Lithiation of *N*-Boc-Protected Ferrocenylalkylamines: Preparation of Unsymmetrical 1,1′-Disubstituted Ferrocenes

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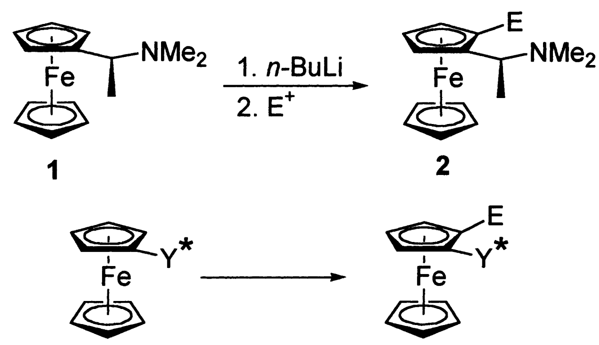
Treatment of *N*-Boc-1-ferrocenylethylamine or *N*-Boc-ferrocenylmethylamine with 2 equiv of *n*-BuLi results in selective N,1′-dimetalation. Trapping of the dianions with various electrophiles is a convenient route to unsymmetrical 1,1′-disubstituted ferrocenes. Under similar conditions, the pivalamide of 1-ferrocenylethylamine undergoes predominantly N,2-dilithiation while urea derivatives give mixtures of regioisomers.

Ugi showed some three decades ago that ferrocenyl derivatives such as the dimethylamine species **1** can be lithiated with high diastereoselectivity, and the resulting organolithium may be trapped with various electrophiles to provide 1,2-disubstituted ferrocenes **2** (Scheme 1).[1] Subsequently, other researchers have used this reaction to prepare various 1,2-disubstituted ferrocenes, including phosphines,[2] carboxylic acids,[3] carboxaldehydes,[4] and boronic acids.[5] Many groups other than Me_2N- (e.g. acetals,[6] oxazolines,[7] sulfoxides,[8] SAMP hydrazones,[9] and pyrrolidines[10]) have also been used to access 1,2-disubstituted ferrocenes. In fact, the diastereoselective metalation/electrophilic quenching of chiral ferrocene derivatives (i.e. **3** → **4**) has become a standard method for the synthesis of 1,2-disubstituted planar chiral ferrocenes, compounds of current interest for applications in asymmetric synthesis.[11]

In connection with a project to prepare a 1,2-disubstituted ferrocene, the Boc derivative **5**, easily prepared from 1-ferrocenylethylamine,[12] was treated with *n*-BuLi and the resulting dianion was treated with CO_2 followed by CH_2N_2. A single product was isolated in good yield; however, its ^1H NMR spectrum did not exhibit a 5H singlet around 4.2 ppm that would be expected for the unsubstituted Cp ring of the 1,2-disubstituted ferrocene **6**.[13] Rather, it was obvious from the spectral data that the new product formed was the unexpected 1,1′-disubstituted ferrocene **7a** (Scheme 2).

Scheme 1



While the 1,1′-disubstituted product **7a** was not expected, on the basis of many examples of directed ortho lithiations,[1−11] there is one previous report of a similar reaction: it was noted that ferrocenecarbaldehyde upon treatment with lithium 4-methylpipirazide followed by *t*-BuLi undergoes selective 1′-lithiation.[14] Electrophilic quenching gave modest (17−69%) yields of mixtures of products (1,1′:1,2 = (90:10)−(96:4)). This chemistry has also been extended for the preparation of highly substituted ferrocenes with planar chirality.[15]

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(1) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1980**, *92*, 5389−5393.
(2) (a) Apsimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157−5254 and references therein. (b) Togni, A.; Bieler, N.; Burckhardt, U.; Köllner, C.; Pioda, G.; Schneider, R.; Schnyder, A. *Pure Appl. Chem.* **1999**, *71*, 1531−1537.
(3) Cullen, W. R.; Wickenheiser, E. B. *Can. J. Chem.* **1990**, *68*, 705−707.
(4) (a) Lu, X.; Chen, G. *Tetrahedron* **1998**, *54*, 12539−12546. (b) Fukuzawa, S.; Tsuchiya, D.; Sasamoto, K.; Hirano, K.; Ohtaguchi, M. *Eur. J. Org. Chem.* **2000**, 2877−2883.
(5) Søtofte, I.; Norrild, J. C. *J. Chem. Soc., Perkin Trans. 2* **2001**, 727−732.
(6) (a) Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835−5836. (b) Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem.* **1997**, *62*, 6733-6745.
(7) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10−11.
(8) Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511−3514.
(9) Enders, D.; Peters, R.; Lochtman, R.; Runsink, J. *Eur. J. Org. Chem.* **2000**, 2839−2850.
(10) Farrell, A.; Goddard, R.; Guiry, P. J. *J. Org. Chem.* **2002**, *67*, 4209−4217.
(11) For a recent review, see: Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377−2407.
(12) (a) Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Org. Chem.* **1972**, *37*, 7, 3052−3058. (b) Woltersdorf, M.; Kranich, R.; Schmalz, H.-G. *Tetrahedron* **1997**, *53*, 7219−7230. (c) Enders, D.; Lochtman, R.; Raabe, G. *Synlett* **1996**, 126−128. (d) Fukuda, T.; Takehara, A.; Haniu, N.; Iwao, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4083−4091.
(13) Pickett, T. E.; Richards, C. J. *Tetrahedron Lett.* **1999**, *40*, 5251−5254.
(14) Iftime, G.; Moreau-Bossuet, C.; Manoury, E.; Balavoine, G. G. A. *J. Chem. Soc., Chem. Commun.* **1996**, 527−528.

