Preparation of 5-Brominated and 5,5′-Dibrominated 2,2′-Bipyridines and 2,2′-Bipyrimidines

Peter F. H. Schwab, Frank Fleischer, and Josef Michl*

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

michl@eefus.colorado.edu

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Efficient syntheses of 5-brominated and 5,5′-dibrominated 2,2′-bipyridines and 2,2′-bipyrimidines, useful for the preparation of metal-complexing molecular rods, have been developed. 5-Bromo-2,2′-bipyridine, 5-bromo-5′-*n*-butyl-2,2′-bipyridine, and 5-bromo-5′-*n*-hexyl-2,2′-bipyridine were obtained by Stille coupling of 2,5-dibromopyridine with 2-trimethylstannylpyridine or the requisite 5-alkyl-2-trimethylstannylpyridine, obtained via regioselective zincation of a 3-alkylpyridine·BF_3 complex in the less hindered of the two reactive positions with lithium di-*tert*-butyl-(2,2,6,6-tetramethylpiperidino)zincate. 5,5′-Dibromo-2,2′-bipyridine was obtained by the reductive symmetric coupling of 2,5-dibromopyridine with hexa-*n*-butyldistannane. The yields of these coupling reactions ranged from 70 to 90%. 5-Bromo- and 5,5′-dibromo-2,2′-bipyrimidines were obtained in yields of 30 and 15%, respectively, by bromination of 2,2′-bipyrimidine, prepared from 2-chloropyrimidine in 80% yield by an improved reductive symmetric coupling procedure.

Introduction

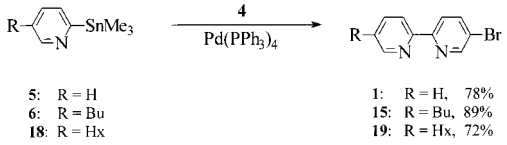
In connection with the synthesis of rigid-rod molecules[1] containing pyridine and pyrimidine modules, we needed to use 5-brominated and 5,5′-dibrominated 2,2′-bipyridines and 2,2′-bipyrimidines as starting materials. Although the brominated bipyridine derivatives have been long known, they were mostly obtained by direct bromination under harsh conditions and in low yield. We now report improved access to these building blocks, including new 5-bromo-2,2′-bipyridines that carry solubilizing alkyl chains. Very little was known about brominated bipyrimidines; we were able to obtain two of them by direct bromination in low yield.

Results and Discussion

5-Brominated and 5,5′-Dibrominated 2,2′-Bipyridines (Schemes 1 and 2). The best reported synthesis of 5-bromo-2,2′-bipyridine (**1**) is the reaction of the 2,2′-bipyridine (**2**) dihydrobromide with neat bromine described by Ziessel and Romero.[2] However, we share the experience of others[3] who obtained very poor results when following the published procedure. The reaction is run in a pressurized vessel at 180 °C for 3 days. This makes it difficult to monitor, and the harsh conditions cause extensive degradation and formation of many brominated derivatives. We varied the conditions, but the major product was always 5,5-dibromo-2,2′-bipyridine (**3**), isolated in a poor overall yield. We concluded that a more efficient method to produce 5-bromo-2,2′-bipyridine (**1**) would be useful.

It seemed to us that the two bromine substituents in 2,5-dibromopyridine (**4**) would exhibit differential reactivity toward oxidative addition in a Pd-catalytic cycle of a Stille-type coupling reaction.[4−8] Indeed, when treated with 2-trimethylstannylpyridine[9] (**5**) in the presence of Pd(0)(PPh_3)$_4$ at 130 °C, **4** reacted almost exclusively at the 2-position, yielding the desired product **1** cleanly

Scheme 1



Scheme 2

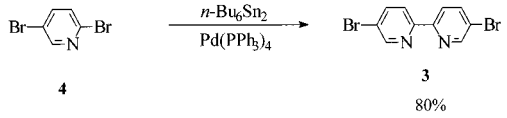
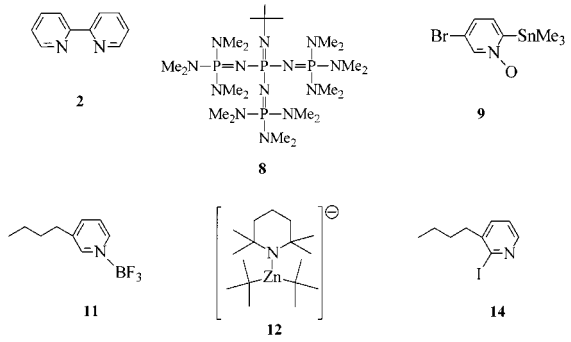


Chart 1



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(Scheme 1). The stannylated pyridine **5** was prepared from 2-bromopyridine in high yield by lithiation and transmetalation, following a procedure published[10] for the synthesis of 2-tributylstannylpyridine. When **4** was used in slight excess relative to **5**, no significant byproducts were formed. Excess **4** was easily separated from the crude reaction mixture by sublimation.

A small amount of 5,5′-dibromo-2,2′-bipyridine (**3**) was also formed, indicating that a symmetrical coupling of **4** takes place in the presence of an organotin compound and a Pd(0) catalyst. The bipyridine **3** is a valuable building block and has seen considerable use as a module in supramolecular architecture,[11,12] and several syntheses have been published. Burstall first obtained **3** in 1938[13] by direct bromination of 2,2′-bipyridine hydrobromide salts in a stream of bromine gas, but as mentioned above, even the latest variation of the direct bromination procedure[2] only yields a mixture of monobromo and dibromo derivatives and suffers from harsh conditions and the uncontrolled nature of the reaction. A high-temperature Ullmann coupling of **4** is also known,[14] but all of these procedures either are lengthy or suffer from low yields.

We have therefore examined the observed side reaction in more detail and found that about 50 mol % hexa-*n*-butyldistannane and a catalytic amount of Pd(0) give superior results (Scheme 2). Other trimethyltin compounds were active but less effective. At lower reactant ratios, the reaction proceeded much more slowly. No major side products were formed, and even though the reaction was rather slow, it was possible to run it on a 5 g scale. In principle, the reaction can be stopped before it has run to completion because the starting material can be easily recovered from the crude product mixture by sublimation. The dibromo derivative **3** was purified by flash chromatography and crystallization and obtained in a yield of about 80%. Overall, the method is vastly superior to the direct bromination procedure and should be applicable to the synthesis of other symmetrical 5,5′-disubstituted bipyridine derivatives.

5-Bromo-5′-*n*-butylbipyridine. A. 5-*n*-Butyl-2-trimethylstannylpyridine (6). The C-alkylation of pyridine derivatives has been a frequently encountered challenge in organic synthesis, as these compounds are a part of many natural products, pharmaceuticals, and ligands.[15−18] Even though a few substitution reactions on halogenated pyridines have been reported for the introduction of alkyl groups, all of them suffer from limited applicability.[19−22] Coupling reactions with organolithium compounds[23] and organocuprates[24] are restricted to very few systems; coupling with Wittig reagents[18] and the Ullmann[25] reaction occur only with reactive halides or under very harsh conditions, and nickel- or palladium-catalyzed reactions are often accompanied by elimination reactions on the alkylorganometallic reagents and the reduction of the aryl halide.

