Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 761–767
Tetrahedron

Synthesis of (2-aminoethyl)ferrocenes from the reaction of lithium amides with vinylferrocene

Kévin M. Joly,[a] Renate M. Gleixner,[a] Simon M. E. Simpkins,[a] Diane M. Coe[b] and Liam R. Cox[a,*]

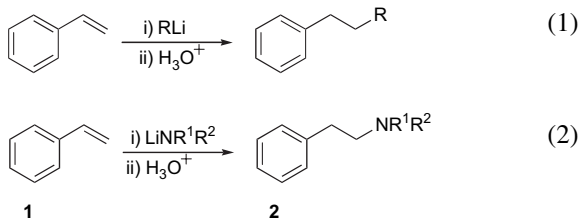
[a]*School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK*
[b]*GlaxoSmithKline, Medicinal Chemistry 1, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK*

Received 12 September 2006; revised 12 October 2006; accepted 27 October 2006
Available online 15 November 2006

Abstract—Lithium amides react with vinylferrocene in the presence of TMEDA to provide the corresponding (2-aminoethyl)ferrocenes in good to excellent yields. A range of secondary amines can be employed in this amidolithiation reaction, with cyclic derivatives affording particularly good yields of the 2-aminoethyl-substituted ferrocene product. This operationally simple procedure provides one of the most straightforward routes to this class of mono-substituted ferrocene.
© 2006 Elsevier Ltd. All rights reserved.

1. Introduction

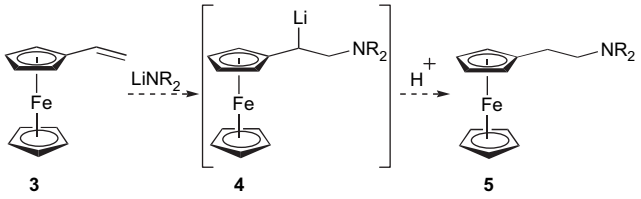
Although an aryl-substituted alkene, such as styrene **1**, is far less electrophilic than the alkene contained within an α,β-unsaturated carbonyl compound,[1] strong nucleophiles, such as organolithium reagents, do react with the pendant olefin to provide an addition product (Scheme 1, Eq. 1).[2] Regioselectivity is excellent, with the formation of the more stable benzylic anion intermediate accounting for the observed regiochemistry in the protonated end-product. The analogous reaction with lithium amides has also been developed to provide a convenient route to the corresponding β-phenethylamine **2**,[3] which is a particularly important and widespread structural motif in medicinal chemistry (Scheme 1, Eq. 2).[4]



Scheme 1. Regioselective carbolithiation and amidolithiation of styrene.

We have postulated that replacing the phenyl group in a β-phenethylamine motif with a redox-active ferrocenyl substituent would provide a means for electrochemically sensing chemistry or recognition events carried out on proximal side-chain functionality.[5] Combining this sensing capability with the facility with which an amino-substituted ferrocene can be rendered water-soluble,[6] and therefore potentially bioavailable, would then allow us to employ this class of organometallic as a potential substitute for the β-phenethylamine motif and potentially broaden the utility of this metallocene in medicinal and biological chemistry.[7–11] It is worth noting that ferrocenes containing side-chain amino groups have found application in other fields.[7–15] Of particular note are the range of chiral ligands incorporating this scaffold, which are now used widely in asymmetric catalysis.[14,15] New methods that allow the straightforward synthesis of 2-aminoethyl-substituted ferrocenes are therefore highly desirable.

Based on the precedent set by the reaction of styrene with lithium amides, we postulated that vinylferrocene **3** might react in a similar fashion, to provide a straightforward route to the corresponding 2-aminoethyl-substituted ferrocene product **5** (Scheme 2). Although at the outset we expected the increased electron density on the cyclopentadienyl ligand in the metallocene, compared with that in the benzene ring in styrene **1**, would attenuate the electrophilicity of the pendant olefin, if successful, the reaction would provide a very simple route to the desired compounds.

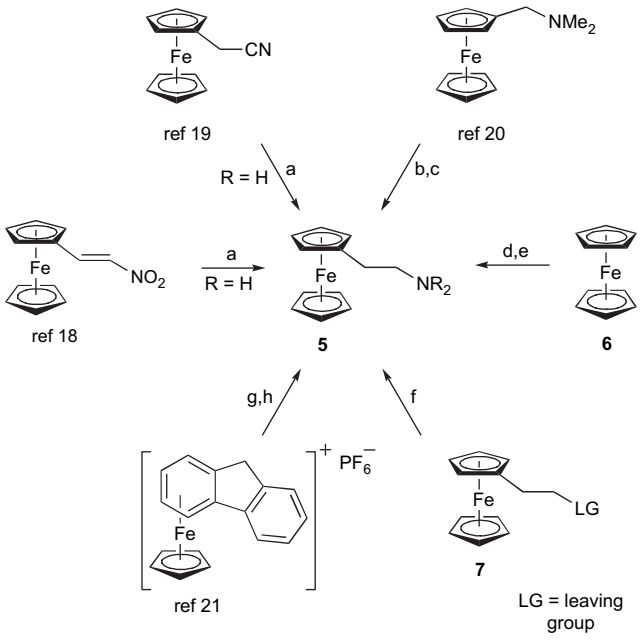


Scheme 2. Proposed amidolithiation route to 2-aminoethyl-substituted ferrocenes.

Keywords: Amidolithiation; Vinylferrocene; Regioselective addition; Lithium amides.
* Corresponding author. Tel.: +44 121 414 3524; fax: +44 121 414 4403; e-mail addresses: diane.m.coe@gsk.com; l.r.cox@bham.ac.uk

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.078

Ferrocenes **5**, containing a single 2-aminoethyl side-chain, have to-date been accessed in a number of ways.[16–21] Of the various approaches, which are summarised in Scheme 3, nucleophilic substitution methods provide the most commonly employed route to this class of molecule. Thus direct monolithiation of ferrocene **6**, followed by reaction with a 2-chloroethylamino compound, provides one route to the desired product **5**.[16] Alternatively, substitution of a leaving group contained in a side-chain of ferrocene derivative **7**, with a nitrogen nucleophile, provides a second approach.[17] Unfortunately both of these strategies have drawbacks, with competing elimination side-reactions being a particular problem.[22] The synthesis of the 2-chloroethylamino substitution precursors required for these approaches is also not always particularly straightforward.[23] Moreover, these electrophiles have limited shelf-lives and are potentially hazardous owing to their structural similarity to various mustards. We now report that the reaction of lithium amides with vinylferrocene provides a new and particularly simple approach to these compounds, which circumvents many of the drawbacks associated with existing approaches to 2-aminoethyl-substituted ferrocenes.

