One-Pot Synthesis of 1,1′-Bis(2-amino)ethyl-Substituted Ferrocenes from the Reaction of Spiro[2.4]hepta-4,6-diene with Lithium Amides: An Expedient Route into Functionalized Ferrocenophanes

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Received October 8, 2004

The reaction of lithium amides with spiro[2.4]hepta-4,6-diene **2** affords the corresponding (2-aminoethyl)CpLi cyclopropane-ring-opened product that can be trapped in situ with $FeCl_2$ to provide a direct route into 1,1′-bis-aminoethyl ferrocenes **3**. In addition to the desired bis-amine products, a number of interesting ferrocene byproducts have been identified. Their formation can be attributed to the associated Brønsted basicity of the lithium amide nucleophiles and their ability to participate in SET processes, opening-up alternative reaction pathways. The desired aminoethyl-substituted ferrocene products are derived primarily from direct nucleophilic cyclopropane ring-opening rather than via amidolithiation of vinylCp intermediates.

Introduction

Cyclopentadienyl (Cp) metal complexes possessing side-chains that incorporate additional groups capable of behaving as donors to the metal are attracting considerable interest.[1−4] If a ligand system is designed such that the pendant donor group binds only weakly to the metal center, it may be regarded as a temporary or hemilabile ligand,[5] capable of stabilizing reactive, coordinatively unsaturated intermediates by reversible coordination to the metal. This property is particularly important in metal-catalyzed processes, and not surprisingly, the application of metal complexes containing this class of ligand as catalysts in a range of reactions,[6] in particular olefin polymerization,[7] has received appreciable attention. Although a wide range of donor groups can be envisaged, the synthesis of metal complexes derived from Cp ligands containing appended nitrogen donors has been the most widely studied.[4b]

As a long-term goal of this project, we are interested in developing methods for preparing chiral, substituted Cp ligands that contain multiple donor groups (hard *and* soft groups based on N, O, S) in the side-chain substituent that can be derived from an amino acid. We wish to investigate their mode of coordination with a range of metals in different oxidation states[8] and their dynamic behavior in solution. Such ligands will form complexes in which the metal also provides a stereogenic center. Moreover, since the ligand will be enantiomerically pure, metal complexation will proceed through diastereoisomeric transition states that should differ in energy, allowing the potential for diastereocontrol and the isolation of products containing a single configuration at the metal center. Complexation of an amino acid to a Cp metal species usually results in the formation of a mixture of diastereoisomers, although in certain cases, excellent levels of stereocontrol can be obtained.[9] Even if diastereocontrol can be achieved, the configurational

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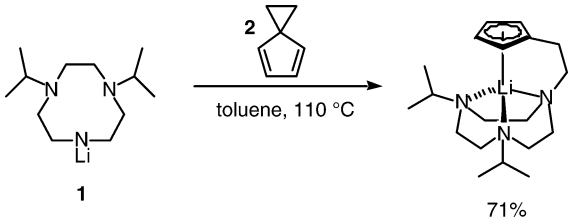
10.1021/om049222m CCC: $30.25
Publication on Web 12/22/2004

stability of the metal center will also be important for any application in asymmetric synthesis. In the case of Cp-amino acid complexes, epimerization at the metal center is sometimes rapid at room temperature; in others, it occurs only at high temperatures, at which point application in asymmetric synthesis becomes a realistic goal.[10] We hope that by linking the Cp ligand to the amino acid derivative not only will complexation be more diastereoselective, but the resulting metal complexes should also be more configurationally stable owing to the chelating nature of the ligand system.

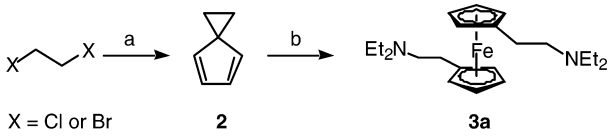
As a first target, we chose to develop a synthesis of a more simple Cp-amino hybrid ligand system in which an ethylene spacer separates the Cp ligand from the nitrogen donor site.[11] The vast majority of Cp-amino ligand systems contain a methylene or $SiMe_2$ spacer between the Cp ligand and appended nitrogen group.[12] Systems containing an additional linking atom are comparatively unusual, which probably reflects the relative difficulty associated with their preparation. $CpCH_2CH_2NR_2$ ligands are normally accessed by a nucleophilic displacement reaction between NaCp and the corresponding 2-chloroethylamino compound.[13] Although this multistep approach provides a very useful route to some (2-amino)ethyl-substituted Cp ligands, especially if the desired 2-chloroethylamino compound is commercially available,[14] we found elimination of HCl to be a major competing process in the nucleophilic displacement step in a number of systems that we examined.[15] An alternative and potentially more convergent approach that would not be reliant on the synthesis of 2-chloroethylamino ligand precursors was therefore sought.

Employing spiro[2.4]hepta-4,6-diene **2** as a precursor to both the Cp ligand *and* the two carbons required for our ethylene spacer seemed to be a particularly attractive option worth exploring. Release of ring-strain, accompanied by the formation of a relatively stable Cp anion, would hopefully render opening of the cyclopropane by a nitrogen nucleophile facile and present a direct synthesis of our desired ligand system. A search in the literature revealed that a large number of soft nucleophiles (based on S, As, P) have already been used successfully to open the cyclopropane ring in **2**;[2,16] in sharp contrast, the use of harder nitrogen and oxygen nucleophiles has received scant attention, with only isolated examples being reported to date.[17,18] The only example that we could find in which an amine nucleophile had been reacted with **2** involved the rather unusual lithium amide **1**, which provided the desired Cp-amino hybrid ligand in good yield (Scheme 1).[17] We therefore set about investigating whether more conventional nitrogen nucleophiles could be used to prepare substituted (2-amino)ethylCp ligands from **2** and provide a potentially facile and general entry into this class of ligands.

Scheme 1. Lithium-Amide-Mediated Opening of the Cyclopropane Ring in Spiro[2.4]hepta-4,6-diene



Scheme 2. Two-Step Synthesis of 1,1′-Bis(2-diethylamino)ethylferrocene 3a[a]



[a] Reagents and conditions: (a) CpH (1.2 equiv), NaH (2.6 equiv), THF, RT, 12 h, 62% (X = Cl), 46% (X = Br); (b) $LiNEt_2$ (1.0 equiv), THF, reflux, 15 h, then anhydrous $FeCl_2$, (0.55 equiv), reflux, 8 h (42%).

Results and Discussion

Synthesis of 1,1′-Bis(2-amino)ethyl-Substituted Ferrocenes. Although spiro[2.4]hepta-4,6-diene **2** is commercially available, we found it more convenient to prepare this starting material ourselves. Using a modification of the published procedure,[19] treatment of a THF solution of freshly cracked cyclopentadiene and 1,2-dichloroethane[20] with 2.6 equiv of NaH provided spiro[2.4]hepta-4,6-diene **2** in good yield (Scheme 2).[21] Using these conditions, diene **2**[22] was obtained in high purity (>95%)[23] by distillation.

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(11) Such a C_2 linker between the two ligand donor sites should hopefully maximize the likelihood that the side-chain amino group would interact with the metal center. See for example: (a) Ti complex: Herrmann, W. A.; Morawietz, M. J. A.; Priermeier, T.; Mashima, K. *J. Organomet. Chem*. **1995**, *486*, 291−295. (b) Cr complex: Döhring, A.; Göhre, J.; Jolly, P. W.; Kryger B.; Rust, J.; Verhovnik, G. P. J. *Organometallics* **2000**, *19*, 388−402. (c) Co complex: Jutzi, P.; Kristen, M. O.; Dahlhaus, J.; Neumann, B.; Stammler, H.-G. *Organometallics* **1993**, *12*, 2980−2985.

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(14) For example, $ClCH_2CH_2NH_2$·HCl, $ClCH_2CH_2NEt_2$·HCl, $ClCH_2CH_2NMe_2$·HCl, and $ClCH_2CH_2N^iPr_2$·HCl are commercially available.

