Synthesis of Cyclo-2,2′:4′,4″:2″,2‴:4‴,4⁗:2⁗,2⁗′:4⁗′,4-sexipyridine

T. Ross Kelly,* Yean-Jang Lee, and Richard J. Mears

Department of Chemistry, E. F. Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02167

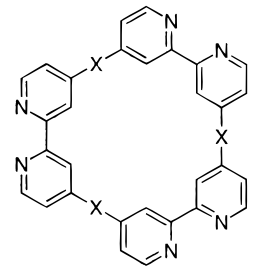
Received December 3, 1996[⊗]

Preparation of the title compound (**2**) by use of Stille couplings and a Kröhnke pyridine synthesis is described. By application of the Stille coupling reaction, preparation and functionalization of quater- and quinquepyridines **26**, **27**, and **28** were achieved. Elaboration of quinquepyridine **27** to the pyridinium salt **30** bearing a protected enal allowed for the synthesis of **2** by a one-pot deprotection/Kröhnke reaction in nine steps from 4,4′-bipyridine. Use of the Kröhnke pyridine synthesis has been applied to prepare sexipyridine dibromide **19**, but attempts to induce a macrocyclization via metal-mediated (Pd/Ni/Cu) aryl−aryl coupling procedures proved unsuccessful. Acetylene-bridged sexipyridines **3a** and **3b** incorporating 2,2′-bipyridine units proved to be inaccessible via sp−sp^2 or sp−sp coupling protocols.

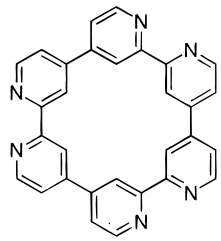
Introduction

The design of metal-chelating organic ligands that assemble into structurally defined architectures when chelated to metals continues to be a major research topic in the field of supramolecular chemistry.[1] Such structures have possible applications as selective catalysts and filters[2] or as media for electron transfer in mixed valency structures with the potential to act as molecular wires or switches.[3] To this end, we hoped to prepare a ligand with D_{3h} symmetry,[4] exploiting the well-documented[5] chelating properties of the 2,2′-bipyridine system with a diverse range of metals. The molecules we envisioned to possess both the desired symmetry and the potential to form predictable chelated network structures (e.g., organic zeolites[6]) were cyclic sexipyridines of the general form **1** where X could be varied to change the pore size of the network and/or to embed functionalities within the matrix. This paper describes our efforts to prepare the parent compound **2** and the two simple acetylenic analogs **3a** and **3b**.

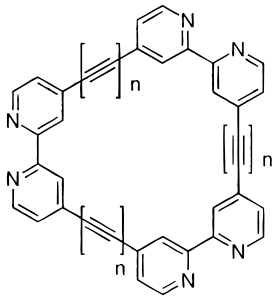
To date, only two examples, **4a** and **4b**, of cyclic oligopyridines have been reported,[7] and in both cases the nitrogen atoms are directed toward the center of the molecule, i.e. "endo".[8] A number of cyclic bipyridines joined by flexible spacer units have been reported.[9] However, none of these structural types possesses the required symmetry or structural rigidity necessary for the formation of predictable molecular networks.



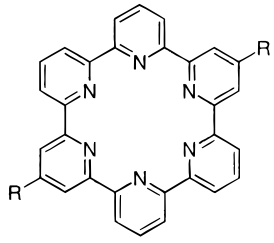
1



2



3a, n = 1
3b, n = 2



4a, R = H
4b, R = *p*-Tolyl, *p*-EtC_6H_4

* Author to whom correspondence should be addressed. Tel: (617) 552-3621. Fax: (617) 552-2705.

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

(1) (a) Zaworotko, M. J. *Chem. Soc. Rev.* **1994**, 283. (b) Moore, J. S.; Lee, S. *Chem. Ind. (London)* **1994**, 557. (c) Abrahams, B. F.; Hoskins, B. F.; Michail, D, M.; Robson, R. *Nature* **1994**, 369, 727. (d) Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1079. (e) Fujita, M.; Kwon, Y. J.; Washizu, S.; Ogura, K. *J. Am. Chem. Soc.* **1994**, *116*, 1151. (f) Drain, C. M.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1994**, 2313. (g) Hanan, G. S.; Arana, C. R.; Lehn, J.-M.; Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1122. (h) Baxter, P. N. W.; Lehn, J.-M.; Fisher, J.; Youinou, M.-T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2284. (i) De Munno, G.; Julve, M.; Nicolo, F.; Lloret, F.; Faus, J.; Ruiz, R.; Sinn, E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 613.

(2) (a) Service, R. F. *Science* **1994**, *265*, 1363. (b) Holderich, W.; Hesse, M.; Näumann, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 226 and references therein. (c) Amato, I. *Science* **1993**, *259*, 891. (d) Subramanian, S.; Zaworotko, M. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2127.

(3) (a) Ward, M. D. *Chem. Soc. Rev.* **1995**, 121. (b) Sauvage, J.-P.; Collin, J.-P.; Chambron, J.-C.; Guillerez, S.; Condret, C.; Balzani, V.; Barigelletti, F.; De Cola, L.; Flamigni, L. *Chem. Rev.* **1994**, *94*, 993. (c) Benniston, A. C.; Grosshenny, V.; Harriman, A.; Ziesel, R. *Angew Chem., Int. Ed. Engl.* **1994**, *33*, 1884. (d) Marfurt, J.; Zhao, W.; Walder, L. *J. Chem. Soc., Chem. Commun.* **1994**, 51. (e) Ward, M. D. *Chem. Ind. (London)* **1996**, 568.

(4) Other ligands with D_{3h} symmetry include 2,4,6-tri(4-pyridyl)-1,3,5-triazine (Batten, S. R.; Hoskins, B. F.; Robson, R. *J. Am. Chem. Soc.* **1995**, *117*, 5385) and 1,4,5,8,9,12-hexaazatriphenylene (HAT) (Nasielski-Hinkens, R.; Benedek-Vamos, M.; Maetens, D.; Nasielski, J. *J. Organomet. Chem.* **1981**, *217*, 179).

(5) Gillard, R. D. *Coord. Chem. Rev.* **1975**, *6*, 187.

(6) (a) Venkaraman, D.; Gardner, G. B.; Lee, S.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 11600. (b) Moore, J. S. *Nature* **1995**, *374*, 495. (c) Ward, M. D. *Nature* **1995**, *374*, 764.

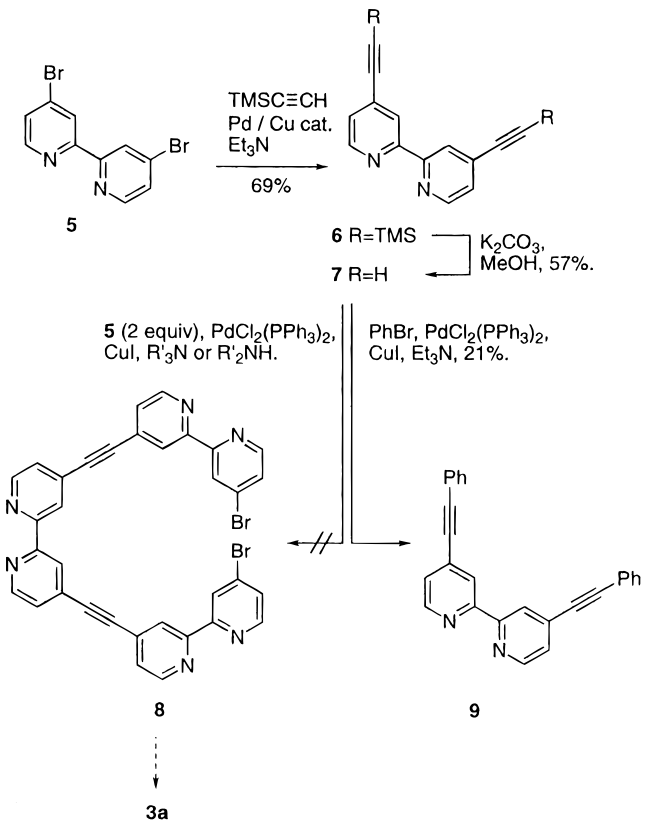
(7) (a) Newkome, G. R.; Lee, H.-W. *J. Am. Chem. Soc.* **1983**, *105*, 5956. (b) Toner, J. L. *Tetrahedron Lett.* **1983**, *24*, 2707.

(8) As a convenient way of distinguishing between molecules such as **4a**, where the nitrogens are on the inside (*endo*), and **2**, where the nitrogens are on the outside (*extra*, as in extraterrestrial), we suggest **4a** be named *endo*-sexipyridine and **2** *extra*-sexipyridine.

