Synthesis of Amino-Functionalized 2,2′-Bipyridines

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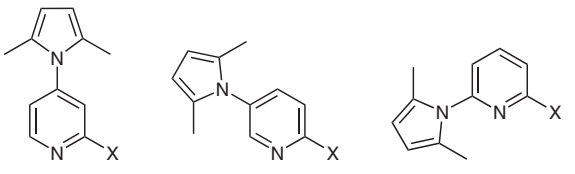
Abstract: Amino-functionalized 2,2′-bipyridines are versatile building blocks for the synthesis of sophisticated chelating ligands with the 2,2′-bipyridine core. The 4-, 5-, and 6-substituted 2-chloro- and 2-bromopyridine building blocks were prepared and coupled to symmetrically and non-symmetrically diamino-functionalized compounds by homo- and cross-coupling procedures. Further transformations were carried out to demonstrate the synthetic versatility of these compounds and the employed procedures.

Key words: cross-coupling reactions, bipyridine, palladium, protecting group, amines

Bipyridines, especially 2,2′-bipyridines, are one of the most widely applied classes of ligands for the construction of metal complexes and they have found broad application, notably in supramolecular chemistry, photochemistry, and catalysis.[1] Nature also uses this building block in a number of naturally occurring substances.[2] Newkome and Schubert et al. have extensively reviewed the numerous methods for the synthesis of symmetrically as well as non-symmetrically substituted 2,2′-bipyridines that have emerged in recent years;[3] non-symmetrically substituted ligand systems could give access to more advanced applications and may lead to novel ideas for their use in future applications. In particular, cross-coupling reactions have become established in recent years as an efficient tool for the construction of a number of different bipyridine cores, replacing previous, frequently multistep, procedures. Recently, we described a convenient access to the bipyridine framework via modified Negishi cross-coupling reactions to a series of mono- and variously disubstituted bipyridines with a broad spectra of functional groups, exploring the synthetic depth of this approach.[4] Herein, we would like to report on the extension of this methodology to the synthesis of novel amino-functionalized 2,2′-bipyridines with subsequent transformations to other functionalities.

The amino group, in general, is one of the central functional groups and can act as a chemical all-rounder; in particular, it can act as a precursor for other functional groups such as halides, imines, amides, etc. Thus, amination reactions have attracted much interest over the last decade.[5] The synthesis of diamino-substituted 2,2′-bipyridines, however, has thus far only been established for symmetrical examples, involving conventional multistep procedures and metal-catalyzed reactions.[6] Recently, we presented a new homo-coupling approach to 5,5′-diamino-substituted 2,2′-bipyridine, an interesting building block for the construction of helicates.[7] The expansion of this concept to the 4,4′- and 6,6′-isomers will be presented in this paper. The 4,5′-, 4,6′- and 5,6′-substituted congeners, however, are still missing comparable efficient synthetic entries and have not been previously synthesized. In all cases the choice of the protecting group is crucial for the coupling step and subsequent transformations. Previously we utilized the easily installed and deprotected pyrrole group as an efficient tool for the protection of the amino groups in Negishi cross-coupling reactions.[4] The complete series of 4-, 5-, and 6-pyrrole-substituted 2-halopyridines as chloro and bromo derivatives can be efficiently prepared, generally in excellent yields, by the known reaction of the free amine with hexane-2,5-dione in toluene (Figure 1).[4]



1a X = Cl
1b X = Br

2a X = Cl
2b X = Br

3a X = Cl
3b X = Br

Figure 1 Protected amino-substituted halopyridines as building blocks for the synthesis of diamino-2,2′-bipyridines

In our original homo-coupling protocol the nickel complex, dibromobis(triphenylphosphine)nickel(II) [$NiBr_2(PPh_3)_2$] was used together with zinc powder and tetraethylammonium iodide.[7] This catalyst system gave the protected 5,5′-diamino-2,2′-bipyridine (**8**) from **2a** in 85% yield.

The modification of this protocol by the supplementary addition of lithium chloride resulted in an improved performance of the homo-coupling reaction, exemplified for the synthesis of **5** (85% yield without vs. 94% yield with LiCl as additive).[8] Therefore, using the pyrrole-protected chloropyridines **1a** or **2a** the products **4** and **5** were isolated in very high to quantitative yields (Scheme 1). However, **3a** was somewhat less stable than the other chlorides, thus, we used the respective bromide **3b** instead; Iyoda et al. were able to demonstrate that bromides are equally well suited to homo-coupling reactions under similar con-

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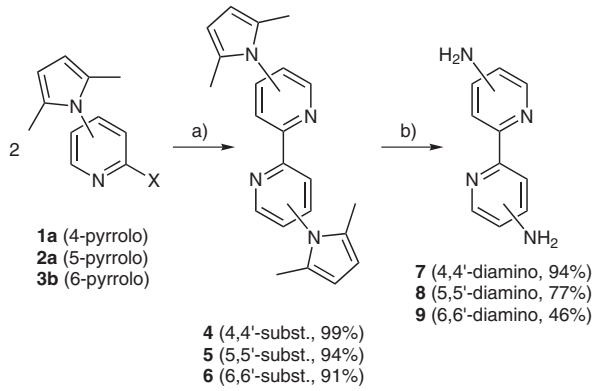
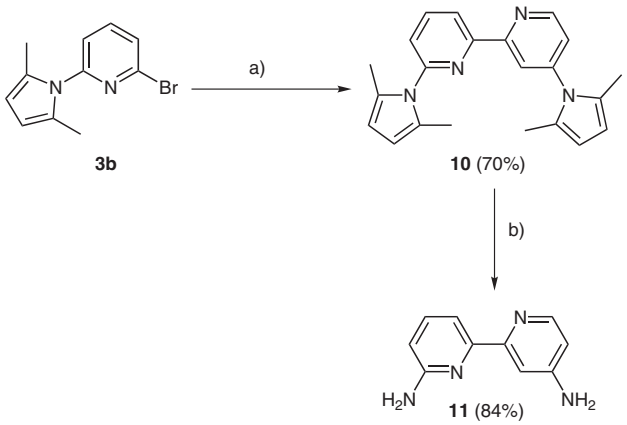


Scheme 1 Synthesis of symmetrical diamino-2,2′-bipyridines by homo-coupling reactions. *Reagents and conditions*: (a) $NiBr_2(PPh_3)_2$, Zn powder, LiCl, *n*-Bu_4NI, heat; (b) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, H_2O, heat.



Scheme 2 Synthesis of non-symmetrically substituted diamino-2,2′-bipyridines via the Negishi cross-coupling reaction, exemplified for the preparation of **10** and **11**. *Reagents and conditions*: (a) *t*-BuLi, THF, –78 °C then $ZnCl_2$, r.t. then **1a**, Pd(P*t*-$Bu_3)_2$, THF, heat; (b) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, H_2O, heat.

ditions.[9] In fact, using **3b** in this reaction gave the desired protected bipyridine **6** also in very good yield.

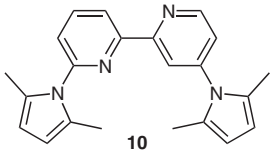
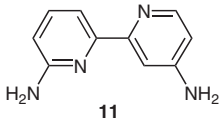
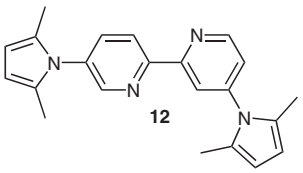
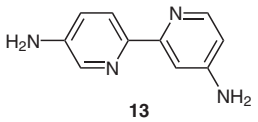
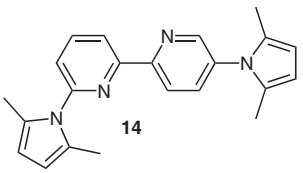
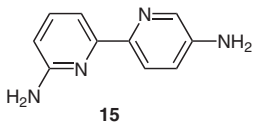
The protected bipyridines **4**, **5**, and **6** can easily be deprotected by a standard procedure to yield the free diamines in good to excellent yields.[7] This approach conveniently delivers diaminobipyridine building blocks, which can be imagined to have a wide variety of areas of application, especially in supramolecular chemistry.[10]

For the synthesis of non-symmetrically substituted diamino-2,2′-bipyridines, we employed our established cross-coupling approach. As already reported the pyrrole group easily allows the preparation of the corresponding 2-organozinc reagents from 2-bromopyridines.[4b] The starting compounds **1b**, **2b**, or **3b** were lithiated using *tert*-butyllithium for lithiation and zinc chloride for the transmetalation, giving the respective organozinc species. The appropriate chloro derivative **1a**, **2a**, or **3a** was then added together with the palladium catalyst and the resulting solution was heated in tetrahydrofuran to yield the bipyridine product after workup, which was then deprotected following the usual protocol (Scheme 2).

