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An organoiron approach to thyroid hormone analogues

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Abstract

An approach to thyroid hormone analogues was proposed involving sequential substitution of cationic cyclopentadienyl(1,4-dichlorobenzene)iron(II) complexes with phenoxide/thiophenoxide and hydroxide/amine, followed by decomplexation. Although the selectivity for monosubstitution with phenolates and thiophenolates was poorer than previously observed, it was often possible to control the reaction with sterically less demanding phenolates of intermediate nucleophilicity. The subsequent introduction of a polar substituent into the monosubstituted product was successful with amine nucleophiles. A modified approach, based on the reverse order of substitution was also attempted. Whereas clean monosubstitution with hydroxide/hydroxide equivalents was unsuccessful, cyclopentadienyl(*N*-alkyl-1-chloro-4-aminobenzene)iron(II) complexes could be prepared in fair yields and further substituted with nucleophiles such as thiophenolates.
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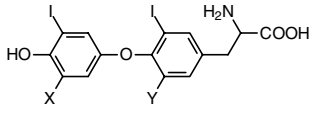
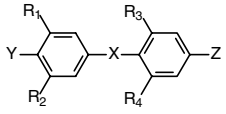
Keywords: Thyroid hormones; (1,4-Dichlorobenzene)iron(II) complexes; Sequential substitution; Phenoxide/thiophenoxide; Hydroxide/amine

1. Introduction

Selenoenzymes is a slowly but steadily growing family of enzymes. To date, the structure and function of a dozen of them are known with some certainty [1]. Like other selenoenzymes, the three varieties of the iodothyronine deiodinase enzymes (ID-1, ID-2 and ID-3) contain a selenocysteine residue at the active site. These enzymes catalyze the interconversion of active and inactive forms of thyroid hormones [2]. The follicular cells of the thyroid provide the only source of thyroxin (**1a**). However, this is only thought to be a prohormone requiring outer ring deiodination to provide the active hormone 3,5,3′-triiodothyronine (**1b**). This reduction is brought about by the ID-1 and ID-2 varieties of the enzyme. The ID-3 variety is known to cause inner-ring deiodination of thyroxin to give inactive **1c**. Both compounds **1b** and **1c** can undergo further monodeiodination to provide **1d.**



1a X=Y=I
1b X=H; Y=I
1c X=I; Y=H
1d X=Y=H



2 X=O, S, Se
Y=OH, NH_2
Z=CH_2CH_2COOR
R_1-R_4=H, Cl, Br, I, Me, *i*-Pr, or *t*-Bu

The thyroid hormone receptor (TR) functions as a ligand-dependent transcriptional regulator that controls the expression of a specific set of genes involved in development and homeostasis in response to **1b** (T_3) [3]. There are two known TR subtypes, α (TRα) and β (TRβ), expressed from two different genes. In adults, the TRβ isoform is the most prevalent form in most tissues, especially in the liver. The TRα isoform has been found in highest concentration in skeletal muscle and brain and is closely linked to cardiac function. At normal levels, thyroid hormones maintain body weight, metabolic rate, body temperature, and mood, and

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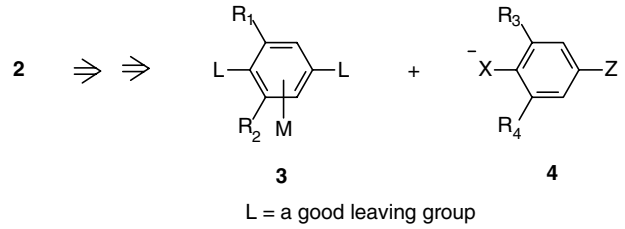
influence serum lipid levels as well as basal hepatic glucose output. Thus, in hypothyroidism there is weight gain, high levels of LDL cholesterol, and depression. In hyperthyroidism, these hormones cause weight loss, hypermetabolism, lowering of serum LDL cholesterol, cardiac tachycardia, heart failure, muscle weakness, bone loss in postmenopausal women, and anxiety. Thyroid hormones are currently used primarily as replacement therapy for patients with hypothyroidism. Therapy with **1b** returns metabolic functions to normal. However, replacement therapy, particularly in older individuals, is limited by the deleterious effects of thyroid hormones. Some effects of thyroid hormones should be therapeutically useful in non-thyroid disorders provided that adverse effects could be minimized or eliminated. Such disorders include atherosclerosis, dyslipidemia, hypercholesterolemia, obesity, diabetes, congestive heart failure, osteoporosis and various skin disorders [4]. Development of tissue and/or subtype selective thyroid hormone receptor agonists could lead to novel therapies for these common disorders. For avoiding cardiotoxicity, TR agonists that interact selectively with the β-isoform of the thyroid hormone receptor are especially attractive [5].

Compounds of potential use as thyroid hormone agonists [6] are appropriately substituted diaryl ethers (**2**; X = O), diaryl sulfides (**2**; X = S) and diaryl selenides (**2**; X = Se) which show only a slight resemblance to compounds **1**. One or several of the iodines in the 3,3′ and 5,5′-positions may be replaced by hydrogen, chlorine, bromine, or alkyls. The phenolic hydroxyl may be replaced by an amine and the amino acid side-chain may be substituted by some other polar group (e.g., a carboxylic acid alkyl chain).

