Efficient Synthesis of 4-, 5-, and 6-Methyl-2,2′-bipyridine by a Negishi Cross-Coupling Strategy Followed by High-Yield Conversion to Bromo- and Chloromethyl-2,2′-bipyridines

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Introduction

Bipyridine ligands and their many complexes find wide application in chemistry.[1] These nitrogen heterocycles are common in studies of electron transfer in proteins and small molecules,[2] in supramolecular assembly,[3] and in sensing and recognition.[4] They also play a central role as ligands for copper catalysts in new living radical polymerization methodologies.[5] Despite their prevalence, many desirable bipyridine (bpy) derivatives have long proven elusive. Until recently many of the halomethyl bipyridines were only obtainable in low to moderate yields. Common approaches to these compounds include radical halogenation which can give rise to mixtures of products that are difficult to separate[6] or preparation via alcohol precursors which are accessed by a multistep synthesis from the methyl precursors.[6,7] Recently we introduced a new and highly efficient approach to the halogenation of dimethyl bipyridines.[8,9a] Specifically, 4,4′-dimethyl-2,2′-bipyridine was deprotonated with lithium diisopropylamide (LDA) followed by trapping with trimethylsilyl chloride (TMSCl). Reaction of the resulting bis-TMS derivative with BrF_2CCF_2Br or Cl_3CCCl_3 in the presence of CsF provided the bromide or chloride cleanly and in high yield. These 4,4′-bis(halomethyl)-2,2′-bipyridines and their metal complexes were utilized by us as initiators for living polymerization reactions.[9] To further explore the use of metal complexes as templates for polymerization initiators, it was also of interest to prepare monofunctional halomethyl bipyridines. Moreover, we wanted to determine the generality of the TMS methodology for methyl bpys with different substitution patterns.[10] Anions of 4- and 6-methyl bpy possess resonance structures with formal negative charges on electronegative nitrogen atoms on the same ring. For the anion of 5-methyl bpy, similar stabilization is achieved only through delocalization onto the adjacent heteroaromatic ring. We were curious to see whether this difference might correlate with differences in reactivity for the methyl bpy derivatives.

Monofunctional bipyridine reagents may be accessed from monomethyl bpy starting materials. As the vast literature documenting many alternative routes to these compounds attests, efficient synthesis of these unsymmetrical bipyridines represents a long-standing challenge in the field.[11] Traditionally, methyl bpys have been prepared by the Krönke method which involves reaction of pyridinium salts with α,β-unsaturated ketones followed by treatment with ammonium acetate to effect cyclization.[12] They have also been made by coupling of pyridyllithium reagents with pyridyl sulfoxides,[6b,13] by Ni and other metal-catalyzed cross-coupling reactions,[14] by the Ullman reaction,[12] and, more recently, by use of α-oxoketene dithioacetals among a variety of other routes.[15] Many methods lead to mixtures of isomers or they also produce dimethyl byproducts. Some approaches require rather involved multistep syntheses and harsh conditions, few methods are general for different substitution patterns, and nearly all of them produce products in moderate yields, at best. Though modern palladium-catalyzed cross-coupling strategies require an expensive

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(10) During the course of our investigations, it was demonstrated that the TMS to halide methodology[8] extends to 6,6′-dimethyl-2,2′-bipyridine which was used to generate 6,6′-bis(bromomethyl)-2,2′-bipyridine in good yield. Hochwimmer, G.; Nuyken, O.; Schubert, U. S. *Macromol. Rapid Commun.* **1998**, *19*, 309.

(11) Another common route to monofunctional bipyridines involves monosubstitution of dimethyl bipyridine reagents. This approach is often complicated by over- or underfunctionalization and separation of desirable products from starting material and byproducts can be troublesome.[6a] Our attempts to access monofunctional bpy derivatives in this manner involved reaction of commercially available 4,4′-dimethyl-2,2′-bipyridine with 0.95 equiv[6a] of LDA followed by quenching with TMSCl. After varying reaction conditions and reagent loadings, in all cases mixtures of the desired product, the difunctional TMS compound, and the dimethyl starting material were obtained. These species proved difficult to separate by either chromatography or recrystallization (Krause, B.; Fraser, C. L. Unpublished results). Monolithiation followed by reaction with electrophiles has been successful in some cases (e.g., with aldehydes). See: Beer, P. D.; Kocian, R. J.; Mortimer, R. J.; Ridgway, C. *J. Chem. Soc., Dalton Trans.* **1993**, 2629. Other approaches take advantage of the limited solubility of monofunctionalized intermediates.[15b]

