Dalton Transactions

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Roemer, B. W. Skelton, M. Piggott and G. Koutsantonis, *Dalton Trans.*, 2016, DOI: 10.1039/C6DT03820D.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/dalton

View Article Online
DOI: 10.1039/C6DT03820D

Dalton

COMMUNICATION

1,1'-Diacetyloctamethylferrocene: An overlooked and overdue synthon leading to the facile synthesis of an octamethylferrocenophane.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

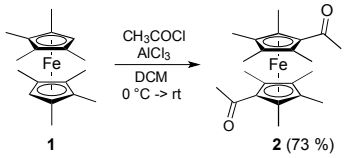
www.rsc.org/

Max Roemer[a]*, Brian W. Skelton[b], Matthew J. Piggott[a] and George A. Koutsantonis[a]*

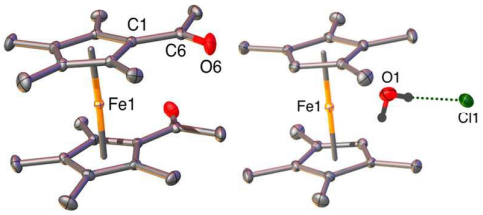
Abstract: This paper describes the facile preparation of 1,1'-diacetyloctamethylferrocene (2) by acylation of octamethylferrocene (1) with acetyl chloride. Chloroformylation with $POCl_3$/DMF of 2 affords a variety of products, including 1,1'-bis-(1-chlorovinyl)octamethylferrocene (3b) in high yield. Compound 3b cyclises in aqueous sodium hydroxide/DMF to an octamethyl[1,4]-ferrocenophane bearing a 1-dimethylaminobuta-1,3-diene-handle (4).

Ferrocene (FcH) is perhaps the archetypical organometallic compound.[1-5] Derivatives of the redox-stable 18-electron complex find numerous applications in a variety of fields, including molecular electronics,[6] electrochemistry,[7] catalysis,[8, 9] and medicine.[10] Highly alkylated FcHs are of interest for a number of reasons. The increased electron density in the cyclopentadienyl (Cp) ligands results in lowered oxidation potentials,[11] hence making the complexes powerful electron-donating substituents. Alkyl groups also impart greater solubility in organic solvents, compared to FcH, a crucial consideration for the incorporation of FcHs into functional molecules and polymers.[12] Derivatives of octamethylferrocene (**1**) have been used in catalytic hydrogen production,[13] the formation of allylium salts,[14] non-linear optical applications[15] and in mixed-valence species.[16] Furthermore, **1** was used to functionalise a stable radical,[17] dendrimers[18] and metal surfaces.[19] Despite these examples, there are significantly fewer reports of derivatives of **1** in the literature, compared to derivatives of FcH. 1,1'-Diacetylferrocene ($FcAc_2$), prepared by acylation of FcH,[18,20] is a key synthon and was seminal in the demonstration of the aromaticity of ferrocene[20]; the CAS database contains >950 reactions and >700 publications utilising or mentioning $FcAc_2$. Strikingly, 1,1'-diacetyloctamethylferrocene (**2**) (Scheme 1), has never been reported, and to the best of our knowledge there is only a single report describing the preparation of an octamethylferrocenophane.[21] One strategy for the synthesis of highly alkylated FcH's and related sandwich complexes is synthesis of the ligand followed by complexation to Fe.[22] These are multi-step procedures, which suffer from low overall yields. The only example for a functionalisation of **1** in reasonable yield is formylation,[13, 18, 23] 1,1'-diformyloctamethylferrocene was obtained in low yield by oxidation of two methyl groups of decamethylferrocene.[24, 25] Lithiation of the Cp ring, another common means to functionalise ferrocenes, is unsuccessful with **1**, presumably due to steric hindrance, and because the electron-donating methyl groups destabilise the resultant anion.[22]

Herewith we report on the preparation of **2** by acylation of **1**. While the analogous reaction for FcH[26, 27] has been known for over fifty years and remains a contemporary and invaluable tool to functionalise its derivatives[28], this method appears to have been essentially overlooked as a mean to functionalise **1**. For preparation of **2**, the work-up procedure is crucial. Compound **2** is sensitive to silica gel, presumably due to the slightly acidic nature of silica gel which leads to oxidation to a Fe(III) species.