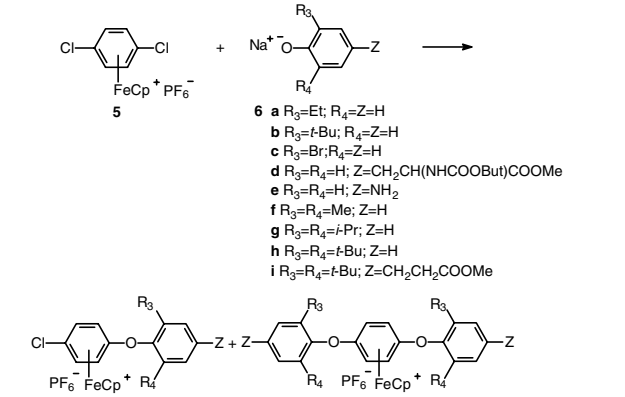
Due to the many useful properties conferred on the aromatic ligand by complexation, transition metal arene complexes have been extensively employed for the functionalization of aromatic molecules. Introduction of hydroxide, alkoxide, phenoxide, carboxylate, amine, thiolate and various carbanion nucleophiles into cationic cyclopentadienyliron complexes by nucleophilic displacement has been recently reviewed [7]. We thought this chemistry could be useful for the preparation of a variety of thyroxine analogues. A retrosynthetic analysis of compounds **2** (Scheme 1) leads to a transition metal-complexed aromatic **3**, functionalized in the 1,4-positions with a good leaving group, and a properly substituted phenolate/thiophenolate/selenophenolate **4** as suitable starting materials. The transition metal would not only facilitate aromatic nucleophilic substitution to give a diaryl chalcogenide, but could also assist in the transformation of the remaining leaving group L into a suitably protected OH or NH_2 group before it is finally removed from the molecule. In the following, we describe an organoiron approach to thyroid hormone analogues as outlined above, using η^6-(1,4-dichlorobenzene)-η^5-(cyclopentadienyl)iron hexafluorophosphate (**5**) as a model compound.



Scheme 1.

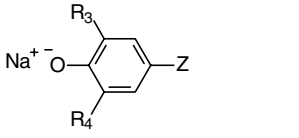
2. Results and discussion

The only practical method for preparation of cationic arene iron(II) cyclopentadienyl complexes involves the ligand exchange reaction with ferrocene discovered by Nesmeyanov et al. [8]. However, product yields vary dramatically depending on the arene substituents. With haloaromatics, dehalogenation is frequently observed. Therefore, under optimized conditions, Pearson and Gelormini [9] could only obtain a 24% yield of 1,4-dichlorobenzene complex **5**. Selective displacement of chlorides with phenolates from cyclopentadienyl(1,4-dichlorobenzene)iron complexes is of crucial importance for the strategy outlined in Scheme 2 [9,10]. As judged by Pearson's study with compound **5** [9], monosubstitution occurred selectively when phenolates carrying *para*-methoxy and *para*-carbomethoxy groups were added at low temperature. In our experience, *ortho*-or *ortho*/*para* substituted phenolates **6** often gave rise to inseparable

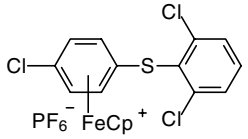


Scheme 2.

mixtures of unreacted compound **5**, the desired monosubstitution (**7**) and disubstitution (**8**) products (Scheme 2). Thus, when an equimolar amount of sodium 2-ethylphenolate (**6a**) in dry THF was allowed to react with a suspension of complex **5** in dry THF at −35 °C for 3 h, a 2.5/1-mixture of compounds **7a** and **5** was formed according to ^{1}H NMR analysis. Raising the temperature to −20 °C caused an increase in the conversion of starting material and a 37% yield of compound **7a** was isolated after chromatographic purification on alumina with acetone elution. Stirring of the reactants at 0 °C for 5 h returned an inseparable 8/1-mixture of compounds **7a** and **8a**. By allowing a threefold excess of compound **6a** to react overnight at ambient temperature with complex **5**, pure disubstitution product **8a** was isolated in a modest 22% yield after crystallization from ethyl ether. Sodium 2-*tert*-butylphenoxide (**6b**) and 2-bromophenoxide (**6c**) behaved similarly. Thus, at −20 °C, an inseparable 1/8-mixture of mono- and disubstitution products **7b** and **8b** was formed in ca. 20% yield, whereas, at ambient temperature, pure compound **7c** was isolated in 15% yield after chromatographic purification. Again, using an excess of the respective phenolates at ambient temperature, disubstituted products **8b** (17%) and **8c** (86%) could be isolated. At −20 °C, *para*-substituted phenolate **6d**, derived from *N*-(*tert*-butyloxycarbonyl)-L-tyrosine, afforded a 1/1-mixture of mono-(**7d**) and disubstitution (**8d**) products. However, only compound **8d** could be isolated in pure form in a modest 13% yield. Sodium 4-aminophenolate (**6e**) was less reactive than compound **6d** as a nucleophile. Crude product **7e** obtained at ambient temperature was always contaminated by unreacted complex **5**. After filtration through alumina and crystallization from ethyl ether, pure material was isolated in 17% yield. Several *o*,*o*-disubstituted phenolates were also studied in the displacement reaction. Sodium 2,6-dimethylphenolate (**6f**), 2,6-di-*i*-propylphenolate (**6g**), and 2,6-di-*tert*- butylphenolate (**6h**) all afforded monosubstitution products (compounds **7f**, **7g**, **7h**) in fair isolated yields (64%, 46% and 44%, respectively). However, the optimal reaction temperature had to be increased in the series (−20, 0 °C and ambient temperature, respectively). Obviously, this is to compensate for the decrease in nucleophilicity of the phenolate due to steric hindrance at the *ortho*-positions. For the similar reason, the sterically encumbered phenolate **6h** in excess failed to produce a disubstitution product with complex **5**. Phenolates **6f** and **6g**, though, produced complexed triaryl diethers **8f** and **8g** in 46% and 54% yields, respectively, under these conditions. Phenolate **6i**, similarly hindered as compound **6h** but carrying an additional 2-carbomethoxyethyl group in the 4-position, also failed to give a disubstitution product. Still, the isolated yield of monosubstitution product **7i** under the best conditions (equimolar amounts of reactants, ambient temperature overnight) was only low (19%). A series of 2,6-difluoro-, dichloro-, dibromo- and diiodosubstituted phenolates **6j**–**6m** were also tried in the substitution reaction of complex **5**. Surprisingly, none of these compounds reacted under the usual reaction conditions (THF, ambient temperature). This was also true at more forcing conditions (THF, 60 °C; DMF, 80 °C) when complex **5** started to decompose. The phenolates derived from *N*-acetyl- and *N*-benzoyl-3,5-diiodo-L-tyrosine ethyl ester were similarly unreactive. The low reactivity of all these phenolates is probably due to a combination of electronic and steric substituent effects. With small, electron withdrawing *o*-substituents the former is predominating, whereas with larger less deactivating ones, the latter effect is more important. The more nucleophilic sodium 2,6-dichlorothiophenolate was quite reactive towards complex **5**. Thus, with equimolar amounts of reactants at −20 °C, an inseparable 7/4/1-mixture of mono-(**9**) and disubstitution (**10a**) products and unreacted starting complex was formed. With an excess of the thiophenolate, disubstitution product **10a** was isolated in 38% yield. The even more nucleophilic thiophenolate derived from 2,6-dimethylthiophenol, showed a similar reactivity. In this case the disubstitution product **10b** could be isolated in pure form (50% isolated yield). Out of curiosity, we also tried sodium 3,5-dibromo-4-methylphenolate in the displacement reaction with complex **5**. It turned out that pure monosubstitution product **11** could be isolated in 49% yield at ambient temperature when an equimolar amount was used and that the disubstitution product **12** was isolated in a modest 18% yield when an excess of the reagent was employed.



