Cephem-3-*C*-carboxamide (5) and Imide (6). The nitrone **2** (0.548 g) was dissolved in 30 ml of distilled acetic anhydride, acetic acid (4 drops) was added, and the solution was heated at 80° for 10 min and then cooled in an ice bath. Evaporation to dryness followed by chromatography on silica gel using a toluene–ethyl acetate gradient gave 0.161 g (27%) of the faster moving imide **6** and 0.287 g (52%) of the amide **5**.

5: needles from CH_2Cl_2–hexane; mp 196–197°; ir ($CHCl_3$) 1788 cm^{-1} (β-lactam); NMR (DMSO-d_6) δ 2.73 (d, J = 4 Hz, 3, N-Me), 3.85 (s, 2, thiophene methylene), 5.09 (d, J = 4 Hz, 1, H_6), 5.55 (q, J = 4, 8 Hz, 1, H_7), 5.70 (s, 1, H_4), 8.21 (d, J = 4 Hz, 1, NHMe). Anal. Calcd for $C_{28}H_{25}N_3O_5S_2$: C, 61.41; H, 4.60; N, 7.67. Found: C, 61.20; H, 4.42; N, 7.54.

6: ir ($CHCl_3$) 1792 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.07 (s, 3, $COCH_3$), 2.87 (s, 3, N-Me), 3.75 (s, 2, thiophene methylene), 5.10 (d, J = 4 Hz, 1, H_6), 5.50 (q, J = 4, 7 Hz, 1, H_7), 5.70 (s, 1, H_4).

3-Formyl-2-(methylamino)-2-cephem (8). The nitrone **2** (2.45 g, 4.48 mmol) in 100 ml of dry toluene was refluxed for 3 hr, evaporated to dryness, and chromatographed on silica gel using a hexane–toluene–ethyl acetate gradient to give 1.22 g of isomer I (eluted first) and 0.54 g of isomer II.

8a isomer I: needles from toluene–hexane; mp 176–177° (4-*C*-PNB, mp 192–193°); ir ($CHCl_3$) 1782 cm^{-1} (β-lactam); NMR (60 and 220 MHz) ($CDCl_3$) δ 2.90 (d, J = 4 Hz, 3, N-Me), 3.91 (s, 2, thiophene methylene), 5.27 (s, 1, H_4), 5.44 (d, J = 4 Hz, 1, H_6), 5.52 (q, J = 4, 8 Hz, 1, H_7), 8.86 (s, 1, CHO), 11.53, 11.62 (AB, J = 4 Hz, 1, NH); λ_{EtOH} 325 nm (ϵ 14,700). Anal. Calcd for $C_{28}H_{25}N_3O_5S_2$: C, 61.40; H, 4.60; N, 7.67. Found: C, 61.65; H, 4.38; N, 7.77.

8b isomer II: ir ($CHCl_3$) 1780 cm^{-1} (β-lactam); NMR (60 and 100 MHz) ($CDCl_3$) δ 2.86 (d, J = 4 Hz, 3, N-Me), 3.75 (s, 2, thiophene methylene), 4.97 (d, J = 2 Hz, 1, H_4), 5.02 (d, J = 4 Hz, 1, H_6), 5.40 (m, 1, H_7), 8.90 (s, 1, CHO) (220 MHz on D_2O shake shows the multiplet at 5.40 as a q, J = 2, 4 Hz, and shows H_4 to H_7 coupling); λ_{EtOH} 332 nm (ϵ 11,000).

2-(*N*-Methyl,*N*-acetyl)-3-formyl-2-cephem (9). Acetylation of **8a** and **8b** was accomplished in cold (5°) THF using 1.1 equiv of acetyl chloride and 2.0 equiv of $NaHCO_3$ for 40 min. The reaction mixture was combined with ETOAc, washed with $NaHCO_3$, H_2O, and brine, evaporated, and chromatographed on silica gel to acetylated derivatives **9a** (79%) from **8a** and **9b** (69%) from **8b**. The NMR spectra are similar, both showing N-methyl singlets, the major difference being the H_4 proton (**9a** δ 5.67, **9b** δ 5.15).