Scheme 1. Preparation of 1,1'-diacetyloctamethylferrocene (2) by acylation of octamethylferrocene (**1**).



[a] *Chemistry, M310, School of Chemistry and Biochemistry, The University of Western Australia, 35 Stirling Hwy, Crawley, WA 6009, Australia*
[b] *Centre for Microscopy, Characterisation and Analysis, University of Western Australia, Crawley, Western Australia 6009, Australia*
** E-mail: max.roemer@uwa.edu.au, george.koutsantonis@uwa.edu.au*
† Electronic Supplementary Information (ESI) available: Full experimental details and X-ray crystallographic data in cif-format.. See DOI: 10.1039/x0xx00000x

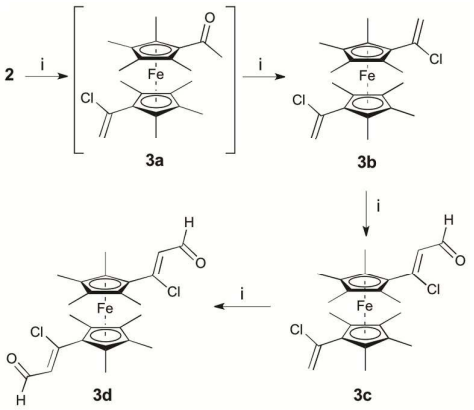
View Article Online
DOI: 10.1039/C6DT03820D

Fig 1. Representations of the molecular structures of **2** (left) and the ferrocenium species $\mathbf{1}^+ \bullet Cl^- \bullet H_2O$ isolated as by-product (thermal ellipsoids with a probability of 50 %, H atoms omitted for clarity).

By using Al_2O_3 instead, the formation of oxidative by-products could be largely avoided and the yield increased about a factor of two. Alternatively, we purified **2** by sublimation, in a similar yield, or removed unreacted **1** using a hexane wash. Complex **2** can be stored for several months in air without any visible sign of decomposition. Its molecular structure is depicted in Scheme 1. The dearth of acylation examples of **1** presumably arises from the reported low yield of diketone obtained using 4-chlorobutyryl chloride,[23] where it was proposed that oxidation to $\mathbf{1}^+$ (i.e., octamethylferrocenium) inhibits electrophilic aromatic substitution. We experienced difficulties using a similar substrate, 4-bromobutyryl chloride, with the isolated yield of the 1,1'-diacyl derivative being very low (< 5%). Traces of product forms however, attempts to purify it by chromatography or sublimation led to almost complete decomposition. Indeed, we isolated an oxidised species of the form $\mathbf{1}^+ \bullet Cl^- \bullet H_2O$ from the acylation of **1** (Fig. 1 and Scheme 1), suggesting that oxidative side-reactions occur. However in our experiments, oxidative by-products, e.g. $\mathbf{1}^+$, were less than 20 % in yield. IR and MS data suggest the formation of acetyloctamethylferrocene cation (SI) as well as $\mathbf{1}^+$ in the reaction mixture, from which we were able to isolate a crystal of the latter.

The solid state structure of **2** (Fig. 1) was determined and by most measures is comparable to the solid state structure of $FcAc_2$[29] with average Fe-Cp distances and $Cp_{centroid}$-Fe-$Cp_{centroid}$ angles not significantly different. The obvious differences arise from the disposition of the acyl moieties. In **2** these are almost eclipsed, marginally offset to accommodate the steric requirements of the acyl methyl groups, in $FcAc_2$ the acyl groups are diametrically opposed.

The bromohexanoyl derivative of **1** has been prepared by acylation with 6-bromohexanoyl chloride, albeit in low yield.[30]



Scheme 2. Chloroformylation of **2** with (i) $POCl_3$/DMF.

We targeted the formation of alkenyls *via* chloroformylation of **2**.[31-34] Treatment of FcAc with a Vilsmeier reagent, generated from $POCl_3$ and DMF, yields 2-formyl-1-chlorovinylferrocene. The reaction of $FcAc_2$ under similar conditions gives mixtures of 1-(2-formyl-1-chlorovinyl)-1′-(1-chlorovinyl)ferrocene and 1,1′-bis(2-formyl-1-chlorovinyl)ferrocene. These reports are conflicting as different product ratios and/or intermediates have been proposed. The chloroformylation of **2**, rapidly and quantitatively affords the 1,1'-bis(1-chlorovinyl) derivative **3b** (Scheme 2), the structure of which was confirmed by X-ray crystallography (Figure 2).

