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Regioselective Functionalization of 2,2′-Bipyridine and Transformations into Unsymmetric Ligands for Coordination Chemistry

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Dedicated to Professor Lennart Eberson on the occasion of his 65th birthday

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Novel synthetic strategies for a series of unsymmetrically substituted 2,2′-bipyridines have been developed. These bipyridines have found use in some novel homoleptic and heteroleptic ruthenium(II) complexes. Two methods for regiochemical control of nucleophilic addition to bpy have been explored: (i) mono *N*-oxidation followed by cyanation and subsequent hydrolysis gave 6-carboxy-2,2′-bipyridine (**4**); (ii) mono *N*-methylation followed by the conversion into 6-bromo-2,2′-bipyridine (**12**) and subsequent nucleophilic addition of lithioacetonitrile followed by hydrolysis of 6-cyanomethyl-2,2′-bipyridine (**8**) gave the homologous 2,2′-bipyridine-6-acetic acid (**9**). An established method of regioselective mono-ring alkylation of bpy using methyllithium yielded 6-methyl-2,2′-bipyridine (**14**), and the generation of the anion of **14** and subsequent addition to a chloromethyl oxazoline was applied to synthesize a second homologue, methyl 2,2′-bipyridine-6-propanoate (**16**). Structural determinations using ^{1}H, ^{13}C and 2D NMR spectroscopy permitted complete assignments of all signals in the ^{1}H NMR spectra.

The bipyridine[1] and terpyridine[2] families of heterocyclic ligands have been employed extensively within the field of photo-induced electron transfer studies of ruthenium(II) and osmium(II) mono-, bi- and polynuclear complexes.[3] We have initiated a study of methods for the preparation of 6-substituted 2,2′-bipyridines, which are potential ligands in homoleptic and heteroleptic ruthenium(II) complexes. Depending on the coordination preferences of the ligand used (**4**, **5**, **9**, **14** or **16**) or the sequence of the synthetic procedure, they may function as bi- or terdentate ligands in heteroleptic Ru^{II} complexes containing ruthenium–nitrogen and ruthenium–oxygen bonds.[4] Our investigations in the field of ruthenium polypyridine chemistry have been extended into a program aimed at developing simple artificial model systems[5] based on the ruthenium polypyridine moiety, which mimic the essential functions of the photosynthetic reaction center (Photosystem II) in green plants.[6]

Although there are several general methods to synthesize substituted polypyridines, only a limited number of reports regarding bipyridines bearing a single functionalized side chain have appeared.[7] We set out to utilize the readily available starting material 2,2′-bipyridine (bpy) (**1**), and thus have looked at the problem of regioselective functionalization of the 6-position of bpy (*ortho* to the pyridine nitrogen), as an alternative to ring syntheses[8] or coupling reactions.[1,8a,9] We will compare our results with alternative synthetic methods which have been reported, in terms of factors such as overall yield and expeditiousness. We also report fully assigned ^{1}H NMR data for compounds **2**–**16**, supported by 2D NMR and decoupling techniques. Three general approaches to regioselective functionalization of bpy have been utilized in this study (Fig. 1): (i) *N*-oxidation followed by cyan-

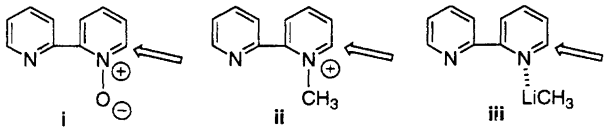

Fig. 1. Regio-directing *N*-oxide, *N*-methyl and *N*-lithium complexes employed as starting points for the regioselective functionalization of 2,2′-bipyridine.

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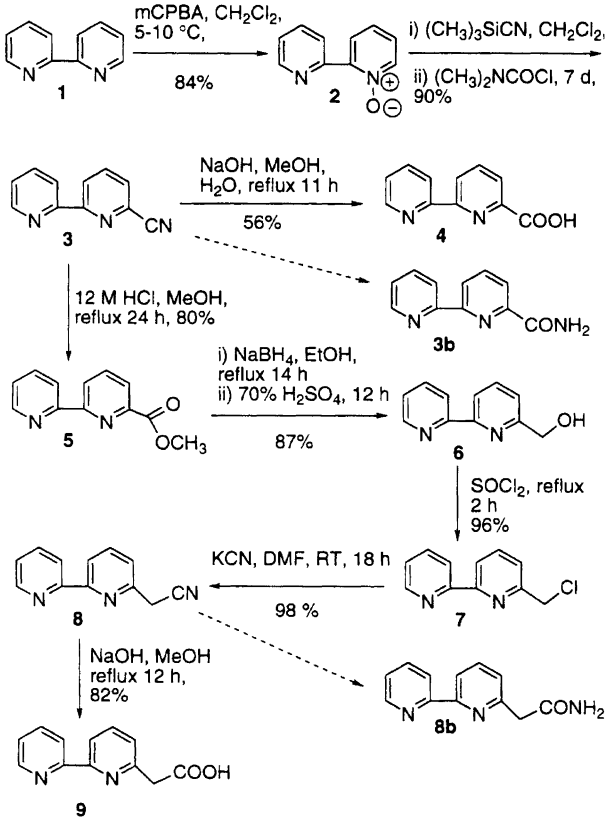
ation; (ii) *N*-methylation followed by hydroxylation and oxidation to a pyridone, and (iii) the formation of a *N*-Li complex acting as regiodirector in the pyridine ring alkylation using methyllithium.

Procedures starting with N-*oxidation and regioselective cyanation of 2,2-bipyridine (Scheme 1).* 2,2′-Bipyridine-*N*-oxide (**2**)[10] was obtained in 80% yield by the oxidation of bpy (**1**) with *meta*-chloroperbenzoic acid (mCPBA) in dichloromethane. The introduction of a cyano group regiospecifically in the 6-position by an application of Fife's modification[11] (employing carbamoyl chloride and trimethylsilylcyanide in dichloromethane) of the Reissert–Henze cyanation of pyridine *N*-oxides yielded 6-cyano-bpy (**3**)[12] in improved yield (90%) compared to previous reports.