2-(*N*-Methyl,*N*-acetyl)-3-cephem Lactone (10). 9a (0.325 g) in 15 ml of dioxane plus 8 ml of water was cooled to ca. 5° and treated with 4 equiv of $NaBH_4$ in 2 ml of water for 15 min; 1 ml of 1 N HCl was added and when the reaction had ceased the mixture was diluted with EtOAc, washed with 1 N HCl and brine, evaporated, and chromatographed on silica gel to give 0.095 g (42%) of lactone. A similar run on **9b** gave 51% identical lactone: ir ($CHCl_3$) 1810 cm^{-1} (β-lactam); mass 407 (theory 407.46); NMR ($CDCl_3$) δ 2.12 (s, 3, N-Ac), 2.93 (s, 3, N-Me), 3.87 (s, 2, thiophene methylene), 4.85 (br s, 2, lactone methylene), 5.20 (d, J = 4 Hz, 1, H_6), 6.02 (q, J = 4, 9 Hz, 1, H_7), 6.70 (s, 1, H_2); λ_{EtOH} 255 nm (ϵ 10,500).

Tricyclic Pyrazole 12. The 3-formyl-2-cephem **1** was combined with 1.1 equiv of tosylhydrazine in 2B EtOH and refluxed for 1 hr. It was then evaporated to dryness and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 88% tosylhydrazone as a white froth: 0.609 g (0.89 mmol) of tosylhydrazone in 50 ml of dry benzene was treated with 1.2 equiv of 50% NaH and refluxed for 15 min. It was then cooled to room temperature, washed with 1 N HCl and brine, evaporated, and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.092 g (20%) of pyrazole as a crystalline white solid: needles from acetone–hexane: mp 198–199°; ir ($CHCl_3$) 1765 cm^{-1} (β-lactam); NMR (DMSO-d_6) δ 3.80 (s, 2, thiophene methylene), 5.37 (d, J = 4 Hz, 1, H_6), 5.57 (q, J = 4, 8 Hz, 1, H_7), 5.93 (s, 1, H_4), 7.79 (br s, 1, olefinic proton of pyrazole), 13.15 (br s, 1, NH of pyrazole). Anal. Calcd for $C_{27}H_{22}N_4O_4S_2$: C, 61.12; H, 4.18; N, 10.56; S, 12.09. Found: C, 60.96; H, 4.11; N, 10.53; S, 12.00.

Acknowledgment. We thank Mr. T. K. Elzey for running the 100-MHz and 220-MHz NMR spectra.

Registry No.—**1**, 55331-32-3; **2**, 55569-95-4; **3**, 55569-96-5; **4a**, 55569-97-6; **4a** sulfide, 55569-98-7; **4b**, 55569-99-8; **4b** sulfide, 55570-00-8; **4c**, 55570-01-9; **4c** sulfide, 55570-02-0; **5**, 55570-03-1; **6**, 55570-04-2; **7**, 55570-05-3; **8a**, 55570-06-4; **8b**, 55570-07-5; **9a**, 55570-08-6; **9b**, 55570-09-7; **10**, 55570-10-0; **11**, 55570-11-1; **12**, 55570-12-2.

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Nucleophilic Adducts of *N*-*tert*-Butyloxycarbonyl-1,1,1,3,3,3-hexafluoroisopropylimine. Facile Hydrolysis of Imidazole-Based Adducts[1,2]

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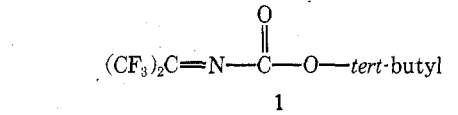
During the course of studies toward new blocking groups for the imidazole moiety of histidine,[3] we synthesized *N*-*t*-Boc-hexafluoroisopropylimine (**1**) and prepared its adducts with various nucleophiles including imidazole (adduct **2a**), N^{α}-Z-L-his-OCH_3 (adduct **2b**), water (adduct **3a**), methanol (adduct **3b**), and *tert*-butyl mercaptan (adduct **3c**). It