In order to identify the most favorable combination of starting materials, we examined the reactions using both the chloride and the bromide of the coupling partners with their appropriate counterparts (Table 1).

These results clearly demonstrate that **3a** is not really suited for these purposes because it is the by far least reactive and least stable compound of this series (Table 1, entries 2 and 6). In fact **3a** only gave the desired coupling product **15** when reacted with the most reactive bromo compound

Table 1 Synthesis of the Protected and Unprotected Diamino-2,2′-bipyridines by Negishi Cross-Coupling Reactions and Subsequent Deprotection

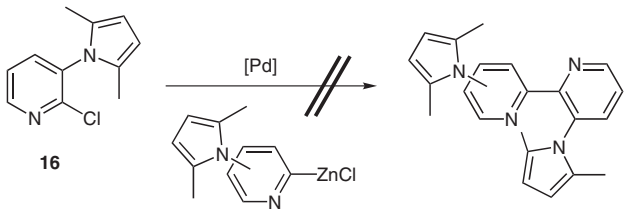
Entry	Chloropyridine	Bromopyridine	Cross-coupling product	Yield (%)	Diaminobipyridine	Yield (%)
1	**1a**	**3b**	 **10**	70	 **11**	84
2	**3a**	**1b**		0[a]		
3	**1a**	**2b**	 **12**	75	 **13**	30[b]
4	**2a**	**1b**		61		
5	**2a**	**3b**	 **14**	68	 **15**	61
6	**3a**	**2b**		38		

[a] Only dehalogenated 4-pyrrolopyridine derived from **1b** was isolated.
[b] Low yield due to isolation problems during the purification process.

2b but did not yield any coupling product **11** when reacted with **1b**.

However, employing the matching pairs **1a** and **3b**, **1a** and **2b**, or **2a** and **3b** (Table 1, entries 1, 3, and 5) gave the desired protected diamino-bipyridines **10**, **12**, and **14** in 68–75% yield, which were subsequently deprotected to give the non-symmetrically substituted diamino-2,2′-bipyridines **11**, **13**, and **15**.

For reasons of curiosity we also attempted the coupling reaction of the 3-pyrrole-substituted chloropyridine **16** with a pyridinylzinc reagent, but it was not a surprise that these attempts were unsuccessful and no coupling product was isolated. It is reasonable to assume that in the 3-position and *ortho* to the proposed new bond, high steric hindrance is exerted by the pyrrole group thus preventing formation of the final bond. The starting chloropyridine **16** was isolated unchanged in nearly quantitative yield (Scheme 3).

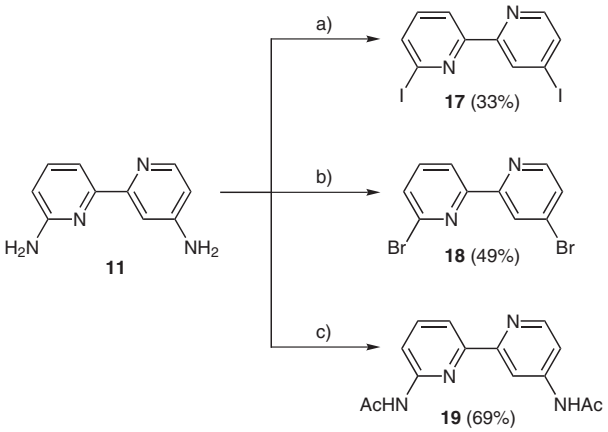


Scheme 3 Attempted synthesis of 3-pyrrole-substituted 2,2′-bipyridines

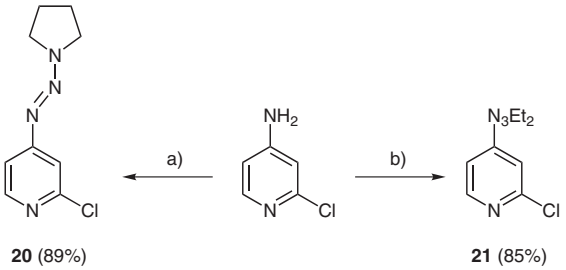
To demonstrate the versatility of the prepared diamino-2,2′-bipyridines for further transformations, we chose **11** for subsequent elaboration. Some of the most interesting and important derivatives of the bipyridines are halides, especially as precursor compounds for the construction of more complex structures.

Bromination as well as iodination were evaluated as possible transformations (Scheme 4). At first glance, it would appear that the yields could be improved, however, it must be considered that these are dihalogenations, and, for example, for the iodination each single step gave at least a yield of around 60% to account for an overall yield for the two-step process of 33% for the diiodide **17**. The bromination of **11** gave even better results and the dibromide **18** was isolated with 49% yield, which would translate into a yield of 70% for each of the bromination steps. The synthesis of these sophisticated bipyridines bearing bromide and iodide substituents in different positions at each ring requires only four steps from commercially available amines and gives access to highly interesting building blocks for subsequent functionalizations. The last derivatization reaction of diamine **11** was the acetylation with acetyl chloride in pyridine, affording the diacetamide **19** in good yield (69%, Scheme 4).

Finally, we investigated the synthetic flexibility of our approach, studying the possibility of selective transformations at only one of the two amino groups, using orthogonal protecting group methodology.[11] For this purpose we used a triazene protecting group in addition to the pyrrole group. Triazenes are also versatile functionalities and have been demonstrated to be stable under conditions involving organometallic reagents and a number of catalysts;[12] they are also easy to install. Thus, for this purpose, we prepared the diethyl- and the pyrrolidine-substituted triazenes **20** and **21** from 2-chloro-4-aminopyridine in high yields (Scheme 5).[13]



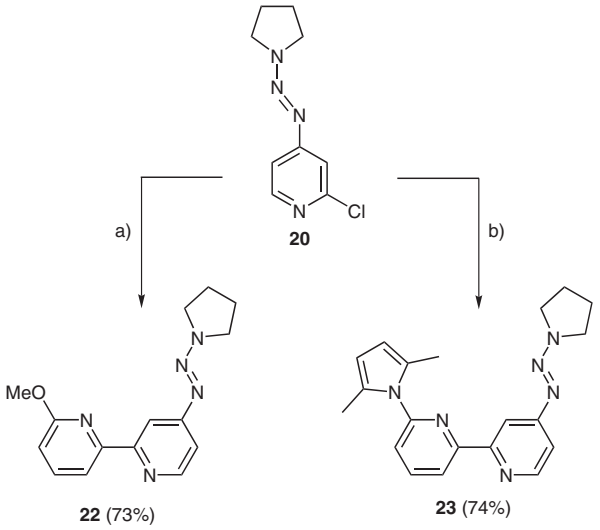
Scheme 4 Synthesis of halogenated and acetylated derivatives of diamino-2,2′-bipyridine **11**. *Reagents and conditions*: (a) $NaNO_2$, 2 M H_2SO_4, –10 °C; then KI, H_2O, 0 °C; (b) Br_2, HBr (62%), $NaNO_2$, –10 °C; then 0 °C; (c) AcCl, pyridine.



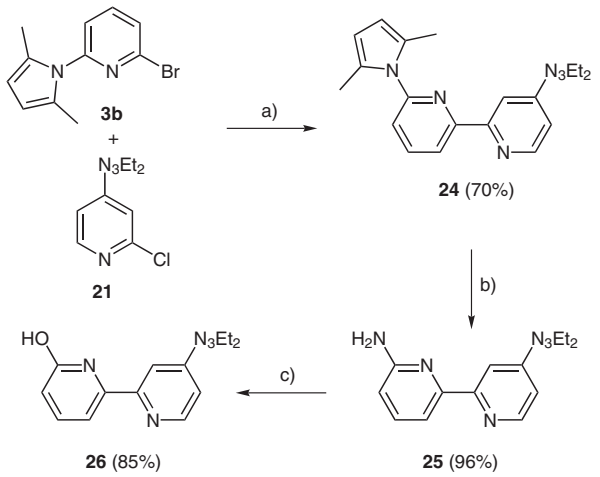
Scheme 5 Synthesis of the triazene-protected pyridines **20** and **21** from 2-chloro-4-aminopyridine. *Reagents and conditions*: (a) 1 M H_2SO_4, $NaNO_2$, –5 °C; then pyrrolidine, K_2CO_3, 0 °C; (b) 1 M H_2SO_4, $NaNO_2$, –5 °C; then Et_2NH, K_2CO_3, 0 °C.