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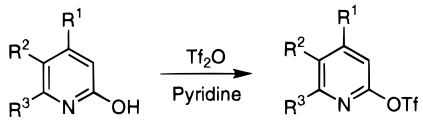
transition metal reagent or, in the case of Stille coupling, tin compounds that are toxic, they are an attractive alternative nonetheless since both yields and selectivities are considerably higher than those observed by other routes.[16]

This account describes our efforts to develop a more efficient preparation of methyl 2,2′-bipyridine ligands, and the achievement of this goal via cross-coupling of an aryl Zn reagent and an aryl triflate[17] in the presence of a catalytic amount of Pd by the Negishi method.[18] This method is general; the 4-, 5-, and 6-methyl-2,2′-bipyridines are all attainable in unprecedented yields. Despite potential differences in the acidities of the methyl protons in the 5- vs 4- and 6-methyl bpys, all three regioisomers are readily converted to the respective (trimethylsilyl)-methyl analogues and are obtained in high yield. It is further demonstrated that these reagents serve as precursors to the useful bromomethyl and chloromethyl bpy derivatives.

Results and Discussion

After attempting several different Pd-catalyzed methodologies,[19] it was discovered that the Negishi cross-coupling reaction between a pyridyl triflate, **PyOTf**, and a pyridyl zinc reagent was consistently the most effective. This reaction also benefits from the fact that it is conveniently carried out in a single pot. The 4-, 5-, and 6-methyl-2-(trifluoromethylsulfonyl)oxypyridines (**1**−**3**) were prepared from the respective 2-hydroxypyridines[20] by reaction with triflic anhydride, Tf_2O, and were obtained in high yield after purification by flash chromatography on silica gel[21] (Table 1). Lithium−halogen exchange was effected by reaction of *tert*-butyllithium with 2-bromopyridine at −78 °C. After transmetalation to Zn, a THF solution of $Pd(PPh_3)_4$ (generated in situ from $Pd_2(dba)_3$ and PPh_3) (dba = dibenzylideneacetone) and the appropriate triflate were added, and the reactions were refluxed for 15 h. After aqueous workup in the presence of ethylenediaminetetraacetic acid (EDTA) to chelate Zn(II)[22] and purification by column chromatography, the desired methyl-2,2′-bipyridines, **Mebpy**, were all obtained in high yield (Table 2).

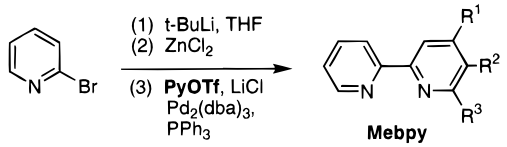
Table 1. Synthesis of 2-Pyridyl Triflates



PyOTf

PyOTf	R^1	R^2	R^3	yield (%)
1	Me	H	H	94
2	H	Me	H	90
3	H	H	Me	95

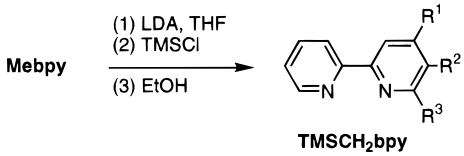
Table 2. Synthesis of Methyl-2,2′-bipyridines



Mebpy

Mebpy	PyOTf	R^1	R^2	R^3	yield (%)
4	**1**	Me	H	H	98
5	**2**	H	Me	H	94
6	**3**	H	H	Me	93

Table 3. Synthesis of (Trimethylsilyl)methyl-2,2′-bipyridines



$TMSCH_2$bpy

$TMSCH_2$bpy	Mebpy	R^1	R^2	R^3	yield (%)
7	**4**	$TMSCH_2$	H	H	93
8	**5**	H	$TMSCH_2$	H	99
9	**6**	H	H	$TMSCH_2$	97

