# Synthesis of Differently Disubstituted 2,2′-Bipyridines by a Modified Negishi Cross-Coupling Reaction[‡]

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*Dedicated to Prof. Dr. Manfred Weidenbruch on the occasion of his 65th birthday*

**Keywords:** Biaryls / Cross-coupling / Negishi reaction / 2,2′-Bipyridines

A general practical approach to a number of differently disubstituted 2,2′-bipyridines from substituted 2-bromo- and 2-chloropyridines by application of modified Negishi cross-coupling conditions has been developed. These 2,2′-bipyridines carry versatile functional groups that can be elaborated further, as demonstrated for some examples.


## Introduction

The synthesis of multiply substituted 2,2′-bipyridines is a process that has gained increasing importance with the extensive use of bipyridine moieties as ligands in transition metal coordination compounds, which are being found to exhibit more and more interesting characteristics.[1] These transition metal complexes are, for example, very valuable building blocks for the assembly of supramolecular[1] and macromolecular devices.[2] However, differently substituted 2,2′-bipyridines are also found in natural products such as the caerulomycins,[3] the collismycins[3b] or in the very important camptothecin and its derivatives, which are used in cancer therapy.[4] Furthermore, substituted 2,2′-bipyridines are used as ligands in a number of transition metal-catalysed reactions such as the recently found C−H-activation reactions of arenes with iridium complexes,[5] while multiply substituted chiral 2,2′-bipyridines have also been used successfully on several occasions in asymmetric synthesis, an active area of research that has been comprehensively reviewed only recently.[6]

Several methods have been applied to the synthesis of di- and polysubstituted bipyridines. One of the most widespread approaches to symmetrically substituted bipyridines is the homocoupling of halogenated pyridine precursors, often catalysed by nickel complexes.[7] Further procedures also allowing the elaboration of unsymmetrically substituted bipyridines include the Kröhnke reaction,[6,8] cyclisation reactions[9] or modification of an existing bipyridine core, often by multi-step procedures.[10] With the advent of cross-coupling reactions over the last 30 years, more and more efficient methods have been developed for the formation of aryl−aryl bonds.[11] Thus, also a growing number of syntheses containing a cross-coupling reaction as the key step for the formation of multiple substituted bipyridine fragments have been reported in the last decade. In particular, the Stille reaction has been extensively used in this context, mainly because of the stability and chemoselectivity of the organotin reagents.[12] Although examples with the Negishi cross-coupling reaction have also been reported,[1,3] there has not been any systematic investigation concerning the general applicability of organozinc reagents to the synthesis of multiply substituted bipyridines. However, with the rapid development of new and ever more efficient catalytic systems, mainly derived from palladium and sophisticated ligands such as phosphanes and carbenes, it has now become possible to use virtually any simple and easily available aryl chloride as a substrate in these reactions.[13] One example of these powerful catalysts is the palladium complex bis(tri-*tert*-butylphosphane)palladium(0) [Pd(P*t*Bu$_3$)$_2$], an established source of a catalytic system for C-C coupling reactions today thanks to the stability of the complex and its easy accessibility from [Pd$_2$dba$_3$·CHCl$_3$] and P*t*Bu$_3$.[13,14] In the meantime, investigations by Hartwig et al. have also provided more detailed information on the catalytic reaction, confirming that the actual catalytically active species derived from this palladium complex is most probably a monophosphane palladium complex.[15]

We have recently been able to show that the use of this complex in a modified Negishi coupling reaction is an excellent way in which to synthesise monosubstituted 2,2′-bipyridines from chloropyridines, with a wide variety of functional groups being tolerated.[1]

[‡] Synthesis of Substituted 2,2′-Bipyridines, 2. Part 1 Ref.[1]

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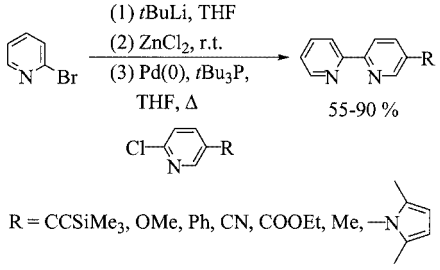



Here we would like to report on the extension of this reaction in order to show that our one-pot procedure can also be applied as a general approach to the preparation of a variety of differently disubstituted 2,2′-bipyridines from organozinc pyridyl reagents and several chloropyridines containing functional groups that also allow further derivatisation.

## Results and Discussion

The first object of our studies was the preparation of the substituted organozinc pyridyl reagent. We speculated on whether the bromopyridines used in the initial lithiation step could possibly be substituted by more easily available chloropyridines. Since alkyllithium reagents fail as lithiating agents in these cases, it appeared from the literature that the use of lithium/naphthalene might be a promising reagent for this purpose, since there has been some reported work in which this reagent has been successfully applied to the lithiation of aryl chlorides and even pyridyl chlorides, with the use either of catalytic or of stoichiometric amounts of naphthalene.[16] All our attempts with these reagents gave only unsatisfactory results, however, as we were not able to bring the lithiation of the model substrate 2-chloro-5-methylpyridine to completion, as shown by quenching experiments with $CD_3OD$, even if prolonged reaction times were used.[17]

We therefore decided to return to our initial approach and to make use of the lithiation of substituted bromopyridines with *t*-BuLi, which has been shown to be a fast and quantitative reaction.[18] Consequently, we were in need of bromopyridines with functional groups that were stable against the lithiation reagent but which could be transformed into further useful functionalities. These demands are met by the bromopyridines **1**−**3** (Figure 1), containing a methyl, a methoxy (which can be regarded as a protected hydroxy function) or an amino group, respectively, the last of these protected in the form of the very valuable pyrrole group, as first reported by Meakins et al.[19]

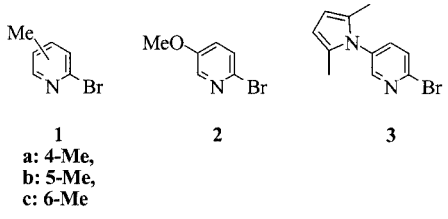
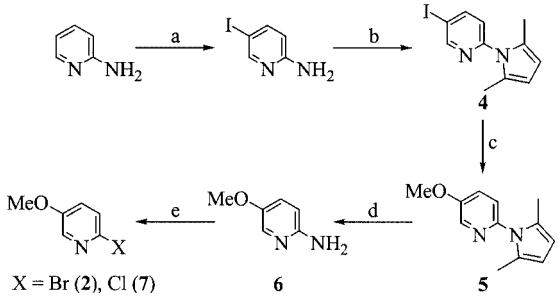



Figure 1. 2-Bromopyridines

While compounds **1** and **3** are commercially available or easy to prepare in a simple protection step, for compound **2** we had to develop a new synthesis, starting from 2-aminopyridine (Scheme 1). The synthesis was achieved starting with the well known electrophilic iodination of 2-aminopyridine,[20] followed by Ragan's procedure for the protection/deprotection sequence of the amino group, and an Ullman methoxylation, each in good to very good yields.[21] This sequence was especially advantageous not only because of the high yields but also because of the ease of preparation, since none of these steps requires tedious purification procedures such as column chromatography, and the resulting 2-amino-5-methoxypyridine (**6**) could easily be isolated by distillation. The subsequent Sandmeyer halogenations could be performed through known or slightly modified procedures.[22]




Scheme 1. Preparation of methoxy-substituted pyridyl halides from 2-aminopyridine: (a) $HIO_4 \cdot 2\,H_2O$, $I_2$, $CH_3COOH$, $H_2O$, concd. $H_2SO_4$, 68%; (b) 2,5-hexanedione, *p*TsOH, toluene, reflux, 2 h, 83%; (c) NaOMe, CuCl, MeOH, DMF, 80°C, 2 h, 96%; (d) $HONH_2 \cdot HCl$, $Et_3N$, EtOH, $H_2O$, reflux, 20 h, 81%; (e) for **2**: HBr (62%), $Br_2$, −10 °C, then $NaNO_2$, −5 °C to room temp., 69%; for **7**: concd. HCl, −5 °C, then $NaNO_2$, CuCl, 0 °C to room temp., 70 °C; 50%

As substituted chloropyridines we chose compounds **7**−**17** as shown in Figure 2, which carry functional groups interesting either because of their intrinsic properties, e. g. with regard to solubility, or because of their potential for further derivatisation. Most of these are either commercially available (**9**, **13**, and **16**, for example) or are relatively