(15) For example, reaction of $ClCH_2CH_2NTsCH(CH_2Ph)CH_2OTHP$ with NaCp resulted in exclusive formation of the enamine elimination product.

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(17) For the use of a nitrogen nucleophile: Qian, B.; Henling, L. M.; Peters, J. C. *Organometallics* **2000**, *19*, 2805−2808.

(18) For the use of an oxygen nucleophile: ref 11b.

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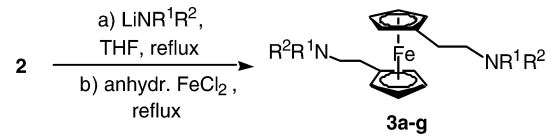
(20) The use of 1,2-dibromoethane as an alternative bis-electrophile offered no significant advantage and provided diene **2** in reduced yield (46%).

(21) We found it particularly important to use an excess of cyclopentadiene in this reaction to ensure complete consumption of the 1,2-dichloroethane, since any residual starting material proved impossible to separate from the product.

(22) **2** can be stored under a nitrogen atmosphere at 4 °C for several months without significant decomposition.

Table 1. One-Pot Synthesis of 1,1′-Bis(2-amino)ethyl-Substituted Ferrocenes 3



lithium amide	product	isolated yield (%)
$LiNEt_2$	**3a**	42
$LiN(CH_2)_4CH_2$	**3b**	52
$LiN(CH_2)_2N(CH_3)CH_2CH_2$	**3c**	52
$LiN(CH_2)_2OCH_2CH_2$	**3d**	65
$LiN(CH_2)_3CH_2$	**3e**	39
LiNHBn	**3f**	12
LiNHBu	**3g**	7

Since we expected the (2-amino)ethylCp ligands to be unstable and difficult to isolate, we elected to test the efficiency of our cyclopropane-opening reaction by trapping the intermediate Cp anion directly with Fe(II). This would generate a ferrocene derivative, which we expected would be much more readily characterized. Ferrocenes containing pendant amino groups are themselves of interest and find use in a wide range of applications.[24] In a first experiment, heating a solution of **2** with diethylamine in THF under reflux for 12 h, followed by the addition of anhydrous $FeCl_2$, failed to provide the desired ferrocene product. No polar, ring-opened products were obtained, and the starting diene **2** slowly decomposed on prolonged heating. Moving to the more nucleophilic lithium amide improved matters: heating a 1:1 mixture of $LiNEt_2$ and **2** in THF for 15 h, followed by the addition of $FeCl_2$ and further heating for 8 h, provided the desired 1,1′-bis(2-diethylamino)ethyl-substituted ferrocene product **3a** in moderate yield (Scheme 2).

Carrying out the reaction at room temperature in an effort to reduce the loss of starting material, presumably through thermally induced polymerization pathways, failed to improve matters; in this case the desired ring-opening reaction simply became extremely sluggish. Neither the use of other solvents (Et_2O, toluene) nor the inclusion of 1 equiv of TMEDA (per lithium amide) in the reaction mixture provided any improvement in the yield of the desired product. Since the basicity of the lithium amide nucleophile was another source of side-reactions (see below), we also attempted the ring-opening reaction using the corresponding magnesium amide $Mg(NEt_2)_2$, prepared from Bu_2Mg and $HNEt_2$,[25] and the aluminum amide prepared from Me_3Al and $HNEt_2$.[26] While both of these amide nucleophiles are significantly less basic than their lithium congeners, they unfortunately also lacked the necessary nucleophilicity to effect ring-opening.

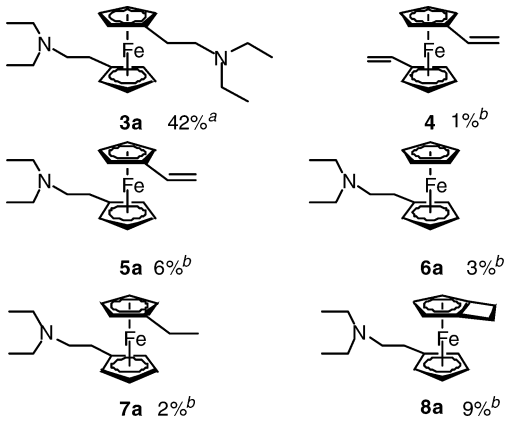


Figure 1. Reaction of spiro[2.4]hepta-4,6-diene with $LiNEt_2$ and then $FeCl_2$ provided a range of ferrocene products. [a]Isolated yield after purification by column chromatography. [b]Yield calculated from GC analysis of the crude reaction mixture.

A range of primary and secondary lithium amides was then investigated using our optimized conditions, and the results are summarized in Table 1. The desired 1,1′-bis(2-amino)ethyl-substituted ferrocenes **3a**−**g** were isolated from this one-pot operation, after aqueous workup and purification by flash column chromatography or recrystallization, in low to good yields, depending on the starting amine. The best results were generally obtained with cyclic secondary lithium amides; acyclic lithium amides, in particular those derived from primary amines, provided lower yields of the desired products, which is reflective of their reduced nucleophilicity. Attempted ring-opening with lithium amides derived from oxazolidinone and imidazole failed. Crystals of the bis-morpholine complex **3d** were grown from EtOAc/petroleum ether (bp 40−60 °C), and the structure was solved by single-crystal X-ray diffraction, thus confirming our structural assignment made from spectroscopic analyses (see Supporting Information).

Characterization of Reaction Byproducts. In addition to the desired 1,1′-bis(2-amino)ethyl ferrocenes **3**, we observed a range of other interesting ferrocene products, which helped to account for some of the mass balance in the reaction. For example, when spiro[2.4]-hepta-4,6-diene (**2**) was treated with $LiNEt_2$, followed by $FeCl_2$, five other ferrocene products, **4**−**8**, were identified, in addition to the desired product **3a** (Figure 1).

The formation of the first byproduct, 1,1′-divinyl ferrocene **4**,[27] can be understood by assuming that the

(23) Even after distillation, spiro[2.4]hepta-4,6-diene always contained a residual amount of CpH (<5%).

(24) *Water-soluble* ferrocene and ferrocenium species (amino-substituted ferrocenes are readily rendered water-soluble by quaternization or simple protonation) exhibit a range of useful biological properties: (a) DNA binding: 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**, 2969−2974. (b) Antitumor activity: Kopf-Maier, P.; Köpf, H.; Neuse, E. W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 456−457. 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*, 42−48. (c) Antimalarial activity: (i) Biot, C.; Delhaes, L.; Maciejewski, L. A.; Mortuaire, M.; Camus, D.; Dive, D.; Brocard, J. S. *Eur. J. Med. Chem.* **2000**, *35*, 707−714. (ii) 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*, 59−65. (d) Redox sensors for the commercially important flavoenzyme glucose oxidase: Forrow, N. J.; Sanghera, G. S.; Walters, S. J. *J. Chem. Soc., Dalton Trans.* **2002**, 3187−3194. (e) Anion-recognition; Beer, P. D. *Acc. Chem. Res.* **1998**, *31*, 71−80. (f) Ligands in Pd-catalyzed cross-coupling processes: Weng, Z.; Teo, S.; Koh, L. L.; Hor, T. S. A. *Organometallics* **2004**, *23*, 3603−3609.

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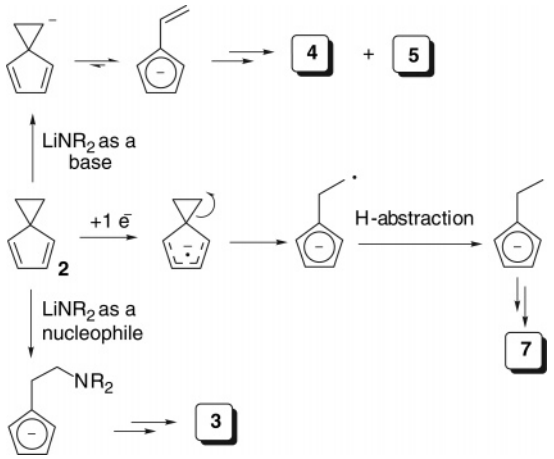
(27) Rausch, M. D.; Siegel, A. *J. Organomet. Chem.* **1968**, *11*, 317−324.

