a steam bath for 2.25 h while a stream of N_2 was passed through the solution via a fritted glass tube. Volatiles were removed on a rotary evaporator at aspirator vacuum, and the dark residue was vacuum distilled to give 44.2 g (55%) of the pyrrole as a clear pale yellow oil: bp 118 °C (1.1 Torr); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.6–7.1 (4 H, m), 6.98 (2 H, t, J = 2.4 Hz), 6.42 (2 H, t, J = 2.4 Hz), 2.70 (2 H, q, J = 7.4 Hz), 1.33 (3 H, t, J = 7.4 Hz); MS m/z (rel int) 203 M^+, 174 (100). Anal. Calcd for $C_{12}H_{13}NS$: C, 70.89; H, 6.45; N, 6.89; Found: C, 70.77; H, 6.42; N, 6.91.

1-(2-(Ethylsulfinyl)phenyl)pyrrole (5b). The corresponding sulfide (10.0 g, 49.3 mmol) in CH_2Cl_2 (145 mL) was cooled to 0 °C in an ice bath. *m*-Chloroperoxybenzoic acid (11.8 g, 80%, 52.3 mmol) in CH_2Cl_2 (200 mL) was then added dropwise over 90 min. After an additional 1 h in ice, the mixture was stored in the freezer (-20 °C) overnight. Precipitated *m*-chlorobenzoic acid was removed by filtration, and the filtrate was washed with 5% K_2CO_3 solution. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo to give a brown oil (10.8 g, 100%) that slowly crystallized: mp 76–77.5 °C (from ethanol); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 8.30–7.85 (1 H, m), 7.80–7.20 (3 H, m), 6.83 (2 H, t, J = 2.6 Hz), 6.33 (2 H, t, J = 2.6 Hz), 2.73–1.55 (2 H, AB portion of ABX_3 system, J = 14, 7.6 Hz), 0.88 (3 H, t, J = 7.6 Hz); IR (KBr) 1045 cm^{-1}; MS m/z (rel int) 219 M^+, 162 (100). Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39; Found: C, 65.61; H, 5.83; N, 6.34.

1-(Trifluoroacetyl)pyrrolo[2,1-*b*]benzothiazole (7). To a solution of **5b** (440 mg, 2 mmol) in toluene (25 mL), under dry nitrogen, was added neat TFAA (0.57 mL, 4 mmol) dropwise over 5 min via syringe. The mixture was then refluxed, gradually becoming progressively darker yellow. At the end of 1 h the blood red to dark brown solution was cooled, washed with 5% aqueous K_2CO_3, and dried over Na_2SO_4, and the volatiles were removed in vacuo. The resulting crude solid was recrystallized from hexanes to give 410 mg (76%) of **7**: mp 114–115 °C; IR (KBr) 1675 cm^{-1}; MS m/z (rel int) 269 M^+, 200 (100). Anal. Calcd for $C_{12}H_6F_3NOS$: C, 53.53; H, 2.25; N, 5.20; Found: C, 53.49; H, 2.38; N, 5.11.

Hydrolysis of 7 to 1-Pyrrolo[2,1-*b*]benzothiazolecarboxylic Acid (8). Compound **7** (500 mg, 1.86 mmol) was refluxed with 0.6 M NaOH solution in 50% aqueous ethanol for 24 h. After being cooled to room temperature, the deep red solution was diluted with water (60 mL) and acidified with 3 N HCl. The off-white solid that formed was collected by filtration, slurried with benzene, and rotary evaporated to azeotropically remove residual water to give a beige solid (0.29 g, 72%) which was not purified further: mp 125–130 °C; IR (KBr) 3600–2750, 1660 cm^{-1}; MS m/z (rel int) 217 (100), 200 (58), 173 (88), 172 (55), 145 (20).

Pyrrolo[2,1-*b*]benzothiazole (9) by Decarboxylation of 8. The carboxylic acid **8** (60 mg, 0.276 mmol) was heated under aspirator vacuum in a sublimator to a bath temperature of 120 °C. Sublimation commenced at about 80 °C; after 5–10 min deposition of fine white crystals (24 mg; 50%) of **9** onto the cold finger was complete: mp 52 °C (lit.[19a] mp 54 °C; lit.[19b] mp 57–58.5 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.61–7.23 (5 H, m containing a H-1 at δ 7.42 (1 H, dd, $J_{1/2}$ = 2.98 Hz, $J_{1,3}$ = 1.31 Hz), 6.52 (1 H, dd, $J_{2,1}$ = 2.98 Hz, $J_{2,3}$ = 3.57 Hz, H-2), 6.16 (1 H, dd, $J_{2,3}$ = 3.57, $J_{1,3}$ = 1.31 Hz, H-3); IR (neat) 3050, 1600, 1500, 1300, 890, 630 cm^{-1}; MS m/z (rel int) 173 (100).

1-(Trichloroacetyl)pyrrolo[2,1-*b*]benzothiazole (10). Replacing TFAA with an equivalent molar quantitity of trichloroacetic anhydride in the procedure described above for **7** gave **10** as a yellow solid. Recrystallization from hexanes gave analytically pure material (60%) as pale yellow crystals: mp 137–140 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.15–9.10 (1 H, dt, J = 8.2, 1.6 Hz), 8.00 (1 H, d, J = 4.80 Hz), 7.64–7.59 (1 H, dm, J = 7.7 Hz), 7.47–7.28 (2 H, m), 6.47 (1 H, d, J = 4.80 Hz); IR (KBr) 1650 cm^{-1}; MS m/z (rel int) 317 M^+, 200 (100). Anal. Calcd for $C_{12}H_6NOSCl_3$: C, 45.24; H, 1.90; N, 4.40. Found: C, 45.28; H, 1.99; N, 4.35.

