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COMMUNICATION

An efficient, scalable synthesis of ferrocenylphosphine and dichloroferrocenylphosphine

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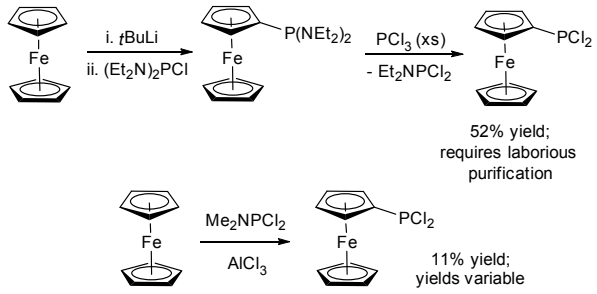
A new synthetic route to $FcPH_2$ and $FcPCl_2$ (Fc = Ferrocenyl) is presented. This method avoids the challenging monolithiation of ferrocene, as well as any tedious purification steps. All reactions are high yielding and easily conducted on a relatively large scale, using economical and commercially available synthetic precursors.

Since its discovery in the 1950s,[1,2] which kickstarted research into the field of organometallic chemistry,[3] ferrocene has cemented itself as one of the most important organometallic compounds due to its high stability and the relative ease with which it can be functionalised. The Cambridge structural database currently contains over 2500 entries for phosphorus functionalised ferrocene derivatives. These include strained ferrocenophanes serving as precursors for ring opening polymerisation,[4,5] or chiral phosphine ligands with a ferrocene backbone.[6] Ferrocene is an interesting group to introduce due to its redox activity and strong electron donating properties, which allow it to stabilise electron deficient species. In fact, the first "all-carbon" phosphenium cation to be isolated was stabilised by two Fc substituents.[7]

Despite all of this, the archetypal ferrocenyl phosphorus synthons, $FcPH_2$ and $FcPCl_2$, remain significantly underutilised. This is due largely to a lack of convenient synthetic routes to these molecules. So far, the main hurdle appeared to be the monolithiation of ferrocene, which is notoriously challenging and requires the use of highly pyrophoric *t*BuLi.[8–10]

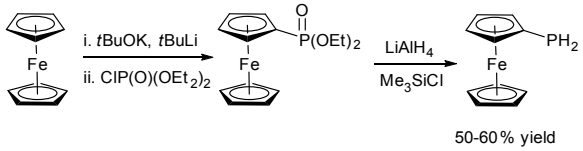
Arguably, the best synthesis of $FcPCl_2$ was published by Pietschnig and Niecke in 1997.[11] In their protocol (Scheme 1, top) ferrocene is monolithiated with *t*BuLi, followed by the addition of $(Et_2N)_2PCl$. The resulting $FcP(NEt_2)_2$ is converted to $FcPCl_2$ by reaction with excess PCl_3. The work up for the reaction is rather laborious, involving removal of excess PCl_3 and the Et_2NPCl_2 byproduct by distillation, then vacuum distillation of the $FcPCl_2$ to remove the various ferrocene containing sideproducts. At 52%, the yield is acceptable but not ideal, and the use of *t*BuLi makes the reaction dangerous to conduct on a large scale. This problem is further exacerbated by the need for careful control of the lithiation reaction conditions.

Another literature method utilises the Friedel-Crafts reaction of ferrocene with Me_2NPCl_2 (Scheme 1, bottom).[12,13] The yields are low (11%) and repeated attempts to improve on this reaction demonstrated the yields to be highly variable and often much lower.[14,15] Nonetheless, this method was still being used relatively recently.[15,16]



Scheme 1: Previous syntheses of $FcPCl_2$.[11–13]

The most recent synthesis of ferrocenylphosphine, $FcPH_2$, was reported by Wright and co-workers in 2009. In this procedure diethyl ferrocenylphosphonate is reduced by $LiAlH_4/Me_3SiCl$.[17] The diethyl ferrocenylphosphonate was itself prepared by monolitiation of ferrocene, followed by reaction with chlorodiethylphosphate (Scheme 2).[18] $FcPH_2$ was obtained in relatively good overall yields (50–60%), but the procedure requires the use of *t*BuLi and column chromatography, which hinders scale-up of the reaction.