6 **j** R_3=R_4=F; Z=H
k R_3=R_4=Cl; Z=H
l R_3=R_4=Br; Z=H
m R_3=R_4=I; Z=Me



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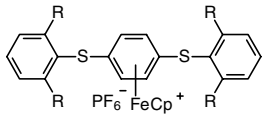
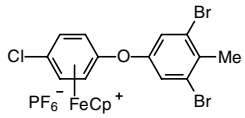
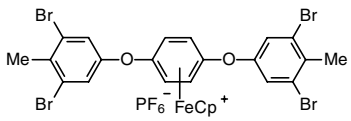


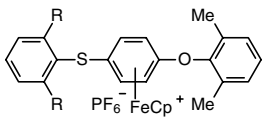
10a R=Cl
b R=Me



11



12

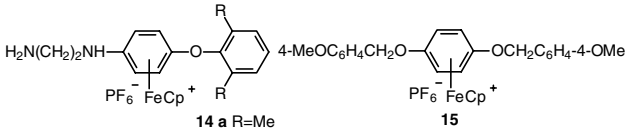


13a R=Cl
b R=Me

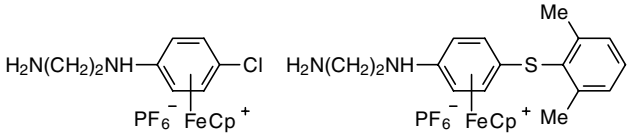
We conclude from this part of the study that selectivity for monosubstitution of complex **5** with phenolates is more difficult to control than previously thought. Phenolates where the nucleophilicity is lowered due to steric or electronic reasons fail to react in the displacement reaction even at elevated temperature whereas highly nucleophilic phenolates tend to undergo disubstitution even at low temperature. However, by the proper choice of stoichiometry and reaction temperature, it is often possible to effect selective mono- substitution with phenolates of intermediate reactivity.

As a further step in the synthetic direction towards thyroid hormone analogues (Scheme 1), we proposed substitution of the remaining leaving group in the arene iron(II) cyclopentadienyl complex. Chloroarene complex **7f** was used as a model compound for these types of transformation. Substitution with sodium 2,6-dichlorothiophenolate and 2,6-dimethylthiophenolate occurred readily to afford compounds **13a** and **13b**, respectively, in 77% and 53% yields. However, introduction of hydroxyl proved more difficult. Direct substitution with hydroxide as described by Helling and Hendrickson [11] was found to cause decomposition of complex **7f**. Potassium 2-trimethylsilylethoxide has been used in iron chemistry for converting complexed halobenzenes to phenols via tetra-*n*-butylammonium fluoride deprotection [12]. However, both the sodium and potassium alcoholates were unreactive towards complex **7**. Salts of 4-methoxybenzyl alcoholate [13] also turned out to react sluggishly with complex **7** in THF or DMF and we were unable to free the substitution product from unreacted starting material by Al_2O_3-chromatography.

Amines turned out to be more reactive [14,15]. Thus, stirring of complex **7f** for 5 h in THF with a twofold excess of ethylenediamine and potassium carbonate afforded substitution product **14a** in 94% yield. Chlorobenzene complex **7h**, when submitted to similar reaction conditions, afforded complex **14b** in 89% yield.



