Synthesis of 5-Substituted 2,2′-Bipyridines from Substituted 2-Chloropyridines by a Modified Negishi Cross-Coupling Reaction

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A new and practical approach to a number of differently 5-substituted 2,2′-bipyridines starting from substituted 2-chloropyridines has been found through the application of modified Negishi cross-coupling conditions.

Introduction

2,2′-Bipyridines are certainly among the most widely used ligand structure motifs in metal coordination compounds.[1] In particular, transition metal-bipyridine complexes exhibit lots of interesting characteristics, which has resulted in numerous studies of − for example − their photochemical[2] and electrochemical behavior,[3] as well as their application in catalysis.[4] About two decades ago, however, a new and exciting field emerged. Bipyridine and oligopyridine metal complexes serve as important structure-determining units in self-assembled supramolecular architectures, an area of study that has seen tremendous development since.[5]

Functionalized bipyridine derivatives have commonly been required for all the purposes described above. Although existing methods for the synthesis of symmetrically functionalized 2,2′-bipyridines permit the elaboration of many different derivatives,[6] the synthesis of bipyridines with differently functionalized pyridine subunits is still not common. In principle, this can mainly be achieved through two different pathways: a) monofunctionalization of 2,2′-bipyridine, which often involves multi-step procedures and/or requires rather harsh conditions,[7] or b) coupling of two different pyridine components by use of palladium- and nickel-catalyzed cross-coupling procedures such as the Stille, Suzuki, or Negishi reactions − coupling reactions generally employed for the synthesis of biaryls.[8] Most of these reactions, however, require bromides, iodides, or triflates as coupling components, and these are often not easily accessible but necessary in order to provide satisfying yields.

In the course of our studies concerning the formation of self-assembled supramolecular aggregates[9] we needed to synthesize 5-substituted 2,2′-bipyridines as ligand units capable of coordinating metal ions. We hoped to make these from more easily available and cheaper pyridyl chlorides. It appeared from the literature that, if chlorides were to be used in the coupling of two pyridine fragments, the method of choice should be the Stille reaction.[10] However, this reaction generally suffers from the need to use toxic and expensive pyridylstannanes, and in addition, did not work too well in our hands.[11] Although often attempted, including by ourselves, the Suzuki coupling reaction has seldom been successfully used in the synthesis of 2,2′-bipyridines,[12] mainly because of the evident instability of the 2-pyridylboronic acid and its esters.[13] However, some examples of the coupling of substituted pyridines in the sense of a Negishi cross-coupling reaction have been reported in the literature.[14] The use of organozinc compounds combines better transmetallation activity than obtained by use of organotin and organoboron reagents with good chemoselectivity, most of the common functional groups not being attacked by organozincs.[15] Only recently, Fraser et al. have reported a valuable Negishi coupling procedure between 2-pyridylzinc chloride and different methylpyridyl triflates to yield 3-, 4- and 5-monosubstituted 2,2′-bipyridines in excellent yields.[14e,14f] In the last three years, outstanding contributions to the transformation of unreactive aryl chlorides − especially in the area of carbon-carbon bond formation with respect to the synthesis of biaryls − have been made by Buchwald,[16] Fu,[17] and others.[18] Very recently, Fu described a general method for the palladium-catalyzed Negishi cross-coupling of aryl and vinyl chlorides with bis(tri-*tert*-butylphosphane)palladium(0) [Pd(P*t*Bu$_3$)$_2$] as a catalyst.[17e] These facts encouraged us to take this reaction a step further. Here we describe the development of a general method for the synthesis of 5-monosubstituted 2,2-bipyridines in a one-pot procedure from an organozinc pyridyl re-

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agent and several 2-chloropyridines by the palladium-catalyzed Negishi cross-coupling reaction.

Results and Discussion

Since we were especially interested in the synthesis of 5-[(trimethylsilyl)ethynyl]-2,2′-bipyridine (**2**),[6h] we began our synthetic studies by finding the optimal conditions for the desired coupling of 2-pyridylzinc chloride with 2-chloro-5-[(trimethylsilyl)ethynyl]-pyridine (**1**).[19] The synthesis of **2** had the advantage that this reaction was very suitable as a test reaction for different catalytic systems, because of the stability of the TMS-ethynyl substituent and the ease of purification of the product **2**. Therefore, lithium-bromine exchange was achieved by treatment of 2-bromopyridine with *tert*-butyllithium (*t*BuLi) at −78 °C. After transmetallation to give the corresponding pyridylzinc compound, with anhydrous zinc(II) chloride dissolved in anhydrous THF,[20] the palladium complex, the phosphane, and the 2-chloropyridine in THF were added. The reaction mixture was heated under reflux until TLC monitoring revealed no further consumption of the starting material (usually within 24 h). After aqueous workup in the presence of ethylenediaminetetraacetic acid (EDTA) to remove Zn^{II} [14e][14f] and purification by column chromatography, the desired 5-functionalized 2,2′-bipyridine was obtained.

