Synthesis of Halomethyl and Other Bipyridine Derivatives by Reaction of 4,4′-Bis[(trimethylsilyl)methyl]-2,2′-bipyridine with Electrophiles in the Presence of Fluoride Ion

Cassandra L. Fraser,* Natia R. Anastasi, and Jaydeep J. S. Lamba

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

Received September 8, 1997[⊗]

Bipyridine (bpy) ligands figure prominently in many areas of chemistry. Common precursors to many derivatives are the halomethyl-substituted analogues. This report describes a new, high yield route to these valuable compounds via a trimethylsilyl (TMS) intermediate. 4,4′-Dimethyl-2,2′-bpy was reacted with lithium diisopropylamide, and the dianion thus formed was trapped with TMSCl to generate 4,4′-bis[(trimethylsilyl)methyl]-2,2′-bpy (**1**). The TMS group was removed using dry F^- sources (TBAF/SiO_2 in THF or CsF in DMF) in the presence of BrF_2CCF_2Br or Cl_3CCCl_3 to produce the bromide **2** or chloride **3** analogues of 4,4′-bis(halomethyl)-2,2′-bipyridine, respectively. The CsF/DMF methodology extends to other electrophiles, including benzaldehyde to give 4,4′-bis(2-hydroxy-2-phenethyl)-2,2′-bpy, **6**, as well as to alkyl halides. Benzyl Br, dodecyl Br, and α-chloroacetonitrile gave mixtures of di- and monoalkylated products along with the diprotonated product, 4,4′-dimethyl-2,2′-bpy.

Introduction

Some of the most widely used ligands in chemistry are bipyridine (bpy) and its various derivatives. From foundational studies in coordination chemistry[1] to the present day, this family of nitrogen heterocycles has played a central role. Currently bpy derivatives figure prominently in supramolecular chemistry,[2] conformationally constrained peptides,[3] in sensors and receptors,[4] in polymer chemistry,[5,6] studies of redox electrocatalysis,[7] electron transfer,[8] photochemistry, electroluminescence,[9] and a variety of other fields. Halomethyl bipyridines are particularly useful since they serve as precursors to numerous other analogues. Despite their widespread application, the synthesis and purification of halide derivatives are rarely trivial. Typically they are prepared either by radical halogenation of the appropriate methyl derivatives,[7,10] or from hydroxymethyl precursors.[11] Radical methods usually give rise to mixtures of halogenated products that are difficult to separate by column chromatography. One solution to this problem has been to carry out selective reduction of polyhalogenated byproducts with diisobutylaluminum hydride (DIBALH), but this has resulted in only slight improvements in overall yields.[12] A more efficient approach involves the conversion of alcohol functionalities to halides; however the synthesis of the hydroxymethyl compounds from methyl precursors typically involves multiple steps, each of which give intermediates in moderate to high yields.[11] Generation of bpy$(CH_2Li)_n$ anions with strong bases, followed by trapping with electrophiles, has not proven successful for halide products.[11a,13]

In trying to develop more efficient routes to 4,4′-bis(halomethyl)-2,2′-bpy ligands for use as metalloinitiators for living polymerization reactions,[6] it was discovered that halides and other bpy analogues can be conveniently obtained via the trimethylsilyl (TMS) derivative, **1**. Our approach employs TMS as a carbanion protecting group that may be removed by F^- in situ for reaction with electrophiles. Though this methodology has precedent in reactions with carbonyl substrates,[14] the use of halide and RX electrophiles is less common. Described below are investigations of the reactivity of **1** with halide, aldehyde, and alkyl halide electrophiles.

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1997.

(1) Reedijk, J. In *Comprehensive Coordination Chemistry*; Wilkinson, Sir G.; Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford and NY, 1987; Vol. 2, pp 73−98 and references therein.

(2) (a) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154−96. (b) Achar, S.; Puddephatt, R. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 847−9. (c) Hasenknopf, B.; Lehn, J. M.; Kneisel, B. O.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1838−40. (d) Woods, C. R.; Benaglia, M.; Cozzi, F.; Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1830−3. (e) See: Tzalis, D.; Tor, Y. *J. Am. Chem. Soc.* **1997**, *119*, 852−3 and references therein.

