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The application of a variety of iron complexes with chelating amine ligands as pre-catalysts in the representative cross-coupling of 4-tolylmagnesium bromide with cyclohexyl bromide was investigated. The results from this study indicate the performance of the pre-catalyst is inversely proportional to the strength of the chelate or macrocyclic effect of the amine ligand, as determined by the propensity of the ligand to be displaced from the iron centre by reaction with excess benzyl magnesium chloride. The findings from this study are consistent with a catalytic cycle wherein the chelating amine ligand is not co-ordinated to the iron centre during turnover.

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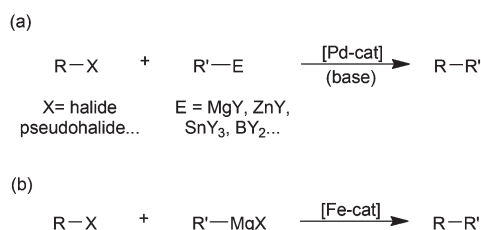
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While there is no doubt that palladium-catalysed cross-coupling is an exceptionally powerful synthetic methodology (Scheme 1(a)),¹ the benefits of the use of palladium are offset by its high price, relative toxicity and the environmental impact of its extraction.² Accordingly there has been much recent³ effort expended on developing iron-based catalysts for cross-couplings,⁴ due to the far lower cost, toxicity and supply issues associated with iron. By far the most widely studied iron-catalysed cross-coupling reaction is the Kumada reaction, that is the coupling of Grignard reagents with alkyl or aryl halides and related electrophilic substrates (Scheme 1(b)).⁴

While several classes of complexes and ligands have been investigated, amine complexes of iron have been found to be particularly useful pre-catalysts in a range of iron-catalysed Kumada reactions, often giving high yields and good selectivity for the cross-coupled product. For instance Nakamura and Nakamura showed that 1,2-bis(dimethylamino)ethane, TMEDA, could be employed to good effect, providing that it was used in stoichiometric or greater amounts with respect to the Grignard substrate and that the amine-Grignard mixture was added slowly to the reaction mixture, typically with a syringe pump.⁵ We,⁶ and subsequently Cahiez,⁷ demonstrated that TMEDA, as well as other amine ligands, could actually be used in catalytic quantities and that slow addition was not always required for good activity.

Clearly, given the successes enjoyed with TMEDA and other chelating amines, it is important to establish the role(s) played by the ligands in the catalytic cycle of the iron-catalysed Kumada reaction. In the first study to address this issue, Nagashima and co-workers investigated the reaction of 3 equivalents of mesitylMgBr with FeCl₃ and excess TMEDA.⁸ They showed that this gave the bis-mesityl complex **1**, which reacts with octyl bromide to give the cross-coupled product and the second mesityl complex **2**. Reaction of **2** with the Grignard reagent regenerates **1**. On the basis of these observations, the authors proposed the catalytic cycle outlined in Scheme 2.

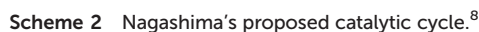
By contrast, we demonstrated that in the presence of excess MesMgBr, such as would be seen under catalytic conditions, complex **1** reacts to generate the homoleptic ‘ate’ complex **3** (Scheme 3).⁹ Indeed ¹H NMR studies revealed that during catalysis only complex **3** is observed and not complex **1**. Furthermore, complex **3** reacts far faster than complex **1** with OctBr, effectively eliminating **1** as a feasible catalytic intermediate in the primary cycle. We instead proposed the cycle shown in



Scheme 1 (a) Generalised palladium-catalysed cross-coupling; (b) the iron-catalysed Kumada reaction.

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Ultimately, these model studies are limited because mesityl Grignard is a poor, non-representative substrate in iron-catalysed cross-couplings, with low yields of the cross-coupled product furnished after protracted reaction times.^{8,9} Accordingly, we decided to investigate the effect of varying the amine-donor ligands in the presence of a smaller, far more representative aryl nucleophile. Clearly, if the mechanism in Scheme 3 is still operative with less bulky Grignard reagents, and the amine is required to dissociate from the iron centre in order

Finally, the previously reported complex **10** was examined,¹³ which contains an ethylene-bridged cyclam ligand (Me₂EBC).