The methyl bipyridines, **4**−**6**, were readily converted to the respective (trimethylsilyl)methyl derivatives, **$TMSCH_2$bpy** (**7**−**9**), by deprotonation with 1 equiv of LDA followed by trapping with TMSCl as previously described[8] (Table 3). Products were obtained in nearly quantitative yield after purification by chromatography on silica gel. As for 4,4-bis($TMSCH_2$)-2,2′-bipyridine,[8] the $TMSCH_2$bpy compounds, **7**−**9**, serve as useful starting materials for the preparation of chloro- and bromomethyl derivatives, **XCH_2bpy** (Table 4). Reaction of the $TMSCH_2$-bpy compounds with either hexachloroethane in CH_3CN or dibromotetrafluoroethane in DMF in the presence of dry CsF yielded the chlorides and bromides respectively, in very high yield.[23]

Conclusion

This account describes both a new route to 4-, 5-, and 6-methyl bipyridines and the successful conversion of

(16) For some other examples of metal-catalyzed cross-coupling of pyridyl reagents see the following. Cu: (a) Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237. Pd: (b) Fernando, S. R. L.; Maharoof, U. S. M.; Deshayes, K. D.; Kinstle, T. H.; Ogawa, M. Y. *J. Am. Chem. Soc.* **1996**, *118*, 5783. (c) Ishikura, M.; Kamada, M.; Terashima, M. *Synthesis* **1984**, 936. (d) Bell, A. S.; Roberts, D. A.; Ruddock, K. S. *Tetrahedron Lett.* **1988**, 29, 5013.

(17) For a review of the use of aryl triflates in Pd-catalyzed Stille coupling see: Ritter, K. *Synthesis* **1993**, 735.

(18) (a) Negishi, E. *J. Org. Chem.* **1977**, *42*, 1821. (b) Negishi, E.; Takahashi, T.; King, A. O. *Org. Synth.* **1988**, *66*, 67. (c) Larsen, M.; Jorgensen, M. *J. Org. Chem.* **1997**, *62*, 4171.

(19) Palladium-catalyzed Suzuki coupling[16c] of both aryl borates or aryl boric acid reagents and variously substituted aryl bromides was attempted. In most cases, large amounts of dimethyl byproducts were formed in these preparations. The pyridyl bromides were prepared from the respective amino pyridines by the Craig reaction (Craig, L. C. *J. Am. Chem. Soc.* **1934**, *56*, 231). Negishi coupling of 2-pyridyl zinc chloride with the methyl-substituted pyridyl bromides generated some of the desired Mebpy products but in low yield as compared with the triflates (e.g., bromides, ∼15%; triflates, ∼60% when no EDTA was used in the workup).

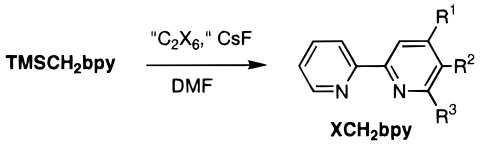
(20) 2-Hydroxy-4-methylpyridine and 2-hydroxy-6-methylpyridine are commercially available; however they and the 5-methyl analogue are all conveniently prepared from the appropriate 2-aminopyridine derivatives by reaction with H_2SO_4 and $NaNO_2$ as previously reported by Barash and modified by Adger. (a) Barash, M.; Osbond, J. M.; Wickens, J. C. *J. Chem. Soc.* **1959**, 3530. (b) Adger, B. M.; Ayrey, P.; Bannister, R.; Forth, M. A.; Hajikarimian, Y.; Lewis, N. J.; O'Farrell, C.; Owens, N.; Shamji, A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2791. 2-Hydroxy-5-methylpyridine: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.99 (s, 3 H), 6.43 (d, J = 8.8 Hz, 1 H), 7.06 (s, 1 H), 7.23 (dd, J = 2.2, 9.5 Hz, 1 H), 13.48 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.5, 115.5, 119.2, 131.9, 143.8, 164.2. Anal. Calcd for C_6H_7NO: C, 66.04; H, 6.46; N, 12.84. Found: C, 66.09; H, 6.31; N, 13.05.