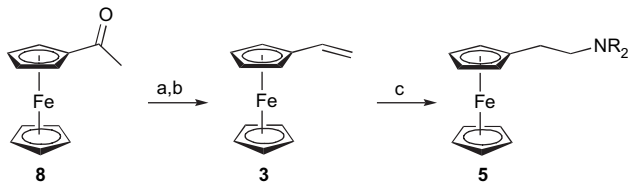


Scheme 3. Reagents and conditions: (a) $LiAlH_4$ (R=H); (b) MeI; (c) KNH_2, NH_3(l); (d) ^{n}BuLi; (e) $ClCH_2CH_2NR_2$; (f) *N*-nucleophile; (g) KO^{t}Bu; (h) $Na^+[CpCH_2CH_2NR_2]^-$.

2. Results and discussion

Vinylferrocene **3** was first prepared on a large scale as outlined in Scheme 4; thus reduction of acetylferrocene **8** with $NaBH_4$ provided the corresponding alcohol in quantitative yield, from which vinylferrocene **5** was readily obtained by dehydration.[24]

Reaction of **3** with equimolar quantities of lithium morpholinide in THF at room temperature was very slow, although clean, affording only the desired addition product **5a**, albeit with poor conversion according to GC analysis of the reaction mixture after 8 h (entry 1, Table 1). The product,



Scheme 4. Reagents and conditions: (a) $NaBH_4$, EtOH, 13 h, quant.; (b) $CuSO_4$, hydroquinone, Δ, toluene, 83%; (c) $LiNR_2$, THF, Δ (see Table 2).

however, was readily separated from the very non-polar starting material, which accounted for the remaining mass balance. Increasing the reaction temperature to 75 °C and using 2 equiv of lithium amide led to a significant improvement in the rate of reaction: 42% conversion to the amine **5a** was now observed after 8 h as determined by GC analysis (entry 2, Table 1). The reaction was again highly chemoselective, with starting materials being the only other products observed by GC. We next investigated the effect of various additives on the reaction as these are well known to affect the aggregation state of lithium amides, and therefore their reactivity.[25] In our case, the inclusion of 1 equiv of TMEDA per equivalent of lithium amide led to a significant improvement in the reaction, with quantitative conversion to the addition product now being observed after 8 h at reflux (entry 3, Table 1). Interestingly, the use of HMPA as an additive completely shut down the reaction (entry 4, Table 1). These results, in particular the elevated reaction temperatures required to effect this transformation, clearly demonstrate the greatly reduced electrophilicity of the pendant olefin in vinylferrocene compared with that in styrene. This was further highlighted when no reaction at all was observed when vinylferrocene was treated with morpholine in the presence of sub-stoichiometric quantities (10 mol %) of ^{n}BuLi at reflux, conditions that have been successfully used in the net hydroamination of styrene.[3f,26,27]

In an effort to optimise the method further, the amidolithiation was carried out in a range of solvent mixtures.[28] A solution of equimolar quantities of the lithium amide derived from *N*-methyl piperazine and ^{n}BuLi, and TMEDA, in THF,

Table 1. Optimisation of the amidolithiation of vinylferrocene **3**[a]

Entry	Starting amine	Solvent	Additive[b]	Temp (°C)	% Conversion after 8 h[c]
1	Morpholine	THF	—	rt	10
2	Morpholine	THF	—	Reflux	42
3	Morpholine	THF	TMEDA	Reflux	100
4	Morpholine	THF	HMPA	Reflux	0[d]
5	*N*-Methyl piperazine	THF	TMEDA	Reflux	73
6	*N*-Methyl piperazine	THF/Et_2O 1:2	TMEDA	Reflux	70
7	*N*-Methyl piperazine	THF/toluene 1:2	TMEDA	Reflux	71
8	*N*-Methyl piperazine	THF/hexane 1:2	TMEDA	Reflux	46
9	*N*-Methyl piperazine	THF/DMPU 4:1	TMEDA	Reflux	0[d]

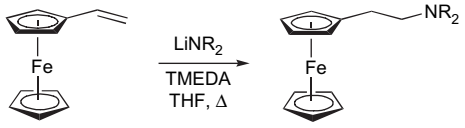
[a] Lithium amide (2 equiv prepared from equimolar quantities of ^{n}BuLi and the corresponding amine) employed.
[b] TMEDA: 2 equiv employed.
[c] % Conversion calculated by GC.
[d] Starting material was recovered.

was added to vinylferrocene **3** in a range of other solvents (entries 5–9, Table 1). The reaction mixtures were heated under reflux for 8 h and then worked-up and their relative progress assessed by GC. The results collected in Table 1 show that the reaction tolerates a range of other co-solvents with ether and toluene providing comparable results to our original conditions employing just THF. The amidolithiation fared less well when hexane was employed as a co-solvent, whilst inclusion of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) had a similar effect to the use of HMPA, and completely shut down the reaction.

With an optimised reaction protocol in hand, the scope of the reaction was investigated using a range of lithium amides. The results are summarised in Table 2. Lithium amides derived from cyclic secondary amines (entries 1–8) proved to be the most effective in terms of both reaction rate and isolated yield of product, with particularly good yields being obtained for five- and six-ring systems (entries 1–6). Reaction with the less nucleophilic, seven- and eight-ring systems was more difficult, although in these cases, the use of a larger excess of the Li amide allowed the desired products to be obtained in good yield (entries 7 and 8). Interestingly in these cases, we also identified two by-products from the reaction, namely ethylferrocene **9** and enamines **10** (Fig. 1). We propose that ethylferrocene **9**, which we also recently observed in related work involving the reaction of lithium amides with spiro[2,4]hepta-4,6-diene in the presence of $FeCl_2$,[29] results from competing reduction of the olefin through a single-electron-transfer process involving the lithium amide. The enamine products **10** presumably arise from the lithium amide behaving as a base and reacting with the THF solvent to provide butanal, which can then condense with the secondary amine to provide **10**. Whilst the use of toluene or ether in place of THF suppressed this latter side-reaction, these solvents led to no improvement in the yield of the desired product: in the case of Et_2O, the lower reaction temperature greatly reduced the rate of reaction, and when toluene was employed, reduction of the starting material to ethylferrocene predominated.

