Multiple Acetylation of Pentaphenylferrocene. Synthesis and Asymmetric Reduction of 1-Acetyl-1',2',3',4',5'-penta(*para*-acetylphenyl)ferrocene

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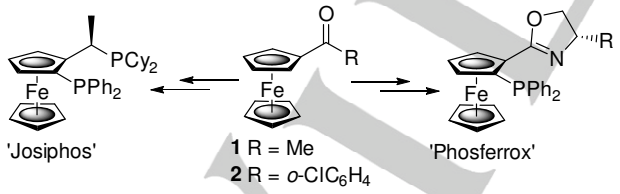
Dedication ((optional))

Abstract: The Friedel-Crafts acetylation of pentaphenylferrocene has been revisited using 1.1 equivalents of AcCl/$AlCl_3$ in CH_2Cl_2 at room temperature leading to the synthesis of 1-acetyl-1',2',3',4',5'-pentaphenylferrocene (78% yield). Increased quantities of reagents and longer reaction times resulted in acetylation of the phenyl groups exclusively at the *para*-position, this methodology culminating in the synthesis of 1-acetyl-1',2',3',4',5'-penta(*para*-acetylphenyl)ferrocene (32% for a two step process). Subsequent asymmetric reduction of all six ketone functionalities with $BH_3.SMe_2$ catalysed by 60 mol % (*S*)-CBS proceeded in 81% yield to give (*R*,*R*,*R*,*R*,*R*,*R*)-1-(α-hydroxyethyl)-1',2',3',4',5'-penta(*para*-(α-hydroxyethyl)phenyl)ferrocene, a highly functionalised enantiopure building block for the synthesis of ligands and materials.

Introduction

The Friedel-Crafts acylation of ferrocene is a useful way of adding functionality to one or both cyclopentadienyl rings.[1] Depending on the electrophile used, the resulting compounds have been employed as the starting material for a variety of compounds,[2] including ligands that have found widespread application in asymmetric catalysis.[3] For example, asymmetric reduction of ketone **1** can be performed yielding the corresponding alcohol, an essential building block for the synthesis of chiral ligands such as PPFA[4] and Josiphos (Scheme 1).[5] Chiral ligands can also be obtained from **2** following hydrolytic cleavage to form the carboxylic acid,[6] an intermediate in the synthesis of Phosferrox ligands.[7]



Scheme 1. The importance of ferrocene based ketones in ligand preparation.

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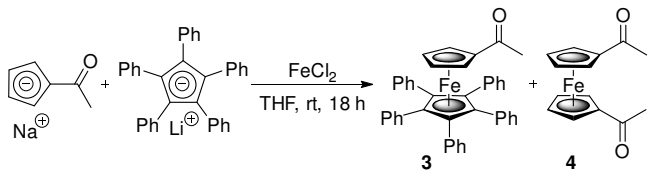
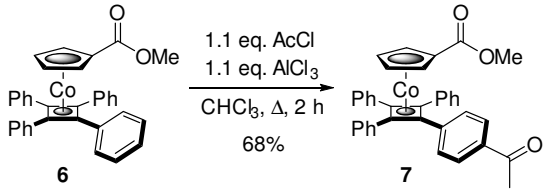
Bulky ferrocene and related sandwich complexes are potentially advantageous in catalysis over less bulky derivatives, and it has been shown that an increase in the size of the cyclopentadienyl group (*e.g.* as Cp* or Cp^{Φ}) leads to more selective catalysis.[8] To this end the synthesis of 1',2',3',4',5'-penta-substituted acetylferrocenes have been described using ferrous chloride, sodium acetylcyclopentadienides, and the corresponding (Me, Et and Ph) penta-substituted lithium cyclopentadienides.[9] However, in addition to the desired compounds, a significant quantity of the *bis*-ketone **4** was produced. For 1-acetyl-1',2',3',4',5'-pentaphenylferrocene **3** the selectivity of the reaction was 89 : 11 with a 66% yield of the desired ketone (Scheme 2). Although a previous study showed that 1,2,3,4,5-pentamethylferrocene could undergo Friedel-Crafts acetylation (albeit in 29% yield),[10] application of the same conditions (AcCl/$AlCl_3$), and alternative conditions (Ac_2O/BF_3),[11] to pentaphenylferrocene resulted in no reaction.[9] Conversely, work carried out by one of us has shown that the Friedel-Crafts reaction of pentaphenylferrocene **5** with *ortho*-chlorobenzoyl chloride resulted in the formation of the desired product in 91% yield.[12] This methodology has been used for the synthesis of the pentaphenylferrocene congener of Phosferrox.[13] In addition, Zhang *et al.* described the synthesis of ferrosalen-type ligands involving the use of succinic anhydride in the Friedel-Crafts acylation of **5** resulting in a 75% yield.[14]