General Procedure for Cyclization Using TFA/Ac_2O. Trifluoroacetic anhydride (7.5 mmol) and acetic anhydride (5 mL) were allowed to stand overnight at room temperature. The appropriate sulfoxide (5 mmol) was added in portions to this ice-cooled mixture. After 2.5 h in an ice bath the pH of the dark red solution was adjusted to 7 with 3 N NaOH, and the mixture was stirred for an additional 30 min at room temperature. Extraction with CH_2Cl_2 (2 × 25 mL), drying of the extract over Na_2SO_4, and evaporation of the solvent in vacuo gave a dark oil, which was passed through a short (1- × 5-in) column of alumina eluted with $CHCl_3$. Yields of pure **9** from different sulfoxides were as follows: **5a**, 60%; **5b**, 70%; **5c**, 0%; **5d**, 31%; **5e**, 9%.

Effect of Solvent on Cyclization of 5b. To the appropriate solvent (5 mL, 10 mL for DMF) in ice was added TFAA (1.93 g, 9.2 mmol) dropwise. This mixture was stirred in ice for 20 min before **5b** (1.0 g, 4.9 mmol) in the solvent (15 mL, 30 mL for DMF) was added over 15 min. After being stirred an additional 15 min in ice, the reaction was stirred at room temperature for the times listed in Table II. The mixture was then quenched with water (50 mL), and solid sodium acetate was added until the mixture had a pH of 7. After standing overnight, the mixture was extracted with CH_2Cl_2 (2 × 25 mL). In DMF and TFA most of the product appeared as an off-white precipitate which was collected prior to extraction. Some discoloration occurred in the TFA/sulfoxide mixture during addition; addition of the solid sulfoxide to the TFAA/TFA mixture avoided this problem. In the cases of acetonitrile and acetic acid, the reaction was much slower and the concentrated extract had to be chromatographed to separate product from unreacted starting material. The data are summarized in Table II.

Regiochemistry of Acetylation of Ferrocenylarylethylenes

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We describe the synthesis and Friedel–Crafts acetylation of a series of ferrocenylarylethylenes, $C_5H_5FeC_5H_4CH{=}CH(C_6H_4$-*p*-X), where X = NO_2 (**3a**), Br (**3b**), and NMe_2 (**3c**). Compounds **3a–c** provide a direct comparison of the reactivity of ferrocene, olefin, and aryl functionalities. The regiochemistry of substitution of these compounds depends on the nature of the aryl substituent. Acetylation occurs predominantly at the olefin and the unsubstituted cyclopentadienyl ring; substitution does not occur at the aryl ring or at the substituted cyclopentadienyl ring. Reaction at the olefin is accompanied by olefin isomerization. With the strongly activating dimethylamino substituent (**3c**), substitution at the unsubstituted cyclopentadienyl ring (**5c**) is slightly favored over substitution at the olefin (**4c**). The regiochemistry of olefin substitution suggests that a ferrocenyl substituent is better able to stabilize an adjacent positive charge than a *p*-(dimethylamino)aryl substituent. With the bromine substituent (**3b**), substitution at the olefin (**4b**) is slightly favored over substitution at the unsubstituted cyclopentadienyl ring (**5b**). The nitro group is sufficiently deactivating that **3a** fails to react under our conditions.

In the course of our synthesis of nonlinear optical materials, we investigated the Friedel–Crafts acetylation chemistry of ferrocene derivatives **3a–c** as a potential means of further functionalizing these compounds for ultimate use as electrochemically switchable nonlinear optical materials anchored at the surface of modified

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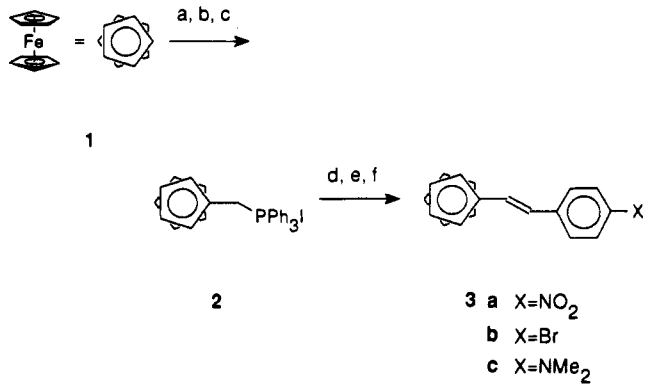
Scheme I[a]



[a] (a) $(NMe_2)_2CH_2$, CH_3COOH, H_3PO_4; (b) CH_3I, CH_3OH; (c) PPh_3, EtOH; (d) *n*-BuLi, THF; (e) *p*-XC_6H_4CHO, THF; (f) chromatography (alumina).

electrodes.[1] We sought to acetylate **3a** and then introduce a long alkyl chain to impart surfactant character to the molecule. We expect these compounds to be readily adsorbed at the surface of gold electrodes modified with a monolayer of adsorbed alkanethiol. We report here on the unusual reactivity and regiochemistry of substitution for **3a–c**.