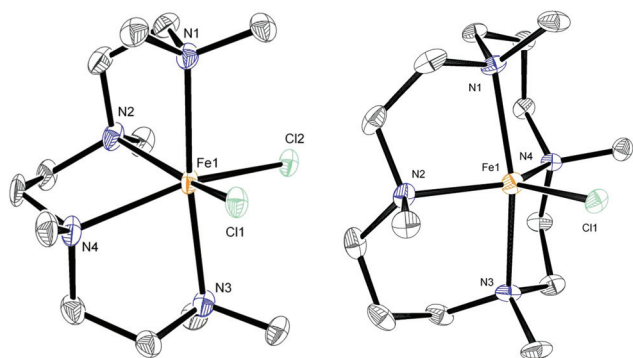


Fig. 2 X-ray crystal structures of complexes **8** and **9**. Thermal ellipsoids set at 50% probability; hydrogen atoms, chloride counter-ion of **9** and three molecules of MeCN solvate in **9** omitted for clarity.

In this case the bicyclic nature of the ligand would be expected to confer even greater macrocyclic stabilisation, compared with the TMC ligand, giving by far the most stable complex of the series.

Catalytic studies

The complexes **7–10**, as well as the species formed *in situ* from FeCl₂ and TMEDA in THF were tested as pre-catalysts in the representative cross-coupling of 4-tolyl magnesium bromide with cyclohexylbromide, under two sets of conditions. In the first set of (A), the reaction was performed at 0 °C with slow addition of the Grignard reagent using a syringe pump, conditions similar to those reported by Nakamura.⁵ Meanwhile in the second set of conditions (B) the Grignard reagent was added rapidly and the reaction was warmed to 40 °C, to mirror the conditions that we previously exploited.⁶ The results from this study are summarised in Table 1.

Compared with the excellent and good conversions observed after 1 hour with the TMEDA-containing system under slow and rapid addition of the Grignard reagent respectively (entries 1 and 2) it is clear that much lower activity is seen with the pre-catalyst **7**, which contains the more conformationally rigid diamine ligand sparteine (entries 3 and 4). Even worse activity is observed with complex **8**, which contains the tetradentate chelating ligand HMTETA, under slow addition conditions (entry 5). Interestingly some activity is recovered when the reaction was repeated with rapid addition of the Grignard reagent.

In all the examples above, the catalysis is accompanied by the formation of black, heterogeneous reaction mixtures, most likely due to the formation of iron nanoparticles, which have previously been demonstrated to be catalytically competent in Kumada¹⁴ and related cross-coupling reactions.¹⁵ By contrast, the reactions catalysed by complexes **9** or **10** remained homogeneous over the course of the reactions under both sets of conditions, and in all cases gave very little of the cross-coupled product **11**. It is clear that an increase in the chelate or macrocyclic complex stability leads to a sharp decrease in catalyst

Table 1 Iron-catalysed Kumada cross-coupling

Conditions
A: THF, 0 °C, slow addition
B: Et₂O, 40 °C

11

Entry	[Fe-cat]	Conditions ^a	Conversion to 11 ^b , %	Appearance at end of reaction
1	FeCl ₂ + excess TMEDA ^c	A	93	Heterogeneous
2	FeCl ₂ + 2TMEDA ^d	B	77	Heterogeneous
3	7	A	51	Heterogeneous
4	7	B	54	Heterogeneous
5	8	A	19	Heterogeneous
6	8	B	53	Heterogeneous
7	9	A	15	Homogeneous
8	9	B	3	Homogeneous
9	10	A	1	Homogeneous
10	10	B	3	Homogeneous

^a Conditions, A: CyBr (1.0 mmol), 4-tolylMgBr (drop-wise, 1.2 mmol), [Fe-cat] (0.05 mmol), THF, 0 °C, 1 h; B: CyBr (1.0 mmol), 4-tolylMgBr (2.0 mmol), [Fe-cat] (0.05 mmol), Et₂O, 40 °C, 1 h. ^b Conversion to **11** determined by ¹H NMR spectroscopy (1,3,5-trimethoxybenzene internal standard). ^c 2.0 mmol. ^d 0.1 mmol.

performance. This is despite the fact that, in all the cases examined, the pre-catalysts should be capable of providing the *cis*-disposed reactive sites that might be envisaged as necessary for catalytic activity if an iron-amine-based cycle such as that shown in Scheme 2 were operative.