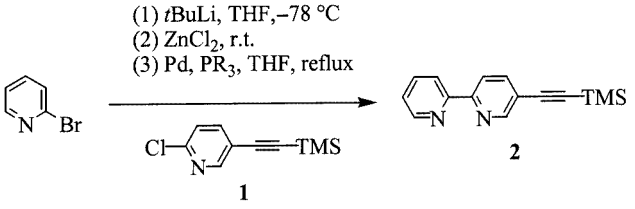
Of the different palladium/phosphane systems (Table 1) tested with respect to their efficiency in the formation of the desired 2,2-bipyridine, the use of 2 equiv. tri-*tert*-butylphosphane (tBu$_3$P) and a Pd^0 complex (Table 1, entry 4) was found to be best. It is an interesting fact that reaction conditions with a tBu$_3$P/Pd^0 ratio of 1:1 (Table 1, entry 3) gave the same yield as with 2 equiv. tBu$_3$P, indicating that a monophosphane palladium complex might be the active species in the catalytic cycle.[17e] Also noticeable is the result obtained with the Buchwald ligand 2-(di-*tert*-butylphosphanyl)biphenyl (tBu$_2$(2-biph)P)[16c] (Table 1, entry 5). As well as compound **2**, large amounts of the homocoupling product 5,5′-bis[(trimethylsilyl)ethynyl]-2,2′-bipyridine were isolated; this compound has also been used as a versatile building block in supramolecular chemistry.[6h]

With the optimized procedure established, we were now interested in whether this approach could be applied generally to the coupling of pyridylzinc compounds with 5-substituted 2-chloropyridines. We therefore tested our procedure in the synthesis of a number of different 5-functionalized 2-chloropyridines (Table 2). Although the method had its obvious limitations in the cases of primary amino- and nitro-substituted pyridines, with which either no reaction (amino compound)[21] or competing decomposition reactions (only about 5% of the nitro compound **3** could be isolated) took place, the process usually gave the desired bipyridines in good to excellent yields, of up to 90% in the case of the 5-methyl-2,2′-bipyridine **11**. Only in the case of the phenylsulfanyl-substituted bipyridine **5** were other side products formed, complicating the purification and hence lowering the isolated yield to such an extent that alternative approaches (such as starting from the amino-substituted bipyridine through a Sandmeyer reaction and subsequent substitution) seemed to be more practical. Other than **3**, in fact, only **10** has previously been reported to have been synthesized from the corresponding 5-functionalized 2-chloropyridine by means of a Stille cross-coupling reaction, although in lower yield.[10a]

It should be noted that the use of commercially available 2-pyridylzinc bromide proved to be slightly less efficient, as we were only able to obtain bipyridines **2**, **9**, and **11** in lower yields of 67%, 42%, and 55%, respectively. However, we were able to show that the preformed and isolated Pd complex Pd(PtBu$_3$)$_2$ [17e] could also be used as an equally efficient catalyst for the formation of bipyridines.

During the course of our studies we were also able to circumvent the problems associated with the amino group, by the use of a pyrrole-substituted compound. This proved

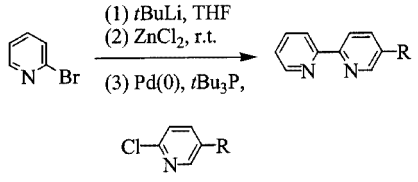
Table 1. Synthesis of 5-[(trimethylsilyl)ethynyl]-2,2′-bipyridine (**2**)

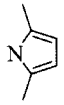


Entry	Catalytic system	mol-% Pd	Yield of 2 (%)	Recovered 1 (%)
1	$Pd(PPh_3)_2Cl_2$	8	44	25
2	Pd_2dba_3 $CHCl_3$, 8 mol % dppf	8	72	6
3	Pd_2dba_3 $CHCl_3$, 3 mol % tBu$_3$P	3	83	9
4	Pd_2dba_3 $CHCl_3$, 6 mol % tBu$_3$P	3	83[a]	2
5	Pd_2dba_3 $CHCl_3$, 6 mol % tBu$_2$(2-biph)P	3	58[b]	0

[a] As well as **1**, 9% of the homocoupling product 5,5′-bis[(trimethylsilyl)ethynyl]-2,2′-bipyridine were isolated. [b] 35% of the homocoupling product 5,5′-bis[(trimethylsilyl)ethynyl]-2,2′-bipyridine were isolated.