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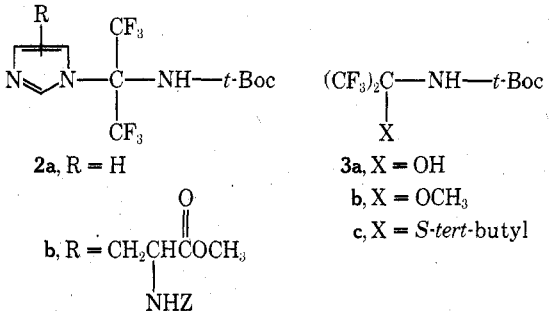


2a, R = H

3a, X = OH
b, X = OCH_3
c, X = *S*-*tert*-butyl

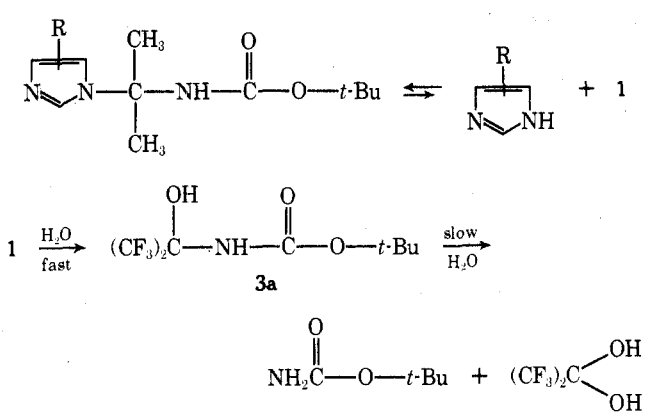
b, R = $CH_2CHCOCH_3$ (NHZ)

was found that although **3b** and **3c** are hydrolytically stable, the imidazole-based adducts **2a** and **2b** undergo facile hydrolysis; **2a** decomposes upon standing in air giving *O*-*tert*-butyl carbamate and **2b** cleaves in acetonitrile solution to which a small amount of water is added giving the carbamate and N^{α}-Z-his-OCH_3. This is surprising in view of the stability of many 1,1,1,3,3,3-hexahalopropanes bearing two heteroatoms at carbon 2 including **3b** and **3c** (unchanged after 124 and 179 hr in an aqueous environment), the incredible stability in both acid and base of ketals and *gem*-amino ethers of fluorinated ketones,[3-5] and the stability of analogs of **2b** containing a single trifluoromethyl group derived from trifluoroacetaldehyde.[6] Simple *gem*-diamines based on hexafluoroacetone have been reported to decompose with HCl in ether.[7] Details of the hydrolysis of **2b** were examined by NMR spectroscopy.

Water, 2–3 equiv, was added to a solution of **2b** in CD_3CN and the NMR spectrum monitored for 147.5 hr, during which time three separate resonances were seen for the *tert*-butyl protons. During the first 4.75 hr the resonance at δ1.42 of **1b** is seen to diminish while a resonance at δ1.48 appears along with a very small signal at δ1.43. After 18 hr the original resonance has disappeared and after 70 hr that at δ1.48 has been almost entirely replaced by that at δ1.43. This latter resonance belongs to *O-tert*-butyl carbamate which is isolated at the end of the experiment; moreover, the only Pauly position spot[8] on TLC is N^{α}-Z-his-OCH_3.[9] There are corresponding changes in the resonance of the imidazole C-2 and C-4 protons as deblocking occurs; the resonance of the former shifts from δ7.78 to δ7.72, and that of the latter at δ7.11 is replaced by a new band at δ6.90. This process parallels the formation of the δ1.48 *tert*-butyl resonance but is complete and stabilized within the 18-hr period.

We favor the hydrolytic mechanism shown in Scheme I; this scheme is directly supported by the NMR data, which show two observable reactions occurring at different rates and a *tert*-butyl-containing intermediate on the path from **1b** to *tert*-butyl carbamate. Assignment of the δ1.48 intermediate as compound **3a** is based on (1) its experimentally determined chemical shift as δ0.05 downfield of *tert*-butyl carbamate in a similar medium, (2) the precedented[7,10,11] equilibrium of fluorimines and addends with their adducts, and (3) the known hydration of fluorimines[10] including **1**.[12]