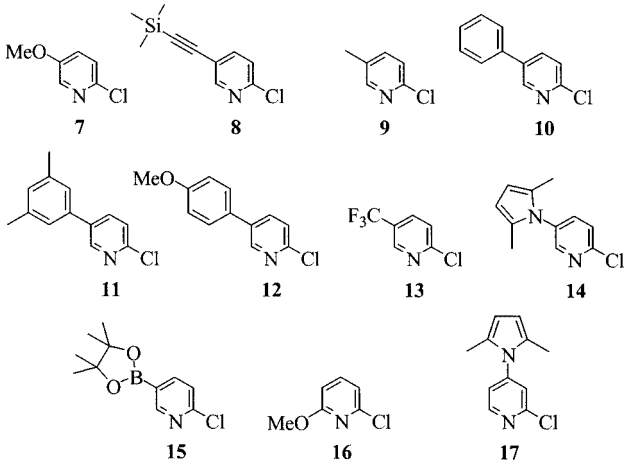
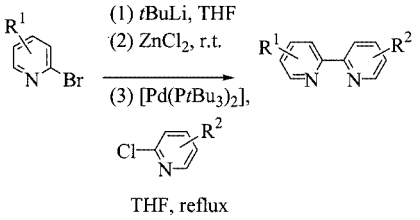



Figure 2. 2-Chloropyridines used as coupling partners for cross-coupling reactions

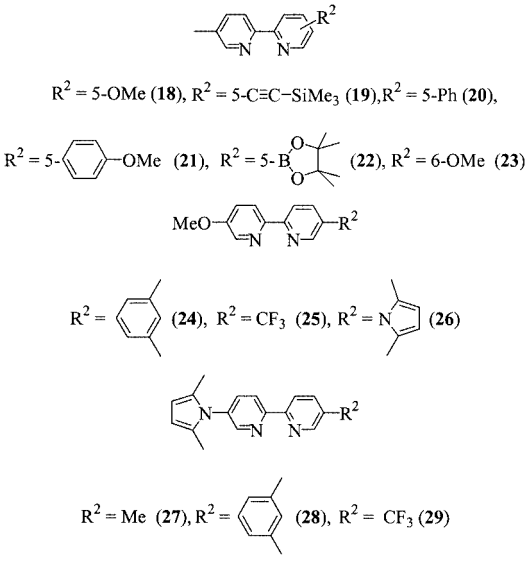
  

easy to prepare. For the aryl-substituted chloropyridines **11** and **12**, regioselective Suzuki reactions between 2-chloro-5-iodopyridine and the appropriate aryl boronic acids were developed, giving the desired coupling products in good yields.

Table 1. Synthesis of disubstituted 2,2′-bipyridines




| Product | Bromopyridine | Chloropyridine | Yield (%) |
|---|---|---|---|
| **18** | **1b** | **7** | 56 |
| **19** | **1b** | **8** | 77 |
| **20** | **1b** | **10** | 71 |
| **21** | **1b** | **12** | 46 |
| **22** | **1b** | **15** | 0[a] |
| **23** | **1b** | **16** | 85 |
| **24** | **2** | **11** | 72 |
| **25** | **2** | **13** | 55 |
| **26** | **2** | **14** | 60[b] |
| **27** | **3** | **9** | 77 |
| **28** | **3** | **11** | 42 |
| **29** | **3** | **13** | [c] |




[a] NMR and MS experiments indicated the formation of the desired product **22**, but all attempts to isolate it by column chromatography failed. [b] If the reaction was performed starting from bromopyridine **3** and chloropyridine **7**, the yield was lower (ca. 50%) and the obtained coupling product still contained impurities even after repeated chromatographic purification. [c] The product was isolated as an inseparable 2:1 mixture together with the homocoupling product 5,5′-bis(trifluoromethyl)-2,2′-bipyridine.[24]

With these compounds in hands, we started to set up a number of cross-coupling reactions with 5-substituted 2-bromopyridines, using 3 mol-% [Pd(P*t*Bu$_3$)$_2$] (Table 1).[23] Although the method has its obvious limitations in the case of the boronic ester-functionalized pyridine **15**, with which we were able to prove the formation of the corresponding bipyridine **22** by NMR and MS investigations of the crude product mixture but failed to isolate either the desired product or the corresponding deprotected boronic acid, the process usually gave the desired 2,2′-bipyridines in good to very good yields, up to 85% in the case of the 6-methoxy-5-methyl-2,2′-bipyridine (**23**) after column chromatography on silica gel (Table 1). Only in the case of the pyrrole- and trifluoromethyl-substituted bipyridine **29** did we face the problem of obtaining the desired compound only as an inseparable 2:1 mixture together with the bis(trifluoromethyl)-substituted homocoupling product, whereas the formation of homocoupling products was not observed in significant amounts in the other cases.

As already shown for the monosubstituted bipyridine,[1] the pyrrole protecting group can readily be removed by treatment with hydroxylamine, as we were able to demonstrate with the pyrrole-protected, methoxy-substituted bipyridine **26**, and the corresponding free amine **30**.

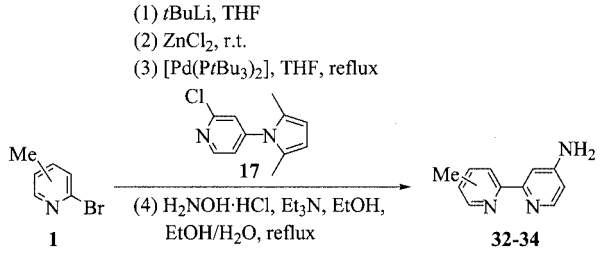
The above deprotection strategy, however, also enabled us to circumvent the problems associated with the purification of bipyridines containing pyrrole substituents through the removal of the protective group from the crude cross-coupling product mixture obtained after filtration through a short column of silica. This caused a substantial change in the chromatographic behaviour and allowed the isolation of amino-substituted bipyridines, thought to represent desirable starting materials for further transformations anyway. This could be demonstrated for compound **29**, with which the removal of the pyrrole group furnished free amine **31**, which could be separated from the homocoupling product, yielding 16% of the deprotected coupling product **31** over two steps.

In order to extend the scope of the reaction further, we used bromopyridines **1**, each with a methyl group in the 4-, 5- or 6-position, respectively, for the preparation of the transmetallation reagent and chloropyridine **17**, possessing a pyrrole group in the 4-position, as partners for the coupling reaction (Table 2). In each case the expected coupling products could be isolated and identified by NMR and MS techniques, but we were again facing the problem that the isolated products still contained some level of impurities, which could not even be removed by repeated column chromatography with different eluents. We thus again changed our strategy to that used above for the isolation of free amine **31**. By doing so, we were able to isolate the desired bipyridines **32**−**34** as pure products in acceptable yields.

All of these bipyridines provide valuable functional groups that can be addressed selectively and offer numerous possibilities for further derivatisation. In some representative reactions we were able, for instance, to perform a lithium-mediated alkylation to give **35**[25] and a lithium-mediated silylation to yield **36**, followed by a subsequent

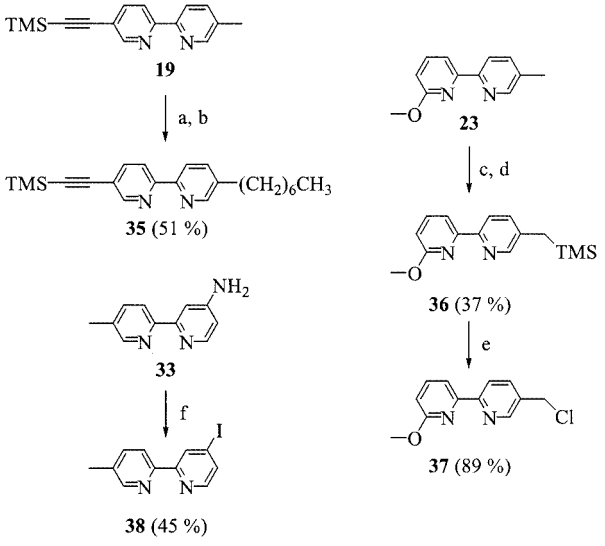
Table 2. Synthesis of disubstituted 2,2′-bipyridines containing a 4-amino group




| Product | Bromopyridine | Chloropyridine | Yield (%)[a] |
|---|---|---|---|
| **32** | **1a** | **17** | 47 |
| **33** | **1b** | **17** | 28 |
| **34** | **1c** | **17** | 45 |

[a] Isolated overall yields after both steps.

chlorination to **37**, each starting from methyl groups. The last two transformations were performed by use of a procedure published by Fraser et al.[26] We were also able to achieve an iodination through a Sandmeyer reaction of **33**, resulting in the further elaborated bipyridine **38** (Scheme 2).