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Scheme 2

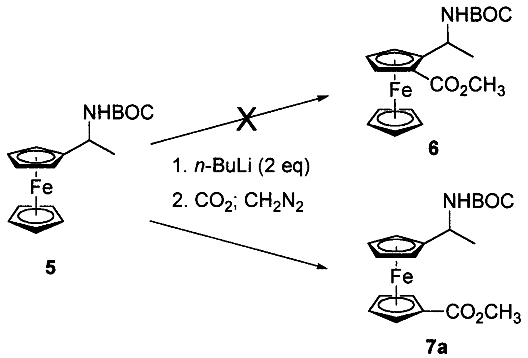
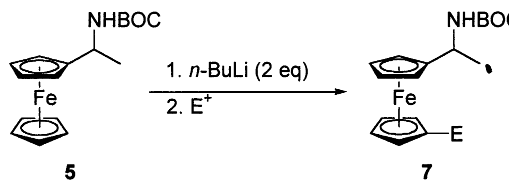


Table 1. Preparation of 1,1′-Disubstituted Ferrocenes 7 from 5



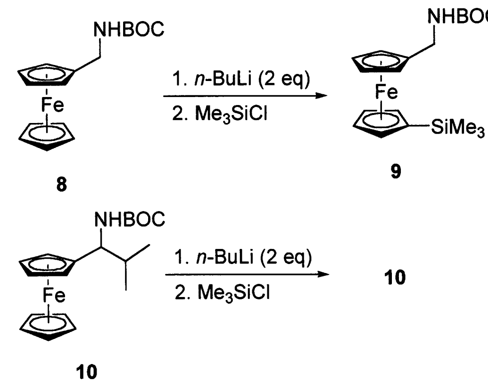
entry	E^+	E	product	yield (%)[a]
1	CO_2, CH_2N_2	CO_2Me	**7a**	96
2	Me_3SiCl	Me_3Si	**7b**	95
3	Me_3SnCl	Me_3Sn	**7c**	86
4	I_2	I	**7d**	71
5	Me_2NCHO	C(O)H	**7e**	84
6	$Ph_2C{=}O$	Ph_2COH	**7f**	97
7	PhCHO	CH(OH)Ph	**7g**[b]	80

[a] Isolated yield of chromatographed product. [b] Isolated as a 3:1 mixture of diastereomers.

Ferrocenylethylamine[12] and other related primary amines are readily available in enantioenriched form[16] and so could be used to prepare novel derivatives of use as chiral ligands and auxiliaries. In addition, such chiral derivatives might be useful as materials with nonlinear optical and liquid crystalline properties.[17] Previous routes to 1,1′-disubstituted ferrocenes typically begin with symmetrical compounds (e.g. 1,1′-dibromoferrocene,[17] 1,1′-bis(tributylstannyl)ferrocene,[18] 1,1′-ferrocenedicarbaldehyde[19]) and thus often experience problems with statistics. Therefore, we decided to examine the lithiation of **5** and related compounds more closely.

Treatment of **5** with *n*-BuLi (2 equiv, THF, −40 °C) followed by a variety of electrophiles afforded 1,1′-disubstituted products cleanly with no evidence of other isomers or multiple substitution (Table 1). The trimethylstannyl (**7c**) and iodo (**7d**) products are particularly interesting, as they are potential substrates for cross-

Scheme 3



coupling reactions.[20] Essentially identical results were obtained using *t*-BuLi or *n*-BuLi/TMEDA for metalation, but no electrophile incorporation was observed with *n*-BuLi using ether as solvent. Also, only starting material was recovered when LDA was used as the base. Thus, it seems that metalation of **5** requires an alkyllithium base in THF.

To further probe the metalation of *N*-Boc-ferrocenylalkylamines, Boc derivatives of ferrocenylmethylamine[21] (**8**) and 1-ferrocenyl-2-methylpropylamine[22] (**10**) were prepared (Scheme 3). Methylamine derivative **8** behaved like its homologue **5**: metalation with *n*-BuLi (2 equiv, THF, −40 °C) followed by treatment with Me_3SiCl gave the 1,1′-disubstituted ferrocene **9** as the sole product in excellent yield. In contrast, the isopropyl-substituted amine **10** resisted metalation even with excess *n*-BuLi at 0 °C. Perhaps the isopropyl group in **10** sterically encumbers coordination of the Boc group to *n*-BuLi, and thus lithiation is not facilitated as it is in compounds **5** and **8**.

Other amine derivatives that have been shown to be useful for lithiations of benzylamines were also examined (Scheme 4).[23] Ureas **11a**−**c** were readily prepared from 1-ferrocenylethylamine and the corresponding dialkylcarbamyl chloride while pivalamide **14** was made using pivaloyl chloride. Dimethylurea **11a** could be completely metalated under the “usual” conditions (2 equiv of *n*-BuLi, THF, −40 °C) to give, after Me_3SiCl trapping, a mixture of 1,2-disubstituted **12a** and 1,1′-disubstituted **13a** in a ratio of 1:3, respectively. Diethylurea **11b** behaved similarly and gave a similar (**12b**:**13b** = 1:4) mixture of products. Diisopropylurea **11c**, like isopropyl-substituted derivative **10**, proved to be more resistant to metalation: an excess (5 equiv) of *n*-BuLi was needed to obtain significant metalation. Here a 1:2 (**12c**:**13c**) mixture was obtained. For each of these ureas, the 1,2-disubstituted product **12** was isolated as a single diastereomer.[24] Finally, pivalamide **14** afforded a mixture of products, of which 1,2-disub-

(15) (a) Iftime, G.; Daran, J. C.; Manoury, E.; Balavoine, G. G. A. *Organometallics* **1996**, *15*, 4808−4815. (b) Iftime, G.; Daran, J. C.; Manoury, E.; Balavoine, G. G. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1698−1701. (c) Chiffre, J.; Coppel, Y.; Balavoine, G. G. A.; Daran, J. C.; Manoury, E. *Organometallics* **2002**, *21*, 4552−4555.

(16) In our hands, CBS reduction of acetylferrocene gave (*R*)-1-ferrocenylethanol with >98% ee, essentially as described in ref 12b. $[\alpha]^{22}_D = -12.9°$ (c = 1.1, EtOAc), −31.6° (c = 1.05, C_6H_6); lit.[12a] $[\alpha]^{22}_D = -30.5°$ (c = 1.1, C_6H_6). Conversion of this alcohol to 1-ferrocenylethylamine and derivatization with (*S*)-MTPA-Cl gave a single amide (^{19}F NMR −68.5 ppm vs −68.6 ppm for the other diastereomer).