Since it appeared to be the most direct route, we started with **3** and attempted to substitute one of the bromines with a *n*-butyl substituent using two recent transition-metal-based methods[15,22] for the alkylation of heterocycles. Both produced the desired product in a very low yield and gave mostly the reduction products **1** and 2,2′-bipyridine (**2**), presumably because 2,2-bipyridine interferes with the coupling reaction by binding the metal; interference by metal ions has been reported in similar cases.[26]

We concluded that **3** was not a promising starting material and decided to prepare a 2-halo-5-alkylpyridine, stannylate it at position 2, and run a Stille-type coupling with 2,5-dibromopyridine, taking advantage of the differential bromine reactivity described above. Several routes to 2-halo-5-alkylpyridines appeared feasible. We did not use 5-alkyl-2-pyridones because none with longer alkyl chains are commercially available and chose the deprotonation of 2-alkylpyridines as the most direct path. 3-*n*-Butylpyridine (**7**) is commercial, and other 3-alkylpyridines can be easily synthesized on a large scale in one step. Although a number of literature procedures were available for the deprotonation of pyridines[27−31] and pyridine-*N*-oxides,[32,33] the selective deprotonation of one of the two α-positions was not known. As we needed to deprotonate exclusively at position 6, we searched for an encumbered base to take advantage of the steric hindrance provided by the alkyl group. Our first choice, lithium 2,2,6,6-tetramethylpiperidide (LiTMP),[34] reacts with trimethylstannyl chloride, and thus a large excess of both the base and the trapping electrophile was necessary to achieve a ∼50% yield of **6** by ^{1}H NMR. Attempted separation of the product from the reagents resulted in the loss of the $SnMe_3$ group. Our second choice, the uncharged and sterically very hindered phosphazene base P_4-*tert*-butyl (**8**) developed by Schwesing-

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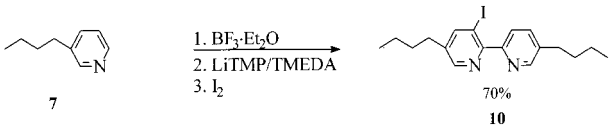
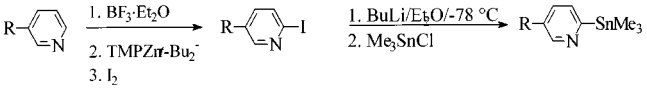
Scheme 3



7 10

Scheme 4



7: R = Bu; **16**: R = Hx — **13**: R = Bu, 79%; **17**: R = Hx, 78% — **6**: R = Bu; **18**: R = Hx

er,[35] did not react with trimethylstannyl chloride at room temperature, permitting us to add the base to the pyridine derivative in the presence of the trapping agent. However, **8** failed to deprotonate the pyridine, and no reaction was observed.

We next attempted to increase the acidity of the hydrogen in position 6. 3-*n*-Butylpyridine-*N*-oxide was deprotonated by **8** at position 6, and we were able to capture the anion with trimethylstannyl chloride to obtain the stannylated pyridine-*N*-oxide **9**. However, we were subsequently unable to reduce the *N*-oxide without losing the C−Sn bond at the same time. Since **9** failed to couple with **4**, we abandoned this approach.

Inspired by a report by Kessar et al.,[29] who used the easily formed and easily hydrolyzed BF_3 complex to activate the pyridine ring and synthesize α-pyridyl alcohols, and by a study[32] describing a deprotonation of pyridine·BF_3 complexes with LiTMP/TMEDA, we then attempted to deprotonate under these conditions and trap the anion with iodine to obtain a more stable product that could be converted to the desired trimethylstannyl derivative in a subsequent step. However, after hydrolysis, this reaction yielded an iodo-5,5′-di-*n*-butyl-2,2′-bipyridine, most likely the 3-iodo isomer **10** judging by the ^{1}H NMR spectrum (Scheme 3). Formation of 2,2′-bipyridine from pyridine was previously reported by Gros et al.[30] after treatment with BuLi/LiDMEA and by Tagawa et al.[32] after treatment with LiTMP, but Tagawa's group claimed that this reaction could be suppressed when the pyridine·BF_3 complex was used in the presence of TMEDA. However, in our case, deprotonation of the 3-*n*-butylpyridine·BF_3 complex (**11**) at position 6 was apparently followed by a nucleophilic attack by the resulting anion on the 6 position of another molecule of the pyridine·BF_3 complex. The remaining base then probably deprotonated the resulting 5,5′-dibutyl-2,2′-bipyridine at position 3, and the resulting anion was finally trapped with I_2. Indeed, Zoltewicz and Dill[36] recently reported an ortho lithiation of 2,2′- and 2,4′-bipyridines with LiTMP followed by quenching with various electrophiles, and among the compounds they obtained was 3-iodo-2,2′-bipyridine.

We finally turned to a new base, lithium di-*tert*-butyl-(2,2,6,6-tetramethylpiperidino)zincate (TMP-zincate, **12**), useful for the chemoselectively directed ortho metalation of alkyl benzoates and direct α-metalation of π-deficient aza-aromatics.[33,37] This base permits a conversion of pyridine to 2-iodopyridine in 76% yield. When we applied the procedure to **7**, we obtained a product mixture whose ^{1}H NMR suggested the presence of 50% starting material and several monoiodinated isomers but only about 5% of the expected 5-*n*-butyl-2-iodopyridine (**13**). When we activated positions 2 and 6 by using the 3-*n*-butylpyridine·BF_3 complex **11**, there was no reaction when 1 equiv of the base was employed. However, with 2 equiv of TMP-zincate, we observed a clean conversion of the starting material to **13** (Scheme 4). The alternative structure, 3-*n*-butyl-2-iodopyridine (**14**), was excluded by NOE NMR: irradiation of the benzylic methylene protons enhances the signals of two ring protons, H4 and H6, and irradiation of H6 only enhances the signals of the benzylic protons and the methylene protons next to them. Compound **13** appeared to be stable in solution as judged by ^{1}H NMR, but upon evaporation of the solvent, it turned dark orange, indicating partial decomposition. We were unable to isolate it pure in neat form.

When trimethylstannyl chloride was used instead of iodine as the trapping agent, only one product was formed and the ^{1}H NMR spectrum clearly showed a singlet in the region where the resonance of the proton located next to the ring nitrogen is expected. However, the separation of 2-trimethylstannyl-5-*n*-butylpyridine (**6**) from the zincate and its further purification proved to be difficult because of its low stability, and it is preferable to obtain the trimethylstannyl derivative **6** by metal−halogen exchange from the purified iodo compound **13** (Scheme 4). The use of diethyl ether as the solvent gave better results than the use of THF. A solution in xylenes is easier to store for an extended period than the neat compound.