Based on both the relative productivities of the pre-catalysts and the appearance of the reaction mixtures, it is tempting to conclude that the amine ligands do indeed dissociate from the iron centre prior to its entry into the primary catalytic cycle, as hypothesised and outlined in Scheme 3. In this scenario, amine dissociation would be triggered by reaction with excess Grignard reagent, therefore we next focussed on establishing the ease and extent of ligand dissociation from the amine complexes in the presence of a representative Grignard reagent.

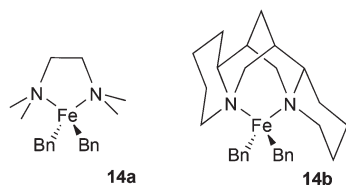
Reactions with benzyl Grignard reagent

We previously found that the reaction of either FeCl₂ or FeCl₂/TMEDA with excess 4-tolyl Grignard at low temperature (−30 °C) gives species tentatively assigned as the homoleptic arylferrates [FeAr₃][−] and [FeAr₄]^{2−} respectively, as characterised by ¹H NMR spectroscopy. In the latter case the TMEDA ligand is not coordinated to the paramagnetic iron centre, but instead most likely coordinates to the magnesium salt counter-ion. Whilst these species have so far proven too thermally fragile for us to isolate, we found that we were able to isolate and characterise the comparable Fe(II) benzyl-containing anionic ‘ate’ complex, [FeBn₃][−] (**12**), as well as the Fe(III) analogue [FeBn₄][−] (**13**), and probe its significance as a possible active intermediate in cross-coupling.⁹ In view of the improved stability of iron-benzyl adducts compared to iron-4-tolyl inter-



mediates, we decided to explore the reactivity of the iron amine-complexes listed above with benzyl Grignard.

Fig. 3 shows the ^1H NMR spectra recorded on addition of varying amounts of BnMgCl to complex **6** in THF. Complex **6** is NMR silent, but the addition of one equivalent of the Grignard reagent gives a spectrum assigned as that of the complex $[\text{FeClBn}(\text{TMEDA})]$, **15**, which could be isolated in modest yield when the reaction was repeated on a larger scale. Addition of a further 0.5 or 1 equivalent of the Grignard reagent to the NMR-scale reaction mixture led to increasing amounts of a species previously identified by Sen and co-workers as the bis-benzyl complex **14a**.¹⁶ As described previously,⁹ the addition of excess BnMgCl rapidly led to the formation of the 'ate' complex **12**.



As yet, no structural evidence has been provided for **14a**, however Chirik and co-workers have reported the crystal structure of the equivalent sparteine-based analogue, **14b**.¹² The ^1H NMR spectrum of **14b**, formed *in situ* from **7** and two equivalents of benzyl Grignard, is shown in Fig. 4(a). Addition of excess (20 equivalents) of Grignard again led to the formation of the anionic complex **12**, but the reaction is significantly slower than with the Fe-TMEDA mixture, presumably as a function of increased chelate complex stability with the more conformationally constrained sparteine ligand.

The ^1H NMR spectrum of the HMTETA-containing complex **8** in THF at room temperature is shown in Fig. 5(a), whilst (b) shows the spectrum after addition of 2 equivalents of BnMgCl . The latter spectrum is more complicated and is likely to correspond to the formation of one or more iron-benzyl/HMTETA adducts. On addition of a further two equivalents of the

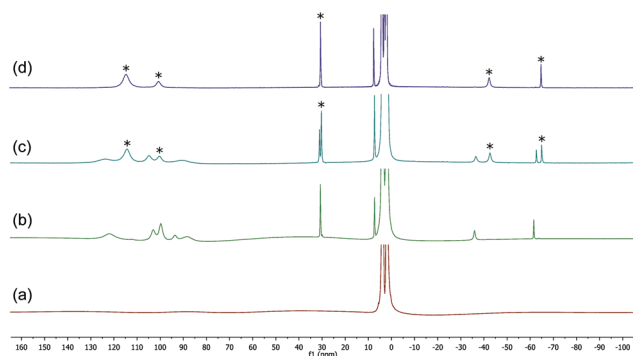


Fig. 3 (a) ^1H NMR spectrum of complex **6** in THF (NMR silent). (b) Part of spectrum of complex **15**, formed *in situ* from **6** and 1 equiv. BnMgCl/Fe (peak at 1067 ppm omitted). (c) and (d) Addition of a further 0.5 and 1 equivalent of BnMgCl/Fe . Peaks marked '*' correspond to $[\text{FeBn}_2(\text{TMEDA})]$, (**14a**).