In view of the facile substitution of compound **7f** with thiophenolates, a slightly modified route to thyroid hormone analogues was also considered, involving monosubstitution of complex **5** with hydroxyl/amine before substitution of the remaining chloride with a phenolate/thiophenolate. However, despite variations in solvent, temperature and stoichiometry of the reactants, dichlorobenzene complex **5** and/or the product of disubstitution were always contaminating the desired monosubstitution product in the crude product mixtures obtained with alcoholates derived from 2-trimethylsilylethanol and 4-methoxybenzyl alcohol. Only when complex **5** was added to a threefold excess of sodium 4-methoxybenzylalcoholate in tetrahydrofuran was it possible to isolate a pure product from the reaction mixture. However, this was the undesired disubstitution product **15** which was isolated in 48% yield. Surprisingly, stirring of complex **5** at ambient temperature with a twofold excess of ethylenediamine in THF afforded a monosubstitution product **16** in high yield (89%). Substitution of the remaining chloride using sodium 2,6-dimethylthiophenolate afforded complex **17** in a 35% yield. However, attempts to use less nucleophilic phenolates in this substitution reaction were met with failure.



This part of the work can be summarized as follows: Whereas cationic cyclopentadienyl(1-chloro-4-aryloxybenzene)iron(II) complexes **7** allow substitution of the remaining chloride with good nucleophiles such as thiophenolates and amines, they are generally not reactive enough towards hydroxide or alcoholates that are convertible to OH. A slightly modified approach to thyroid hormone analogues, based on the reversal of the order of substitution of dichlorobenzene complex **5** with hydroxyl/amine and phenolate/thiophenolate did not turn out to be generally applicable. Thus, cationic cyclopentadienyl(1-chloro-4-alkoxybenzene)iron(II) complexes where the alkoxy group was convertible to OH were inaccessible and cyclopentadienyl(*N*-alkyl-1-chloro-4-aminobenzene)iron(II) complexes were only reactive towards good nucleophiles such as thiophenolates.

Despite some limitations in terms of product yields and generality, we feel the synthetic methodology outlined in this paper is of interest for the preparation of certain members of the structurally diverse family of potentially useful thyroid hormone agonists **2**.

3. Experimental

^{1}H NMR (200 MHz) and ^{13}C NMR (50.28 MHz) spectra were recorded in acetone-d_6. Melting points are uncorrected. Elemental analyses were performed by Analytical Laboratories, Lindlar, Germany. All reactions

were performed under a nitrogen atmosphere. Ether and tetrahydrofuran were freshly distilled under nitrogen from Na/benzophenone. Except for the addition of water, η^6-(1,4-dichlorobenzene)-η^5-cyclopentadienyliron(II) hexafluorophosphate (**1**) was prepared according to the literature [9]. Methyl 3-(2,6-*tert*-butyl-4-hydroxyphenyl)propionate was prepared according to a known procedure [16,17].

3.1. Typical procedure for preparation of monosubstitution products 7 and 11. η^6-[1-chloro-4-(2,6-dimethylphenoxy)-benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (7*f*)

2,6-Dimethylphenol (0.21 mmol, 25.7 mg) was stirred with sodium hydride (0.4 mmol, 16 mg of 60% dispersion in mineral oil) in THF (2 mL) for 15–20 min. This solution was then added dropwise to a stirred suspension of the complex **5** (0.2 mmol, 82.6 mg) in THF (4 mL) cooled to −78 °C. The mixture was warmed to −20 °C and stirring continued. The reaction was then quenched by addition of a few drops of water and the mixture was passed through a pad of Celite, which was subsequently washed with CH_2Cl_2. The solvent was removed in vacuo and the residue redissolved in CH_2Cl_2 (25 mL). This solution was washed with NH_4PF_6 (1.5 mL of a saturated solution further diluted with 3.5 mL of H_2O), then 0.05 M NaOH (2 × 5 mL) and finally with water (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The oily residue was triturated with dry ether to give the title compound, 64 mg (64%), m.p. 185–186 °C (d). ^{1}H NMR δ: 7.21 (3H, s), 6.87 (2H, d, J = 7.0 Hz), 6.45 (2H, d, J = 7.0 Hz), 5.41 (5H, s), 2.98 (6H, s). For some reason, the aromatic protons in the uncomplexed ring of this and many other (**7g**, **7h**, **8f**, **8g**, **13a**, **13b**, **14a**, **14b**) complexes appear as singlets. ^{13}C NMR δ: 149.5, 133.3, 128.9, 135.8, 130.0, 86.0, 78.6, 74.6, 15.0. Anal. Calc. for $C_{19}H_{18}ClF_6FeOP$: C, 45.44; H, 3.64. Found: C, 45.97; H,3.86.

The following compounds were similarly prepared.

3.2. η^6-[1-Chloro-4-(2-ethylphenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (7*a*)

The substitution reaction was run at −15 to −20 °C for 3 h. The crude product was dissolved in the minimum amount of acetone and passed through a short column of Al_2O_3. Evaporation of the solvent gave pure product. Yield: 37%, m.p. 141–142 °C (d). ^{1}H NMR: 7.56–7.25 (4H, m), 6.85 (2H, d, J = 9.0 Hz), 6.50 (2H, d, J = 9.0 Hz), 5.41 (5H, s), 2.57 (2H, q, J = 7.6 Hz), 1.09 (3H, t, J = 7.6 Hz).