Scheme 2: Recent synthesis of $FcPH_2$.[17,18]

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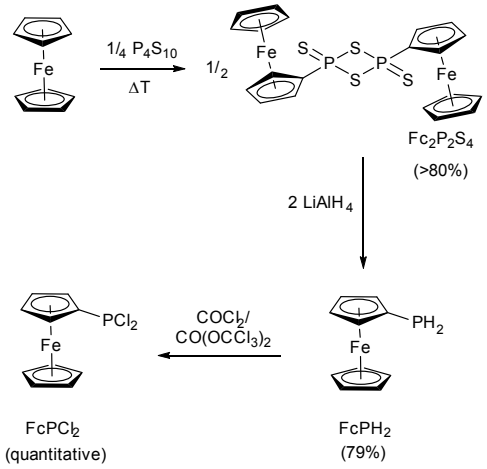
In all of the lithiation based syntheses, the biggest issue has been the selective addition of a *single* phosphorus moiety to the ferrocene ring, avoiding the disubstituted species formed through overlithiation to 1,1'-dilithioferrocene. An elegant bypass of the lithiation strategy was identified in the regiospecific reaction of ferrocene with P_4S_{10}, which yields the perthiophosphonic anhydride $Fc_2P_2S_4$ (Scheme 3). The reaction is accomplished by refluxing the two components in xylenes, with the air stable product being collected by filtration in >80% yield.[19] The reaction is relatively facile, and has been scaled to ca. 250 g ferrocene with little difficulty.

Perthiophosphonic anhydrides (general formula $R_2P_2S_4$) are well known in the literature, with the most famous example being Lawesson's reagent[20] (R = 4-$MeOC_6H_4$). Although the reactivity of selected perthiophosphonic anhydrides has been studied in some detail,[21] their use as thionation reagents has been most prominent.[22,23] Nevertheless, no reports on reductions of such species with hydridic reagents have appeared in the literature to date. We have found that reduction of $Fc_2P_2S_4$ using $LiAlH_4$ gave the primary phosphine $FcPH_2$ as a low melting solid in 79% yield (66% overall yield, Scheme 3). This reaction was conducted on a 100 g scale without issue, something which would be very difficult and potentially dangerous to do using *t*BuLi as in the Wright synthesis.[17,18] Crucially, the reaction proceeds cleanly when 4 eq. $LiAlH_4$ are used per $Fc_2P_2S_4$. The $FcPH_2$ obtained was found to be exceptionally pure by microanalysis, as well as ^1H, ^{31}P and ^{13}C NMR spectroscopy, with no need for further purification.



Scheme 3: Two-step synthesis of $FcPH_2$ from ferrocene via the perthiophosphonic anhydride $Fc_2P_2S_4$. Also shown is subsequent quantitative transformation into $FcPCl_2$.

With an efficient synthesis of $FcPH_2$ in hand, it was subsequently found that $FcPH_2$ can be chlorinated by triphosgene (considered a safer substitute for phosgene gas) or phosgene (commercially supplied as a solution in toluene) to give $FcPCl_2$ in quantitative yield (Scheme 3). This reaction is simple to conduct, although an efficient fumehood is necessary. The reaction is completed in a few hours with either chlorinating reagent. Removal of volatiles *in vacuo* affords $FcPCl_2$ as a red-brown oil, which solidifies on standing at room temperature. The purity of the compound, as determined by microanalysis and multinuclear NMR spectroscopy, was exceptionally high with no need for further purification. This represents a marked improvement over the Pietschnig synthesis which, in addition to requiring purification by vacuum distillation, gave $FcPCl_2$ in a lower yield (52% vs. 65% overall yield). Although the toxicity of phosgene/triphosgene is a concern in this procedure, we feel these compounds are easier to handle on a large scale than the pyrophoric *t*BuLi, and have repeatedly carried out this transformation on a relatively large scale (ca. 60 g $FcPH_2$).