(21) 4-Methyltriflate, **1**: (a) Yuan, J.; Thurkauf, A. Patent WO 96 16, 058 (US 344,397,23). 5-Methyltriflate, **2**: (b) Fey, P.; et al. Bayer AG.; EP 0624583 A1; May 2, 1994. 6-Methyltriflate, **3**: (c) Zhu, J.; Bigot, A.; Elise, M.; Dau, T. H. *Tetrahedron Lett.* **1997**, *38*, 1181. (d) Yoneda, N.; Fukuhara, T.; Mitsubishi Chem Ind, Jpn. Kokai Tokkyo Koho; JP 05,255,251 (93,255,251); Oct 5, 1993.

(22) When EDTA was omitted, Zn complexes of the products were observed (white solids) and the yields were considerably depressed.

(23) The chlorides may also be prepared in DMF solution at 25 °C as described for the bromides. It has been the experience of some investigators in our group that large scale chloride reactions are cleaner in CH_3CN than in DMF.

Table 4. Synthesis of Halomethyl-2,2′-bipyridines



XCH_2bpy	$TMSCH_2bpy$	C_2X_6	R^1	R^2	R^3	yield (%)
10	**7**	Cl_3CCCl_3	$ClCH_2$	H	H	94
11	**8**	Cl_3CCCl_3	H	$ClCH_2$	H	98
12	**9**	Cl_3CCCl_3	H	H	$ClCH_2$	95
13	**7**	BrF_2CCF_2Br	$BrCH_2$	H	H	92
14	**8**	BrF_2CCF_2Br	H	$BrCH_2$	H	98
15	**9**	BrF_2CCF_2Br	H	H	$BrCH_2$	99

these reagents to the widely used bromo- and chloromethyl derivatives by way of (trimethylsilyl)methyl bipyridine intermediates. Bipyridine derivatization schemes that were previously difficult due to the challenges associated with accessing these unsymmetrical reagents should now be considerably more practical as a result of these vast improvements in reaction efficiency and product yields.

Experimental Section

General Considerations. All chemicals were obtained from Aldrich and were used as received unless otherwise indicated. Silica gel used for flash chromatography (particle size 0.040−0.063 mm) was obtained from Merck. THF was dried and purified by passage through alumina solvent purification columns.[24] Acetonitrile and diisopropylamine were distilled over CaH_2 prior to use. Dry DMF and pyridine were obtained from Aldrich in Sureseal bottles. All reactions were run under a nitrogen atmosphere and were monitored by TLC on SiO_2 (UV detection). Silica plates were deactivated with 10% Et_3N in hexanes prior to use, and plates were heated or dried under vacuum to evaporate DMF prior to developing. Silica chromatography columns were deactivated with 10% Et_3N in hexanes and then were washed with hexanes prior to use for product purification. ^1H and ^{13}C NMR spectra were recorded on a GE QE 300 spectrometer in the solvents specified.

4-Methyl-2-(trifluoromethanesulfonyl)oxypyridine (1).[21a] To 2-hydroxy-4-methylpyridine (2.49 g, 22.8 mmol) in dry pyridine (90 mL) at 0 °C was rapidly added trifluoromethanesulfonic anhydride (7.91 g, 28.0 mmol). The solution was stirred at 0 °C for 20 min and then was poured into a separatory funnel containing H_2O (80 mL). The mixture was extracted with CH_2Cl_2 (3 × 60 mL); then combined organic fractions were dried over Na_2SO_4. Filtration and concentration in vacuo, followed by flash chromatography on deactivated silica gel (20% EtOAc:80% hexanes), gave pure **1** as a colorless oil: 5.20 g (94%); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3 H), 6.99 (s, 1 H), 7.19 (d, J = 5.1 Hz, 1 H), 8.25 (d, J = 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 116.0, 119.2 (q, J_{CF} = 321.0 Hz), 125.8, 148.5, 153.9, 156.7.

5-Methyl-2-(trifluoromethanesulfonyl)oxypyridine (2).[21b] The triflate **2** was prepared from 2-hydroxy-5-methylpyridine[20] by the method described above for **1** and was obtained as a colorless oil: 6.3 g (90%); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3 H), 7.06 (d, J = 8.1 Hz, 1 H), 7.67 (dd, J = 2.4, 8.5 Hz, 1 H), 8.17 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.2, 114.2, 118.1 (q, J_{CF} = 320.3 Hz), 134.1, 141.0, 148.1, 153.6. Anal. Calcd for $C_7H_6NO_3SF_3$: C, 34.86; H, 2.51; N, 5.81. Found: C, 34.99; H, 2.19; N, 5.70.