The reaction of piperazine with 2 equiv of ^{n}BuLi and TMEDA generated the corresponding bis-lithiated amide, which, when heated with an equimolar quantity of vinylferrocene **3**, provided the two possible addition products **5b** and **11** in 36% and 21% yields, respectively. Interestingly it was found that the TMEDA additive could be removed from this reaction without having any deleterious effect on the yield or reaction rate.[30] Changing the relative stoichiometry of the reacting partners allowed more selective access to these two addition products: reacting 1 equiv of the lithium amide with 2 equiv of vinylferrocene **3** provided the double addition product **11** in 74% yield (Scheme 5), whilst employing 4 equiv of lithium amide relative to vinylferrocene **3** enabled the mono-addition product **5b** to be isolated in 85% yield (entry 3, Table 2).

Table 2. Synthesis of (2-aminoethyl)ferrocenes by the amidolithiation of vinylferrocene **3**



3 **5a-i**

Entry	Starting amine	Time (h)	Equiv of Li amide	Product	Isolated yield (%)
1	Morpholine	8	2	**5a**	87
2	Piperazine	12	1	**5b**	36[a]
3	Piperazine	12	4[b]	**5b**	85
4	*N*-Methyl piperazine	12	2	**5c**	90
5	Piperidine	12	2	**5d**	92
6	Pyrrolidine	12	2	**5e**	88
7	Hexamethyleneimine	5	4	**5f**	73
8	Heptamethyleneimine	3	4	**5g**	40
9	Et_2NH	24	4	**5h**	49
10	$(C_6H_{13})_2NH$	31	4	**5i**	43
11	$^iPr_2NH$	48	4		0
12	$BnNH_2$	48	4		0

[a] Double addition product **11** (21%) was also isolated.
[b] TMEDA was not used in this reaction.

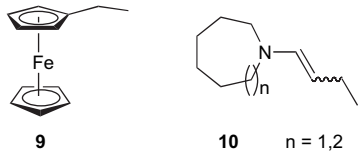
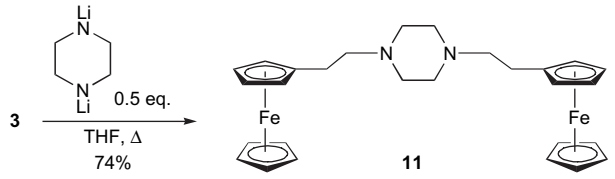


Figure 1. By-products identified from the reaction of vinylferrocene in THF with seven- and eight-ring lithium amides.



Scheme 5. Using an excess of vinylferrocene provided bis-ferrocene adduct **11**.

As expected, lithium amides derived from acyclic secondary amines (entries 9–11, Table 2) proved to be less reactive, which is in accord with their reduced nucleophilicity on steric grounds; thus lithium diethylamide and lithium dihexylamide reacted rather slowly, although the desired addition products were still obtained in reasonable yields, especially when a 4-fold excess of the lithium amide was employed. Not surprisingly, lithium diisopropylamide provided no addition product and the starting vinylferrocene was recovered intact. Lithium amides derived from primary amines are generally poorer nucleophiles for the amidolithiation of styrene; thus we were not surprised to observe no reaction between the lithium amide of benzylamine and vinylferrocene (entry 12, Table 2).

At the outset of the project we had hoped that the use of chiral additives, such as (−)-sparteine, might permit the enantioselective amidolithiation of vinylferrocene. Trapping the lithiated intermediate **4** (Scheme 2) with a range of electrophiles would then provide an entry into enantiomerically enriched amino-ferrocene derivatives, which find application as ligands for asymmetric synthesis. Unfortunately, all attempts to trap the presumed lithiated intermediate **4** with D^+ or Me_3SiCl, have so far proved fruitless.

3. Conclusion

We have shown that vinylferrocene behaves, albeit under more forcing conditions, like styrene in its reaction with lithium amides, to provide the corresponding (2-aminoethyl)ferrocene products. Compared with other multi-step routes to these compounds, this amidolithiation approach is characterised by its operational simplicity and high product yields, especially with cyclic secondary amines, and now provides a useful approach to incorporating this redox-active β-phenethylamine substitute into biologically active small organic molecules.

4. Experimental

4.1. General

Melting points were determined using open capillaries on a Gallenkamp MDP350 melting-point apparatus and are uncorrected. Elemental analyses were recorded on a Carlo Erba EA1110 simultaneous CHNS analyser and performed by The University of Birmingham microanalytical services. Infra-red spectra were recorded either neat, as thin films, or as a Nujol mull between sodium chloride plates, on a Perkin Elmer FT-IR PARAGON 1000 spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ at ambient temperature on a Bruker AC-300 (300 MHz) or Bruker AMX 400 (400 MHz) spectrometer. The term 'stack' is used to describe a region where resonances arising from non-equivalent nuclei are coincident, whilst 'multiplet', m, is used to describe a region where a resonance arises from a single nucleus (or equivalent nuclei) but where coupling constants cannot be assigned. Residual protic solvent $CHCl_3$ (δ_H=7.26 ppm) was used as an internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on a Bruker AC-300 (75 MHz), Bruker AV-300 (75 MHz), or Bruker AMX 400 (100 MHz) spectrometer. The central resonance of $CDCl_3$ (δ_C=77.0 ppm) was used as an internal reference. EI (electron impact) and GC–MS mass spectra were recorded on a VG Prospec mass spectrometer, and TOF ES$^+$ mass spectra were recorded on a Micromass LCT spectrometer, and are reported as (*m*/*z* (%)). HRMS were recorded on a Micromass LCT spectrometer, using a lock mass incorporated into the mobile phase. GC spectra were recorded on a CARLO ERBA GC8000 SERIES, equipped with an AS800 autosampler.

All reagents were obtained from commercial sources and used without further purification unless stated otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. Diethylamine and dihexylamine were distilled from KOH and stored over KOH. Diisopropylamine was distilled from NaOH and stored over 4 Å molecular sieves. Pyrrolidine and piperidine were distilled from BaO. Morpholine was distilled from KOH. All solutions are aqueous and saturated, unless stated otherwise.

All reactions were conducted in oven-dried (140 °C) or flame-dried glassware under a N_2 atmosphere, and at ambient temperature (19–25 °C) unless otherwise stated, with magnetic stirring. Volumes of 1 mL or less were measured and dispensed with Hamilton gastight syringes. Flash column chromatography was carried out using Fluorochem 60 (40–63 μm mesh) silica gel. Analytical thin layer chromatography (TLC) was performed on Merck or Whatman 60A 0.25 mm pre-coated glass-backed plates and visualised by UV (254 nm), potassium manganate(VII) solution and ammonium molybdate(IV)/cerium(IV) sulfate solution. Solutions were concentrated under reduced pressure at 50–500 mbar. Residual solvent was removed under high vacuum (1 mbar).