(9) (a) Kaes, C.; Hosseini, M. W.; Ruppert, R.; De Cian, A.; Fischer, J. *J. Chem. Soc., Chem. Commum.* **1995**, 1445. (b) Newkome, G. R.; Gupta, V. K.; Sauer, J. D. In *Pyridine and its Derivatives: The Chemistry of Heterocyclic Compounds*; Newkome, G. R., Ed.; John Wiley: New York, 1984; Vol. 14, Part 5, Chapter 3, pp 447−633.

S0022-3263(96)02236-0 CCC: $14.00

Scheme 1

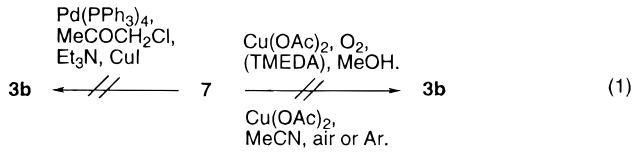


Results and Discussion

Our initial attempts to prepare ligands such as **1**−**3** focused on the preparation of sexipyridine **3a**. When the three 2,2′-bipyridine systems are connected by 0−*n* acetylene spacer units, variation of spacer units has the potential to allow tuning of the cavity sizes of any network structures formed, an important consideration in the design of size-selective filters[2a] or catalysts.[2b] We had hoped to prepare the precursor dibromide **8** (Scheme 1) and complete the synthesis by a mono-Sonogashira[10] coupling with (trimethylsilyl)acetylene, removal of the trimethylsilyl group, and a final cyclization/coupling to the desired product. Dibromide **5** was prepared (three steps, 24% overall yield) according to literature procedures,[11] and a subsequent Sonogashira coupling using the method of Ziesel[12] yielded the doubly substituted (trimethylsilyl)acetylene **6**. In our hands, formation of significant amounts of monocoupled material was observed using only 2.5 equiv of (trimethylsilyl)acetylene; we found it necessary to use 6 equiv of (trimethylsilyl)-acetylene to drive the reaction to completion. Removal of the trimethylsilyl group with K_2CO_3 in methanol surrendered the diacetylene **7** in 39% overall yield from dibromide **5**; the spectral data for both acetylene compounds **6** and **7** agree with those reported.[12]

Palladium-catalyzed coupling of the acetylene **7** with dibromide **5** to produce **8** proved to be an insurmountable problem, despite myriad attempts. We attempted the coupling reactions using $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ as the palladium source with and without CuI as the cocatalyst, in benzene[13] and DMF[14] containing 2 molar equiv of a base (Et_3N or *i*-Pr_2NH),[12] or conducted the experiment in neat amine[15] (90−130 °C/4−24 h/sealed tube), but in no cases were any coupling products observed. Our failure to couple these reagents may lie in the poor reactivity of **7** toward aromatic coupling, as a trial reaction of **7** with bromobenzene afforded the diphenyl derivative **9** in only 21% yield.

Having acetylene **7** in hand, we also investigated the oxidative homocoupling (eq 1) of this molecule, hoping to prepare sexipyridine **3b**. A Glaser coupling under the conditions of Hay[16] or the Vogtle[17] procedure in air, or under an atmosphere of argon, failed to afford any coupled products. Disappointingly, attempts to induce a palladium-mediated coupling using chloroacetone[18] also failed to give any of the desired product. This inability to access acetylene-bridged oligobipyridines by sp−sp^2 or sp−sp coupling protocols led us to change focus and investigate the synthesis of the "unbridged" sexipyridine **2**.



(1)

Our first attempts to synthesize sexipyridine **2** sought to take advantage of the wide range of aryl−aryl coupling methodologies to form the target molecule via an intramolecular coupling reaction.[19] With this strategy in mind, we hoped to prepare dibromide **19** by a Kröhnke reaction[20] between the bis-pyridinium salt **16** and aldehyde **18** (Scheme 2). Diamine **10** was prepared from 4,4′-bipyridine using the Chichibabin reaction;[21] a subsequent diazotization and hydrolysis generated the pyridone **11** in 86% overall yield. The pyridone was then subjected to bromination with $POBr_3$,[22] affording dibromide **12** in 60% yield; surprisingly, the dichloro analogue of **12** is

(10) (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 521−549. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH Publishers: New York, 1996; p 582.

(11) (a) Wenkert, D.; Woodward, R. B. *J. Org. Chem.* **1983**, *48*, 283. Nakashima, K.; Shinkai, S. *Chem. Lett.* **1994**, 1267.

(12) Suffert, J.; Ziesel, R. *Tetrahedron Lett.* **1991**, *32*, 757.

(13) (a) Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P. *Synthesis* **1984**, 729. (b) Takehashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

(14) Chen, Q.-Y.; Yang, Z.-Y. *Tetrahedron Lett.* **1986**, *27*, 1171.

(15) Tilley, J. W.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386.

(16) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320.

(17) Berscheid, R.; Vögtle, F. *Synthesis* **1992**, 59.

(18) Rossi, R.; Carpita, A.; Bigelli, C. *Tetrahedron Lett.* **1985**, *26*, 523.

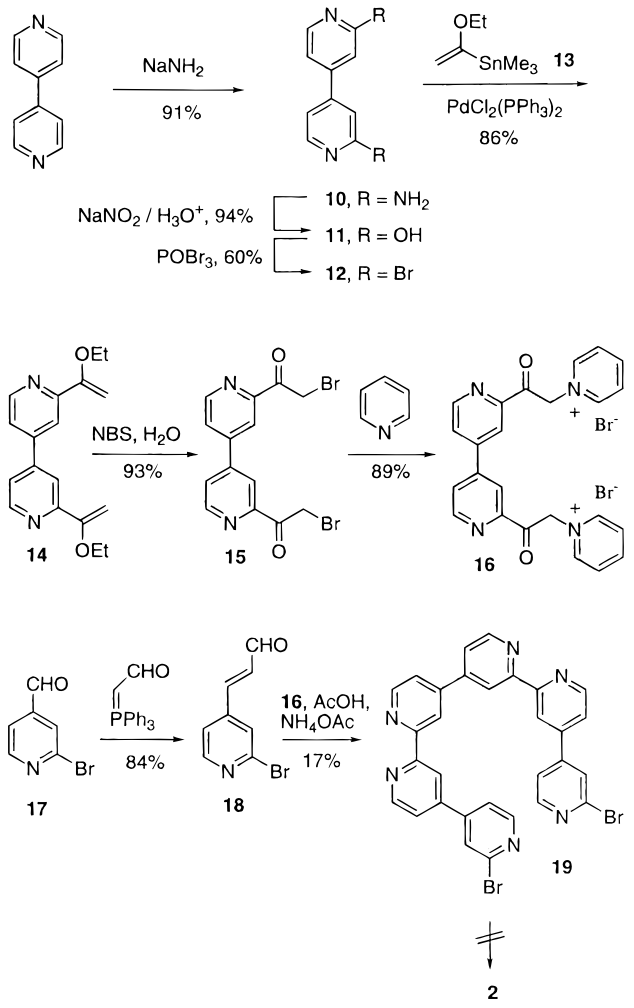
(19) (a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (b) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 505−509.

(20) (a) Kröhnke, F. *Synthesis* **1976**, 1. (b) Constable, E. C.; Lewis, J. *Tetrahedron* **1982**, *1*, 303. (c) Constable, E. C.; Ward, M. D.; Corr, J. *Inorg. Chim. Acta* **1988**, *141*, 201. (d) Constable, E. C.; Ward, M. D.; Tocher, D. A. *J. Chem. Soc., Dalton Trans.* **1991**, 1675. (e) Constable, E. C.; Chotalia, R. *J. Chem. Soc., Chem. Commun.* **1992**, 65.

(21) Leffler, M. T. *Org. React.* **1942**, *1*, 91.

(22) $POBr_3$ was prepared by a procedure developed by Dr. S. Christie in our laboratories, which is carried out as follows: Into a beaker containing PBr_3 (37 mL, 0.40 mol) cooled to 5 °C, bromine (20.6 mL, 0.40 mol) was introduced dropwise while the mixture was stirred with a glass rod, giving a deep orange solid. To this solid was slowly introduced water (7.2 mL, 0.40 mol) (CARE: EXOTHERMIC), and mixing was continued between additions. The resulting orange slush was transferred to a round-bottomed flask and distilled under vacuum (20 Torr) using a warm condenser (to prevent solidification in and blocking of the condenser). Fractions were collected between 92 and 120 °C (head temperature). Yield fraction 1 (<100 °C head temperature, 37.7 g, 33%), total yield (98.7 g, 87%). The first fraction collected (<100 °C) was a pale orange semisolid and was found to be superior to higher boiling fractions (colorless, crystalline solid mass) for the bromination of pyridone **11**.