Scheme 2. Previous synthesis of 1-acetyl-1',2',3',4',5'-pentaphenylferrocene.[9]

All attempts to perform a Friedel-Crafts acylation on similarly bulky (η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt have been reported to result in only a trace amount of cyclopentadienyl ring-substituted product,[15] and in our hands attempts at this reaction resulted in only decomposition of the starting material. However, following deactivation of the cyclopentadienyl ring of **6** by incorporation of an ester functionality, Friedel-Crafts acetylation could be performed on one or more of the phenyl groups giving, for example, compound **7** in 68% yield (Scheme 3).[16]



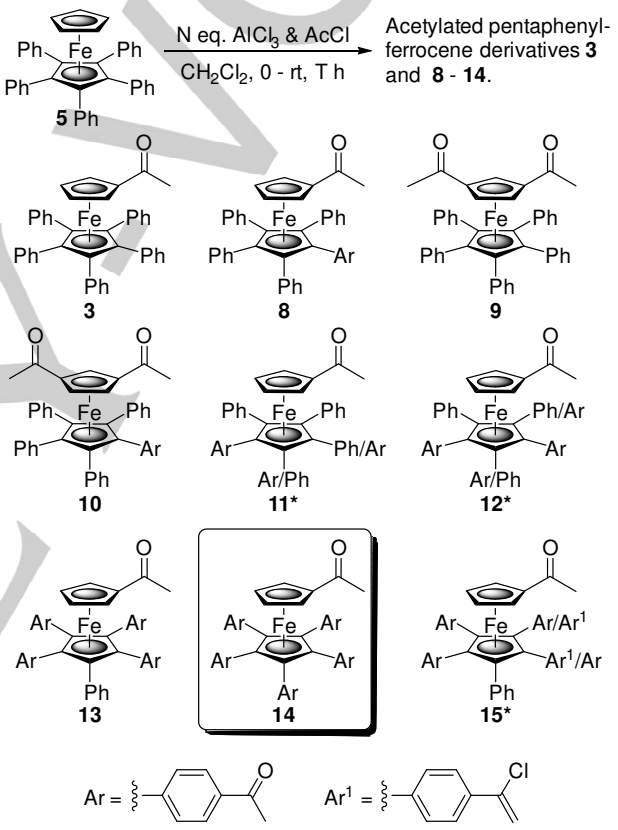
Scheme 3. Friedel-Crafts acetylation of (η^5-carbomethoxycyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt.[16]

In light of the above results we decided to revisit the Friedel-Crafts acetylation of pentaphenylferrocene **5**, and in addition, investigate whether the phenyl groups could also be functionalised by electrophilic aromatic substitution. Compounds formed in this way, including chiral non-racemic derivatives, are potential building blocks for the synthesis of novel ligands and materials.