Scheme 2. Further functionalisation of cross-coupled 2,2′-bipyridines: (a) THF, LDA, −78 °C to 0 °C; (b) hexyl iodide, room temp.; (c) THF, LDA, −78 °C to 0 °C; d) TMSCl, 0 °C; (e) CsF, $C_2Cl_6$, $CH_3CN$, 60 °C; (f) $NaNO_2$, 4 N $H_2SO_4$, $H_2O$, −10 °C, then KI, −10 °C to 80 °C

## Conclusion

In conclusion, we have presented a versatile approach to a number of differently disubstituted 2,2′-bipyridines starting from easily available pyridyl bromides and chlorides by application of modified Negishi cross-coupling conditions. This methodology is almost generally applicable to the synthesis of valuable difunctionalised bipyridines that can be further derivatised in manifold ways.

## Experimental Section

**General Remarks:** 2-Bromo-4-methylpyridine (**1a**), 2-bromo-5-methylpyridine (**1b**), 2-bromo-6-methylpyridine (**1c**), 4-amino-2-chloropyridine, 2-chloro-5-methylpyridine (**9**), 2-chloro-5-(trifluoromethyl)pyridine (**13**), 2-chloro-6-methoxypyridine (**16**), (3,5-dimethylphenyl)boronic acid, and (4-methoxyphenyl)boronic acid were purchased from Sigma−Aldrich Chemie GmbH or Alfa Aesar GmbH and were used as received. The syntheses of 2-chloro-5-phenylpyridine (**10**), 1-(2-chloropyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole (**14**) and 2-chloro-5-[(trimethylsilyl)ethynyl]pyridine[12c] (**8**) have already been mentioned in our preceding paper.[1] The synthesis of the required 5-amino-2-bromopyridine for the preparation of compound **3** started with the bromination of the commercially available 2-hydroxy-5-nitropyridine with $PBr_5$ or $PBr_3/Br_2$, followed by reduction of the nitro group with iron in acetic acid.[27] The synthesis of 2-bromo-5-methoxypyridine (**2**) from 2-amino-5-methoxypyridine (**6**) was performed by the procedure described by Leeson and Emmett.[28] 2-(2-Chloropyridine-5-yl)-4,4′,5,5′-tetramethyl-1,3-dioxaborolane (**15**) was prepared by a method recently published by Rault et al.[29] Zinc(II) chloride was dried thoroughly before use. THF was dried with and distilled from sodium benzophenone ketyl. The complex $[Pd(PtBu_3)_2]$ was prepared from $[Pd_2dba_3{\cdot}CHCl_3]$ and $PtBu_3$ by a method published by Fu et al.[14] *t*BuLi solutions were purchased from Merck or Sigma−Aldrich Chemie GmbH and were titrated prior to use against *N*-pivaloyl-*o*-toluidine.[30] Reactions with air- and moisture-sensitive transition metal compounds were performed under an argon atmosphere in oven-dried glassware by use of standard Schlenk techniques.

Thin layer chromatography was performed on Merck aluminum TLC plates (60 $F_{254}$ silica gel). Detection was done with UV light (254 nm). Products were purified by column chromatography on Merck silica gel 60 (70−230 mesh). $^1H$ and $^{13}C$ NMR spectra were recorded in deuterated chloroform or dimethyl sulfoxide solutions on a Bruker Avance 500 spectrometer at 300 K at 500.1 and 125.8 MHz, respectively. $^{19}F$ NMR spectra were recorded on a Bruker Avance 300 spectrometer in deuterated chloroform at 300 K at 282.4 MHz. $^1H$ NMR chemical shifts are reported on the δ scale in ppm relative to residual nondeuterated solvent as internal standards. $^{13}C$ NMR chemical shifts are reported on the δ scale in ppm relative to deuterated solvent as internal standard. $^{19}F$ NMR chemical shifts are reported on the δ scale in ppm relative to $CCl_3F$ as external standard. Mass spectra were measured on a Finnigan-MAT 212 instrument with MMS data system and ISIS processing system or on a Finnigan MAT 95 with DEC-Station 5000 data system in EI or CI mode with isobutane as reactant gas. Melting points were measured with a Leitz SM-Lux hot-stage microscope and are not corrected.

### Synthesis of Substituted Bromo- and Chloropyridines

**General Procedure for the Protection of Amines as Pyrroles, Demonstrated for 1-(2-Bromopyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole (3):** 5-Amino-2-bromopyridine[27] (2 g, 11.6 mmol), 2,5-hexanedione (1.65 mL, 14.0 mmol), and *p*TsOH (23 mg, 0.08 mmol) were dissolved in toluene (10 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 with $MgSO_4$, the

solvent was removed in vacuo. The dark residue was dried under high vacuum and was used for the coupling reaction without further purification (2.68 g, 92%). An analytically pure sample was obtained after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (3:1:0.02 v/v) as eluent. M.p. 72−74 °C. $^1$H NMR ($CDCl_3$. 500.1 MHz): δ = 2.03 (s, 6 H), 5.93 (s, 2 H), 7.42 (dd, *J* = 8.2, 2.7 Hz, 1 H), 7.60 (d, *J* = 8.2 Hz, 1 H), 8.28 (d, 2.7 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$. 125.8 MHz): δ = 12.9, 107.1, 128.4, 128.7, 135.0, 137.9, 140.7, 149.4 ppm. MS (CI): *m*/*z* (%) = 250.9 (100) [$MH^+$, $^{79}$Br], 252.9 (75) [$MH^+$, $^{81}$Br]. $C_{11}H_{11}N_2Br$ (251.12): calcd. C 52.61, H 4.42, N 11.16; found C 52.92, H 4.51, N 11.13.

**1-(2-Chloropyridin-4-yl)-2,5-dimethyl-1*H*-pyrrole (17):** The *N*-protected chloropyridine **17** was prepared by the General Procedure as used for **3**, from 4-amino-2-chloropyridine (2 g, 15.6 mmol) and 2,5-hexanedione (2.2 mL, 18.8 mmol), and was obtained as a red-brown solid (3.01 g, 93%) after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (3:1:0.02 v/v) as eluent. M.p. 107 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.03 (s, 6 H), 5.93 (s, 2 H), 7.42 (dd, *J* = 8.2, 2.7 Hz, 1 H), 7.60 (d, *J* = 8.2 Hz, 1 H), 8.28 (d, 2.7 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 13.1, 108.0, 121.5, 123.1, 128.3, 148.7, 150.4, 152.3 ppm. MS (CI): *m*/*z* (%) = 129.1 (100) [$MH^+ - C_6H_8$, $^{35}$Cl], 131.1 (23) [$MH^+ - C_6H_8$, $^{37}$Cl], 221.2 (92) [$M^+ + CH_4$, $^{35}$Cl], 223.2 (21) [$M^+ + CH_4$, $^{35}$Cl]. $C_{11}H_{11}N_2Cl$ (206.67): calcd. C 63.93, H 5.36, N 13.55; found C 64.09, H 5.49, N 13.33.

**1-(5-Iodopyridin-2-yl)-2,5-dimethyl-1*H*-pyrrole (4):** The *N*-protected iodopyridine **4** was synthesised from 2-amino-5-iodopyridine[20] (7 g, 31.8 mmol) and 2,5-hexanedione (4.5 mL, 38.2 mmol) by the General Procedure as used for **3**. The product was isolated as a dark brown solid (7.91 g, 83%), which was used without further purification. An analytically pure sample was obtained after column chromatography on silica gel with hexane/ethyl acetate (1:1 v/v) as eluent. M.p. 118−119 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.13 (s, 6 H), 5.89 (s, 2 H), 7.01 (d, *J* = 8.2 Hz, 1 H), 8.09 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.79 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 13.2, 90.9, 107.4, 123.5, 128.5, 146.1, 151.2, 155.4 ppm. MS (CI): *m*/*z* (%) = 299.1 (100) [$MH^+$]. $C_{11}H_{11}N_2I$ (298.12): calcd. C 44.32, H 3.72, N 9.40; found C 44.48, H 3.59, N 9.16.