Analogous reactions have been observed with electron-rich acetophenones, and are thought to proceed by initial de-aromatisation rather than the enolisation that occurs in the accepted mechanism for the chloroformylation of less electron rich ketones.[35] We propose the mechanism depicted in the Scheme S1 (SI). Extended reaction times led to the further formylation of **3b**. We studied the reaction of **2** in DMF-d^7 with varying amounts of $POCl_3$, which proceeds via a short-lived intermediate bearing one 1-chlorovinyl group (**3a**), enroute to **3b** (Figures S1-S4). In the presence of an excess of the Vilsmeier reagent, **3b** is slowly converted to **3c** and finally to **3d** (Scheme 2). Our results show a strong dependence of the reaction rate on the $POCl_3$ concentration (Figures S4 and S5). Transformation of **2** to **3c** is achieved in 1h and to **3d** overnight, respectively. We note that after aqueous work-up a significant amount of **3d** is transferred into the aqueous phase, presumably due to oxidation to $\mathbf{3d}^+$ in the presence of $POCl_3$. Intriguingly, after standing for 1 h, the product quantitatively precipitated from the aqueous phase in form of black needles, analytically pure and suitable for X-ray diffraction, in its water insoluble reduced form **3d**. Its molecular structure is depicted in Fig. 2.

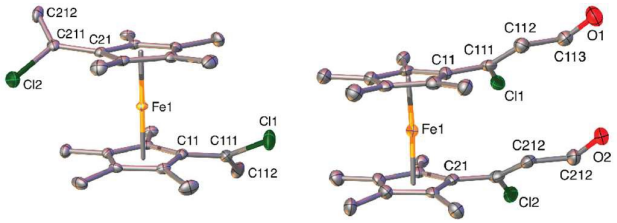


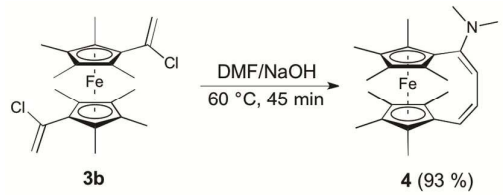
Fig. 2 Representations of the molecular structures of **3b** (left) and **3d** (right). Compound **3b** crystallises with two different molecules in the asymmetric unit, the figure shows only one of them (thermal ellipsoids with a probability of 50 %, H atoms omitted for clarity).

The difference in reactivity between $FcAc_2$ and **2** towards the Vilsmeier reagent is a result of the greater electron-richness of the latter; cyclic voltammetry revealed reversible one electron redox process (Fe(II)/Fe(III)) for **2**, **3b**, **3c** and **3d** (Fig. S6). Compound **2** oxidises at 45 mV (vs the Fc/Fc^+ couple), considerably lower than that of $FcAc_2$ at 490 mV, and higher than that of decamethylferrocene (-480 mV).[11] Transformation of the acetyl groups to chlorovinyl groups results in a lower redox potential of -310 mV (**3b**). Addition of one formyl group shifts the potential to - 15 mV for **3c**, and addition of a further formyl group results in a potential of 99 mV for **3d**. The formylation reaction of **2** proceeds faster than that of $FcAc_2$, and $POCl_3$ concentration and reaction time both play a crucial

View Article Online
DOI: 10.1039/C6DT03820D

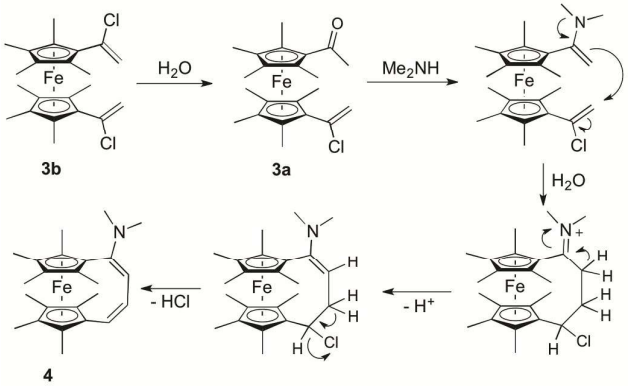
role regarding the product distribution. It seems that differences in the reaction conditions are the root cause for the conflicting results reported regarding the chloroformylation of $FcAc_2$.[31, 36, 37]