Scheme 2



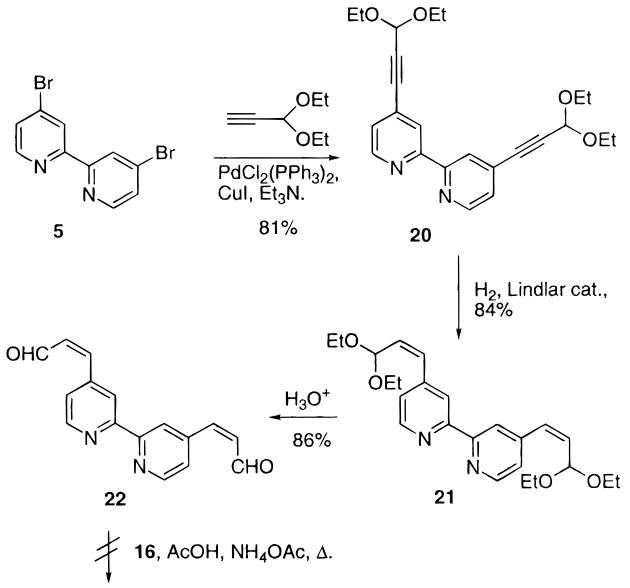
the only 2,2′-dihalo-4,4′-bipyridine to be reported[23] in the literature, and our procedure represents the first route to access such compounds without the use of autoclave techniques. Conversion to bis(ethoxyvinyl)bipyridine **14** utilized the stannane **13**[24] which serves as a masked acyl[25] or α-haloacyl[26] group for introduction of these substituents into aromatic systems via a Stille coupling process.[27] Coupling of the stannane **13** with dibromide **12** proceeded smoothly to give an 86% yield of the desired bis(ethoxyvinyl)bipyridine **14**, and bromination with NBS under aqueous conditions gave the bis(bromoacetyl)bipyridine **15** in 93% yield. This compound was surprisingly stable in light of its subsequent facile substitution reaction with pyridine: **15** could be recrystallized from hot ethanol:water mixtures without evidence of any solvolysis and stored in a freezer indefinitely. Finally, reaction of **15** with a stoichiometric amount of pyridine in acetone gave an 89% yield of the bis-pyridinium salt **16**. An alternative procedure involving acid hydrolysis of the (ethoxyvinyl)bipyridine **14**, followed by an Ortoleva−King[28] reaction on the resulting bis(methyl ketone) using I_2/pyridine gave lower yields (<45%) of the corresponding bis-pyridinium iodide of **16**. Bromo aldehyde **17** was prepared from 2-aminopicoline in four steps, 12% overall yield, by a reported procedure;[29] subsequent Wittig reaction with (triphenylphosphoranylidene)acetaldehyde afforded an 84% yield of aldehyde **18**. A Kröhnke reaction between bis-pyridinium salt **16** and aldehyde **18** in acetic acid afforded the dibromide **19** in 17%. A number of unidentified pyridine products are also formed in this reaction; olefinic signals (^{1}H NMR) in the crude products lead us to postulate that a competing 1,2-addition to the aldehyde **18** may occur. Use of DMF or methanol[20a] as the solvent was found to give lower yields (ca. 3% and 6%, respectively); in these latter cases, even greater amounts of competing olefinic products were observed in the crude products.

Intramolecular coupling of the dibromide **19** was examined exhaustively using palladium-, nickel-, and copper-mediated coupling processes. A one-pot halogen−metal exchange[30]/Stille coupling between 0.5 molar equiv of hexamethylditin and dibromide **19**, using either Pd(PPh$_3$)$_4$ or PdCl$_2$(PPh$_3$)$_2$, inexplicably gave only mixtures of starting material and the bis(trimethylstannane) derivative of **19**. Nickel coupling by in-situ preparation of Ni(0) (NiBr$_2$(PPh$_3$)$_2$/Zn/Et$_4$NI/DMF or THF)[31] was found to give mixtures of starting materials and debrominated products using 1 and 4 equiv[32] of Ni(0) (a treatment with KCN[33] during workup was used to cleave any metal complexes). Use of preformed Ni(0) (Ni(COD)$_2$/2,2′-bipyridine/DMF)[34] gave polypyridines by intermolecular coupling; even at a 50× dilution factor (0.001 M vs 0.050 M) these polymeric materials were the only products observed. Finally, dibromide **19** was found to be unreactive to Ullmann coupling in DMF[35] or DMF with catalytic palladium.[36] Use of biphenyl as solvent[37] in the Ullmann reaction was also found to be unsuccessful. At temperatures <280 °C no reaction was observed, even after 48 h; at higher temperatures only debromination products were observed. Such a result is consistent with the observation by Constable[20e] that 2-bromoterpyridines are unreactive toward Ullmann coupling procedures. It is striking that cyclization of **19** to **2** could not be achieved despite the many advances in methods for achieving biaryl couplings[19b] and this research group's considerable experience[26a,38] in achieving such couplings. Perhaps geometric constraints of a relatively rigid system prevent the organometallic intermediates from achieving the necessary conformation.

Our lack of success with metal-mediated coupling reactions led us to examine the Kröhnke reaction as a means of cyclization, as demonstrated by Toner[7b] in the

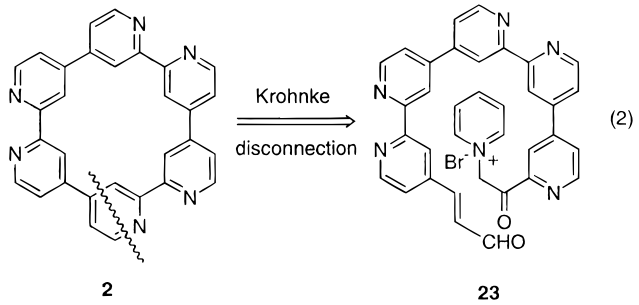
(23) Darragh, J. I. Brit. Patent 1,491,254, 1977; *Chem. Abstr.* **1978**, *88*, 190594j. Ruetman, S. H. U.S. Patent 3,819,558, 1971; *Chem. Abstr.* **1974**, *81*, 91363g.
(24) Soderquist, J. A.; Hsu, G. J.-H. *Organometallics* **1982**, *1*, 830.
(25) (a) Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, *55*, 3114. (b) Cheney, D. L.; Paquette, L. A. *J. Org. Chem.* **1989**, *54*, 3334.
(26) (a) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623. (b) Gaudry, M.; Marquet, A. *Bull. Soc. Chim. Fr.* **1969**, *11*, 4169.
(27) Kosugi, M.; Sumiya, T.; Obara, Y.; Suzuki, M.; Sano, H.; Migata, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 767.
(28) King, L. C. *J. Am. Chem. Soc.* **1944**, *66*, 894.
(29) Ashimori, A.; Ono, T.; Uchida, T.; Ohtaki, Y.; Fukaya, C.; Watanabe, M.; Yokoyama, K. *Chem. Pharm. Bull.* **1990**, *38*, 2446.
(30) Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49.
(31) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80.
(32) Stoichiometric amounts of Ni(0) were used for coupling reactions, cf. Constable, E. C.; Hannon, M. J.; Edwards, A. J.; Raithby, P. R. *J. Chem. Soc., Dalton Trans.* **1994**, 2669.
(33) Constable, E. C.; Elder, S. M.; Healy, J.; Tocher, D. A. *J. Chem. Soc., Dalton Trans.* **1990**, 1669.
(34) (a) Yamamoto, T.; Etori, H. *Macromolecules* **1995**, *28*, 3371. (b) Yamamoto, T.; Maruyama, T.; Zhao, Z.; Ito, T.; Fukuda, T.; Yoneda, Y.; Begum, F.; Ikeda, T.; Sasaki, S.; Takezoe, H.; Fukuda, A.; Kubota, K. *J. Am. Chem. Soc.* **1994**, *116*, 4832.
(35) Fanta, P. E. *Synthesis* **1974**, 9.-
(36) Shimizu, N.; Kitamura, T.; Watanabe, K.; Yamaguchi, T.; Shigyo, H.; Ohta, T. *Tetrahedron Lett.* **1993**, *34*, 3421.
(37) Burstall, F. H. *J. Chem. Soc.* **1938**, *108*, 1662.