(3) (a) Cheng, R. P.; Fisher, S. L.; Imperiali, B. *J. Am. Chem. Soc.* **1996**, *118*, 11349−56. (b) Ghadiri, M. R.; Soares, C.; Choi, C. *J. Am. Chem. Soc.* **1992**, *114*, 825−31, 4000−2. (c) Sardesai, N.; Lin, S. C.; Zimmermann, K.; Barton, J. K. *Bioconjugate Chem.* **1995**, *6*, 302−12. (d) Harding, M. M.; Lehn, J. M. *Aust. J. Chem.* **1996**, *49*, 1023−27.

(4) (a) Torrado, A.; Imperiali, B. *J. Org. Chem.* **1996**, *61*, 8940−8. (b) Szemes, F.; Hesek, D.; Chen, Z.; Dent, S. W.; Drew, M. G. B.; Goulden, A. J.; Graydon, A. R.; Grieve, A.; Mortimer, R. J.; Wear, T.; Weightman, J. S.; Beer, P. D. *Inorg. Chem.* **1996**, *35*, 5868−79.

(5) Matyjaszewski, K.; Patten, T. E.; Xia, J. *J. Am. Chem. Soc.* **1997**, *119*, 674−80.

(6) Lamba, J. J. S.; Fraser, C. L. *J. Am. Chem. Soc.* **1997**, *119*, 1801−2.

(7) See: Gould, S.; Strouse, G. F.; Meyer, T. J.; Sullivan, B. P. *Inorg. Chem.* **1991**, *30*, 2942−9 and references therein.

(8) (a) Gray, H. B.; Winkler, J. R. *Annu. Rev. Biochem.* **1996**, *65*, 537−61. (b) Holmlin, R. E.; Stemp, E. D. A.; Barton, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 5236−44. (c) Dandliker, P. J.; Holmlin, R. E.; Barton, J. K. *Science* **1997**, *275*, 1465−8.

(9) (a) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85−277. (b) Sauvage, J.-P.; Collin, J.-P.; Chambron, J.-C.; Guillerez, S.; Coudret, C.; Balzani, V.; Barigelletti, F.; De Cola, L.; Flamigni, L. *Chem. Rev. (Washington, D.C.)* **1994**, *94*, 993−1019. (c) Balzani, V.; Juris, A.; Venturi, M.; Campagna, S.; Serroni, S. *Chem. Rev.* **1996**, *96*, 659−833.

(10) (a) Wang, Z.; Reibenspies, J.; Motekaitis, R. J.; Martell, A. E. *J. Chem. Soc., Dalton Trans.* **1995**, 1511−8. (b) Rodriguez, J.-C.; Alpha, B.; Plancherel, D.; Lehn, J.-M. *Helv. Chim. Acta* **1984**, *67*, 2264−9. (c) Newkome, G. R.; Puckett, W. E.; Kiefer, G. E.; Gupta, V. K.; Xia, Y.; Coreil, M.; Hackney, M. A. *J. Org. Chem.* **1982**, *47*, 4116−20.

(11) (a) Della Ciana, L.; Hamachi, I.; Meyer, T. J. *J. Org. Chem.* **1989**, *54*, 1731−5. (b) Della Ciana, L.; Dressick, W. J.; von Zelewsky, A. *J. Heterocyc. Chem.* **1990**, *27*, 163. (c) Newkome, G. R.; Kiefer, G. E.; Kohli, D. K.; Xia, Y.-J.; Fronczek, F. R.; Baker, G. R. *J. Org. Chem.* **1989**, *54*, 5105−10. (d) Imperiali, B.; Prins, T. J.; Fisher, S. L. *J. Org. Chem.* **1993**, *58*, 1613−6.

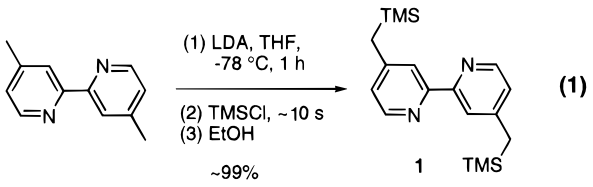
(12) Uenishi, J.-I.; Tanaka, R.; Nishiwaki, K.; Wakabayashi, S.; Oae, S.; Tsukube, H. *J. Org. Chem. Soc.* **1993**, *58*, 4382−8.