B. Coupling of 6 and 4 (Scheme 1). Stille-type coupling of **6** and **4** to 5-bromo-5′-*n*-butylbipyridine (**15**) was accomplished by applying the procedure described above for 2-trimethylstannylpyridine; however, the yield was lower, and a considerable amount of **3** was isolated along with 3-*n*-butylpyridine (**7**). Clearly, **4** was depleted due to symmetric coupling and the unreacted **6** decomposed during the workup. No coupling through bromine in position 5 was observed, even when there was no **4** left in the reaction mixture. When excess **4** was used, the yield of **15** improved to a value similar to that observed above in the absence of the butyl group. 5,5′-Dibromobipyridine (**3**) was still formed in a considerable amount but could be separated by column chromatography, and excess **4** was easily recovered by sublimation. The comparison of the ^{1}H and ^{13}C NMR spectra with those of **4** gave conclusive evidence of the structure and therefore indirectly confirmed the structural assignment of **13** in the previous step as well.

5-Bromo-5′-*n*-hexylbipyridine. The treatment of 3-*n*-hexylpyridine (**16**) with 2 equiv of the TMP-zincate base, followed by quenching with iodine, yielded a single product characterized as 5-hexyl-2-iodopyridine (**17**) by comparison of its ^{1}H and ^{13}C NMR spectra with those of **13**. When the progress of the reaction was followed closely by ^{1}H NMR, the formation and disappearance of an intermediate became obvious. This species has a symmetrical peak pattern in the aromatic region and a shifted peak with a changed splitting pattern for the benzylic protons on the hexyl chain. We did not investigate this intermediate further, but its appearance suggests that the reaction is more complex than a mere deprotonation followed by electrophile trapping. Product

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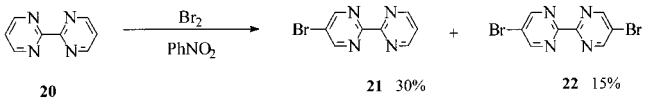
Scheme 5



17 was stable in solution but decomposed slightly when neat. As a result, attempts to obtain an elemental analysis were unsuccessful, but the HRMS clearly proved the composition.

The iodine was cleanly exchanged to form 5-*n*-hexyl-2-trimethylstannylpyridine (**18**) by halogen−metal exchange using BuLi and transmetalation with trimethylstannyl chloride at −78 °C in diethyl ether (Scheme 4). Again, we did not isolate the trimethylstannyl derivative **18** in pure form due to its inherent instability; we simply separated the inorganic salts formed in the reaction by precipitation and transferred the compound in dry xylenes for reaction with **4** under Pd(0) catalysis to yield the desired 5-bromo-5′-*n*-hexylbipyridine (**19**) in good yield (Scheme 1). It was again necessary to use an excess of **4** in order to compensate for the loss due to symmetric coupling.

5-Brominated and 5,5′-Dibrominated 2,2′-Bipyrimidines (Scheme 5). Since bromination of 2,2′-bipyrimidine (**20**) is expected[38] to occur in the desired positions, we decided to try this admittedly harsh procedure first. We also considered the synthesis of 5-bromo-2,2′-bipyrimidine (**21**) and 5,5′-dibromo-2,2′-bipyrimidine (**22**) by a coupling similar to that shown for **1** and **3** in Schemes 1 and 2, respectively, but were discouraged by the reported[39] instability of the starting 2,5-dibromopyrimidine. The possible alternative, 2-iodo-5-bromopyrimidine,[39] requires a rather elaborate synthesis itself. For the direct bromination, simple access to 2,2′-bipyrimidine (**20**) in large amounts was clearly essential. To run the reaction on a multigram scale, we found it necessary to adjust the procedure published by Nasielski et al.,[40] which is based on reductive coupling of 2-chloropyrimidine, in the following three respects. (i) The starting 2-chloropyrimidine was sublimed immediately prior to use. (ii) A half equivalent of the nickel reagent with respect to the product was used. This amount is most likely required because the nickel ion is deactivated when it is complexed to two bipyrimidine units. (iii) In the workup of the reaction, EDTA disodium salt was added to the aqueous layer and **20** was recovered by repeated extractions with chloroform. This ligand was necessary since the metal complexes of **20** are very water soluble and could not be extracted into an organic layer. With these modifications, the yield of **20** exceeds 80% when the reaction is run on a multigram scale.

The bromination step was accomplished by heating **20** with bromine in nitrobenzene to 135 °C. Unfortunately, at this temperature, considerable degradation of the starting material was observed and the yield of the reaction was rather low, but there was no reaction at lower temperatures. Even when we tried to favor the formation of the singly brominated product **21**, 5,5′-dibromo-2,2′-bipyrimidine (**22**) was a substantial byproduct since bromine had to be used in excess in order to ensure a reasonable reaction rate. Milder bromination agents such as NBS did not yield any brominated products. Fortunately, the separation of **21** from **22** was facile because the latter is poorly soluble in most organic solvents. A saturated solution of the mixture in chloroform contained an ∼95:5 mixture of **21** and **22**, easily separated by flash chromatography, while the residual solid consisted solely of **22**.

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Conclusion

We have developed efficient syntheses of 5-brominated and 5,5′-dibrominated bipyridine and of 5′-*n*-butyl- and 5′-*n*-hexyl-substituted 5-bromobipyridine. We also report low-yield but still practical syntheses of 5-brominated and 5,5′-dibrominated bipyrimidine. These compounds are useful for the synthesis of rodlike heterocyclic structures. In the process, we have found a procedure for selective deprotonation of 3-*n*-alkylpyridines at position 6 with lithium di-*tert*-butyl-(2,2,6,6-tetramethylpiperidino)zincate (**23**) as a mild bulky base.

Experimental Section

All reactions were carried out under an argon atmosphere with dry solvent, freshly distilled under anhydrous conditions unless otherwise noted. Standard Schlenk and vacuum line techniques were employed for all manipulations of air- or moisture-sensitive compounds. Yields refer to isolated, chromatographically and spectroscopically homogeneous materials, unless otherwise stated.

Melting points were determined with a Laboratory Devices MEL-TEMP II apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired with a Varian Unity Inova 500 spectrometer and referenced to residual ^{1}H and ^{13}C present in deuterated solvents. All NMR spectra were recorded at room temperature. IR spectra were recorded with a Nicolet Avatar 320 FT-IR spectrometer. GC MS spectra were measured with an HP GC/MS 5988A instrument with a fused silica capillary column (cross-linked 5% phenyl methyl silicone). EI$^+$MS spectra were measured with a VG 7070 EQ-HF Hybrid Tandem Mass spectrometer. FAB measurements were conducted with a Fisons Instruments VG autospec instrument. ESI spectra were acquired with a Hewlett-Packard 59987A Electrospray instrument connected to a HP 5989B Mass Spectrometer. Elemental Analyses were performed by Desert Analytics, Tucson, AZ, and Galbraith Laboratories, Knoxville, TN.