The coupling reaction of **20** with the pyridylzinc reagent derived from 2-bromo-6-methoxypyridine under our standard coupling conditions was smooth and gave the pyrrolidine triazene-substituted 2,2′-bipyridine **22** in 73% yield (Scheme 6). Nearly the same yield (74%) was obtained when reacting **21** with the organozinc species derived from **3b**. These experiments again proved the versatility of our coupling procedure, which allows for the transformation of substrates with very different amino or amino/hydroxy protecting groups to be used.

A complete reaction sequence, which also contains a further transformation of the cross-coupling product, is shown in Scheme 7. The diethyl-substituted triazene **21** reacted with the organozinc reagent derived from **3b** to give the 2,2′-bipyridine **24** in 70% yield. After selective and nearly quantitative deprotection of the pyrrole group



Scheme 6 Cross-coupling reactions starting from pyrrolidinyltriazene-protected **20**: *Reagents and conditions*: (a) 6-methoxypyridin-2-ylzinc chloride (prepared from 2-bromo-6-methoxypyridine), Pd(P*t*-Bu_3)$_2$, THF, heat; (b) 6-(2,5-dimethyl-1*H*-pyrrol-1-yl)pyridin-2-ylzinc chloride (prepared from **3b**), Pd(P*t*-Bu_3)$_2$, THF, heat.



Scheme 7 Synthesis of the differently amino-protected 2,2′-bipyridine **24**, selective deprotection (to **25**), and hydroxylation (to **26**). *Reagents and conditions*: (a) *t*-BuLi, THF, –78 °C; then $ZnCl_2$, r.t.; then Pd(P*t*-Bu_3)$_2$, heat; (b) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, H_2O, heat; (c) $NaNO_2$, 2 M H_2SO_4, H_2O, 0 °C; then r.t. and 80 °C.

under standard conditions the resulting monoprotected bipyridine **25** was subjected to hydroxylation. This final step gave the protected amino-substituted hydroxybipyridine **26** in an excellent 85% yield, giving an overall yield of 57% for the whole sequence.

In summary, we have presented a novel and convenient homo- and cross-coupling approach to symmetrical and non-symmetrical diamino-2,2′-bipyridines. These compounds are excellent and versatile building blocks and starting materials for a wealth of further transformations, some of which have been demonstrated in this paper. Finally, we demonstrated the application of orthogonal protecting group methodology for the preparation of variously substituted diamino-2,2′-bipyridines.

All coupling reactions were performed under an argon atmosphere using standard Schlenk techniques and oven-dried glassware prior to use. TLC was performed on aluminum TLC plates silica gel 60 F_{254} from Merck; detection: UV light (254 and 366 nm). Products were purified by column chromatography on silica gel 60 (70–230 mesh) from Merck. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer or a Bruker DMX 500 spectrometer at 300 K at 500.1 and 125.8 MHz, or a Bruker AM 400 at 298 K at 400.1 MHz and 100.6 MHz, respectively. ^{1}H NMR chemical shifts are reported relative to residual undeuterated solvent as internal standard. ^{13}C NMR chemical shifts are reported relative to deuterated solvent or a small amount of acetone in D_2O as internal standard. Signals were assigned on the basis of ^{1}H, ^{13}C, H,H-COSY, HMQC, and HMBC NMR experiments. MS spectra were taken on a Finnigan MAT 212 with data system MMS–ICIS (EI, CI, Me_3CH, NH_3), a Finnigan MAT 95 with data system DEC-Station 5000 (CI, Me_3CH or NH_3; HiRes-CI, Me_3CH or NH_3; FD), or an A.E.I. MS-50 (EI; HiRes-EI). Melting points were measured with a hot-stage microscope SM-Lux from Leitz or a SMP-20 from Büchi and are not corrected. Elemental analyses were carried out with a Fisons Instrument EA1108 or a Heraeus Vario EL.

Most solvents were dried, distilled and stored under argon according to standard procedures. *t*-BuLi solns were purchased from Aldrich and were titrated prior to use against *N*-pivaloyl-*o*-toluidine.[14] All chemicals were used as received from commercial sources. Pd(P*t*-Bu_3)$_2$[15] and $NiBr_2(PPh_3)_2$[16] were prepared after published procedures. Pyrrole-protected pyridines **2b**, **3b**, **1a**, and **2a** were prepared according to a published procedure.[4] In general, pyrrole-protected pyridines should be stored in dark vials to avoid photodegradation upon exposure to sunlight. The synthesis of 5,5′-diamino-2,2′-bipyridine (**8**) has recently been published.[7]

All products were fully characterized; the numbering used in NMR spectral interpretation is given in Figure 2.

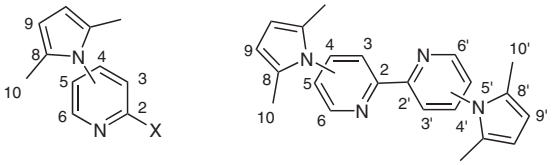


Figure 2 Numbering of the pyridine and bipyridine core

2-Bromo-4-(2,5-dimethyl-1*H*-pyrrol-1-yl)pyridine (1b)

4-Amino-2-bromopyridine (2.50 g, 14.50 mmol), hexane-2,5-dione (2.0 mL, 16.80 mmol, 1.2 equiv), and PTSA (24 mg, 0.14 mmol, 1 mol%) were dissolved in toluene (10 mL) and heated in a Dean–Stark apparatus for 2 h. After cooling, the dark brown mixture was washed with sat. aq $NaHCO_3$ (20 mL), H_2O (5 × 20 mL), and brine (20 mL). After drying ($MgSO_4$) the solvent was removed in vacuo. The dark residue was subjected to column chromatography (silica gel, *n*-hexane–EtOAc, 2:1, with 5% Et_3N, R_f = 0.7) to give the product as a pale yellow solid; yield: 3.13 g (86%); mp 122 °C.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.09 (s, 6 H, H10), 5.93 (s, 2 H, H8), 7.13 (dd, ^3J = 5.5 Hz, ^4J = 1.7 Hz, 1 H, H5), 7.37 (d, ^4J = 1.7 Hz, 1 H, H3), 8.46 (d, ^3J = 5.5 Hz, 1 H, H6).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 13.1 (C10), 108.1 (C7), 121.9 (C5), 126.9 (C6), 128.3 (C8), 142.6 (C2), 148.3 (C4), 150.7 (C3).

MS (EI): *m*/*z* (%) = 252.0 ($[C_{11}H_{11}{}^{81}BrN_2]^+$, 100), 250.0 ($[C_{11}H_{11}{}^{79}BrN_2]^+$, 99), 251.0 ($[C_{11}H_{10}{}^{81}BrN_2]^+$, 86), 249.0 ($[C_{11}H_{10}{}^{79}BrN_2]^+$, 77).

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $[C_{11}H_{10}{}^{79}BrN_2]^+$: 249.0022; found: 249.0023.

Anal. Calcd for $C_{11}H_{11}BrN_2$: C, 52.62; H, 4.42; N, 11.16. Found: C, 52.78; H, 4.42; N, 11.23.

2-Chloro-6-(2,5-dimethyl-1*H*-pyrrol-1-yl)pyridine (3a)

2-Amino-6-chloropyridine (1.80 g, 10.40 mmol), hexane-2,5-dione (2.0 mL, 16.80 mmol, 1.2 equiv), and PTSA (24 mg, 0.14 mmol, 1 mol%) were dissolved in toluene (10 mL)) and heated in a Dean–Stark apparatus for 2 h. After cooling, the dark brown mixture was washed with sat. aq $NaHCO_3$ (20 mL), H_2O (5 × 20 mL), and brine (20 mL). After drying ($MgSO_4$) the solvent was removed in vacuo. The dark residue was subjected to sublimation to give the desired product as colorless needles; yield: 2.58 g (89%); mp 60–61 °C. *The compound is prone to degradation, becoming darkly colored, and should therefore be stored in a freezer and sublimed prior to use.*

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.15 (s, 6 H, H10), 5.88 (s, 2 H, H9), 7.13 (d, ^3J = 7.7 Hz, 1 H, H5), 7.32 (d, ^3J = 7.7 Hz, 1 H, H3), 7.77 (dd, ^3J = 7.7 Hz, ^3J = 7.7 Hz, 1 H, H4).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 13.2 (C10), 107.5 (C9), 120.0 (C5), 122.6 (C6), 128.7 (C8), 140.1 (C4), 150.4 (C3), 151.7 (C2).