(17) Lai, L.-L.; Dong, T.-Y. *J. Chem. Soc., Chem. Commun.* **1994**, 2347−2348

(18) Liu, C.-M.; Guo, Y.-L.; Wu, X.-I.; Liang, Y.-M.; Ma, Y.-X. *J. Organomet. Chem.* **2000**, *612*, 172−175.

(19) Argyropoulos, N.; Coutouli-Argyropoulou, E. *J. Organomet. Chem.* **2002**, *654*, 117−122.

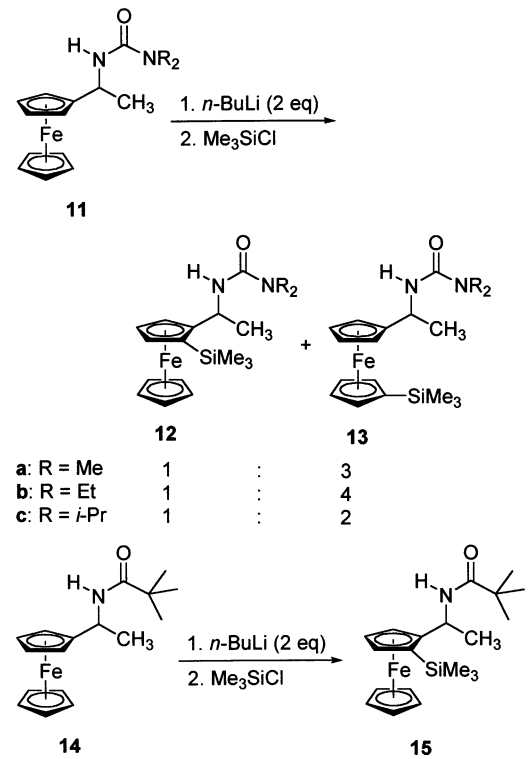
(20) Stille and Suzuki couplings of ferrocene derivatives have been described: (a) Kasak, P.; Miklas, R.; Putala, M. *J. Organomet. Chem.* **2001**, *637*−*639*, 318−326. (b) Liu, C.-M.; Liang, Y.; Wu. X.; Liu, W.; Ma, Y. *J. Organomet. Chem.* **2001**, *637*−*639*, 723−726. (c) Liu, C.-M.; Guo, Y.-L.; Wu, X.; Liang, Y.; Ma, Y. *J. Organomet. Chem.* **2000**, *612*, 172−175. (d) Jensen, J. F.; Søtofte, I.; Sørensen, H. O.; Johannsen, M. *J. Org. Chem.* **2003**, *68*, 1258−1265.

(21) Widhalm, M.; Nettekoven, U.; Mereiter, K. *Tetrahedron: Asymmetry* **1999**, *10*, 4369−4391.

(22) Cushman, M.; Chen, J. K. *J. Org. Chem.* **1987**, *52*, 1517−1521.

(23) Katsoulos, G.; Schlosser, M. *Tetrahedron Lett.* **1993**, *34*, 6263−6264.

Scheme 4



stituted derivative **15** was the major (~90%) product and could be isolated as a single diastereomer in 78% yield.

Overall, there seems to be no obvious correlation between the structure of the N-protecting group and the regioselectivity of lithiation for the ferrocenylalkylamines examined. Nonetheless, it is noteworthy that Boc derivatives such as **5** and **8** are quite special in their ability to undergo 1′-lithiation with very high regioselectivities. Electrophilic trapping allows for the preparation of unsymmetrical 1,1′-disubstituted ferrocenes in excellent yields.

Experimental Section

All reactions were carried out under argon using flame-dried glassware. NMR data were recorded on 300 MHz (300 MHz for ^{1}H, 75 MHz for ^{13}C) instruments in $CDCl_3$ unless otherwise noted. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Ether and THF were distilled from Na/benzophenone. Alkyllithiums were purchased from Aldrich Chemical Co. and were titrated using *N*-benzylbenzamide.[25] 1-Ferrocenylethylamine[12b] and ferrocenylmethylamine[19] were prepared from the corresponding acetates using aqueous NH_3 with sonication.

***N*-Boc-1-ferrocenylethylamine (5).** A solution of 1-ferrocenylethylamine (1.162 g, 5.07 mmol), Et_3N (1 mL), and $(BOC)_2O$ (1.33 g, 6 mmol) in THF (25 mL) was stirred at ambient temperature for 2 h. The mixture was diluted with ether, washed twice with water, dried (Na_2SO_4), and concentrated. Purification of the resulting residue by flash chromatography (CH_2Cl_2) provided a yellow solid that was recrystallized from hexanes to afford **5** (1.64 g, 98% yield) as orange crystals. Mp: 87−88 °C. IR (cast): 3349 (br), 1699, 1172 cm^{-1}. ^{1}H NMR: δ 4.68 (br s, 1H), 4.57 (br s, 1H), 4.17 (s, 5H), 4.2−4.1 (m, 4H), 1.47 (s, 9H), 1.42 (d, J = 7 Hz, 3H). ^{13}C NMR: δ 154.9, 92.0, 79.0, 68.4 (5C), 67.8, 67.4, 66.8, 65.7, 44.9, 28.4 (3C), 21.5. MS (FAB): *m/z* 329 (M$^+$, 100), 273 (28), 213 (35). Anal. Calcd for $C_{17}H_{23}FeNO_2$: C, 62.02; H, 7.04; N, 4.25. Found: C, 62.22; H, 6.81; N, 4.34. (*R*)-**5**: $[\alpha]^{22}_D$ = −16.1 (c = 1.8, EtOAc).

