monoprotected diol 15, in 29% overall yield from ferrocene (Scheme 4).

There are no precedents for this selective lithiation chemistry in ferrocenes. Diphenyl sulfide is known to undergo *ortho*-metallation or double *ortho*-metallation with *n*-BuLi-TMEDA.¹¹ The chromium tricarbonyl complexes of phenyl silyl ethers or alkylaminobenzenes are known to undergo selective *meta*-lithiation with different RLi bases, however.¹² More general approaches to *meta*-lithiation are desirable.

Attempts to carry out the metallation of ferrocenyl sulfides in the presence of (–)-sparteine gave both low yields and low ee. As far as our original goal is concerned, the chemistry described can only be used after an initial enantioselective sulfoxide-driven step, and efforts are continuing along these lines.

We thank the EC through RTN Network HPRN-CT-2001-00172, and the Leverhulme Trust F08341A for support of C. P.

Notes and references

[†] Typical procedure for *meta*-lithiation of **4a**: the reaction was carried out under an anhydrous argon atmosphere using standard vacuum line and Schlenk techniques. To a solution of **4a** (716 mg, 2 mmol) in anhydrous THF (8 mL) under Ar was added dropwise at -10 °C a commercial solution of *s*-BuLi (1.4 M; 1.6 mL, 2.24 mmol; 1.12 eq.). Next, the solution was stirred at 0 °C for 7 h until it become opaque yellow–orange. After cooling to -30 °C, acetone (0.4 mL) was then added and the solution stirred for 5 min. NH₄Cl (sat. in H₂O; 10 mL) was then added and the aqueous layers were extracted with Et₂O (3 × 15 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and dried over MgSO₄. After concentration *in vacuo*, a reddish oil was obtained, which was purified by silica chromatography (40 : 1; CH₂Cl₂–Et₂O from 99 : 1 to 80 : 20). Some unreacted starting material was easily recovered (87 mg, 12%). The 1,2-isomer (21 mg, 3%).

Selected characterisation data. 7: red solid, m.p. 104–105 °C. v_{max}/cm⁻¹ 3005, 2995, 2975, 1720, 1550, 1320, 1100. R_f 0.51 (CH₂Cl₂). $\delta_{\rm H}$ (400 MHz, CDCl₃) 2.28 (s, 3H, CH₃), 4.35 (s, 5H, Cp'-H), 4.76 (dd, 1H, J 2.6, 1.3 Hz, Cp-H5), 4.90 (dd, 1H, J 2.6, 1.3 Hz, Cp-H4), 4.99 (t, 1H, J 1.3 Hz, Cp-H3); 7.04 (d_{AA'BB'}, 2H, J 8.4 Hz, Ar-H), 7.09 (d_{AA'BB'}, 2H, J 8.3 Hz, Ar-H), 9.91 (s, 1H, CHO). δ_C (100 MHz, CDCl₃) 21.0, 70.8, 71.3, 75.0, 78.6, 80.3, 83.9, 128.2, 129.7, 134.6, 136.1, 192.7. HRMS *m*/*z* calc. for C₁₈H₁₆OSFe [M + H]⁺ 337.0349, found 337.0341. 9b: yellow solid, m.p. 151–153 °C. v_{max}/ cm⁻¹ 3225, 3005, 1650, 1420, 1310, 1220. R_f 0.41 (CH₂Cl₂-Et₂O 8 : 2). $\delta_{\rm H}$ (400 MHz, C₆D₆) 1.44 (s, 3H, Me), 1.47 (s, 3H. Me), 2.08 (s, 3H, Ar-CH₃), 4.17 (s, 5H, Cp'-H), 4.19 (dd, 1H, J 2.4, 1.3 Hz, Cp-H4), 4.38 (dd, 1H, J 2.4, 1.3 Hz, Cp-H5), 4.48 (t, 1H, J 1.3 Hz, Cp-H2), 6.92 (d_{AA'BB'}, 2H, J 8.1 Hz, Ar-H), 7.34 (d_{AA'BB'}, 2H, J 8.1 Hz, Ar-H). $\delta_{\rm C}$ (100 MHz, C₆D₆) 20.9, 31.1, 31.5, 67.6, 68.7, 70.5 (5C), 72.8, 74.8, 77.4, 102.5, 127.4, 130.0, 135.2, 137.8. HRMS m/z calc. for $C_{20}H_{22}OSFe [M + H]^+$ 367.0819, found 368.0821. 15: orange oil. v_{max}/cm⁻¹ 3200 (br), 1510, 1410, 1210. R_f 0.15 (CH₂Cl₂). δ_H (400 MHz, CDCl₃) 1.50 (t, 1H, J 5.8 Hz, OH); 4.16 (s, 5H, Cp'-H), 4.20 (m, 1H, Cp-H), 4.23 (m, 1H, Cp-H), 4.28 (m, 1H, CH₂O), 4.29 (m, 1H, Cp-H), 4.30 (m, 1H, CH₂O), 4.39 (s, 2H, CH₂OSi). $\delta_{\rm C}$ (100 MHz, CDCl₃) -5.1, 18.4, 26.0, 60.7, 61.1, 67.6, 67.8, 68.1, 68.9 (5C), 88.3, 88.4. HRMS m/z calc. for C₁₈H₂₈O₂SiFe [M + NH₄]⁺ 378.1552, found 378.1559.

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