4.2. General procedure for the formation of (2-aminoethyl)ferrocenes 5a–i

^{n}BuLi (340 μL of a 2.23 M solution in hexane, 0.76 mmol: see Table 2 for the relative quantities of lithium amide and vinylferrocene employed) was added to a solution of the amine (0.76 mmol) and TMEDA (115 μL, 0.76 mmol) in THF (2 mL) at 0 °C. The solution was stirred at rt for 15 min and then transferred via cannula to a solution of vinylferrocene **3** (80 mg, 0.38 mmol) in THF (1.5 mL) at rt. The resulting brown-orange solution was heated at reflux and the progress of the reaction monitored by TLC or GC. Upon consumption of all starting material, the reaction mixture was cooled to rt, and Et_2O (15 mL) and water (15 mL) were added. The mixture was basified to pH 9 with NaOH solution (2 M) and the two phases were separated. The aqueous phase was extracted with Et_2O (2×10 mL). The combined organic fractions were washed with brine (20 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide an orange oil, which was purified by flash column chromatography.

4.2.1. [2-(Morpholin-4′-yl)ethyl]ferrocene 5a. Aminoferrocene **5a** was prepared from morpholine (66 μL, 0.76 mmol), TMEDA (115 μL, 0.76 mmol), ^{n}BuLi (340 μL of a 2.23 M solution in hexane, 0.76 mmol) and vinylferrocene **3** (80 mg, 0.38 mmol) according to the general procedure. After 8 h, work-up and purification by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) afforded amine **5a** as a yellow powder (98 mg, 87%): mp 74–76 °C; R_f=0.62 (94% EtOAc, 5% EtOH, 1% Et_3N); (found: C, 64.2; H, 7.0; N, 4.6. $C_{16}H_{21}FeNO$ requires C, 64.2; H, 7.1; N, 4.7%); ν_{max} (film)/cm^{-1} 3092w, 2952m, 2853m, 2807m, 1458m, 1447m, 1356w, 1306w, 1276w, 1258w, 1118s, 1106s, 1070w, 1038m, 1004m, 913w, 868m, 818m; δ_H (300 MHz) 2.43–2.60 (8H, stack, CpCH_2CH_2N(CH_2CH$_2$)$_2$O), 3.72–3.76 (4H, m, N(CH$_2$CH_2)$_2$O), 4.01–4.17 (9H, stack, Cp*H*); δ_C (75 MHz) 26.8 (CH$_2$, Cp*C*H$_2$), 53.8 (CH$_2$, N(*C*H$_2$CH$_2$)$_2$O), 60.2 (CH$_2$, CpCH$_2$*C*H$_2$N), 67.0 (CH$_2$, N(CH$_2$*C*H$_2$)$_2$O), 67.2 (CH, Cp$_{sub}$), 68.1 (CH, Cp$_{sub}$), 68.5 (CH, Cp$_{unsub}$), 86.5 (quat. C, Cp); *m*/*z* (EI) 299 ([M]$^+$, 33%), 199 (10, [M−CH$_2$N(CH$_2$CH$_2$)O]$^+$), 121 (15, [CpFe]$^+$), 100 (100, [O(CH$_2$CH$_2$)$_2$NCH$_2$]$^+$), 56 (12, [Fe]$^+$).

4.2.2. [2-(Piperazin-1′-yl)ethyl]ferrocene 5b. Aminoferrocene **5b** was prepared from piperazine (88 mg, 1.02 mmol), ^{n}BuLi (940 μL of a 2.17 M solution in hexane, 2.04 mmol) and vinylferrocene **3** (54 mg, 0.26 mmol) according to the general procedure. After 12 h, work-up and purification by flash column chromatography (99% EtOH, 1% Et_3N) afforded amine **5b** as an orange oil

(64 mg, 85%): R_f=0.09 (1% Et_3N in EtOH); ν_{max} (film)/cm^{-1} 3440s br, 3093s, 2928s, 2814s, 1668s, 1564m, 1464s, 1410m, 1266s, 1105s, 1000s, 821s, 736s; δ_H (300 MHz) 2.12 (1H, br s, N*H*), 2.42–2.53 (8H, stack), 2.91 (4H, t, *J* 4.8, N(*C*H_2C*H*$_2$)$_2$NH), 4.03–4.05 (2H, m, 2×Cp$_{sub}$*H*), 4.05–4.08 (2H, m, 2×Cp$_{sub}$*H*), 4.09 (5H, s, Cp$_{unsub}$*H*); δ_C (75 MHz) 26.8 (CH_2, Cp*C*H_2), 45.4 (CH_2, *C*H_2N), 53.6 (CH_2, *C*H_2N), 60.2 (CH_2, *C*H_2N), 67.2 (CH, Cp$_{sub}$), 68.1 (CH, Cp$_{sub}$), 68.5 (CH, Cp$_{unsub}$), 86.5 (quat. C, Cp); *m*/*z* (TOF ES$^+$) 299 ([M+H]$^+$, 100%), 213 (14); *m*/*z* 299.1218 ([M+H]$^+$. $C_{16}H_{23}FeN_2$ requires 299.1211).

4.2.3. [2-(*N*-Methylpiperazin-1′-yl)ethyl]ferrocene 5c. Amino-ferrocene **5c** was prepared from *N*-methyl piperazine (73 μL, 0.66 mmol), TMEDA (100 μL, 0.66 mmol), ^{n}BuLi (300 μL of a 2.23 M solution in hexanes, 0.66 mmol) and vinylferrocene **3** (70 mg, 0.33 mmol) according to the general procedure. After 12 h, work-up and purification by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) afforded amine **5c** as orange needles (93 mg, 90%): mp 66–68 °C; R_f=0.17 (94% EtOAc, 5% EtOH, 1% Et_3N); (found: C, 65.4; H, 7.9; N, 8.8. $C_{17}H_{24}FeN_2$ requires C, 65.4; H, 7.8; N, 9.0%); ν_{max} (film)/cm^{-1} 3094m, 3044w, 2939s, 2878m, 2797s, 2683w, 1639w, 1460s, 1450m, 1412w, 1372m, 1356w, 1336w, 1284s, 1181w, 1164s, 1146m, 1121m, 1105m, 1087w, 1039m, 1011m, 924w, 820s, 736s; δ_H (300 MHz) 2.27 (3H, s, NC*H*$_3$), 2.32–2.71 (12H, stack, CpC*H*$_2$C*H*$_2$N(C*H*$_2$C*H*$_2$)$_2$N), 3.94–4.10 (9H, stack, Cp*H*); δ_C (75 MHz) 27.0 (CH_2, Cp*C*H_2), 45.9 (CH_3, N*C*H$_3$), 53.0 (CH_2, N(*C*H_2CH$_2$)$_2$NCH$_3$), 55.0 (CH_2, N(CH$_2$*C*H$_2$)$_2$NCH$_3$), 59.7 (CH_2, CpCH$_2$*C*H$_2$N), 67.1 (CH, Cp$_{sub}$), 68.0 (CH, Cp$_{sub}$), 68.4 (CH, Cp$_{unsub}$), 86.5 (quat. C, Cp); *m*/*z* (TOF ES$^+$) 313.1 ([M+H]$^+$, 100%); *m*/*z* 313.1373 ([M+H]$^+$. $C_{17}H_{25}FeN_2$ requires 313.1367).