Friedel–Crafts reactions have been thoroughly studied, and the literature contains a large body of information on the subject.[2] Numerous studies have focused on acylation reactions of ferrocene derivatives.[3] The reactivity of ferrocene toward substitutions of this type is comparable or greater than that of activated aromatic compounds, and ferrocene is 10^6 times more reactive than benzene itself.[3e] In a competitive acetylation experiment, Pauson showed that acetylation of a 10:1 mixture of anisole:ferrocene using a limited amount of acetyl chloride produces only acetylferrocene.[4] A recent paper by Cunningham[5] reporting on the mechanism of Friedel–Crafts acetylation of (trimethylsilyl)- and (tributylstannyl)ferrocene derivatives demonstrates that this is still an area of active interest, and that mechanistic details are only now becoming clearly understood.

Olefins also show higher reactivity than aromatics in Friedel–Crafts reactions. Acetylation of styrene derivatives occurs exclusively at the β carbon atom of the olefin; the formation of the more stable benzylic cation results in the observed regiochemistry. Acetylation of the aromatic ring is not observed.[6] Further increasing of the electron density of the olefin, e.g. methylstyrene, leads to increased reactivity. While olefins and ferrocenes are both more reactive than aromatics, the relative reactivities of ferrocenes and olefins are not well defined. In this report, we present the synthesis and Friedel–Crafts acetylation chemistry of ferrocenylarylethylenes, **3a–c**. Compounds **3a–c** provide a direct comparison of the reactivity of ferrocene, olefin, and aryl functionalities. In addition, they reveal an interesting dependence of the regiochemistry of substitution on the nature of the aryl substituent.

Results and Discussion

The synthesis of compounds **3a–c** employs a Wittig olefination[7,8] (Scheme I). (Ferrocenylmethyl)triphenylphosphonium iodide was synthesized by aminomethylation of ferrocene followed by displacement of the ammonium iodide salt with triphenylphosphine in refluxing ethanol. Reaction of the (ferrocenylmethyl)triphenylphosphonium ylide and the appropriate benzaldehyde in tetrahydrofuran (THF) gave initial product mixtures that were comprised of approximately a 1:1 mixture of the cis and trans olefins. The crude reaction mixture was subjected to flash chromatography to separate the mixture of cis and trans olefins from minor impurities. The purified mixture of cis and trans olefins was then subjected to gravity column chromatography (alumina) which, given sufficient elution time, resulted in complete isomerization to the trans isomer. The products **3a–c** are highly colored, crystalline solids.

Scheme II summarizes the Friedel–Crafts acetylation chemistry of **3a–c**. Reaction of the nitro derivative **3a** (1 equiv) with CH_3COCl (1 equiv) and $AlCl_3$ (2 equiv) in CH_2Cl_2 at 25 °C (method A) failed to give any observable substitution products. Reaction of the bromo derivative **3b** under the same acetylation conditions gave three predominant products: two monoacetylated products, **4b** (23%) and **5b** (10%), and one diacetylated product, **6b** (16%). After separation by column chromatography, products **4b** and **6b** were isolated in pure form and characterized (see below). **5b** was not isolated in pure form but was clearly observed by ^1H NMR in intermediate chromatography fractions; its yield was estimated by ^1H NMR integration. Reaction of the dimethylamino derivative **3c** under the same acetylation conditions also gave three predominant products: two monoacetylated products, **4c** (15%) and **5c** (25%), and one diacetylated product, **6c** (20%). After separation by column chromatography, the products **4c** and **5c** were isolated in pure form and characterized (see below).

^1H NMR spectra of products **5b** and **5c** clearly reveal monoacetylation, due to the presence of only one acetyl methyl singlet, at δ 2.27 and 2.29 ($CDCl_3$), respectively. In each case, the Cp singlet integrating to five protons in the spectrum of the starting material disappears and two new multiplets each integrating to two protons appear in the spectrum of the product. In addition, the signal for the two olefin protons remains unchanged, as well as that for the four phenyl protons. The products **4b** and **4c** are also clearly monoacetylated. Again only one acetyl methyl singlet is present, at δ 2.27 and 2.21 ($CDCl_3$), respectively. Furthermore, the olefin signal in the spectrum of the

(1) For general references concerning modified electrodes, see: (a) Murray, R. W. *Acc. Chem. Res.* **1980**, *13*, 135–141. (b) Faulkner, L. R. *Chem. Eng. News* **1984**, Feb. 27, 28–45. (c) Murray, R. W. *Electroanalytical Chemistry*; Bard, A. J., Ed.; Dekker: New York, 1984; Vol. 13. (d) Wrighton, M. S. *Science* **1986**, *231*, 32–37. (e) Murray, R. W.; Ewing, A. G.; Durst, R. A. *Anal. Chem.* **1987**, *59*, 379A–390A.

(2) (a) Olah, G. A. *Friedel–Crafts and Related Reactions*; Interscience: New York, 1963–1964; Vols. 1–4. (b) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley: New York, 1973. (c) Johnson, W. S. *Org. React.* **1944**, *2*, 114–177. (d) Berliner, E. *Org. React.* **1949**, *5*, 229–289. (e) Chevrier, B.; Weiss, R. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 1–10. (f) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1980**, *102*, 3056–3062.