(13) Attempts to react 4,4′-bis-$(LiCH_2)$-2,2′-bpy with halide electrophiles, including NBS, Br_2, and BrF_2CCF_2Br, were unsuccessful in yielding **2**. Addition of the lithiated bpy to a THF solution of Cl_3CCCl_3 produced the less reactive dichloro product **3** in impure form.

S0022-3263(97)01685-X CCC: $14.00

Results and Discussion

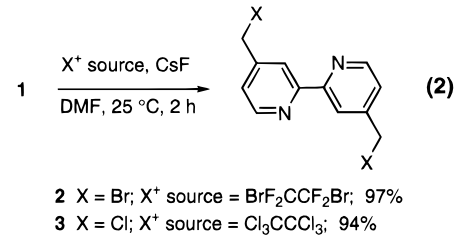
The TMS derivative, **1** is prepared in essentially quantitative yield[15] by deprotonation of 4,4′-dimethyl-2,2′-bipyridine with LDA followed by trapping of the resulting dianion with TMSCl (eq 1). To prevent oversilylation[16] it is crucial that the reaction be quenched with EtOH immediately after silylation is complete. This occurs ∼5−10 s after TMSCl addition and is indicated by a color change from brown to pale blue-green. The resulting crystalline TMS-bpy product, **1**, serves as a stable "dianion equivalent" and as a starting material in the synthesis of other bpy analogues.



(1)

Since removal of the TMS groups with F^- produces a highly basic carbanion-like functionality, dry fluoride sources were utilized for this reaction. Two different F^- reagents, Bu_4NF supported on SiO_2 (dry TBAF)[17] and CsF, were compared under different reaction conditions. Our initial studies employed dry TBAF for the reaction of **1** with the halide electrophiles, BrF_2CCF_2Br and Cl_3CCCl_3, in THF solution.[6] Reactions run at −78 °C and at room temperature proceeded similarly and were complete within ≤15 min. For ease of product isolation and subsequent purification by column chromatography, the amount of TBAF/SiO_2 reagent was kept to a minimum. The halide products **2** and **3** were produced cleanly and in high yield by this route (**2**: 73%; **3**: 96%). Attempts to extend this methodology to other electrophiles, including benzyl or allyl bromide, or methyl α-bromoacetate met with very limited success. Some alkylated products were obtained with the ester reagent, but in the other cases primarily the diprotonated product, 4,4′-dimethyl-2,2′-bipyridine was formed, indicating that protonation is more favorable than alkylation under these conditions.

Since the TBAF/SiO_2 methodology was somewhat limited in scope and the activity of dry TBAF diminishes over time, other more convenient sources of fluoride ion were sought. Anhydrous cesium fluoride was selected for its good solubility in polar organic solvents such as CH_3CN[18] and DMF, the latter also being favorable for anionic alkylations. Reaction of the TMS compound, **1**, with CsF and halide electrophiles, BrF_2CCF_2Br or Cl_3CCCl_3 (X^+ sources), in dry DMF solution produces **2** or **3** cleanly and nearly quantitatively after 2 h at room temperature (eq 2). Since BrF_2CCF_2Br is volatile, the



(2)

2 X = Br; X^+ source = BrF_2CCF_2Br; 97%
3 X = Cl; X^+ source = Cl_3CCCl_3; 94%

halide product **2** may be very conveniently isolated pure, in essentially quantitative yield after a standard aqueous workup. Hexachloroethane, in contrast, is a solid and must be separated either by column chromatography or by acidification, ether washes, neutralization, and back extraction of the bpy product. Typically 2 equiv of the halide electrophile was used per TMS group in these reactions. This increases the reaction rate and is necessary for clean conversion to product by the standard conditions. A mixture of mono- and dichlorinated bpy products was obtained when only 1 equiv of halide per TMS group was utilized. To gain a better understanding of the origin of the protonated byproducts and to see whether the reaction between **1** and Cl_3CCCl_3 might be induced thermally, a control reaction was run at 65 °C in DMF solution in the absence of CsF. GC/MS analysis showed primarily the diprotonated 4,4′-dimethyl-2,2′-bipyridine product. There was no evidence of either mono- or dichlorinated bpy. This suggests that the protonation side reaction may not necessarily be CsF dependent.