Scheme I



A hydrolytic mechanism involving water as a nucleophile in an SN2 displacement would not be acceptable at a tertiary center and is incompatible with the marked stability of the less hindered monotrifluoromethyl analogs. An SN1 mechanism is highly unlikely considering the carbonium ion destabilization by unattached trifluoromethyl groups, dramatically shown recently by the bimolecular displacement of nitrogen from hexafluoroisopropyldiazonium ion.[13] The need for a protic nitrogen is indicated by the hydrolytic stability of **3b** and **3c**; N^{α}-Z,N^{im}-[1,1,1,3,3,3-hexafluoro-2-(*p*-chlorophenoxymethoxy)propyl]-L-his-OCH_3[3] is stable to water, aqueous citric acid, and aqueous sodium hydroxide. Thus, the equilibrium in Scheme I probably requires prior ionization of the nitrogen proton. Steric hindrance may provide a driving force for the initial equilibrium of **2a,b** relative to trifluoroacetaldehyde-based derivatives, analogous to the unfavorable bisulfite addition equilibrium with ketones relative to aldehydes. Along these lines Banfield et al.[14] have shown that the addition of nucleophiles to aromatic *N*-acylimines is unsuccessful with sterically hindered compounds. The reactivity of **2a,b** may be enhanced by the leaving ability of imidazole relative to simple amines; e.g., compare the reactivity of acylimidazoles[15] relative to normal amides.

Finally, adduct **3b** is stable to 0.5 *M* citric acid and to cyclohexylamine. Thus imine **1** may be an effective acid-labile blocking agent for alcohol functionalities in general.

Experimental Section

Thin layer chromatograms were obtained on commercially prepared fluorescent silica gel coated plates. Proton magnetic resonance spectra were obtained on a Varian T-60 spectrometer; variable temperature ^{19}F spectra were obtained on a Bruker B-90C NMR spectrometer at 84.66 Hz.

***N*-*t*-Boc-hexafluoroisopropylimine (1).** To *tert*-butyl carbamate (2.34 g, 0.02 mol) dissolved in 100 ml of anhydrous ether in a 200-ml glass bomb fitted with a Dry Ice–acetone cold finger condenser and drying tube was added hexafluoroacetone (6.6 g, 0.04 mol). The sealed bomb was partially immersed in a 75–90° water bath for 2 hr. The cooled bomb was opened, the ether was removed by flash evaporation and the liquid residue, 1,1,1,3,3,3-hexafluoro-2-hydroxy-*N*-*tert*-butyloxycarbonylisopropylamine, (**3a**), was distilled: bp 80.5° (24 mm); mp 36.5–39°; 3.39 g (60%). The use of 10 equiv of hexafluoroacetone did not affect the yield; large-scale reactions were carried out in steel bombs.

Anal. Calcd for $C_8H_{11}NO_3F_6$: C, 33.91; H, 3.92; N, 4.95; F, 40.26. Found: C, 34.15; H, 4.08; N, 5.14; F, 39.99.

A round-bottom flask fitted with thermometer, drying tube, stirring bar, and pressure-equalizing dropping funnel containing the carbinol (56.2 g, 0.20 mol) in 50 ml of dry quinoline was charged with 80 ml of dry quinoline, 36.5 ml (0.40 mol) of $POCl_3$, and boiling stones. The alcohol solution was added dropwise over a 0.75-hr period and the reaction mixture was stirred for another 1 hr. The product was then vacuum distilled into a chilled receiver (−78°) until a pot temperature of 105° (23 mm) was reached. Redistillation through a porcelain-packed column gave 26.0 g (49%) yield of imine, bp 46–49° (24 mm). GLC showed the product to be free of $POCl_3$: ^1H NMR ($DCCl_3$) δ 1.57 (s); ^{19}F NMR (neat, 330 K) s, 720 Hz downfield from TFA; (neat, 255 K) q, 866 Hz from TFA, J = 6.5 Hz; q, 563 Hz from TFA, J = 6.5 Hz. Variable-temperature data[16] gave an activation energy for syn–anti isomerization of 16.83 kcal/mol, ir (CCl_4) 2967, 1760, 1730 (shoulder), 1235 cm^{-1}.