(3) (a) Plesske, K. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 312–327, 394–399. (b) Little, W. F. In *Survey of Progress in Chemistry*; Scott, A., Ed.; Academic: New York, 1963; Vol. 1, p 133. (c) Rosenblum, M. *Chemistry of the Iron-Group Metallocenes: Ferrocene, Ruthenocene, and Osmocene*; Wiley: New York, 1965. (d) Bublitz, D. E.; Rinehart, K. L. *Org. React.* **1969**, *17*, 1–154. (e) Watts, W. E. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 8, p 1016.

(4) Pauson, P. L. *Q. Rev. Chem. Soc.* **1955**, *9*, 391–414.

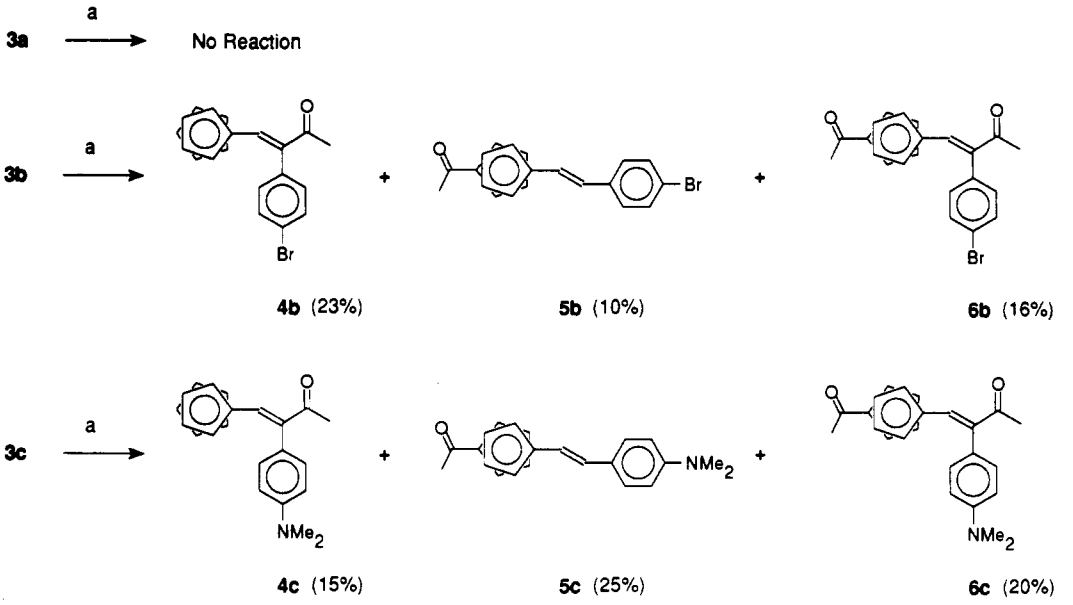
(5) Cunningham, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 4864–4870.

(6) (a) Rozenberg, B. A.; Dzhigirei, N. V.; Dorofeenko, G. N.; Babin, E. P. *Zh. Obshch. Khim.* **1962**, *32*, 3417–3420. (b) Bergmann, F.; Klein, J. *J. Am. Chem. Soc.* **1953**, *75*, 4333–4334.

(7) (a) Drefahl, G.; Plotner, G.; Winnefeld, I. *Chem. Ber.* **1962**, *95*, 2788–2791. (b) Pauson, P. L.; Watts, W. E. *J. Chem. Soc.* **1963**, 2990–2996.

(8) (a) Green, M. L. H.; Marder, S. R.; Thompson, M. E.; Bandy, J. A.; Bloor, D.; Kolinsky, P. V.; Jones, R. J. *Nature* **1987**, *330* (26), 360–362. (b) Marder, S. R.; Perry, J. W.; Schaefer, W. P.; Tiemann, B. G.; Groves, P. C.; Perry, K. J. *Proceedings SPIE, Nonlinear Optical Properties of Organic Materials II* **1989**, *1147*, 108–115. (c) Calabrese, J. C.; Cheng, L. T.; Green, J. C.; Marder. S. R.; Tam, W. *J. Am. Chem. Soc.* **1991**, *113*, 7227–7232.

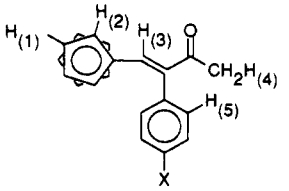
Scheme II[a]



[a] (a) 2.0 equiv of $AlCl_3$, 1.0 equiv of CH_3COCl, CH_2Cl_2, 25 °C, 5 h.

starting material collapsed to a singlet integrating to one proton in the spectrum of the product. The remaining portions of the spectrum are unchanged.