Scheme 3. Reaction of Lithium Amides with Spiro[2.4]hepta-4,6-diene



lithium amide behaves as a base, rather than as a nucleophile, and abstracts a proton from one of the cyclopropane methylene groups (Scheme 3). The resulting cyclopropanyl anion will then be in equilibrium with a much more stable vinylCp anion in which the negative charge has been delocalized into the Cp ring. The additional aromatic stabilization in the vinylCp species presumably serves to help "siphon off" any of the conjugate base that is formed: it is therefore effectively acting as a thermodynamic sink and readily accounts for the formation of both this byproduct and **5** (see below). Ferrocenes **4** and **5** were produced in varying amounts depending on the relative basicity of the lithium amide employed; thus amides derived from cyclic amines generally provided smaller quantities of these byproducts, which was clearly associated with a concomitant increase in the yield of the desired product **3**.

The identification of the remaining side-products (**5**–**8**) proved to be much more difficult, owing to our inability to separate them by either silica gel flash column chromatography or HPLC, irrespective of the amine employed; as a consequence, they were characterized as a mixture. Analysis of this mixture by GC-MS revealed the presence of four compounds of molecular mass 285, 311, 311, and 313 Da (using $HNEt_2$ as the amine). Fragmentation characteristic of the (2-amino)ethylCp ligand was present in the EI mass spectra in all cases and suggested a series of ferrocenes each containing a single (2-amino)ethyl-substituted Cp ligand.

Since the bis(2-amino)ethyl ferrocene **3** and bis-vinyl ferrocene **4** were observed, the isolation of ferrocene **5** containing one of each ligand was predictable. We were keen to check whether the ferrocenes **4** and **5** containing a vinylCp ligand were derived from the pathway described in Scheme 3 and were not the products from a secondary elimination reaction between our target bis-(2-amino)ethyl ferrocene **3** and unreacted lithium amide since this would obviously be compromising the yield of our target compounds. To this end, bis(2-pyrrolidino)-ethyl ferrocene **3e** was treated with lithium morpholinide at reflux for 24 h. Analysis of the reaction mixture by GC showed that this particular lithium amide did not effect elimination—nor amine substitution for that matter—under the reaction conditions, and the starting ferrocene was recovered intact. In contrast, when a THF solution of bis(2-pyrrolidino)ethyl ferrocene **3e** at reflux was treated with $LiNEt_2$, analysis of the reaction mixture after prolonged heating (24 h) revealed the presence of some monoelimination product **5e** (31% isolated yield), although the major component of the reaction mixture remained the starting material (60% isolated yield). From these reactions, it would appear that vinyl-substituted ferrocenes can be formed from the desired bis-amino ferrocene product although only when the more strongly basic acyclic lithium amides are employed; the major source of these compounds remains the direct pathway outlined in Scheme 3.

The occurrence of the third byproduct **6** containing an unsubstituted Cp ligand, in trace (<3%) amounts, was readily rationalized by the fact that the spiro[2.4]-hepta-4,6-diene **2** used in the complexation studies invariably contained a residual amount of cyclopentadiene (<5%).[23] The origins of the two remaining side-products, however, are more interesting. GC-MS and NMR analysis of **7** indicated the presence of an ethylCp ligand. We propose that the formation of such a ligand, and therefore of ethyl-substituted ferrocene **7**, proceeds via a single-electron transfer (SET) process (Scheme 3): one-electron reduction of **2** by the lithium amide, followed by cyclopropane ring-opening and abstraction of a hydrogen atom,[28] provides a route to EtCpLi. The formation of such products in larger quantities has been observed when **2** is treated with butyllithium reagents,[29] which are well known to react through SET processes.

The structure of the fourth byproduct **8** eluded us for some time. While mass spectral analysis indicated the presence of a Cp ligand with a molecular formula C_7H_7, i.e., equivalent to a vinylCp group, we had already attributed this structure to ferrocene **5**. We therefore had to assume that **8** contained a Cp ligand and a double-bond equivalent, namely, an appended ring. Ultimately, chemical derivatization studies allowed us to confirm this and the identity of the compound as **8** (Scheme 4). Thus, reaction of a mixture of ferrocenes **5a**, **7a**, and **8a** (in this case, the mixture contained negligible amounts of ferrocene **6a**) with methyl iodide generated the corresponding tetraalkylammonium salts. Without isolation, treatment of this mixture with KO^tBu in ^{t}BuOH effected a Hoffmann elimination to provide the corresponding olefin products.[30] Subsequent hydrogenation of the olefin functionality present in these molecules reduced the number of compounds from three to two, providing **9** and **10**. At this stage we were luckily able to separate the compounds by reversed-phase HPLC and obtained a pure sample of the derivatized final mystery product **10**. Extensive NMR studies, and comparison of these data with related compounds reported in the literature,[31,32] allowed us to assign the structure of **10** to a ferrocenocyclobutene.

It is interesting to speculate on the mechanism of formation of **8**. Some time ago, Oda and Breslow showed

(28) We have not identified the source of hydrogen: carrying out the reaction in d_8-THF did not lead to any deuterium incorporation in the product.

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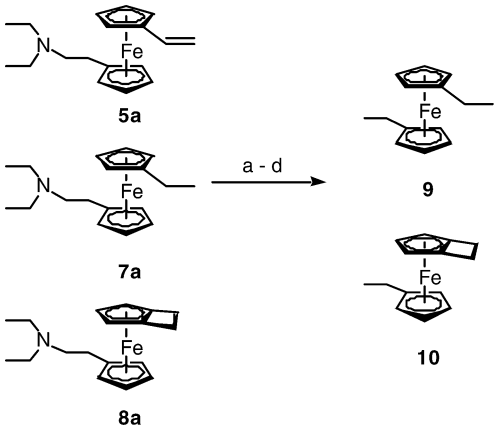
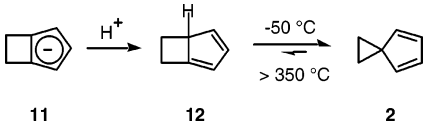
(32) Oda, M.; Breslow, R. *Tetrahedron Lett.* **1973**, 2537–2540.

Scheme 4. Chemical Derivatization Enabled the Structure of Ferrocene 8 To Be Determined[a]

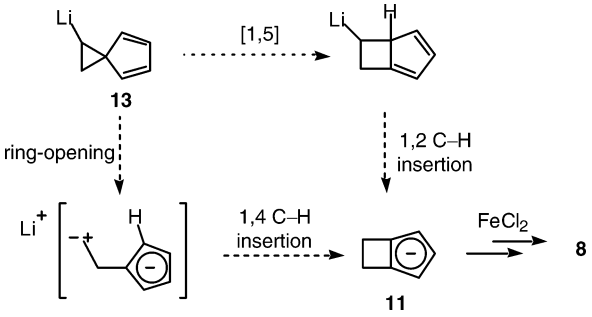


[a] Reagents and conditions: (a) MeI (5 equiv), THF, RT, 15 h; (b) ^{t}BuOK (8 equiv), ^{t}BuOH, reflux, 15 h; (c) H_2 (1 atm), 5% Pd/C, EtOH, 5 h; (d) reversed-phase HPLC.