Table 2. Synthesis of 5-substituted 2,2′-bipyridines



Product	R	Yield (%)	Time (h)
2	C≡CSiMe$_3$	83	24
3	NO$_2$[a]	<5	24
4	NH$_2$	0[b]	24
5	SPh	< 20	24
6	OMe	72	24
7	Ph	78	22
8		72	21
9	C≡N	55	16
10	COOEt	60	18
11	Me	90	24

[a] In an earlier experiment with Pd(OAc)$_2$ + 2.5 equiv. PPh$_3$ as catalytic system, we were able to isolate 28% of **3**. This, however, was still less than we obtained from the respective Stille coupling reaction (45%).[10b,11] [b] No reaction observed.

to be an ideal protecting group for our purposes, because it was easy to prepare and the thus protected amino compound 1-(2-chloropyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole was transformed into the desired bipyridine **8** under our standard coupling conditions in a good yield of 72%. Removal of the protecting group was achieved by treatment with hydroxylamine to give the free amino compound **4** in 99% yield.

Conclusion

In conclusion, a new approach to a number of differently 5-substituted 2,2′-bipyridines by application of modified Negishi cross-coupling conditions has been found. Although this methodology has its limitations with regard to the use of pyridines bearing nitro, free amino, or sulfide groups, it nicely complements the existing synthetic procedures, especially since it can be applied to the easily available 2-chloropyridines and avoids the use of highly toxic organotin compounds.

Experimental Section

General Remarks: 2-Bromopyridine, 2-chloro-5-methylpyridine, 2-chloro-5-nitropyridine, 5-amino-2-chloropyridine, 2-chloropyridine-5-carbonitrile, 2-chloro-5-ethylnicotinate, tetrakis(triphenylphosphane)palladium(0) [Pd(PPh$_3$)$_4$], and 2-pyridylzinc bromide (0.5 M in THF) were purchased from Sigma-Aldrich Chemie GmbH or Alfa Aesar GmbH and used as received. 2-Chloro-5-[(trimethylsilyl)ethynyl]pyridine was prepared in three steps from 2-aminopyridine by a procedure published by Baxter.[19] 2-Chloro-5-methoxypyridine **6** was synthesized from 2-amino-5-iodopyridine[19] in four steps including an Ullman methoxylation according to a procedure published by Ragan et al.[22] 2-Chloro-5-phenylsulfanylpyridine was obtained from 2-chloro-5-iodopyridine[19] and thiophenol in a palladium-catalyzed reaction, but only in low yield (16%).[23] Zinc(II) chloride was dried thoroughly before use. THF was dried over, and distilled from sodium benzophenone ketyl. Tris(dibenzylideneacetone)dipalladium(0) (Pd$_2$dba$_3$·CHCl$_3$),[24] 1,1′-bis(diphenylphosphanyl)ferrocene (dppf),[25] *t*Bu$_2$(2-biph)P,[16c] and *t*Bu$_3$P[26] were prepared by published procedures. *t*BuLi solutions were purchased from Merck and were titrated prior to use against *N*-pivaloyl-*o*-toluidine.[27] All reactions were performed under argon atmospheres in oven-dried glassware by use of standard Schlenk techniques.

Thin layer chromatography was performed on aluminum TLC plates (60 F$_{254}$ silica gel) from Merck. Detection was done by UV (254 nm). Products were purified by column chromatography on 60 silica gel (70−230 mesh) from Merck. ^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform solutions on a Bruker DRX 500 spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H NMR chemical shifts are reported on the δ scale (ppm) relative to residual nondeuterated solvent as internal standard. ^{13}C NMR chemical shifts are reported on the δ scale relative to deuterated solvent as internal standard. Mass spectra were taken on a Finnegan MAT 212 instrument with an MMS data system and ISIS processing system or on a Finnigan MAT 95 with a DEC-Station 5000 data system in CI mode with isobutane as reactant gas. Elemental analyses were carried out with an EA 1108 machine from FISONS INSTRUMENTS. Melting points were measured with an SM-Lux hot-stage microscope from Leitz and are not corrected.