The regiochemistry of the olefin-substituted products **4b** and **4c** was elucidated by ^1H NMR nuclear Overhauser enhancement (NOE) experiments. In both cases, irradiation of the acetyl methyl protons, $H_{(4)}$, produced an enhancement in the olefinic proton $H_{(3)}$ as well as in the signal for the $H_{(5)}$ phenyl protons. These results indicate



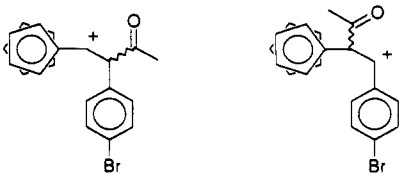
X = Br or NMe_2

that acetylation occurred at the benzylic position, and that the acetyl substituent and the olefin proton bear a cis relationship. Further NOE experiments confirm this structural assignment. Irradiation of the olefinic proton produced an enhancement in the $H_{(2)}$ cyclopentadienyl (Cp) protons, and, in the case of the dimethylamino product **4c**, a slight enhancement in the $H_{(4)}$ acetyl methyl protons as well. In addition, irradiation of the $H_{(2)}$ Cp protons produced an enhancement in the olefinic proton signal as well as in the signal for the $H_{(1)}$ Cp protons. Thus, the ferrocene and aryl substituents bear a trans relationship in the starting olefins **3b** and **3c** but bear a cis relationship in the product olefins **4b** and **4c**. Isomerization may occur during chromatography, as is the case with the starting materials **3a–c**, or, alternatively, isomerization may occur during the reaction by bond rotation before proton loss in the cationic intermediate.

The presence of two distinct acetyl methyl signals in the ^1H NMR spectra of the products **6b** and **6c** clearly indicates diacetylation. In each case, two multiplets each integrating to two protons in the product spectrum replace the Cp singlet integrating to five protons in the spectrum of the starting material. Additionally, the olefin signal of the starting material collapses to a singlet integrating to one proton. The remaining portions of the spectrum are unchanged. We assume the regiochemistry of olefin substitution in the diacetylated products corresponds to that of the monoacetylated products **4b** and **4c**.

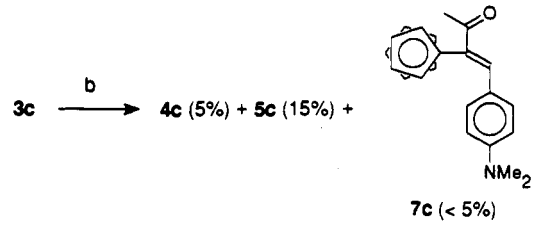
Inspection of the trends of yields of products reveals that the regiochemistry of substitution is dependent on the aryl substituent. In the case of **3a** (X = NO_2), no substitution products are observed under our reaction conditions. In the case of **3b** (X = Br), the major product is the monoacetylated product **4b** where substitution has occurred on the olefin in the benzylic position. The product formed in intermediate yield is the diacetylated product **6b** where substitution has occurred at the benzylic position on the olefin and on the unsubstituted Cp ring. The minor product is the monoacetylated product **5b** where substitution has occurred on the unsubstituted Cp ring only. Formation of other mono- and diacetylated isomers is probable, but such species cannot account for a significant fraction of the product mixture. No other isomers were *clearly* detectable by ^1H NMR spectroscopy. In the case of **3c** (X = $N(CH_3)_2$), the major product is the monoacetylated product **5c** where substitution has occurred on the unsubstituted Cp ring. The product formed in intermediate yield is the diacetylated product **6c**, and the minor product is the monoacetylated product **4c** where substitution has occurred on the olefin, again in the benzylic position.

The lack of products substituted at the olefinic carbon adjacent to the ferrocene moiety indicates that forming a positive charge adjacent to ferrocene in an intermediate or transition state is favored over forming a positive charge adjacent to the aryl ring. Even with the strongly donating



p-$N(CH_3)_2$ substituent, the ferrocene moiety is apparently still better able to stabilize an adjacent positive charge. This is consistent with earlier observations concerning the facile solvolysis of ferrocenyl methanols[3,9] and the ability

Scheme III[a]



[a] (b) 1.0 equiv of $AlCl_3$, 1.0 equiv of CH_3COCl, CH_2Cl_2, 25 °C.

of weak acids to protonate vinylferrocene.[3,10] When only 1.0 equiv of $AlCl_3$ (method B) is used to acetylate **3c**, a small amount (<5%) of the regioisomeric olefin **7c** is produced, however (Scheme III). Under these conditions, the Cp-substituted product **5c** is formed in 15% yield, the olefin-substituted product **4c** is formed in 5% yield, none of the diacetylated product is formed, and 75% starting material is recovered. Product **7c** is observable (<5%) by ^1H NMR spectroscopy after chromatographic separation of the product mixture by preparative TLC. We were unable to isolate **7c** as a pure substance. Our observation of **7c** suggests that stabilization of an adjacent positive charge by the *p*-(dimethylamino)phenyl moiety is competitive with, but still less effective than, the stabilization by the ferrocene moiety.

In summary, acetylation reactions of ferrocenylarylethylenes **3a–c** provide a direct, intramolecular comparison of the reactivity of ferrocene, aryl, and olefin functionalities in the Friedel–Crafts acetylation reaction. Acetylation of **3b** and **3c** occurs at both the ferrocene and olefin sites. Acetylation of the aryl functionality does not occur, even when substituted with a dimethylamino substituent. ^1H NMR studies establish the regiochemistry of the olefin acetylation. Substitution at the benzylic position is strongly preferred. Somewhat surprisingly, the remote nitro substituent in **3a** serves to dramatically deactivate the ferrocene moiety toward acetylation.