General Procedure for the Lithiation of *N*-Boc-1-ferrocenylethylamine (5) and Reaction with Electrophiles. To a cold (−50 °C), stirred solution of **5** (0.3 mmol) in THF was added *n*-BuLi (1.6 M in hexanes, 0.75 mmol), and the resulting orange solution was stirred at −50 °C for 2 h. It was then cooled to −78 °C, the appropriate electrophile (0.9 mmol) was added, and the resulting mixture was stirred at −78 °C for 20 min and then warmed to room temperature. Standard aqueous workup using ether/aqueous NH_4Cl provided crude materials which were purified by flash chromatography on silica gel using hexanes−ether mixtures.

Methyl 1′-(*N-tert*-butoxycarbonyl-1-aminoethyl)-1-ferrocenecarboxylate (7a). This compound was prepared according to the general procedure using solid CO_2 as the electrophile. The crude resulting crude carboxylic acid was treated with excess CH_2N_2 (prepared from *N*-methyl-*N*-nitrosourea[26]). From 119 mg of **5**, there was obtained, after flash chromatography (hexanes/ether, 2:1), 135 mg (96%) of **7a** as a red oil. IR (neat): 3363 (br), 1714, 1280, 1172 cm^{-1}. ^{1}H NMR: δ 4.98 (br s, 1H), 4.81 (br s, 2H), 4.53 (m, 1H), 4.41 (br s, 2H), 4.22 (br s, 1H), 4.17 (br s, 2H), 4.09 (br s, 1H), 3.82 (s, 3H), 1.48 (s, 9H), 1.42 (d, J = 7 Hz, 3H). ^{13}C NMR: δ 171.7, 154.9, 93.8, 79.0, 71.6, 71.1, 70.6, 70.2, 69.3, 69.1, 67.9, 67.8, 51.6, 44.2, 28.4, 21.2. MS (ESI): *m/z* 387 (M$^+$, 28), 332 (16), 271 (100). Anal. Calcd for $C_{19}H_{25}FeNO_4$: C, 58.93; H, 6.51; N, 3.62. Found: C, 59.16; H, 6.27; N, 3.60.

1-(*N-tert*-butoxycarbonyl-1-aminoethyl)-1′-trimethylsilylferrocene (7b). This compound was prepared according to the general procedure using chlorotrimethylsilane as the electrophile. From 139 mg of **5** there was obtained, after flash chromatography (hexanes/ether, 6:1), 161 mg (95%) of **7b** as a yellow solid. Mp: 63−65 °C. IR (cast): 3352 (br), 1714, 1247, 1165 cm^{-1}. ^{1}H NMR: δ 4.72 (br s, 1H), 4.58 (br s, 1H), 4.34 (br s, 2H), 4.16 (br s, 1H), 4.13−4.09 (m, 5H), 1.50 (s, 9H), 1.44 (d, J = 7 Hz, 3H), 0.25 (s, 9H). ^{13}C NMR: δ 154.9, 92.0, 79.1, 73.3, 73.1, 72.5, 71.4, 68.7, 68.1, 67.8, 66.9, 65.8, 44.9, 28.4, 21.6, −0.2. MS (FAB) *m/z* 401 (M$^+$, 100), 345 (30), 285 (34). Anal. Calcd for $C_{20}H_{31}FeNO_2Si$: C, 59.85; H, 7.78; N, 3.49. Found: C, 59.91; H, 7.71; N, 3.26.

1-(*N-tert*-butoxycarbonyl-1-aminoethyl)-1′-trimethylstannylferrocene (7c). This compound was prepared according to the general procedure using chlorotrimethylstannane as the electrophile. From 145 mg of **5**, there was obtained, after flash chromatography (hexanes/ether, 6:1), 187 mg (86%) of **7c** as a red solid. Mp: 45−47 °C. IR (cast): 3353 (br), 1713, 1172 cm^{-1}. ^{1}H NMR: δ 4.72 (br s, 1H), 4.58 (br s, 1H), 4.36 (br s, 2H), 4.2−4.0 (m, 6H), 1.49 (s, 9H), 1.44 (d, J = 7 Hz, 3H), 0.29 (s, 9H, J_{Sn-H} = 55 Hz). ^{13}C NMR: δ 155.0, 91.9, 79.1, 74.5 (J_{Sn-C} = 49 Hz), 74.4 (J_{Sn-C} = 49 Hz), 71.2 (J_{Sn-C} = 38 Hz), 69.3, 67.9, 67.5, 67.0, 65.6, 44.9, 28.4, 21.6, −8.7 (J_{Sn-C} = 340/355 Hz). MS (ESI): *m/z* 493 (M + H$^+$, 12), 422 (3), 376 (3), 213 (100). Anal. Calcd for $C_{20}H_{31}FeNO_2Sn$: C, 48.82; H, 6.35; N, 2.85. Found: C, 48.94; H, 6.55; N, 2.85. (*R*)-**7c**: $[\alpha]^{22}_D$ = −15.5 (c = 1.6, EtOAc).

1-(*N-tert*-butoxycarbonyl-1-aminoethyl)-1′-iodoferrocene (7d). This compound was prepared according to the general procedure using iodine as the electrophile. From 157 mg of **5**, there was obtained, after flash chromatography (hexanes/ether, 5:1), 153 mg (71%) of **7d** as a red oil which solidified on standing. Mp: 62−64 °C. IR (neat): 3349 (br), 1693, 1245, 1168 cm^{-1}. ^{1}H NMR: δ 4.72 (br s, 1H), 4.62 (m,

(24) When *t*-BuLi was used in place of *n*-BuLi, mixtures of **12** and **13** were formed and **12** was isolated as an inseparable mixture of diastereomers with modest (~3:1) stereoselectivity.

(25) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281−283.

(26) Arndt, F. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, pp 165−167.

1H), 4.39 (br s, 2H), 4.20−4.04 (m, 6H), 1.47 (s, 9H), 1.43 (d, J = 7 Hz, 3H). ^{13}C NMR: δ 154.8, 93.6, 79.2, 75.0, 74.9, 71.2, 70.9, 69.7, 69.4, 69.2, 44.7, 39.8, 28.5, 21.9. MS (FAB): *m*/*z* 455 (M$^+$, 100), 399 (30), 385 (10), 329 (50). (*R*)-**7d**: $[\alpha]^{22}{}_D$ = −7.5 (*c* = 2.7, EtOAc).