**1-(5-Methoxypyridin-2-yl)-2,5-dimethyl-1*H*-pyrrole (5):** 1-(5-Iodopyridin-2-yl)-2,5-dimethyl-1*H*-pyrrole (**4**, 7.5 g, 25.2 mmol), sodium methoxide (4.08 g, 75.6 mmol), and copper(I) chloride (376 mg, 3.8 mmol) were suspended in a mixture of dry methanol (30 mL) and dry DMF (20 mL) and heated to 80 °C for 2 h. After the mixture had cooled, diisopropyl ether (50 mL), an aq. solution of $NH_4Cl$ (5%, 25 mL), and water (35 mL) were added, and the mixture was stirred overnight. Afterwards the solids were filtered off over celite and the filtrate was extracted several times with dichloromethane. The combined organic phases were washed with a 10% aq. $NH_4OH$ solution and filtered through silica gel. The filtrate was dried with $Na_2SO_4$ and the solvents were removed in vacuo. After drying in high vacuum the product was isolated as a dark solid, which was pure enough to be used directly for the next step. Further purification could be carried out by column chromatography on silica gel with hexane/ethyl acetate (1:1 v/v) as eluent (4.91 g, 96%). M.p. 75 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.08 (s, 6 H), 3.91 (s, 3 H), 5.87 (s, 2 H), 7.15 (d, *J* = 8.7 Hz, 1 H), 7.32 (dd, *J* = 8.7, 3.0 Hz, 1 H), 8.27 (d, *J* = 3.0 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 12.9, 55.8, 106.2, 122.3, 122.4, 128.6, 136.2, 145.0, 154.7 ppm. MS (CI): *m*/*z* (%) = 203.2 (100) [$MH^+$]. $C_{12}H_{14}N_2O$ (202.25): calcd. C 71.26, H 6.98, N 13.85; found C 71.63, H 6.92, N 13.90.

**2-Amino-5-methoxypyridine (6):**[22] A mixture of 1-(5-methoxypyridin-2-yl)-2,5-dimethyl-1*H*-pyrrole (**8**, 3.5 g, 17.3 mmol), hydroxylamine hydrochloride (12.02 g, 173 mmol), triethylamine (4.8 mL, 34.6 mmol), ethanol (30 mL), and water (15 mL) was heated at reflux for 20 h. The cooled solution was quenched with cold HCl (50 mL), washed with diisopropyl ether, and the pH was adjusted to 9−10 with 6 N NaOH. The resulting mixture was extracted several times with dichloromethane. The combined organic phases were dried with $K_2CO_3$ and the solvent was removed in vacuo. The oily residue was distilled in high vacuum to yield the product as a slightly yellow oil (1.75 g, 81%). $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 3.74 (s, 3 H), 4.45 (br. s, 2 H), 6.45 (d, *J* = 8.8 Hz, 1 H), 7.07 (dd, *J* = 8.8, 3.3 Hz, 1 H), 7.72 (d, *J* = 3.3 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 56.3, 109.5, 125.9, 132.8, 149.4, 152.9 ppm. MS (CI): *m*/*z* (%) = 125.2 (100) [$MH^+$].

**2-Chloro-5-methoxypyridine (7):**[22] 2-Amino-5-methoxypyridine (**6**, 895 mg, 7.2 mmol) was dissolved in concd. HCl (20 mL) and the system was cooled to ca. −5 °C. A solution of sodium nitrite (600 mg, 8.7 mmol) in water (4 mL) was slowly added, the temperature being kept under 0 °C. After completion the reaction mixture was briefly stirred, and a precooled solution of copper(I) chloride (1 g, 10.1 mmol) in concd. HCl (8 mL) was then added. The stirring was continued for 30 min at 0 °C, then for 2 h at room temperature and for a short period of time at 70 °C. After cooling to room temperature again, the mixture was hydrolysed with water (50 mL) and extracted several times with dichloromethane. The organic phases were combined, washed with water and sat. aq. $NaHCO_3$ solution, dried with $Na_2SO_4$, and concentrated in vacuo. The residue was purified by distillation and the product was obtained as a bright yellow oil (514 mg, 50%). $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 3.83 (s, 3 H), 7.16 (dd, *J* = 8.7, 3.1 Hz, 1 H), 7.21 (d, *J* = 8.7 Hz, 1 H), 8.03 (d, *J* = 3.1 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 56.0, 124.4, 124.4, 136.1, 142.5, 155.0 ppm. MS (CI): *m*/*z* (%) = 144.1 (100) [$MH^+$, $^{35}$Cl], 146.1 (37) [$MH^+$, $^{37}$Cl].

**2-Chloro-5-(3,5-dimethylphenyl)pyridine (11):** For the Suzuki coupling reaction, 2-chloro-5-iodopyridine (1.45 g, 6.1 mmol), (3,5-dimethylphenyl)boronic acid (1 g, 6.7 mmol), potassium fluoride (1.16 g, 20 mmol), and [Pd(P*t*Bu$_3$)$_2$] (85 mg, 2.5 mol %) were repeatedly evacuated and flushed with argon in a Schlenk flask. THF (5 mL) was then added and the black suspension was heated at reflux until TLC monitoring showed no further consumption of the starting material. The now brightly yellow coloured suspension was allowed to cool to room temperature and was then diluted with diethyl ether, filtered through celite, and the solvents were evaporated in vacuo. Column chromatography on silica gel with hexane/ethyl acetate (20:1 v/v) as eluent gave the pure pyridine as a white solid (866 mg, 64%). M.p. 54 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.38 (s, 6 H), 7.05 (s, 1 H), 7.14 (s, 2 H), 7.36 (d, *J* = 8.2 Hz, 1 H), 7.80 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.57 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 21.3, 124.0, 124.9, 130.1, 135.9, 136.4, 137.1, 138.8, 148.0, 150.1 ppm. MS (CI): *m*/*z* (%) = 218.2 (100) [$MH^+$, $^{35}$Cl], 220.3 (40) [$MH^+$, $^{37}$Cl]. $C_{13}H_{12}ClN$ (217.70): calcd. C 71.72, H 5.56, N 6.43; found C 71.21, H 5.53, N 6.07.

**2-Chloro-5-(4-methoxyphenyl)pyridine (12):** 2-Chloro-5-iodopyridine (1.43 g, 6.0 mmol) and (4-methoxyphenyl)boronic acid (1 g, 6.6 mmol) were coupled in the same way as described above for **11**. The product was obtained as a white solid after column chromatography on silica with hexane/ethyl acetate/triethylamine (2:1:0.15 v/

v) as eluent (920 mg, 70%). M.p. 124 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 3.84 (s, 3 H), 6.99 (m, 2 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 7.46 (m, 2 H), 7.77 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.55 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 55.4, 114.7, 124.1, 128.1, 128.9, 135.3, 136.7, 147.6, 149.6, 160.0 ppm. MS (CI): *m*/*z* (%) = 220.0 (100) [$MH^+$, $^{35}$Cl], 222.0 (33) [$MH^+$, $^{37}$Cl]. $C_{12}H_{10}ClNO$ (219.67): calcd. C 65.61, H 4.59, N 6.38; found C 66.04, H 4.63, N 6.37.