Experimental Section

General Methods. ^1H NMR spectra were obtained with a Bruker WP-200 spectrometer (200 MHz) or with a Bruker WP-270 spectrometer (270 MHz) in the indicated solvents. Chemical shifts (δ) are reported as ppm downfield from internal tetramethylsilane. ^{13}C NMR spectra were obtained with a Bruker WP-270 spectrometer (68 MHz) in the indicated solvents using tetramethylsilane as an internal standard. High-resolution mass spectra were recorded on a Kratos MS-80RFA (DS55/DS90 detector). Infrared (IR) spectra were recorded on a Nicolet Model 740 FT-IR spectrometer (TGS detector). Elemental analyses were performed by Desert Analytics. Melting points were measured using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Column chromatography was carried out using grade III neutral or basic alumina. Thin-layer chromatography was carried out using E. Merck silica gel (60F-254) or alumina (60F-254) plates. All glassware used was flame-dried and purged with nitrogen prior to use. All reactions were run under a nitrogen atmosphere. CH_2Cl_2 was dried over and distilled from CaH_2 immediately prior to use. THF was dried over KOH, predistilled from CaH_2, and finally distilled from Na/benzophenone immediately prior to use.

General Method of Acetylation. Method A. CH_3COCl (1.0 equiv, Aldrich) was added to 2.0 equiv of $AlCl_3$ in freshly distilled CH_2Cl_2 at 0 °C. The solution was warmed to 25 °C and stirred for 30 min. A solution of 1.0 equiv of the ferrocenylarylethylene in CH_2Cl_2 was then added at 25 °C and stirred for 5 h. The reaction was quenched by the addition of H_2O. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers were extracted once with 5% $NaHCO_3$ and once with H_2O before being dried over Na_2SO_4. Removal of solvent by evaporation under reduced pressure yielded the highly colored crude product mixtures. **Method B**: used 1.0 equiv of $AlCl_3$; otherwise identical to method A.

[(*N*,*N*-Dimethylamino)methyl]ferrocene Methiodide. [(*N*,*N*-Dimethylamino)methyl]ferrocene was synthesized from 11.6 g (62.5 mmol) of ferrocene (Aldrich), 10.8 g (105.5 mmol) of bis(dimethylamino)methane (Aldrich), 10.8 g of 85% H_3PO_4, and 100 mL of CH_3COOH according to a literature procedure.[11] The crude amine was converted to the ammonium iodide salt by reaction with 13.5 mL (218 mmol) of CH_3I in refluxing CH_3OH for 30 min. The precipitate was collected by filtration and rinsed with Et_2O to yield 18.77 g (78%) of the ammonium iodide salt as a light orange crystalline solid: mp 185 °C dec (lit.[11] mp 200 °C dec); ^1H NMR (D_2O) δ 4.60 (s, 2 H), 4.1–4.3 (m, 9 H), 2.8 (s, 9 H).

(Ferrocenylmethyl)triphenylphosphonium Iodide (2). **2** was synthesized from 18.76 g (48.7 mmol) of [(*N*,*N*-dimethylamino)methyl]ferrocene methiodide and 25.24 g (96 mmol) of triphenylphosphine in refluxing EtOH according to a literature procedure.[7b] After cooling to room temperature, the reaction mixture was poured into 800 mL of Et_2O. Recrystallization of the phosphonium iodide salt from ethanol gave 24.25 g (85%) of **2** as large, gold-colored crystals: mp 230–235 °C dec (lit.[7b] mp 254–256 °C dec); ^1H NMR (Me_2CO-d_6) δ 7.75–7.95 (m, 15 H), 5.03 (d, 2 H ($^2J_{PH}$ = 12.5 Hz)), 4.27 (s, 5 H), 4.16 and 4.08 (2 m, 4 H).

***trans*-1-Ferrocenyl-2-(4-nitrophenyl)ethylene (3a).** This ferrocene derivative was synthesized in a manner analogous to a literature procedure.[8] A solution of 15.00 g (25.5 mmol) of (ferrocenylmethyl)triphenylphosphonium iodide in 150 mL of THF was cooled to −78 °C. 16.0 mL (25.6 mmol) of *n*-BuLi/hexane was added over a period of 45 min, and the resulting mixture stirred for 2 h at 0 °C. A solution of 3.86 g (25.5 mmol) of 4-nitrobenzaldehyde (Aldrich) in 75 mL of THF was added at 0 °C, and the resulting mixture was stirred for 4 h at 0 °C and then for 16 h at room temperature. The reaction was quenched by addition of 20% aqueous HCl. Aqueous workup followed by drying over Na_2SO_4 resulted in an approximately 1:1 mixture of cis:trans olefin products, as estimated by ^1H NMR. The mixture was purifed by flash chromatography (alumina/CH_2Cl_2). Subsequent gravity (3 h) chromatography (alumina/CCl_4) resulted in complete isomerization to the trans isomer. Recrystallization from ether/hexane gave 6.62 g (78%) of pure **3a** as a deep purple crystalline solid: mp 195.0–196.0 °C; ^1H NMR ($CDCl_3$) δ 8.2 and 7.6 (2 d, 4 H), 7.1 and 6.7 (2 d, 2 H ($^3J_{HH(trans)}$ = 16 Hz)), 4.6 and 4.4 (2 m, 4 H), 4.2 (s, 5 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 146.0, 144.4, 132.9, 125.9, 124.3, 123.4, 81.7, 70.0, 69.4, 67.5; IR (CH_2Cl_2) 1590 and 1515 (NO_2) cm^{-1}; mass spectrum, calcd for $C_{18}H_{15}FeNO_2$ 333.0452, found 333.0453; *m*/*z* (relative intensity) 333 (M^+, 100), 287 (29), 165 (27), 121 (18).