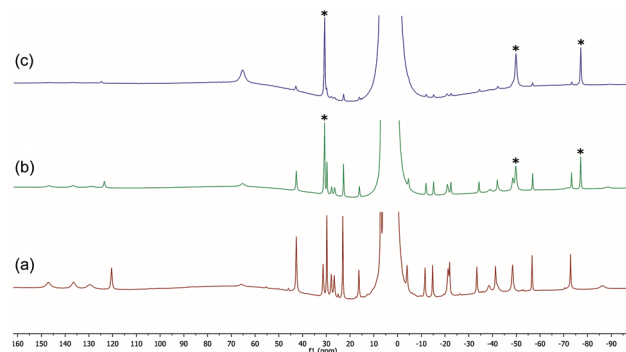


Fig. 4 (a) ^1H NMR spectrum of complex **14b** in THF. (b) **14b** + 20 BnMgCl , after 10 min. (c) As above, after 5 h; peaks marked with '*' correspond to 'ate' complex **12**.

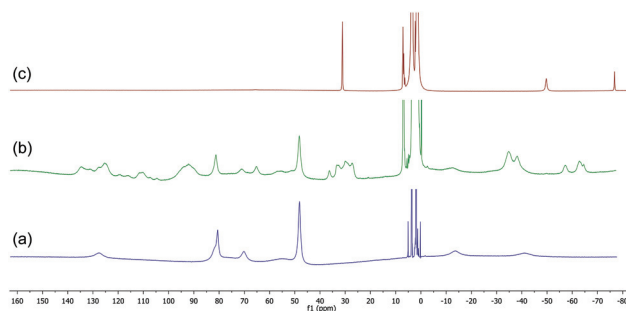


Fig. 5 (a) ^1H NMR spectrum of complex **8**. (b) and (c) Spectra recorded after addition of 2 and 4 equiv. BnMgCl respectively.

Grignard reagent, the tetraamine ligand was lost from the iron centre and the 'ate' complex **12** was once again the only paramagnetic iron-containing complex observed (spectrum (c)). The data clearly show that, as with both the TMEDA- and sparteine-containing complexes, the presence of excess Grignard reagent favours the dissociation of HMTETA and the concomitant formation of the amine-ligand-free homoleptic 'ate' complex **12**.

The ^1H spectra of macrocyclic complexes **9** and **10** are shown in Fig. 6 (spectra (a) and (c) respectively), meanwhile

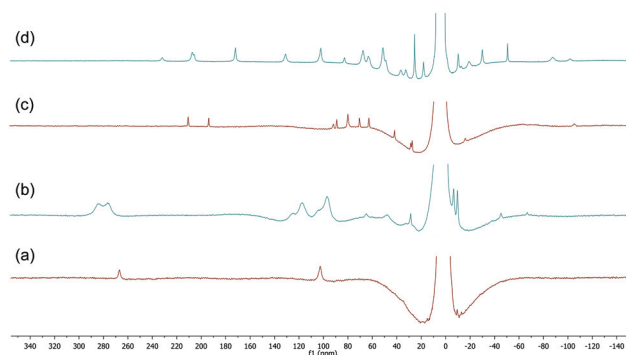


Fig. 6 (a) and (c) ^1H NMR spectra of complexes **9** and **10** respectively (THF, r.t.); (b) and (d) spectra recorded 10 minutes after addition of 10 equiv. BnMgCl to **9** and **10** respectively.



the spectra of the red and orange reaction mixtures recorded 10 minutes after addition of excess BnMgCl (10 equivalents) to **9** and **10** are shown in plots (b) and (d) respectively. It is clear that new paramagnetic complexes were formed in both cases, again presumably containing benzyl ligands in addition to the macrocyclic amine ligands. However, in stark contrast to all of the reactions discussed above with iron complexes of TMEDA, sparteine or HMTETA, none of the homoleptic anionic complex **12** was observed suggesting that the macrocyclic ligands were not displaced by the Grignard reagent. Indeed, no **12** was observed when the spectra were run again after 24 hours.