Cyclisation reactions of ferrocenes with trifluorovinyl[38, 39], vinyl[40] and ethynyl[21] groups in 1,1'-positions yield a variety of [1,4]-ferrocenophanes. To investigate whether we could achieve ferrocenophane formation from **3b**, we used similar conditions to those above.[21, 38-40] Remarkably the only product we isolated was that of unexpected hydrolysis, compound **2**. We propose the reaction to proceed via an S_N1-subsitution of the chloride by H_2O, followed by H^+ loss and tautomerisation of the enol to afford the acetyl substituents. Reactions of a 1-halovinylferrocenes in this manner appear to be unprecedented. The hydrolysis of 1-chlorostyrene to yield acetophenone requires heating with strong acid catalysts,[41] but an electron-rich 1-chlorovinylpyrrole hydrolysed in wet ethanol.[42] An analogous hydrolysis of **2** in other solvent/water mixtures (MeCN, THF, dioxane) hampered our initial attempts to prepare ferrocenophanes. But surprisingly, when **3b** is treated with NaOH in DMF, we achieved cyclisation giving an electron rich octamethyl [1,4]-ferrocenophane in excellent yield (**4**, Scheme 3).



Scheme 3. Formation of an electron rich [1,4]-ferrocenophane from **3b**.

The intramolecular C-C-coupling reaction to afford **4** is facile, but depends on several factors, such as DMF/water ratio, reaction time and temperature, and concentration of NaOH. We propose a mechanism (Scheme 4) involving initial hydrolysis of one $CCl=CH_2$-group to **3a**, which gets converted in the presence of dimethylamine, arising from base induced decomposition of DMF, to the respective enamine.



Scheme 4. Proposed mechanism for formation of ferrocenophane **4**.

The enamine cyclises to an immino [1,4]-ferrocenophane intermediate in the presence of water, eliminating a proton and then HCl to afford **4**. Optimised reaction conditions are provided in the SI. Altering the reaction time, temperature or NaOH concentration from those, resulted in intractable complex mixtures. The rate of the DMF decomposition is dependent on these factors,[43] providing the explanation for our observation. We note that [1,3]-ferrocenophanes bearing an enamine handle have been prepared from $FcAc_2$ and dimethylamine. The formation of an enamine under aqueous conditions is rather surprising, but not unprecedented given that it is stabilised by conjugation.[44] Even so, **4** is highly reactive and attempts to purify it by chromatography on silica or Al_2O_3 led to complete degradation. Work-up avoiding chromatography afforded air-sensitive **4** in excellent yield but always accompanied by trace impurities (overall purity ca. 97 %, SI). Its molecular structure is depicted in Fig. 3. The molecule is slightly strained with a tilt ranging from 1.4-8.1° (two different disordered conformers).

Cyclic voltammetry revealed a reversible one-electron process at a potential of - 425 mV, but only when keeping the cathodic peak potential low (~ - 160 mV, Fig. S7). Scanning at a larger bias range induced decomposition, giving rise to a new process at ~ -193 mV, followed by a further one in the vicinity of 8 mV with a sharp decline of E_{pa} and E_{pc} of the initially reversible process at - 425 mV with repeated scans, which ultimately vanishes (Fig. S8). We are currently investigating this oxidation triggered decomposition, which is likely the reason for the inherent instability of **4**. There are a number of ferrocenyl substituted amines known in the literature[45, 46] and, in the present case, we cannot exclude the possibility of an amine centered oxidation[11] contributing to the decomposition. Compound **4** exhibits a remarkably low oxidation potential for an all-carbon bridged ferrocenophane, we are not aware of a lower reported value.

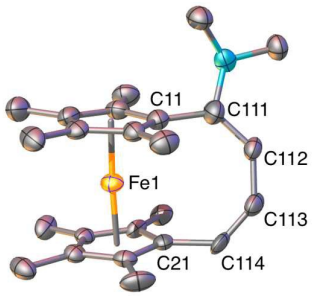


Fig. 3 Representation of the molecular structure of **4**. The molecule crystallises with two different molecules in the asymmetric unit, this figure shows only one. A disorder at one Cp ring and the butadiene handle is not depicted **(**thermal ellipsoids with a probability of 50 %, H atoms omitted for clarity).