6-Methyl-2-(trifluoromethanesulfonyl)oxypyridine (3).[21c,d] The triflate **3** was prepared from 2-hydroxy-6-methylpyridine by the method used for **1** and was obtained as a colorless oil: 3.71 g (95%); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.52 (s, 3 H), 6.95 (d, J = 8.1 Hz, 1 H), 7.21 (d, J = 7.7 Hz, 1 H), 7.74 (t, J = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.3, 111.3, 118.3 (q, J_{CF} = 320.3 Hz), 123.4, 140.6, 154.8, 158.6.

4-Methyl-2,2′-bipyridine (4). To THF (20 mL) at −78 °C was added *t*-BuLi (1.75 M in pentane, 7.5 mL, 13 mmol) followed by dropwise addition of 2-bromopyridine (1.05 g, 6.64 mmol). After stirring at −78 °C for 30 min, $ZnCl_2$ (2.00 g, 14.6 mmol) was added, and the reaction was stirred for 2 h at 25 °C. The triflate, **1** (1.31 g, 5.43 mmol), LiCl (0.5 g, 12 mmol), and a THF solution of $Pd(PPh_3)_4$ (prepared in situ by stirring $Pd_2(dba)_3$ (0.17 g, 0.19 mmol) and PPh_3 (0.40 g, 1.5 mmol) in THF (5 mL) for 1 h) were then added. The reddish-brown reaction mixture was heated at reflux for 15 h. After cooling, an aqueous solution of EDTA (18 g, 48 mmol in 150 mL) was added and the reaction mixture was stirred for 5 min. The reaction was poured into a separatory funnel, the pH was adjusted to 8 with saturated aqueous $NaHCO_3$, and the basic mixture was extracted with CH_2Cl_2 (3 × 75 mL). Combined organic fractions were dried over Na_2SO_4, were filtered, and then were concentrated in vacuo. Pure **2** was isolated as a white solid after purification by flash chromatography using deactivated silica gel (30% EtOAc:70% hexanes): 0.90 g (98%); mp 62.5−64 °C, lit. mp 62−64 °C;[15] ^1H NMR coincident with data reported by Potts et al.[15]

5-Methyl-2,2′-bipyridine (5). The methyl bpy **5** was obtained as a very pale yellow oil after preparation from 2-bromopyridine and the triflate **2** by the method described above for **4**: 1.31 g (94%); ^1H NMR coincident with data reported by Potts et al.[15]

6-Methyl-2,2′-bipyridine (6). The methyl bpy **6** was isolated as a white solid after preparation from 2-bromopyridine and the triflate **3** by the method described above for **4**: 1.05 g (93%); recrystallized from hexanes; mp 37−38 °C, lit. mp 50−51 °C;[6b] ^1H NMR coincident with data reported by Potts et al.[15]

4-(Trimethylsilyl)methyl-2,2′-bipyridine (7).[25] To diisopropylamine (0.72 mL, 5.1 mmol) in THF (35 mL) at −78 °C was added *n*-BuLi (1.7 M in hexanes, 2.7 mL, 4.6 mmol). The solution was stirred at −78 °C for 10 min, was warmed to 0 °C for 10 min, and then was cooled back down to −78 °C. 4-Methyl-2,2′-bipyridine (**4**) (0.695 g, 4.1 mmol) in THF (5 mL) was added dropwise to the cold LDA solution. The resulting maroon-black reaction mixture was stirred at −78 °C for 1 h; then TMSCl (0.65 mL, 5.1 mmol) was added. After the solution became pale blue-green in color (∼10 s after TMSCl addition), the reaction was quenched by rapid addition of absolute EtOH (2.5 mL). The cold reaction mixture was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (40 mL) and was allowed to warm to ∼25 °C. The product was extracted with CH_2Cl_2 (3 × 40 mL); then the combined organic fractions were dried over Na_2SO_4. Filtration and concentration in vacuo, followed by flash chromatography using deactivated silica gel (30% EtOAc:70% hexanes), gave pure **7** as a clear, colorless oil: 0.92 g (93%);[25] ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 9 H), 2.21 (s, 2 H), 6.95 (dd, J = 1.5, 5.0 Hz, 1 H), 7.29 (m, 1 H), 7.8 (td, J = 1.9, 8.1 Hz, 1 H), 8.06 (s, 1 H), 8.38 (d, J = 8.1 Hz, 1 H), 8.47 (d, J = 5.0 Hz, 1 H), 8.68 (d, J = 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −2.3, 27.2, 120.3, 120.8, 123.1, 123.2, 136.4, 148.3, 148.7, 150.9,