MS (EI): *m/z* (%) = 206.0 ($[C_{11}H_{11}{}^{35}ClN_2]^+$, 100), 205.0 ($[C_{11}H_{10}{}^{35}ClN_2]^+$, 82), 207.0 ($[C_{11}H_{10}{}^{37}ClN_2]^+$, 40), 208.0 ($[C_{11}H_{11}{}^{37}ClN_2]^+$, 33).

HRMS (EI): *m/z* $[M - H]^+$ calcd for $[C_{11}H_{10}{}^{35}ClN_2]^+$: 205.0527; found: 205.0535.

Anal. Calcd for $C_{11}H_{11}ClN_2$: C, 63.93; H, 5.36; N, 13.55. Found: C, 64.22, H, 5.42, N, 13.77.

4,4′-Bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (4): Typical Procedure for the Homo-Coupling Reaction

To a suspension of $NiBr_2(PPh_3)_2$ (0.72 g, 0.97 mmol, 25 mol%), zinc powder (0.54 g, 8.23 mmol, 1.7 equiv), LiCl (0.35 g, 8.23 mmol, 1.7 equiv), and Et_4NI (1.25 g, 4.84 mmol, 1 equiv) in anhyd THF (20 mL) was added a soln of **1a** (1 g, 4.84 mmol) in anhyd THF (10 mL). The mixture was stirred under reflux for 20 h. After cooling aq NH_3 (20 mL), H_2O (15 mL), and CH_2Cl_2 (60 mL) were added and it was stirred at r.t. for 15 min. The mixture was extracted several times with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and the solvents were removed in vacuo. The pure product was obtained after column chromatography (silica gel, *n*-hexane–EtOAc, 5:1, with 5% Et_3N, R_f = 0.6) as a yellow solid; yield: 819 mg (99%); mp 243–245 °C.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.15 (s, 12 H, H10), 5.97 (s, 4 H, H9), 7.20 (d, ^3J = 4.9 Hz, ^4J = 1.6 Hz, 2 H, H5), 8.41 (d, ^4J = 1.6 Hz, 2 H, H3), 8.75 (d, ^3J = 4.9 Hz, 2 H, H6).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 13.2 (C10), 107.5 (C9), 120.0 (C3), 123.0 (C5), 128.4 (C8), 147.7 (C4), 150.3 (C6), 156.9 (C2).

MS (CI): *m/z* (%) = 342.8 ($[MH]^+$, 100), 398.9 ($[MH + Me_3CH]^+$, 20).

HRMS (CI): *m/z* $[MH]^+$ calcd for $[C_{22}H_{23}N_4]^+$: 343.1923; found: 343.1923.

Anal. Calcd for $C_{22}H_{22}N_4$·0.5 EtOAc: C, 74.58; H, 6.78; N, 14.50. Found: C, 74.87; H, 6.68; N, 14.71.

5,5′-Bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (5)

Following the typical procedure for **4** using **2a** and heating to reflux for 24 h gave **5** as a yellow solid after column chromatography (silica gel, *n*-hexane–EtOAc, 5:1, with 5% Et_3N, R_f = 0.8); yield: 782 mg (94%). The analytical data are in accordance with previously reported data.[8]

6,6′-Bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (6)

Following the typical procedure for **4** using **3b** and stirring under reflux for 24 h gave **6** as a yellow solid after column chromatography (silica gel, *n*-hexane–EtOAc, 5:1, with 5% Et_3N, R_f = 0.8); yield: 683 mg (91%); mp 172 °C.

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.23 (s, 12 H, H10), 5.96 (s, 4 H, H9), 7.24 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 2 H, H5), 7.93 (dd, ^3J = 7.8 Hz, ^3J = 7.8 Hz, 2 H, H4), 8.46 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 2 H, H3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.5 (C10), 107.1 (C9), 119.5 (C3), 121.9 (C5), 128.7 (C8), 138.9 (C4), 151.4 (C6), 155.1 (C2).

MS (EI): *m/z* (%) = 342.1 ($[C_{22}H_{22}N_4]^+$, 100).

HRMS (EI): *m/z* $[M]^+$ calcd for $[C_{22}H_{22}N_4]^+$: 342.1844; found: 342.1843.

4,4′-Diamino-2,2′-bipyridine (7) (as the Dihydrochloride); Typical Procedure for Removal of the Pyrrole Protecting Group[7]

Deprotection of 4,4′-bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (**4**, 360 mg, 1.05 mmol) was achieved by treatment with NH_2OH·HCl (1.47 g, 21.0 mmol, 20 equiv) in a mixture of Et_3N (0.5 mL), EtOH (10 mL), and H_2O (2.5 mL). The resulting soln was refluxed until TLC monitoring revealed complete consumption of the starting material (usually after 20 h). After cooling to r.t. the reaction was quenched by pouring into ice-cold 1 M HCl (10 mL). The resulting soln was washed with *i*-Pr_2O (15 mL) and the pH was adjusted to 9–10 by careful addition of 6 M NaOH. The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried (Na_2SO_4). After removal of the solvent in vacuo, the brown residue was subjected to column chromatography (silica gel) to give the desired diamine. For further purification, the diamine was dissolved in EtOH. Et_2O (15 mL) was added and the mixture was filtered. A 2 M soln of HCl in Et_2O (1.05 mL, 2.10 mmol) was added to the filtrate and pure **7**·2 HCl precipitated, which was collected and dried in vacuo; yield: 254 mg (94%); mp >250 °C.

^{1}H NMR (400.1 MHz, D_2O, as dihydrochloride): δ = 7.02 (dd, ^3J = 7.1 Hz, ^4J = 2.5 Hz, 1 H, H5), 7.22 (d, ^4J = 2.5 Hz, 2 H, H3), 8.16 (d, ^3J = 7.1 Hz, 1 H, H6).

^{13}C NMR (100.6 MHz, D_2O, as dihydrochloride): δ = 111.8 (C3), 112.3 (C5), 143.4 (C6), 144.7 (C2), 162.7 (C4).

MS (EI): *m/z* (%) = 186.1 ($[C_{10}H_{10}N_4]^+$, 100).

HRMS (EI): *m/z* $[M - H]^+$ calcd for $[C_{10}H_9N_4]^+$: 185.0822; found: 185.0828.

6,6′-Diamino-2,2′-bipyridine (9) (as the Dihydrochloride)

Following the typical procedure for **7** using **6** (550 mg, 1.61 mmol) gave diamine **9**. For further purification, the diamine was dissolved in EtOH, Et_2O (15 mL) was added and the mixture was filtered. A 2 M soln of HCl in Et_2O (1.61 mL, 3.22 mmol) was added to the filtrate and pure **9**·2 HCl precipitated, which was collected and dried under vacuum; yield: 191 mg (46%); mp >250 °C.

^{1}H NMR (400.1 MHz, D_2O, as dihydrochloride): δ = 7.09 (d, ^3J = 8.9 Hz, 1 H, H5), 7.25 (d, ^3J = 8.8 Hz, 2 H, H3), 7.94 (dd, ^3J = 8.8 Hz, ^3J = 8.9 Hz, 1 H, H4).

^{13}C NMR (100.6 MHz, D_2O, as dihydrochloride): δ = 115.1 (C3), 117.8 (C5), 141.1 (C2), 146.0 (C4), 157.6 (C6).

MS (EI): *m/z* (%) = 186.1 ($[C_{10}H_{10}N_4]^+$, 100).

HRMS (EI): *m/z* $[M]^+$ calcd for $[C_{10}H_{10}N_4]^+$: 186.0905; found: 186.0905.

Anal. Calcd for $C_{10}H_{12}N_4Cl_2$: C, 46.35; H, 4.67; N, 21.62. Found: C, 46.94; H, 4.49; N; 20.07.

4,6′-Bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (10); Typical Procedure for the Negishi Cross-Coupling Reaction

A 1.55 M soln of *t*-BuLi in pentane (5.0 mL, 7.78 mmol, 2.15 equiv) was added to anhyd THF (10 mL) at –78 °C. Subsequently, a soln of **3b** (1 g, 3.98 mmol, 1.1 equiv) in anhyd THF (5 mL) was added dropwise. The mixture was stirred at –78 °C for 30–45 min and then

a soln of anhyd $ZnCl_2$ (1.36 g, 9.96 mmol, 2.75 equiv) in anhyd THF (10 mL) was added slowly and the mixture was stirred at r.t. for 2–3 h. After that time a soln of $Pd(P\textit{t}\text{-}Bu_3)_2$ (61 mg, 0.119 mmol, 3 mol% Pd) and **1a** (746 mg, 3.62 mmol) in anhyd THF (5 mL) was added and the mixture was heated at reflux until no further consumption was observed by TLC monitoring.