To further explore the scope of this reaction, benzaldehyde, a carbonyl electrophile, was also tested. A mixture of TMS ether products **4** and **5** was isolated after reaction of the TMS bpy starting material **1** with benzaldehyde under the standard conditions (eq 2) and aqueous workup. Treatment of the mixture of **4** and **5** thus isolated with 1 M HCl yielded the diol **6**. This product **6** was obtained more directly by addition of H_2O to the reaction mixture once alkylation was complete (TLC) and stirring for ∼30 min prior to workup (eq 3).

The CsF methodology also extends to reactions of **1** with alkyl halide electrophiles, RX (eq 4), though these reactions are not as selective as those with halide or benzaldehyde electrophiles. Benzyl and dodecyl bromide and chloroacetonitrile were selected for careful screening since these commercially available compounds span a range of reactivities and some of the likely reaction products are of interest to us for other purposes. Reaction times were extended to ensure the complete consumption of TMS starting material and intermediates as

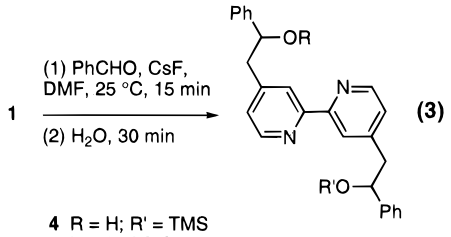
(14) (a) Majetich, G.; Hull, K.; Casares, A. M.; Khetani, V. *J. Org. Chem.* **1991**, *56*, 3958−73 and references therein. (b) Ricci, A.; Fiorenza, M.; Grifagni, M. A.; Bartolini, G. *Tetrahedron Lett.* **1982**, *23*, 5079−82. (c) Hosomi, A.; Hayashi, S.; Hoashi, K.; Kohara, S.; Tominaga, Y. *J. Org. Chem.* **1987**, *52*, 4424−6. (d) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509−25. (e) Danishefsky, S. J.; Shair, M. D. *J. Org. Chem.* **1996**, *61*, 16−44.

(15) In some reactions the TMS product **1** was contaminated with trace amounts of the 4,4′-dimethyl-2, 2′-bipyridine starting material and/or a yellow impurity. If only the dimethyl compound is present, crude **1** may be separated either by column chromatography (SiO_2, 3.5% EtOAc in hexanes, TMS compound elutes first) or more conveniently, by recrystallization from a minimal amount of hexanes at −4 °C. The TMS bpy **1** precipitates and may be collected by filtration. The yellow impurity may be removed from the solid thus collected by washing with copious quantities of very cold hexanes, leaving the TMS product **1** as a white crystalline solid.

(16) Oversilylation is most clearly indicated by more than one singlet in the 0−0.10 ppm region of the ^1H NMR spectrum. Oversilated product (∼2 g) may be recycled to valuable dimethyl bpy starting material by stirring a CH_3CN solution (∼100 mL) with 48% HF (∼2−3 mL) at 25 °C for several hours. The dimethyl compound precipitates from the reaction mixture as its HF salt, a white solid, and is collected by filtration. The free base is obtained by dissolving the white precipitate in CH_2Cl_2, washing with aqueous Na_2CO_3, followed by concentration of the organic layer.

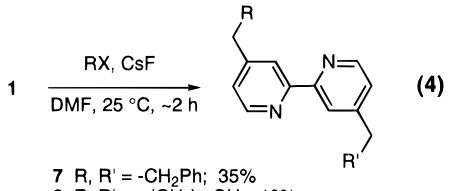
(17) Clark, J. H. *J. Chem. Soc., Chem. Commun.* **1978**, 789.

(18) Acetonitrile was also tested as a solvent for reactions using CsF and the TMS bpy substrate **1**. This approach works well for the preparation of the chloro bpy ligand **3**, and many alkylated products may be accessed by this route. However, elevated temperatures (∼50 °C) are required for reactions in CH_3CN which not only precludes the synthesis of the bromide ligand **2** (BrF_2CCF_2Br: bp = 47 °C), but also leads to side products and depressed yields in the alkylation reactions as compared with reactions run in DMF solution.