Scheme 3



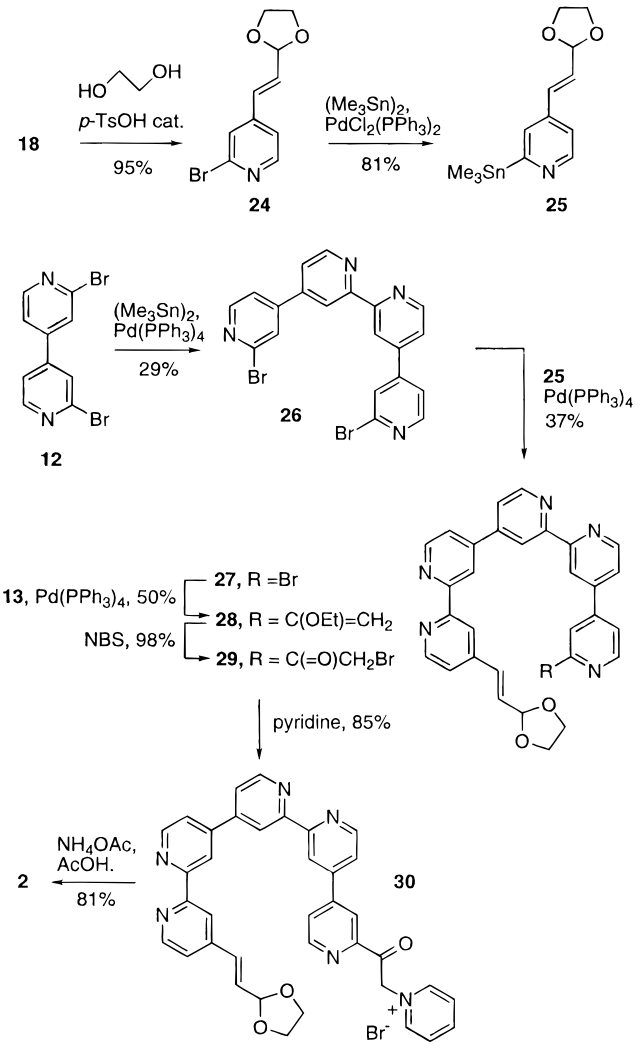
synthesis of the substituted *endo*-sexipyridines **4b**. A Kröhnke reaction between dialdehyde **22** (Scheme 3) and the previously prepared bis-pyridinium salt **16** would afford the desired sexipyridine **2**. Preparation of the aldehyde involved a Sonogashira coupling of the dibromide **5** with propiolaldehyde diethyl acetal to afford the diacetal **20** in 81% yield. A subsequent partial hydrogenation over Lindlar's catalyst and hydrolysis of the acetal group gave the (*Z*,*Z*)-dialdehyde **22** in 72% overall yield from diacetal **20** although a facile isomerization (~1−2 h) to the (*E*,*E*)-isomer was observed in acidic, aqueous solutions. The final step involved a double Kröhnke reaction between dialdehyde **22** and bis-pyridinium salt **16**. The reaction was examined at concentrations of 0.07 and 0.007 M in acetic acid, DMF, methanol, and formamide.[39] In all cases, only black insoluble material was produced, possibly oligo/polypyridines formed by "linear" Kröhnke reactions; no insoluble products were observed to be formed when the reagents (dialdehyde **22** or bis-pyridinium salt **16**) were separately subjected to the reaction conditions.

We hoped that synthesis of a suitably protected analogue of quinquepyridine **23** would circumvent the problem of linear (oligopolymerization) and that a single, intramolecular Kröhnke reaction could be favored by dilution (eq 2).



(2)

Scheme 4



Attempts to prepare the trimethylstannane derivative of aldehyde **18** ($(Me_3Sn)_2/PdCl_2(PPh_3)_2$/dioxane/130 °C) for subsequent coupling with quaterpyridine **26** (Scheme 4) were unsuccessful, resulting in unidentified degradation products from which the aldehyde and olefinic signals were observed to be absent in the ^1H NMR spectrum. The instability of the α,β-unsaturated aldehyde group necessitated protection of the aldehyde group to enable further progress by a route involving a number of Stille coupling reactions. Choosing a 1,3-dioxolane as a protecting group for the aldehyde to be carried through the synthesis balanced the stability of this group to the conditions employed in subsequent Stille couplings and the aqueous conditions used for NBS bromination, with the requirement that it be removed under the conditions of the Kröhnke reaction to allow a one-pot deprotection/Kröhnke pyridine formation to occur. Synthesis of the pyridinium salt **30** utilized aldehyde **18** and dibromide **12**, both prepared earlier, as starting materials. Protection of the aldehyde **18** under standard acetalization conditions[40] yielded dioxolane **24**, which was subjected to a palladium-mediated halogen−metal exchange with

(38) For examples, see: (a) Kelly, T. R.; Bowyer, M. C.; Bhaskar, K. V.; Bebbington, D.; Garcia, A.; Lang, F.; Kim, M. H.; Jette, M. P. *J. Am. Chem. Soc.* **1994**, *116*, 3657. (b) Kelly, T. R.; Garcia, A.; Lang, F.; Walsh, J. J.; Bhaskar, K. V.; Boyd, M. R.; Götz, R.; Keller, P. A.; Walter, R.; Bringmann, G. *Tetrahedron Lett.* **1994**, *35*, 7621. (c) Kelly, T. R.; Xu, W.; Sundaresan, J. *Tetrahedron Lett.* **1993**, *34*, 6173. (d) Kelly, T. R.; Kim, M. H. *J. Org. Chem.* **1992**, *57*, 1593. (e) Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024. (f) Kelly, T. R.; Li, Q.; Bhushan, V. *Tetrahedron Lett.* **1990**, *31*, 161.

(39) van Esch, J. H.; Hoffmann, M. A. M.; Nolte, R. J. M. *J. Org. Chem.* **1983**, *48*, 283.

(40) Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley: New York, 1991; pp 188−193.

hexamethylditin to give stannane **25** in 77% overall yield from **18**. Stille coupling with the quaterpyridine **26**, prepared from dibromide **12** in 29% yield by a one-pot halogen−metal exchange/Stille coupling, afforded the quinquepyridine **27**. The yields of this reaction were found to be very sensitive to the palladium catalyst used, the best yields being observed with freshly prepared[41] $Pd(PPh_3)_4$. A further Stille coupling with stannane **13** gave a 50% yield of the disubstituted quinquepyridine **28**. Bromination of quinquepyridine **28** with NBS in wet THF to give **29** was immediately followed by **29**'s conversion to the mono-pyridinium salt **30** in 83% overall yield by a procedure analogous to the one used in the preparation of bis-pyridinium salt **16**. It was observed that the bromo ketone **29** was not stable at room temperature and underwent slow (20−30%) decomposition over the course of 2−3 days to give unidentified degradation products; this instability is in marked contrast to the stability of bis(bromoacetyl)bipyridine **15**.

The final step of the synthesis was the acetal deprotection−Kröhnke reaction. Using acetic acid at reflux, all the starting material was observed to have been consumed within 5−6 h. Upon examination of the ^{1}H NMR spectrum of the crude products, we were pleased to observe the desired product as the only aromatic component; sexipyridine **2** was secured in 81% yield after workup. The success of the reaction may originate in the slow deprotection of the dioxolane group, thus maintaining a low concentration of the reactive aldehyde **23**, so favoring the intramolecular cyclization. Attempts to purify **2** beyond simple solvent washing were frustrated by the extreme insolubility of this compound. This solubility problem and the tendency of the compound to exhibit NMR signal broadening in solution (DMSO-d_6) prevented the acquisition of ^{13}C NMR data for this compound. Attempts to sublime this compound under vacuum (0.05 Torr) resulted in charring between 480 and 490 °C without any evidence of sublimation, but the simplicity (three resonances) of the ^{1}H NMR (see Supporting Information) and low (see Supporting Information) and high resolution mass spectra document its existence. Notwithstanding our success in preparing the compound, the problems associated with its purification and the impracticality of this route for the preparation of significant quantities of cyclosexipyridine **2** have prevented further investigations toward the application of this compound to the generation of network structures.

In conclusion, we have accomplished the first synthesis of cyclo-2,2′:4′,4″:2″,2‴:4‴,4⁗:2⁗,2⁗′:4⁗′,4⁗″:2⁗″,2⁗‴:4⁗‴,4-sexipyridine (**2**) and highlighted the versatility of the Kröhnke reaction for the preparation of oligopyridines inaccessible via aryl−aryl coupling methodologies. Moreover, during the course of our investigations we have prepared a number of synthetically useful dibromo bi-, quater-, and sexipyridines (**12**, **26**, and **19**) which should be of general interest as intermediates in the preparation of functionalized oligopyridines.