After cooling to r.t., a suspension of EDTA (8.67 g, 29.87 mmol, 8.75 equiv) in H_2O (100 mL) was added and the resulting mixture was stirred for 15 min. After adjusting the pH to 8 with sat. aq Na_2CO_3, the mixture was extracted several times with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and the solvents were removed in vacuo. The pure product was obtained after column chromatography (silica gel, *n*-hexane–EtOAc, 10:1, with 5% Et_3N, R_f = 0.5) as a pale yellow solid; yield: 866 mg (70%); mp 199 °C.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.11 (s, 6 H, H10), 2.19 (s, 6 H, H10′), 5.92 (s, 2 H, H9), 5.93 (s, 2 H, H9′), 7.19 (dd, ^3J = 5.3 Hz, ^4J = 1.9 Hz, 1 H, H5), 7.26 (d, ^3J = 7.5 Hz, 1 H, H5′), 7.97 (dd, ^3J = 7.5 Hz, ^3J = 7.5 Hz, 1 H, H4′), 8.33 (d, ^4J = 1.9 Hz, 1 H, H3), 8.50 (d, ^3J = 7.5 Hz, 1 H, H3′), 8.77 (d, ^3J = 5.3 Hz, 1 H, H6).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 13.2, 13.5 (C10, C10′), 107.2, 107.5 (C9, C9′), 119.3 (C3′), 120.3 (C3), 121.9 (C5′), 122.8 (C5), 128.3 (C8), 128.6 (C8′), 138.9 (C4′), 147.7 (C4), 150.2 (C6), 151.4 (C6′), 155.0 (C2′), 157.0 (C2).

MS (EI): *m*/*z* (%) = 342.3 ($[C_{22}H_{22}N_4]^+$, 100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_{22}H_{22}N_4]^+$: 342.1844; found: 342.1848.

Anal. Calcd for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36. Found: C, 77.09; H, 6.74; N; 16.00.

4,6′-Diamino-2,2′-bipyridine (11)

Following the typical procedure for **7** using **10** (1.06 g, 3.10 mmol) gave **11** after column chromatography (silica gel, CH_2Cl_2–MeOH, 2:1, R_f = 0.1) as an amorphous solid; yield: 486 mg (84%).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 5.81 (br s, 2 H, C6′-NH_2), 6.00 (br s, 2 H, C4-NH_2), 6.42–6.45 (m, 2 H, H5, H5′), 7.41–7.45 (m, 3 H, H3, H3′, H4′), 8.01 (d, ^3J = 5.4 Hz, 1 H, H6).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 105.7 (C3), 108.7, 109.0 (2 C, C5,C5′), 109.4 (C3′), 138.0 (C4′), 148.9 (C6), 154.4 (C2), 155.6 (C4), 156.1 (C2′), 159.5 (C6′).

MS (EI): *m*/*z* (%) = 186.0 ($[C_{10}H_{10}N_4]^+$, 100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_{10}H_{10}N_4]^+$: 186.0905; found: 186.0909.

Anal. Calcd for $C_{10}H_{10}N_4 \cdot 0.5\ MeOH \cdot 0.25\ CH_2Cl_2$: C, 57.38; H, 5.64; N, 25.07. Found: C, 57.64; H, 6.04; N, 25.03.

4,5′-Bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (12)

Following the typical procedure for **10** using **1b** (500 mg, 1.99 mmol, 1.1 equiv) and **2a** (373 mg, 1.81 mmol) gave **12** after column chromatography (*n*-hexane–EtOAc, 10:1, with 5% Et_3N, R_f = 0.7) as a pale yellow solid; yield: 376 mg (61%); mp 125 °C.

The desired product could also be obtained from **2b** (500 mg, 1.99 mmol, 1.1 equiv) and **1a** (373 mg, 1.81 mmol); yield: 466 mg (75%).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.09 (s, 6 H, H10), 2.15 (s, 6 H, H10′), 5.96 (s, 4 H, H9, H9′), 7.21 (dd, ^3J = 5.5 Hz, ^4J = 1.1 Hz, 1 H, H5), 7.70 (dd, ^3J = 8.2 Hz, ^4J = 2.2 Hz, 1 H, H4′), 8.37 (d, ^4J = 1.1 Hz, 1 H, H3), 8.55 (d, ^4J = 2.2 Hz, 1 H, H6′), 8.60 (d, ^3J = 8.2 Hz, 1 H, H3′), 8.79 (d, ^3J = 5.5 Hz, 1 H, H6).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 13.0, 13.2 (C10, C10′), 106.9, 107.4 (C9, C9′), 120.4 (C3), 121.4 (C3′), 122.8 (C5), 128.4, 128.9 (C8, C8′), 136.0 (C5′), 136.3 (C4′), 147.8 (C4), 148.5 (C6′), 150.3 (C6), 154.3 (C2′), 157.0 (C2).

MS (EI): *m*/*z* (%) = 342.3 ($[C_{22}H_{22}N_4]^+$, 100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_{22}H_{22}N_4]^+$: 342.1844; found: 342.1838.

Anal. Calcd for $C_{22}H_{22}N_4 \cdot 0.25\ CH_2Cl_2$: C, 73.48; H, 6.24; N, 15.41. Found: C, 74.12; H, 6.39; N, 15.46.

4,5′-Diamino-2,2′-bipyridine (13) (as the Dihydrochloride)

Following the typical procedure for **7** using **12** (730 mg, 2.13 mmol) gave diamine **13**. For further purification, the diamine was dissolved in EtOH. Et_2O (20 mL) was added and the mixture was filtered. A 2 M soln of HCl in Et_2O (2.13 mL, 4.26 mmol) was added to the filtrate and pure **13**·2 HCl precipitated, which was collected and dried under vacuum; yield: 179 mg (30%); mp >250 °C.

^{1}H NMR (400.1 MHz, D_2O, as dihydrochloride): δ = 6.77 (dd, ^3J = 7.0 Hz, ^4J = 2.4 Hz, 1 H, H5), 7.07 (d, ^4J = 2.4 Hz, 1 H, H3), 7.46 (dd, ^3J = 8.7 Hz, ^4J = 2.7 Hz, 1 H, H4′), 7.79 (dd, ^3J = 8.7 Hz, ^5J = 0.4 Hz, 1 H, H3′), 7.95 (d, ^3J = 7.0 Hz, 1 H, H6), 8.21 (dd, ^4J = 2.7 Hz, ^5J = 0.4 Hz, 1 H, H6′).

^{13}C NMR (100.6 MHz, D_2O, as dihydrochloride): δ = 105.5 (C3), 108.5 (C5), 123.8 (C3′), 125.8 (C4), 136.4 (C6), 136.6 (C5′), 139.6 (C6′), 144.0 (C2′), 145.6 (C2), 160.3 (C4).

MS (EI): *m*/*z* (%) = 186.1 ($[C_{10}H_{10}N_4]^+$, 100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_{10}H_{10}N_4]^+$: 186.0905; found: 186.0905.

5,6′-Bis(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (14)

Following the typical procedure for **10** using **2b** (500 mg, 1.99 mmol, 1.1 equiv) and **3a** (373 mg, 1.81 mmol) gave **14** after column chromatography (*n*-hexane–EtOAc, 10:1, with 5% Et_3N, R_f = 0.8) as a pale yellow solid; yield: 234 mg (38%); mp 143 °C.

The desired product could also be obtained from **3b** (500 mg, 1.99 mmol, 1.1 equiv) and **2a** (373 mg, 1.81 mmol); yield: 419 mg (68%).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.09 (s, 6 H, H10), 2.23 (s, 6 H, H10′), 5.95 (s, 2 H, H9), 5.96 (s, 2 H, H9′), 7.26 (d, ^3J = 7.7 Hz, 1 H, H5′), 7.66 (dd, ^3J = 8.3 Hz, ^4J = 2.7 Hz, 1 H, H4), 7.98 (dd, ^3J = 7.7 Hz, ^3J = 7.7 Hz, 1 H, H4′), 8.49 (d, ^3J = 7.7 Hz, 1 H, H3′), 8.56 (d, ^3J = 8.3 Hz, 1 H, H3), 8.57 (s, 1 H, H6).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 13.0 (C10), 13.4 (C10′), 106.9 (C9), 107.1 (C9′), 119.4 (C3′), 121.6 (C3), 121.9 (C5′), 128.6 (C5), 128.9 (C8), 135.9 (C8′), 136.5 (C4), 139.0 (C4′), 148.2 (C6), 151.5 (C6′), 154.2 (C2), 154.8 (C2′).