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

(25) Generally the TMS compounds are stable when stored at room temperature under N_2. It should be noted however that slow decomposition to the parent methyl compound has been observed for 4-$TMSCH_2$bpy and more rarely for 4,4′-bis($TMSCH_2$)bpy.

155.2, 156.1. Anal. Calcd for $C_{14}H_{18}N_2Si$: C, 69.37; H, 7.48; N, 11.56. Found: C, 69.39; H, 7.73; N, 11.88.

5-(Trimethylsilyl)methyl-2,2′-bipyridine (8). The $TMSCH_2$-bpy **8** was prepared from the methyl bpy **5** according to the method described above for **7** and was obtained as a white solid: 0.708 g (99%); mp 50−52 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 9 H), 2.13 (s, 2 H), 7.27 (td, J = 1.9, 8.0 Hz, 1 H), 7.45 (d, J = 8.1 Hz, 1 H), 7.79 (td, J = 1.9, 8.1 Hz, 1 H), 8.25 (d, J = 8.1 Hz, 1 H), 8.34 (d, J = 7.6 Hz, 1 H), 8.36 (d, J = 2.4 Hz, 1 H), 8.66 (d, J = 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.5, 24.5, 30.2, 121.1, 123.6, 136.5, 137.2, 137.3, 149.0, 149.6, 152.8, 156.9. Anal. Calcd for $C_{14}H_{18}N_2Si$: C, 69.37; H, 7.48; N, 11.56. Found: C, 69.29; H, 7.60; N, 11.43.

6-(Trimethylsilyl)methyl-2,2′-bipyridine (9). The $TMSCH_2$-bpy **9** was obtained as a clear, colorless oil after preparation from the methyl bpy **6** by the method described above for **7** (15% EtOAc:85% hexanes): 0.56 g (97%);[25] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 9 H), 2.41 (s, 2 H), 6.98 (d, J = 7.8 Hz, 1 H), 7.27 (m, 1 H), 7.63 (t, J = 7.8 Hz, 1 H), 7.79 (td, J = 1.8, 7.8 Hz, 1 H), 8.09 (d, J = 7.2 Hz, 1 H), 8.41 (d, J = 8.1 Hz, 1 H), 8.66 (d, J = 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −1.9, 29.8, 116.1, 120.7, 122.0, 122.9, 136.36, 136.41, 148.6, 154.8, 156.5, 160.4. Anal. Calcd for $C_{14}H_{18}N_2Si$: C, 69.37; H, 7.48; N, 11.56. Found: C, 69.02; H, 7.52; N, 11.86.

4-Chloromethyl-2,2′-bipyridine (10). To 4-(trimethylsilyl)-methyl-2,2′-bipyridine (**7**) (0.58 g, 2.4 mmol) and Cl_3CCCl_3 (1.13 g, 4.8 mmol) in CH_3CN[23] (15 mL) at 25 °C was added dry CsF (0.72 g, 4.8 mmol). The heterogeneous reaction mixture was stirred at 60 °C for ∼4 h (or until TLC indicated that all TMS starting material was consumed). After cooling to ∼25 °C, the mixture was poured into a separatory funnel containing EtOAc and H_2O (∼30 mL each). The product was extracted with EtOAc (3 × 30 mL); then the combined organic fractions were shaken with brine (100 mL) and dried over Na_2SO_4. Filtration and concentration in vacuo, followed by flash chromatography using deactivated silica gel (60% EtOAc:40% hexanes), gave pure **10** as a clear, colorless oil: 0.46 g (94%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.64 (s, 2 H), 7.34 (m, 2 H), 7.83 (td, J = 1.5, 7.7 Hz, 1 H), 8.41 (m, 2 H), 8.69 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.9, 119.8, 120.8, 122.5, 123.6, 136.6, 146.5, 148.8, 149.3, 155.2, 156.3. Anal. Calcd for $C_{11}H_9N_2Cl$: C, 64.56; H, 4.43; N, 13.69. Found: C, 64.25; H, 4.44; N, 13.60.