The 6-carboxy-bpy (**4**)[8a,13] was obtained by prolonged refluxing (11 h) of an alkaline aqueous methanolic solution of nitrile **3**, followed by neutralization, evaporation and extraction of the solid residue with abs. methanol. Recrystallization from ethanol–water afforded pure **4**. If the duration of the hydrolysis reaction was shorter, ca. 3 h, a substantial amount (20%) of the amide intermediary **3b** could be isolated. One practical difficulty encountered was the isolation of the bipyridine carboxylic acids analytically pure, free from inorganic content (accordingly, they are sometimes reported as an ester derivate, e.g. Ref. 14). This is probably due to a combination of



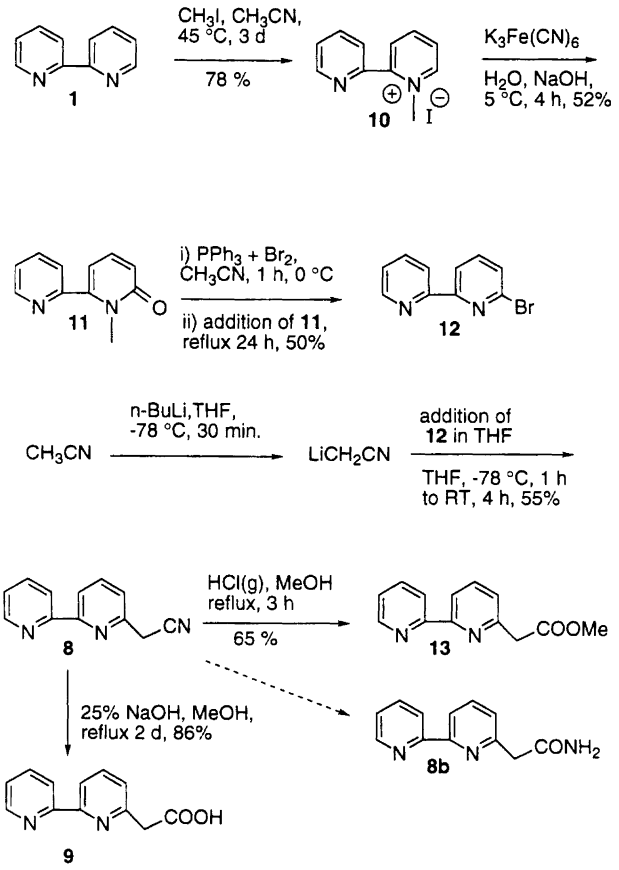
Scheme 1.

two properties of these compounds: the strong chelating power of these acids, giving complexes with the cations present (Na^+, K^+ etc. depending on the synthetic procedure); and the very low solubility of these acids, which generally leads to rapid precipitation (giving inclusion phenomena etc.) upon acidification of the water phase which usually is the isolation step of the synthetic procedure. The hydrolysis of a nitrile is expected to proceed in very high yield (albeit slowly), but in the case of pyridine-type carboxylic acids, the isolated yields typically[15] are ca. 65–85%, depending on the presence of other substituents and the overall solubility of the product, which affects the isolation and purification procedures.

The 6-cyano-bpy (**3**) was also utilized in one synthetic route to 2,2′-bipyridine-6-acetic acid (**9**). The first step was methanolysis of **3** to the methyl ester **5** by refluxing for 24 h in conc. aq. hydrochloric acid and methanol, under an atmosphere of argon (to protect from possible oxidative degradation). Methanolysis under Pinner conditions, refluxing methanol under constant bubbling with dry HCl gas, was also attempted. After 2 h the starting material was consumed, but the isolated yield of **5** was ca. 68%, and the corresponding amide **3b** (m.p. 151–153 °C) was isolated in ca. 20% yield. The 6-hydroxymethyl-bpy (**6**)[8a,9a] was then obtained in 87% yield by the $NaBH_4$ reduction of **5** in refluxing ethanol, followed by standard acidic work-up. The conversion of **6** to 6-chloromethyl-bpy (**7**) by refluxing in $SOCl_2$ represents a rather useful improvement on the established syntheses of **6** involving free-radical *N*-chlorosuccinimide (NCS) chlorination of 6-methyl-bpy (**14**) in CCl_4 (60% yield).[7d] When **7** was treated with KCN in DMF for 18 h in room temperature, 6-cyanomethyl-bpy (**8**) was obtained in 98% yield. In the next section we present an additional synthetic route to **8**.

Finally, 2,2′-bipyridine-6-acetic acid (**9**) was obtained in 82% yield by the methanolysis of **8** by refluxing with NaOH overnight in methanol, followed by hydrolytic work-up in water of the iminoester intermediate. To conclude, by the reactions in Scheme 1, overall yields from bipyridine of ca. 42% of 6-carboxy-bpy (**4**), and ca. 40% of the 2,2′-bipyridine-6-acetic acid (**9**) were obtained.

Procedures starting with N-*alkylation and regioselective 2,2-bipyridine-6-one formation (Scheme 2).* Bipyridine (**1**) was converted into 1-methyl-2,2′-bipyridinium iodide (**10**)[16] in 78% yield by treatment with an excess of methyl iodide in warm acetonitrile for several days. The *N*-methylation makes the bipyridine ring susceptible to nucleophilic attack by hydroxide ion, and the resulting dihydropyridine is oxidized by ferricyanide in a one-pot reaction yielding 1-methyl-2,2′-bipyridin-2-one (**11**)[12b] in 52%. Regioselective bromination using the bromo-(triphenyl)phosphonium bromide complex gave 6-bromo-bpy (**12**)[8a,9a,12b,13a] in ca. 50% yield. This procedure is an adaptation of a method developed in-house for the selective bromination of phenanthroline.[17]

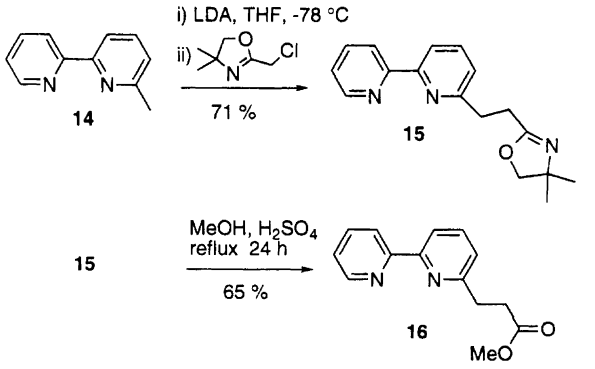


Scheme 2.

The 6-cyanomethyl-bpy (**8**) was then obtained in 65% yield by the addition of lithioacetonitrile to **12** at −78 °C in dry THF. The use of the nucleophile lithioacetonitrile is an adaptation of a method for the ring synthesis of annelated pyridines.[8g] We could never successfully add lithioacetonitrile to *N*-oxide **2** (ring-opening products) nor directly to bpy itself: an adduct of *n*-butyllithium (*n*-BuLi), 6-butyl-bpy was isolated in low yield if an excess of *n*-BuLi was used.

In contrast to 6-cyano-bpy (**3**), the 6-cyanomethyl-bpy (**8**) was converted into the methyl-2,2′-bipyridine-6-acetate (**13**) in 65% yield under Pinner conditions. Finally, 2,2′-bipyridine-6-acetic acid (**9**) was obtained in 86% yield by the hydrolysis of **8** in refluxing 25% NaOH and methanol for 2 days and subsequent work-up. To conclude, by the reactions in Scheme 2, an overall yield of ca. 10% of 2,2′-bipyridine-6-acetic acid (**9**) was obtained.