3.3. η^6-[1-Chloro-4-(2-tert-butylphenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (7*b*)

The substitution reaction was run at −20 °C for 2.5 h. This afforded a 8/1 mixture of mono- and disubstitution products, corresponding to a 21% yield of the title compound. ^{1}H NMR δ: 7.60–7.10 (4H, m), 6.95 (2H, d, J = 9.0 Hz), 6.62 (2H, d, J = 9.0 Hz), 5.45 (5H, s), 1.28 (9H, s).

3.4. η^6-[1-Chloro-4-(2-bromophenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (7*c*)

The substitution reaction was carried out at room temperature for 16 h. The crude product was dissolved in the minimum amount of acetone and passed through a short column of Al_2O_3. Removal of the solvent afforded the pure product. Yield: 15%, m.p. 199–202 °C (d). ^{1}H NMR δ: 7.85 (1H, dd, ^2J = 8.0 Hz, ^3J = 2.0 Hz), 7.63–7.30 (3H, m), 6.88 (2H, d, J = 7.0 Hz), 6.56 (2H, d, J = 7.0 Hz), 5.43 (5H, s). ^{13}C NMR δ: 149.3, 133.5, 131.2, 129.2, 127.5, 121.6, 113.6, 103.4, 86.0, 78.9, 75.6. Anal. Calc. for $C_{17}H_{13}BrClF_6FeOP$: C, 37.16; H, 2.38. Found: C, 37.00; H, 2.51.

3.5. η^6-[1-Chloro-4-(4-aminophenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (7*e*)

The substitution reaction was run at room temperature for 16 h and after quenching the mixture was filtered through neutral Al_2O_3. Yield: 17%, m.p. 178–179 °C (d). ^{1}H NMR δ: 7.05 (2H, d, J = 9.0 Hz), 6.85–6.75 (4H, m), 6.39 (2H, d, J = 9.0 Hz), 5.56 (5H, s). ^{13}C NMR δ: 146.6, 142.1, 133.6,120.5, 114.4, 102.6, 85.9, 78.4, 74.2. Anal. Calc. for $C_{17}H_{15}ClF_6FeNOP$: C, 42.05; H, 3.11. Found: C, 41.79; H, 3.30.

3.6. η^6-[1-Chloro-4-(2,6-di-iso-propylphenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (7*g*)

The substitution reaction was run at 0 °C for 3 h. Yield: 46%, m.p. 188–189 °C (d). ^{1}H NMR δ: 7.36 (3H, s), 6.90 (2H, d, J = 7.0 Hz), 6.49 (2H, d, J = 7.0 Hz), 5.40 (5H, s), 3.01 (2H, m, J = 7.0 Hz), 1.18 (12H, d, J = 7.0 Hz). ^{13}C NMR δ: 147.2, 139.5, 134.3, 126.8, 124.3, 103.1, 86.1, 78.6, 74.5, 26.2, 21.6. Anal. Calc. for $C_{23}H_{26}ClF_6FeOP$: C, 49.80; H, 4.72. Found: C, 49.61, H, 4.72.

3.7. η^6-[1-Chloro-4-(2,6-di-tert-butylphenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (7*h*)

The substitution reaction was run at room temperature for 16 h using a 1:1.5-ratio of **5** and 2,6-di-*tert*-butylphenol (**4**). Yield: 44%, m.p. 246–247 °C (d). ^{1}H NMR δ: 7.72 (2H, s), 7.07 (2H, d, J = 9.0Hz), 6.96

(2H, d, $J = 9.0$ Hz), 6.72 (1H, s), 5.21 (5H, s), 1.52 (18H, s). ^{13}C NMR δ: 155.5, 137.4, 123.8, 123.8, 105.0, 104.5, 87.4, 84.5, 78.8, 33.5. Anal. Calc. for $C_{25}H_{30}ClF_6FeOP$: C, 51.53; H, 5.19. Found: C, 51.51; H, 5.33.

3.8. η^6-[1-Chloro-4-[2,6-di-tert-butyl-4-(2-carbomethoxyethyl)phenoxy]benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**7i**)

The substitution reaction was run at room temperature for 16 h. Yield: 18%, m.p. 87–88 °C (d). ^{1}H NMR δ: 6.96 (2H, s), 6.89 (2H, d, $J = 7.0$ Hz), 6.73 (2H, d, $J = 7.0$ Hz), 5.37 (5H, s), 3.62 (3H, s), 2.61 (2H, t, $J = 7.6$ Hz), 2.25 (2H, d, $J = 7.6$ Hz), 1.31 (18H, s). ^{13}C NMR δ: 184.4, 171.7, 148.5, 140.0, 114.8, 109.6, 106.0, 87.2, 84.5, 78.8, 78.2, 50.1, 43.9, 34.2, 32.5.

3.9. η^6-[1-Chloro-4-(3,5-dibromo-4-methylphenoxy)-benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**11**)

The substitution reaction was run at 0 °C for 3 h. Yield: 49%, m.p. 189–191 °C (d). ^{1}H NMR δ: 7.68 (2H, s), 7.90 (2H, d, $J = 6.7$ Hz), 6.72 (2H, d, $J = 6.7$ Hz), 5.44 (5H, s), 2.58 (3H, s). ^{13}C NMR δ: 153.2, 134.4, 130.8, 124.3, 123.0, 103.6, 86.1, 78.9, 76.7, 21.3. Anal. Calc. for $C_{18}H_{14}Br_2ClF_6FeOP$: C, 33.66; H, 2.20. Found: C, 33.40; H, 2.31.