1′-(*N-tert*-butoxycarbonyl-1-aminoethyl)ferrocenecarbaldehyde (7e). This compound was prepared according to the general procedure using *N*,*N*-dimethylformamide as the electrophile. From 151 mg of **5**, there was obtained, after flash chromatography (hexanes/ether, 1:1), 138 mg (84%) of **7e** as a red oil. IR (neat): 3345 (br), 1682, 1246, 1171 cm^{-1}. ^{1}H NMR: δ 9.97 (s, 1H), 4.80−4.50 (m, 5H), 4.22 (br s, 4H), 1.48 (s, 9H), 1.39 (d, J = 7 Hz, 3H). ^{13}C NMR: δ 193.4, 155.0, 94.3, 79.4, 79.2, 73.7, 70.2, 70.0, 69.96, 69.8, 69.2, 69.0, 68.0, 67.4, 44.4, 28.3, 21.6. MS (FAB): *m*/*z* 357 (M$^+$, 65), 307 (33), 154 (100). Anal. Calcd for $C_{20}H_{23}FeNO_3$: C, 60.52; H, 6.49; N, 3.92. Found: C, 60.40; H, 6.60; N, 3.90.

[1′-(*N-tert*-butoxycarbonyl-1-aminoethyl)ferrocenyl]diphenylmethanol (7f). This compound was prepared according to the general procedure using benzophenone as the electrophile. From 154 mg of **5**, there was obtained, after flash chromatography (hexanes/ether, 4:1), 232 mg (97%) of **7f** as a red oil. IR (neat): 3434 (br), 3334 (br), 1693, 1170, 701 cm^{-1}. ^{1}H NMR: δ 7.35−7.22 (m, 10H), 5.22 (br s, 1H), 4.43 (br s, 1H), 4.29−3.99 (m, 8H), 3.27 (s, 1H), 1.45 (s, 9H), 1.30 (d, J = 7 Hz, 3H). ^{13}C NMR: δ 155.1, 147.2, 146.8, 127.5, 127.4, 126.9, 98.6, 93.4, 79.1, 77.8, 69.3, 69.1, 68.4, 68.1, 67.5, 44.6, 28.6, 21.6. MS (FAB): *m*/*z* 511 (M$^+$, 100), 494 (27), 225 (25). Anal. Calcd for $C_{30}H_{33}FeNO_3$: C, 70.45; H, 6.50; N, 2.74. Found: C, 70.60; H, 6.48; N, 2.61.

[1′-(*N-tert*-butoxycarbonyl-1-aminoethyl)ferrocenyl]phenylmethanol (7g). This compound was prepared according to the general procedure using benzaldehyde as the electrophile. From 148 mg of **5**, there was obtained, after flash chromatography (hexanes:ether, 3:2), 157 mg (80%) of **7g** as a red oil. ^{1}H NMR data show the presence of two diastereomers in a 72:28 ratio. IR (neat): 3394 (br), 1691, 1170 cm^{-1}. ^{1}H NMR: δ 7.41−7.25 (m, 5H), 5.50 (br s, 0.72H), 5.28 (br s, 0.28H), 4.6−4.1 (m, 10H), 1.50 (s, 9H), 1.43 (d, J = 7 Hz, 0.8H), 1.41 (d, J = 7 Hz, 2.2H). ^{13}C NMR: δ 155.1, 143.5, 131.7, 128.4, 128.3, 128.2, 127.6, 127.5, 126.2, 126.1, 94.0, 93.1, 79.2, 72.5, 72.2, 72.1, 71.7, 69.8, 68.6, 68.3, 68.0, 67.9, 67.7, 67.3, 66.8, 66.1, 44.9, 28.5, 21.8, 21.7. MS (ESI): *m*/*z* 435 (M$^+$, 81), 418 (47), 214 (52), 158 (100) Anal. Calcd for $C_{24}H_{29}FeNO_3$: C, 66.22; H, 6.71; N, 3.22. Found: C, 65.93; H, 6.96; N, 3.01.

***N*-Boc-1-ferrocenylmethylamine (8).** A solution of 1-ferrocenylmethylamine[19] (0.70 g, 3.3 mmol), Et_3N (0.7 mL) and $(BOC)_2O$ (1.07 g, 4.9 mmol) in THF (10 mL) was stirred at ambient temperature for 2 h. The mixture was diluted with ether, washed twice with water, dried (Na_2SO_4), and concentrated. Purification of the resulting residue by flash chromatography (hexanes:ether:CH_2Cl_2, 8:2:1) provided a yellow solid which was recrystallized from hexanes to afford **8** (0.70 g, 68% yield) as orange crystals. Mp 91−92 °C. IR (cast): 3387 (br), 1693, 1504, 1163 cm^{-1}; ^{1}H NMR: δ 4.68 (br s, 1H), 4.18 (br s, 5 + 2H), 4.14 (s, 2H), 3.99 (d, J = 5 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR: δ 154.4, 85.6, 79.0, 68.3 (5C), 67.8, 39.6, 28.3 (3C). MS (FAB): *m*/*z* 315 (M$^+$, 100), 259 (35), 199 (31). Anal. Calcd for $C_{16}H_{21}FeNO_2$: C, 60.97; H, 6.72; N, 4.44. Found: C, 60.76; H, 6.78; N, 4.45.