4.2.4. [2-(Piperidin-1′-yl)ethyl]ferrocene 5d. Amino-ferrocene **5d** was prepared from piperidine (65 μL, 0.66 mmol), TMEDA (100 μL, 0.66 mmol), ^{n}BuLi (300 μL of a 2.23 M solution in hexanes, 0.66 mmol) and vinylferrocene **3** (70 mg, 0.33 mmol) according to the general procedure. After 12 h, work-up and purification by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) afforded amine **5d** as an orange oil (90 mg, 92%): R_f=0.24 (94% EtOAc, 5% EtOH, 1% Et_3N); ν_{max} (film)/cm^{-1} 3093m, 2933s, 2853s, 2798s, 2760s, 1643w, 1468m, 1442m, 1411w, 1375m, 1350m, 1308m, 1292w, 1262m, 1226w, 1155m, 1120s, 1106s, 1041s, 1023m, 1000s, 927w, 910m, 863m, 817s, 733s; δ_H (300 MHz) 1.36–1.71 (6H, stack, N(CH$_2$C*H*$_2$)$_2$C*H*$_2$), 2.31–2.61 (8H, stack, CpC*H*$_2$C*H*$_2$N(C*H*$_2$CH$_2$)$_2$CH$_2$), 3.93–4.15 (9H, stack, Cp*H*); δ_C (75 MHz) 24.4 (CH_2, N(CH$_2$CH$_2$)$_2$*C*H$_2$), 25.9 (CH_2, N(CH$_2$*C*H$_2$)$_2$CH$_2$), 27.0 (CH_2, Cp*C*H_2), 54.5 (CH_2, N*C*H$_2$), 60.6 (CH_2, N*C*H$_2$), 67.1 (CH, Cp$_{sub}$), 68.0 (CH, Cp$_{sub}$), 68.4 (CH, Cp$_{unsub}$), 86.9 (quat. C, Cp); *m*/*z* (TOF ES$^+$) 298.2 ([M+H]$^+$, 100%); *m*/*z* 298.1253 ([M+H]$^+$. $C_{17}H_{24}FeN$ requires 298.1258). Data were in agreement with those reported in the literature.[21]

4.2.5. [2-(Pyrrolidin-1′-yl)ethyl]ferrocene 5e. Amino-ferrocene **5e** was prepared from pyrrolidine (55 μL, 0.66 mmol), TMEDA (100 μL, 0.66 mmol), ^{n}BuLi (300 μL of a 2.23 M solution in hexane, 0.66 mmol) and vinylferrocene **3** (70 mg, 0.33 mmol) according to the general procedure. After 12 h, work-up and purification by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) afforded amine **5e** as orange needles (82 mg, 88%): mp 64–66 °C; R_f=0.16 (94% EtOAc, 5% EtOH, 1% Et_3N); (found: C, 68.0; H, 7.5; N, 4.8. $C_{16}H_{21}FeN$ requires C, 67.9; H, 7.5; N, 5.0%); ν_{max} (film)/cm^{-1} 3094m, 3047w, 2963s, 2877m, 2788s, 1640w, 1461m, 1412w, 1382w, 1351m, 1331w, 1266s, 1205w, 1144m, 1117m, 1106s, 1040m, 1022w, 1001m, 882w, 819s, 738s, 703m; δ_H (300 MHz) 1.72–1.86 (4H, m, N(CH$_2$C*H*$_2$)$_2$), 2.46–2.66 (8H, stack, CpC*H*$_2$C*H*$_2$N(C*H*$_2$CH$_2$)$_2$), 3.99–4.14 (9H, stack, Cp*H*); δ_C (75 MHz) 23.4 (CH_2, N(CH$_2$*C*H$_2$)$_2$), 29.2 (CH_2, Cp*C*H_2), 54.2 (CH_2, N(*C*H_2CH$_2$)$_2$), 57.5 (CH_2, CpCH$_2$*C*H$_2$N), 67.1 (CH, Cp$_{sub}$), 68.0 (CH, Cp$_{sub}$), 68.4 (CH, Cp$_{unsub}$), 86.8 (quat. C, Cp); *m*/*z* (TOF ES$^+$) 284.1 ([M+H]$^+$, 100%); *m*/*z* 284.1108 ([M+H]$^+$. $C_{16}H_{22}FeN$ requires 284.1102).

4.2.6. [2-(Hexamethyleneimin-1′-yl)ethyl]ferrocene 5f. Amino-ferrocene **5f** was prepared from hexamethyleneimine (165 μL, 1.45 mmol), TMEDA (200 μL, 1.32 mmol), ^{n}BuLi (560 μL of a 2.36 M solution in hexane, 1.32 mmol) and vinylferrocene **3** (70 mg, 0.33 mmol) according to the general procedure. After 5 h, work-up and purification by column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) afforded amine **5f** as an orange oil (75 mg, 73%): R_f=0.14 (94% EtOAc, 5% EtOH, 1% Et_3N); ν_{max} (film)/cm^{-1} 3093m, 2925s, 2852s, 2811s, 1638w, 1469m, 1451m, 1356m, 1126m, 1106s, 1040w, 1021w, 1001m, 816s; δ_H (300 MHz) 1.55–1.72 (8H, stack, N(CH$_2$C*H*$_2$C*H*$_2$)$_2$), 2.45–2.55 (2H, m), 2.61–2.72 (6H, stack), 4.01–4.08 (4H, stack, Cp$_{sub}$*H*), 4.09 (5H, br s, Cp$_{unsub}$*H*); δ_C (75 MHz) 27.0 (CH_2, N(CH$_2$CH$_2$*C*H$_2$)$_2$), 27.4 (CH_2, Cp*C*H_2), 28.0 (CH_2, N(CH$_2$CH$_2$CH$_2$)$_2$), 55.5 (CH_2, N(*C*H_2CH$_2$CH$_2$)$_2$), 59.6 (CH_2, CpCH$_2$*C*H$_2$N), 67.1 (CH, Cp$_{sub}$), 68.1 (CH, Cp$_{sub}$), 68.5 (CH, Cp$_{unsub}$), 87.0 (quat. C, Cp); *m*/*z* (TOF ES$^+$) 312.1 ([M+H]$^+$, 100%); *m*/*z* 312.1421 ([M+H]$^+$. $C_{18}H_{26}FeN$ requires 312.1415).