Scheme 5. Isomerization of Spiro[2.4]hepta-4,6-diene and Bicyclo[3.2.0]hepta-1,3-diene



Scheme 6. Possible Routes to Ferrocenocyclobutene 8

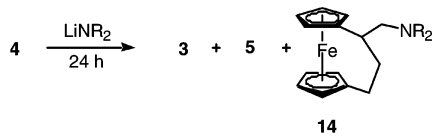


that protonation of anion **11** provided bicyclo[3.2.0]-hepta-1,3-diene **12**, which underwent an energetically favorable and rapid [1,5]-alkyl shift at −50 °C to provide spiro[2.4]hepta-4,6-diene **2** (Scheme 5).[32] Kloosterziel and co-workers have shown that the reverse reaction can also be effected by thermolysis at 345−400 °C (Scheme 5).[33]

The fact that such high temperatures are required to isomerize **2** to **12** suggests a [1,5]-alkyl shift pathway directly on this neutral species is not the source of the anion **11** required for the formation of ferrocenocyclobutene **8**, although we do not discount the possibility that this rearrangement may be more facile on the carbanion **13** (Scheme 6), which we have already proposed to be an intermediate in the synthesis of vinyl ferrocenes **4** and **5** (Scheme 3). Other mechanisms proceeding via carbanion **13** can be envisaged. For example, a tandem ring-opening/carbene 1,4-insertion mechanism would also provide a route to anion **11** (Scheme 6).

(33) Krekels, J. M. E.; de Haan, J. W.; Kloosterziel, H. *Tetrahedron Lett*. **1970**, 2751−2754.

Table 2. Amidolithiation of 1,1′-Divinyl Ferrocene



entry	amine	reaction conditions	isolated yield **3** (%)[a]	isolated yield **5** (%)[a]	isolated yield **14** (%)[a]
1	morpholine	THF, reflux	69	5	15
2[b]	morpholine	THF, RT	30	41	0
3	Et_2NH	THF, reflux	5	28	42
4[c]	$^i Pr_2NH$	THF, reflux	0	0	0

[a] Isolated yields following purification by flash column chromatography. [b] Starting material **4** was also recovered (10%). [c] Starting material was recovered.

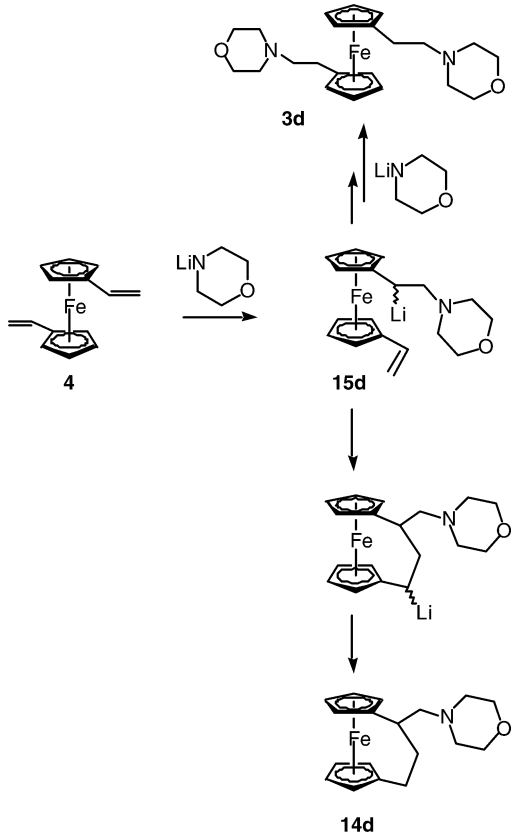
An Alternative Route to the Desired Products and Adventitious Entry into Some Novel [3]Ferrocenophanes. In an effort to improve the yield of our desired product, we entertained the possibility that the lithium amide nucleophile might add to vinylCp ligands in analogy with a similar reaction that has been reported with styrene.[34] If this were to be the case, and assuming elimination pathways were not important, as seems to be the case, then using an excess of the lithium amide nucleophile might allow an increased yield of the desired bis-amino ferrocenes; vinyl ferrocenes **4** and **5** would effectively be intermediates and, providing the reaction was given sufficient time, would then converge on the desired bis-amino ferrocene compound **3**. To test this possibility, 1,1′-divinyl ferrocene **4** was treated separately with a selection of lithium amides under a range of reaction conditions (Table 2). The progress of the reactions was monitored by GC.

We were gratified to observe that the more nucleophilic lithium morpholinide did indeed add fairly readily to the vinyl substituents in **4** to provide the bis-amino ferrocene **3d** in very good yield, along with a small amount of the monoaddition product **5d**, after heating at reflux for 24 h. In addition to these two expected addition products we also isolated the novel [3]ferrocenophane **14d**, whose formation can be rationalized by the cascade process outlined in Scheme 7. Thus intermolecular amidolithiation of one vinyl group affords the organolithium intermediate **15d**, which can then react in one of two ways: protonation of this intermediate, presumably with the THF solvent acting as the proton source, provides the monoaddition product **5d**, which can then react in a similar fashion to provide the desired 1,1′-bis(2-amino)ethyl ferrocene adduct **3d**. Alternatively, **15d** may react with the remaining olefin through an intramolecular carbolithiation pathway to provide [3]ferrocenophane **14d** after workup.[35]

(34) (a) Beller, M.; Breindl, C. *Tetrahedron* **1998**, *54*, 6359−6368. (b) Seijas, J. A.; Vázquez-Tato, M. P.; Entenza, C.; Martínez, M. M.; Ónega, M. G.; Veiga, S. *Tetrahedron Lett.* **1998**, *39*, 5073−5076. (c) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *69*, 1571−1587. (d) Hamana, H.; Iwasaki, F.; Nagashima, H.; Hattori, K.; Hagiwara, T.; Narita, T. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 1109−1113.

(35) For recent examples of intramolecular carbolithiation reactions: (a) Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc*. **2002**, *124*, 12106−12107. (b) Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomol. Chem*. **2003**, 2111−2119. (c) Bailey, W. F.; Luderer, M. R.; Mealy, M. J. *Tetrahedron Lett*. **2003**, *44*, 5303−5305. (d) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett*. **2003**, *44*, 7143−7146. (e) Yus, M.; Ortiz, R.; Huerta, F. F. *Tetrahedron* **2003**, *59*, 8525−8542.

Scheme 7. Amidolithiation of 1,1′-Divinyl Ferrocene 4 Provided an Alternative Entry into the Desired Products and a Route to a Novel Amine-Functionalized [3]Ferrocenophane



The fact that the bis-amino ferrocene **3d** was the major product suggests the second carbolithiation step is either slow or possibly reversible. These experiments seemed to confirm our predictions that vinyl ferrocenes could be treated as intermediates. However, using an excess of lithium morpholinide in the reaction with **2**, or adding excess after the addition of $FeCl_2$, and heating the mixture at reflux for a prolonged period (15 h), failed to lead to a significant improvement in the yield of **3d**. Carrying out the amidolithiation reaction at room temperature for 24 h served to reduce the rate of addition, although now we were able to completely suppress ferrocenophane formation. Although styrene derivatives have been shown to react with lithium amides at 0 °C,[34b] carrying out our reaction at this lower temperature simply resulted in the recovery of starting material after 24 h. The reduced susceptibility of our vinyl group toward amidolithiation compared with that in styrene was further emphasized when we observed no reaction at all when morpholine in the presence of substoichiometric quantities (10 mol %) of ^{n}BuLi at reflux was employed.[34a]

Performing the same reaction between 1,1′-divinyl ferrocene **4** and $LiNEt_2$ proved less successful. The reduced nucleophilicity of this lithium amide provided the double-addition product **3a** in greatly reduced yield along with the monoaddition product **5a** and the corresponding [3]ferrocenophane **14a** in 28% and 42% yield, respectively, after 24 h at reflux. The increased amount of [3]ferrocenophane product probably reflects the reduced rate of amidolithiation such that intramolecular carbolithiation becomes competitive. Not surprisingly, the use of the very poor amide nucleophile LDA led to no reaction, with starting material being recovered.