MS (EI): *m*/*z* (%) = 172.0 ($[C_{10}H_9N_3]^+$, 100), 342.1 ($[C_{22}H_{22}N_4]^+$, 10).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_{22}H_{22}N_4]^+$: 342.1844; found: 342.1849.

Anal. Calcd for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36. Found: C, 76.15; H, 6.06; N, 15.98.

5,6′-Diamino-2,2′-bipyridine (15)

Following the typical procedure for **7** using **12** (700 mg, 2.04 mmol) gave **15** after column chromatography (silica gel, CH_2Cl_2–MeOH, 2:1, R_f = 0.1) as an amorphous solid; yield: 233 mg (61%).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 5.49 (br s, 2 H, C5-NH_2), 5.77 (br s, 2 H, C6′-NH_2), 6.34 (d, ^3J = 7.7 Hz, 1 H, H5′), 6.96 (dd, ^3J = 8.2 Hz, ^4J = 2.8 Hz, 1 H, H4), 7.33 (d, ^3J = 7.7 Hz, 1 H, H3′), 7.38 (dd, ^3J = 7.7 Hz, ^3J = 7.7 Hz, 1 H, H4′), 7.93 (d, ^3J = 8.2 Hz, 1 H, H3), 7.95 (d, ^4J = 2.8 Hz, 1 H, H6).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 106.4 (C5′), 107.1 (C3′), 119.9 (C4), 120.6 (C3), 135.3 (C6), 137.5 (C4′), 144.1 (C2), 144.8 (C5), 154.4 (C2′), 158.9 (C6′).

MS (EI): *m/z* (%) = 186.0 ($[C_{10}H_{10}N_4]^+$, 100).

HRMS (EI): *m/z* $[M]^+$ calcd for $[C_{10}H_{10}N_4]^+$: 186.0905; found: 186.0906.

Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 63.44; H, 5.65; N, 29.14.

2-Chloro-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)pyridine (16)

3-Amino-2-chloropyridine (5.00 g, 38.89 mmol), hexane-2,5-dione (4.68 mL, 46.67 mmol, 1.2 equiv), and PTSA (67 mg, 0.39 mmol, 1 mol%) were dissolved in toluene (20 mL) and heated in a Dean–Stark apparatus for 2 h. After cooling, the dark brown mixture was washed with sat. aq $NaHCO_3$ (25 mL), H_2O (5 × 20 mL), and brine (20 mL). After drying ($MgSO_4$) the solvent was removed in vacuo. The dark residue was subjected to column chromatography (silica gel, *n*-hexane–EtOAc, 3:1, with 5% Et_3N, R_f = 0.7) to give the product as a pale yellow solid; yield: 7.48 g (93%); mp 65 °C.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.96 (s, 6 H, H10), 5.95 (s, 2 H, H9), 7.39 (dd, ^3J = 7.7 Hz, ^3J = 4.9 Hz, 1 H, H5), 7.65 (dd, ^3J = 7.7 Hz, ^4J = 2.2 Hz, 1 H, H4), 8.48 (dd, ^3J = 4.9 Hz, ^4J = 2.2 Hz, 1 H, H6).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 12.5 (C10), 106.6 (C9), 122.9 (C5), 128.7 (C8), 133.8 (C3), 139.1 (C4), 149.3 (C6), 151.4 (C2).

MS (EI): *m/z* (%) = 205.1 ($[C_{11}H_{10}{}^{35}ClN_2]^+$, 100), 206.1 ($[C_{11}H_{11}{}^{35}ClN_2]^+$, 84), 207.1 ($[C_{11}H_{10}{}^{37}ClN_2]^+$, 41), 208.1 ($[C_{11}H_{11}{}^{37}ClN_2]^+$, 29).

HRMS (EI): *m/z* $[M - H]^+$ calcd for $[C_{11}H_{10}{}^{35}ClN_2]^+$: 205.0527; found: 205.0536.

Anal. Calcd for $C_{11}H_{11}ClN_2 \cdot 0.2\ C_6H_{14}$: C, 65.44; H, 6.21; N. 12.51. Found: C, 65.57; H, 6.85; N, 13.31.

4,6′-Diiodo-2,2′-bipyridine (17)

A soln of 4,6′-diamino-2,2′-bipyridine (**11**, 250 mg, 1.34 mmol) in 2 M H_2SO_4 (10 mL) was stirred at –10 °C. A soln of $NaNO_2$ (241 mg, 3.49 mmol, 2.6 equiv) in H_2O (5 mL) was added dropwise at this temperature. The mixture was stirred at 0 °C for 0.5 h. After that time a soln of KI (4.01 g, 24.17 mmol, 18 equiv) in H_2O (5 mL) was added and the mixture stirred at r.t. for 45 min and then heated to 80 °C for 1 h. The mixture was neutralized with sat. aq Na_2CO_3 and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were washed with sat. aq $Na_2S_2O_3$ and dried (Na_2SO_4). The pure product was obtained after column chromatography (silica gel, $CHCl_3$–MeOH, 9:1, R_f = 0.6) as a pale yellow solid; yield: 192 mg (33%); mp 184 °C.

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 6.64 (dd, ^3J = 9.2 Hz, ^4J = 0.8 Hz, 1 H, H5), 6.76 (dd, ^3J = 6.9 Hz, ^4J = 0.8 Hz, 1 H, H3), 7.46 (dd, ^3J = 9.2 Hz, ^3J = 6.9 Hz, 1 H, H4), 7.70 (dd, ^3J = 5.2 Hz, ^4J = 2.5 Hz, 1 H, H5′), 8.16 (dd, ^4J = 2.5 Hz, ^5J = 0.7 Hz, 1 H, H3′), 8.28 (dd, ^3J = 5.2 Hz, ^5J = 0.7 Hz, 1 H, H6′).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 103.4 (C3), 106.4 (C4′), 122.9 (C5), 129.1 (C3′), 133.6 (C5′), 140.3 (C6), 140.4 (C4, C6), 148.8 (C2′), 149.4 (C6′), 162.7 (C2).

MS (EI): *m/z* (%) = 407.9 ($[C_{10}H_6N_2I_2]^+$, 100).

HRMS (EI): *m/z* $[M]^+$ calcd for $[C_{10}H_6N_2I_2]^+$: 407.8620; found: 407.8630.

4,6′-Dibromo-2,2′-bipyridine (18)

4,6′-Diamino-2,2′-bipyridine (**11**, 200 mg, 1.07 mmol) was dissolved in aq HBr (62%, 5 mL) and cooled to –10 °C. Br_2 (858 mg, 0.3 mL, 5.37 mmol, 5 equiv) was added. A soln of $NaNO_2$ (371 mg, 5.37 mmol, 5 equiv) in H_2O (2 mL) was added dropwise at a temperature below –5 °C. The mixture was stirred at r.t. for 0.5 h, then cooled to 0 °C and a soln of NaOH (2.4 g) in H_2O (5 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 20 mL). The organic phases were dried (Na_2SO_4) and the solvents were removed in vacuo. The pure product was obtained after column chromatography (silica gel, CH_2Cl_2, R_f = 0.6) as a colorless solid; yield: 163 mg (49%); mp 108 °C.

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.48 (dd, ^3J = 5.2 Hz, ^4J = 1.9 Hz, 1 H, H5), 7.51 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 1 H, H5′), 7.66 (dd, ^3J = 7.8 Hz, ^3J = 7.8 Hz, 1 H, H4′), 8.35 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 1 H, H3′), 8.45 (d, ^4J = 5.2 Hz, 1 H, H6), 8.58 (d, ^3J = 1.9 Hz, 1 H, H3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 120.1 (C3′), 124.8 (C3), 127.5 (C5′), 128.7 (C5), 134.1 (C4), 139.3 (C4′), 141.7 (C6′), 149.9 (C6), 155.8 (C2), 156.0 (C2′).

MS (EI): *m/z* (%) = 313.9 ($[C_{10}H_6N_2{}^{79}Br^{81}Br]^+$, 100), 232.9 ($[C_{10}H_6N_2{}^{79}Br]^+$, 56), 234.9 ($[C_{10}H_6N_2{}^{81}Br]^+$, 53), 311.9 ($[C_{10}H_6N_2{}^{79}Br_2]^+$, 53), 315.9 ($[C_{10}H_6N_2{}^{81}Br_2]^+$, 50).