4.2.7. [2-(Heptamethyleneimin-1′-yl)ethyl]ferrocene 5g. Amino-ferrocene **5g** was prepared from heptamethyleneimine (185 μL, 1.45 mmol), TMEDA (200 μL, 1.32 mmol), ^{n}BuLi (560 μL of a 2.36 M solution in hexane, 1.32 mmol) and vinylferrocene **3** (70 mg, 0.33 mmol) according to the general procedure. After 3 h, work-up and purification by column chromatography (80% hexane, 19% EtOAc, 1% Et_3N) afforded amine **5g** as a viscous yellow oil (43 mg, 40%): R_f=0.15 (80% hexane, 19% EtOAc, 1% Et_3N); ν_{max} (film)/cm^{-1} 3094w, 2919s, 2851s, 2804m, 1638w, 1474m, 1452m, 1358m, 1126m, 1106s, 1040w, 1022w, 1000m, 817s; δ_H (300 MHz) 1.54–1.64 (10H, stack, N(CH$_2$C*H*$_2$C*H*$_2$)$_2$C*H*$_2$), 2.44–2.52 (2H, m), 2.56–2.67 (6H, stack), 4.02–4.08 (4H, stack, Cp$_{sub}$*H*), 4.10 (5H, br s, Cp$_{unsub}$*H*); δ_C (75 MHz) 26.3 (CH_2, N(CH$_2$CH$_2$*C*H$_2$)$_2$CH$_2$), 27.4 (CH_2), 28.1 (CH_2, N(CH$_2$*C*H$_2$CH$_2$)$_2$CH$_2$), 28.2 (CH_2), 54.0 (CH_2, N(*C*H_2CH$_2$CH$_2$)$_2$CH$_2$), 60.3 (CH_2, CpCH$_2$*C*H$_2$N), 67.0 (CH, Cp$_{sub}$), 68.2 (CH, Cp$_{sub}$), 68.4 (CH, Cp$_{unsub}$), 87.4 (quat. C, Cp); *m*/*z* (TOF ES$^+$) 326.1 ([M+H]$^+$, 100%); *m*/*z* 326.1579 ([M+H]$^+$. $C_{19}H_{28}FeN$ requires 326.1571).

4.2.8. (2-Diethylaminoethyl)ferrocene 5h. Amino-ferrocene **5h** was prepared from $HNEt_2$ (135 μL, 1.32 mmol),

TMEDA (200 μL, 1.32 mmol), ^{n}BuLi (590 μL of a 2.23 M solution in hexanes, 1.32 mmol) and vinylferrocene **3** (70 mg, 0.33 mmol) according to the general procedure. After 24 h, work-up and purification by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) afforded, in order of elution, starting material **3** as a red powder (21 mg, 33%), and then amine **5h** as an orange oil (46 mg, 49%): R_f=0.22 (94% EtOAc, 5% EtOH, 1% Et_3N); ν_{max} (film)/cm^{-1} 3095m, 2969s, 2932s, 2803m, 1640w, 1470m, 1382m, 1266w, 1205w, 1106m, 1069w, 1040w, 1001w, 911w, 818m, 734m; δ_H (300 MHz) 1.06 (6H, t, *J* 7.2, $N(CH_2CH_3)_2$), 2.44–2.67 (8H, stack, $CpCH_2CH_2N(CH_2CH_3)_2$), 4.02–4.12 (9H, stack, Cp*H*); δ_C (75 MHz) 11.8 (CH_3, $N(CH_2CH_3)_2$), 26.9 (CH_2, $CpCH_2$), 46.9 (CH_2, $N(CH_2CH_3)_2$), 54.1 (CH_2, $CpCH_2CH_2N$), 67.2 (CH, Cp_{sub}), 68.1 (CH, Cp_{sub}), 68.5 (CH, Cp_{unsub}), 87.0 (quat. C, Cp); *m/z* (TOF ES$^+$) 286.1 ([M+H]$^+$, 100%); *m/z* 286.1268 ([M+H]$^+$. $C_{16}H_{24}FeN$ requires 286.1258).

4.2.9. (2-Dihexylaminoethyl)ferrocene 5i. Amino-ferrocene **5i** was prepared from dihexylamine (340 μL, 1.45 mmol), TMEDA (200 μL, 1.32 mmol), ^{n}BuLi (560 μL of a 2.36 M solution in hexane, 1.32 mmol) and vinylferrocene **3** (70 mg, 0.33 mmol) according to the general procedure. After 31 h, work-up and purification by column chromatography (90% hexane, 9% EtOAc, 1% Et_3N) afforded amine **5i** as an orange oil (56 mg, 43%): R_f=0.18 (90% hexane, 9% EtOAc, 1% Et_3N); (found: C, 72.4; H, 9.9; N, 3.5. $C_{24}H_{39}FeN$ requires C, 72.5; H, 9.9; N, 3.5%); ν_{max} (film)/cm^{-1} 3095w, 2928s, 2857s, 2798s, 1634w, 1466s, 1378m, 1106s, 1040w, 1022w, 1001m, 816s; δ_H (300 MHz) 0.87 (6H, t, *J* 6.6, 2×CH_3), 1.21–1.32 (12H, stack, 2×$CH_2CH_2CH_2CH_2CH_3$), 1.36–1.47 (4H, m, 2×NCH_2CH_2), 2.38–2.46 (6H, stack), 2.55–2.63 (2H, m), 4.01–4.05 (4H, stack, $Cp_{sub}H$), 4.08 (5H, br s, $Cp_{unsub}H$); δ_C (75 MHz) 14.1 (CH_3), 22.7 (CH_2, CH_2CH_3), 26.9 (CH_2, $CpCH_2$), 27.2 (CH_2, $CH_2CH_2CH_3$), 27.3 (CH_2, $CH_2(CH_2)_2CH_3$), 31.8 (CH_2, $CH_2(CH_2)_3CH_3$), 54.2 (CH_2, $N(CH_2(CH_2)_4CH_3)_2$), 55.3 (CH_2, $CpCH_2CH_2N$), 67.1 (CH, Cp_{sub}), 68.0 (CH, Cp_{sub}), 68.4 (CH, Cp_{unsub}), 87.2 (quat. C, Cp); *m/z* (TOF ES$^+$) 398.2 ([M+H]$^+$, 100%); *m/z* 398.2512 ([M+H]$^+$. $C_{24}H_{40}FeN$ requires 398.2510).