Results and Discussion

It has been suggested that pentaphenylferrocene is a less reactive substrate than ferrocene with respect to electrophilic substitution.[9] This is supported by our observation that the ^{13}C NMR signal ($CDCl_3$) for the cyclopentadienyl group of ferrocene (68.3 ppm) is lower than the corresponding signal for pentaphenylferrocene (75.1 ppm). However, in view of the successful Friedel-Crafts acylation of **5** with *ortho*-chlorobenzoyl chloride, the corresponding reaction with acetyl chloride as the electrophile was re-examined examined using a similar procedure.[12] Thus use of 1.1 equivalents each of aluminium chloride and acetyl chloride in CH_2Cl_2 resulted in the formation of the desired product in 78% yield (Scheme 4, Table 1, entry 1). In addition to 1-acetyl-1',2',3',4',5'-pentaphenylferrocene **3**, around 1% of the doubly acylated product **8** was obtained as a result of a second acetylation occurring on one of the phenyl rings. The proton NMR spectrum of compound **8** showed a pair of doublets in the aromatic region at 7.66 and 7.12 ppm, and a methyl singlet at 2.55 ppm, indicating acetylation had taken place solely at the *para* position. This outcome is a result of *o*/*p*-activation of the phenyl ring by ferrocene (σ_p^+ = -0.65)[17] and a steric effect resulting exclusively in *para*-regioselectivity. Use of 2 equivalents of the acetylating reagent mixture and a longer reaction time increased the yield of the doubly acylated product **8** to 10%, with **3** again formed as the major product (86% - entry 2).

The synthesis of the hexa-acetylated pentaphenylferrocene complex was attempted using 6.6 equivalents of the acetylating reagent mixture. After allowing the reaction to stir at room temperature overnight this resulted in a mixture of compounds from the addition of between two and five acetyl groups, with compound **12*** formed as the major product (68% - entry 3). Functionalisation of two or three of the phenyl groups in this way can result in isomers, but only a single set of ^1H and ^{13}C NMR signals were observed for **11*** and **12***, an outcome that appears to be a consequence of the isomers being spectroscopically indistinguishable.[18] By increasing the number of equivalents of aluminium chloride and acetyl chloride to 20, and with an extended reaction time of 72 h, the synthesis of the hexa-acetylated compound **14** was achieved, albeit in only a 4% yield (entry 4). Monitoring by thin layer chromatography showed that after 24 h no detectable change was observed in the ratio of products being formed, and from this mixture the major product isolated in 46% yield was penta-acetylated **13**. It was observed that addition of acetyl chloride to a suspension of pentaphenylferrocene and aluminium chloride in CH_2Cl_2 gave a dark green solution, which over time slowly went brown. This colour change from green to brown is indicative of the reaction stopping as no subsequent change in the ratio of products formed was revealed by TLC.



Scheme 4. Friedel-Crafts acetylation of pentaphenylferrocene to give **3** and **8** – **14** (* = mixture of isomers).

Ferrocene is estimated to be approximately six orders of magnitude more reactive than benzene in an electrophilic aromatic substitution reaction.[2] However, initial acetylation of the cyclopentadienyl group of **5** significantly reduces this activity, such that subsequent reactions take place predominantly on the (iron activated) phenyl groups. The isolation of **9** and **10** revealed some double acetylation of the cyclopentadienyl ring, but this would appear to have essentially deactivated the whole molecule to further Friedel-Crafts acetylation under the conditions used.

In an attempt to overcome the low yield of the hexa-acetylated product resulting from a single step process, the major penta-acetylated product **13** isolated instead was subject to a further Friedel–Crafts reaction (Table 1, entry 5). The use of 1.5 equivalents of acetylating mixture immediately gave a brown suspension and did not lead to further acetylation over a period of 24 h. Instead the only product isolated, in addition to recovered starting material, contained in its ^{1}H NMR spectrum signals at 5.78 and 5.52 ppm arising from the 1-chlorovinyl substituent of **15***. In addition, NMR spectroscopy revealed a 1:1 ratio of regioisomers that were separable by careful chromatography.

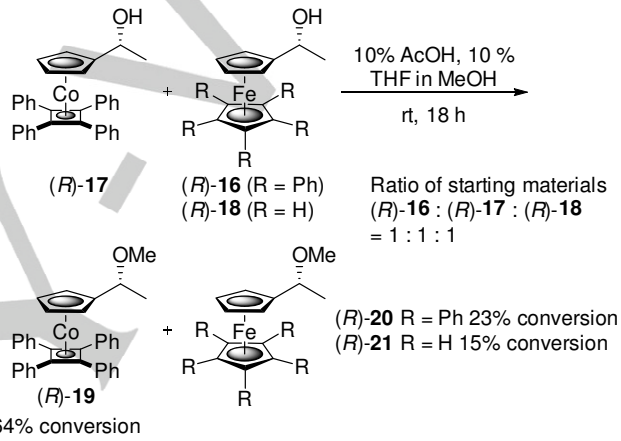
Table 1. Friedel-Crafts acetylation of pentaphenylferrocene to give **3** and **8** - **14**.[a]