HRMS (EI): *m/z* $[M]^+$ calcd for $[C_{10}H_6N_2{}^{79}Br_2]^+$: 311.8898; found: 311.8900.

Anal. Calcd for $C_{10}H_6N_2Br_2$: C, 38.25; H, 1.93; N, 8.92. Found: C, 38.77; N, 8.76; H, 2.10.

4,6′-Bis(acetylamino)-2,2′-bipyridine (19)

4,6′-Diamino-2,2′-bipyridine (**11**, 200 mg, 1.07 mmol) was dissolved in anhyd pyridine (10 mL). AcCl (0.17 mL, 2.36 mmol, 2.2 equiv) was added dropwise and the mixture was stirred at r.t. for 12 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvents were removed in vacuo. The pure product was obtained after column chromatography (silica gel, EtOAc with 5% Et_3N, R_f = 0.1) as a colorless solid; yield: 199 mg (69%); mp >250 °C.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.12, 2.15 (s, 6 H, C4-CH_3, C6′-CH_3), 7.55 (dd, ^3J = 5.4 Hz, ^4J = 2.1 Hz, 1 H, H5), 7.88 (dd, ^3J = 7.8 Hz, ^3J = 7.8 Hz, 1 H, H4′), 8.02 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 1 H, H5′), 8.08 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 1 H, H3′), 8.51 (d, ^3J = 5.4 Hz, 1 H, H6), 8.52 (d, ^4J = 2.1 Hz, 1 H, H3), 10.47 (br s, 2 H, NH).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 24.4, 24.6 (2 CH_3), 110.5 (C3), 113.8 (C5), 114.5 (C3′), 116.6 (C5′), 139.4 (C4′), 147.2 (C4), 150.4 (C6), 152.0 (C6′), 154.5 (C2′), 156.4 (C2), 169.9 (CONH).

MS (EI): *m/z* (%) = 228.1 ($[C_{12}H_{12}N_4O]^+$, 100), 270.1 ($[C_{14}H_{14}N_4O_2]^+$, 62), 186.1 ($[C_{10}H_{10}N_4]^+$, 58).

HRMS (EI): *m/z* $[M]^+$ calcd for $[C_{14}H_{14}N_4O_2]^+$: 270.1117; found: 270.1117.

Anal. Calcd for $C_{14}H_{14}N_4O_2 \cdot 0.25\ CH_2Cl_2 \cdot 0.25\ H_2O$: C, 57.82; H, 5.11; N, 18.93. Found: C, 57.02; H, 5.79; N, 18.64.

2-Chloro-4-[(pyrrolidin-1-yl)diazenyl)pyridine (20); Typical Procedure

4-Amino-2-chloropyridine (1.00 g, 7.78 mmol) was dissolved in 1 M H_2SO_4 (45 mL) and cooled to –5 °C. A soln of $NaNO_2$ (1.82 g, 26.45 mmol, 3.4 equiv) in H_2O (10 mL) was added dropwise. After stirring at 0 °C for 1.5 h, the mixture was added to a cold soln of pyrrolidine (3.25 mL, 38.89 mmol, 5 equiv) and K_2CO_3 (5.38 g, 38.89 mmol, 5 equiv) in H_2O (80 mL) and stirred again at r.t. for 1.5 h. The mixture was extracted with Et_2O (2 × 40 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The expected product was obtained after column chromatography (silica gel, *n*-hexane–EtOAc, 3:1, with 0.5% Et_3N, R_f = 0.6) as a colorless solid; yield: 1.47 g (89%); mp 122 °C.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.07 (dt, ^3J = 6.4 Hz, 4 H, CH_2), 3.68 (t, ^3J = 6.4 Hz, 2 H, NCH_2), 3.97 (t, ^3J = 6.4 Hz, 2 H, NCH_2),

7.19 (dd, ^3J = 5.5 Hz· ^4J = 1.7 Hz, 1 H, H5), 7.30 (d, ^4J = 1.7 Hz, 1 H, H3), 8.23 (d, ^3J = 5.5 Hz, 1 H, H6).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.0, 23.4 (2 CH_2), 46.6, 51.5 (2 NCH_2), 114.0 (C3), 114.4 (C5), 149.5 (C6), 151.7 (C2), 159.3 (C4).

MS (EI): *m*/*z* (%) = 112.0 ($[C_5H_3{}^{35}ClN]^+$, 100), 210.1 ($[C_9H_{11}{}^{35}ClN_4]^+$, 33), 114.0 ($[C_5H_3{}^{37}ClN]^+$, 32), 212.1 ($[C_9H_{11}{}^{37}ClN_4]^+$, 11).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_9H_{11}{}^{35}ClN_4]^+$: 210.0672; found: 210.0672.

Anal. Calcd for $C_9H_{11}ClN_4$: C, 51.31; H, 5.26; N, 26.60. Found: C, 51.25; H, 5.38; N, 26.08.

2-Chloro-4-(3,3-diethyltriaz-1-en-1-yl)pyridine (21)

Following the typical procedure for **20** using 4-amino-2-chloropyridine (1.00 g, 7.78 mmol) with Et_2NH (4 mL, 38.89 mmol, 5 equiv) gave **21** after column chromatography (silica gel, *n*-hexane–EtOAc, 1:1, with 0.5% Et_3N, R_f = 0.6) as a pale yellow oil; yield: 1.40 g (85%).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.21, 1.35 (t, ^3J = 7.1 Hz, 6 H, 2 NCH_2CH_3), 3.77–3.83 (m, 4 H, 2 NCH_2CH_3), 7.18 (dd, ^3J = 5.5 Hz, ^4J = 1.7 Hz, 1 H, H5), 7.29 (d, ^4J = 1.7 Hz, 1 H, H3), 8.22 (d, ^3J = 5.5 Hz, 1 H, H6).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 11.0, 14.3 (2 NCH_2CH_3), 42.0, 49.7 (2 NCH_2CH_3), 114.6 (C5), 114.9 (C3), 149.7 (C6), 151.9 (C2), 159.7 (C4).

MS (EI): *m*/*z* (%) = 140.0 ($[C_5H_3N_3{}^{35}Cl]^+$, 100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_9H_{13}{}^{35}ClN_4]^+$: 212.0828; found: 212.0820.

Anal. Calcd for $C_9H_{13}ClN_4$: C, 50.83; H, 6.16; N, 26.34. Found: C, 50.46; H, 6.24; N, 26.11.

6-Methoxy-4′-[(pyrrolidin-1-yl)diazenyl]-2,2′-bipyridine (22)

Following the typical procedure for **10** using 2-bromo-6-methoxypyridine (500 mg, 2.67 mmol, 1.1 equiv) and **20** (512 mg, 2.43 mmol) gave the pure product after column chromatography (silica gel, EtOAc with 5% Et_3N, R_f = 0.6) as a pale yellow solid; yield: 500 mg (73%); mp 88 °C.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.97–2.15 (m, 4 H, 2 CH_2), 3.67–4.02 (m, 4 H, 2 NCH_2), 4.05 (s, 3 H, OCH_3), 6.75 (d, ^3J = 7.7 Hz, 1 H, H5), 7.29 (dd, ^3J = 5.5 Hz, ^4J = 1.6 Hz, 1 H, H5′), 7.67 (dd, ^3J = 7.7 Hz, ^3J = 7.7 Hz, 1 H, H4), 8.0 (d, ^3J = 7.7 Hz, 1 H, H3), 8.34 (d, ^4J = 1.6 Hz, 1 H, H3′), 8.53 (d, ^3J = 5.5 Hz, 1 H, H6′).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.5, 23.8 (2 CH_2), 47.0, 51.7 (2 NCH_2), 53.3 (OCH_3), 110.8 (C5), 113.3 (C3′), 113.9 (C3), 114.1 (C5′), 139.2 (C4), 149.5 (C6′), 153.6 (C2), 156.9 (C2′), 158.5 (C4′), 163.5 (C6).

MS (EI): *m*/*z* (%) = 185.1 ($[C_{11}H_9N_2O]^+$, 100), 283.1 ($[C_{15}H_{17}N_5O]^+$, 19).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_{15}H_{17}N_5O]^+$: 283.1433; found: 283.1433.

Anal. Calcd for $C_{15}H_{17}N_5O$·0.25 EtOAc: C, 62.93; H, 6.27; N, 22.94. Found: C, 62.85; H, 6.11; N, 24.65.