1-(*N-tert*-butoxycarbonylaminomethyl)-1′-trimethylsilylferrocene (9). This compound was prepared according to the general procedure using chlorotrimethylsilane as the electrophile. From 98 mg of **8**, there was obtained, after flash chromatography (hexanes/ether, 6:1), 107 mg (89%) of **9** as an orange oil which, upon standing, became a yellow solid. Mp: 71−72 °C. IR (cast): 3394 (br), 1692, 1162 cm^{-1}. ^{1}H NMR: δ 4.74 (br s, 1H), 4.33 (s, 2H), 4.16 (s, 2H), 4.10 (d, J = 5 Hz), 4.09 (s, 4H), 1.47 (s, 9H), 0.24 (s, 9H). ^{13}C NMR: δ 155.5, 85.6, 79.2, 73.3 (2C), 72.6, 71.4 (2C), 68.2 (2C), 68.1 (2C), 39.7, 28.4 (3C), −0.3 (3C). MS (FAB): *m*/*z* 387 (M$^+$, 100), 331 (36), 271 (28). Anal. Calcd for $C_{19}H_{29}FeNO_2Si$: C, 58.76; H, 7.79; N, 3.61. Found: C, 58.95; H, 7.50; N, 3.64.

***N*-Boc-1-ferrocenyl-2-methylpropylamine (10).** A solution of 1-ferrocenyl-2-methylpropylamine[22] (1.00 g, 3.9 mmol) and $(BOC)_2O$ (0.98 g, 4.5 mmol) in THF (25 mL) was stirred at ambient temperature for 2 h. The mixture was diluted with ether, washed twice with water, dried (Na_2SO_4), and concentrated. The resulting yellow solid was recrystallized from hexanes to afford **10** (1.25 g, 90% yield) as yellow needles. Mp: 125−126 °C. IR (KBr): 3326, 1670, 1541, 1171 cm^{-1}. ^{1}H NMR: δ 4.82 (br d, 1H, J = 5 Hz), 4.34 (dd, J = 5, 7 Hz, 1H), 4.18 (s, 5H), 4.14 (br s, 1H), 4.10 (br s, 2H), 3.98 (br s, 1H), 1.79 (octet, J = 7 Hz, 1H), 1.51 (s, 9H), 0.82 (d, J = 7 Hz, 3H), 0.78 (d, J = 7 Hz, 3H). ^{13}C NMR: δ 155.4, 90.1, 78.9, 68.7 (5C), 68.4, 67.2, 67.0, 65.0, 55.0, 34.6, 28.4 (3C), 18.8, 17.8. MS (ESI): *m*/*z* 357 (M$^+$, 100). Anal. Calcd for $C_{19}H_{27}FeNO_2$: C, 63.87; H, 7.62; N, 3.92. Found: C, 64.05; H, 7.42; N, 4.00.

General Procedure for the Preparation of Ureas 11. To a cold (−78 °C), stirred solution of 1-ferrocenylethylamine (4 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (6 mmol) followed by the appropriate dialkylcarbamyl chloride (4.8 mmol). The reaction mixture was warmed to ambient temperature and stirred for 12 h. Water was added, and the mixture was stirred vigorously for 30 min. The usual aqueous workup involving dilution with ether and sequential washing with water, 1 M HCl, saturated $NaHCO_3$, and brine, followed by drying ($MgSO_4$) and concentration, afforded the crude ureas **11**, which were further purified by chromatography or crystallization.

***N*-1-Ferrocenylethyl-*N*′,*N*′-dimethylurea (11a).** Treatment of 1-ferrocenylethylamine with dimethylcarbamyl chloride as described above gave **11a** as orange crystals, which were recrystallized from hexanes (86% yield): Mp: 107−110 °C. IR (KBr): 3379, 1625, 1527 cm^{-1}; ^{1}H NMR: δ 4.71 (quintet, J = 7 Hz, 1H), 4.61 (br d, J = 7 Hz, 1H), 4.21−4.09 (m, 4H), 4.15 (s, 5H), 2.91 (s, 6H), 1.44 (d, J = 7 Hz, 3H); ^{13}C NMR: δ 157.3, 92.4, 68.2 (5C), 67.8, 67.42, 67.35, 65.6, 44.5, 36.0 (2C), 21.4. MS (ESI): *m*/*z* 300 (M$^+$, 3), 213 (100). Anal. Calcd for $C_{15}H_{20}FeN_2O$: C, 60.02; H, 6.72; N, 9.33. Found: C, 59.96; H, 6.92; N, 9.49.

***N*-1-Ferrocenylethyl-*N*′,*N*′-diethylurea (11b).** Treatment of 1-ferrocenylethylamine with diethylcarbamyl chloride as described above gave **11b**, which was purified by flash chromatography on silica gel (hexanes/ether, 1:1) to provide a tan solid (88% yield): Mp: 76−77 °C. IR (KBr): 3455, 1639, 1504 cm^{-1}. ^{1}H NMR: δ 4.74 (quintet, J = 7 Hz, 1H), 4.57 (br d, J = 7 Hz, 1H), 4.17 (br s, 1H), 4.15 (s, 5H), 4.15−4.09 (m, 3H), 3.27 (q, J = 7 Hz, 4H), 1.43 (d, J = 7 Hz, 3H), 1.16 (t, J = 7 Hz, 6H). ^{13}C NMR: δ 155.8, 92.4, 67.8 (5C), 67.4, 67.1, 66.8, 65.3, 43.8, 40.7 (2C), 21.2, 13.6 (2C). MS (FAB): *m*/*z* 328 (100, M$^+$), 263 (10), 213 (37). Anal. Calcd for $C_{17}H_{24}FeN_2O$: C, 62.21; H, 7.37; N, 8.53. Found: C, 62.08; H, 7.20; N, 8.42.

***N*-1-Ferrocenylethyl-*N*′,*N*′-diisopropylurea (11c).** Treatment of 1-ferrocenylethylamine with diisopropylcarbamyl chloride as described above gave **11c**, which was purified by flash chromatography on silica gel (hexanes/ether, 3:2) to provide a thick red oil (83% yield): IR (neat): 3375, 1637 cm^{-1}. ^{1}H NMR: δ 4.82 (br s, 1H), 4.48 (br s, 1H), 4.4.2−4.1 (m, 4H), 4.19 (s, 5H), 3.92 (br s, 2H), 1.47 (br s, 3H), 1.28 (br 2, 12H). ^{13}C NMR: δ 155.9, 92.5, 67.9 (5C), 67.4, 67.0, 66.6, 65.4, 44.6 (2C), 43.7, 21.5, 21.11 (2C), 21.05 (2C). MS (FAB): *m*/*z* 356 (100), 213 (35). Anal. Calcd for $C_{19}H_{28}FeN_2O$: C, 64.05; H, 7.92; N, 7.86. Found: C, 64.22; H, 8.15; N, 7.79.