4 R = H; R' = TMS
5 R, R' = TMS
6 R, R' = H; 99%

indicated by TLC. Typically mixtures of dialkylated, monoalkylated, and diprotonated (i.e. dimethyl) bpy were obtained in different amounts with these and other alkyl halide reagents. In most cases, particularly with more reactive electrophiles, highly colored, polar byproducts were also formed. These water soluble species could be alkyl pyridinium species resulting from reaction of RX reagents with the bpy nitrogens. For each reaction, the major product was separated from reaction byproducts by fractional crystallization or by column chromatography prior to characterization. Generally this was the dialkylated product; however, for reaction of **1** with chloroacetonitrile, the monoalkylated product **9** predominated. Yields are reported after purification based on starting material **1** (eq 4).[19] Though direct reaction of alkyl halides with dimethyl bpy dianion is more efficient in certain cases,[20] it might be possible to further optimize the conditions of our reactions to give better selectivity for mono- or dialkylated products.



7 R, R' = -CH_2Ph; 35%
8 R, R' = -$(CH_2)_{11}CH_3$; 46%
9 R = -CH_2CN, R'= H; 40%

Conclusion

These investigations illustrate that 4,4′-bis($TMSCH_2$)-2,2′-bipyridine is a versatile starting material for the synthesis of bpy derivatives bearing halide, alcohol, nitrile, and other functionalities. Though different dry F^- sources, reaction conditions, and solvents may be used for these reactions, for convenience, optimal yield, and purity of products, CsF in DMF is the method of choice for both halogenation and alkylation reactions. This approach, which allows for the synthesis of halomethyl bpys in two nearly quantitative yield steps, constitutes a dramatic improvement over existing methodologies for making these widely used compounds. This TMS/CsF chemistry should readily extend to bipyridines with different substitution patterns, to related nitrogen heterocycles, and to new classes of electrophiles.

Experimental Section

General Considerations. All chemicals were obtained from Aldrich or Acros and were used as received unless otherwise indicated. Silica gel used to prepare dry TBAF and for flash column chromatography (particle size 0.040−0.063 mm) was obtained from Merck. Reactions were run in DMF obtained from Aldrich in Sureseal bottles. THF was dried and purified by passage through alumina solvent purification columns.[21] CH_3CN was distilled from CaH_2. All reactions were run under a nitrogen atmosphere and were monitored by TLC on SiO_2 (typically 20% EtOAc in hexane; UV detection). Silica plates and chromatography columns were deactivated with 10% Et_3N in hexanes prior to use. (NOTE: For the TMS bpy starting material, **1**, $R_f \approx 0.5$. All products appear at $R_f < 0.5$. Reaction intermediates sometimes appear at $R_f > 0.5$.) For reactions run in DMF, silica plates were dried under high vacuum for at least ~10 min prior to developing. Typical procedures for dry TBAF and CsF reactions are provided below. Alkylation reactions were typically run using ~100 mg of **1**. Deviations from these procedures and purification methods for each compound are indicated below. Initial product percentages for reaction mixtures were determined by GC after the standard workup. Isolated product yields are based on **1**.

Preparation of n-Bu_4NF/SiO_2 ("Dry TBAF"). Dry TBAF was prepared by the procedure of Clark[17] with the following modifications. n-Bu_4NF (1 M in THF, 20 mL, 20 mmol) and Et_3N (1 mL) were added to silica gel (8 g) in MeOH (~60 mL). The solvents were removed by evaporation at 25 °C,[22] and the residual solvent in the resulting white gummy solid was azeotroped with benzene (3 × 100 mL). The SiO_2-supported TBAF was then dried under high vacuum for ~14 h at 25 °C. The reagent remains "active" for ~2 weeks if stored under nitrogen at 4 °C. Dry TBAF gradually turns yellow as it decomposes.