2,5-Dibromopyridine and 2-chloropyrimidine were purchased from Aldrich and sublimed prior to use. 2-Bromopyridine, 3-bromopyridine, and 3-*n*-butylpyridine were purchased from Aldrich and distilled from CaH_2 prior to use. *t*-BuLi, *n*-BuLi, 2,2,6,6-tetramethylpiperidine, $ZnCl_2$, Me_3SnCl, and $Pd(PPh_3)_4$ were purchased from Aldrich and used without further purification. THF, diethyl ether, and hydrocarbon solvents were dried by distillation from sodium metal.

5-Bromo-2,2′-bipyridine (1).[2] 2,5-Dibromopyridine (**4**, 12.3 g, 0.052 mol) was charged into a flask, evacuated, and put under argon. The 2-trimethylstannylpyridine (**5**, 11.5 g, 0.047 mol) obtained as described below was transferred under argon with dry *m*-xylene (100 mL), and argon gas was bubbled through the solution for 1 h. Then, $Pd(PPh_3)_4$ (0.547 g, 1 mol %) was added from a tip tube, and the reaction mixture was heated while stirring for 12 h at 120 °C and poured into 2 M NaOH. The phases were separated, and the aqueous layer was extracted with toluene (2 × 25 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The solid crude product was chromatographed (alumina, 5:1 hexanes/ethyl acetate), and **1** was isolated as a white crystalline powder: 8.61 g (78%); mp 73 °C (lit.[2] 74−75 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (ddd, J = 7.4 Hz, J =

4.8 Hz, J = 1.0 Hz, 1 H, H5′), 7.79 (td, J = 7.4 Hz, J = 1.8 Hz, 1 H, H4′), 7.90 (dd, J = 2.4 Hz, J = 8.5 Hz, 1 H, H4), 8.29 (d, J = 8.5 Hz, 1 H, H3′), 8.34 (d, J = 8.5 Hz, 1 H, H3), 8.64 (dt, J = 4.8 Hz, J = 1.0 Hz, 1 H, H6′), 8.69 (d, J = 2.4 Hz, 1 H, H6). Romero and Ziessel[2] reported a ^{13}C NMR spectrum with only 9 signals; our data reveal the expected 10 peaks: ^{13}C {^{1}H} NMR ($CDCl_3$, 124 MHz) δ 120.92 (C_{bipy}), 121.09 (C_{bipy}−Br), 122.29 (C_{bipy}), 123.96 (C_{bipy}), 136.97 (C_{bipy}), 139.45 (C_{bipy}), 149.21 (C_{bipy}), 150.15 (C_{bipy}), 154.58 (C_{bipy}), 155.13 (C_{bipy}).

5,5-Dibromo-2,2′-bipyridine (3).[2] 2,5-Dibromopyridine (**4**, 1.00 g, 4.33 mmol) was charged into a flask, evacuated, and put under argon. Anhydrous *m*-xylene (35 mL) was added from a syringe, followed by hexa-*n*-butyldistannane (1.18 mL, 50 mol %). Argon was bubbled through the stirred solution for 1 h before $Pd(PPh_3)_4$ (0.117 g, 0.101 mmol) was added from a tip tube. The reaction mixture was heated to 130 °C for 3 days until all starting material was consumed and poured into aqueous EDTA (1 M, 25 mL). After the mixture was stirred for 15 min, the phases were separated. The aqueous phase was extracted with chloroform (3 × 50 mL), and the combined organic phases were dried over Na_2SO_4. After evaporation of the solvents, the crude product was flash chromatographed (alumina, 5:1 hexanes/ethyl acetate), yielding 5,5-dibromo-2,2′-bipyridine (**3**) as a white solid (95% by ^{1}H NMR, 0.52 g, 78%). The product **3** was further purified by PTLC (alumina, 8:1 hexanes/ethyl acetate) and obtained as colorless plates after recrystallization from chloroform: mp 201 °C (lit.[2] 205 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91 (dd, J = 2.4 Hz, J = 8.5 Hz, 2 H, H4), 8.26 (d, J = 8.5 Hz, 2 H, H3), 8.68 (d, J = 2.4 Hz, 2 H, H6).

2-Trimethylstannylpyridine (5).[9] Freshly distilled 2-bromopyridine (8.5 g, 5.2 mL, 0.053 mol) was charged into a flask, evacuated, and put under argon. Dry diethyl ether (100 mL) was added from a syringe under stirring, and the solution was cooled to −78 °C in a dry ice/acetone bath. *n*-BuLi (2.0 M in cyclohexane, 29 mL, 0.058 mol) was added dropwise from a syringe, and the reaction mixture was stirred for 2 h under continued cooling. Then, trimethylstannyl chloride (1.0 M in THF, 58 mL, 0.058 mol) was added dropwise from a syringe. After 3 h, the reaction mixture was allowed to warm slowly to room temperature overnight. The solvents were evaporated directly from the reaction flask under reduced pressure. Dry hexanes (100 mL) were added from a syringe, and the slurry was stirred for 10 min. Following filtration through a frit under argon, the hexanes were evaporated under reduced pressure and the crude product (**5**, 11.5 g, 88%, 96% purity by ^{1}H NMR) was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.33 (s, 9 H, J_{SnH} = 27 Hz, $SnCH_3$), 7.12 (ddd, 1 H, J = 6.1 Hz, J = 4.8 Hz, J = 1.5 Hz, H5), 7.42 (dt, 1 H, J = 6.9 Hz, J = 0.9 Hz, H3), 7.50 (td, 1 H, J = 6.9 Hz, J = 1.5 Hz, H4), 8.72 (dt, 1 H, J = 4.8 Hz, J = 0.9 Hz, H6).[9]

5,5′-Dibutyl-3-iodo-2,2′-bipyridine (10). Freshly distilled, dry 3-*n*-butylpyridine (**7**,135 mg, 0.001 mol) was transferred by a syringe to a two-neck flask filled with argon. Under stirring, dry diethyl ether (10 mL) was added from a syringe and the clear, colorless solution was cooled to 0 °C. Then, BF_3 etherate (0.125 mL, 0.001 mol) was added dropwise and the reaction mixture was stirred at 0 °C for 30 min. In a second flask, freshly distilled 2,2,6,6-tetramethylpiperidine (0.186 mL, 0.0011 mol) was stirred under argon and cooled to 0 °C in an ice bath. *n*-BuLi (2 M in cyclohexane, 0.6 mL, 0.0012 mol) was added dropwise from a syringe, and the reaction mixture was stirred for 20 min before the solution was warmed to room temperature. Dry THF (15 mL) was added from a syringe along with TMEDA (0.098 mL, 0.0012 mol). The yellow, clear solution was stirred for 15 min and transferred to a syringe.