Experimental Section[42]

2,2′-Diamino-4,4′-bipyridine (10). A stirred mixture of 4,4′-bipyridine (15.0 g, 0.095 mol) and sodium amide[43] (51.0 g, 1.3 mol) in *p*-cymene (200 mL) was refluxed for 2 days under nitrogen. The black solid was filtered off under a blanket of nitrogen[44] and washed with hexane. The dry solid was cautiously introduced to a rapidly stirred solution of dilute HCl (300 mL of 2.0 M HCl) at 0 °C. The solution was acidified with concd HCl to pH 5 and filtered, and the filtrate neutralized with solid NaOH. After the resulting precipitate was collected and washed with $CHCl_3$, the residue was dried in a pistol at 25 Torr to give the diamine **10** (16.1 g, 91%) as a brown solid of sufficient purity for subsequent reaction. An analytical sample was obtained by repeated refluxing with activated carbon in ethanol and filtration, until a colorless solution was obtained. The product was isolated by evaporating the solvent *in vacuo* to give the pure product as a colorless, amorphous solid: mp 289−290 °C (sealed tube); ^{1}H NMR (DMSO-d_6) δ 6.08 (br s, 4H), 6.64 (d, J = 1.6 Hz, 2H), 6.69 (dd, J = 5.2, 1.6 Hz, 2H), 7.98 (d, J = 5.2 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 104.9, 109.6, 146.7, 148.7, 160.5; IR (KBr) 3459 cm^{-1}; EIMS m/z (rel int) 186 (100, M$^+$). Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.11; H, 5.31; N, 29.91.

2,2′-Dihydroxy-4,4′-bipyridine (11). To a rapidly stirred solution of diamine **10** (10.0 g, 0.053 mol) in concd sulfuric acid (25 mL) and water (150 mL) at 0 °C was added a solution of sodium nitrite (125 mL of a 0.88 M solution in water, 0.11 mol) dropwise over 6 h with the temperature being carefully maintained between 0 and 5 °C. The reaction mixture was then stirred at this temperature for another 2 h, warmed to room temperature, and stirred overnight. Filtration of the resulting suspension and drying of the solid *in vacuo* (pistol, 100 °C, P_2O_5 desiccant) afforded the pyridone **11** (9.50 g, 0.051 mol, 94%) as a light brown solid. A pure sample was obtained by recrystallization from acetic acid, giving **11** as a colorless solid: mp 376−377 °C (sealed tube, lit.[45] mp 355 °C); ^{1}H NMR (DMSO-d_6) δ 6.44 (dd, J = 7.2, 1.2 Hz, 2H), 6.59 (d, J = 1.2 Hz, 2H), 7.46 (d, J = 7.2 Hz, 2H), 11.73 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 103.3, 117.2, 136.1, 149.2, 162.4; IR (KBr) 3434, 1645 cm^{-1}; EIMS m/z (rel int) 188 (100, M$^+$), 159 (20), 133 (44), 104 (30). Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.89. Found: C, 63.60; H, 4.26; N, 14.92.

2,2′-Dibromo-4,4′-bipyridine (12). A stirred mixture of pyridone **11** (0.800 g, 4.25 mmol) and freshly prepared $POBr_3$[22] (8.0 g, 28 mmol) in anisole (8.0 mL) was heated at 145 °C for 2 days. After cooling, the reaction mixture was poured into ice water (300 mL) and basified with saturated sodium carbonate solution until the pH was 8−9. The mixture was extracted with CH_2Cl_2 (3 × 300 mL); the combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. Purification of the residue by flash[46] chromatography (silica gel, 1:1 CH_2Cl_2:Et_2O) and recrystallization from ethanol gave dibromide **12** (0.831 g, 2.64 mmol, 60%) as colorless, fine needles: mp 188.5−191 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (dd, J = 5.2, 1.6 Hz, 2H), 7.70 (dd, J = 1.6, 0.8 Hz, 2H), 8.51 (dd, J = 5.2, 0.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 120.5, 125.8, 143.3, 146.8, 151.0; EIMS m/z (rel int) 316, 314, 312 (48, 100, 52, M$^+$), 235, 233 (77, 79), 208, 206 (28, 30). Anal. Calcd for $C_{10}H_6Br_2N_2$: C, 38.25; H, 1.93; N, 8.92; Br, 50.90. Found: C, 38.24; H, 1.83; N, 8.89; Br, 50.68.

2,2′-Bis(α-ethoxyvinyl)-4,4′-bipyridine (14). Dibromide **12** (1.300 g, 4.14 mmol), bis(triphenylphosphine)palladium(II) chloride (0.290 g, 0.41 mmol), and vinylstannane **13**[24] (1.50 mL, 9.11 mmol) were introduced to a sealable tube containing anhydrous dioxane (20 mL) and the reaction mixture degassed.[26a] The tube was sealed and heated for 20 h at 130 °C; after cooling, the solution was filtered and evaporated *in vacuo*. The filtrate residue was subjected to flash chromatography (silica gel, 1:1 CH_2Cl_2:Et_2O) to give the bis(ethoxyvinyl)-bipyridine **14** (1.053 g, 86%) as a colorless solid. An analytical

(41) Coulson, D. R. *Inorganic Syntheses*; Angelici, R., Ed.; John Wiley: New York, 1990; Vol. 28, p 107.

(42) For typical experimental protocols, see ref 26a.

(43) The yield is particularly dependent on the quality of the sodium amide; the $NaNH_2$ should be handled under an atmosphere of nitrogen, and if a yellow color develops it should be disposed of, see: *Merck Index*, 11th ed.; Merck & Co., Inc.: Rahway, NJ, 1989; entry 8519.

(44) Filtration under vacuum results in exothermic reaction of the excess sodium amide with atmospheric moisture, resulting in charring/destruction of the product.

(45) Dehmlow, E. V.; Sleegers, A. *Liebigs Ann. Chem.* **1992**, 953.

(46) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

sample was obtained by recrystallization from cyclohexane to surrender pure **14** as colorless plates: mp 133−134 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (t, J = 7.2 Hz, 6H), 4.01 (q, J = 7.2 Hz, 4H), 4.43 (d, J = 2.2 Hz, 2H), 5.48 (d, J = 2.2 Hz, 2H), 7.47 (dd, J = 5.2, 1.6 Hz, 2H), 7.94 (d, J = 1.6 Hz, 2H), 8.67 (d, J = 5.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 63.5, 85.3, 116.8, 120.6, 146.2, 149.5, 154.4, 158.0; EIMS m/z (rel int) 296 (3, M^+), 281 (78), 255 (80), 104 (92), 99 (100). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.32; H, 6.74; N, 9.35.

2,2′-Bis(bromoacetyl)-4,4′-bipyridine (15). Into a round-bottomed flask were introduced bis(α-ethoxyvinyl)bipyridine **14** (0.339 g, 1.14 mmol), THF (35 mL), and water (8 mL). To this vigorously stirred solution was added NBS (0.427 g, 2.40 mmol) in one portion, and stirring was continued at room temperature for 15 min, during which time a pale yellow solid precipitated from solution. Evaporation of the THF *in vacuo*, filtration of the resulting solid, and washing with water gave the bis(bromoacetyl)bipyridine **15** (0.422 g, 93%). An analytical sample was obtained by recrystallization from 1:1 water: EtOH to give pure bis(bromoacetyl)bipyridine **15** as colorless needles: mp 121−123 °C dec; ^{1}H NMR ($CDCl_3$) δ 4.88 (s, 4H), 7.82 (dd, J = 4.8, 1.6 Hz, 2H), 8.39 (d, J = 1.6 Hz, 2H), 8.86 (d, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.8, 120.3, 125.2, 146.0, 150.3, 152.4, 192.2; IR (KBr) 1715 cm^{-1}; CIMS m/z (rel int) 401, 399, 397 (49, 100, 52, M + H$^+$), 321, 319 (78, 81), 241 (77). Anal. Calcd for $C_{14}H_{10}Br_2N_2O_2$: C, 42.24; H, 2.53; N, 7.04; Br, 40.15. Found: C, 41.93; H, 2.38; N, 6.92; Br, 39.95.

2,2′-Bis(2-pyridiniumylacetyl)-4,4′-bipyridine Dibromide (16). To a solution of dibromide **15** (0.952 g, 2.39 mmol) in anhydrous acetone (40 mL) at room temperature was introduced pyridine (0.426 mL, 5.27 mmol), and the reaction mixture was stirred under a nitrogen atmosphere for 12 h. Evaporation of the reaction mixture *in vacuo* gave a light brown solid which was washed with $CHCl_3$ (3 × 20 mL) to give bis-pyridinium salt **16** (1.18 g, 89%) which was pure enough to use in subsequent reactions: mp 185−215 °C dec; ^{1}H NMR (DMSO-d_6) δ 6.56 (s, 4H), 8.29 (dd, J = 7.2, 5.2 Hz, 4H), 8.36 (dd, J = 5.2, 1.6 Hz, 2H), 8.47 (d, J = 1.6 Hz, 2H), 8.75 (t, J = 7.2 Hz, 2H), 9.02 (d, J = 5.2 Hz, 4H), 9.07 (d, J = 5.2 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 66.7, 119.4, 126.6, 127.8, 145.2, 146.4, 146.4, 150.8, 151.6, 191.2; IR (KBr) 1725 cm^{-1}. Anal. Calcd for $C_{24}H_{20}Br_2N_4O_2$: C, 50.91; H, 3.62; N, 10.07. Found: C, 50.85; H, 3.51; N, 9.79.