General Procedure for the Negishi Coupling Reaction, Demonstrated for the Synthesis of 5-[(Trimethylsilyl)ethynyl]-2,2′-bipyridine (2):[6h] *t*BuLi (1.7 M in pentane, 6.4 mL, 10.2 mmol) was added at −78 °C to 10 mL of THF. 2-Bromopyridine (0.52 mL, 5.24 mmol) was then added dropwise. After this mixture had been stirred at −78 °C for 30−45 min, a solution of anhydrous ZnCl$_2$ (1.79 g, 13.1 mmol) in 10 mL THF was added slowly, and the reaction mixture was stirred for 2−3 h at room temperature. After that time, a solution of Pd$_2$dba$_3$·CHCl$_3$ (69 mg, 3 mol % Pd), *t*Bu$_3$P (55 mg, 6 mol %), and 2-chloro-5-[(trimethylsilyl)ethynyl]pyridine[19] (950 mg, 4.8 mmol) in THF was added, and the yellow-orange reaction mixture was heated under reflux until no further consumption was observed by TLC monitoring. After the mixture had cooled to room temperature, a suspension of EDTA (10 g, 34 mmol) in water (150 mL) was added, and the resulting mixture was stirred for 15 min. After neutralization to pH 8 with saturated Na$_2$CO$_3$, the mixture was extracted several times with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, and the solvents were removed in vacuo. The pure product was obtained after column chromatography on silica gel, with petroleum ether 40:60/ethyl acetate/triethylamine (75:25:1 vv) as eluent, as a yellow solid. (0.95 g, 83%). m.p. 55−56 °C, ref. m.p. 45−46 °C.[6h] ^{1}H and ^{13}C NMR spectroscopic data were in agreement with data reported by Ziessel et al.[6h]

5-Phenylsulfanyl-2,2′-bipyridine (5): The 5-phenylsulfanyl-substituted bipyridine **5** was synthesized from 2-bromopyridine and 2-chloro-5-phenylsulfanylpyridine according to the General Procedure for **2** and obtained as a yellow solid, which was still contaminated by small amounts of impurities even after several chromatographic purification steps (62 mg, <20%). ^{1}H NMR (CDCl$_3$; 500.1 MHz): δ = 6.98 (d, *J* = 8.3 Hz, 1 H), 7.23 (ddd, *J* = 7.8,

4.9, 1.2 Hz, 1 H), 7.42−7.45 (m, 3 H), 7.61−7.62 (m, 2 H), 7.66 (dd, J = 7.8, 1.2 Hz, 1 H), 7.74 (ddd, J = 7.8, 7.8, 1.8 Hz, 1 H), 8.11 (dd, J = 8.3, 2.4 Hz, 1 H), 8.66 (dd, J = 4.9, 1.8 Hz, 1 H), 8.66 (dd, J = 2.4, 4.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$. 125.8 MHz): δ = 120.1, 121.2, 122.6, 129.2, 129.7, 130.9, 131.3, 134.9, 135.0, 136.9, 147.9, 149.1, 150.0, 154.4 ppm. HRMS: $C_{16}H_{13}N_2S$ (MH^+): calcd. 265.0799; found 265.0799.

5-Methoxy-2,2′-bipyridine (6):[7b] The 5-methoxy-substituted bipyridine **6** was prepared from 2-bromopyridine and 2-chloro-5-methoxypyridine according to the General Procedure for **2**. The pure product was obtained after column chromatography on silica gel, with ethyl acetate/triethylamine (100:1, v/v) as eluent, as a slightly yellow oil (376 mg, 72%). ^{1}H NMR ($CDCl_3$; 500.1 MHz): δ = 3.88 (s, 3 H), 7.22 (ddd, J = 7.7, 4.9, 1.1 Hz, 1 H), 7.29 (dd, J = 8.8, 2.9 Hz, 1 H), 7.76 (ddd, J = 7.7, 7.7, 1.7 Hz, 1 H), 8.29 (d, J = 7.7 Hz, 1 H), 8.33 (d, J = 8.8 Hz, 1 H), 8.35 (d, J = 2.9 Hz, 1 H), 8.61 (dd, J = 4.9, 1.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$; 125.8 MHz): δ = 55.6, 120.4, 120.9, 121.7, 122.9, 136.8, 136.9, 136.9, 148.9, 155.9, 156.1 ppm.