1,1,1,3,3,3-Hexafluoro-2-*N*-*t*-Boc-aminoisopropylimidazole (2a). Imidazole (68 mg, 1 mmol) dissolved in THF (1 ml) was treated with imine **1** (273 mg, 1 mmol) in ⅓ ml of THF. The reaction was mildly exothermic and complete in 10 min. Flash evaporation left an oil. An aliquot was dissolved in Skelly B and cooling to −78° caused oiling. The mother liquor was decanted and the oil crystallized on standing. These crystals were used to seed crystallization from 10% ethyl acetate in hexane, giving 157 mg (47%) of product, mp 96–102°.

Anal. Calcd for $C_{11}H_{13}N_3O_2F_6$: C, 39.65; H, 3.93; N, 12.61; F, 34.21. Found: C, 39.62; H, 3.89; N, 12.35; F, 33.20.

NMR (parts per million from THF downfield multiplet maximum) δ 5.49 (br s, 1.2 H, NH), 4.31 (br s, 1.1 H, C_2H), 3.61 (br s, 1.0 H, C_5H), 3.45 (br s, 1.0, C_4H), −2.27 (s, *O-tert*-butyl).

1,1,1,3,3,3-Hexafluoro-2-methoxy-*N*-*t*-Boc-isopropylamine (3b). Equimolar amounts of imine **1** and methanol were mixed at room temperature. The material solidified after a few hours. After 30 hr the solid was recrystallized from CS_2: yield 68%; mp 65–69°; NMR ($CDCl_3$) δ 5.32 (1 H, NH), 3.60 (3 H, OCH_3), 1.50 (9 H, *O-tert*-butyl).

1,1,1,3,3,3-Hexafluoro-2-*tert*-butylmercapto-*N*-*t*-Boc-isopropylamine (3c). The procedure was the same as for **3b** using *tert*-butyl mercaptan: yield 50%; mp 80.5°; NMR ($CDCl_3$) δ 5.18 (1.0 H, NH), 1.52, 1.50 (s, 18 H, *O-tert*-butyl, *S-tert*-butyl).

***N*$^{\alpha}$-Z,*N*^{im}-(1,1,1,3,3,3-hexafluoro-2-*t*-Boc-aminoisopropyl)-L-his-OCH_3 (2b).** N^{α}-Z-L-his-OCH_3 (153 mg, 0.5 mmol) in $CDCl_3$ was treated with imine **1** (142 mg, 0.54 mmol) at room temperature. After 20.5 hr the solution was added to cold (0°) Skelly B dropwise with swirling. A white, amorphous precipitate developed which became tacky on warming to room temperature. The mother liquor was decanted and the residue was high vacuum dried to a crisp foam: NMR (CD_3CN) δ 7.78 (br s, 1.0 H, C_2H), 7.39 (s, 5.4 H, phenyl), 7.11 (br s, 1.23 H, C_4H), 6.43 and 6.1 (1.95 H, Z-NH, *t*-BOC-NH), 5.09 (s, 2.0 H, benzyl), 4.53 (m, 0.92 H, $C_{\alpha}H$), 3.65 (s, 3.0 H, OCH_3), 3.03 (d, J = 6 Hz, 1.92 H, β-CH_2), 1.43 (s, 8.0 H, *O-t*-Bu); TLC (silica gel F-254, 5% CH_3OH in $CHCl_3$, detected by fluorescence quenching and Pauly reagent) R_f 0.75 with some tailing; R_f of N^{α}-Z-his-OCH_3 0.23.

Registry No.—**1**, 52786-55-7; **2a**, 55606-65-0; **2b**, 55648-91-4; **3a**, 52786-44-4; **3b**, 55606-66-1; **3c**, 55606-67-2; *tert*-butyl carbamate, 543-28-2; hexafluoroacetone, 684-16-2; imidazole, 288-32-4; methanol, 67-56-1; *tert*-butyl mercaptan, 513-44-0; N^{α}-Z-L-his-OCH_3, 15545-10-5.