4.2.10. *N,N′*-Di-(2-ferrocenylethyl)piperazine 11. Bis-alkylated piperazine **11** was prepared from piperazine (22 mg, 0.26 mmol), ^{n}BuLi (240 μL of a 2.17 M solution in hexane, 0.52 mmol) and vinylferrocene **3** (110 mg, 0.52 mmol) according to the general procedure. After 18 h, work-up and purification by column chromatography (60% hexane, 39% EtOAc, 1% Et_3N) afforded bis-alkylated piperazine **11** as a pale orange solid (97 mg, 74%): mp 138–140 °C (decomp.); R_f=0.12 (60% EtOAc, 39% hexane, 1% Et_3N); ν_{max} (film)/cm^{-1} 3094w, 3054w, 2961m, 2809s, 2769m, 1466w, 1423w, 1266vs, 1158m, 1129w, 1104w, 1041w, 741vs; δ_H (300 MHz) 2.42–2.64 (16H, stack, $CpCH_2CH_2N(CH_2CH_2)_2NCH_2CH_2Cp$), 4.00–4.10 (18H stack, [including 4.10 (10H, s, 2×$Cp_{unsub}H$)], Cp*H*); δ_C (75 MHz) 27.0 (CH_2, $CpCH_2$), 53.2 (CH_2, $N(CH_2CH_2)_2N$), 59.8 (CH_2, $CpCH_2CH_2$), 67.2 (CH, Cp_{sub}), 68.1 (CH, Cp_{sub}), 68.5 (CH, Cp_{unsub}), 86.6 (quat. C, Cp); *m/z* (TOF ES$^+$) 511 ([M+H]$^+$, 100%); *m/z* 511.1498 ([M+H]$^+$. $C_{28}H_{35}N_2Fe_2$ requires 511.1499).

Acknowledgements

We thank the EPSRC and GlaxoSmithKline (studentship to K.M.J.), the Leverhulme Trust (F/00 094/T) and EPSRC (EP/C532260/1) (SMES) and der Studienstiftung des deutschen Volkes (R.M.G.) for funding.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.078.

References and notes

1. Perlmutter, P. *Conjugate addition reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series; Pergamon: Oxford, 1992.
2. Wei, X.; Johnson, P.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1109.
3. (a) van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B.; Fernandes, M. A. *Tetrahedron Lett.* **2004**, *45*, 9561; (b) Kumar, K.; Michalik, D.; Castro, I. G.; Tillack, A.; Zapf, A.; Arlt, M.; Heinrich, T.; Böttcher, H.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 746; (c) Seijas, J. A.; Vázquez-Tato, M. P.; Martínez, M. M. *Synlett* **2001**, 875; (d) Garcia, A.; Domínguez, D. *Tetrahedron Lett.* **2001**, *42*, 5219; (e) Seijas, J. A.; Vázquez-Tato, M. P.; Entenza, C.; Martínez, M. M.; Ónega, M. G.; Veiga, S. *Tetrahedron Lett.* **1998**, *39*, 5073; (f) Beller, M.; Breindl, C. *Tetrahedron* **1998**, *54*, 6359; (g) Hamana, H.; Iwasaki, F.; Nagashima, H.; Hattori, K.; Hariwara, T.; Narita, T. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1109; (h) Schlott, R. J.; Falk, J. C.; Narducy, K. W. *J. Org. Chem.* **1972**, *37*, 4243.
4. *Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 13th ed.; O'Neil, M. J., Smith, A., Heckelman, P. E., Budavari, S., Eds.; Merck: Whitehouse Station, NJ, 2001.
5. For a selection of recent examples where the redox properties of ferrocene have been used in sensing and related applications, see: (a) Westwood, J.; Coles, S. J.; Collinson, S. R.; Gasser, G.; Green, S. J.; Hursthouse, M. B.; Light, M. E.; Tucker, J. H. R. *Organometallics* **2004**, *23*, 946; (b) Bernhardt, P. V.; Creevey, N. L. *Dalton Trans.* **2004**, 914; (c) Morita, T.; Kimura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8732; (d) Evans, A. J.; Matthews, S. E.; Cowley, A. R.; Beer, P. D. *Dalton Trans.* **2003**, 4644; (e) Bucher, C.; Devillers, C. H.; Moutet, J.-C.; Royal, G.; Saint-Aman, E. *Chem. Commun.* **2003**, 888; (f) Miyaji, H.; Collinson, S. R.; Prokes, I.; Tucker, J. H. R. *Chem. Commun.* **2003**, 64; (g) Beer, P. D.; Bernhardt, P. V. *J. Chem. Soc., Dalton Trans.* **2001**, 1428; (h) Li, C.; Medina, J. C.; Maguire, G. E. M.; Abel, E.; Atwood, J. L.; Gokel, G. W. *J. Am. Chem. Soc.* **1997**, *119*, 1609; (i) Fabbrizzi, L.; Licchelli, M.; Pallavicini, P.; Taglietti, A. *Inorg. Chem.* **1996**, *35*, 1733; (j) For a review on the use of ferrocene as an electrochemical reporter group in anion recognition chemistry, see: Beer, P. D.; Cadman, J. *Coord. Chem. Rev.* **2000**, *205*, 131.
6. This is readily achieved by either protonation or alkylation.
7. Ferrocene has been used to induce turn structures in oligopeptides: Barisic, L.; Dropucic, M.; Rapic, V.; Pritzkow, H.; Kirin, S. I.; Metzler-Nolte, N. *Chem. Commun.* **2004**, 2004.
8. For ferrocene compounds with anti-malarial activity, see: (a) Blackie, M. A. L.; Beagley, P.; Chibale, K.; Clarkson, C.; Moss, J. R.; Smith, P. J. *J. Organomet. Chem.* **2003**, *688*,

144; (b) Biot, C.; Delhaes, L.; Maciejewski, L. A.; Mortuaire, M.; Camus, D.; Dive, D.; Brocard, J. S. *Eur. J. Med. Chem.* **2000**, *35*, 707; (c) Biot, C.; Delhaes, L.; Abessolo, H.; Domarle, O.; Maciejewski, L. A.; Mortuaire, M.; Delcourt, P.; Deloron, P.; Camus, D.; Dive, D.; Brocard, J. S. *J. Organomet. Chem.* **1999**, *589*, 59.