**Synthesis of Disubstituted 2,2′-Bipyridines**

**General Procedure for Negishi Coupling Reactions with Substituted Pyridine Derivatives, Demonstrated for the Synthesis of 5-Methyl-5′-[(trimethylsilyl)ethynyl]-2,2′-bipyridine (19):** *t*BuLi (1.7 M in pentane, 1.9 mL, 2.82 mmol) was added to abs. THF (8 mL) at −78 °C. Subsequently, a solution of 2-bromo-5-methylpyridine (**1b**, 250 mg, 1.45 mmol) in abs. THF (2 mL) was added dropwise. After the mixture had been stirred at −78 °C for 30−45 min, a solution of anhydrous $ZnCl_2$ (494 mg, 3.63 mmol) in abs. THF (5 mL) was added slowly and the reaction mixture was stirred for 2−3 h at room temperature. After that time a solution of [Pd(P*t*Bu$_3$)$_2$] (19 mg, 0.038 mmol, 3 mol % Pd) and 2-chloro-5-[(trimethylsilyl)ethynyl]pyridine (**8**, 264 mg, 1.29 mmol) in abs. THF (5 mL) was added and the reaction mixture was heated at reflux until no further consumption was observed by TLC monitoring. After cooling to room temperature, a suspension of EDTA (3 g, 10.3 mmol) in water (60 mL) was added and the resulting mixture was stirred for 15 min. After neutralisation to pH 8 with saturated $Na_2CO_3$, the mixture was extracted several times with dichloromethane, dried with $Na_2SO_4$, and the solvents were removed in vacuo. The pure product was obtained after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (10:1:0.05 v/v) as eluent, as a pale yellow solid (265 mg, 77%). M.p. 106−107 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 0.27 (s, 9 H), 2.39 (s, 3 H), 7.65 (d, *J* = 7.7 Hz, 1 H), 7.85 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.31 (d, *J* = 7.7 Hz, 1 H), 8.37 (d, *J* = 8.2 Hz, 1 H), 8.51 (s, 1 H), 8.70 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = −0.2, 18.4, 98.9, 101.9, 119.8, 119.9, 121.0, 133.8, 137.6, 139.7, 149.6, 152.0, 152.8, 155.0 ppm. MS (CI): *m*/*z* (%) = 267.2 (100) [$MH^+$]. HRMS (EI): $C_{16}H_{18}N_2Si$ ($M^{\cdot+}$): calcd. 266.1239; found 266.1243. $C_{16}H_{18}N_2Si$ (266.41): calcd. C 72.13, H 6.81, N 10.52; found C 72.47, H 6.99, N 10.24.

**5-Methoxy-5′-methyl-2,2′-bipyridine (18):** The disubstituted bipyridine **18** was prepared from 2-bromo-5-methylpyridine (**1b**, 500 mg, 2.9 mmol) and 2-chloro-5-methoxypyridine (**7**, 378 mg, 2.6 mmol) according to the General Procedure as used for **19**. The pure product was obtained after column chromatography on silica with hexane/ethyl acetate/triethylamine (2:1:0.15 v/v) as eluent, as a slightly yellow syrup (289 mg, 56%). $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.35 (s, 3 H), 3.88 (s, 3 H), 7.28 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.57 (dd, *J* = 8.2, 1.7 Hz, 1 H), 8.11 (d, *J* = 8.2 Hz, 1 H), 8.28 (d, *J* = 8.8 Hz, 1 H), 8.33 (d, *J* = 2.7 Hz, 1 H), 8.44 (d, *J* = 1.7 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 18.2, 55.6, 120.0, 121.0, 121.4, 132.5, 136.8, 137.5, 149.0, 149.3, 153.4, 155.9 ppm. MS (CI): *m*/*z* (%) = 201.3 (100) [$MH^+$]. HRMS (EI): $C_{12}H_{12}N_2O$ ($M^{\cdot+}$): calcd. 200.0950; found 200.0958.

**5-Methyl-5′-phenyl-2,2′-bipyridine (20):** The disubstituted bipyridine **20** was synthesised from 2-bromo-5-methylpyridine (**1b**, 250 mg, 1.45 mmol) and 2-chloro-5-phenylpyridine (**10**, 245 mg, 1.29 mmol) following the General Procedure as used for **19** and obtained after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (3:1:0.02 v/v), as a pale yellow solid (226 mg, 71%). M.p. 105−106 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.40 (s, 3 H), 7.40 (m, 1 H), 7.48 (m, 2 H) 7.64 (dd, *J* = 7.7 Hz, 2 H), 7.65 (d, *J* = 8.2 Hz, 1 H), 8.01 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.34 (d, *J* = 8.2 Hz, 1 H), 8.46 (d, *J* = 8.2 Hz, 1 H), 8.52 (s, 1 H), 8.90 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 18.4, 120.8, 120.8, 127.0, 127.0, 128.2, 129.1, 133.6, 135.3, 136.3, 137.6, 137.8, 147.5, 149.4, 153.3, 155.0 ppm. MS (CI): *m*/*z* (%) = 247.3 (100) [$MH^+$]. HRMS (EI): $C_{17}H_{14}N_2$ ($M^{\cdot+}$): calcd. 246.1157; found 246.1160. $C_{17}H_{14}N_2$ (246.31): calcd. C 82.90, H 5.73, N 11.37; found C 82.94, H 5.79, N 11.39.

**5-(4-Methoxyphenyl)-5′-methyl-2,2′-bipyridine (21):** The desired product was obtained from 2-bromo-5-methylpyridine (**1b**, 500 mg, 2.9 mmol) and 2-chloro-5-(4-methoxyphenyl)pyridine (**12**, 580 mg, 2.6 mmol) by the General Procedure as used for **19**. After column chromatography on silica with petroleum ether 40:60/ethyl acetate/triethylamine (2:1:0.15 v/v) as eluent, **21** was isolated as a bright yellow solid (335 mg, 46%). M.p. 134−135 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 1.84 (s, 3 H), 3.31 (s, 3 H), 6.76 (m, 2 H), 7.10 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.25 (m, 2 H), 7.59 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.50 (d, *J* = 2.2 Hz, 1 H), 8.77 (d, *J* = 8.2 Hz, 1 H), 8.85 (d, *J* = 8.2 Hz, 1 H), 9.01 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 17.6, 54.4, 114.4, 120.4, 120.5, 128.0, 130.2, 132.8, 134.2, 135.7, 136.8, 147.2, 149.6, 154.0, 154.9, 159.8 ppm. MS (CI): *m*/*z* (%) = 277.3 (100) [$MH^+$]. $C_{18}H_{16}N_2O$ (276.34): calcd. C 78.24, H 5.84, N 10.14; found C 78.69, H 6.03, N 9.77.

**6-Methoxy-5′-methyl-2,2′-bipyridine (23):** Treatment of 2-bromo-5-methylpyridine (**1b**, 500 mg, 2.9 mmol) and 2-chloro-6-methoxypyridine (**16**, 378 mg, 2.6 mmol) according to the General Procedure as used for **19** gave **23** as a bright yellow, syrupy substance (447 mg, 85%) after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (2:1:0.15 v/v) as eluent. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.37 (s, 3 H), 4.02 (s, 3 H), 6.73 (d, *J* = 7.7 Hz, 1 H), 7.58 (dd, *J* = 7.7, 1.7 Hz, 1 H), 7.67 (dd, *J* = 7.7, 7.7 Hz, 1 H), 7.96 (d, *J* = 7.7 Hz, 1 H), 8.28 (d, *J* = 7.7 Hz, 1 H), 8.47 (d, *J* = 1.7 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 18.3, 53.2, 110.6, 113.3, 120.5, 133.1, 137.2, 139.3, 149.5, 153.6, 153.6, 163.5 ppm. MS (CI): *m*/*z* (%) = 201.3 (100) [$MH^+$]. HRMS (CI): $C_{12}H_{13}N_2O$ [$MH^+$]: calcd. 201.1028; found 201.1027. $C_{12}H_{12}N_2O$ (200.24): calcd. C 71.98, H 6.04, N 13.99; found C 71.52, H 6.48, N 13.58.

**5-(3,5-Dimethylphenyl)-5′-methoxy-2,2′-bipyridine (24):** 2-Bromo-5-methoxypyridine (**2**, 500 mg, 2.7 mmol) and 2-chloro-5-(3,5-dimethylphenyl)pyridine (**11**, 525 mg, 2.4 mmol) were treated following the General Procedure as used for **19**, and the resulting disubstituted bipyridine **24** was isolated as a yellow solid (404 mg, 57%) after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (2:1:0.15 vv). M.p. 78−80 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.39 (s, 6 H), 3.91 (s, 3 H), 7.04 (s, 1 H), 7.24 (s, 2 H), 7.32 (dd, *J* = 8.2, 3.3 Hz, 1 H), 7.96 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.35 (d, *J* = 8.2 Hz, 1 H), 8.38 (m, 2 H), 8.84 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 21.4, 55.6, 120.2, 120.9, 121.6, 124.9, 129.7, 135.2, 135.9, 137.0, 137.7, 138.6, 147.5, 148.8, 154.6, 156.0 ppm. MS (CI): *m*/*z* (%) = 291.3 (100) [$MH^+$]. HRMS (EI): $C_{19}H_{18}N_2O$ ($M^{\cdot+}$): calcd. 290.1419; found 290.1419.