3-[4-(2-Bromopyridinyl)]-2-propenal (18). To a solution of aldehyde **17**[29] (2.318 g, 12.46 mmol) in toluene (100 mL) was introduced (triphenylphosphoranylidene)acetaldehyde (3.80 g, 12.5 mmol). The solution was stirred at room temperature under nitrogen for 24 h and then evaporated *in vacuo* to give a tan, amorphous solid. Flash chromatography (silica gel, CH_2Cl_2) afforded the aldehyde **18** (2.21 g, 84%) as a colorless solid: mp 115−116 °C; ^{1}H NMR ($CDCl_3$) δ 6.82 (dd, J = 16.0, 7.4 Hz, 1H), 7.35 (d, J = 16.0 Hz, 1H), 7.38 (dd, J = 4.8, 1.2 Hz, 1H), 7.61 (d, J = 1.2 Hz, 1H), 8.46 (d, J = 4.8 Hz, 1H), 9.77 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 120.7, 126.4, 132.9, 143.3, 143.8, 146.9, 151.0, 192.4; IR (KBr) 1678 cm^{-1}; EIMS m/z (rel int) 213, 211 (42, 42, M$^+$), 132 (100), 104 (39), 77 (42). Anal. Calcd for C_8H_6BrNO: C, 45.31; H, 2.85; N, 6.60; Br, 37.68. Found: C, 45.24; H, 2.69; N, 6.59; Br, 37.38.

2,2‴″-Dibromo-4,4′:2′,2″:4″,4‴:2‴,2⁗:4⁗,4‴″-sexipyridine (19). Into a round-bottomed flask were introduced bis-pyridinium salt **16** (0.400 g, 0.72 mmol), aldehyde **18** (0.335 g, 1.58 mmol), NH_4OAc (2.00 g, 26 mmol), and acetic acid (40 mL). The solution was heated at reflux for 3 h, giving a dark brown solution which was evaporated *in vacuo* and the residue dissolved in CH_2Cl_2 (200 mL). This stirred solution was triturated by dropwise addition of petroleum ether (1000 mL) via a dropping funnel, and the precipitate was collected by filtration. This precipitate was purified by dissolving in a minimum (ca. 80 mL) of refluxing chloroform and cooling to give a tan precipitate which was collected by filtration yielding essentially pure sexipyridine **19** (0.096 g, 21%). An analytical sample was obtained by washing **19** with hot pyridine[47] and chloroform to give the analytically pure product as a colorless, amorphous solid: mp 317−318 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (dd, J = 4.8, 1.6 Hz, 2H), 7.65 (dd, J = 5.2, 1.6 Hz, 2H), 7.77 (dd, J = 4.8, 1.6 Hz, 2H), 7.89 (dd, J = 1.6, 0.8 Hz, 2H), 8.54 (dd, J = 5.2, 0.8 Hz, 2H), 8.77 (dd, J = 1.6, 0.8 Hz, 2H), 8.86 (dd, J = 4.8, 0.8 Hz, 2H), 8.87 (dd, J = 4.8, 0.8 Hz, 2H), 8.90 (dd, J = 1.6, 0.8 Hz, 2H); EIMS m/z (rel int) 624, 622, 620 (52, 100, 48, M$^+$), 543, 541 (34, 31), 192, 191 (48, 59), 105 (100). Anal. Calcd for $C_{30}H_{18}Br_2N_6$: C, 57.90; H, 2.92; N, 13.50; Br, 25.68. Found: C, 57.84; H, 3.00; N, 13.36; Br, 25.82.

4,4′-Bis(3,3-diethoxypropynyl)-2,2′-bipyridine (20). A solution of dibromide **5** (0.100 g, 0.32 mmol), bis(triphenylphosphine)palladium(II) chloride (0.010 g, 0.014 mmol), copper(I) iodide (0.003 g, 0.02 mmol) and propionaldehyde diethyl acetal (0.20 mL, 1.4 mmol) in Et_3N (5.0 mL) was heated at 100 °C in a sealed tube for 24 h. Filtration and evaporation of the filtrate *in vacuo* gave a brown solid which was subjected to flash chromatography (silica gel, 95:5 CH_2Cl_2:EtOAc) affording the bis-acetylene **20** as a pale brown solid. Recrystallization from ethanol gave pure **20** (0.105 g, 81%) as colorless, wooly needles: mp 113−114 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 12H), 3.67 (dq, J = 9.6, 7.2 Hz, 4H), 3.82 (dq, J = 9.6, 7.2 Hz, 4H), 7.36 (dd, J = 5.2, 1.6 Hz, 2H), 8.46 (dd, J = 1.6, 0.8 Hz, 2H), 8.64 (dd, J = 4.8, 0.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.1, 61.2, 82.6, 89.0, 91.5, 123.5, 125.9, 131.2, 149.2, 155.5; EIMS m/z (rel int) 409 (25, [M + H]$^+$),[48] 363 (100), 261 (70), 233 (83). Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.29; H, 6.70; N, 6.78.

(*Z*,*Z*)-4,4′-Bis(3,3-diethoxy-1-propenyl)-2,2′-bipyridine (21). To a stirred suspension of Lindlar catalyst (0.600 g of 5% Pd on $CaCO_3$ poisoned with Pb, Aldrich no. 20,573-7) in ethyl acetate (5.0 mL) was introduced a solution of acetylene **20** (0.200 g, 0.49 mmol) in ethyl acetate (5.0 mL) under an atmosphere of hydrogen. The uptake of hydrogen (24 mL, 0.98 mmol) was measured quantitatively using a modification of a reported hydrogenation apparatus,[49] after which the solution was filtered through Celite and evaporated *in vacuo*. The crude residue was recrystallized from hexane to give the pure (*Z*,*Z*)-diacetal **21** (0.168 g, 84%) as colorless needles: mp 69−70 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 12H), 3.64 (m, 4H), 5.21 (d, J = 7.2 Hz, 2H), 6.00 (dd, J = 12.0, 7.2 Hz, 2H), 6.69 (d, J = 12.0 Hz, 2H), 7.38 (dd, J = 5.2, 1.6 Hz, 2H), 8.35 (s, 2H), 8.65 (d, J = 5.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.2, 60.9, 97.8, 121.0, 123.4, 130.4, 133.3, 144.5, 149.2, 156.1; EIMS m/z (rel int) 413 (100, [M + H]$^+$), 367 (93), 321 (86). Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.82; H, 7.82; N, 6.69.

4,4′-Bis(3-oxo-1-propenyl)-2,2′-bipyridine (22). To a vigorously stirred solution of diacetal **21** (0.200 g, 0.49 mmol) in acetone (16 mL) was introduced a solution of oxalic acid (8.0 mL of a 4.0% solution in acetone, 3.6 mmol) and water (8.0 mL). After 30 min, the acetone was evaporated *in vacuo* (<25 °C) and the aqueous solution basified with solid Na_2CO_3 and extracted with ethyl acetate (2 × 30 mL); the combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The crude product was found to contain a (∼1:9) mixture of (*E*,*E*)- and (*Z*,*Z*)-isomers (no (*E*,*Z*) was observed) of aldehyde **22** (0.111 g, 86%) and was pure enough

(47) As the purity of this compound increased, its solubility decreased markedly. In crude reaction mixtures, it is soluble in $CHCl_3$ and CH_2Cl_2, but upon purification it becomes only sparingly soluble in hot DMSO-d_6. The low solubility of this compound prevented the acquisition of its ^{13}C NMR spectrum.

(48) Confirmation of assignment as [M + H]$^+$: HRMS calcd for $C_{24}H_{29}N_2O_4$ 409.2127, found 409.2125.