2-Chloro-5-phenylpyridine:[28] This precursor was prepared by means of a Suzuki coupling reaction, starting from 2-chloro-5-iodopyridine and phenylboronic acid dimethyl ester.[29] A mixture of potassium phosphate (1.64 g, 7.7 mmol), 2-chloro-5-iodopyridine (530 mg, 2.2 mmol), and $Pd(PPh_3)_4$ (127 mg, 0.11 mmol) was evacuated and flushed twice with argon. Abs. DMF (30 mL) and dimethyl phenylboronate (380 mg, 2.5 mmol) were added by syringe, and the reaction mixture was heated to 80 °C. After 12 h the mixture was allowed to cool, and diethyl ether was added. The mixture was washed with 2 N NaOH, and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with brine and dried over $MgSO_4$, and the solvent was removed in vacuo. The product was purified by column chromatography on silica gel with hexane/ethyl acetate (10:1, v/v) as eluent (337 mg, 80%). M.p. 55−56 °C, ref. m.p. 62−63 °C. ^{1}H NMR spectroscopic data were in agreement with the data reported by Yamanaka et al.[28] ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 124.2, 127.0, 128.5, 129.2, 135.7, 136.5, 137.2, 147.9, 150.3 ppm.

5-Phenyl-2,2′-bipyridine (7):[30] The 5-phenyl-substituted bipyridine **7** was prepared from 2-bromopyridine and 2-chloro-5-phenylpyridine according to the General Procedure for **2**. The pure product was obtained after column chromatography on silica gel, with petroleum ether 40:60/ethyl acetate/triethylamine (50:50:0.5, v/v) as eluent, as a beige solid (284 mg, 78%). M.p. 93 °C. ^{1}H NMR ($CDCl_3$, 500.1 MHz): δ = 7.31 (ddd, J = 7.6, 4.9, 1.2 Hz, 1 H), 7.41 (dd, J = 7.3, 1.2 Hz, 1 H), 7.49 (m, 2 H), 7.65 (m, 2 H), 7.83 (ddd, J = 7.6, 7.6, 1.8 Hz, 1 H), 8.02 (dd, J = 8.2, 2.4 Hz, 1 H), 8.45 (dd, J = 7.6, 1.2 Hz, 1 H), 8.48 (d, J = 8.2 Hz, 1 H), 8.70 (dd, J = 4.9, 1.8 Hz, 1 H), 8.92 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 121.0, 121.1, 123.7, 127.1, 128.2, 129.1, 135.3, 136.5, 137.0, 137.5, 147.6, 149.1, 154.7, 155.7 ppm. MS: m/z (%) = 233.2 (100) [MH^+].

1-(2-Chloropyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole: 5-Amino-2-chloropyridine (1 g, 7.8 mmol), 2,5-hexanedione (1.1 mL, 9.4 mmol), and *p*TsOH (15 mg, 0.08 mmol) were dissolved in toluene (15 mL) and heated in a Dean−Stark apparatus for 2 h. After cooling, the dark brown reaction mixture was washed with sat. aqueous $NaHCO_3$ solution, five times with water, and with brine. After the mixture had been dried over $MgSO_4$, the solvent was removed in vacuo. The dark residue was dried in high vacuum and was used for the coupling reaction without further purification (1.47 mg, 91%). An analytically pure sample was obtained after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (10:1:0.05, v/v) as eluent. M.p. 67−68 °C. ^{1}H NMR ($CDCl_3$, 500.1 MHz): δ = 2.04 (s, 6 H), 5.93 (s, 2 H), 7.45 (d, J = 8.3 Hz, 1 H), 7.53 (dd, J = 8.3, 2.7 Hz, 1 H), 8.29 (d, 2.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 12.9, 107.0, 124.5, 128.8, 134.6, 138.1, 148.9, 150.3 ppm. MS: m/z (%) = 207.3 (100) [MH^+]. $C_{11}H_{11}N_2Cl$ (206.67): calcd. C 63.93, H 5.36, N 13.55; found C 64.07, H 5.41, N 13.56.