Synthesis of 4,4′-Bis[(trimethylsilyl)methyl]-2,2′-bipyridine (1). To diisopropylamine (1.75 mL, 12.5 mmol) in THF (16 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes, 6.9 mL, 11 mmol). The solution was stirred at −78 °C for 20 min. 4,4′-Dimethyl-2,2′-bipyridine (0.921 g, 5 mmol) was dissolved in dry THF (22 mL) and was transferred dropwise via cannula to the LDA solution. The flask and cannula were rinsed with THF (2 × 2 mL). The brown mixture was stirred at −78 °C for 20 min, was warmed to −10 °C for 25 min, and then was cooled to −78 °C before addition of TMSCl (1.65 mL, 13 mmol). As soon as the brown reaction mixture became pale blue-green in color (~5−10 s after TMSCl addition), the reaction was quenched with EtOH (3 mL). Saturated aqueous $NaHCO_3$ was added to the cold reaction mixture, which was then allowed to warm to ~25 °C. The product was extracted into EtOAc (3 × 200 mL), and then combined organic fractions were washed with brine (200 mL) and were dried over Na_2SO_4. Filtration and concentration afforded the product, **1**, as a slightly off-white crystalline solid: 1.632 g (99%);[15] mp 90−92 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 18 H), 2.21 (s, 4 H), 6.94 (d, J = 5.01 Hz, 2 H), 8.05 (br s, 2 H), 8.46 (d, J = 5.00 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −2.2, 27.1, 120.4, 123.0, 148.3, 150.8, 155.5.

General Procedure for TBAF/SiO_2 Reactions. Synthesis of 4,4′-Bis(chloromethyl)-2,2′-bipyridine (3). To 4,4′-bis[(trimethylsilyl)methyl]-2,2′-bipyridine (**1**) (0.500 g, 1.52 mmol) and Cl_3CCCl_3 (1.44 g, 6.1 mmol) in THF (20 mL) at −78 °C was added TBAF/SiO_2 (3.0 g, ~4.6 mmol). If the reaction was not complete after 15 min (TLC), additional TBAF/SiO_2 (0.2 g) was added. After complete conversion, the heterogeneous mixture was concentrated in vacuo. Crude **3** was loaded onto a deactivated silica gel column (pretreated with 10% triethylamine in hexane) and was eluted with CH_2Cl_2. Concentration of the appropriate fractions afforded the chloride **3** as a white solid: 0.357 g (94%); mp 98−100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.63 (s, 4 H), 7.38 (dd, J = 5.01, 1.93 Hz, 2 H), 8.43 (s, 2 H), 8.70 (d, J = 4.62 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.9, 120.1, 122.8, 146.7, 149.4, 155.8. Anal. Calcd for $C_{12}H_{10}N_2Cl_2$: C, 56.94; H, 3.98; N, 11.07. Found: C, 56.82; H, 4.04; N, 11.01.

(19) Though the phenethyl product **7** is produced in good yield (83%, GC) by the CsF reaction, this drops dramatically during purification due to the difficulties of separation from the dimethyl bpy byproduct of similar polarity.

(20) (a) el Torki, F. M.; Schmehl, R. H.; Reed, W. F. *J. Chem. Soc., Faraday Trans. 1* **1989**, *85*, 349−62. (b) For related compounds see: Griggs, C. G.; Smith, D. J. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 3041−3.

(21) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−20.

(22) Rotoevaporation at elevated temperature results in decomposition of the "dry TBAF" reagent.

General Procedure for CsF Reactions. Synthesis of 4,4′-Bis(bromomethyl)-2,2′-bipyridine (2).[7] To a dry DMF solution (5 mL) of 4,4′-bis[(trimethylsilyl)methyl]-2,2′-bipyridine (**1**) (0.104 g, 0.317 mmol) and BrF_2CCF_2Br (0.152 mL, 1.27 mmol) was added anhydrous CsF (0.193 g, 1.27 mmol). The reaction was stirred at ~25 °C for ~2 h (or until TLC indicated that all TMS starting material and intermediates were consumed). The reaction mixture was poured into a separatory funnel containing EtOAc and H_2O (100 mL each). The aqueous layer was extracted with EtOAc (3 × 50 mL), and then combined organic fractions were washed with H_2O (2 × 100 mL), were shaken with brine (200 mL), and then were dried over Na_2SO_4. Filtration, and concentration in vacuo gave pure **2** as a white solid: 0.105 g (97%); mp 116−118 °C. ^{1}H NMR coincident with data reported by Gould et al.[7]