9. Ferrocenes in nucleotide chemistry: (a) Beilstein, A. E.; Grinstaff, M. W. *J. Organomet. Chem.* **2001**, *637-639*, 398; (b) Yu, C. J.; Wan, Y.; Yowanto, H.; Li, J.; Tao, C.; James, M. D.; Tan, C. L.; Blackburn, G. F.; Meade, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 11155; (c) Georgopoulou, A. S.; Mingos, D. M. P.; White, A. J. P.; Williams, D. J.; Horrocks, B. R.; Houlton, A. *J. Chem. Soc., Dalton Trans.* **2000**, 2969.
10. For ferrocene compounds exhibiting anti-tumour activity, see: Köpf-Maier, P.; Köpf, H.; Neuse, E. W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 456; This property possibly arises through the ability of ferrocenium species to generate hydroxyl radicals which are commonly implicated in DNA damage: Osella, D.; Ferrali, M.; Zanello, P.; Laschi, F.; Fontani, M.; Nervi, C.; Cavigiolo, G. *Inorg. Chim. Acta* **2000**, *306*, 42.
11. Redox sensors for the commercially important flavoenzyme glucose oxidase: Forrow, N. J.; Sanghera, G. S.; Walters, S. J. *J. Chem. Soc., Dalton Trans.* **2002**, 3187.
12. Chiral ferrocenylamines have been used as precursors for preparing ferrocenes with NLO properties: Togni, A.; Rihs, G. *Organometallics* **1993**, *12*, 3368.
13. For an example of the use of ferrocenes in redox switching, see: Medina, J. C.; Gay, I.; Chen, Z.; Echegoyen, L.; Gokel, G. W. *J. Am. Chem. Soc.* **1991**, *113*, 365.
14. A wide range of ligands containing the aminomethylferrocene skeleton have been prepared, many in enantiomerically pure form. Some, such as MANDYPHOS and TANIAPHOS are particularly useful ligands for asymmetric hydrogenation and are now commercially available. For a selection of recent leading references: (a) Co, T. T.; Shim, S. C.; Cho, C. S.; Kim, T.-J.; Kang, S. O.; Han, W.-S.; Ko, J.; Kim, C.-K. *Organometallics* **2005**, *24*, 4824; (b) Steurer, M.; Tiedl, K.; Wang, Y.; Weissensteiner, W. *Chem. Commun.* **2005**, 4929; (c) Moyano, A.; Rosol, M.; Moreno, R. M.; López, C.; Maestro, M. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1865; (d) Hu, X.; Bai, C.; Dai, H.; Chen, H.; Zheng, Z. *J. Mol. Catal. A* **2004**, *218*, 107; (e) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862; (f) Anderson, J. C.; Blake, A. J.; Arnall-Culliford, J. C. *Org. Biomol. Chem.* **2003**, *1*, 3586; (g) Pastor, S. D.; Togni, A. *J. Am. Chem. Soc.* **1989**, *111*, 2333; (h) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.
15. Chiral ferrocenylamines have also been used as precursors to other chiral ligand systems. See for example: (a) Tu, T.; Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X.; Dong, X.-C.; Yu, Y.-H.; Sun, J. *Organometallics* **2003**, *22*, 1255; (b) Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915; (c) Burckhardt, U.; Hintermann, L.; Schnyder, A.; Togni, A. *Organometallics* **1995**, *14*, 5415.
16. Salmon, A.; Jutzi, P. *J. Organomet. Chem.* **2001**, *637–639*, 595.
17. (a) Bildstein, B.; Malaun, M.; Kopacka, H.; Ongania, K.-H.; Wurst, K. *J. Organomet. Chem.* **1998**, *552*, 45; (b) Tverdokhlebov, V. P.; Tselinskii, I. V.; Gidaspov, B. V.; Vasileva, N. Y. *J. Org. Chem. (USSR)* **1978**, *14*, 1222.
18. (a) Popp, F. D.; Moynahan, E. B. *J. Heterocycl. Chem.* **1974**, *11*, 267; (b) Loev, B.; Flores, M. *J. Org. Chem.* **1961**, *26*, 3595.
19. Chen, C.-H.; Postlethwaite, T. A.; Hutchison, J. E.; Samulski, E. T.; Murray, R. W. *J. Phys. Chem.* **1995**, *99*, 8804.
20. Hauser, C. R.; Lindsay, J. K.; Lednicer, D. *J. Org. Chem.* **1958**, *23*, 358.
21. Furtado, S. J.; Gott, A. L.; McGowan, P. C. *Dalton Trans.* **2004**, 436.
22. The formation of an aziridine or aziridinium ion through intramolecular substitution of the leaving group by the pendant amine is another competing pathway; however, depending on the stability and substitution pattern of the three-membered ring, this may not necessarily be a redundant pathway as it too may function as an electrophile.
23. We have found a reductive amination procedure using chloroacetaldehyde to be a particularly convenient approach to this type of electrophile and much better than nucleophilic mono-substitution approaches involving 1,2-dihaloethanes. Watanabe, T.; Kinoyama, I.; Kakefuda, A.; Okazaki, T.; Takizawa, K.; Hirano, S.; Shibata, H.; Yanagisawa, I. *Chem. Pharm. Bull.* **1997**, *45*, 996.
24. Wang, Y.-P.; Lin, T.-S.; Shyu, R.-S.; HwuYu Wang, J.-M.; Cheng, M.-C. *J. Organomet. Chem.* **1989**, *371*, 57.
25. Hilmersson, G.; Davidsson, O. *J. Org. Chem.* **1995**, *60*, 7660; Similar effects have been observed in organolithiums: Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. O.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201.
26. For recent examples of base-mediated hydroamination of olefins, see: (a) Ong, T. G.; O'Brien, J. S.; Korobkov, I.; Richeson, D. S. *Organometallics* **2006**, *25*, 4728; (b) Martinez, P. H.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221; (c) Trost, B. M.; Tang, W. P.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785; (d) Ates, A.; Quinet, C. *Eur. J. Org. Chem.* **2003**, 1623; (e) Hartung, C. G.; Breindl, C.; Tillack, A.; Beller, M. *Tetrahedron* **2000**, *56*, 5157.
27. For two recent reviews on base-mediated hydroamination of olefins, see: (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368; (b) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795.
28. Solvent also affects the aggregation state and reactivity of lithium amides [see Ref. 25].
29. Joly, K. M.; Kariuki, B. M.; Coe, D. M.; Cox, L. R. *Organometallics* **2005**, *24*, 358.
30. Presumably in this case the diamide substrate functions in the same way as the TMEDA additive.