In summary, acylation of octamethylferrocene is viable, allowing the preparation of the 1,1'-diacetyl octamethylferrocene in good yield and exploitation of this synthon. Formylation of it affords a variety of products, the product distribution can be efficiently controlled. 1,1'-bis(1-chlorovinyl)octamethylferrocene undergoes a cyclisation reaction to a highly reactive octamethyl-[1,4]-ferrocenophane in excellent yield.

View Article Online
DOI: 10.1039/C6DT03820D

This research was supported under Australian Research Council's *Discovery Projects* funding scheme (project number DP 150104117). We acknowledge the facilities and the scientific and technical assistance of the Australian Microscopy and Microanalysis Research Facility at the Centre for Microscopy, Characterization and Analysis, The University of Western Australia, a facility funded by the University, State and Commonwealth Governments.

Notes and references

‡ Experiments were performed under Ar atmospheres using standard Schlenk techniques. For full experimental details see supporting information. The supporting supplementary material contains the crystallographic information files in cif-format for compounds **1**$^{+}$ * Cl^{-} * H_2O, **2**, **3b**, **3d** and **4** (CCDC numbers 1498867-71). Molecular graphics: OLEX2.[47]

1. L.-X. Dai, X.-L. Hou and Editors, *Chiral Ferrocenes In Asymmetric Catalysis: Synthesis And Applications*, Wiley-VCH Verlag GmbH & Co. KGaA, 2010.
2. N. J. Long, *Metallocenes: An Introduction to Sandwich Complexes*, Wiley-Blackwell, 1998.
3. A. Togni and R. L. Halterman, *Metallocenes*, Wiley, 1998.
4. A. Togni, T. Hayashi and Editors, *Ferrocenes: homogeneous catalysis, organic synthesis, materials science*, VCH, 1995.
5. P. Štěpnička, *Ferrocenes: Ligands, Materials and Biomolecules*, John Wiley & Sons Ltd., 2008.
6. P. Song, L. Yuan, M. Roemer, L. Jiang and C. A. Nijhuis, *J. Am. Chem. Soc.*, 2016, **138**, 5769-5772.
7. M. V. Sheridan, K. Lam and W. E. Geiger, *J. Am. Chem. Soc.*, 2013, **135**, 2939-2942.
8. R. C. Atkinson, V. C. Gibson and N. J. Long, *Chem Soc Rev*, 2004, **33**, 313-328.
9. Q. Zhang, X. Cui, L. Zhang, S. Luo, H. Wang and Y. Wu, *Angew. Chem. Int. Ed. Engl.*, 2015, **54**, 5210-5213.
10. G. Jaouen, A. Vessieres and S. Top, *Chem Soc Rev*, 2015, **44**, 8802-8817.
11. N. G. Connelly and W. E. Geiger, *Chem. Rev.*, 1996, **96**, 877-910.
12. P. Nguyen, P. Gómez-Elipe and I. Manners, *Chem. Rev.*, 1999, **99**, 1515-1548.
13. J. C. Lansing, J. M. Camara, D. E. Gray and T. B. Rauchfuss, *Organometallics*, 2014, **33**, 5897-5906.
14. S. Barlow, L. M. Henling, M. W. Day, W. P. Schaefer, J. C. Green, T. Hascall and S. R. Mardert, *J. Am. Chem. Soc.*, 2002, **124**, 6285-6296.
15. B. J. Coe, S. P. Foxon, R. a. Pilkington, S. Sánchez, D. Whittaker, K. Clays, G. Depotter and B. S. Brunschwig, *Organometallics*, 2015, **34**, 1701-1715.
16. S. Barlow, *Inorg. Chem.*, 2001, **40**, 7047-7053.
17. J. Guasch, L. Grisanti, S. Jung, D. Morales, G. D'Avino, M. Souto, X. Fontrodona, A. Painelli, F. Renz, I. Ratera and J. Veciana, *Chem. Mater.*, 2013, **25**, 808-814.