Procedures starting with N-*lithium complexation and regioselective ring alkylation (Scheme 3).* Ring alkylation of bpy using methyllithium in ether followed by oxidative re-aromatization of the intermediary dihydropyridine species gave 6-methyl-bpy (**14**) by the method of Kauffmann *et al.*[18] The 6-methyl group of **14** was deprotonated using LDA in THF, and 2-chloromethyl-4,4-dimethyl-2-oxazoline, obtained by the method of Breton



Scheme 3.

et al.,[19] was added rapidly. This procedure gave a fairly clean product in good yield (91%). The use of LDA to deprotonate methyl substituents on bpy has been applied to 4,4′-dimethyl-bpy, but yields in the subsequent reactions with various electrophiles have generally been lower.[7a,20] The improved yield obtained by our method could be explained by an effect of the coordination of the lithium ion by the adjacent pyridine nitrogen, giving a more 'naked' and reactive nucleophile. Chromatography of the crude oxazoline may be excluded at this stage of the preparation, since it causes an unnecessary lowering of the product yield. The phenomenon of unsatisfactory mass balance of chromatographic steps is frequently encountered in the preparative chemistry of the polypyridine family, due to the strong binding of these chelators to chromatographic stationary phases.[21]

The oxazoline **15** was converted into the methyl ester **16** according to the method of Meyers *et al.*,[22] with a minor modification of the work-up procedure: water was added to the reaction mixture after cooling, and solid Na_2CO_3 was used to make the solution alkaline before extraction with dichloromethane, which yielded **16** in 92%. After chromatography, a clear oil was obtained in moderate yield (65%).

Results and discussion

To the best of our knowledge compounds **5**, **8**, **9**, **13**, **15** and **16** have not been described previously. The previous methods reported for the remaining compounds **2**, **3**, **4**, **6**, **7**, **10**, **11**, **12** and **14** are reviewed in the following discussion.

The use of 2 M NaOH in the work-up of the *N*-oxide **2** led to a slight improvement of the yield, and the use of dichloromethane is generally preferable to chloroform. The cyanation of pyridine *N*-oxides using carbamoyl chloride as the acylating agent and trimethylsilylcyanide as cyanide source under mild conditions yielded 6-cyano-bpy (**3**) in improved yield (90%) compared to previous reports, where **3** was prepared under the classic Reissert–Henze conditions, benzoyl chloride and KCN (62% yield),[12a] or from 6-bromo-bpy (**12**) and conc. aq. KCN (65%).[12b]

The overall yield of 6-carboxy-bpy (**4**) obtained by our procedure (Scheme 1) was ca. 42%, which is clearly competitive compared to earlier methods. In Burstall's classic study,[13a] no final yield is stated for the hydrolysis of **3** in 12 M HCl followed by purification of **4** via the Cu^{II} complex. Carboxylation, using carbon dioxide, of the lithium salt of the 6-bipyridyl anion, obtained from lithiation of 6-bromo-bpy (**12**), has been reported by Tsuchia and Seno (no yield stated),[23] while Parks *et al.*[13c] obtained a 27% yield of **4** by a method combining carboxylation of the 6-bipyridyl anion and purification via the Cu^{II} complex in a manner similar to that of Burstall.[13a] Compound **4** was reported to form in 50% yield by the anionic oxidation of 6-methyl-bpy **14**, as part of a ring-synthesis strategy to synthesize 6-acetyl-bpy.[8a] Compound **14**, in turn, is usually obtainable in ca. 71% yield by Potts' method,[8c] so an estimated overall yield of ca. 36% of **4** could be expected.

The 6-hydroxymethyl-bpy (**6**) was obtained in 53% yield from bpy (**1**) (Scheme 1). Compound **6** has also been reported by Uenishi *et al.*[9a] by the trapping of the 6-bipyridyl anion, again obtained via lithiation of 6-bromo-bpy (**12**), with dimethyl formamide (DMF), giving 6-formyl-bpy, which was reduced by $NaBH_4$ in a facile one-pot reaction. The yield of **6** was 63% in one step from **12**, or for comparison, in 51% overall yield from 2,6-dibromopyridine, which was the starting material for the very elegant coupling reaction yielding **12** in 80% yield (*vide infra*). Potts reported the hydrolysis of bromomethylene-substituted pyridines, by Na_2CO_3 in dioxane (no yield stated), to hydroxymethylene-substituted pyridine species which were used as intermediates in the synthesis of complex multi-pyridine ligands.[8a]

We obtained 6-chloromethyl-bpy (**7**) in 51% overall yield from bpy (**1**) (Scheme 1) by the very efficient conversion of the 6-hydroxymethyl-bpy (**6**) in refluxing $SOCl_2$. Newkome *et al.*[7d] reported a crude product yield of 60% (based on **14**), by the NCS chlorination of 6-methyl-bpy (**14**) in CCl_4, in the presence of a catalytic amount of benzoyl peroxide. As a by-product they also obtained 25% of 6-dichloromethyl-bpy, and the two were separated by chromatography (no final yield stated). The final step of Scheme 1 is the nitrile hydrolysis of **8**, yielding **9** in 82% [ca. 10% from bpy (**1**)]. The two main problems are (i) the long reaction times needed, in order to completely hydrolyze the nitrile and the amide intermediate **8b**, and (ii) the practical difficulties encountered in the isolation and purification of **9**.

N-Methyl bipyridinium iodide (**10**) was first prepared by Westheimer and Benfey in 60% yield by a sealed-tube procedure (2 h, 100 °C, methyl iodide in MeOH).[16] Our preparation employing methyl iodide in warm acetonitrile yields 78%, a moderate improvement. 1-Methyl-2,2′-bipyridin-2-one (**11**) was first reported by Case[12b] (54.3% yield) in a procedure involving ferricyanide oxidation in an alkaline aq. solution of **10**. We obtained **11** in 52% yield using the analogous method of Lewis and O'Donoghue[24] who, curiously, make no reference the work by Case.

6-Bromo-bpy (**12**) is one of the early precursors available in the bipyridine field: Burstall[13a] first used the gas-phase bromination at 500 °C to obtain **12** in 'modest' yield (not stated). Case[12b] obtained **12** in 47% yield, from the pyridone **11** added to ice-cold PBr_3 and Br_2 in phosphoryl bromide ($POBr_3$), followed by heating at 120–130 °C for 2.5 h (47% yield). Parks *et al.*[13c] reported a $CuCl_2$-mediated coupling reaction between 2-bromopyridine and 2,6-dibromopyridine lithiated at −90 °C in THF giving **12** in 23% yield. Uenishi *et al.* recently reported[9a] **12** in 80% yield, by a very elegant coupling method involving ethyl 2-pyridyl sulfoxide[25] acting as a quencher for the lithiopyridine species obtained via metal-halogen exchange of 2,6-dibromopyridine and *n*-butyl lithium (0.94 eq.) in ether/THF/hexanes (2 : 1 : 1). We used an adaptation from a procedure developed in-house for the selective bromination of phenanthroline by Sjögren *et al.*[17] to obtain **12** in 50% from **11**, ca. 21% overall yield from bpy which might be improved by a careful optimization of the conversions **10** into **11**, and especially **11** into **12** which was expected to give ca. 75% yield in analogy with Sjögren's report.