**5-Methoxy-5′-(trifluoromethyl)-2,2′-bipyridine (25):** The disubstituted bipyridine **25** was prepared from 2-bromo-5-methoxypyridine (**2**, 500 mg, 2.7 mmol) and 2-chloro-5-(trifluoromethyl)pyridine (**13**, 439 mg, 2.4 mmol) according to the General Procedure as used for **19**. The pure product was obtained as a yellow solid after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (2:1:0.15 v/v) as eluent (320 mg, 52%). M.p. 89−91 °C.

$^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 3.92 (s, 3 H), 7.32 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.98 (dd, *J* = 8.8, 2.2 Hz, 1 H), 8.37 (d, *J* = 2.7 Hz, 1 H), 8.40 (d, *J* = 8.8 Hz, 1 H), 8.45 (d, *J* = 8.8 Hz, 1 H), 8.86 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 55.7, 119.9, 120.7, 122.4, 123.8 (*J* = 272 Hz), 125.4 (*J* = 33 Hz), 133.9 (*J* = 4 Hz), 137.4, 146.0 (*J* = 4 Hz), 147.4, 156.7, 159.1 ppm. $^{19}$F NMR ($CDCl_3$, 282.4 MHz): δ = −62.3 ppm. MS (CI): *m/z* (%) = 255.2 (100) [$MH^+$]. HRMS (CI): $C_{12}H_{10}F_3N_2O$ [$MH^+$]: calcd. 255.0745; found 255.0739.

**1-(5′-Methoxy-2,2′-bipyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole (26):** The disubstituted bipyridine **23** was prepared from 2-bromo-5-methoxypyridine (**2**, 500 mg, 2.7 mmol) and 1-(2-chloropyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole (**14**, 500 mg, 2.4 mmol) by the General Procedure as used for **19**, and was obtained as a yellow solid (405 mg, 60%) after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (5:1:0.03 v/v) as eluent. M.p. 118−119 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.07 (s, 6 H), 3.93 (s, 3 H), 5.95 (s, 2 H), 7.34 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.64 (dd, *J* = 8.2, 2.7 Hz, 1 H), 8.38 (m, 2 H), 8.44 (d, *J* = 8.2 Hz, 1 H), 8.52 (d, *J* = 2.7 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 13.0, 55.7, 106.6, 120.5, 120.9, 121.8, 129.0, 134.8, 136.2, 137.1, 148.1, 148.2, 155.1, 156.3 ppm. MS (CI): *m/z* (%) = 280.3 (100) [$MH^+$]. $C_{17}H_{17}N_3O$ (279.34): calcd. C 73.10, H 6.13, N 15.04; found C 73.56, H 6.30, N 15.06.

**1-(5′-Methyl-2,2′-bipyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole (27):** Compound **27** was prepared from 1-(2-bromopyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole (**3**, 364 mg, 1.45 mmol) and 2-chloro-5-methylpyridine (**9**, 165 mg, 1.29 mmol) by the General Procedure as used for **19** and isolated after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (3:1:0.02 v/v) as a pale yellow solid (262 mg, 77%). M.p. 100−101 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.08 (s, 6 H), 2.41 (s, 3 H), 5.95 (s, 2 H), 7.65 (m, 2 H), 8.31 (d, *J* = 8.2 Hz, 1 H), 8.49 (d, *J* = 8.3 Hz, 1 H), 8.52 (m, 1 H), 8.54 (d, *J* = 2.1 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 18.0, 18.4, 106.7, 120.7, 120.9, 129.0, 133.8, 135.2, 136.3, 137.6, 148.3, 149.8, 152.8, 155.4 ppm. MS (CI): *m/z* (%) = 263.8 (100) [$MH^+$]. HRMS (EI): $C_{17}H_{17}N_3$ ($M^{\cdot+}$): calcd. 263.1422; found 263.1423. $C_{17}H_{17}N_3$ (263.34): calcd. C 77.54, H 6.51, N 15.96; found C 78.11, H 6.57, N 15.65.

**1-[5′-(3,5-Dimethylphenyl)-2,2′-bipyridin-5-yl]-2,5-dimethyl-1*H*-pyrrole (28):** Compound **28** was prepared from 1-(2-bromopyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole (**3**, 408 mg, 1.6 mmol) and 2-chloro-5-(3,5-dimethylphenyl)-pyridine (**11**, 280 mg, 1.5 mmol) by the General Procedure as used for **19** and was obtained as a yellow solid (225 mg, 42%) after column chromatography on silica gel with hexane/ethyl acetate (10:1 vv). M.p. 106−107 °C $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.10 (s, 6 H), 2.42 (s, 6 H), 5.97 (s, 2 H), 7.08 (s, 1 H), 7.28 (s, 2 H), 7.69 (dd, *J* = 8.2, 2.7 Hz, 1 H), 8.03 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.49 (d, *J* = 8.2 Hz, 1 H), 8.58 (m, 2 H), 8.92 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 13.0, 21.4, 106.8, 121.1, 121.2, 125.0, 129.0, 130.0, 135.4, 135.5, 136.3, 137.0, 137.3, 138.8, 147.8, 148.4, 153.8, 154.9 ppm. MS (CI): *m/z* (%) = 354.3 (100) [$MH^+$]. HRMS (CI): $C_{24}H_{24}N_3$ [$MH^+$]: calcd. 354.1970; found 354.1920. $C_{24}H_{23}N_3 \cdot 1/2H_2O$ (353.46 + 1/2 × 18.01 = 362.47): calcd. C 79.53, H 6.67, N 11.59; found C 79.35, H 6.71, N 11.36.

**General Procedure for the Removal of the Pyrrole Protecting Group from Protected Aminobipyridines, Demonstrated for 5-Amino-5′-methoxy-2,2′-bipyridine (30):** 1-(5′-Methoxy-2,2′-bipyridin-5-yl)-2,5-dimethyl-1*H*-pyrrole (**26**, 182 mg, 0.65 mmol), hydroxylamine hydrochloride (910 mg, 13.0 mmol, 20 equiv.), triethylamine (0.4 mL), ethanol (6 mL), and water (1.6 mL) were heated at reflux until TLC monitoring revealed complete consumption of the starting material (usually after 20 h). After cooling to room temperature the reaction mixture was quenched by pouring into 10 mL of ice-cold 1 N HCl. The resulting 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 with $Na_2SO_4$. After removal of the solvent in vacuo, the brown residue was subjected to column chromatography on silica with dichloromethane/MeOH/triethylamine (3:1:0.04 v/v) as eluent. The pure product was obtained as a yellow solid (122 mg, 93% yield). M.p. 139−140 °C. $^1$H NMR ([$D_6$]DMSO, 500.1 MHz): δ = 3.84 (s, 3 H), 5.66 (br. s, 2 H), 7.01 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.41 (dd, *J* = 8.8, 2.8 Hz, 1 H), 7.97 (d, *J* = 8.8 Hz, 1 H), 7.98 (d, *J* = 2.7 Hz, 1 H), 8.11 (d, *J* = 8.8 Hz, 1 H), 8.25 (d, *J* = 2.8 Hz, 1 H). $^{13}$C NMR ([$D_6$]DMSO, 125.8 MHz): δ = 55.5, 119.4, 120.2, 120.6, 121.3, 135.1, 136.1, 143.3, 144.8, 149.0, 154.6. MS (CI): *m/z* (%) = 202.5 (100) [$MH^+$]. $C_{11}H_{11}N_3O \cdot 1/3\ H_2O$ (201.22 + 1/3 × 18.01 = 207.22): calcd. C 63.75, H 5.67, N 20.28; found C 63.99, H 5.60, N 20.24.