Then, the solution containing the pyridine·BF_3 complex was cooled to −78 °C and the base was added dropwise. The orange-red solution was stirred for 20 min before freshly sublimed iodine (550 mg, 0.002 mol) dissolved in diethyl ether (10 mL) was added via cannula. After stirring for an additional 2 h below −30 °C, the reaction mixture was poured into aqueous Na_2SO_3 and shaken vigorously. The phases were separated, and the aqueous layer was extracted with chloroform (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, and the solvents were evaporated. The crude product mixture was separated by PTLC (silica, 5:1 hexanes/ethyl acetate). Some unreacted **7** was also recovered (15 mg, 10%), but the main product isolated was 5,5′-dibutyl-3-iodo-2,2′-bipyridine as a yellow-orange oil (**10**, 137 mg, 69%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 3 H, J = 7.3 Hz), 0.87 (t, 3 H, J = 7.3 Hz), 1.25 (m, 2 H), 1.35 (m, 2 H), 1.47 (m, 2 H), 1.61 (m, 2 H), 2.64 (t, 2 H, J = 7.7 Hz), 2.82 (t, 2 H, J = 7.7 Hz), 7.57 (d, 1 H, J = 2.1 Hz), 7.62 (d, 1 H, J = 8.1 Hz), 7.92 (d, 1 H, J = 2.1 Hz), 8.45 (s, 1 H), 8.67 (d, 1 H, J = 2.1 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$, 124 MHz) δ 13.69 (CH_3−), 13.79 (CH_3−), 22.12 (−CH_2−), 22.39 (−CH_2−), 31.94 (−CH_2−), 32.47 (−CH_2−), 32.79 (−CH_2−pyr), 33.11 (−CH_2−pyr), 92.67 (C−I), 123.56 (C_{pyr}−H), 136.39 (C_{pyr}−H), 137.24 (C_{pyr}−H), 139.31 (C_{pyr}−H), 146.05 (C_{pyr}−H), 148.63 (C_{pyr}−H), 152.33 (C_{pyr}−H), 155.09 (C_{pyr}−H), 155.55 (C_{pyr}−H); MS (EI$^+$) *m*/*z* (rel intensity) 394 ([M]$^+$, 45), 365 ([M − C_2H_5]$^+$, 100), 351 ([M − C_3H_7]$^+$, 15), 322 (5), 308 (3), 267 ([M − I]$^+$, 4), 238 (6), 195 (5), 128 ([I]$^+$, 3), 77 (2); IR (KBr) 634, 750, 789, 848, 866, 888, 901, 931, 1026, 1039, 1079, 1109, 1130, 1155, 1193, 1259, 1305, 1378, 1431, 1463, 1485, 1531, 1568, 1595, 2857, 2928, 2956, 3031; HRMS calcd 394.0906, found 394.0921.

5-*n*-Butyl-2-iodopyridine (13). Freshly distilled 3-*n*-butylpyridine (**7**, 2.5 g, 0.0185 mol) was rinsed into a flask with dry ether (25 mL) and cooled to 0 °C under stirring. BF_3 etherate (2.5 mL, 0.019 mol) was added dropwise, and the mixture was stirred at 0 °C for 2 h. In the meantime, $ZnCl_2$ (0.5 M in THF, 67.2 mL) was placed in a separate flask and cooled to −78 °C under stirring. Under argon, *t*-BuLi (1.7 M in pentane, 58 mL, 0.0983 mol) was added dropwise but rapidly, and the clear, yellow reaction mixture was slowly warmed to room temperature and stirred for 15 min before recooling to −78 °C. In a third flask, 2,2,6,6-tetramethylpiperidine (6.9 mL, 0.0407 mol) was put under argon and cooled to 0 °C. Under stirring, *n*-BuLi (1.6 M in hexanes, 26.0 mL) was added dropwise, and the reaction mixture was stirred for 30 min before warming up to room temperature. After 30 min, the flask was cooled to −78 °C under continued stirring and the di-*tert*-butylzinc solution was added slowly through a cannula over 20 min. The mixture was stirred vigorously until all solids were dissolved, yielding a clear, yellow solution. The solution was stirred for 30 min at −78 °C before warming to room temperature for 15 min. After the solution was recooled to −78 °C, the ether solution of the pyridine·BF_3 complex was added through a cannula in small portions. The reaction mixture turned orange immediately and then brown. The reaction mixture was stirred for 2 h at −78 °C at which time the color had turned to dark red. In a fourth flask, freshly sublimed iodine (18.8 g, 0.074 mol) was placed under argon, dissolved in dry diethyl ether (100 mL), and cooled to 0 °C. The solution was added to the pyridinium zincate through a cannula over 5 min. Then, the reaction mixture was slowly warmed to room temperature overnight and poured into a saturated aqueous solution of sodium sulfite (100 mL). Following vigorous mixing, the two layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed once more with sodium sulfite solution (2 × 50 mL), and after drying over Na_2SO_4, the organic solvents were evaporated under reduced pressure. The crude product was chromatographed (alumina, 10:1 hexanes/ethyl acetate), and **13** was recovered as a yellowish oil: 3.8 g (79%, 98% purity by ^{1}H NMR); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, J = 7.3 Hz, 3 H, CH_3), 1.30 (m, 2 H, CH_2−CH_3), 1.52 (m, 2 H, CH_2), 2.49 (t, J = 7.7 Hz, 2 H, C_{pyr}−CH_2), 7.10 (dd, J = 8.1 Hz, J = 2.5 Hz, 1 H, C_{pyr}−H), 7.56 (d, J = 8.1 Hz, 1 H, C_{pyr}−H), 8.25 (d, J = 2.5 Hz, 1 H, C_{pyr}−H); ^{13}C {^{1}H} NMR ($CDCl_3$, 124 MHz) δ 13.73 (CH_3−CH_2), 22.05 (CH_2), 31.94 (CH_2), 32.94 (CH_2−C_{pyr}), 114.40 (C_{pyr}−I), 134.27 (C_{pyr}), 137.59 (C_{pyr}), 137.80 (C_{pyr}), 150.88 (C_{pyr}); IR (NaCl) 513, 622, 641, 729, 788, 818, 833, 934, 1019, 1070, 1128, 1210, 1377, 1451, 1552, 1575, 2858, 2929, 2956, 3034 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 261 ([M]$^+$, 35), 218 ([M − C_3H_7]$^+$,

12), 167 (3), 149 (13), 134 ([M − I]$^+$, 100), 91 ([M − C_3H_7I]$^+$, 25), 77 (16), 69 (20), 55 (30); HRMS calcd 261.0015, found 261.0020.