Conclusions

The lability of the amine ligands of the complexes **5–10** in the presence of excess benzyl Grignard reflects decreasing catalytic activity in the coupling of cyclohexylbromide with 4-tolylmagnesium bromide, with the least labile systems showing the poorest catalytic activity. Of particular note, whilst the complexes **9** and **10** do react with benzyl Grignard, the amine ligands are not displaced by excess Grignard, unlike the amine ligands in the other complexes examined. These two complexes show only very poor activity as catalysts in the cross-coupling reactions and it is important to note that in these cases the reaction mixtures stay homogeneous throughout the catalysis. Conversely TMEDA, sparteine and HMTETA are all displaceable by excess benzyl Grignard, and their complexes are catalytically competent with an activity in the order $\text{HMTETA} < \text{sparteine} < \text{TMEDA}$ reflecting the decreasing chelate effect of the ligands. In these cases the catalytic reactions all turned black, suggestive of the formation of iron nanoparticles.

Taken together the data reported here provide further strong evidence that amine ligands are not coordinated to the iron centre in the primary catalytic cycle of Kumada reactions employing iron-amine pre-catalysts, lending support to variants of the catalytic cycle outlined in Scheme 3.

Experimental

General

All reactions were carried out under a dry atmosphere of nitrogen using standard Schlenk line and glove box techniques, unless otherwise specified. Anhydrous solvents were obtained from a Grubbs solvent drying system, degassed and stored over molecular sieves in a flame dried Strauss flask. Commercial reagents were used as received without further purification unless otherwise specified. The ligand Me_2EBC was prepared according to a literature method.¹⁷ ^1H NMR spectra were recorded on a Jeol Lambda 300, Jeol ECP 400, Varian 400-MR, or Varian 500 spectrometer. Half-height peak widths for paramagnetic compounds are reported in Hz in parentheses after the chemical shift. Elemental analyses were obtained from the

microanalytical service at the University of Bristol. Infrared spectra were recorded on a PerkinElmer Spectrum 100 FTIR Spectrometer, selected frequencies are reported.

Preparation of $[\{\text{FeCl}(\mu\text{-Cl})(\text{TMEDA})\}_2]$, **6.** Prepared following a literature procedure.¹¹ FeCl_2 (4.10 g, 32.3 mmol) and TMEDA (4.90 ml, 32.7 mmol) were heated for 1 h in THF (150 ml) at reflux temperature. After cooling, the volume was reduced by a third and the mixture cooled to -20°C to give a crop of crystals of **6** (3.72 g, 47.4%). Anal. Found: C, 30.10; H, 6.92; N, 11.20. Calcd for $\text{C}_{12}\text{H}_{32}\text{Cl}_4\text{Fe}_2\text{N}_4$: C, 29.66; H, 6.64; N, 11.53.

Preparation of $[\text{FeCl}_2((-)\text{-sparteine})]$, **7.** A literature preparation was followed.¹² To a mixture of FeCl_2 (1.09 g, 8.60 mmol) in THF (5 ml) was added a solution of $(-)$ -sparteine (2.02 g, 8.60 mmol) in THF (2 ml) and the reaction mixture stirred for 18 h to give a suspension. The white solid was isolated by filtration, washed with diethyl ether and dried under reduced pressure to yield **7** (2.61 g, 83.9%). The ^1H NMR spectroscopic data (CDCl_3) were in agreement with reported values.¹² ^1H NMR (400 MHz, 25.0°C , THF) δ 352.3 (271, 1H), 313.5 (296, 1H), 297.1 (275, 1H), 175.9 (167, 1H), 139.2 (632, 2H), 118.3 (821, 1H), 43.3 (79, 1H), 41.8 (74, 1H), 37.5 (56, 1H), 24.5 (106, 1H), 22.9 (94, 1H), 10.9 (65, 1H), 7.2 (30, 1H), -6.6 (42, 1H), -7.2 (53, 1H), -15.1 (83, 1H), -15.6 (59, 1H), -22.0 (68, 2H), -34.3 (69, 2H), -38.0 (766, 1H), -44.6 (81, 1H), -69.6 (797, 1H), -134.4 (970, 1H). Anal. Found: C, 49.62; H, 6.91; N, 7.73. Calcd for $\text{C}_{15}\text{H}_{26}\text{Cl}_2\text{FeN}_2$: C, 49.89; H, 7.26; N, 7.76.