**5-Amino-5′-(trifluoromethyl)-2,2′-bipyridine (31):** The removal of the pyrrole group from crude 1-[5′-(trifluoromethyl)-2,2′-bipyridin-5-yl]-2,5-dimethyl-1*H*-pyrrole (**29**, approx. 300 mg, approx. 0.9 mmol) − obtained as an inseparable 2:1 mixture together with homocoupling product 5,5′-bis(trifluoromethyl)-2,2′-bipyridine from the reaction of pyrrole **3** (500 mg, 2.7 mmol) with chloropyridine **13** (439 mg, 2.4 mmol) according to the General Procedure as used for **19** − was accomplished by the General Procedure as used for **30** and gave the pure product as an orange-brown solid (89 mg, 16% over both reaction steps) after purification by column chromatography on silica gel with hexane/dichloromethane/MeOH (4:4:1 v/v) as eluent. M.p. 102−104 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 3.90 (br. s, 2 H), 7.09 (dd, *J* = 8.2, 2.7 Hz, 1 H), 7.95 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.15 (d, *J* = 2.7 Hz, 1 H), 8.26 (d, *J* = 8.2 Hz, 1 H), 8.38 (d, *J* = 8.2 Hz, 1 H), 8.83 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 119.3, 121.7, 122.4, 123.9 (*J* = 273 Hz), 128.9 (*J* = 33 Hz), 133.7 (*J* = 4 Hz), 136.6, 143.6, 145.3, 145.9 (*J* = 4 Hz), 159.5 ppm. $^{19}$F NMR ($CDCl_3$, 282.4 MHz): δ = −62.2. MS (CI): *m/z* (%) = 240.1 (100) [$MH^+$]. HRMS (EI): $C_{11}H_8F_3N_3$ ($M^{\cdot+}$): calcd. 239.0670; found 239.0660.

**4-Amino-4′-methyl-2,2′-bipyridine (32):** Bromopyridine **1a** (500 mg, 2.9 mmol) and pyrrole **17** (545 mg, 2.6 mmol) were reacted following the General Procedure as used for **19**. Deprotection of crude 1-(4′-methyl-2,2′-bipyridin-4-yl)-2,5-dimethyl-1*H*-pyrrole (580 mg, approx. 2.2 mmol), which was obtained after filtration of the cross-coupling reaction product mixture through a short column of silica with hexane/ethyl acetate/triethylamine (5:2:0.2 v/v) as eluent by the General Procedure as used for **30**, gave **32** as a light yellow solid (232 mg, 47% yield over both the coupling and the deprotection step) after column chromatography on silica with dichloromethane/MeOH (2:1 v/v) as eluent. M.p. 199−201 °C. $^1$H NMR ([$D_6$]DMSO, 500.1 MHz): δ = 2.37 (s, 3 H), 6.20 (br. s, 2 H), 6.52 (dd, *J* = 6.0, 2.2 Hz, 1 H), 7.20 (d, *J* = 4.4 Hz, 1 H), 7.61 (d, *J* = 2.2 Hz, 1 H), 8.09 (d, *J* = 6.0 Hz, 1 H), 8.15 (s, 1 H), 8.46 (d, *J* = 4.4 Hz, 1 H). $^{13}$C NMR ([$D_6$]DMSO, 125.8 MHz): δ = 20.7, 105.7, 108.9, 121.1, 124.4, 147.4, 148.6, 148.9, 155.1, 155.3, 155.7. MS (CI): *m/z* (%) = 186.4 (100) [$MH^+$]. − $C_{11}H_{11}N_3 \cdot 1/3\ H_2O$ (185.23 + 1/3 × 18.01 = 191.23): calcd. C 69.09, H 6.15, N 21.97; found C 68.88, H 6.14, N 21.35.

**4-Amino-5′-methyl-2,2′-bipyridine (33):** Crude 1-(5′-methyl-2,2′-bipyridin-4-yl)-2,5-dimethyl-1*H*-pyrrole (327 mg, approx. 1.2 mmol)

was obtained from the reaction of bromopyridine **1b** (500 mg, 2.9 mmol) with pyrrole **17** (545 mg, 2.6 mmol) following the General Procedure as used for **19**, after filtration of the cross-coupling reaction product mixture through a short column of silica with hexane/ethyl acetate/triethylamine (5:1:0.3 v/v) as eluent. Deprotection of the pyrrole according to the General Procedure as used for **30** gave **33** as a white solid (136 mg, 28% over both reaction steps) after column chromatography on silica gel with dichloromethane/MeOH (2:1 v/v) as eluent. M.p. 148−150 °C. $^1$H NMR ([D$_6$]DMSO, 500.1 MHz): δ = 2.33 (s, 3 H), 6.17 (br. s, 2 H), 6.50 (dd, *J* = 5.5, 2.2 Hz, 1 H), 7.58 (d, *J* = 2.2 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 1 H), 8.07 (d, *J* = 5.5 Hz, 1 H), 8.19 (d, *J* = 8.2 Hz, 1 H), 8.45 (s, 1 H) ppm. $^{13}$C NMR ([D$_6$]DMSO, 125.8 MHz): δ = 17.7, 105.1, 108.8, 119.8, 132.9, 137.2, 148.9, 149.1, 153.3, 155.1, 155.2 ppm. MS (CI): *m*/*z* (%) = 186.4 (100) [MH$^+$]. HRMS (EI): $C_{11}H_{11}N_3$ (M$^{\cdot+}$): calcd. 185.0953; found 185.0953. $C_{11}H_{11}N_3$·1/2 $H_2O$ (185.23 + 1/2 × 18.01 = 194.24): calcd. C 68.02, H 6.23, N 21.63; found C 67.73, H 5.93, N 21.05.

**4-Amino-6′-methyl-2,2′-bipyridine (34):** Crude 1-(6′-methyl-2,2′-bipyridin-4-yl)-2,5-dimethyl-1*H*-pyrrole (540 mg, approx. 2.1 mmol) was obtained from treatment of bromopyridine **1c** (500 mg, 2.9 mmol) and pyrrole **17** (545 mg, 2.6 mmol) by the General Procedure as used for **19**, after filtration of the cross-coupling reaction product mixture through a short column of silica with hexane/ethyl acetate/triethylamine (5:2:0.2 v/v) as eluent. Deprotection of the pyrrole by the General Procedure as used for **30** gave the pure product as a white solid (220 mg, 45% over both reaction steps) after column chromatography on silica gel with dichloromethane/MeOH (2:1 v/v) as eluent. M.p. 136−138 °C. $^1$H NMR ([D$_6$]DMSO, 500.1 MHz): δ = 2.54 (s, 3 H), 6.40 (br. s, 2 H), 6.54 (dd, *J* = 5.5, 2.2 Hz, 1 H), 7.26 (d, *J* = 7.7 Hz, 1 H), 7.60 (d, *J* = 2.2 Hz, 1 H), 7.76 (dd, *J* = 7.7, 7.7 Hz, 1 H), 8.07 (d, *J* = 5.5 Hz, 1 H), 8.09 (d, *J* = 7.7 Hz, 1 H) ppm. $^{13}$C NMR ([D$_6$]DMSO, 125.8 MHz): δ = 24.2, 105.4, 108.9, 117.4, 122.9, 137.0, 149.0, 155.2, 155.3, 155.4, 157.0 ppm. MS (CI): *m*/*z* (%) = 186.4 (100) [MH$^+$]. $C_{11}H_{11}N_3$·2/3 $H_2O$ (185.23 + 2/3 × 18.01 = 197.24): calcd. C 66.98, H 6.30, N 21.30; found C 67.31, H 6.11, N 21.29.

**5-Heptyl-5′-[(trimethylsilyl)ethynyl]-2,2′-bipyridine (35):** A solution of 5-methyl-5′-[(trimethylsilyl)ethynyl]-2,2′-bipyridine (**19**, 150 mg, 0.56 mmol) in abs. THF (2 mL) was added by syringe at −78 °C to a solution of lithium diisopropylamide, previously prepared from diisopropylamine (83 μL, 0.59 mmol) and *n*BuLi (1.55 M in hexane, 380 μL, 0.59 mmol) in abs. THF (6 mL) at −78 °C. The reaction mixture was allowed to warm up to 0 °C, and hexyl iodide (87 μL, 0.59 mmol) was added. The mixture was allowed to warm to room temperature and was stirred for 48 h. The solvent was removed and the residue was partitioned in a mixture of water and dichloromethane. The phases were separated and the aqueous phase was extracted repeatedly with dichloromethane. The combined organic phases were dried with $MgSO_4$, the solvent was removed in vacuo, and the product was isolated after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (20:1:0.05 v/v) as eluent as a waxy compound (100 mg, 51%). $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 0.27 (s, 9 H), 0.87 (s, 3 H), 1.29 (m, 8 H), 1.64 (m, 2 H), 2.64 (t, *J* = 7.6 Hz, 2 H), 7.63 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.84 (dd, *J* = 8.2, 2.1 Hz, 1 H), 8.31 (d, *J* = 8.2 Hz, 1 H), 8.34 (d, *J* = 8.2 Hz, 1 H), 8.49 (d, *J* = 1.8 Hz, 1 H), 8.71 (d, *J* = 2.1 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = −2.0, 14.0, 22.6, 29.0, 31.0, 31.7, 32.9, 99.0, 101.9, 119.9, 120.0, 121.2, 137.1, 138.8, 139.8, 149.1, 152.0, 152.8, 154.7 ppm. MS (CI): *m*/*z* (%) = 350.8 (100) [MH$^+$]. HRMS (EI): $C_{22}H_{30}N_2Si$ (M$^{\cdot+}$): calcd. 350.2178; found 350.2183.