Conclusions

We have successfully applied three different types of regioselective functionalization to the development of unsymmetric bipyridine ligands for our Ru^{II} coordination chemistry studies. Some novel substituted bipyridines, compounds **5**, **8**, **9**, **13**, **15** and **16**, have been presented. The procedure shown in Scheme 1 emerges as the best route so far to the bipyridine carboxylic acids **4** and **9**. The application of lithioacetonitrile in the nucleophilic substitution of 6-bromo-bpy (**12**) has not previously been reported. The very facile conversion of 6-hydroxymethyl-2,2′-bipyridine (**6**) into 6-chloromethyl-2,2′-bipyridine (**7**) using $SOCl_2$ represents an alternative to the established method using NCS free-radical chlorination, and gives comparable to better overall yield. The use of the nucleophile derived from 6-methyl-bpy (**14**) in the reaction with an oxazoline represents a practical way to introduce the two-carbon spacer unit in this type of substituted bipyridines. The complete set of ^1H and ^{13}C NMR data (see Experimental) has proven useful in the further development and characterization of novel ruthenium(II) complexes involving substituted bipyridine ligands.

Experimental

Methods. The NMR spectra of the ligands **1**–**16** were recorded in deuterated chloroform, methanol or water on Bruker ACF 250 (250 MHz proton), AM 400 (400 MHz proton) or DMX 500 (500 MHz proton) instruments; unless stated otherwise in the experimental part the spectra were obtained at 400 MHz proton

(100 MHz carbon). Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS (tetramethylsilane). IR spectra (KBr disks) were recorded on a Perkin–Elmer 1725 FT-IR spectrometer or Bruker ISF 25 FT-IR spectrometer. Melting points were obtained on a Büchi apparatus and are uncorrected. Analytical TLC was performed on precoated aluminium oxide gel 60 F_{254} plates (Al_2O_3, neutral, Merck) with UV detection. Aluminium oxide gel (Al_2O_3, neutral, Brockmann I, 150 mesh, Aldrich) was used for preparative column chromatography. The electrospray ionization mass spectrometry (ESI-MS) and gas chromatography electron ionization (GC-EI) experiments were performed on a ZabSpec mass spectrometer (VG Analytical, Fisons instrument). Electrospray conditions were: needle potential, 3 kV; acceleration voltage, 4 kV; bath and nebulizing gas, nitrogen. Liquid flow was 50 μL min^{-1} using a syringe pump (Phoenix 20, Carlo Erba, Fisons instrument). Solvent composition was: 50% acetonitrile–50% water containing 1% acetic acid. Accurate mass measurements were obtained by the use of polyethylene glycol (PEG) as an internal standard. GC-EI: Gas chromatography was performed with a capillary column coated with SE-54 (11 m × 0.25 mm) using a temperature program (injector temp., 250 °C; column temp. program 70 °C for 2 min, then increased 10 °C min^{-1} to 270 °C), ionization potential, 70 eV.

Materials. Reactions under anhydrous conditions were performed under argon. Dichloromethane and diisopropylamine were distilled from CaH_2 under a constant flow of nitrogen. Tetrahydrofuran (THF) and diethyl ether (ether) were freshly distilled from sodium/benzophenone ketyl radical under a flow of dry nitrogen. For extraction and chromatography purposes, diethyl ether, ethyl acetate and dichloromethane (supplied by Kebo AB, Sweden, grade purum) and hexanes (b.p. 60–80 °C) (Shell, polymer grade) were distilled prior to use. Deionized water was used in all experiments. Dichloromethane (CH_2Cl_2), acetonitrile, and methanol of 99+% HPLC grade (Aldrich), ethanol (99.5%, Kemetyl, Sweden) and 2,2′-bipyridine (Aldrich, 99%, pro analysi) were used as received. The bipyridine *N*-oxides are potent toxins (target: kidney function) and have been associated with poisoning by ingestion of wild mushrooms. Appropriate safety measures should therefore be taken in the handling of compound **2**. All substances containing the halomethyl functional group are **powerful irritants** and **lachrymators**, and like other alkylating agents they should be handled with prudence considering their **possible mutagenecity**.

Analyses. The analyses (carbon, hydrogen and nitrogen, reported in mass %) were performed by Analytische Laboratorien GmbH, D-51789 Lindlar, Germany.

Syntheses.

2,2′-Bipyridine-N-*oxide* (**2**). The mono *N*-oxide **2** was prepared according to Ref. 10 with a slight modification. To a solution of bpy (**1**) (7 g, 45 mmol) in CH_2Cl_2 (50 mL) was added dropwise a solution of 3-chloroperbenzoic acid (mCPBA) (10 g, 80–90%, Aldrich) in CH_2Cl_2 (80 mL) at 5–10 °C. The reaction mixture was stirred at room temperature overnight. 2 M NaOH (100 mL) was added at 0 °C and the mixture was stirred for 15 min. The organic layer was separated and washed with 2 M NaOH (100 mL) once more. The combined basic washings were extracted with CH_2Cl_2 (3 × 100 mL). The CH_2Cl_2 phase was dried over solid Na_2CO_3 and evaporated to give *N*-oxide **2** (5.3–6.5 g, 31–38 mmol, 69–84%). Recrystallization from ether/hexanes of a sample gave white crystals, m.p. 55–56 °C (lit.[26] 58.5–59.5 °C). TLC: $R_f \approx 0.80$ (**2**), ≈0.96 (**1**) (Al_2O_3, 5% MeOH in CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$): δ 8.90 (dd, $J=0.9$, 7.2 Hz, 1 H, H-3); 8.73 (ddd, $J=0.9$, 1.7, 3.9 Hz, 1 H, H-6); 8.32 (dd, $J=0.9$, 6.5 Hz, 1 H, H-6′); 8.19 (dd, $J=2.2$, 8.0 Hz, 1 H, H-3′); 7.84 (ddd, $J=1.8$, 7.7, 7.9 Hz, 1 H, H-4), 7.42–7.27 (m, 3 H, H-4′, H-5, H-5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 149.4, 147.3, 140.7, 136.2, 127.9, 125.6, 125.5, 125.2, 124.2.

6-Cyano-2,2′-bipyridine (**3**). A solution of 2,2′-bipyridine-*N*-oxide (**2**) (0.86 g, 5 mmol) and Me_3SiCN (0.55 g, 0.78 mL, 5.5 mmol) (**CAUTION**! Highly toxic cyanide equivalent: handle with care!) in CH_2Cl_2 (10 mL) was stirred for 5 min at room temperature. *N,N′*-Dimethylcarbamoyl chloride (0.59 g, 0.5 mL, 5.5 mmol) was added, and stirring continued for 7 days. Ether (80 mL) was added and the resultant solution was washed with 5% $NaHCO_3$, brine (satd. aq. NaCl) and dried over solid Na_2CO_3. The solvent was evaporated to give crude **3** (1.13 g). The crude product was crystallized from ether/hexanes to give a pure product (0.82 g, 4.5 mmol, 90%), m.p. 132–133 °C (lit.[12b] 130–131 °C).