***trans*-1-Ferrocenyl-2-(4-bromophenyl)ethylene (3b).** **3b** was synthesized from 3.00 g (5.10 mmol) of (ferrocenylmethyl)triphenylphosphonium iodide and 0.944 g (5.10 mmol) 4-bromobenzaldehyde (Aldrich) as described for **3a**. Recrystallization from hexane gave 0.8825 g (47%) of pure **3b** as large deep orange crystals: mp 142.0–143.0 °C; ^1H NMR ($CDCl_3$) δ 7.45 and 7.30 (2 d, 4 H), 6.87 and 6.61 (2 d, 2 H ($^3J_{HH(trans)}$ = 16 Hz)), 4.45 and 4.30 (2 m, 4 H), 4.10 (s, 5 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 136.8, 131.7, 127.9, 127.3, 124.7, 120.2, 82.9, 69.1, 69.1, 66.8; mass spectrum, calcd for $C_{18}H_{15}BrFe$ 367.9687, 365.9707, found 367.9709, 365.9700; *m*/*z* (relative intensity) 368, 366 (M^+, 100, 98), 286 (30), 165 (83), 121 (10).

***trans*-1-Ferrocenyl-2-(4-(dimethylamino)phenyl)ethylene (3c).** **3c** was synthesized from 1.54 g (2.62 mmol) of (ferrocenylmethyl)triphenylphosphonium iodide and 0.3910 g (2.62 mmol) of 4-(dimethylamino)benzaldehyde (Aldrich) as described for **3a**. Recrystallization from EtOH gave 0.3352 g (39%) of pure **3c** as an orange-red crystalline solid: mp 163.0–164.0 °C; ^1H NMR ($CDCl_3$) δ 7.25 and 6.63 (2 d, 4 H), 6.58 (s, 2 H), 4.36 and 4.17 (2 m, 4 H), 4.05 (s, 5 H), 2.89 (s, 6 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 149.6, 126.7, 126.6, 126.3, 122.3, 112.7, 84.6, 69.1, 68.5, 66.4, 40.6;

(9) Hill, E. A.; Richards, J. H. *J. Am. Chem. Soc.* **1961**, *83*, 4216–4221.
(10) Buell, G. R.; McEwen, W. E.; Kleinberg, J. *J. Am. Chem. Soc.* **1962**, *84*, 40–43.
(11) Lednicer, D.; Hauser, C. R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 434–436.

mass spectrum, calcd for $C_{20}H_{21}FeN$ 331.1023, found 331.1023; m/z (relative intensity) 331 (M^+, 100), 266 (30), 250 (12), 209 (12), 165 (7). Anal. Calcd for $C_{20}H_{21}FeN$: C, 72.52; H, 6.39; N, 4.23. Found: C, 72.69; H, 6.20; N, 3.92.

Acetylation of *trans*-1-Ferrocenyl-2-(4-nitrophenyl)-ethylene (3a). Reaction of 0.0906 g (0.272 mmol) of **3a** under the acetylation conditions (method A) resulted in recovery of starting material only.

Acetylation of *trans*-1-Ferrocenyl-2-(4-bromophenyl)-ethylene (3b). Acetylation (method A) of **3b** (98.9 mg, 0.270 mmol) gave an orange solid residue. Column chromatography (alumina/CH_2Cl_2 followed by alumina/2:1 CH_2Cl_2-hexane) permitted the isolation of two major products: monoacetylated product **4b** (23%) and diacetylated product **6b** (10%).

For **4b**, an orange-red crystalline solid: mp 117.0-119.0 °C; ^1H NMR ($CDCl_3$) δ 7.59 and 7.06 (2 d, 4 H), 7.55 (s, 1 H), 4.30 and 3.85 (2 m, 4 H), 4.11 (s, 5 H), 2.27 (s, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 197.3, 141.7, 136.9, 135.9, 132.0, 131.4, 121.8, 77.2, 71.4, 71.3, 69.7, 27.5; IR (CH_2Cl_2) 1656 (C=O) cm^{-1}; mass spectrum, calcd for $C_{20}H_{17}BrFe$ 409.9748, 407.9812, found 409.9789, 407.9813; m/z (relative intensity) 410, 408 (M^+, 99, 100), 345, 343 (30, 34), 165 (23).

For **6b**, an orange crystalline solid: ^1H NMR (CD_2Cl_2) δ 7.50 and 6.98 (2 d, 4 H), 7.26 (s, 1 H), 4.62, 4.35, 4.22, and 3.82 (4 m, 8 H), 2.25 and 2.20 (2 s, 6 H); IR (CH_2Cl_2) 1669 (C=O) cm^{-1}; mass spectrum, calcd for $C_{22}H_{19}BrFeO_2$ 451.9898, 449.9918, found 451.9882, 449.9910; m/z (relative intensity) 452, 450 (M^+, 93, 100), 345 (64), 165 (47).

The monoacetylation product **5b** was also observed in an intermediate column fraction: ^1H NMR ($CDCl_3$) δ 7.45 and 7.31 (2 d, 4 H), 6.74 and 6.69 (2 d, 2 H), 4.75 and 4.31 (2 m, 4 H), 4.47 (m, 4 H), 2.27 (s, 3 H).