18. M. Zamora, S. Herrero, J. Losada, I. Cuadrado, C. M. Casado and B. Alonso, *Organometallics*, 2004, 2688-2693.
19. Y. Yokota, Y. Mino, Y. Kanai, T. Utsunomiya, A. Imanishi and K. I. Fukui, *J. Phys. Chem. C*, 2015, **119**, 18467-18480.
20. R. B. Woodward, M. Rosenblum and M. C. Whiting, *J. Am. Chem. Soc.*, 1952, **74**, 3458-3459.
21. J. K. Pudelski and M. R. Callstrom, *Organometallics*, 1994, **13**, 3095-3109.
22. M. Hobi, O. Ruppert, V. Gramlich and A. Togni, *Organometallics*, 1997, **16**, 1384-1391.
23. C. Zou and M. S. Wrighton, *J. Am. Chem. Soc.*, 1990, **112**, 7578-7584.
24. S. T. Erik Stankovic, Roel Van Boxel, Inge Asselberghs, Andre Persoons, *J. Organomet. Chem.*, 2001, 426–434.
25. A. Z. K. M. I. Rybinskaya, and P. V .Petrovskii, *Organometallics*, 1994, 3903-3908.
26. G. D. Broadhead, J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.*, 1958, 650-656.
27. M. Rosenblum and J. O. Santer, *J. Am. Chem. Soc.*, 1959, **81**, 5517-5518.
28. M. Roemer, B. Donnadieu and C. A. Nijhuis, *Eur. J. Inorg. Chem.*, 2016, 1314-1318.
29. A. M. Makal, D. Plazuk, J. Zakrzewski, B. Misterkiewicz and K. Wozniak, *Inorg. Chem.*, 2010, **49**, 4046-4059.
30. J. H. Olshansky, T. X. Ding, Y. V. Lee, S. R. Leone and A. P. Alivisatos, *J. Am. Chem. Soc.*, 2015, **137**, 15567-15575.
31. K. Schlögel and W. Steyrer, *Monatsh. Chem.*, 1965, 1520-1535.
32. M. Rosenblum, N. Brawn, J. Papenmeier and M. Applebaum, *J. Organomet. Chem*, 1966, **6**, 173-180.
33. J. Polin and H. Schottenberger, *Org. Synth.*, 1996, **73**, 262.
34. H. Schottenberger, J. Lukassser, E. Reichel, A. G. Müller, G. Steiner, H. Kopacka, K. Wurst, K. H. Ongania and K. Kirchner, *J. Organomet. Chem.*, 2001, **637–639**, 558–576.
35. A. Lilienkampf, M. P. Johansson and K. Wähälä, *Org. Lett.*, 2003, **5**, 3387-3390.
36. M. Puciová, E. Solčániová, N. a. Pronayová, D. Loos and Ŝ. Toma, *Tetrahedron*, 1993, **49**, 7733-7742.
37. S. Basurto, O. Riant, D. Moreno, J. Rojo and T. Torroba, *J. Org. Chem.*, 2007, **72**, 4673-4688.
38. M. Roemer, D. Heinrich, Y. K. Kang, Y. K. Chung and D. Lentz, *Organometallics*, 2012, **31**, 1500-1510.
39. M. Roemer and D. Lentz, *Chem. Commun.*, 2011, **47**, 7239-7241.
40. R. M. Gleixner, K. M. Joly, M. Tremayne, B. M. Kariuki, L. Male, D. M. Coe and L. R. Cox, *Chem. Eur. J.*, 2010, **16**, 5769-5777.
41. W. Emerson and E. P. Agnew, *J. Am. Chem. Soc*, 1944, **67**, 518-520.
42. D. T. Kozhich, L. V. Akimenko, A. F. Mironov and R. P. Evstigneeva, *Zh. Org. Khim.*, 1977, **13**, 2604-2608.
43. E. Buncel and E. A. Symons, *Chem. Commun.*, 1970, 164-165.
44. G. Erker, M. Riedel, S. Koch, T. Joedicke and E.-U. Wuerthwein, *J. Org. Chem.*, 1995, **60**, 5284-5290.
45. K. Heinze and M. Schlenker, *Eur. J. Inorg. Chem.*, 2004, DOI: 10.1002/ejic.200300897, 2974-2988.
46. M. C. Semencic, D. Siebler, K. Heinze and V. Rapic, *Organometallics*, 2009, **28**, 2028-2037.
47. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339-341.

View Article Online
DOI: 10.1039/C6DT03820D

Table of Contents Entry

Surprisingly easy access to versatile synthons: High yielding acylation, formylation and intramolecular cyclisation reaction to a ferrocenophane