5-*n*-Butyl-5′-bromo-2,2′-bipyridine (15). 5-*n*-Butyl-2-iodopyridine (**13**, 2.8 g, 0.0107 mol) was charged into a flask, kept under vacuum for 20 min, and put under argon. Dry diethyl ether (100 mL) was added from a syringe, and the solution was transferred to a two-neck flask through a cannula. The solution was stirred and cooled to −78 °C with a dry ice/acetone bath. *n*-BuLi (2.0 M in cyclohexane, 5.75 mL, 0.0115 mol) was added dropwise while the color changed from yellow to orange and finally red when the addition was complete. After stirring for 1 h, the reaction mixture turned brown. Trimethylstannyl chloride (1 M in THF, 13 mL, 0.013 mol) was added dropwise from a syringe, and the solution was allowed to warm to room temperature overnight. The diethyl ether and THF were evaporated directly from the reaction flask under reduced pressure. Dry hexanes (50 mL) were added through a syringe, and the slurry was stirred for 30 min at room temperature. The white precipitate was filtered off through a frit under argon, and the hexanes were evaporated from the filtrate under vacuum, leaving a brown viscous liquid (3.18 g, 99%, 94% purity by ^{1}H NMR). Dry xylenes were added, and the crude 5-*n*-butyl-2-trimethylstannylpyridine (**6**) was used in the next step: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.31 (s, 9 H, J_{SnH} = 27 Hz, $SnCH_3$), 0.90 (t, J = 7.3 Hz, 3 H, CH_3), 1.34 (m, 2 H, CH_2−CH_3), 1.56 (m, 2 H, CH_2), 2.54 (t, J = 7.7 Hz, 2 H, C_{pyr}−CH_2), 7.33 (m, 2 H, H4, H5), 8.57 (s, 1 H, H2); ^{13}C {^{1}H} NMR ($CDCl_3$, 124 MHz) δ 13.85 (CH_3−CH_2), 22.22 (CH_2), 32.76 (CH_2), 33.27 (CH_2−C_{pyr}), 131.18 (C_{pyr}), 133.58 (C_{pyr}), 136.46 (C_{pyr}), 151.01 (C_{pyr}), 169.51 (C_{pyr}−$SnMe_3$).

2,5-Dibromopyridine (**4**, 3.02 g, 0.0128 mol) was charged into a flask, evacuated, and put under argon. The crude **6** prepared above (3.18 g, 0.0107 mol) in dry xylenes (75 mL) was added through a cannula, and argon gas was bubbled through the solution for 2 h. Then, $Pd(PPh_3)_4$ (400 mg, 0.346 mmol) was added from a tip tube. The reaction mixture was stirred at 120 °C for 16 h and subsequently poured into 2 M NaOH (50 mL) saturated with ETDA. The two layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, and the solvents were evaporated under reduced pressure. The crude product was chromatographed (alumina, 15:1 hexanes/ethyl acetate) and 5-bromo-5′-*n*-butyl-2,2′-bipyridine (**15**) was recovered as a colorless oil: 2.45 g, (79%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, J = 7.3 Hz, 3 H), 1.35 (m, 2 H), 1.62 (m, 2 H), 2.64 (t, J = 7.8 Hz, 2 H), 7.58 (dd, J = 7.8 Hz, J = 2.2 Hz, 1 H), 7.88 (dd, J = 8.5 Hz, J = 2.4 Hz, 1 H), 8.25 (dd, J = 8.5 Hz, J = 2.2 Hz, 2 H), 8.46 (s, 1 H), 8.68 (s, 1H); ^{13}C {^{1}H} NMR ($CDCl_3$, 124 MHz) δ 13.85 (CH_3−CH_2), 22.20 (CH_2), 32.57 (CH_2), 33.16 (CH_2−C_{pyr}), 120.59 (C_{bipy}), 120.68 (C_{bipy}), 122.06 (C_{bipy}), 136.86 (C_{bipy}), 138.66 (C_{bipy}−C_{bu}), 139.41 (C_{bipy}), 149.39 (C_{bipy}), 150.10 (C_{bipy}), 152.82 (C_{bipy}), 154.81 (C_{bipy}); IR (NaCl) 633, 649, 735, 836, 920, 1005, 1025, 1056, 1090, 1130, 1242, 1269, 1364, 1399, 1454, 1545, 1565, 1594, 2858, 2930, 2957, 3003, 3043 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 290 ([M]$^+$, 75), 275 ([M −CH_3]$^+$, 3), 261 ([M − C_2H_5]$^+$, 10), 247 ([M − C_3H_7]$^+$, 100), 234 (3), 220 (7), 181 (4), 168 (9), 154 (3), 141 (25), 115 (5), 77 (5), 55 (5); HRMS calcd 290.0419, found 290.0428. Anal. Calcd for $C_{14}H_{15}N_2Br$: C, 57.75; H, 5.19; N, 9.62. Found: C, 58.00; H, 5.24; N, 9.53.

3-*n*-Hexylpyridine (16).[41] Into a 2 L three-neck flask was placed CuBr (71.7 g, 0.5 mol) under argon, and dry THF (500 mL) was added. The suspension was cooled to −78 °C, and *n*-hexylmagnesium bromide (2 M in diethyl ether, 500 mL, 1.0 mol) was added dropwise over 1 h under mechanical stirring. After additional stirring for 30 min, freshly distilled 3-bromopyridine (19.8 g, 0.125 mol) was added dropwise from a syringe. The reaction mixture was kept at −78 °C for 30 min, warmed to −25 °C, and then stirred overnight. After the mixture was warmed to room temperature, the black solids were filtered off and washed thoroughly with diethyl ether (500 mL). The filtrate was washed with NH_4OH (14% in water, 2 × 200 mL), and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The organic layer was extracted with 2 M HCl (4 × 50 mL). The aqueous phases were combined and basified with concentrated NaOH under stirring and cooling with ice. The solution was transferred to a separatory funnel and extracted with diethyl ether (4 × 100 mL). The organic layers were combined and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude liquid was fractionally distilled, and 3-*n*-hexylpyridine (**16**) was collected as a colorless liquid with a sweet fragrance: 6.2 g, (30%); bp 73 °C at 0.5 Torr; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, J = 7.3 Hz, 3 H, CH_3), 1.28 (m, 6 H, C_3H_6−CH_3), 1.59 (m, 2 H, CH_2), 2.57 (t, J = 7.7 Hz, 2 H, C_{pyr}−CH_2), 7.16 (dd, J = 8.1 Hz, J = 2.3 Hz, 1 H, H5), 7.45 (dt, 1 H, J = 8.1 Hz, J = 2.1 Hz, H4), 8.39 (dd, 1 H, J = 7.7 Hz, J = 2.1 Hz, H6), 8.41 (s, 1 H, H2).[41]

5-*n*-Hexyl-2-iodopyridine (17). Freshly distilled 3-*n*-hexylpyridine (**16**, 3.02 g, 0.0185 mol) was rinsed into a flask with dry diethyl ether (25 mL) and cooled to 0 °C under stirring. BF_3 etherate (2.5 mL, 0.019 mol) was added dropwise, and the mixture was stirred at 0 °C for 2 h.

In the meantime, $ZnCl_2$ (0.5 M in THF, 67.2 mL) was put in a separate flask and cooled to −78 °C under stirring. *t*-BuLi (1.7 M in pentane, 58 mL, 0.098 mol) was added dropwise but rapidly, and the clear, yellow reaction mixture was slowly warmed to room temperature and stirred for 15 min before being recooled to −78 °C.