3.10. Typical procedure for preparation of disubstitution products **8**, **10**, **12**. η^6-[1,4-Bis(2,6-dimethylphenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**8f**)

2,6-Dimethylphenol (0.6 mmol, 73.3 mg) was stirred with sodium hydride (1.2 mmol, 48 mg of 60% dispersion in mineral oil) in THF (2 mL) for 15–20 min. The resulting solution of the phenolate was then added to a stirred suspension of the complex **5** (0.2 mmol, 82.6 mg) at room temperature. The reaction was stirred for 12–16 h and then quenched by addition of a few drops of 10% aqueous HCl to dissolve precipitate formed. The resulting mixture was filtered through Celite and the pad washed with CH_2Cl_2. The solvent was removed in vacuo and the residue redissolved in CH_2Cl_2 (25 mL). This solution was then washed with a dilute solution of NH_4PF_6 (1.5 mL of a saturated solution further diluted with 3.5 mL of H_2O), 0.05 M NaOH (2×5 mL) and water (10 mL). Drying over $MgSO_4$ and removal of the solvent in vacuo afforded a semi-solid residue, which was triturated with dry ether to give the title compound, 63 mg (54%), m.p. 253–254 °C (d). ^{1}H NMR δ: 7.18 (6H, s), 6.31 (4H, s), 5.37 (5H, s), 2.19 (12H, s). ^{13}C NMR δ: 150.3, 131.2, 128.8, 126.1, 125.6, 77.1, 73.2, 15.1. Anal. Calc. for $C_{27}H_{27}F_6FeO_2P$: C, 55.50; H, 4.66. Found: C, 55.31; H, 4.65.

The following compounds were similarly prepared.

3.11. η^6-[1,4-Bis(2-ethylphenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**8a**)

The reaction was quenched with water. Yield: 22%, m.p. 203–204 °C (d). ^{1}H NMR: 7.52–7.20 (8H, m), 6.37 (4H, s), 5.37 (5H, s), 2.61 (4H, q, $J = 7.6$ Hz), 1.19 (6H, t, $J = 7.6$ Hz). ^{13}C NMR δ: 150.8, 134.5, 130.1, 129.5, 127.0, 125.6, 119.1, 77.1, 74.1, 21.5, 12.7. Anal. Calc. for $C_{27}H_{27}F_6FeO_2P$: C, 55.50; H, 4.66. Found: C, 55.29; H, 4.68.

3.12. η^6-[1,4-Bis(2-tert-butylphenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**8b**)

Yield: 17%, m.p. 219–221 °C (d). ^{1}H NMR δ: 7.51 (2H, dd, $^2J = 7.0$ Hz, $^3J = 2$ Hz), 7.26 (4H, dt, $^2J = 7.0$ Hz, $^3J = 2$ Hz), 7.06 (2H, dd, $^2J = 7.0$ Hz, $^3J = 2$ Hz), 6.60 (4H, s), 5.46 (5H, s), 1.42 (18H, s). ^{13}C NMR δ: 153.5, 139.1, 129.3, 127.1, 126.8, 124.3, 117.9, 77.4, 76.8, 33.4. Anal. Calc. for $C_{31}H_{35}F_6FeO_2P$: C, 58.14; H, 5.51. Found: C, 57.92; H, 5.46.

3.13. η^6-[1,4-Bis(2-bromophenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**8c**)

The reaction was quenched with water. Yield: 86%, m.p. 193–194 °C (d). ^{1}H NMR δ: 7.86 (2H, dd, $^2J = 8.0$ Hz, $^3J = 2$ Hz), 7.61–7.30 (6H, m), 6.48 (4H, s), 5.43 (5H, s). ^{13}C NMR δ: 149.8, 133.5, 129.4, 129.1, 127.2, 121.3, 113.5, 77.7, 74.3. Anal. Calc. for $C_{23}H_{17}Br_2F_6Fe$- O_2P: C, 40.27; H, 2.50. Found: C, 39.97; H, 2.64.

3.14. η^6-[1,4-Bis(4-[N-(tert-butoxycarbonyl)-L-2-amino-2-carbomethoxyethyl]phenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**8d**)

The typical procedure for preparation of monosubstitution products was followed, but the substitution reaction was run at −20 °C for 5 h.

The title compound was isolated by passing the solution of the 1/1-mixture of mono- and disubstitution products in the minimum amount of acetone through a short column of Al_2O_3. Yield: 17 mg (13%), m.p. 163–165 °C (d). ^{1}H NMR δ: 7.46 (4H, d, $J = 8.2$ Hz), 7.28 (4H, d, $J = 8.2$ Hz), 6.36 (4H, s), 6.27 (2H, broad d, $J = 6.7$ Hz), 5.36 (5H, s), 4.42 (2H, broad m), 3.71 (6H, s), 3.26–2.95 (4H, m) 1.35 (18H, s). ^{13}C NMR δ: 171.1, 154.3, 151.6, 135.0, 130.5, 130.0, 119.3, 77.6, 77.1, 74.1, 54.1, 50.4, 35.8, 26.6. Anal. Calc. for $C_{41}H_{49}F_6FeN_2O_{10}P$:

C, 52.92; H, 5.31; N, 3.01. Found: C, 52.79; H, 5.31; N,3.01.