Preparation of *cis*- $[\text{FeCl}_2(\text{HMTETA})]$, **8.** A flame dried Schlenk was charged with FeCl_2 (1.52 g, 12.0 mmol) and THF (20 ml) and the mixture was stirred for 10 min to give a grey/pink suspension. HMTETA was added in one portion (3.26 ml, 12.0 mmol), the reaction mixture stirred for 30 min at room temperature and then heated at reflux for 8 h, after which time it was allowed to cool and the supernatant removed *via* a filter cannula. The remaining fine solid was washed with cold THF (3×3 ml) and then dried under vacuum to give **8** as a white solid (3.45 g, 80.5%). ^1H NMR (400 MHz, 25.0°C , THF) δ 127.6 (1471), 81.6 (942), 80.5 (372), 70.1 (854), 55.0 (3314), 48.1 (403), -13.6 (1605), -41.1 (2143). Anal. Found: C, 40.02; H, 8.51; N, 15.56. Calcd for $\text{C}_{12}\text{H}_{30}\text{Cl}_2\text{FeN}_4$: C, 40.36; H, 8.47; N, 15.64. Crystals suitable for X-ray structure determination were grown from a THF solution. IR (cm^{-1}): 2972 w, 2859 m, 2824 m, 1468 sh, 1446 sh, 1281 sh, 1174 w, 1138 w, 1116 m, 1066 m, 1057 m, 1031 sh, 1010 m, 984 sh, 935 sh, 897 sh, 794 m, 780 sh, 604 m, 576 m.

Preparation of $[\text{FeCl}(\text{TMC})]\text{Cl}$, **9.** A Schlenk was charged with tetramethylcyclam (111 mg, 0.43 mmol) and anhydrous MeCN (5 ml). FeCl_2 was added in one portion (55 mg, 0.43 mmol) and the reaction mixture stirred for 30 min at room temperature. The reaction mixture was then heated at 40°C for 1 h resulting in a pale yellow solution, which was allowed to cool, filtered *via* cannula and left at -20°C to give a crop of crystals suitable for X-ray structure determination. The crystals were washed with cold THF (2 ml) and dried under vacuum to give the product as a colourless solid (107 mg, 64.9%). ^1H NMR (400 MHz, 25.0°C , THF): δ = 265.9 (589), 103.2 (952). Anal. Found: C, 43.99; H, 8.19; N, 14.24. Calcd for $\text{C}_{14}\text{H}_{32}\text{Cl}_2\text{FeN}_4$: C,



43.88; H, 8.42; N, 14.62. IR (cm⁻¹): 2865 br, 1472 sh, 1458 sh, 1426 w, 1115 sh, 1067 sh, 999 sh, 963 sh, 930 w, 804 sh, 727 sh.

Preparation of [FeCl₂(Me₂EBC)], 10. A literature procedure was followed.¹³ A solution of Me₂EBC (1.02 g, 4.0 mmol) in anhydrous acetonitrile (20 ml) was added to a suspension of [FeCl₂(py)₂] (1.14 g, 4.0 mmol) in anhydrous acetonitrile and the mixture stirred for 16 h at room temperature. (Note: all sources of adventitious water must be avoided as water coordinates preferentially in the ligand cavity and cannot be displaced by the iron.) The reaction mixture was filtered and the solvent removed from the filtrate under reduced pressure to give the product as a light brown solid (1.35 g, 88.5%). ¹H NMR (400 MHz, 25.0 °C, THF): δ = 209.5 (234), 192.7 (234), 90.7 (411), 88.0 (248), 78.8 (453), 69.2 (248), 61.6 (218), 40.7 (262), 27.3 (290), 26.3 (276), -17.2 (397), -106.6 (893). Anal. Found: C, 45.36; H, 8.25; N, 15.14. Calcd for C₁₄H₃₀Cl₂FeN₄: C, 45.11; H, 7.93; N, 14.70. Crystals suitable for X-ray structure determination were grown from a cooled THF solution.