Somewhat surprisingly, the crystal structures of $FcPH_2$ and $FcPCl_2$ have not been reported previously.[24] Using the pure material obtained via our procedure, crystals suitable for X-ray diffraction were obtained with relative ease. The structures are shown in Figure 1,[25,26] both compounds are as expected, with P–C bond lengths of 1.818(9) Å for $FcPH_2$ and 1.778(4) [1.784(4)] Å for $FcPCl_2$.[27]

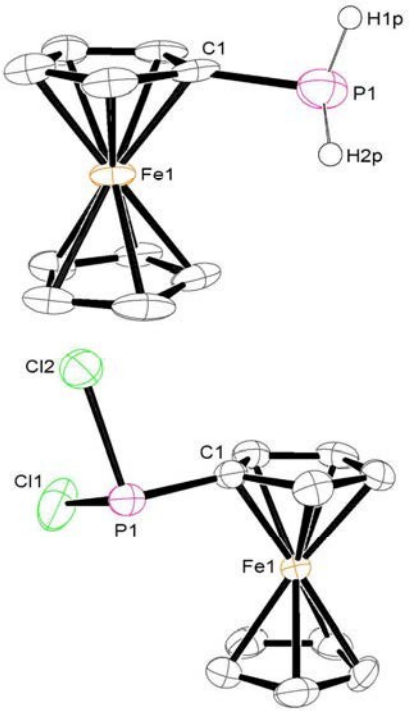


Figure 1: Solid state structures of $FcPH_2$ (top) and $FcPCl_2$ (bottom). Thermal ellipsoids are drawn with 50% probability. Carbon bound H atoms and second molecule in asymmetric unit ($FcPCl_2$) are omitted for clarity. Selected bond lengths (Å) and angles (°): $FcPH_2$: C1–P1 1.818(9); $FcPCl_2$: C1–P1 1.778(4) [1.784(4)], Cl1–P1–Cl2 97.95(8) [98.34(7)].[27]

Conclusions

The electrophilic substitution reaction of ferrocene with P_4S_{10} has been used to introduce a single phosphorus moiety onto ferrocene with complete regiospecificity and in high yield. Subsequently, the two archetypal phosphorus synthons $FcPH_2$ and $FcPCl_2$ were obtained in high yields and purity through the reduction of $Fc_2P_2S_4$ with $LiAlH_4$, followed by chlorination with triphosgene/phosgene. By avoiding the difficult monolithiation of ferrocene and associated use of pyrophoric *t*BuLi, it was possible to scale this new synthetic route to multi-gram quantities (ca 60 g).

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Experimental

$Fc_2P_2S_4$: A slight modification of the literature procedure was employed.[19] Ferrocene (37.7 g, 202 mmol) and P_4S_{10} (20.0 g, 45.0 mmol) were heated under reflux in xylenes (300 mL) for 3 hours before being allowed to cool. $Fc_2P_2S_4$ was collected by filtration as an air stable, dark orange solid, which was washed with toluene (2 × 100 mL) and diethyl ether (2 × 50 mL) and dried *in vacuo.* Yield 41.8 g (75.0 mmol, 83%).