Conclusions

In summary, we have shown that the action of lithium amides on spiro[2.4]hepta-4,6-diene **2** provides the corresponding (2-aminoethyl)CpLi species that can be trapped in situ with $FeCl_2$ to provide 1,1′-bis(amino)-ethyl ferrocenes. A number of interesting side-products, which we propose result from SET processes and the associated Brønsted basicity of the lithium amide nucleophiles, have also been identified and led us to investigate the ring-opening reaction in more detail. Control experiments have shown that the major pathway to the target bis-amines is through a nucleophilic opening of the cyclopropane moiety in **2** rather than a possible competing amidolithiation of vinylCp intermediates. The simplicity of this operation and rapidity of complex assembly provides a useful entry into this class of amino-substituted ferrocenes, although the length of some of the reaction steps still detracts somewhat from the method. We are actively seeking alternative synthetic approaches that address this specific issue.

Experimental Section

General Comments. Infrared spectra were recorded either neat as thin films between sodium chloride disks or as a Nujol mull between sodium chloride disks. The intensity of each band is described as s (strong), m (medium), or w (weak) and with the prefix v (very) and suffix br (broad) where appropriate. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, 400 and 100 MHz, or 300 and 75 MHz, respectively. Chemical shifts are reported as δ values (ppm) referenced to the following solvent signals: $CHCl_3$, δ_H 7.26; $CDCl_3$, δ_C 77.0. The term, "stack" is used to describe a region where resonances arising from nonequivalent nuclei are coincident, and multiplet, m, to describe a region where resonances arising from a single nucleus (or equivalent nuclei) are coincident but coupling constants cannot be readily assigned. Connectivities were deduced from COSY90, HSQC, and HMBC experiments. Mass spectra were recorded utilizing electrospray ionization (and a methanol mobile phase), or *m*-nitrobenzyl alcohol (3-NOBA) as the matrix, and are reported as *m/z* (%). HRMS were recorded using a lock mass incorporated into the mobile phase. Melting points were determined using open capillaries and are uncorrected.

Reversed-phase preparative HPLC was performed using a C18(2) 100 × 21.2l D 5 μM column at 20 mL min^{-1} and monitored using a photodiode array detector (used at 200 and 330 nm) using a helium-degassed HPLC grade water/acetonitrile gradient, with formic acid additive [t = 0−1 min: 20% of A (0.1% formic acid in H_2O):80% of B (95% MeCN, 5% of 0.05% formic acid in H_2O) then gradient to t = 12 min: 5% A:95% B, then gradient to t = 14 min: 1% A:99% B].

Analytical GC data were collected with FID detection: carrier gas, He; 5% phenyl 95% dimethylpolysiloxane column, 15 m × 0.53 mm i.d.

Reactions were monitored by thin-layer chromatography using precoated glass-backed silica-rapid plates (60A F_{254}) and visualized by UV detection (at 254 nm) and with ammonium molybdate(IV)−cerium(IV) sulfate staining dip. Column chromatography was performed on silica gel (particle size 40−63 μm mesh).

All reactions were conducted in oven-dried (140 °C) or flame-dried glassware under a nitrogen atmosphere, and at ambient

temperature (20 to 25 °C) unless otherwise stated, with magnetic stirring. Volumes of 1 mL or less were measured and dispensed with gastight syringes. Evaporation and concentration under reduced pressure were performed at 50−500 mbar. Residual solvent was removed under high vacuum (<1 mbar).

All reagents were obtained from commercial sources and used without further purification unless stated otherwise. Cyclopentadiene was obtained by cracking dicyclopentadiene (160−170 °C) under N_2 and collected by fractional distillation.[36] All amines were distilled under a N_2 atmosphere from KOH and stored under N_2 at room temperature over activated 4 Å molecular sieves (activated by heating under a vacuum for 15 min with a Bunsen flame immediately before use). Dichloromethane was freshly distilled under nitrogen from CaH_2. Tetrahydrofuran and diethyl ether were freshly distilled under nitrogen from sodium benzophenone ketyl. All solutions are aqueous and saturated unless stated otherwise.

General Procedure for Formation of 1,1′-Bis(2-amino)-ethyl-Substituted Ferrocenes (3). ^{n}BuLi (7.19 mL of a 1.6 M solution in hexane, 12.0 mmol) was added to a solution of the amine (13 mmol) in THF (21 mL) at 0 °C. The solution was then stirred at RT for 15 min and then transferred via syringe to a solution of spiro[2.4]hepta-4,6-diene **2** (10 mmol) in THF (5 mL) at RT. The resulting orange solution was heated under reflux overnight (∼12−14 h) and then cooled to RT, whereupon anhydrous $FeCl_2$ (5 mmol) was added. The dark brown solution was heated under reflux for a further 18 h. After cooling to RT, Et_2O (200 mL) and NH_4Cl solution (200 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 × 100 mL) and then with CH_2Cl_2 (2 × 100 mL). The combined organic fractions were washed with brine (300 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide a red oil, which was purified by flash column chromatography.

1,1′-Bis[2-diethylamino]ethylferrocene (3a). Bis-amino ferrocene **3a** was prepared from Et_2NH (0.65 mL, 6.3 mmol), spiro[2.4]hepta-4,6-diene **2** (0.5 mL, 4.85 mmol), and $FeCl_2$ (0.31 g, 2.4 mmol). After workup, purification by flash column chromatography (94% EtOAc, 4% EtOH, 1% Et_3N) afforded bis-amine **3a** (394 mg, 42%) as a red-orange oil: R_f = 0.26 (94% EtOAc, 5% EtOH, 1% Et_3N); IR (film) 3089m, 1471m, 1383m, 1293m, 1206m, 1069m, 1040m cm^{-1}; ^{1}H NMR (300 MHz) δ 1.03 (t, J 7.2, 12H), 2.41−2.61 (stack, 16H), 3.98 (br s, 8H); ^{13}C NMR (75 MHz) δ 12.3 (CH_3), 27.4 (CH_2), 47.3 (CH_2), 54.8 (CH_2), 68.3 (CH), 69.1 (CH), 87.4 (quat. C); MS (EI) *m/z* 384 ([M]$^+$, 40%), 86 (100, [$(CH_3CH_2)_2NCH_2$)]$^+$); HRMS calcd for $C_{22}H_{37}FeN_2$ [M + H]$^+$ 385.2306, found 385.2294.

1,1′-Bis[2-methylpiperazin-1-yl]ethylferrocene (3c). Bis-amino ferrocene **3c** was prepared from *N*-methylpiperazine (0.28 mL, 2.5 mmol), spiro[2.4]hepta-4,6-diene **2** (0.2 mL, 1.94 mmol), and $FeCl_2$ (0.135 g, 1.1 mmol). After workup, purification by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) afforded bis-amine **3c** (0.221 mg, 52%) as a red-orange powder: mp 78−80 °C; R_f = 0.13 (94% EtOAc, 5% EtOH, 1% Et_3N); IR (film) 3088w, 3045w, 1450s, 1372m, 1356m, 1284s, 1266s, 1163s, 1148s, 1013s cm^{-1}; ^{1}H NMR (300 MHz) δ 2.31 (s, 6H), 2.35−2.65 (stack, 24H), 3.99 (s, 8H); ^{13}C NMR (75 MHz) δ 26.9 (CH_2), 45.8 (CH_3), 52.9 (CH_2), 54.9 (CH_2), 59.8 (CH_2), 67.8 (CH), 68.6 (CH), 86.4 (quat. C); MS (EI) *m/z* 438 ([M]$^+$, 42%), 247 (7, [M − $CpCH_2CH_2N(CH_2CH_2)_2NCH_3$]$^+$), 176 (7, [M − $FeCpCH_2CH_2N(CH_2CH_2)_2NCH_3$]$^+$), 113 (100, [$CH_2N(CH_2CH_2)_2NCH_3$]$^+$), 70 (47, [$N(CH_2CH_2)_2$]$^+$). Anal. Calcd for $C_{24}H_{38}FeN_4$: C, 65.75; H, 8.74; N, 12.78. Found: C, 65.88; H, 8.86; N, 12.54.