Cross-coupling of 4-tolylMgBr with cyclohexyl bromide Table 1, conditions A

Cyclohexyl bromide (123 µl, 1.0 mmol), the appropriate iron complex (0.05 mmol) and where appropriate, TMEDA (300 µl, 2.0 mmol) were stirred for 3 minutes in THF (2.0 ml) held at 0 °C. 4-TolylMgBr (1.2 mmol) was added dropwise with stirring over 30 min using a syringe pump and the reaction mixture was stirred for a further 30 min at 0 °C. The reaction was quenched by addition of H₂O (5 ml) and the organic products extracted with CH₂Cl₂ (3 × 10 ml). 1,3,5-Trimethoxybenzene (168 mg, 1.0 mmol) was added as an internal standard and the conversion to cross-coupled product was determined by ¹H NMR spectroscopy. **Conditions B.** Cyclohexyl bromide (123 µl, 1.0 mmol), the relevant iron complex (0.05 mmol) and where appropriate, TMEDA (15 µl, 0.1 mmol) were stirred for 3 minutes in Et₂O (3.0 ml) at room temperature. 4-TolylMgBr (2.0 mmol) was added in one portion and the reaction mixture heated at reflux temperature for 1 h. Workup and determination of conversion to cross-coupled product as above.

NMR studies of the reaction of iron-amine chelate complexes with BnMgCl (Fig. 3–6)

The appropriate iron-amine complex (0.5 mmol) was dissolved in THF (2 ml), BnMgCl (0.84 M in THF, specified amount) was added at room temperature, the reaction mixture stirred for 10 min, a sample was removed and the ¹H NMR was recorded.

Preparation of [FeClBn(TMEDA)], 15

Complex 6 (0.972 g, 2.0 mmol) was dissolved in THF (5.0 ml), BnMgCl added (2.0 ml, 2.0 M in THF, 4.0 mmol) and the reaction mixture stirred for 10 min to give an orange solution. Cooling the solution at -20 °C gave 15 as an orange solid (402 mg, 33.7%). ¹H NMR (400 MHz, 25.0 °C, THF) δ 1066.8 (3823 Hz, 4H), 121.6 (2168), 102.7 (892), 99.4 (763), 93.3 (688), 88.1 (1897), 30.4 (73, 4H), -36.3 (337, 4H), -61.9 (76, 2H).

Anal. Found: C, 52.58; H, 8.02; N, 8.95. Calcd for C₂₆H₄₆Cl₂Fe₂N₄: C, 52.28; H, 7.76; N, 9.38.

Preparation of [FeBn₂((-)-sparteine)], 14b

A literature preparation was followed.¹² To 7 (0.203 g, 0.562 mmol) was added diethyl ether (5 ml) and the mixture stirred. To this was added KCH₂C₆H₅ (0.146 g, 1.12 mmol) in diethyl ether (10 ml) and the reaction mixture was stirred for 6 h to give a yellow solution. This was filtered through celite and the solvent removed *in vacuo* to yield 14b as a yellow solid (0.151 g, 57.1%). The ¹H NMR spectroscopic data (benzene-d₆) were in agreement with reported values,¹² and were also recorded in THF. ¹H NMR (400 MHz, 25.0 °C, THF) δ 932.8 (2433, 1H), 896.2 (2107, 1H), 827.8 (2401, 1H), 777.7 (1626, 1H), 350.9 (343, 1H), 341.2 (371, 1H), 218.9 (315, 1H), 147.3 (958, 1H), 136.8 (794, 1H), 129.6 (1203, 1H), 120.8 (215, 1H), 43.2 (135, 2H), 31.7 (134, 1H), 29.9 (99, 2H), 28.4 (168, 1H), 27.1 (187, 1H), 23.1 (103, 2H), 16.7 (150, 1H), 7.1 (93, 1H), 6.0 (105, 1H), -3.6 (177, 1H), -11.3 (134, 1H), -14.6 (122, 1H), -21.4 (311, 1H), -21.8 (161, 1H), -33.3 (137, 1H), -38.3 (575, 1H), -41.0 (165, 1H), -41.8 (649, 1H), -48.3 (277, 1H), -56.7 (87, 1H), -72.9 (104, 2H), -86.0 (1139, 1H), -148.1 (1208, 1H).

Acknowledgements

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Notes and references

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