References and Notes

(1) We acknowledge the support of the U.S. Public Health Service (Grant AM 12970) and the Department of Chemistry in providing a teaching fellowship for H.H S.
(2) Abbreviations used: *t*-Boc, *tert*-butoxycarbonyl; Z, benzyloxycarbonyl; THF, tetrahydrofuran; TFA, trifluoroacetic acid; his-OCH_3, histidine methyl ester.
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Directive Effects in the Hydroboration of Vinylferrocenes

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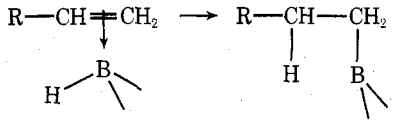
While examining possible synthetic applications of the hydroboration reaction in organometallic systems,[1] we observed that certain vinylmetallocenes, upon hydroboration–oxidation, were converted to a single alcohol product. By contrast, most aryl- and alkyl-substituted alkenes yield a mixture of two isomeric alcohols under similar reaction conditions. Since the positional selectivity of this reaction was so pronounced, a study was initiated in order to probe the nature of this directive ability.

Results and Discussion

A series of ferrocenyl-substituted alkenes (**1–6**, Table I) was prepared and allowed to react with borane in tetrahydrofuran. These alkenes reacted normally and produced the corresponding alcohols in high yields. The alcohols were isolated by column chromatography,[2] and percent yields of isolated products ranged from 60% with **4** to 79% with **3**. In addition, approximately 5% yields of the corresponding alkanes were obtained.

The distributions of the isomeric alcohols are indicated in Table I. By way of comparison, distributions in similar aryl- and alkyl-substituted alkenes are also shown. The distribution of ferrocenyl-substituted alcohols was determined by NMR analysis. The NMR spectra of the purified alcohol fractions from the hydroboration–oxidation procedure were recorded and unique areas of absorption for each of the possible alcohols were integrated repeatedly. Even though the accuracy of the distributions is limited by the accuracy of the integration procedure, these values are the average of several experiments. Variations in distribution among several experiments were found to be quite small (±3%).

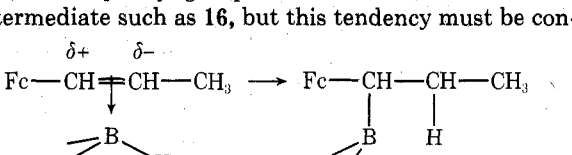
The various isomer distributions can be accounted for in terms of the presently accepted hydroboration mechanism. This mechanism, which is based on stereochemical[3] and thermodynamic[4] considerations, involves the formation of a triangular π complex (**14**) and its collapse via a concerted process[5] to product (**15**). Both steric and electronic factors



14 **15**

are involved in determining the carbon to which the boron moiety will become attached.[5] Upon hydroboration–oxidation the terminal alkenes **1** and **2** produce preponderant amounts of the terminal alcohols. In fact, vinylferrocene (**1**) produces a significantly greater amount of the terminal alcohol than does styrene (**7**) or *tert*-butylethylene (**10**). It is likely that the steric bulk of ferrocene and its powerful electron-releasing ability[6] combine to produce this increased preferential attachment of boron to the terminal carbon.

With disubstituted internal alkyl-substituted alkenes, Brown and Zweifel[7] observed that the boron moiety becomes attached in approximately equal amounts to each carbon of the double bond. When one of the substituents is the very bulky *tert*-butyl group (**12**) the distribution becomes 42:58 (Table I). However, the case of 1-phenylpropene (**9**) demonstrates the importance of electronic factors in the hydroboration reaction. Further, when substantial amounts of both isomers are formed one must consider the extent of hydroboration. Reactions of stoichiometric amounts of borane and of disubstituted alkenes such as **3**, **4**, or **5** indicate that these reactions proceed to the dialkylborane stage while with the trisubstituted alkene **6**, hydroboration apparently stops at the monoalkylborane stage. In the hydroboration of **3**, control by steric factors should cause a small preference for boron addition to the carbon β to the ferrocenyl group; however, the opposite result is observed. This suggests that some type of electronic control must also be involved. Ferrocene is generally regarded as a very strong electron-releasing group;[8] however, electron release by ferrocene would not favor the formation of the observed major product. An electron-withdrawing tendency (similar to the phenyl group's behavior in **9**) would lead to an intermediate such as **16**, but this tendency must be con-



16 **17**

siderably less significant than in the phenyl case, since there is not a large deviation from the usual 50:50 distribution.

When the two substituents are the phenyl and the ferrocenyl systems (**4**), the boron displays a great preference for attachment to the carbon α to the phenyl group. This result occurs because of the very favorable combination of electronic factors in the intermediate (**18**) in which the ferrocenyl system is electron releasing and the phenyl group is