In a third flask, 2,2,6,6-tetramethylpiperidine (6.9 mL, 0.041 mol) was put under argon and cooled to 0 °C. Under stirring, *n*-BuLi (1.6 M in hexanes, 26.0 mL) was added dropwise, and the reaction mixture was stirred for 30 min before warming up to room temperature. After 30 min, the flask was cooled to −78 °C under continued stirring and the di-*tert*-butylzinc solution was added slowly through a cannula over 20 min. The mixture was stirred vigorously until all solids were dissolved, yielding a clear, yellow solution. The solution was stirred for 30 min at −78 °C before warming to room temperature for 15 min. After the solution was recooled to −78 °C, the ethereal solution of the pyridine·BF_3 complex was added through a cannula in small portions. The reaction mixture turned orange immediately and then brown. It was stirred for 3 h at −78 °C, at which time the color had turned to dark red.

In a fourth flask, freshly sublimed iodine (18.8 g, 0.074 mol) was placed under argon, dissolved in 100 mL of dry THF, and cooled to −78 °C. The pyridinium zincate solution was then slowly added under vigorous stirring. After slowly warming to room temperature, the reaction mixture was stirred overnight. Then, the solution was poured into a saturated aqueous solution of sodium sulfite (100 mL). Following vigorous mixing, the two layers were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed once more with sodium sulfite solution (2 × 50 mL), and after drying over Na_2SO_4, the organic solvents were evaporated under reduced pressure. The crude product was subsequently chromatographed (alumina, 10:1 hexanes/ethyl acetate), and 5-*n*-hexyl-2-iodopyridine (**17**) was recovered as an orange oil: 4.2 g (78%, 96% purity by ^{1}H NMR); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 7.3 Hz, 3 H, CH_3), 1.28 (m, 6 H, C_3H_6−CH_3), 1.58 (m, 2 H, CH_2), 2.55 (t, J = 7.7 Hz, 2 H, C_{pyr}−CH_2), 7.14 (dd, J = 8.1 Hz, J = 2.3 Hz, 1 H, C_{pyr}−H), 7.60 (d, J = 8.1 Hz, 1 H, C_{pyr}−H), 8.19 (d, J = 2.5 Hz, 1 H, C_{pyr}−H); ^{13}C {^{1}H} NMR ($CDCl_3$, 124 MHz) δ 13.99 (CH_3−CH_2), 22.47 (CH_2), 28.64 (CH_2), 30.81 (CH_2), 31.46 (CH_2), 32.25 (CH_2−C_{pyr}), 114.41 (C_{pyr}−I), 134.27 (C_{pyr}), 137.63 (C_{pyr}), 137.79 (C_{pyr}), 150.89 (C_{pyr}); IR (NaCl) 405, 422, 449, 455, 463, 489, 601, 623, 643, 731, 790, 817, 924, 1020, 1071, 1128, 1211, 1377, 1452, 1552, 1575, 2856, 2928, 2955, 3034 cm^{-1}; MS (EI$^+$) *m*/*z* (rel intensity) 289 ([M]$^+$, 55), 250 (13), 218 ([M − C_5H_{11}]$^+$, 17), 162 ([M − I]$^+$, 100), 149 (8), 128 (18), 91 ([M − C_5H_{11}I]$^+$, 25), 77 (16), 69 (20), 55 (30); HRMS calcd 289.0328, found 289.0324.

(41) Tereshko, A. B.; Tarasevich, V. A.; Kozlov, N. G. *Zh. Org. Khim.* **1995**, *31*, 289.

5-Bromo-5′-*n*-hexyl-2,2′-bipyridine (19). 5-*n*-Hexyl-2-iodopyridine (**17**, 3.2 g, 0.011 mol) was charged into a flask, kept under vacuum for 20 min, and put under argon. Dry diethyl ether (100 mL) was added from a syringe, and the solution was transferred to a two-neck flask through a cannula. The solution was stirred and cooled to −78 °C with a dry ice/acetone bath. *n*-BuLi (2.0 M in cyclohexane, 5.75 mL, 0.012 mol) was added dropwise while the color changed from yellow to orange and finally to red when the addition was complete. The reaction mixture was stirred for 2 h and gradually turned brown. Then, trimethylstannyl chloride (1 M in THF, 13 mL, 0.013 mol) was added dropwise from a syringe and the solution was allowed to warm to room temperature overnight. The diethyl ether and THF were evaporated directly from the reaction flask under reduced pressure. Dry hexanes (50 mL) were added through a syringe, and the slurry was stirred for 30 min at room temperature. The white precipitate was filtered off through a frit under argon, and the hexanes were evaporated from the filtrate under vacuum, leaving a brown viscous liquid (3.38 g, 95%, purity 94% by ^{1}H NMR). Dry xylenes were added, and the crude 5-*n*-hexyl-2-trimethylstannylpyridine (**18**) was used without further purification in the next step: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.31 (s, 9 H, J_{SnH} = 27 Hz, $SnCH_3$), 0.85 (t, J = 7.3 Hz, 3 H, CH_3), 1.28 (m, 6 H, C_3H_6−CH_3), 1.58 (m, 2 H, CH_2), 2.55 (t, J = 7.7 Hz, 2 H, C_{pyr}−CH_2), 7.33 (m, 2 H, H4, H5), 8.57 (s, 1 H, H2).

2,5-Dibromopyridine (**4**, 4.05 g, 0.0171 mol) was charged into a 250 mL three-neck flask, evacuated, and put under argon. Through a cannula, the crude **18** (3.38 g, 0.0104 mol) dissolved in anhydrous *m*-xylene (100 mL) was added under stirring. Argon gas was bubbled through the solution for 1 h, and $Pd(PPh_3)_4$ (165 mg, 1.25 mol %) was added from a tip tube. The reaction mixture was stirred at 110 °C for 32 h and poured into EDTA (1 M in water, 50 mL) to which NH_4OH (concentrated, 5 mL) had been added. The layers were mixed vigorously and then separated. The aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, and the solvents were evaporated under reduced pressure. The crude product was flash chromatographed (alumina), first with hexanes to elute the excess **4**, and then with 10:1 hexanes/ethyl acetate to elute the 5-bromo-5′-*n*-hexyl-2,2′-bipyridine (**19**) contaminated with 5,5′-dibromo-2,2′-bipyridine (**3**) and a small amount of 2,5-dibromopyridine. Compound **4** was sublimed off (0.5 Torr, 75 °C). The two products were crudely separated in a centrifuge (3200 rpm). Finally, **19** was purified by column chromatography (silica, 25:1 hexanes/ethyl acetate) and obtained as a colorless oil that crystallized as a white solid upon standing at room temperature: 2.32 g (72%); mp 28 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J = 6.9 Hz, 3 H), 1.29 (m, 6 H), 1.62 (m, 2 H), 2.64 (t, J = 7.5 Hz, 2 H), 7.60 (dd, J = 7.0 Hz, J = 2.2 Hz, 1 H), 7.89 (dd, J = 8.5 Hz, J = 2.4 Hz, 1 H), 8.25 (dd, J = 8.5 Hz, J = 4.6 Hz, 2 H), 8.46 (d, J = 1.8 Hz, 1 H), 8.67 (d, J = 2.4 Hz, 1H); ^{13}C {^{1}H} NMR ($CDCl_3$, 124 MHz) δ 14.05 (CH_3−CH_2), 22.56 (CH_2), 28.79 (CH_2), 31.01 (CH_2), 31.60 (CH_2), 32.87 (CH_2−C_{pyr}), 120.59 (C_{bipy}), 120.67 (C_{bipy}), 122.05 (C_{bipy}−Br), 136.85 (C_{bipy}), 138.70 (C_{bipy}−C_{hex}), 139.41 (C_{bipy}), 149.41 (C_{bipy}), 150.10 (C_{bipy}), 152.84 (C_{bipy}), 154.83 (C_{bipy}); IR (KBr) 466, 491, 634, 657, 721, 736, 754, 787, 828, 921, 1004, 1020, 1056, 1089, 1128, 1183, 1225, 1355, 1367, 1384, 1427, 1453, 1544, 1565, 1592, 2854, 2925, 2958, 3045 cm^{-1}; MS (EI$^+$) *m/z* (rel intensity) 318 ([M]$^+$, 55), 303 ([M −CH_3]$^+$, 2), 289 ([M − C_2H_5]$^+$, 5), 275 ([M − C_3H_7]$^+$, 7), 261 ([M − C_4H_9]$^+$, 15), 247 ([M − C_5H_{11}]$^+$, 100), 219 (7), 183 (4), 168 (15), 154 (5), 141 (25), 115 5), 77 (5), 55 (5); HRMS calcd 318.0732, found 318.0720. Anal. Calcd for $C_{16}H_{19}N_2Br$: C, 60.20; H, 6.00; N, 8.77. Found: C, 60.44; H, 6.18; N, 8.70.