TLC: $R_f \approx 0.55$ (**3**), 0.1 (**2**), 0.65 (**1**) (Al_2O_3, 10% CH_2Cl_2 and 36% ether in hexanes). Elemental analysis: calc. for $C_{11}H_7N_3$: C, 72.92; H, 3.89; N, 23.19. Found: C, 73.19; H, 3.96; N, 23.11. ^1H NMR ($CDCl_3$): δ 8.68 (ddd, $J=1.0$, 1.8, 4.8 Hz, 1 H, H-6′), 8.66 (dd, $J=1.1$, 8.2 Hz, 1 H, H-3), 8.45 (ddd, $J=1.0$, 1.2, 8.0 Hz, 1 H, H-3′), 7.94 (dd, $J=7.6$, 8.2 Hz, 1 H, H-4), 7.85 (ddd, $J=1.8$, 7.5, 8.0 Hz, 1 H, H-4′), 7.69 (dd, $J=1.1$, 7.6 Hz, 1 H, H-5), 7.37 (ddd, $J=1.2$, 4.8, 7.5 Hz, 1 H, H-5′). ^{13}C NMR ($CDCl_3$): δ 157.7, 154.0, 149.3, 137.9, 137.2, 133.2, 128.1, 124.8, 124.2, 121.58, 117.4.

6-Carboxy-2,2′-bipyridine (**4**). A solution of 6-cyano-bpy **3** (165 mg, 0.9 mmol) and NaOH (320 mg, 8 mmol, 8.8 eq.) in MeOH (10 mL, 99+%) and water (10 mL, deionized) was refluxed for 11 h under argon. The clear solution was evaporated to half the volume at the rotary evaporator (to remove the MeOH) and filtered through a glass frit (P3). The pH was adjusted to ca. 6.5 with 6 M HCl, and the solution was extracted with CH_2Cl_2

(3 × 20 mL) to remove any remaining **3** or the hydrolysis intermediate 6-carboxamido-bpy (**3b**) (m.p. 151–152 °C). The water phase was evaporated to dryness at the rotary evaporator, and the residue extracted with MeOH (99+%), filtered and evaporated again. This extraction process was repeated, and the resulting solid recrystallized from EtOH: H_2O (10:1 by vol.) to give **4** (102 mg, 0.5 mmol, 56%), m.p. dec. 220–230 °C (lit.[13a] 210–220 °C).

TLC: $R_f \approx 0.0$ (**4**), 0.93 (**3**), 0.57 (**3b**) (Al_2O_3, 5% MeOH in CH_2Cl_2). ESI-MS found 201.065 *m/z*, calc. for $[4+H]^+$ 201.066 *m/z* ($C_{11}H_9N_2O_2$). Elemental analysis: calc. for $C_{11}H_8N_2O_2$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.76; H, 4.17; N, 13.89. ^{1}H NMR (MeOH-d_4): δ 8.69 (ddd, J=0.9, 1.7, 5.0 Hz, 1 H, H-6′); 8.56 (ddd, J=0.9, 1.2, 7.9 Hz, 1 H, H-3′); 8.53 (dd, J=1.2, 7.9 Hz, 1 H, H-3); 8.20 (dd, J=1.2, 7.6 Hz, 1 H, H-5); 8.12 (dd, J=7.6, 7.9 Hz, 1 H, H-4); 8.02 (ddd, J=1.8, 7.6, 7.9 Hz, 1 H, H-4′); 7.51 (ddd, J=1.2, 5.0, 7.5 Hz, 1 H, H-5′). The assignment of the protons is supported by 2D NMR (NOESY). ^{13}C NMR (MeOH-d_4): δ 168.2, 156.5, 155.8, 150.0, 149.2, 140.0, 139.5, 126.1, 126.0, 125.6, 123.4. IR (KBr, cm^{-1}): 1734(s), C=O.

6-Methoxycarbonyl-2,2′-bipyridine (**5**). A solution of 6-cyano-bpy (**3**) (600 mg, 3.3 mmol) and HCl (12 M, 10 mL) in MeOH (50 mL, 99+%) was refluxed for 24 h under argon. Most of the MeOH was removed at the rotary evaporator, and the resulting acidic water solution was immediately cooled at 0 °C. Water (45 mL) and solid Na_2CO_3 were added to ca. pH 7. This solution was extracted with CH_2Cl_2 (4 × 50 mL) and evaporated at the rotary evaporator to give crude **5** (568 mg, 2.65 mmol, 80%). Sublimation (oil bath 90 °C, pump vacuum ca. 1 Torr) gave pure **5** (523 mg, 2.44 mmol, 74%), m.p. 83.5–84 °C. TLC: $R_f \approx 0.33$ (**5**), 0.40 (**3**) (Al_2O_3, 40% ether in hexanes). Elemental analysis: calc. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.36; H, 4.67; N, 12.91. ^{1}H NMR ($CDCl_3$): δ 8.68 (ddd, J=0.9, 1.8, 4.8 Hz, 1 H, H-6′), 8.60 (dd, J=1.2, 7.9 Hz, 1 H, H-3), 8.54 (ddd, J=1.1, 1.2, 8.0 Hz, 1 H, H-3′), 8.13 (dd, J=1.1, 7.7 Hz, 1 H, H-5), 7.96 (dd, J=7.7, 7.9 Hz, 1 H, H-4), 7.84 (ddd, J=1.8, 7.7, 7.8 Hz, 1 H, H-4′), 7.34 (ddd, J=1.2, 4.8, 7.6 Hz, 1 H, H-5′), 4.04 (s, 3 H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 165.8, 156.4, 155.2, 149.2, 147.5, 137.9, 137.1, 125.0, 124.3, 124.2, 121.7, 52.8. IR (KBr, cm^{-1}): 1719(s), C=O.

6-Hydroxymethyl-2,2′-bipyridine (**6**). To a solution of 6-methoxycarbonyl-bpy (**5**) (6.34 g, 29.6 mmol) in ethanol (200 mL) was added $NaBH_4$ (3.15 g, 83.3 mmol), and the solution was refluxed for 14 h. The reaction mixture was allowed to cool to room temperature, water (20 mL) and 70% H_2SO_4 (5 mL) were added, and stirring was maintained overnight. 2 M NaOH was added to adjust the pH to 9, and the resulting mixture was stirred at room temperature for 2 h, then filtered and evaporated at the rotary evaporator. The residue was extracted with 1% MeOH in CH_2Cl_2. Concentration of the extract gave **6** as an oil (4.75 g, 25.8 mmol, 87%). TLC: $R_f \approx 0.53$ (**5**), 0.11 (**6**) (Al_2O_3, 1% MeOH in CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 8.65 (ddd, J=1.0, 1.8, 4.8 Hz, 1 H, H-6′), 8.37 (ddd, J=1.0, 1.2, 7.9 Hz, 1 H, H-3′), 8.28 (dd, J=0.9, 7.8 Hz, 1 H, H-3), 7.79 (ddd, J=1.8, 7.7, 7.8 Hz, 1 H, H-4′), 7.78 (dd, J=7.7, 7.8 Hz, 1 H, H-4), 7.29 (ddd, J=1.2, 4.8, 7.6 Hz, 1 H, H-5′), 7.24 (dd, J=0.8, 7.7 Hz, 1 H, H-5), 4.81 (s, 2 H, CH_2OH), 4.27 (s, exchange br., 1 H, CH_2O*H*). ^{13}C NMR ($CDCl_3$) d: 158.3, 155.6, 154.7, 149.2, 137.6, 136.9, 123.8, 121.0, 120.4, 119.6, 63.9.