Entry	N	T (h)	**3**	**8**	**9**	**10**	**11***	**12***	**13**	**14**
1	1.1	0.5	**78**	1	0	0	0	0	0	0
2	2.0	18	**86**	10	0	0	0	**0**	0	0
3	6.6	16	0	0	11	2	9	**68**	10	0
4	20	72	0	0	0	1	2	42	**46**	4
5[b,c]	1.5	24	-	-	-	-	-	-	-	0[d]
6[b,e]	50	96	-	-	-	-	-	-	-	**69**
7[e]	50	96	0	0	0	0	0	17	27	19

[a] General procedure: N equivalents of acetyl chloride was added to a solution of **5** at 0 °C followed by N equivalents of aluminium chloride. The solution was allowed to warm to RT and stirred for time T. [b] Compound **13** used as starting material. [c] Reaction started at RT. [d] Compound **15*** formed in addition to the recovery of starting material. [e] Reaction set up at RT and then heated at reflux with sequential addition of the acetylating reagents over a period of 72 h.

In contrast, subjecting penta-acetylated **13** to attempted Friedel-Crafts reaction with 20 equivalents of the acetylating mixture, and heating at reflux for 48 hours, revealed the green reaction mixture to contain a small quantity of desired product following TLC analysis. Addition of another 30 equivalents of the acetylating mixture, and allowing the reaction to continue for a further 48 h, gave compound **14** in 69% yield (entry 6). Repeating the same sequential addition of the acetylating mixture with pentaphenylferrocene **5** as the starting material gave compound **14** in 19% yield (entry 7). Very little reaction took place if 50 equivalents of the acetylating mixture were added at the start of the reaction followed by heating at reflux overnight. Thus a two-step procedure, with isolation of **13** as an intermediate, gave hexa-acetylated **14** as a single *para*-substituted regioisomer in an overall yield of 32%, corresponding to an average yield for each of the six reactions of approximately 82%.

The reduction of **3** to alcohol (*R*)-**16** in 98% ee with (*S*)-CBS as catalyst (30 mol %) has been described,[19] a reaction we repeated to give alcohol (*R*)-**16** in 63% yield. We recently reported the use of this same procedure for the asymmetric synthesis of the tetraphenylcyclobutadiene cobalt analogue (*R*)-**17**.[20] To investigate the relative rate of stereospecific α–substitution in these complexes to that of the parent ferrocene congener (*R*)-**18**,[21] a three-way competitive methanolysis experiment was performed by addition to an equimolar ratio of all three alcohols a mixture of methanol containing 10% acetic acid and 10% THF. The latter was included to ensure complete dissolution (Scheme 5). After stirring at room temperature for 18 hours the highest conversion was observed for the cobalt complex (*R*)-**19** (64%), the lowest for the ferrocene complex (*R*)-**21** (15%) and an intermediate conversion for the pentaphenylferrocene complex (*R*)-**20** (23%). Assuming that the percentage conversions are indicative of the relative stability of the corresponding α–carbenium ions (formed *via* rate-limiting loss of water), the phenyl groups of the Cp$^{\Phi}$Fe fragment aid this stabilisation, with both Cp$^{\Phi}$Fe and CpFe being less effective than $(Ph)_4$CbCo.[22]