5-Chloromethyl-2,2′-bipyridine (11). Chloride **11** was prepared from the $TMSCH_2$bpy **8** as described above for **10** and was obtained as a white solid after purification with deactivated silica gel (CH_2Cl_2): 0.166 g (98%); mp 59−61 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.66 (s, 2 H), 7.33 (t, J = 6.6 Hz, 1 H), 7.84 (qd, J = 1.5, 1.5, 1.9, 2.3 Hz, 2 H), 8.40 (d, J = 4.4 Hz, 1 H), 8.43 (d, J = 7.4 Hz, 1 H), 8.69 (bs, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.6, 121.5, 121.7, 124.4, 133.6, 137.4, 137.6, 149.5, 149.7, 156.1, 156.7. Anal. Calcd for $C_{11}H_9N_2Cl$: C, 64.56; H, 4.43; N, 13.69. Found: C, 64.56; H, 4.57; N, 13.53.

6-Chloromethyl-2,2′-bipyridine (12). The chloride **12** was isolated as a clear, colorless oil after synthesis from the $TMSCH_2$-bpy compound **9** and purification with deactivated silica gel (15% EtOAc:85% hexanes) as described above for **10**: 0.12 g (95%); ^{1}H NMR coincident with data reported by Newkome et al.[7a]

4-Bromomethyl-2,2′-bipyridine (13).[26] 4-(Trimethylsilyl)-methyl-2,2′-bipyridine, **7** (0.39 g, 1.6 mmol), BrF_2CCF_2Br (0.49 g, 3.2 mmol), CsF (0.84 g, 3.2 mmol), and DMF (15 mL) were combined and stirred at 25 °C for ∼3 h (or until TLC indicated absence of all TMS starting material). The reaction mixture was poured into a separatory funnel containing H_2O (∼50 mL), and the product was extracted with EtOAc (3 × 40 mL). The combined organic fractions were washed with H_2O (100 mL), were shaken with brine (100 mL), and then were dried over Na_2SO_4. Filtration and concentration in vacuo, followed by flash chromatography on deactivated silica gel (30% EtOAc:70% hexanes), yielded the bromide **13** as a clear, colorless oil: 0.45 g (92%);[26] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.49 (s, 2 H), 7.33 (m, 2 H), 7.83 (td, J = 1.5, 7.7 Hz, 1 H), 8.40 (d, J = 7.5 Hz, 1 H), 8.43 (s, 1 H), 8.67 (d, J = 4.8 Hz, 1 H), 8.70 (d, J = 4.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.4, 120.4, 120.9, 123.2, 123.6, 136.6, 146.8, 148.8, 149.3, 155.1, 156.4.

5-Bromomethyl-2,2′-bipyridine (14). The bromide **14** was synthesized from the $TMSCH_2$bpy compound **8** by the method described for **13**, thus producing a white solid: 0.198 g (98%); mp 71−73 °C, lit. mp 72−73 °C;[6b] ^{1}H NMR coincident with data reported by Imperiali[7c] and Uenishi.[6b]

6-Bromomethyl-2,2′-bipyridine (15). The bromide **15** was prepared from the $TMSCH_2$bpy compound **9** according to the method described above for **13** and was obtained as a white solid: 0.49 g (99%); mp 66−68 °C, lit. mp 65.5−67 °C;[6b] ^{1}H NMR coincident with data reported by Uenishi.[6b]

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Supporting Information Available: 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra for compounds **1**, **3**, and **13** (6 pages). Ordering information is given on any current masthead page. 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.

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(26) Unlike the 5- and 6-bromomethyl bpys (**14** and **15**), **13** is very reactive and develops a brown color when solutions are concentrated, when in $CDCl_3$ solution as NMR samples, and even when stored in the freezer under nitrogen. The major impurity gives rise to peaks at 5.4 and 5.6 ppm in the ^{1}H NMR spectrum and may correspond to the dimer formed by nucleophilic attack of the bpy nitrogen at the benzylic bromide position. Many colored and poorly soluble impurities may be removed by filtering a 30% EtOAc:70% hexanes solution of the sample through a plug of deactivated silica gel.