**6-Methoxy-5′-[(trimethylsilyl)methyl]-2,2′-bipyridine (36):** *n*BuLi (0.86 mL, 1.44 M in hexane, 1.25 mmol) was added by syringe to a solution of diisopropylamine (0.18 mL, 1.25 mmol) in abs. THF (5 mL) at −78 °C. The solution was stirred for 10 min, allowed to warm to room temperature and cooled again to −78 °C. Subsequently, a solution of 6-methoxy-5′-methyl-2,2′-bipyridine (**24**, 200 mg, 1 mmol) in abs. THF (5 mL) was added dropwise by syringe. After the mixture had been stirred for 1 h at −78 °C, trimethylsilyl chloride (0.16 mL, 1.25 mmol) was added quickly to the reaction mixture and after further 5 min the reaction was quenched by addition of ethanol (2 mL). The reaction mixture was poured into a flask containing sat. aq. $NaHCO_3$ solution and then extracted three times with dichloromethane. The combined organic phases were washed with brine, dried with $Na_2SO_4$, and the solvents were evaporated in vacuo. Purification by column chromatography on silica gel with hexane/ethyl acetate (10:1 v/v) as eluent gave the product as a colourless oil (100 mg, 37%). $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 0.03 (s, 9 H), 2.11 (s, 2 H), 4.03 (s, 3 H), 6.72 (d, *J* = 8.2 Hz, 1 H), 7.43 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.67 (dd, *J* = 8.2, 7.7 Hz, 1 H), 7.96 (d, *J* = 7.7 Hz, 1 H), 8.27 (d, *J* = 8.2 Hz, 1 H), 8.33 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = −2.0, 24.0, 53.2, 110.4, 113.1, 120.5, 136.0, 136.5, 139.3, 148.3, 153.6, 163.5 ppm. MS (CI): *m*/*z* (%) = 273.1 (100) [MH$^+$]. HRMS (EI): $C_{15}H_{20}N_2OSi$ (M$^{\cdot+}$): calcd. 272.1345; found 272.1345.

**5-Chloromethyl-6′-methoxy-2,2′-bipyridine (37):** 6-Methoxy-5′-[(trimethylsilyl)methyl]-2,2′-bipyridine (**36**, 80 mg, 0.29 mmol), perchloroethane (142 mg, 0.6 mmol), and caesium fluoride (91 mg, 0.6 mmol) were placed in a Schlenk flask and repeatedly evacuated and flushed with argon. After addition of abs. acetonitrile (5 mL), the mixture was heated to 60 °C for 3.5 h. After cooling, the reaction solution was quenched with water and ethyl acetate. The phases were separated and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were dried with $Na_2SO_4$ and the solvent was removed in vacuo. The product (79 mg, 89%) was obtained as a bright yellow solid after column chromatography on silica gel with hexane/ethyl acetate/triethylamine (2:1:0.15 v/v) as eluent. M.p. 56−57 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 4.03 (s, 3 H), 4.63 (s, 2 H), 6.78 (d, *J* = 8.2 Hz, 1 H), 7.69 (dd, *J* = 8.2, 7.1 Hz, 1 H), 7.83 (dd, *J* = 8.2, 2.2 Hz, 1 H), 8.00 (d, *J* = 7.1 Hz, 1 H), 8.40 (d, *J* = 8.2 Hz, 1 H), 8.64 (d, *J* = 2.2 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 43.1, 53.2, 111.4, 114.0, 120.9, 132.9, 137.1, 139.4, 148.8, 152.1, 153.6, 163.5 ppm. MS (CI): *m*/*z* (%) = 235.1 (100) [MH$^+$, $^{35}$Cl], 237.1 (32) [MH$^+$, $^{37}$Cl]. HRMS (CI): $C_{12}H_{12}N_2ClO$ [MH$^+$]: calcd. 235.0638; found 235.0637. $C_{12}H_{11}ClN_2O$ (234.68): calcd. C 61.41, H 4.72, N 11.94; found C 61.78, H 5.07, N 11.50.

**4-Iodo-5′-methyl-2,2′-bipyridine (38):** A solution of sodium nitrite (39 mg, 0.6 mmol) in water (1.2 mL) was cooled to −10 °C and a solution of 4-amino-5′-methyl-2,2′-bipyridine (**33**, 80 mg, 0.4 mmol) in 4 N $H_2SO_4$ (4 mL) was added slowly, so that the temperature did not exceed −5 °C. Subsequently, a solution of potassium iodide (642 mg, 3.9 mmol) in water (0.5 mL) was also added slowly. After stirring at this temperature for 30 min and for another 45 min at room temperature, the reaction mixture was heated to 80 °C for 1 h. After cooling to room temperature the mixture was neutralised with sat. $NaHCO_3$ and extracted five times with dichloromethane. The combined organic phases were washed twice with sat. aq. $Na_2S_2O_3$ solution, then with water, dried with $Na_2SO_4$, and the solvents were evaporated in vacuo. Purification by column chromatography on silica gel with hexane/ethyl acetate/triethylamine (2:1:0.15 v/v) gave the pure product (57 mg, 45%). M.p.

76−78 °C. $^1$H NMR ($CDCl_3$, 500.1 MHz): δ = 2.38 (s, 3 H), 7.61 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.64 (dd, *J* = 5.0, 1.1 Hz, 1 H), 8.25 (d, *J* = 7.7 Hz, 1 H), 8.28 (d, *J* = 5.0 Hz, 1 H), 8.48 (d, *J* = 1.1 Hz, 1 H), 8.78 (d, *J* = 1.1 Hz, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 125.8 MHz): δ = 18.4, 106.6, 121.1, 130.3, 132.6, 134.3, 137.9, 149.2, 149.4, 151.8, 156.4 ppm. MS (CI): *m/z* (%) = 297.1 (100) [$MH^+$]. HRMS (EI): $C_{11}H_9N_2I$ ($M^{\cdot+}$): calcd. 295.9810; found 295.9812. $C_{11}H_9N_2I$ (296.11): calcd. C 44.62, H 3.06, N 9.46; found C 44.08, H 2.58, N 9.20.

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[17] The best result we were able to obtain was the formation of 5-methyl-5′-[(trimethylsilyl)ethynyl]-2,2′-bipyridine (**19**) in 45% yield after lithiation of our model substrate 2-chloro-5-methylpyridine (**9**) with 2 equiv. of lithium and 4 equiv. of naphthalene, transmetallation with anhydrous zinc(II) chloride and subsequent palladium-catalysed cross-coupling reaction with 2-chloro-5-[(trimethylsilyl)ethynyl]-pyridine (**8**). However, the very long reaction time, which was found to be essential, residual unreacted lithium, which possibly interferes in the cross-coupling step, and also the excess of naphthalene caused problems during the isolation and purification of the product.
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wald's $Pd_2dba_3$·$CHCl_3$/P(2-biph)$t$Bu$_2$ system (27% yield of **18** besides some unidentified by-products) proved to be effective when employed under otherwise identical conditions in a 3 mol-% Pd scale. As in our preceding study, only $Pd_2dba_3$·$CHCl_3$/dppf proved to be similarly effective in this context (65% yield of **18**). Interestingly, an increase in the amount of Pd to 10 mol-% [Pd(P$t$Bu$_3$)$_2$] did not result in a significantly higher yield but actually gave **18** only in a slightly lower yield of 49%: [23a] M. Beller, H. Fischer, W. A. Herrmann, K. Öfele, C. Broßmer, *Angew. Chem.* **1995**, *107*, 1992−1993; *Angew. Chem. Int. Ed. Engl.* **1995**, *107*, 1989−1992. [23b] W. A. Herrmann, C. Broßmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989−1992; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844−1847.

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