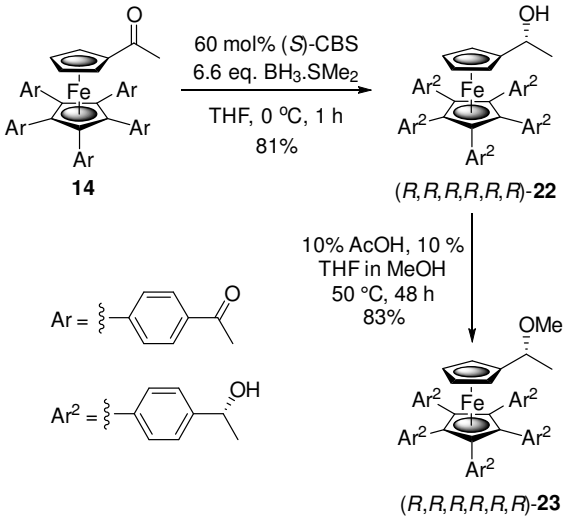


Scheme 5. Competitive methanolysis of alcohols (*R*)-**16**, (*R*)-**17** and (*R*)-**18**.

For the reduction of hexa-acetylated compound **14** we assumed that selective acetyl reduction (cyclopentadienyl *vs.* phenyl) would not be possible as a single carbonyl stretching band was observed in the IR spectrum of **14** (ν_{CO} = 1683 cm^{-1}). Global asymmetric reduction was achieved using (*S*)-CBS as catalyst (60 mol %) with borane dimethylsulphide in THF at 0 °C (Scheme 6). The product was obtained in 81% yield by column chromatography and assigned as predominantly (*R*,*R*,*R*,*R*,*R*,*R*)-**22** by comparison to literature precedent.[21,23,24] The ^{1}H and ^{13}C NMR spectra of the product both contained a single set of signals, which was also the case for the corresponding spectra of the product obtained by reduction using excess $NaBH_4$ in THF heated at reflux. For the latter reaction eight isomers are possible[25] which appear to be indistinguishable using NMR spectroscopy.

To rule out the possibility of intramolecular stereoselective induction leading to a single diastereoisomer under the achiral reduction conditions, **14** was partially reduced with (*S*)-CBS (30 mol %) with the reaction monitored by TLC until all of the starting material had been consumed, but not fully converted to a single species. This mixture was then subjected to reduction with $NaBH_4$ to give fully reduced hexa-alcohol **22***. Comparison of stepwise produced **22*** to (*R*,*R*,*R*,*R*,*R*,*R*)-**22**, by both optical

rotation[26] and circular dichroism (Figure 1), revealed that the *R* configured stereogenic centres created on (*S*)-CBS catalysed reduction do not control the selectivity of reduction with $NaBH_4$. In addition, the similarity of the CD spectrum of (*R*)-**16** to that of (*R*,*R*,*R*,*R*,*R*,*R*)-**22** suggests that, under the conditions used for the recording of these spectra, the *para*-substituted stereogenic centres of the latter do not induce a preference for *M* or *P* propeller chirality in the pentaarylcyclopentadienyl moiety.[27]



Scheme 6. Asymmetric reduction of **14** to give (*R*,*R*,*R*,*R*,*R*,*R*)-**22** and subsequent methanolysis to give (*R*,*R*,*R*,*R*,*R*,*R*)-**23**.

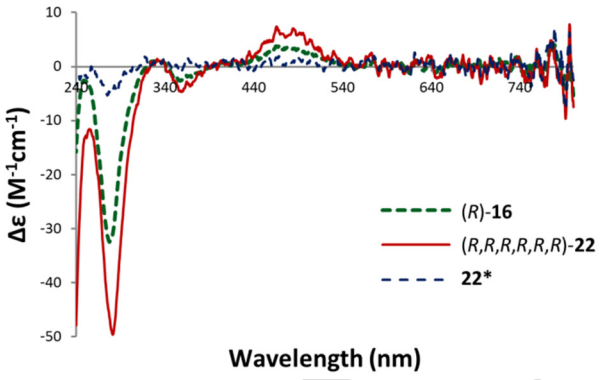


Figure 1. CD spectra of (*R*)-**16**, (*R*,*R*,*R*,*R*,*R*,*R*)-**22** and stepwise produced **22*** obtained as an 84 μM solution in THF at room temperature.