***N*-1-(2-Trimethylsilylferrocenyl)ethyl-*N*′,*N*′-dimethylurea (12a) and *N*-1-(1′-Trimethylsilyl-ferrocenyl)ethyl-*N*′,*N*′-dimethylurea (13a).** Lithiation of urea **11a** and trapping with Me_3SiCl as described for **5** provided the 1,2-disubstituted isomer **12a** and the 1,1′-disubstituted isomer **13b** in a ratio of 23:77, respectively, as determined by integration of the ^{1}H NMR spectrum of crude material. These compounds were separated by flash chromatography on silica gel (CH_2Cl_2/ether, 3:1) to give **12a** (R_f = 0.53, double elution with CH_2-

Cl_2/ether, 2:1) followed by **13a** (R_f = 0.41, double elution with CH_2Cl_2/ether, 2:1). **12a**: orange solid (16% yield). Mp: 105−108 °C. IR (cast): 3332 (br), 1630, 1522 cm^{-1}. ^{1}H NMR: δ 4.81 (m, 1H), 4.38 (br s, 1H), 4.28 (br s, 1H), 4.19 (br s, 1H), 4.11 (s, 5H), 4.06 (br s, 1H), 2.80 (br s, 6H), 1.51 (d, *J* = 6 Hz, 3H), 0.24 (s, 9H). ^{13}C NMR: δ 156.9, 95.2, 74.8, 71.7, 69.6, 69.2 (5C), 46.1, 36.1 (2C), 20.9, 0.1 (3C). MS (FAB): *m/z* 372 (100, M$^+$), 307 (8), 285 (40). Anal. Calcd for $C_{18}H_{28}FeN_2OSi$: C, 58.06; H, 7.58; N, 7.52. Found: C, 58.09; H, 7.76; N, 7.22. **13a**: orange solid (55% yield). Mp: 95−96 °C. IR (cast): 3258, 1625, 1530, 830 cm^{-1}. ^{1}H NMR: δ 4.74 (quintet, *J* = 7 Hz, 1H), 4.54 (br d, *J* = 7 Hz, 1H), 4.29 (br s, 2H), 4.19 (br s, 1H), 4.13−4.05 (m, 5H), 2.90 (s, 6H), 1.44 (d, *J* = 7 Hz, 3H), 0.20 (s, 9H). ^{13}C NMR: δ 157.4, 92.3, 73.3, 72.9, 72.6, 71.4, 71.3, 68.3, 67.9, 67.6, 65.6, 44.7, 36.1 (2C), 21.5, −0.2 (3C). MS (FAB): *m/z* 372 (100, M$^+$), 285 (33), 235 (11). Anal. Calcd for $C_{18}H_{28}FeN_2OSi$: C, 58.06; H, 7.58; N, 7.52. Found: C, 57.86; H, 7.34; N, 7.38.

***N*-1-(2-Trimethylsilylferrocenyl)ethyl-*N′*,*N′*-diethylurea (12b) and *N*-1-(1′-Trimethylsilylferrocenyl)ethyl-*N′*,*N′*-diethylurea (13b).** Lithiation of urea **11b** and trapping with Me_3SiCl as described for **5** provided the 1,2-disubstituted isomer **12b** and the 1,1′-disubstituted isomer **13b** in a ratio of 18:82, respectively, as determined by integration of the ^{1}H NMR spectrum of crude material. These compounds were separated by flash chromatography on silica gel (hexanes/ether, 4:5) to give **12b** (R_f = 0.23) followed by **13b** (R_f = 0.17). **12b**: red oil (18% yield). IR (neat): 3353, 1634, 1504 cm^{-1}. ^{1}H NMR: δ 4.89 (m, 1H), 4.40 (br s, 2H), 4.30 (br s, 1H), 4.12 (s, 5H), 4.09 (br s, 2H), 3.3−3.0 (m, 4H), 1.52 (d, *J* = 6 Hz, 3H), 1.07 (t, *J* = 7 Hz, 6H), 0.27 (s, 9H). ^{13}C NMR: δ 155.6, 95.7, 74.9, 71.8, 69.7, 69.3 (5C), 69.2, 45.8, 40.8 (2C), 21.1, 13.8 (2C), 0.1 (3C). MS (FAB): *m/z* 400 (100, M$^+$), 335 (7), 285 (41). Anal. Calcd for $C_{20}H_{32}FeN_2OSi$: C, 59.99; H, 8.05; N, 7.00. Found: C, 60.23; H, 8.12; N, 6.85. **13b**: red oil (69% yield). IR (neat): 3351, 1622, 1526 cm^{-1}. ^{1}H NMR: δ 4.76 (m, 1H), 4.53 (m, 1H), 4.31 (br s, 2H), 4.18 (br s, 1H), 4.15−4.05 (m, 5H), 3.27 (q, *J* = 7 Hz, 4H), 1.44 (d, *J* = 6 Hz, 3H), 1.15 (t, *J* = 7 Hz, 3H), 0.21 (s, 9H). ^{13}C NMR: δ 156.3, 92.7, 73.4, 73.0, 72.6, 71.4, 71.3, 68.3, 68.0, 67.5, 65.7, 44.4, 41.1 (2C), 21.5, 13.9 (2C), 0.29 (3C). MS (FAB): *m/z* 400 (100, M$^+$), 327 (5), 285 (42), 263 (12). Anal. Calcd for $C_{20}H_{32}FeN_2OSi$: C, 59.99; H, 8.05; N, 7.00. Found: C, 60.12; H, 7.96; N, 7.11.