1,1′-Bis[2-morpholin-4-yl]ethylferrocene (3d). Bis-amino ferrocene **3d** was prepared from morpholine (0.55 mL, 6.3 mmol), spiro[2.4]hepta-4,6-diene **2** (0.5 mL, 4.85 mmol), and $FeCl_2$ (0.31 g, 2.4 mmol). After workup, purification by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) afforded bis-amine **3d** (650 mg, 65%) as a red powder: mp 70−72 °C; R_f = 0.30 (94% EtOAc, 5% EtOH, 1% Et_3N); λ_{max} (CH_2Cl_2)/nm 435 (ϵ/dm^3 mol^{-1} cm^{-1} 160), 322 (166); IR (Nujol mull) 3070w, 1377m, 1131m, 1116s, 1038m cm^{-1}; ^{1}H NMR (300 MHz) δ 2.42−2.55 (stack, 16H), 3.70−3.74 (stack, 8H), 3.99 (s, 8H); ^{13}C NMR (75 MHz) δ 25.9 (CH_2), 52.9 (CH_2), 59.6 (CH_2), 66.1 (CH_2), 67.1 (CH), 67.9 (CH), 85.6 (quat. C); MS (EI) *m/z* 413 ([M + 1]$^+$, 47%), 312 (5, [M − $CH_2N(CH_2CH_2O)$]$^+$), 100 (100, [$O(CH_2CH_2)_2NCH_2$)]$^+$). Anal. Calcd for $C_{22}H_{32}FeN_2O_2$: C, 64.08; H, 7.82; N, 6.79. Found: C, 64.09; H, 7.91; N, 6.70.

1,1′-Bis[2-pyrrolidin-1-yl]ethylferrocene (3e). Bis-amino ferrocene **3e** was prepared from pyrrolidine (0.52 mL, 6.3 mmol), spiro[2.4]hepta-4,6-diene **2** (0.5 mL, 4.85 mmol), and $FeCl_2$ (0.31 g, 2.4 mmol). After workup, purification by flash column chromatography (90% acetone, 9% EtOH, 1% Et_3N) afforded bis-amine **3e** (360 mg, 39%) as a red powder: mp 46−48 °C; R_f = 0.07 (94% EtOAc, 5% EtOH, 1% Et_3N); IR (Nujol mull) 3084s, 1460s, 1378m, 1350m, 1329m, 1280m, 1144m, 1114m, 1038s cm^{-1}; ^{1}H NMR (300 MHz) δ 1.73−1.85 (m, 8H), 2.43−2.66 (stack, 16H), 3.99 (s, 8H); ^{13}C NMR (75 MHz) δ 23.4 (CH_2), 29.1 (CH_2), 54.2 (CH_2), 57.8 (CH_2), 67.9 (CH), 68.7 (CH), 86.8 (quat. C); MS (EI) *m/z* 380 ([M]$^+$, 22%), 84 (100, [$(CH_2CH_2)_2$-NCH_2)]$^+$); HRMS calcd for $C_{22}H_{33}FeN_2$ [M + H]$^+$ 381.1993, found 381.1988.

1,1′-Bis[2-benzylamin-1-yl]ethylferrocene (3f). Bis-amino ferrocene **3f** was prepared from $BnNH_2$ (0.66 mL, 6.3 mmol), spiro[2.4]hepta-4,6-diene **2** (0.5 mL, 4.85 mmol), and $FeCl_2$ (0.31 g, 2.4 mmol). After workup, purification by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) afforded bis-amine **3f** (72 mg, 12%) as an orange oil: R_f = 0.29 (94% EtOAc, 5% EtOH, 1% Et_3N); IR (film) 3312w, 3085m, 3026m, 1454s, 1118m, 1040m, 1027m cm^{-1}; ^{1}H NMR (300 MHz) δ 2.30 (br s, 2H), 2.54 (t, J 7.0, 4H), 2.75 (t, J 7.0, 4H), 3.79 (s, 4H), 3.98 (s, 8H), 7.19−7.39 (stack, 10H); ^{13}C NMR (75 MHz) δ 29.5 (CH_2), 50.2 (CH_2), 53.6 (CH_2), 68.0 (CH), 68.9 (CH), 86.4 (quat. C), 127.2 (CH), 128.4 (CH), 128.7 (CH), 140.5 (quat. C); MS (TOF ES+) *m/z* 453.2 ([M + H]$^+$, 100%); HRMS calcd for $C_{28}H_{33}FeN_2$ [M + H]$^+$ 453.1993, found 453.1998.

1,1′-Bis[2-butylamin-1-yl]ethylferrocene (3g). Bis-amino ferrocene **3g** was prepared from $BuNH_2$ (1.00 mL, 10.1 mmol), spiro[2.4]hepta-4,6-diene **2** (0.8 mL, 7.75 mmol), and $FeCl_2$ (0.31 g, 2.4 mmol). After workup, purification by flash column chromatography (90% acetone, 8% EtOH, 2% Et_3N) afforded bis-amine **3g** (100 mg, 8%) as an orange oil: R_f = 0.28 (90% acetone, 8% EtOH, 2% Et_3N); IR (film) 3420w, 3086w, 1470s, 1411m, 1378m, 1304m, 1265m cm^{-1}; ^{1}H NMR (300 MHz) δ 0.88 (t, J 7.0, 6H), 1.20−1.52 (stack, 8H), 1.73 (br s, 2H), 2.44−2.76 (stack, 12H), 3.98 (s, 8H); ^{13}C NMR (75 MHz) δ 13.9 (CH_3), 20.4 (CH_2), 29.9 (CH_2), 32.1 (CH_2), 49.5 (CH_2), 51.1 (CH_2), 68.0 (CH), 68.9 (CH), 86.4 (quat. C); MS (TOF ES+) *m/z* 385.2 ([M + H]$^+$, 100%); HRMS calcd for $C_{22}H_{37}FeN_2$ [M + H]$^+$ 385.2306, found 385.2318.

1, 1′-Divinylferrocene (4) and 1-[2-Diisopropylamino]-ethyl-1′-ethenylferrocene (5h). ^{n}BuLi (3.48 mL of a 1.68 M solution in hexane, 5.81 mmol) was added to a solution of ^{i}Pr_2NH (0.89 mL, 6.30 mmol) in THF (10 mL) at 0 °C under N_2. The solution was stirred at RT for 15 min and then added via syringe to a solution of spiro[2.4]hepta-4,6-diene **2** (0.5 mL, 4.85 mmol) in THF (2.5 mL) at RT. The resulting orange solution was heated under reflux overnight and then cooled to RT. Anhydrous $FeCl_2$ (0.307 g, 2.42 mmol) was added. The dark brown solution was heated under reflux for a further 22 h. After cooling to RT, Et_2O (100 mL) and ammonium chloride solution (100 mL) were added. The mixture was basified to pH 9 with NaOH solution (2 M), and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL) and then with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (150 mL) and then dried ($MgSO_4$).

(36) Kiselev, V. D.; Kashaeva, E. A.; Konovalov, A. I. *Tetrahedron* **1999**, *55*, 1153−1162.