Finally, the facility with which (*R*)-**16** underwent α-methanolysis (Scheme 5) was exploited for the selective transformation of (*R*,*R*,*R*,*R*,*R*,*R*)-**22** into mono methyl-substituted (*R*,*R*,*R*,*R*,*R*,*R*)-**23** (Scheme 6). As before, the assumption made is that no change in configuration results due to stereospecific substitution *via* a metal-stabilised α–carbenium ion.[20,28] Under the conditions used, the benzyl-like substituted alcohols are unreactive, this method therefore providing a simple method for selective reaction/protection as a prelude to further manipulation.

Conclusions

Use of acetyl chloride and aluminum chloride results in the Friedel-Crafts acetylation of the cyclopentadienyl ring of pentaphenylferrocene. Further *para*-selective functionalisation of the phenyl groups is possible, and use of a stepwise procedure gave the title compound 1-acetyl-1',2',3',4',5'-penta(*para*-acetylphenyl)ferrocene in an overall yield of 32%. Asymmetric reduction with borane-dimethylsulfide catalysed by (*S*)-CBS gave the corresponding hexa-alcohol in 81% yield, as predominantly the product containing six *R* configured stereogenic centres. The facility with which a pentaphenylferrocene derivative undergoes an α–substitution reaction, together with the size of the hexa-alcohol, and the multiple stereogenic centres it contains, makes (*R*,*R*,*R*,*R*,*R*,*R*)-**22** a potentially versatile building block for the generation of new enantiopure ferrocene-based ligands and materials.

Experimental Section

Preparation of 1-acetyl-1',2',3',4',5'-pentaphenylferrocene **3**. Pentaphenylferrocene **5** (1.000 g, 1.77 mmol) and aluminium chloride (0.26 g, 1.94 mmol) were dissolved in dry CH_2Cl_2 (30 mL) and stirred at 0 °C under an inert atmosphere for 5 mins. Acetyl chloride (0.14 mL, 1.94 mmol) was added dropwise over 5 mins and the reaction mixture was stirred for a further 5 mins at 0 °C and then allowed to warm to room temperature for an additional 30 mins. The reaction was carefully quenched, after re-cooling to 0 °C, by the addition of H_2O (50 mL) and the resulting layers separated. The organic layer was dried over magnesium sulfate and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, CH_2Cl_2) yielded the product as a pale red solid (0.837 g, 78%): R_f 0.64 (CH_2Cl_2); ν_{max} (film)/cm^{-1} 3090, 3059, 3038, 2917, 2248, 1669 (CO); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (5H, t, *J* = 7.0 Hz, *p*-Ph*H*), 7.10 - 7.03 (20H, m, *o*+*m*-Ph*H*), 4.84 (2H, brs, Cp*H*), 4.48 (2H, brs, Cp*H*), 2.13 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2 (*C*=O), 134.9 ((*ipso*-Ph*C*), 132.4 (*m*-Ph*C*), 127.3 (*o*-Ph*C*), 126.7 (*p*-PhC), 88.4 (Cp*C*Ph), 84.3 (Cp*C*COCH$_3$), 79.2 (β-Cp*C*), 75.4 (α-Cp*C*), 29.6 (*C*H$_3$).

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Keywords: metallocenes • iron • aromatic substitution • asymmetric catalysis • regioselectivity

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[18] Global reduction of **11*** and **12*** by BH_3-SMe_2 catalysed by (*S*)-CBS gave what appeared to be a single compound from **11***, but **12*** resulted in a 8 : 1 ratio of presumably regioisomeric products. See SI for more information.

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[24] Assuming the six reduction reactions are independent of one another. and all proceed with an er of 49 : $1^{21,23}$, the product may be regarded as enantiopure [ee = $(49^6 - 1)/(49^6 + 1)$ x 100], albeit that the very minor diastereoisomers (~2%) could not be observed by NMR spectroscopy or separated by chromatography.

[25] Six diastereoisomers with two regioisomers possible for two of the diastereoisomers.

[26] (*R*,*R*,*R*,*R*,*R*,*R*)-**22 =** $([\alpha]_D^{20}$ = -40 (*c* = 0.12, $CHCl_3$). **22*** = $([\alpha]_D^{22}$ = +3.3 (*c* = 0.12, $CHCl_3$).

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