(49) For the hydrogenation apparatus used to quantitatively measure the uptake of H_2, see: Vogel, A. I.; Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific & Technical: Harlow, 1991; p 89. We found that degassing of the reaction solution was necessary for a successful hydrogenation, but hydrogenation occurred during evacuation/regassing (H_2) cycles (×3), making quantitative measurement difficult. By insertion of a pressure equalizing dropping funnel containing the alkyne solution above the reaction flask containing the Lindlar catalyst solution, it was possible to degas without concommitant hydrogenation. Following degassing, the alkyne solution was quickly dropped into the catalyst solution whereupon hydrogenation commenced.

for use in subsequent reactions. An analytical sample of the (*Z*,*Z*)-isomer was isolated by recrystallization from hexane/benzene; pure (*E*,*E*)-isomer was obtained by allowing the reaction mixture to isomerize for 4 h at room temperature before workup and then isolation by the same procedure as used for the (*Z*,*Z*)-isomer. ***(Z,Z)*-22**: mp 148−149 °C; ^{1}H NMR ($CDCl_3$) δ 6.37 (dd, J = 11.6, 8.0 Hz, 2H), 7.33 (d, J = 4.8 Hz, 2H), 7.64 (d, J = 11.6 Hz, 2H), 8.49 (s, 2H), 8.75 (d, J = 4.8 Hz, 2H), 10.02 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 121.2, 124.0, 133.1, 142.7, 145.4, 149.6, 155.8, 191.33; IR (KBr) 1682 cm^{-1}; EIMS *m*/*z* (rel int) 264 (53, M$^+$), 207 (100). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.63; H, 4.46; N, 10.30. ***(E,E)*-22**: mp 243−244 °C; ^{1}H NMR ($CDCl_3$) δ 6.97 (dd, J = 16.0, 7.6 Hz, 2H), 7.47 (dd, J = 5.2, 1.2 Hz, 2H), 7.53 (d, J = 16.0 Hz, 2H), 8.61 (d, J = 1.6 Hz, 2H), 8.79 (d, J = 5.2 Hz, 2H), 9.81 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 119.7, 122.1, 132.3, 142.3, 149.0, 150.2, 156.5, 193.0; IR (KBr) 1676 cm^{-1}; CIMS *m*/*z* (rel int) 265 (100, M + H$^+$), 239 (7). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.63; H, 4.41; N, 10.45.

2-Bromo-4-[2-(1,3-dioxolan-2-yl)ethenyl]pyridine (24). Into a flask were introduced aldehyde **18** (4.00 g, 18.9 mmol), anhydrous ethylene glycol (2.06 mL, 36.9 mmol), *p*-TsOH·H_2O (0.120 g, 0.63 mmol), and anhydrous benzene (520 mL). The flask was fitted with a Soxhlet condenser whose thimble contained anhydrous $MgSO_4$; this apparatus was flushed with nitrogen and the solution refluxed for 3 days, replacing the $MgSO_4$ thimble each day. Evaporation of the reaction mixture *in vacuo* and flash chromatography (basic alumina (50−200 μm), $CHCl_3$) of the residue gave the acetal **24** (4.60 g, 95%) as a colorless solid: mp 52−53 °C; ^{1}H NMR ($CDCl_3$) δ 4.00 (m, 4H), 5.44 (d, J = 5.0 Hz, 1H), 6.36 (dd, J = 16.0, 5.0 Hz, 1H), 6.64 (d, J = 16.0 Hz, 1H), 7.22 (dd, J = 5.2, 1.2 Hz, 1H), 7.45 (d, J = 1.2 Hz, 1H), 8.30 (d, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 65.1, 102.3, 120.2, 125.5, 130.1, 131.6, 142.7, 146.0, 150.2; EIMS *m*/*z* (rel int) 257, 255 (94, 95, M$^+$), 176 (21), 99 (100). Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.90; H, 3.94; N, 5.47; Br, 31.20. Found: C, 46.80; H, 3.66; N, 5.47; Br, 31.16.

4-[2-(1,3-Dioxolan-2-yl)ethenyl]-2-(trimethylstannyl)pyridine (25). Into a sealable tube were introduced acetal **24** (0.250 g, 0.98 mmol), bis(triphenylphosphine)palladium(II) chloride (0.025 g, 0.04 mmol), hexamethylditin (0.404 mL, 1.90 mmol), and anhydrous dioxane (10 mL). The solution was degassed and the tube sealed and heated at 135 °C for 12 h. Filtration of the resulting black suspension through a Celite pad gave a yellow oil after evaporation of the filtrate *in vacuo*. Flash chromatography [basic alumina[50] (50−200 μm), CH_2Cl_2] gave the stannane **25** (0.269 g, 81%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.33 (s, 9H), 3.99 (m, 4H), 5.43 (d, J = 5.8 Hz, 1H), 6.33 (dd, J = 16.0, 5.8 Hz, 1H), 6.67 (d, J = 16.0 Hz, 1H), 7.11 (dd, J = 4.8, 1.6 Hz, 1H), 7.41 (d, J = 1.6 Hz, 1H), 8.69 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −9.6, 65.0, 102.8, 119.6, 128.7, 129.5, 132.4, 140.2, 150.6, 173.6; EIMS *m*/*z* (rel int) 341 (51, M$^+$, ^{120}Sn), 326 (100), 165 (85), 135 (79); HRMS calcd for $C_{13}H_{19}NO_2$ ^{116}Sn 337.0433, found 337.0433.

2,2‴-Dibromo-4,4′:2′2″:4″,4‴-quaterpyridine (26). Into a sealable tube were introduced dibromide **12** (0.400 g, 1.27 mmol), freshly prepared tetrakis(triphenylphosphine)palladium(0) (0.033 g, 0.03 mmol), hexamethylditin (0.100 mL, 0.48 mmol), and anhydrous dioxane (10 mL). The solution was degassed and the tube sealed and heated at 140 °C for 48 h. On cooling, the reaction mixture was filtered, the filtrate evaporated *in vacuo*, and the residue subjected to flash chromatography (silica gel, CH_2Cl_2, and then 1:1 $CHCl_3$:Et_2O) to give almost pure quaterpyridine **26**. The product was washed (to remove residual triphenylphosphine oxide) with a small volume of CH_2Cl_2 (4 mL) at room temperature and the insoluble material collected by filtration, giving pure **26** (0.085 g, 29%) as a colorless, amorphous solid. An analytical sample was obtained as fine wooly needles by recrystallization from ethanol: mp 262−263 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (dd, J = 4.8, 1.6 Hz, 2H), 7.63 (dd, J = 5.2, 1.6 Hz, 2H), 7.88 (d, J = 1.6 Hz, 2H), 8.53 (d, J = 5.2 Hz, 2H), 8.75 (d, J = 1.6 Hz, 2H), 8.84 (d, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 119.0, 120.7, 121.7, 126.0, 143.3, 145.3, 148.4, 150.2, 150.9, 156.5; EIMS *m*/*z* (rel int) 470, 468, 466 (65, 100, 57, M$^+$), 389, 387 (90, 88). Anal. Calcd for $C_{20}H_{12}Br_2N_4$: C, 51.31; H, 2.58; N, 11.97; Br, 34.14. Found: C, 51.04; H, 2.84; N, 11.77; Br, 34.45.

2-Bromo-4⁗-[2-(1,3-dioxolan-2-yl)ethenyl]-4,4′:2′,2″:4″,4‴:2‴,2⁗-quinquepyridine (27). Into a sealable tube were introduced quaterpyridine **26** (0.123 g, 0.26 mmol), stannane **25** (0.098 g, 0.29 mmol), freshly prepared tetrakis(triphenylphosphine)palladium(0) (0.020 g, 0.020 mmol), and anhydrous dioxane (10 mL). The tube was sealed and heated at 130−140 °C for 24 h. After cooling, the solution was filtered, the filtrate evaporated *in vacuo*, and the residue subjected to flash chromatography (silica gel, 1:1 CH_2Cl_2:Et_2O, and then 5:95 MeOH:$CHCl_3$). The quinquepyridine **27** (0.055 g, 37%) was isolated as a white, amorphous solid: mp 243−246 °C dec; ^{1}H NMR ($CDCl_3$) δ 4.04 (m, 4H), 5.52 (d, J = 5.6 Hz, 1H), 6.53 (dd, J = 16.0, 5.6 Hz, 1H), 6.85 (d, J = 16.0 Hz, 1H), 7.36 (d, J = 5.2 Hz, 1H), 7.56 (d, J = 5.2 Hz, 1H), 7.64 (d, J = 5.2 Hz, 1H), 7.72 (d, J = 5.2 Hz, 1H), 7.76 (d, J = 5.2 Hz, 1H), 7.89 (s, 1H), 8.52 (s, 1H), 8.53 (d, J = 5.2 Hz, 1H), 8.68 (d, J = 5.2 Hz, 1H), 8.75−8.88 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 65.2, 102.9, 118.9, 119.0, 119.1, 119.2, 120.7, 121.4, 121.5, 121.6, 122.0, 125.9, 130.5, 131.9, 143.2, 144.4, 145.1, 146.6, 146.9, 148.5, 149.6, 150.0, 150.1, 150.2, 150.8, 156.1, 156.2, 156.8, 156.9. EIMS *m*/*z* (rel int) 565, 563 (64, 59, M$^+$), 520 (100). Anal. Calcd for $C_{30}H_{22}BrN_5O_2$: C, 63.84; H, 3.93; N, 12.40. Found: C, 64.08; H, 3.74; N, 12.58.