6-Chloromethyl-2,2′-bipyridine (**7**). To neat 6-hydroxymethyl-bpy (**6**) (4.75 g, 25.2 mmol) was added $SOCl_2$ (30 mL) dropwise with stirring at room temperature. The mixture was then refluxed for 2 h. Excess $SOCl_2$ was evaporated at the rotary evaporator. Water (20 mL) was added and solid Na_2CO_3 was used to neutralize the solution to pH 7.5. The mixture was extracted with ether (3 × 100 mL). The combined ether phases were washed with brine and dried over solid Na_2CO_3. The solution was concentrated to give **7** as an oil (4.95 g, 24.2 mmol, 96%). TLC: $R_f \approx 0.04$ (**6**), 0.65 (**7**) (Al_2O_3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 8.68 (ddd, J=1.0, 1.8, 4.8 Hz, 1 H, H-6′), 8.44 (ddd, J=1.0, 1.2, 7.8 Hz, 1 H, H-3′), 8.34 (dd, J=0.75, 7.9 Hz, 1 H, H-3), 7.85 (dd, J=7.7, 7.9 Hz, 1 H, H-4), 7.82 (ddd, J=1.8, 7.5, 7.8 Hz, 1 H, H-4′), 7.50 (dd, J=0.75, 7.7 Hz, 1 H, H-5), 7.32 (ddd, J=1.2, 4.8, 7.5 Hz, 1 H, H-5′), 4.75 (s, 2 H, CH_2Cl). ^{13}C NMR ($CDCl_3$): δ 165.1, 156.1, 155.7, 149.2, 137.9, 136.9, 123.9, 122.7, 121.3, 120.3, 46.9.

*6-Cyanomethyl-2,2′-bipyridine (**8**), Procedure A.* To a solution of 6-chloromethyl-bpy (**7**) (2.26 g, 11 mmol) in DMF (20 mL) was added KCN (1.44 g, 22 mmol). The reaction solution was stirred at room temperature for 18 h. Water (50 mL) was added and the solution was extracted with ether (3 × 100 mL). The combined ether phases were washed with brine and dried over solid Na_2CO_3. The solvent was removed at the rotary evaporator to give crude **8** (2.10 g, 10.8 mmol, 98%). Purification by column chromatography (Al_2O_3, eluent CH_2Cl_2) gave pure **8** (1.77 g, 9.6 mmol, 87%), m.p. 67–68 °C. TLC: $R_f \approx 0.65$ (**7**), 0.42 (**8**) (Al_2O_3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 8.68 (ddd, J=0.9, 1.8, 4.8 Hz, 1 H, H-6′), 8.44 (ddd, J=0.9, 1.2, 8.1, 1 H, H-3′), 8.38 (dd, J=0.7, 8.0 Hz, 1 H, H-3), 7.86 (dd, J=7.7, 8.0 Hz, 1 H, H-4), 7.83 (ddd, J=1.8, 6.0, 8.1 Hz, 1 H, H-4′), 7.42 (dd, J=0.7, 7.7 Hz, 1 H, H-5), 7.31 (ddd, J=1.2, 4.8, 6.0 Hz, 1 H, H-5′), 4.02 (s, 2 H, CH_2CN). ^{13}C NMR ($CDCl_3$): δ 156.3, 155.3, 149.8, 149.2, 138.3, 137.0, 124.1, 122.0, 121.3, 120.2, 117.1, 26.8.

*2,2′-bipyridine-6-acetic acid (**9**), Procedure A.* To a solution of 6-cyanomethyl-bpy (**8**) (2.10 g, 10.8 mmol) in methanol (50 mL) was added NaOH (1 g, 25 mmol). The solution was refluxed overnight, then concentrated to dryness at the rotary evaporator. Water (50 mL) was added and the solution was extracted with CH_2Cl_2

(2 × 50 mL). The water phase was neutralized to pH 7.5 with 70% sulfuric acid and evaporated to dryness at the rotary evaporator. The residue was extracted with a small amount of methanol (99+%). After filtration and concentration, crude **9** was obtained, and recrystallized from acetone/methanol to give **9** (1.89 g, 8.8 mmol, 82%), m.p. 193–195 °C with slight decomp. ^{1}H NMR (MeOH-d_4) : δ 8.62 (ddd, J=0.9, 1.7, 4.8 Hz, 1 H, H-6′); 8.41 (ddd, J=0.9, 1.2, 8.0 Hz, 1 H, H-3′); 8.08 (dd, J=0.9, 7.9 Hz, 1 H, H-3); 7.95 (ddd, J=1.7, 7.6, 8.0 Hz, 1 H, H-4′); 7.82 (dd, J=7.7, 7.9 Hz, 1 H, H-4); 7.43 (dd, J= 0.9, 7.7 Hz, 1 H, H-5); 7.41 (ddd, J=1.2, 4.8, 7.6 Hz, 1 H, H-5′), 3.79 (s, 2 H, CH_2). ^{13}C NMR (MeOH-d_4): δ 178.7, 159.4, 157.7, 156.3, 150.0, 138.6, 138.5, 125.3, 125.0, 123.1, 119.8, 48.8. IR (KBr, cm^{-1}): 1703(s), C=O.

1-Methyl-2′2-bipyridinium iodide (**10**). A solution of bpy (**1**) (20 g, 128 mmol) and methyl iodide (54 g, 24 mL, 384 mmol, 3 eq. Merck, *pro synthesis*) in CH_3CN (Aldrich SureSeal, 250 mL) was heated to 45 °C under argon for 3 days. A orange–yellow precipitate of the dialkylated product (*N,N′*-dimethylbipyridinium diiodide) was apparent already at 45 °C, and some more precipitated upon cooling to room temperature. The *N,N′*-dimethylbipyridinium diiodide (9.20 g, 20.9 mmol, 16%) was removed by filtration, and the solid washed with several small portions of CH_3CN. Ether (100 mL) was added to the CH_3CN filtrate, and pure **10** crystallized as white–yellow needles (29.63 g, 99.4 mmol, 78%), m.p. 143–145 °C (lit.[16] 144–145 °C).

TLC: $R_f \approx 0.97$ (**1**), 0.65 (**10**), 0.2 (*N,N′*-dimethylbipyridinium diiodide) (Al_2O_3, EtOAc: MeOH: glacial HOAc: H_2O 15: 5: 1: 1 by vol.). ^{1}H NMR ($CDCl_3$): δ 9.59 (ddd, J=Hz, 1 H, H-6); 8.78 (ddd, J=1.0, 1.6, 4.9 Hz, 1 H, H-6′); 8.66 (dt, J=1.6, 8.1 Hz, 1 H, H-4); 8.24 (dt, J=1.7, 7.0 Hz, 1 H, H-5); 8.12 (J=0.9, 1.2, 7.9 Hz, 1 H, H-3′); 8.09 (J=1.5, 7.9 Hz, 1 H, H-3); 8.03 (J=1.6, 7.8 Hz, 1 H, H-4′); 7.56 (ddd, J=1.2, 4.8, 7.6 Hz, 1 H, H-5′); 4.52 (s, 3 H, *N*-CH_3.). The assignment of the protons is supported by homodecoupling experiments. ^{13}C NMR (D_2O): δ 155.3, 152.5, 151.6, 149.7, 149.0, 141.9, 132.7, 130.6, 129.2, 128.9, 50.0.