4,4′-Bis(2-hydroxy-2-phenethyl)-2,2′-bipyridine (6). A mixture of the mono- and bis-TMS protected alcohol products **4** and **5** was isolated using the standard procedure. To obtain the alcohol **6** directly, H_2O (2 mL) was added to the reaction mixture after alkylation was complete (TLC) and the DMF/H_2O mixture was stirred at rt for ~30 min. The reaction was poured into EtOAc/H_2O (100 mL each), and a white solid precipitated immediately and remained suspended in the EtOAc layer. The EtOAc suspension was washed with H_2O (2 × 50 mL) and then was concentrated in vacuo. The resulting white crystalline solid **6** was suspended in a minimal amount of Et_2O and then was collected by filtration and dried in vacuo: 0.121 g (99%); mp 202−204 °C; ^{1}H NMR (d_6-DMSO, 300 MHz) δ 2.93 (m, 4H), 4.81 (br m, 2 H), 5.35 (br m, 2 H), 7.17−7.34 (m, 12 H), 8.22 (s, 2 H), 8.46 (d, J = 5.01 Hz, 2 H). ^{13}C NMR (d_6-DMSO, 75 MHz) δ 45.0, 72.8, 121.8, 125.3, 126.0, 126.9, 126.9, 127.98, 128.04, 145.5, 148.6, 149.3, 155.1. IR (KBr, cm^{-1}) 3282 (OH).

4,4′-Bis(2-phenethyl)-2,2′-bipyridine (7). Reaction of **1** with benzyl bromide gave 83% dialkyl, trace monoalkyl, and 17% diprotonated bpy products (GC). Dialkylated product **7** was obtained by the following procedure. The crude solid obtained after the standard workup was triturated with EtOH, was collected by filtration, and then was washed with additional EtOH. The resulting white solid **7** was recrystallized from hot EtOH (2× or until ^{1}H NMR indicated the absence of the dimethyl bpy impurity at 2.4 ppm) to give pure **7** as white needles: 0.5 g (35%);[19] mp 147−149 °C, lit. mp 147−149 °C. ^{1}H NMR coincident with data reported by Bos et al.[23]

4,4′-Bis(tridecyl)-2,2′-bipyridine (8). Reaction of **1** with 1-bromododecane for 1 d at 25 °C produced 68% dialkyl, 13% monoalkyl, 19% diprotonated bpy products (GC). Improved yields were obtained using only 1 mL of DMF/0.1 g of **1** for the reaction combined with the following modified workup. Alkylated products precipitated from the DMF reaction mixture, were collected by filtration, and then were washed with H_2O. The major dialkyl product **8** was obtained after fractional crystallization from EtOH according to the procedure of el Torki et al.:[20] 0.37 g (46%); 76−77 mp °C, lit. mp 64−5 °C.[24] ^{1}H NMR coincident with data reported by el Torki et al.[20]

4-(2-cyanoethyl)-4′-methyl-2,2′-bipyridine (9). Reaction of **1** with chloroacetonitrile at rt for 1 d produced 26% dialkyl, 49% monoalkyl, and 25% diprotonated bpy products (GC). After purification by chromatography on deactivated SiO_2 (1:1 EtOAc/hexane), the monoalkylated product, **9** was obtained as a thick water white oil that crystallized upon standing: 0.03 g (40%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3 H), 2.72 (t, J = 7.45 Hz, 2 H), 3.04 (t, J = 7.46 Hz, 2 H), 7.13 (m, 1 H), 7.19 (dd, J = 2.01, 5.23 Hz, 1 H), 8.22 (br s, 1 H), 8.25 (br s, 1 H), 8.51 (d, J = 5.23 Hz, 1 H), 8.62 (d, J = 5.24 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.8, 20.8, 30.6, 118.1, 120.4, 121.7, 123.1, 124.6, 147.3, 148.0, 148.6, 149.3, 155.0, 156.5. IR (KBr, cm^{-1}) 2249 (CN).

Acknowledgment. This work was supported by the National Science Foundation, the American Chemical Society Petroleum Research Fund, the Jeffress Foundation, and the University of Virginia. We also gratefully acknowledge Dr. James E. Collins for his assistance on this project.

Supporting Information Available: Copies of 300 MHz ^{1}H and 75 MHz ^{13}C spectra for compounds **1**, **6**, and **9** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971685X

(23) Bos, K. D.; Kraaijkamp, J. G.; Noltes, J. G. *Synth. Commun.* **1979**, 9(6), 497−504.

(24) Melting points in ref 20a for mono- and dialkylated products appear to be transposed. The melting point reported for the monoalkyl bpy (76-77 °C) is coincident with what we measured for the dialkylated product.