1-(2,2′-Bipyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole (8): The protected 5-aminobipyridine **8** was prepared from 2-bromopyridine and 1-(2-chloropyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole by the General Procedure for **2**. The pure product was obtained after column chromatography on silica gel, with petroleum ether 40/60/ethyl acetate/triethylamine (1:1:0.05, v/v) as eluent, as a yellow solid (865 mg, 72%). M.p. 104−105 °C. ^{1}H NMR ($CDCl_3$, 500.1 MHz): δ = 2.08 (s, 6 H), 5.96 (s, 2 H), 7.35 (ddd, J = 7.6, 4.9, 1.2 Hz, 1 H), 7.68 (dd, J = 8.5, 2.5 Hz, 1 H), 7.86 (ddd, J = 7.6, 7.6, 1.8 Hz, 1 H), 8.46 (dd, J = 7.6, 1.2 Hz, 1 H), 8.55 (d, J = 8.5 Hz, 1 H), 8.57 (d, J = 2.5 Hz, 1 H), 8.71 (dd, J = 4.9, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 13.0, 106.8, 121.3, 121.3, 124.0, 128.9, 135.6, 136.3, 137.2, 148.4, 149.1, 155.0, 155.2 ppm. MS: m/z (%) = 250.2 (100) [MH^+], 172.2 (26) [$C_{10}H_{10}N_3^+$]. $C_{16}H_{15}N_3$ (249.31): calcd. C 77.08, H 6.06, N 16.85; found C 76.78, H 6.18, N 16.88.

2,2′-Bipyridin-5-amine (4):[10b] 1-(2,2′-Bipyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole (**8**, 560 mg, 2.25 mmol), hydroxylamine hydrochloride (1.6 g, 23.0 mmol), triethylamine (0.65 mL), ethanol (5 mL), and water (2.2 mL) were heated under reflux for 20 h. After cooling to room temperature, the reaction mixture was quenched by pouring into 10 mL of ice-cold 1 N HCl. This solution was washed with isopropyl ether, and the pH was adjusted to 9−10 by careful addition of 6 N NaOH. The resulting mixture was extracted several times with dichloromethane and the combined organic phases were dried over Na_2SO_4. After removal of the solvent in vacuo, the brown residue was purified on silica gel, with dichloromethane/*i*PrOH/triethylamine (70:15:15, v/v) as eluent. The pure product was obtained as a light yellow solid (380 mg, 99%). M.p. 132 °C, ref. m.p. 134−136 °C. The ^{1}H and ^{13}C NMR spectroscopic data were in agreement with the data reported by Zhang and Breslow.[10b]

2,2′-Bipyridine-5-carbonitrile (9):[7b] Bipyridine **9** was prepared from 2-bromopyridine and 2-chloropyridine-5-carbonitrile by the General Procedure for **2**. The pure product was obtained after column chromatography on silica gel, with petroleum ether 40/60/ethyl acetate/triethylamine (1:1:0.05, v/v) as eluent, and obtained as a slightly beige/yellow solid (357 mg, 55%). M.p. 148−150 °C, ref. m.p. 147−150 °C.[7b] − ^{1}H NMR ($CDCl_3$. 500.1 MHz): δ = 7.37 (dd, J = 7.7, 4.4 Hz, 1 H), 7.85 (ddd, J = 7.7, 7.7, 1.7 Hz, 1 H), 8.05 (dd, J = 8.2, 2.2 Hz, 1 H), 8.45 (d, J = 7.7 Hz, 1 H), 8.57 (d, J = 8.2 Hz, 1 H), 8.70 (dd, J = 4.4, 1.7 Hz, 1 H), 8.91 (d, J = 2.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$. 125.8 MHz): δ = 109.4, 116.9, 120.7, 122.0, 125.0, 137.2, 140.0, 149.4, 151.9, 154.0, 159.0 ppm.

Ethyl 2,2′-Bipyridine-5-carboxylate (10):[10a] The ester-substituted bipyridine **10** was isolated as an off-white solid after preparation from 2-bromopyridine and ethyl 2-chloro-5-ethylnicotinate by the General Procedure for **2**. The pure product was obtained after column chromatography on silica gel, with petroleum ether 40:60/ethyl acetate/triethylamine (2:1:0.05, v/v) as eluent (367 mg, 60%). M.p. 57−60 °C, ref. m.p. 60−61 °C.[31] The ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those published by Ghadiri et al.[10a]

5-Methyl-2,2′-bipyridine (11):[14e,14f,32] 5-Methyl-2,2-bipyridine **11** was isolated after column chromatography, with petroleum ether 40:60/ethyl acetate/triethylamine (75:25:0.5 vv) as eluent, as a pale yellow oil after preparation from 2-bromopyridine and 2-chloro-5-methylpyridine by the procedure described above for **2**. Distillation gave a colorless oil (727 mg, 90%). ^{1}H and ^{13}C NMR spectroscopic data were in agreement with the data reported by Potts et al.[32]

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