1-Methyl-2,2′-bipyridine-6-one (**11**). A solution of 1-methyl-2,2′-bipyridinium iodide (**10**) (19 g, 64 mmol) in water (200 mL), and a separate solution of NaOH (51.2 g, 1.3 mol, 20 eq.) in water (200 mL) were cooled in ice. They were both added, dropwise and simultaneously, over 90 min to a third solution containing $K_3Fe^{III}CN_6$ (50.4 g, 153 mmol, 2.4 eq.) in water (250 mL) which was kept at 5 °C with stirring for 4 h, after which the mixture was extracted with CH_2Cl_2 (3 × 250 mL). The CH_2Cl_2 phases were dried over $MgSO_4$ and filtered, then evaporated at the rotary evaporator giving **11** as a dark oil which slowly crystallized upon standing. A short column gel filtration (Al_2O_3, 20% MeOH in EtOAc) gave a clear oil, which slowly crystallized (6.14 g, 33 mmol, 52%), m.p. 74–75 °C (lit.[12b] 74–75 °C).

TLC: $R_f \approx 0.27$ (**11**) (Al_2O_3, EtOAc). ^{1}H NMR ($CDCl_3$): δ 8.69 (ddd, J=1.0, 1.8, 4.9 Hz, 1 H, H-6′); 7.81 (dt, J=1.8, 7.6 Hz, 1 H, H-4′); 7.45 (ddd, J=0.9, 1.2, 7.7 Hz, 1 H, H-3′); 7.36 (ddd, J=1.1, 4.7, 7.6 Hz, 1 H, H-5′, overlapping H-4); 7.33 (dd, J=6.7, 9.2 Hz, 1 H, H-4, overlapping H-5′); 6.61 (dd, J=1.2, 9.2 Hz, 1 H, H-3); 6.17 (dd, J=1.2, 7.9 Hz, 1 H, H-5); 3.42 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 163.5, 154.0, 149.6, 148.3, 138.3, 137.3, 123.9, 120.3, 108.1, 33.9. IR (KBr, cm^{-1}): 1651(s), C=O.

6-Bromo-2′2-bipyridine (**12**). This preparation was adopted from a procedure developed for phenanthroline by Sjögren *et al.*[17] Triphenylphosphine (13.11 g, 50 mmol, 1.4 eq.) was dissolved in warm CH_3CN (60 mL, anhydrous Aldrich SureSeal) and cooled to 0 °C. Bromine (Br_2 7.40 g, 2.37 mL, 46.3 mmol, 1.3 eq.) was added dropwise over 0.5 h, and a yellow–white suspension gradually formed. A solution of 1-methyl-2,2′-bipyridine-6-one (**11**) (6.62 g, 35.6 mmol) in a small volume of CH_3CN was added in one portion at 0 °C. The reaction mixture turned dark red–brown, and gradually turned into a dark solution during 24 h of refluxing under argon. This solution was allowed to cool, and was poured onto ice whereupon the triphenylphosphine oxide precipitated, and was removed by filtration. The filtrate was neutralized with 10% Na_2CO_3, and extracted with CH_2Cl_2 (3 × 75 mL). The CH_2Cl_2 phases were dried over $MgSO_4$ and filtered, then evaporated at the rotary evaporator giving **12** as a dark oil. A short column gel filtration (Al_2O_3, gradient elution: EtOAc; EtOAc: CH_2Cl_2 1:1; CH_2Cl_2) gave a clear oil, which slowly solidified (4.21 g, 17.9 mmol, 50%). TLC: $R_f \approx 0.05$ (**11**), 0.82 (**12**) (Al_2O_3, 40% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$): δ 8.67 (ddd, J=0.9, 1.7, 4.8 Hz, 1 H, H-6′); 8.41 (dt, J=1.0, 7.8 Hz, 1 H, H-3′); 8.38 (dd, J=1.0, 7.6 Hz, 1 H, H-3); 7.82 (dt, J=1.8, 7.8 Hz, 1 H, H-4′); 7.67 (t, J=7.8 Hz, 1 H, H-4); 7.49 (dd, J=0.9, 7.8 Hz, 1 H, H-5); 7.33 (ddd, J=1.2, 4.8, 7.5 Hz, 1 H, H-5′). ^{13}C NMR ($CDCl_3$): δ 157.4, 154.5, 149.2, 141.6, 139.2, 137.0, 128.0, 124.3, 121.5, 119.7.

6-Cyanomethyl-2,2′-bipyridine (**8**), *Procedure B.* A solution of lithioacetonitrile (LiCH_2CN)[8g] was prepared from CH_3CN (0.671 g, 0.853 mL, 16.3 mmol, 1.5 eq., Aldrich SureSeal) and *n*-butyl lithium (5.94 mL, 2.69 M in hexanes, 16 mmol, 1.47 eq.) in freshly distilled THF (30 mL), with stirring under argon at −78 °C for 45 min. To this solution was added 6-bromo-bpy (**12**) (2.56 g, 10.9 mmol) in freshly distilled THF (30 mL) in one batch, and stirring was continued as the THF solution was allowed to reach room temperature over night. The dark red reaction solution was poured into water (100 mL), and extracted with CH_2Cl_2 (3 × 75 mL). The CH_2Cl_2 phases were dried over $MgSO_4$ and evaporated at the rotary evaporator to give a red oil. Purification by column chromatography (Al_2O_3, 4 cm diameter, 9 cm height, gradient elution (ca. 150 mL of each mixture): hexanes; hexanes: EtOAc 1:1; EtOAc; CH_2Cl_2; CH_2Cl_2: MeOH 8:2; MeOH) gave a pure fraction as white

crystals (650 mg, 3,3 mmol, 30%), m.p. 67–68 °C, and a second fraction of slightly red crystals (245 mg, 1.45 mmol, 11%, 99% pure by NMR). TLC: $R_f \approx 0.64$ (**8**), 0.83 (**12**) (Al_2O_3, 40% EtOAc in hexanes). Elemental analysis: calc. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52 Found: C, 73.57; H, 4.71; N, 21.41. ^1H and ^{13}C NMR spectra identical to those reported above for 6-cyanomethyl-bpy (**8**) (Procedure A).