Concentration under reduced pressure afforded a red-orange oil, which was purified by flash column chromatography (hexane, then 94% EtOAc, 5% EtOH, 1% Et_3N) to afford, in order of elution, first the bis-olefin **4** (0.202 g, 35%) as a red powder: mp 38−40 °C; R_f = 0.50 (hexane); IR (Nujol mull) 3088m, 1631s, 1464m, 1378m, 1239m, 1047m, 1028m cm^{-1}; ^1H NMR (300 MHz) δ 4.09−4.25 (stack, 8H), 5.05 (dd, *J* 10.7, 1.5, 2H), 5.28 (dd, *J* 17.3, 1.5, 2H), 6.36 (dd, *J* 17.3, 10.7, 2H); ^{13}C NMR (75 MHz) δ 67.9 (CH), 69.9 (CH), 84.2 (quat. C), 111.3 (CH_2), 134.1 (CH); MS (TOF ES+) *m/z* 238.0 ($[M + H]^+$, 100%); HRMS calcd for $C_{14}H_{14}Fe$ $[M]^+$ 238.0445, found 238.0441. Anal. Calcd for $C_{14}H_{14}Fe$: C, 70.62; H, 5.93. Found: C, 70.54; H, 6.01. Then amine **5h** (55 mg, 8%) was afforded as a red oil: R_f = 0.44 (94% EtOAc, 5% EtOH, 1% Et_3N); IR (film) 3406m, 3005m, 1629s, 1463m, 1381m, 1267m, 1241m, 1205m, 1046m, 1029m cm^{-1}; ^1H NMR (300 MHz) δ 1.01 (d, *J* 6.6, 12H), 2.30−2.56 (stack, 4H), 2.94−3.11 (m, 2H), 3.86−4.32 (stack, 8H), 5.03 (d, *J* 10.7, 1H), 5.31 (d, *J* 17.3, 1H), 6.41 (dd, *J* 17.3, 10.7, 1H); ^{13}C NMR (100 MHz) δ 20.7 (CH_3), 31.9 (CH_2), 47.5 (CH_2), 48.9 (CH), 67.2 (CH), 68.4 (CH), 69.2 (CH), 69.5 (CH), 83.6 (quat. C), 87.6 (quat. C), 110.9 (CH_2), 134.5 (CH); MS (EI) *m/z* 339 ($[M]^+$, 15%), 114 (100, $[CH_2N(CH(CH_3)_2)_2]^+$); HRMS calcd for $C_{20}H_{30}FeN$ $[M + H]^+$ 340.1728, found 340.1725.

1,1′-Diethylferrocene (9) and 1-Ethyl-1′,2′-cyclobutylferrocene (10). Methyl iodide (0.49 mL, 3.21 mmol) was added to a mixture of ferrocenes **5a**, **7a**, and **8a** (0.200 g, ∼0.64 mmol) in THF (10 mL) and the resulting brown solution heated under reflux for 16 h. After cooling to RT the volatiles were removed under reduced pressure to afford a mixture of tetraalkylammonium salts as a brown oil (0.303 g), which was used directly in the next step without further purification. KO^{t}Bu (0.58 g, 5.15 mmol) was added to a solution of the tetraalkylammonium salts in ^{t}BuOH (5 mL), and the resulting orange mixture was heated under reflux for 15 h. The brownish-orange cloudy reaction mixture was then cooled to RT, and CH_2Cl_2 (20 mL) and water (20 mL) were then added. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic fractions were washed with brine (20 mL) and then dried ($MgSO_4$). Concentration under reduced pressure afforded three olefin products as a dark red oil (0.162 g). These were used directly in the next step without further purification. A solution of the three olefin products (0.162 g) in ethanol (5 mL) was added to 10% palladium on activated charcoal (0.036 g, 0.0034 mmol), and the resulting black slurry was stirred vigorously under a H_2 atmosphere for 7 h. The resulting black mixture was filtered through a plug of Celite, washing thoroughly with ethanol (40 mL). Evaporation of the solvent under reduced pressure provided two products as an orange oil (0.123 g). Purification by reversed-phase HPLC afforded, in order of elution, first ferrocene **10** (0.013 g) as an orange oil: R_f = 0.59 (1% Et_3N in cyclohexane); IR (film) 3088m, 1260s, 1217m, 1094s, 1040s, 1019s cm^{-1}; ^1H NMR (400 MHz) δ 1.19 (t, *J* 7.6, 3H, $CpCH_2CH_3$), 2.37 (q, *J* 7.6, 2H, $CpCH_2CH_3$), 2.82−2.91 (m, 2H, CCH_2CH_2C), 3.03−3.12 (m, 2H, CCH_2CH_2C), 3.74−3.78 (m, 1H, Cp*H*), 3.93−4.03 (stack, 6H, CpH); ^{13}C NMR (100 MHz) δ 14.8 (CH_3, $CpCH_2CH_3$), 21.5 (CH_2, $CpCH_2CH_3$), 28.5 (CH_2, CCH_2CH_2C), 62.2 (CH, Cp), 65.9 (CH, Cp), 69.0 (CH, Cp), 69.2 (CH, Cp), 91.5 (quat. C, $CpCH_2CH_3$), 92.3 (quat. C, $CpCH_2CH_2$); MS (EI) *m/z* 240 ($[M]^+$, 100%), 91 (24, $[CpCH_2CH_2]^+$), 56, (32, $[Fe]^+$); HRMS calcd for $C_{14}H_{16}Fe$ $[M]^+$ 240.0601, found 240.0602; HPLC t_R = 6.86 min. Then ferrocene **9** (0.009 g) was afforded as an orange oil: R_f = 0.59 (1% Et_3N in cyclohexane); IR (film) 3089w, 1260s, 1094s, 1020s cm^{-1}; ^1H NMR (400 MHz) δ 1.17 (t, *J* 7.6, 6H), 2.35 (q, *J* 7.6, 4H), 4.00 (s, 8H); ^{13}C NMR (100 MHz) δ 14.8 (CH_3), 22.1 (CH_2), 67.9 (CH), 69.0 (CH), 91.0 (quat. C); MS (EI) *m/z* 242 ($[M]^+$, 100%), 227 (24, $[CH_3CH_2CpFeCpCH_2]^+$), 212 (17, $[CH_2CpFeCpCH_2]^+$), 121 (15, $[CpFe]^+$), 56 (16, $[Fe]^+$); HPLC t_R = 7.89 min; data were consistent with those reported in the literature.[37]

1-[2-Pyrrolidin-1-yl]ethyl-1′-ethenylferrocene (5e). ^{n}BuLi (0.177 mL of a 1.78 M solution in hexane, 0.32 mmol) was added to a solution of Et_2NH (35 μL, 0.34 mmol) in THF (3 mL) at 0 °C. The pink solution was stirred at RT for 15 min and then added via syringe to a solution of 1,1′-bis[2-pyrrolidin-1-yl]ethylferrocene **3e** (100 mg, 0.26 mmol) in THF (2.5 mL) at RT. The resulting orange solution was heated under reflux for 48 h. After cooling to RT, workup as described for the preparation of bis-amines **3** provided a red-orange oil, which was purified by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) to afford, in order of elution, first **5e** (25 mg, 31%) as a red-orange oil: R_f = 0.28 (94% EtOAc, 5% EtOH, 1% Et_3N); IR (film) 3086m, 1629s, 1461m, 1382m, 1350m, 1330m, 1292m, 1241m, 1202m, 1145m, 1118m, 1041m, 1020m cm^{-1}; ^1H NMR (300 MHz) δ 1.77−1.83 (m, 4H), 2.47−2.63 (stack, 8H), 3.98−4.27 (stack, 8H), 5.03 (dd, *J* 10.7, 1.5, 1H), 5.30 (dd, *J* 17.6, 1.5, 1H), 6.40 (dd, *J* 17.6, 10.7, 1H); ^{13}C NMR (75 MHz) δ 26.1 (CH_2), 31.3 (CH_2), 56.9 (CH_2), 60.3 (CH_2), 69.9 (CH), 71.2 (CH), 71.9 (CH), 72.0 (CH), 86.4 (quat. C), 89.7 (quat. C), 113.8 (CH_2), 137.0 (CH); MS (EI) *m/z* 309 ($[M]^+$, 25%), 84 (100, $[(CH_2CH_2)_2NCH_2)]^+$). Anal. Calcd for $C_{18}H_{23}FeN$: C, 69.91; H, 7.50; N, 4.53. Found: C, 69.69; H, 7.25; N, 4.32. Then starting material **3e** (60 mg, 60%) eluted.