6-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-4′-[(pyrrolidin-1-yl)diazenyl]-2,2′-bipyridine (23)

Following the typical procedure for **10** using **3b** (500 mg, 1.99 mmol, 1.1 equiv) and **20** (381 mg, 1.81 mmol) gave the pure product after column chromatography (silica gel, *n*-hexane–EtOAc, 1:1, with 5% Et_3N, R_f = 0.6) as a pale yellow oil; yield: 465 mg (74%).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.99–2.13 (m, 4 H, 2 NCH_2CH_2) 3.66–3.99 (m, 4 H, 2 NCH_2CH_3), 2.21 (s, 6 H, H10), 5.93 (s, 2 H, H9), 7.20 (d, ^3J = 7.68 Hz, 1 H, H3), 7.31 (dd, ^3J = 5.49 Hz, ^4J = 1.64 Hz, 1 H, H5′), 7.93 (dd, ^3J = 7.68 Hz, ^3J = 7.68 Hz, 1 H, H4), 8.42 (d, ^4J = 1.65 Hz, 1 H, H3′), 8.47 (d, ^3J = 7.68 Hz, 1 H, H5), 8.56 (d, ^3J = 5.49 Hz, 1 H, H6′).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 13.4 (C10), 23.8, 23.9 (2 NCH_2CH_2), 47.0, 51.7 (2 NCH_2CH_2), 106.7 (C9), 113.0 (C3′), 115.6 (C5′), 119.4 (C5), 121.4 (C3), 128.8 (C8), 138.7 (C4), 149.5 (C6′), 151.2 (C6), 156.1 (C2, C2′), 158.7 (C4′).

MS (EI): *m*/*z* (%) = 346.2 ($[C_{20}H_{22}N_6]^+$, 100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_{20}H_{22}N_6]^+$: 346.1905; found: 346.1906.

4-(3,3-Diethyltriaz-1-en-1-yl)-6′-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2,2′-bipyridine (24)

Following the typical procedure for **10** using **3b** (500 mg, 1.99 mmol, 1.1 equiv) and **21** (385 mg, 1.81 mmol) gave the pure product after column chromatography (silica gel, *n*-hexane–EtOAc, 5:1, with 5% Et_3N, R_f = 0.4) as a pale yellow oil; yield: 438 mg (70%).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.23, 1.35 (m, 6 H, 2 NCH_2CH_3), 2.22 (s, 6 H, H10), 3.82 (m, 4 H, 2 NCH_2CH_3), 5.94 (s, 2 H, H9), 7.20 (d, ^3J = 7.7 Hz, 1 H, H5′), 7.31 (dd, ^3J = 5.5 Hz, ^4J = 2.2 Hz, 1 H, H5), 7.92 (dd, ^3J = 7.7 Hz, ^3J = 7.7 Hz, 1 H, H4′), 8.40 (d, ^4J = 2.2 Hz, 1 H, H3), 8.43 (d, ^3J = 7.7 Hz, 1 H, H3′), 8.56 (d, ^3J = 5.5 Hz, 1 H, H6).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 11.1, 14.3 (2 NCH_2CH_3), 13.4 (C10), 41.6, 49.4 (2 NCH_2CH_3), 106.8 (C9), 113.3 (C3), 115.3 (C5), 119.3 (C3′), 121.3 (C5′), 128.8 (C8), 138.6 (C4′), 149.8 (C6), 151.2 (C6′), 156.4 (C2, C2′), 158.3 (C4).

MS (EI): *m*/*z* (%) = 348.2 ($[C_{20}H_{24}N_6]^+$, 100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_{20}H_{24}N_6]^+$: 348.2062; found: 348.2060.

Anal. Calcd for $C_{20}H_{24}N_6$: C, 68.94; H, 6.94; N, 24.12. Found: C, 68.63; H, 7.00; N, 23.45.

6-Amino-4-(3,3-diethyltriaz-1-en-1-yl)-2,2′-bipyridine (25)

Following the typical procedure for **7** using **24** (300 mg, 0.86 mmol) with NH_2OH·HCl (598 mg, 8.61 mmol, 10 equiv) and Et_3N (0.36 mL, 2.58 mmol, 6 equiv) gave **25** after column chromatography (silica gel, CH_2Cl_2–MeOH, 2:1, R_f = 0.1) as a yellow oil; yield: 223 mg (96%).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.18–1.39 (m, 6 H, 2 NCH_2CH_3), 3.79–3.83 (m, 4 H, 2 NCH_2CH_3), 4.56 (br s, 2 H, NH_2), 6.50 (dd, ^3J = 8.1 Hz, ^4J = 0.8 Hz, 1 H, H5), 7.26 (dd, ^3J = 5.4 Hz, ^4J = 2.0 Hz, 1 H, H5′), 7.53 (dd, ^3J = 8.1 Hz, ^3J = 8.1 Hz, 1 H, H4), 7.68 (dd, ^3J = 8.1 Hz, ^4J = 0.8 Hz, 1 H, H3), 8.21 (dd, ^4J = 2.0 Hz, ^5J = 0.6 Hz, 1 H, H3′), 8.53 (dd, ^3J = 5.4 Hz, ^5J = 0.6 Hz, 1 H, H6′).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 11.1, 14.4 (2 NCH_2CH_3), 41.6, 49.5 (2 NCH_2CH_3), 108.7 (C5), 111.8 (C3), 112.9 (C3′), 114.8 (C5′), 138.5 (C4), 149.9 (C6′), 155.1 (C2), 157.4 (C2′), 158.1 (C4′, C6).

MS (EI): *m*/*z* (%) = 170.1 ($[C_{10}H_8N_3]^+$, 100), 270.2 ($[C_{14}H_{18}N_6]^+$, 28).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $[C_{14}H_{18}N_6]^+$: 270.1593; found: 270.1594.

Anal. Calcd for $C_{14}H_{18}N_6$·0.5 EtOAc: C, 61.13; H, 7.05; N, 26.73. Found: C, 61.07; H, 7.00; N, 26.57.

4-(3,3-Diethyltriaz-1-en-1-yl)-6′-hydroxy-2,2′-bipyridine (26)

A soln of **25** (150 mg, 0.55 mmol) in 2 M H_2SO_4 (10 mL) was stirred at –10 °C. A soln of $NaNO_2$ (49 mg, 0.79 mmol, 1.3 equiv) in H_2O (5 mL) was added at this temperature. The mixture was stirred at r.t.

for 45 min and then heated to 80 °C for 1 h. The mixture was neutralized with sat. aq Na_2CO_3 and extracted with CH_2Cl_2 (5 × 15 mL). The combined organic extracts were dried (Na_2SO_4). The pure product was obtained after column chromatography (silica gel, $CHCl_3$–MeOH, 9:1, R_f = 0.4) as a yellow oil; yield: 127 mg (85%).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.37, 1.24 (t, 6 H, 2 NCH_2CH_3), 3.79–3.87 (m, 4 H, 2 NCH_2CH_3), 6.59 (dd, ^3J = 9.1 Hz, ^4J = 0.8 Hz, 1 H, H5′), 6.81 (dd, ^3J = 6.9 Hz, ^4J = 0.8 Hz, 1 H, H3′), 7.31 (dd, ^3J = 5.4 Hz, ^4J = 1.8 Hz, 1 H, H5), 7.45 (dd, ^3J = 9.1 Hz, ^3J = 6.9 Hz, 1 H, H4′), 7.75 (dd, ^4J = 1.8 Hz, ^5J = 0.5 Hz, 1 H, H3), 8.46 (dd, ^3J = 5.4 Hz, ^5J = 0.5 Hz, 1 H, H6), 10.73 (s, 1 H, OH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 11.1, 14.4 (2 NCH_2CH_3), 42.0, 49.8 (2 NCH_2CH_3), 102.5 (C3′), 111.5 (C3), 115.9 (C5), 121.6 (C5′), 140.7 (C4′), 142.5 (C2′), 148.6 (C2), 149.8 (C6), 158.5 (C4), 162.9 (C6′).

MS (EI): *m/z* (%) = 271.1 ($[C_{14}H_{17}N_5O]^+$, 100), 171.0 ($[C_{10}H_7N_2O]^+$, 99).

HRMS (EI): *m/z* $[M]^+$ calcd for $[C_{14}H_{17}N_5O]^+$: 271.1433; found: 271.1436.

Anal. Calcd for $C_{14}H_{17}N_5O{\cdot}0.125\ CH_2Cl_2$: C, 60.17; H, 6.17; N, 24.84. Found: C, 60.24; H, 6.52; N, 24.44.

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