Acetylation of *trans*-1-Ferrocenyl-2-(4-(dimethylamino)phenyl)ethylene (3c). Acetylation (method A) of **3c** (90.1 mg, 0.272 mmol) and separation of the product mixture by column chromatography (alumina/CH_2Cl_2) followed by preparative TLC (alumina/2:1 ether-hexane) permitted isolation of monoacetylated products **4c** (15%) and **5c** (25%), as well as diacetylated product **6c** (10%).

For **4c**, an orange-red crystalline solid: mp 152.0-154.0 °C; ^1H NMR ($CDCl_3$) δ 7.51 (s, 1 H), 7.03 and 6.81 (2 d, 4 H), 4.24 and 3.93 (2 m, 4 H), 4.10 (s, 5 H), 3.02 (s, 6 H), 2.21 (s, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 199.1, 149.9, 140.0, 137.3, 130.3, 125.7, 112.6, 87.5, 71.3, 70.8, 69.6, 40.6, 29.7; mass spectrum, calcd for $C_{22}H_{23}FeNO$ 373.1129, found 373.1129.

For **5c**, an orange crystalline solid: mp 114.5-115.5 °C; ^1H NMR (CD_2Cl_2) δ 7.34 and 6.70 (2 d, 4 H), 6.68 and 6.51 (2 d, 2 H ($^3J_{HH(trans)}$ = 15.5 Hz)), 4.73 and 4.25 (2 m, 4 H), 4.45 (m, 4 H), 2.97 (s, 6 H), 2.29 (s, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 202.1, 149.9, 128.3, 127.1, 125.8, 119.8, 112.6, 86.4, 79.9, 73.3, 70.5, 70.2, 67.7, 40.5, 27.8; mass spectrum, calcd for $C_{22}H_{23}FeNO$ 373.1129, found 373.1135; m/z (relative intensity) 373 (M^+, 100), 266 (72), 250 (19), 165 (20). Anal. Calcd for $C_{22}H_{23}FeNO$: C, 70.79; H, 6.21; N, 3.75. Found: C, 70.76; H, 6.01; N, 3.76.

For **6c**: ^1H NMR ($CDCl_3$) δ 7.32 (s, 1 H), 7.00 and 6.78 (2 d, 4 H), 4.69, 4.41, 4.24, and 3.96 (4 m, 8 H), 3.01 (s, 6 H), 2.32 (s, 3 H), 2.25 (s, 3 H).

Acetylation by method B and separation of the resulting product mixture by chromatography yields monoacetylated products **4c** (5%) and **5c** (15%) along with starting material (75%). The monoacetylation product **7c** was also detected in one of the preparative TLC bands (<5%) by ^1H NMR spectroscopy, but was not isolated: ^1H NMR ($CDCl_3$) δ 7.61 (s, 1 H), 7.57 and 6.99 (2 d, 4 H), 5.03 and 4.79 (2 m, 4 H), 4.15 (s, 5 H), 2.98 (s, 6 H), 2.41 (s, 3 H).

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Supplementary Material Available: Selected ^1H and ^{13}C NMR spectra for **3-6** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. Ordering information is given on any current masthead page.

Regioselective Reductive Electrophilic Substitution of Derivatives of 3,4,5-Trimethoxybenzaldehyde

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The behavior of several protected derivatives of 3,4,5-trimethoxybenzaldehyde has been investigated under conditions of electron transfer from alkali metals in aprotic solvents. The 4-methoxy group can be regioselectively removed in good to high yield under such conditions, and an appropriate choice of the protecting group, metal, and solvent allows its substitution with a variety of electrophiles. 3,4,5-Trimethoxybenzaldehyde dimethyl acetal, **1**, is the starting material of choice for a new general synthetic approach to several polysubstituted resorcinol dimethyl ethers. Investigation of the mechanism of demethoxylation, with the aid of labeling experiments, showed that reductive demethoxylation is strongly influenced by the nature of the aldehyde protective group employed.

As polysubstituted resorcinols are an important class of natural products with significant biological and pharmacological properties,[1] there is a continuous search for new approaches to their synthesis.[2-11] We have recently reported a synthetic procedure involving the one-pot regioselective reductive electrophilic substitution of the 2-

(1) Nakanishi, K.; Goto, T.; Sho, I.; Natori, S.; Nozoe, S. *Natural Product Chemistry*; Academic Press: New York, 1975; Vol. 2, Chapter 9.

(2) Saà, J. M.; Llobera, A.; Garcìa-Raso, A.; Costa, A.; Deyà, P. M. *J. Org. Chem.* **1988**, *53*, 4263.

(3) Crombie, L. W.; Crombie, W. M. L.; Firth, D. F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1263.

(4) Kanakam, C. C.; Mani, N. S.; Ramanathan, H.; Subba Rao, G. S. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1907.

(5) Boulet, C. A.; Poulton, G. A. *Heterocycles* **1989**, *28*, 405.

(6) Bradbury, B. J.; Sindelar, R. D. *J. Heterocyclic Chem.* **1989**, *26*, 1827.

(7) Kawagishi, H.; Ando, M.; Mizuno, T. *Tetrahedron Lett.* **1990**, *31*, 373.

(8) Martorell, G.; Garcìa-Raso, A.; Saà, J. M. *Tetrahedron Lett.* **1990**, *31*, 2357.

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