$FcPH_2$: To a vigorously stirred suspension of $Fc_2P_2S_4$ (6.00 g, 10.7 mmol) in diethyl ether (70 mL), cooled to 0 °C, a suspension of $LiAlH_4$ (1.62 g, 42.7 mmol) in diethyl ether (30 mL) was added dropwise via cannula and the mixture allowed to warm to RT. Insoluble by-products were removed by filtration and washed with diethyl ether (2 × 20 mL). The orange filtrate and washings were cooled to 0 °C, degassed water (10 mL) was added cautiously and the resulting suspension was warmed to RT. The solid formed was removed by filtration and washed with DCM (2 × 20 mL). The filtrate and washings were collected and volatiles removed *in vacuo* to yield $FcPH_2$ as a dark orange, low melting solid (3.67 g, 16.8 mmol, 79%). Crystals suitable for single crystal X-ray diffraction were obtained by melting and recrystallisation of the solid between 25–40 °C.[25] Mp 36–37 °C. Found: C 55.16; H 5.25. Calc. for $C_{10}H_{11}FeP$: C 55.09; H 5.09. IR (thin layer) ν_{max}/cm^{-1} 3094s (*ν*CH), 2262s (*ν*PH), 1206s, 1024s, 817vs, 495s. ^{1}H NMR δ_H (270 MHz; $CDCl_3$) 4.31–4.29 (4H, m, 4 × CpH), 4.20 (5H, s, 5 × CpH), 3.86 (2H, d, $^1J_{HP}$ = 203 Hz, PH_2). $^{13}C\{^1H\}$ NMR (75 MHz; $CDCl_3$) 75.7 (d, $^2J_{CP}$ = 14.0 Hz, CH, subst. Cp ring), 70.7 (d, $^3J_{CP}$ = 3.6 Hz, CH, subst. Cp ring), 69.3 (s, CH, unsubst. Cp ring), 64.1 (d, $^1J_{CP}$ = 4.7 Hz, qC). ^{31}P NMR δ_P (121 MHz; $CDCl_3$) −143.6 (t, $^1J_{PH}$ = 203 Hz). $^{31}P\{^1H\}$ NMR δ_P (109 MHz; $CDCl_3$) −143.8 (s).

$FcPCl_2$: To a stirred solution of $FcPH_2$ (3.00 g, 13.8 mmol) in dichloromethane (70 mL), cooled to −10 °C, a solution of triphosgene (2.7 g, 9.2 mmol) in dichloromethane (50 mL) was added slowly via cannula. Alternatively, a solution of phosgene (15.2 mL of a 1.9 M solution in toluene, 28.9 mmol) was added dropwise over 30 min. The mixture was allowed to warm to RT and stirred overnight. Volatiles were removed *in vacuo* to give $FcPCl_2$ as a red-brown oil which solidified on standing at room temperature (3.93 g, 13.7 mmol, 99%). Crystals suitable for single crystal X-ray diffraction were grown from toluene at −35 °C.[26] Found: C 41.98; H 3.24. Calc. for $C_{10}H_9Cl_2FeP$: C 41.86; H 3.16. IR (thin layer) ν_{max}/cm^{-1} 3099s (*ν*CH), 1411s, 1163s, 1028s, 825s, 446vs. ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 4.61–4.59 (4H, m, 4 × CpH), 4.30 (5H, s, 5 × CpH). $^{13}C\{^1H\}$ NMR (101 MHz; $CDCl_3$) 79.5 (d, $^1J_{CP}$ = 52.3 Hz, qC), 73.3 (d, J_{CP} = 4.5 Hz, CH, subst. Cp ring), 71.1 (d, J_{CP} = 22.5 Hz, CH, subst. Cp ring), 70.0 (s, CH, unsubst. Cp ring). ^{31}P NMR δ_P (162 MHz; $CDCl_3$) 164.6 (s). $^{31}P\{^1H\}$ NMR δ_P (162 MHz; $CDCl_3$) 164.7 (s).

Acknowledgements

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26. Crystal data for $FcPCl_2$: $C_{10}H_9Cl_2FeP$, M_r = 286.91, monoclinic, $P2_1/n$, a = 12.9787(13), b = 13.2924(12), c = 13.6674(13) Å, β = 110.613(8)°, V = 2206.9(4) Å^3, T = −100(1) °C, Z = 8, reflections collected 14488, independent 4007 (R_{int} = 0.0499), R(obs) = 0.0472, wR(all data) = 0.0779. Deposition number CCDC 1437271.
27. Value in square brackets for second molecule of $FcPCl_2$ in the asymmetric unit.

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