3.15. η^6-[1,4-Bis(2,6-di-iso-propylphenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**8g**)

The reaction was quenched with water. The crude product was dissolved in the minimum amount of acetone and passed through a short column of Al_2O_3. Evaporation of the solvent gave the pure product. Yield: 46%, m.p. 106–109 °C (d). ^{1}H NMR δ: 7.33 (6H, s), 6.35 (4H, s), 5.34 (5H, s), 3.05 (4H, m, J = 7.0 Hz), 1.18 (12H, d, J = 7.0 Hz). ^{13}C NMR δ: 147.8, 139.5, 132.4, 126.6, 124.2, 77.0, 73.2, 26.2, 21.7.

3.16. η^6-[1,4-Bis(2,6-dimethylphenylthio)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**10a**)

The crude product was dissolved in the minimum amount of acetone and passed through a short column of neutral Al_2O_3. Evaporation of the solvent and trituration of the residue with ether gave the title compound in 38% yield, m.p. 188–189 °C (d). ^{1}H NMR δ: 7.27–7.40 (6H, m), 6.26 (4H, s), 5.24 (5H, s), 2.43 (12H, s). ^{13}C NMR δ: 142.3, 130.0, 128.2, 126.6, 107.8, 82.9, 78.8, 20.1.

3.17. η^6-[1,4-Bis(2,6-dichlorophenylthio)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**10b**)

The reaction was quenched with water. The crude product was purified as described above. Yield: 50%, m.p. 189–191 °C (d). ^{1}H NMR δ: 7.78–7.63 (6H, m), 6.43 (4H, s), 5.32 (5H, s). ^{13}C NMR δ: 140.2, 132.7, 129.0, 125.7, 105.6, 83.1, 79.5. Anal. Calc. for $C_{23}H_{15}Cl_4F_6FePS_2$: C, 39.57; H, 2.17; S, 9.19. Found: C, 39.37; H, 2.37; S, 8.99.

3.18. η^6-[1,4-Bis(3,5-dibromo-4-methylphenoxy)-benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**12**)

The reaction was quenched with water. Yield: 18%, m.p. 229–231 °C. NMR ^{1}H δ: 7.06 (4H, s), 6.64 (4H, s), 5.43 (5 H. s), 2.56 (6H, s). NMR ^{13}C, δ: 151.9, 133.9, 129.0, 124.2, 122.6, 77.7, 75.8, 21.3. Anal. Calc. for $C_{25}H_{19}Br_4F_6FeO_2P$: C, 34.44; H, 2.20. Found: C, 34.64; H, 2.32.

3.19. η^6-[1-(2,6-Dichlorophenylthio)-4-(2,6-dimethylphenoxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**13a**)

2,6-Dichlorobenzenethiol (0.32 mmol, 57.3 mg) was stirred with NaH (0.6 mmol, 24 mg of 60% dispersion in mineral oil) in THF (2 mL) for 15–20 min. This solution was added via syringe to a solution of complex **7f** (0.16 mmol, 84.7 mg) in THF (4 mL). The reaction was stirred for 3 h, quenched by addition of a few drops of water and the mixture filtered through a Celite pad. The pad was washed well with CH_2Cl_2 and the solvent removed in vacuo. The residue was redissolved in CH_2Cl_2 (25 mL) and the resulting solution was washed with 1/4 saturated aqueous NH_4PF_6 (5 mL), 0.05 M NaOH (2 × 5 mL) and H_2O (10 mL). The organic layer was separated, dried over $MgSO_4$ and the solvent was removed in vacuo. The semi-solid was triturated with ether to give the title compound, 79 mg (77%), m.p. 190–192 °C. ^{1}H NMR δ: 7.78–7.62 (3H, m), 7.19 (3H, s), 6.31–6.46 (4H, m), 5.35 (5H, s), 2.07 (6H, s). ^{13}C NMR δ: 149.8, 140.0, 132.8, 132.5, 128.9, 128.8, 126.5, 125.7, 103.4, 82.7, 78.3, 74.3, 15.0. Anal. Calc. for $C_{25}H_{21}Cl_2F_6FePOS$: C, 46.83; H, 3.30; S, 5.00. Found: C, 47.01; H, 3.41; S, 4.84.

3.20. η^6-[1-(2,6-Dimethylphenylthio)-4-(2,6-dimethylphenoxy)benzene]-η^5-cyclopentdienyliron(II) hexafluorophosphate (**13b**)

Except that 2,6-dimethylbenzenethiol was employed, the procedure for compound **13a** was followed. The crude product was dissolved in the minimum amount of acetone and passed through a short column of neutral Al_2O_3. Removal of the solvent in vacuo afforded the pure title compound in 53% yield, m.p. 204–205 °C (d). ^{1}H NMR δ: 7.40–7.31 (3H, m), 7.18 (3H, s), 6.35–6.26 (4H, m), 5.32 (5H, s), 2.46 (6H, s), 2.16 (6H, s). ^{13}C NMR δ: 149.8, 142.2, 132.4, 129.9, 128.8 (2 signals), 128.3, 127.1, 125.6, 106.3, 82.3, 78.0, 74.2, 20.1, 15.0. Anal. Calc. for $C_{27}H_{27}F_6FePOS$: C, 54.01; H, 4.53; S, 5.34. Found: C, 53.83; H, 4.66; S, 5.15.