***N*-1-(2-Trimethylsilylferrocenyl)ethyl-*N′*,*N′*-diisopropylurea (12c) and *N*-1-(1′-Trimethylsilyl-ferrocenyl)-ethyl-*N′*,*N′*-diisopropylurea (13c).** Lithiation of urea **11c** and trapping with Me_3SiCl as described for **5** (with the exception that 5 equiv of n-BuLi was used) provided the 1,2-disubstituted isomer **12c** and the 1,1′-disubstituted isomer **13c** in a ratio of 35:65, respectively, as determined by integration of the ^{1}H NMR spectrum of crude material. These compounds were separated by flash chromatography on silica gel (hexanes/ether, 1:1) to give **12c** (R_f = 0.42) followed by **13c** (R_f = 0.26) as well as recovered starting material **11c** (29%). **12c**: orange crystals (26% yield). Mp: 97−99 °C. IR (cast): 1644, 1494 cm^{-1}. ^{1}H NMR: δ 4.88 (br quintet, *J* = 6 Hz, 1H), 4.39 (br s, 1H), 4.30 (br s, 1H), 4.12 (s, 5H), 4.06 (br s, 1H), 3.97 (br d, *J* = 6 Hz, 1H), 3.66 (br septet, *J* = 7 Hz, 2H), 1.51 (br d, *J* = 6 Hz, 3H), 1.18 (d, *J* = 7 Hz, 3H), 1.16 (d, *J* = 7 Hz, 6H), 0.27 (s, 9H). ^{13}C NMR: δ 155.4, 95.6, 74.6, 71.5, 69.5, 69.0 (5C), 68.8, 45.4, 45.2 (2C), 21.6, 21.23 (2C), 21.06 (2C), 0.18 (3C). MS (FAB): *m/z* 428 (100), 363 (5), 285 (35). Anal. Calcd for $C_{22}H_{36}FeN_2OSi$: C, 61.68; H, 8.47; N, 6.54. Found: C, 61.31; H, 8.48; N, 6.39. **13c**: red oil (38% yield). IR (neat): 3376, 1637, 1499 cm^{-1}. ^{1}H NMR: δ 4.80 (br s, 1H), 4.38 (br s, 1H), 4.33 (br s, 2H), 4.22−4.05 (m, 7H), 3.88 (m, 2H), 1.45 (br s, 3H), 1.26 (br d, *J* = 6 Hz, 12H), 0.20 (s, 9H). ^{13}C NMR; δ 156.3, 92.9, 73.4, 73.2, 72.6, 71.6, 71.5, 68.4, 68.0, 67.4, 65.9, 45.0 (2C), 44.4, 21.8, 21.55 (2C), 21.49 (2C), −0.24 (3C). MS (FAB): *m/z* 428 (100, M$^+$), 327 (9), 285 (51). Anal. Calcd for $C_{22}H_{36}FeN_2OSi$: C, 61.68; H, 8.47; N, 6.54. Found: C, 61.90; H, 8.62; N, 6.43.

***N*-Pivaloyl-1-ferrocenylethylamine (14).** To a solution of 1-ferrocenylethylamine (1.556 g, 6.79 mmol) in CH_2Cl_2 at −20 °C was added Et_3N (13.6 mmol) followed by pivaloyl chloride (10 mmol). The mixture was warmed to room temperature and was stirred for a further 1 h. The reaction was quenched with aqueous NH_4Cl and the mixture was diluted with ether. The organic layer was washed sequentially with water, 1 M HCl, and $NaHCO_3$, dried (Na_2SO_4), and concentrated. Purification of the resulting residue by flash chromatography (CH_2Cl_2:ether, 20:1) provided pivamide **14** as a yellow solid (1.91 g, 90% yield). Mp: 134−135.5 °C. IR (KBr): 3328, 1632, 1528 cm^{-1}. ^{1}H NMR: δ 5.89 (d, *J* = 6.3 Hz, 1H), 4.80 (dq, *J* = 6.3, 6.8 Hz, 1H), 4.16 (s, 5H), 4.14 (br s, 2H), 4.12 (m, 1H), 4.07 (m, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.22 (s, 9H). ^{13}C NMR: δ 176.8, 91.6, 68.2 (5C), 67.8, 67.6, 67.0, 65.5, 42.9, 38.4, 27.5 (3C), 20.6. MS (FAB): *m/z* 313 (M$^+$, 100), 248 (11), 213 (36). Anal. Calcd for $C_{17}H_{23}FeNO$: C, 65.19; H, 7.40; N, 4.47. Found: C, 64.90; H, 7.26; N, 4.47.

1-(*N*-Pivaloylaminoethyl)-2-trimethylsilylferrocene (15). This compound was prepared according to the general procedure for the lithiation of **5** using chlorotrimethylsilane as the electrophile. From 101 mg of **14**, there was obtained, after flash chromatography (CH_2Cl_2/ether, 30:1), 97 mg (78%) of **15** as a yellow solid. A minor (∼10%) lower R_f product (likely the 1,1′-disubstituted product) was not isolated. Since **15** exhibited a single set of ^{13}C NMR resonances, it is likely to be a single diastereomer. Mp: 114−116 °C. IR (KBr): 3320, 1630, 1519, 838 cm^{-1}. ^{1}H NMR: δ 5.38 (m, 1H), 4.89 (m, 1H), 4.41 (br s, 1H), 4.32 (br s, 1H), 4.13 (s, 5H), 4.09 (br s, 2H), 1.49 (d, *J* = 6 Hz, 3H), 1.11 (s, 9H), 0.26 (s, 9H). ^{13}C NMR: δ 176.3, 94.2, 74.7, 71.7, 69.9, 69.8, 69.1 (5C), 44.9/44.8, 38.3, 27.53/27.47, 20.1, 0.29/0.24. MS (ESI): *m/z* 408 (M + Na$^+$, 100), 385 (M$^+$, 29). Anal. Calcd for $C_{20}H_{31}FeNOSi$: C, 62.34; H, 8.11; N, 3.64. Found: C, 62.50; H, 8.34; N, 3.62.

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