1,1′-(1-Diethylaminomethylpropanylene)ferrocene (14a) and 1-[2-Diethylamino]ethyl-1′-ethenylferrocene (5a). A solution of $LiNEt_2$ [prepared as described above from ^{n}BuLi (0.308 mL of a 2.40 M solution in hexane, 0.74 mmol) and $HNEt_2$ (80 μL, 0.78 mmol)] in THF (4 mL) was added via cannula to a solution of 1,1′-divinyl ferrocene **4** (88 mg, 0.37 mmol) in THF (5 mL) at RT. The resulting orange solution was heated under reflux for 45 h. After cooling, workup as described for the preparation of bis-amine **3** afforded an orange solid, which was purified by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) to afford, in order of elution, first the ferrocenophane **14a** (0.048 g, 42%) as an orange solid: R_f = 0.36 (94% EtOAc, 5% EtOH, 1% Et_3N); λ_{max}(CH_2Cl_2)/nm 442 (ϵ/dm^3 mol^{-1} cm^{-1} 141), 320 (52); IR (film) 3088m, 3047w, 1465m, 1383m, 1266s, 1204m, 1150w, 1071m, 1041m, 1024m cm^{-1}; ^1H NMR (300 MHz) δ 0.99 (t, *J* 7.0, 6H, $N(CH_2CH_3)_2$), 1.63−1.83 (m, 2H, $CpCH_2CH_2CH$), 1.97−2.11 (m, 1H, Cp*H*), 2.23−2.40 (m, 2H, $CpCH_2CH_2CH$), 2.41−2.65 (stack, 6H, $CH_2N(CH_2CH_3)_2$), 3.85−4.13 (stack, 8H, Cp*H*); ^{13}C NMR (75 MHz) δ 11.7 (CH_3, $N(CH_2CH_3)_2$), 24.5 (CH_2, $CpCH_2CH_2CH$), 35.5 (CH, Cp*C*H), 40.3 (CH_2, $CpCH_2CH_2CH$), 47.5 (CH_2, $N(CH_2CH_3)_2$), 58.4 (CH_2, $CpCHCH_2N$), 65.8 (CH, CpH), 67.2 (CH, CpH), 67.5 (CH, CpH), 67.7 (CH, CpH), 68.6 (CH, CpH), 68.7 (CH, CpH), 70.6 (CH, CpH), 71.0 (CH, CpH), 87.3 (quat. C, Cp), 88.3 (quat. C, Cp); MS (EI) *m/z* 311 ($[M]^+$, 38%), 225 (24, $[M - CH_2N(CH_2CH_3)_2]^+$), 86 (100, $[CH_2N(CH_2CH_3)_2]^+$). Anal. Calcd for $C_{18}H_{25}FeN$: C, 69.46; H, 8.10; N, 4.50. Found: C, 69.44; H, 8.12; N, 4.21. Then amine **5a** (0.032 g, 28%) was afforded as an orange oil: R_f = 21 (94% EtOAc, 5% EtOH, 1% Et_3N); IR (film) 3086m, 1630m, 1470m, 1383m cm^{-1}; ^1H NMR (300 MHz) δ 1.06 (t, *J* 7.2, 6H), 2.37−2.67 (stack, 8H), 3.92−4.06 (stack, 4H), 4.12−4.21 (stack, 2H), 4.23−4.32 (stack, 2H), 5.04 (dd, *J* 10.8, 1.4, 1H), 5.32 (dd, *J* 17.4, 1.4, 1H), 6.41 (dd, *J* 17.4, 10.8, 1H); ^{13}C NMR (75 MHz) δ 11.8 (CH_3), 26.5 (CH_2), 46.9 (CH_2), 54.3 (CH_2), 67.2 (CH), 68.5 (CH), 69.2 (CH), 69.4 (CH), 83.7 (quat. C), 87.3 (quat. C), 111.1 (CH_2), 134.4 (CH); MS (TOF ES+) *m/z* 312.1 ($[M + H]^+$, 100%); HRMS calcd for $C_{18}H_{26}FeN_2$ $[M + H]^+$ 312.1415, found 312.1424. Then bis-amine **3a** (0.007 g, 5%) was afforded as an orange oil.

1,1′-(1-Morpholinomethylpropanylene)ferrocene (14d) and 1-[2-Morpholino]ethyl-1′-ethenylferrocene (5d). A solution of lithium morpholinide [prepared as described above

(37) Carroll, M. A.; White, A. J. P.; Widdowson, D. A.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1551−1557.

from ^{n}BuLi (0.350 mL of a 1.78 M solution in hexane, 0.84 mmol) and morpholine (77 μL, 0.88 mmol)] in THF (2 mL) was added via cannula to a solution of 1,1′-divinyl ferrocene **4** (100 mg, 0.42 mmol) in THF (2.5 mL) at RT. The resulting orange solution was heated under reflux overnight. After cooling, workup as described for the preparation of bis-amine **3** afforded an orange solid, which was purified by flash column chromatography (94% EtOAc, 5% EtOH, 1% Et_3N) to afford, in order of elution, first the ferrocenophane **14d** (0.017 g, 12%) as a pale orange solid: R_f = 0.64 (94% EtOAc, 5% EtOH, 1% Et_3N); IR (film) 3053w, 1266s, 1117m cm^{-1}; ^{1}H NMR (300 MHz) δ 1.58−1.85 (stack, 2H), 2.04−2.20 (m, 1H), 2.22−2.59 (stack, 8H), 3.57−3.78 (m, 4H), 3.89−4.14 (stack, 8H); ^{13}C NMR (75 MHz) δ 23.9 (CH_2), 33.8 (CH), 39.8 (CH_2), 53.9 (CH_2), 64.1 (CH_2), 65.9 (CH), 66.9 (CH_2), 67.3 (CH), 67.6 (CH), 67.8 (CH), 68.6 (CH), 68.8 (CH), 70.4 (CH), 70.9 (CH), 87.1 (quat. C), 87.9 (quat. C); MS (EI) *m/z* 325 ([M]$^+$, 20%), 225 (50, [M − $CH_2N(CH_2CH_2)_2O$]$^+$), 100 (100, [$CH_2N(CH_2CH_2)_2O$]$^+$), 56 (37, [Fe]$^+$); HRMS calcd for $C_{18}H_{24}FeNO$ [M + H]$^+$ 326.1207; found 326.1205. Then amine **5d** (0.014 g, 10%) was afforded as an orange oil: R_f = 0.50 (94% EtOAc, 5% EtOH, 1% Et_3N); IR (film) 3085m, 1629m, 1457m, 1118s, 1037m, 1006m cm^{-1}; ^{1}H NMR (300 MHz) δ 2.43−2.55 (stack, 8H), 3.74 (t, *J* 4.6, 4H), 3.94−4.05 (stack, 4H), 4.11−4.19 (stack, 2H), 4.22−4.30 (stack, 2H), 5.04 (dd, *J* 10.7, 1.5, 1H), 5.31 (dd, *J* 17.5, 1.5, 1H), 6.40 (dd, *J* 17.5, 10.7, 1H); ^{13}C NMR (75 MHz) δ 26.0 (CH_2), 53.6 (CH_2), 60.2 (CH_2), 66.9 (CH_2), 67.2 (CH), 68.5 (CH), 69.2 (CH), 69.3 (CH), 83.7 (quat. C), 86.9 (quat. C), 111.3 (CH_2), 134.7 (CH); MS (TOF ES+) *m/z* 326.1 ([M + H]$^+$, 100%); HRMS calcd for $C_{18}H_{24}FeNO$ [M + H]$^+$ 326.1207, found 326.1212. Then bis-amine **3d** (0.119 g, 69%) was afforded as an orange solid.

Acknowledgment. We gratefully acknowledge financial support from the Engineering and Physical Sciences Research Council, The University of Birmingham, and GlaxoSmithKline (CASE award) (to K.M.J.), and Dr. Steve J. Vickers for assistance with the electrochemical characterization.

Supporting Information Available: General experimental details, experimental procedure, and full characterization data for **2** and **3b**, ^{1}H and ^{13}C NMR data for all compounds, X-ray structure for **3b**, and selected UV spectra for **3d** and **14a**. GC-MS data for the formation of **3a** and associated byproducts, GC-MS analysis of chemical derivatization study (converting mixture of **5a**, **7a**, **8a** to **9** and **10**), GC-MS data for reaction of lithium amides with **4**, and selected electrochemical data for **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM049222M