2,2'-Bipyridine-6-acetic acid (**9**), *Procedure B.* A solution of 6-cyanomethyl-bpy (**8**) in 25% aq. NaOH (5 mL) and MeOH (15 mL 99+%) was refluxed for 2 days. The clear solution was evaporated to half the volume at the rotary evaporator (to remove the MeOH) and filtered through a glass frit (P3). The pH was adjusted to 6.5 with 6 M HCl, and extracted with CH_2Cl_2 (3 × 20 mL) to remove any remaining **8** or the hydrolysis intermediate 6-carboxamidomethyl-bpy (**8b**). The water phase was evaporated to dryness at the rotary evaporator, and the residue extracted with MeOH (99+%), filtered and evaporated again. This extraction process was repeated four times to give **9** (117 mg, 0.55 mmol, 86%). ^1H and ^{13}C NMR spectra were identical to those reported above for **9** in Procedure A.

Methyl-2,2'-bipyridine-6-acetate (**13**). A solution of 6-cyanomethyl-bpy (**8**) (205 mg, 1.05 mmol) in MeOH (50 mL, 99+%) was refluxed under constant bubbling of HCl(g) (generated from 12 M HCl added dropwise to 18 M H_2SO_4). The reaction was followed by TLC, and after 4 h the reaction solution was poured onto ice, neutralized with 15 M NH_3 and extracted with CH_2Cl_2 (3 × 100 mL). The CH_2Cl_2 phases were evaporated at the rotary evaporator, to give a purple-discolored viscous oil. Sublimation overnight (oil bath 50 °C, pump vacuum ca. 1 Torr) yielded white filamentous needles (155 mg, 0.68 mmol, 65%), m.p. 76–77 °C. TLC: $R_f \approx 0.58$ (**8**), 0.74 (**13**) (Al_2O_3, 40% ether in hexanes). Elemental analysis: calc. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.30; H, 5.41; N, 12.17. ^1H NMR (500 MHz, $CDCl_3$): δ 8.69 (ddd, J=0.8, 1.8, 4.8 Hz, 1 H, H-6'); 8.44 (dt, J=1.1, 8.0 Hz, 1 H, H-3'); 8.32 (dd, J=0.8, 7.9 Hz, 1 H, H-3); 7.82(4) (dt, J=1.8, 7.7, Hz, 1 H, H-4'); 7.81(6) (t, J=7.8 Hz, 1 H, H-4); 7.34 (dd, J=1.0, 7.6 Hz, 1 H, H-5); 7.32 (ddd, J=1.2, 4.8, 7.4 Hz, 1 H, H-5'); 3.97 (s, 2 H, CH_2(CO)OCH_3); 3.77 (s, 3 H, (CO)OCH_3). The assignment of the protons is supported by 2D NMR (COSY). ^{13}C NMR ($CDCl_3$): δ 171.3, 156.1, 155.9, 153.8, 149.1, 137.5, 136.9, 123.8, 121.4, 119.4, 52.2, 44.0.

6-[2-(4,4-Dimethyloxazoline-2-yl)ethyl]-2,2'-bipyridine (**15**). To a stirred solution of 6-methyl-bpy (**14**)[18] (0.54 g, 3.17 mmol) in freshly distilled THF (15 mL) was added lithium diisopropylamide (LDA) (3.52 mL, 1 M in THF, 3.52 mmol) at −78 °C. The resulting dark blue solution was stirred for another 30 min, and 2-chloromethyl-4,4-dimethyl-2-oxazoline (0.52 g, 3.52 mmol)[19] in THF (6 mL) was added over period of 10 min at −78 °C. The reaction mixture was allowed to reach RT before addition of water. The solvent was evaporated at the rotary evaporator, and the oily residue was dissolved in CH_2Cl_2, washed with water (3 × 20 mL), dried over $MgSO_4$ and evaporated at the rotary evaporator. The crude product yield was 91% (by NMR). Purification by column chromatography (Al_2O_3, eluted with 20% EtOAc and 1% triethylamine in hexanes) gave pure **15** (0.63 g, 2.23 mmol, 71%). $R_f \approx 0.27$ (Al_2O_3, 20% EtOAc in hexanes).

GC-EI MS: retention time 8.50 min, found M^+ 281.150 m/z, calc. for $C_{17}H_{19}N_3O$ 281.153 m/z. ^1H NMR (500 MHz, $CDCl_3$): δ 8.66 (ddd, J=1.0, 1.8, 4.8 Hz, 1 H, H-6'), 8.48 (ddd, J=1.0, 1.1, 7.8 Hz, 1 H, H-3'), 8.22 (dd, J=0.9, 7.8 Hz, 1 H, H-3), 7.80 (ddd, J=1.8, 7.8, 7.6 Hz, 1 H, H-4'), 7.72 (dd, J=7.6, 7.8 Hz, 1 H, H-4), 7.29 (ddd, J=1.1, 4.8, 7.6 Hz, 1 H, H-5'), 7.19 (dd, J=0.9, 7.6 Hz, 1 H, H-5), 3.92 (s, 2 H, CH_2O), 3.22 (t, J=7.6 Hz, 2 H, CH_2Py), 2.84 (t, J=7.9 Hz, 2 H, CH_2CNO), 1.24 (s, 6 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 159.8, 156.8, 155.8, 149.5, 137.5, 132.2, 124.0, 123.3, 121.7, 188.9, 79.4, 67.4, 34.5, 28.8, 27.8.

Methyl-2,2'-bipyridine-6-propanoate (**16**). 2-Chloromethyl-4,4-dimethyl-2-oxazoline (**15**) (0.558 g, 1.98 mmol) was dissolved in 8% H_2SO_4 in MeOH (50 mL) and refluxed for 24 h. After cooling, the solution was diluted with water (40 mL) and solid Na_2CO_3 was added until CO_2 ceased to evolve. This solution was extracted with CH_2Cl_2 (3 × 20 mL), and the combined CH_2Cl_2 phases were dried with $MgSO_4$ and evaporated at the rotary evaporator. The crude product yield was 92% (by NMR). Purification by column chromatography (Al_2O_3, eluted with 20% EtOAc in hexanes) yielded **16** (0.31 g, 1.27 mmol, 65%). TLC: $R_f \approx 0.52$ (Al_2O_3, 20% EtOAc in hexanes). Elemental analysis: calc. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.29; H, 5.89; N, 11.49. ^1H NMR (500 MHz, $CDCl_3$): δ 8.69 (ddd, J=0.9, 1.8, 4.8 Hz, 1 H, H-6'), 8.46 (ddd, J=0.9, 1.2, 8.0 Hz, 1 H, H-3'), 8.26 (dd, J=1.0, 7.8 Hz, 1 H, H-3), 7.83 (ddd, J=1.8, 7.5, 8.0 Hz, 1 H, H-4'), 7.75 (dd, J=7.6, 7.8 Hz, 1 H, H-4), 7.32 (ddd, J=1.2, 4.8, 7.5 Hz, 1 H, H-5'), 7.22 (dd, J=1.0, 7.6 Hz, 1 H, H-5), 3.72 (s, 3 H, OCH_3), 3.24 (t, J=7.3 Hz, 2 H, CH_2py), 2.94 (t, J=7.3 Hz, 2 H, CH_2CO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 159.5, 158.2, 156.7, 155.7, 149.4, 137.6, 137.3, 124.0, 123.4, 121.6, 118.9, 52.0, 33.2, 32.9.

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