4⁗-[2-(1,3-Dioxolan-2-yl)ethenyl]-2-(α-ethoxyvinyl)-4,4′:2′,2″:4″,4‴:2‴,2⁗-quinquepyridine (28). To a sealable tube were introduced quinquepyridine **27** (0.084 g, 0.15 mmol), vinylstannane **13** (0.028 mL, 0.18 mmol), freshly prepared tetrakis(triphenylphosphine)palladium(0) (0.017 g, 0.01 mmol), and anhydrous dioxane (10 mL). The tube was sealed and the reaction mixture heated at 130−140 °C overnight. After cooling, the suspension was filtered and the solid washed with CH_2Cl_2. The filtrate and wash were combined and evaporated and the residue subjected to flash chromatography (silica gel, CH_2Cl_2, and then 1:1 CH_2Cl_2:Et_2O) to give quinquepyridine **28** (0.042 g, 50%) as a yellow solid: mp 105−120 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.48 (t, J = 6.8 Hz, 3H), 4.04 (m, 6H), 4.45 (d, J = 2.0 Hz, 1H), 5.50 (d, J = 2.0 Hz, 1H), 5.51 (d, J = 5.6 Hz, 1H), 6.68 (dd, J = 16, 5.6 Hz, 1H), 6.84 (d, J = 16 Hz, 1H), 7.34 (d, J = 5.2 Hz, 1H), 7.59 (d, J = 5.2 Hz, 1H), 7.61 (d, J = 5.2 Hz, 1H), 7.70 (d, J = 5.2 Hz, 1H), 7.72 (d, J = 5.2 Hz, 1H), 8.03 (s, 1H), 8.50 (s, 1H), 8.67 (d, J = 5.2 Hz, 1H), 8.70 (d, J = 5.2 Hz, 1H), 8.77 (s, 1H), 8.81−8.84 (m, 4H), 8.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.9, 64.0, 65.5, 85.8, 103.2, 117.4, 119.3, 119.4, 119.5, 119.6, 121.3, 121.8, 121.9, 122.1, 122.2, 130.8, 132.3, 144.7, 146.6, 147.0, 147.1, 147.4, 149.9, 150.0, 150.2, 150.3, 154.9, 156.4, 156.8, 156.9, 157.2, 158.5, 158.6; FABMS *m*/*z* (rel int) 556 (100, [M + H]$^+$), 528 (30), 484 (23); HRMS calcd for $C_{34}H_{30}N_5O_3$ [M + H]$^+$ 556.2346, found 556.2348.

2-(Bromoacetyl)-4⁗-[2-(1,3-dioxolan-2-yl)ethenyl]-4,4′:2′,2″:4″,4‴:2‴,2⁗-quinquepyridine (29). To a solution of quinquepyridine **28** (0.030 g, 0.054 mmol) in THF (20 mL) at room temperature were introduced water (1.0 mL) and *N*-bromosuccinimide (0.011 g, 0.062 mmol). This mixture was stirred at room temperature for 1 h. The solvent was evaporated *in vacuo* and the residue partitioned between CH_2Cl_2 and water (50 mL:50 mL). The CH_2Cl_2 layer was separated and dried over anhydrous sodium sulfate; evaporation *in vacuo* gave bromo ketone **29** (0.032 g, 98%) as a colorless solid (unstable in solution or >20−25 °C): mp 76−95 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.98−4.09 (m, 4H), 4.89 (s, 2 H), 5.50 (d, J = 5.6 Hz, 1H), 6.51 (dd, J = 16.4, 5.6 Hz, 1H), 6.83 (d, J = 16.4 Hz, 1H), 7.33 (d, J = 4.8 Hz, 1H), 7.62 (d, J = 4.8 Hz, 1H), 7.69 (d, J = 4.8 Hz, 1H), 7.72 (d, J = 4.8 Hz, 1H), 7.90 (d, J = 5.2 Hz, 1H), 8.45 (s, 1H), 8.49 (s, 1H), 8.66 (d, J = 5.2 Hz, 1H), 8.79−8.85 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 32.1, 65.1, 102.9, 118.9, 118.95, 119.0, 119.1, 120.4, 121.4, 121.5, 121.6, 122.0, 125.4, 130.5, 131.9, 144.4, 145.4, 146.6, 146.9, 147.1, 149.6, 149.9, 149.95, 150.0, 150.2, 152.2, 156.1, 151.2, 156.7, 156.8, 192.3. IR (KBr) 1715 cm^{-1}. Due to the instability of bromo ketone **29**, this sample was not sent out for combustion analysis or HRMS.

(50) Stannane **25** was observed to undergo facile destannylation on silica gel.

4‴″-[2-(1,3-Dioxolan-2-yl)ethenyl]-2-(2-pyridiniumylacetyl)-4,4′:2′,2″:4″,4‴:2‴,2⁗-quinquepyridine Bromide (30). A mixture of bromo ketone **29** (0.032 g, 0.053 mmol) and pyridine (0.010 mL, 0.12 mmol) in acetone (30 mL) was stirred at room temperature for 12 h. The solvent was evaporated *in vacuo*, and the residue dissolved in $CHCl_3$ and then introduced dropwise to cyclohexane while stirring. The resulting precipitate was collected by filtration and dried *in vacuo* to afford mono(pyridinium salt) **30** (0.031 g, 85%) as a light brown solid (unstable >20−25 °C) that was used immediately for the final step: ^{1}H NMR (DMSO-d_6) δ 3.98−4.09 (m, 4H), 5.48 (d, J = 5.6 Hz, 1H), 6.57 (s, 2H), 6.63 (dd, J = 16.4, 5.6 Hz, 1H), 6.95 (d, J = 16.4 Hz, 1H), 7.69 (d, J = 4.8 Hz, 1H), 8.04 (d, J = 4.8 Hz, 1H), 8.06 (d, J = 4.8 Hz, 1H), 8.28 (t, J = 7.0 Hz, 2H), 8.30 (d, J = 4.8 Hz, 1H), 8.37 (d, J = 5.2 Hz, 1H), 8.47 (s, 1H), 8.49 (s, 1H), 8.72 (d, J = 5.2 Hz, 1H), 8.75 (t, J = 7.0 Hz, 1H), 8.80 (s, 1H), 8.85−9.05 (m, 8H). Due to the instability of **30**, this sample was not sent for combustion analysis. Mass spectra for this compound did not display a molecular ion or interpretable fragment ions suitable for HRMS; this was also observed to be the case with bis(pyridinium salt) **16**.

Cyclo-2,2′:4′,4″:2″,2‴:4‴,4⁗:2⁗,2⁗′:4⁗′,4-sexipyridine (2). A solution of mono(pyridinium salt) **30** (0.024 g, 0.035 mmol) and ammonium acetate (0.170 g, 2.2 mmol) in acetic acid (50 mL) was heated at reflux for 19 h. After cooling, the solvent was evaporated *in vacuo* and the resulting black solid washed with $CHCl_3$ and isolated by filtration to give sexipyridine **2** (0.013 g, 81%) as a dark brown solid. This solid was found to be only sparingly soluble in hot DMSO-d_6 and insoluble in all other solvents examined: ^{1}H NMR (DMSO-d_6) δ 7.69 (d, J = 5.2 Hz, 6H), 8.47 (s, 6H), 8.89 (d, J = 5.2 Hz, 6H); UV λ_{max} (EtOH) 240 nm (ϵ = 8800), 286 (ϵ = 2800); IR (KBr) 2961, 1640, 1098, 1035; EIMS m/z (rel int) 462 (1, M^+), 453 (48) 265 (100) (see Supporting Information); HRMS calcd for $C_{30}H_{18}N_6$ 462.1593, found 462.1582.

Acknowledgment. We thank Dr. Steven D. R. Christie and Mr. Andreas Szabados for early experiments and the National Institutes of Health for partial financial support.

Supporting Information Available: 400 MHz ^{1}H NMR spectra for compounds lacking combustion analysis data (**25**, **27**−**30** and **2**); also contained are the MS of **2** and experimental procedures, ^{1}H and ^{13}C NMR data for compounds **6**, **7**, and **9** (20 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.

JO962236K