3.21. η^6-[1-(2,6-Dimethylphenoxy)-4-(N-(2-aminoethyl)-mino)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**14a**)

Except for the use of complex **7f** instead of **5** and a reaction time of 5 h, the procedure was as described for compound **16**. Yield: 94%, m.p. 159–162 °C (d). NMR ^{1}H δ: 7.18 (3H, several peaks), 6.01 (2H, d, J = 7.2 Hz), 5.88 (2H, d, J = 7.2 Hz), 5.09 (5H, s), 3.54–3.41 (4H, m), 2.21 (6H, s).

3.22. η^6-[1-(2,6-Di-tert-butylphenoxy)-4-(N-(2-aminoethyl)-amino)benzene]-η^5-cyclopentadienyliron-(II) hexafluorophosphate (**14b**)

Except for the use of complex **7h** instead of **7f** and a reaction time of 6.5 h, the procedure was as described for compound **16**. Yield: 89%, m.p. 188–190 °C (d). NMR ^{1}H δ: 7.65 (2H, s), 6.58 (2H, d J = 7.0 Hz), 6.54 (1H, s), 6.06 (2H, d, J = 7.0 Hz), 4.90 (5H, s), 3.67–3.51

(4H, m), 1.52 (18H, s). ^{13}C NMR δ: 154.3, 137.1, 125.4, 124.7, 123.4, 97.5, 82.6, 75.3, 66.5, 48.7, 42.9, 33.5.

3.23. η^6-[1,4-Bis(4-methoxybenzyloxy)benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**15**)

p-Methoxybenzyl alcohol (0.6 mmol, 82.9 mg) was stirred with sodium hydride (1.2 mmol, 48 mg of a 60% dispersion in mineral oil) in THF (2 mL) for 15–20 min. The complex **5** (0.2 mmol, 82.6 mg) was added as a solid and the mixture allowed to stir for 16 h. The reaction was quenched by addition of a few drops of water and the mixture filtered through a Celite which was washed well with CH_2Cl_2. The solvent was removed in vacuo and the residue redissolved in CH_2Cl_2 (25 mL). This solution was washed with 1/4 saturated aqueous NH_4PF_6 (5 mL), 0.05 M NaOH (2 × 5 mL), H_2O (10 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo gave a crystalline product, which was washed several times with ether and dried in vacuo. Yield: 33 mg (48%), m.p. 168–169 °C (d). ^{1}H NMR δ: 7.49 (4H, d, J = 8.8 Hz), 7.01 (4H, d, J = 8.8 Hz), 6.37 (4H, s), 5.29 (4H, s), 5.10 (5H, s), 3.83 (6H, s). ^{13}C NMR δ: 159.3, 129.9, 129.2, 125.9, 113.0, 75.8, 71.3, 70.4, 53.8. Anal. Calc for $C_{27}H_{27}F_6FeO_4P$: C, 52.62; H, 4.42. Found: C, 52.40, H, 4.40.

3.24. η^6-[1-Chloro-4-(N-(2-aminoethyl)-amino)-benzene]-η^5-cyclopentadienyliron(II) hexafluorophosphate (**16**)

Complex **5** (0.2 mmol, 82.6 mg) and ethylenediamine (0.4 mmol, 24.0 mg) were stirred with K_2CO_3 (0.5 mmol, 69.1 mg) in dry THF (4 mL) for 14 h at room temperature. The inorganic precipitate was filtered off and washed with CH_2Cl_2. The solvents were removed in vacuo and the oily residue was triturated with dry ether to yield the title compound as an orange precipitate, 78 mg (89%), m.p. 108–109 °C. NMR ^{1}H δ: 6.52 (2H, d, J = 7.0 Hz), 6.27 (1H, broad s), 6.00 (2H, d, J = 7.0 Hz), 5.12 (5H, s), 3.64–3.44 (4H, m). NMR ^{13}C δ: 125.3, 99.8, 85.0, 76.8, 65.6, 48.6, 43.0. Anal. Calc. for $C_{13}H_{16}ClF_6FeN_2P$: C, 35.77; H, 3.69; N, 6.42. Found: C, 35.95; H, 3.78; N, 6.29.

3.25. η^6-[1-(2,6-Dimethylphenylthio)-4-(N-(2-aminoethyl)-amino)benzene]-η^5-cyclopentadienyliron-(II) hexafluorophosphate (**17**)

2,6-Dimethylthiophenol (0.4 mmol, 55.3 mg) was stirred with sodium hydride (0.8 mmol, 32 mg of 60% dispersion in mineral oil) in THF (3 mL) for 15–20 min. A solution of complex **16** (0.2 mmol, 87.3 mg) in THF (4 mL) was added via syringe and stirring continued for 3 h. The reaction was quenched by addition of a few drops of water and the mixture was filtered through a Celite pad which was washed well with CH_2Cl_2. The combined filtrate was diluted with CH_2Cl_2 to 25 mL and washed with 1/4 saturated aqueous NH_4PF_6 (5 mL), 0.05 M NaOH (2 × 5 mL) and H_2O (10 mL), dried over $MgSO_4$ and the solvents were removed in vacuo. The brownish oily residue was triturated with dry ether and pentane to give the title compound as a yellow-orange powder, 38 mg (35%), m.p. 87–89 °C. NMR ^{1}H δ: 7.37–7.26 (3H, m), 6.04–5.90 (4H, m), 5.04 (5H, s), 3.55 (4H, broad s), 2.48 (6H, s).

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