2,2-Bipyrimidine (20).[40] Dry DMF (1.7 L) was degassed by bubbling argon gas through a frit into the stirred liquid overnight. Triphenylphosphine (91.7 g, 0.35 mol), $NiCl_2 \cdot H_2O$ (20.8 g, 0.088 mol), and zinc powder (11.4 g, 0.175 mol) were put under vacuum for 20 min and then added to the solution under argon. Under vigorous stirring at room temperature, the heterogeneous solution turned first red after a few minutes and then gradually brownish. After 1 h, freshly sublimed (0.5 Torr, 60 °C) 2-chloropyrimidine (40 g, 0.35 mol) was added through a funnel under argon and the solution turned darker. It was stirred vigorously for 1 h at room temperature, heated to 50 °C for 50 h, and filtered through Celite. After being washed with chloroform, the filtrate was evaporated under reduced pressure. The dark green crude solid was suspended in a solution of EDTA (150 g) in aqueous NH_3 (400 mL, 7%). The aqueous layer was extracted with diethyl ether (3 × 200 mL) and subsequently with chloroform (8 × 150 mL). The organic solvents were dried over Na_2SO_4 and evaporated under reduced pressure. The ether extract contained almost pure triphenylphosphine. The chloroform extract yielded **20** as a yellow solid, which was recrystallized from ethanol as off-white plates: 22.5 g (82%), mp 112 °C (lit.[42] 113−115 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44 (t, 4 H, J = 5.1 Hz, H4, H6), 9.02 (d, 2 H, J = 5.1 Hz, H5).

5-Bromo-2,2′-bipyrimidine (21). 2,2′-Bipyrimidine (**20**, 8 g, 0.051 mol) was placed in a two-neck flask, evacuated, and put under argon. Freshly distilled nitrobenzene (125 mL) was added from a syringe, and the solution was stirred at room temperature until the solid was dissolved. Bromine (10 mL, 3.12 g, 0.19 mol) was added from a pipet, and the reaction mixture was stirred at 135 °C for 48 h. Most of the nitrobenzene (100 mL) was then evaporated under reduced pressure, and the remaining solution was poured into saturated aqueous Na_2SO_3. After vigorous mixing, the layers were separated and the aqueous layer was extracted with chloroform (3 × 50 mL). The organic phases were combined and washed with aqueous ammonia (2 M, 1 × 50 mL). After the combined phases were dried over Na_2SO_4, the solvents were evaporated under reduced pressure. The dark brown residue was flash chromatographed (alumina, 1:2 hexane/chloroform). The recovered off-white crude product mixture was washed with chloroform, leaving most of the 5,5′-dibromo-2,2′-bipyrimidine (**22**) undissolved, and then chromatographed (silica, chloroform) to obtain 5-bromo-2,2′-bipyrimidine (**21**) as a white solid, which crystallized from chloroform as large colorless prisms: 3.7 g, (30%) mp 215 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (t, J = 4.9 Hz, 1 H, $C5'_{bipyrim}$−H), 9.00 (d, J = 4.9 Hz, 2 H, $C4'_{bipyrim}$−H), 9.04 (s, 2 H, $C4_{bipyrim}$−H); ^{13}C {^{1}H} NMR ($CDCl_3$, 126 MHz) δ 121.56 (C5′), 121.64 (C5), 158.08 (C4′, C6′), 158.70 (C4, C6), 160.14 (C2′), 161.61 (C2); IR (KBr) 431, 642, 705, 764, 807, 837, 925, 991, 1010, 1107, 1138, 1243, 1369, 1384, 1403, 1533, 1562, 2612, 3038 cm^{-1}; MS (EI$^+$) *m/z* (rel intensity) 236 (bromine cluster center, isotope pattern fits the calculated cluster for M, 100), 211 (bromine cluster center, 10), 183 (25), 130 (40), 105 (30), 79 (10), 52 (20); HRMS calcd 235.9698, found 235.9708. Anal. Calcd for $C_8H_5N_4Br$: C, 40.53; H, 2.13. Found: C, 40.68; H, 2.06.

5,5′-Dibromo-2,2′-bipyrimidine (22). Compound **22** was recrystallized from chloroform/benzene as colorless plates: 2.2 g (14%), mp 325 °C (subl.); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.02 (s, 4 H); ^{13}C {^{1}H} NMR ($CDCl_3$, 124 MHz) δ 121.82 (C5), 158.83 (C4), 159.69 (C2); IR (KBr) 446, 641, 732, 758, 931, 1009, 1089, 1138, 1221, 1237, 1362, 1385, 1412, 1439, 1525, 1542, 1614, 1866, 1994, 3018, 3066 cm^{-1}; MS (EI$^+$) *m/z* (rel intensity) 316 (bromine isotope pattern fits the calculated pattern for M, 100), 236 ([M − Br]$^+$, 10), 208 (20), 183 (15), 158 ([M − $C_4N_2H_2Br$]$^+$, 5), 156 ([M − 2Br]$^+$, 5), 130 (3), 104 (10), 77 (5), 52 (9); HRMS calcd 313.8803, found 313.8801. Anal. Calcd for $C_8H_4N_4Br_2$: C, 30.41; H, 1.28; N, 17.73. Found: C, 30.48; H, 1.36; N, 17.50.

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