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# Synthesis of Nitrile-Functionalized Polydentate N-Heterocycles as Building Blocks for Covalent Triazine Frameworks

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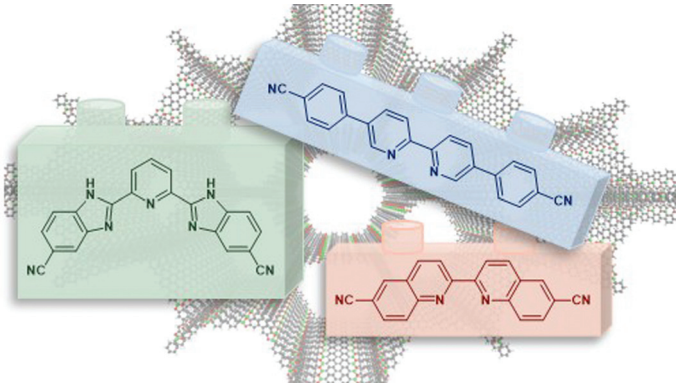
Dedicated to Prof. Alain Krief on the occasion of his 80th birthday

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**Abstract** Covalent triazine frameworks (CTFs) based on polydentate ligands are highly promising supports to anchor catalytic metal complexes. The modular nature of CTFs allows to tailor the composition, structure, and function to its specific application. Access to a broad range of chelating building blocks is therefore essential. In this respect, we extended the current available set of CTF building blocks with new nitrile-functionalized N-heterocyclic ligands. This paper presents the synthesis of the six ligands which vary in the extent of the aromatic system and the denticity. The new building blocks may help in a rational design of enhanced support materials in catalysis.

**Key words** N-heterocycles, 1,4-diazadiene ligands, 2,2′-bipyridine, 2,2′-biquinoline, 2,6-bis(benzimidazolyl)pyridine, nitrile building blocks, covalent triazine frameworks

1,4-Diazadiene ligands, such as 2,2′-bipyridine, 2,2′-biquinoline, and 2,6-bis(benzimidazolyl)pyridine, are among the most widely used ligands in the construction of metal complexes.[1,2] This ligand family strongly chelates with numerous transition metal ions, giving rise to highly stable complexes that often display interesting photophysical and photoredox properties as a result of the metal-to-ligand charge transfer (MLCT).[3] Hence, these scaffolds have found application in many branches of chemistry including fine-chemical synthesis,[4] $CO_2$ reduction,[5] water splitting,[6,7] solar cell development,[8] electroluminescent devices,[9] and cancer therapy.[10] Introducing functional groups on the ligands not only allows for the fine-tuning of the complex's activity, but also enables the incorporation of the ligands in macromolecular structures. Indeed, functionalized 1,4-diazadienes have attracted widespread attention in supramolecular chemistry and material science.[11–17] An example of materials gaining traction are covalent triazine frameworks (CTFs). These extended porous organic frameworks originate from the cyclotrimerization of aromatic nitriles to triazines which provide them with superior chemical and thermal stability.[18,19] The trimerization is typically carried out either through ionothermal synthesis in molten $ZnCl_2$ or through catalysis by triflic acid.[18,20,21] A more recently developed method uses the polycondensation of an amidine, often prepared from the nitrile, and an in situ generated aldehyde.[22] Using nitrile-functionalized 1,4-diazadiene ligands as building blocks in the CTF synthesis renders frameworks with strong coordination sites to anchor catalytic metal complexes.[23–25] This combined with their remarkable robustness make CTFs appealing as metal supports in the development of heterogeneous catalysts.[26]

The modular nature of CTFs enables to tailor the framework to its application by varying the building blocks. Access to a wide range of building blocks is thus essential, and brings further advances in the tailored design of CTFs. Nonetheless, very few polydentate N-ligands with cyano substituents are commercially available, and some are exceedingly expensive. In addition, the synthetic methods towards the ligands, especially with nitrile functionalities, are barely described in the literature. Hence, synthetic routes towards new chelating CTF precursors are highly relevant.

In our research on the development of CTFs as supports for catalytic metal complexes, this lack of building blocks prompted us to expand the range of accessible chelating building blocks. To this end, we synthesized a set of six nitrile-functionalized N-heterocycles suitable as building

 
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blocks in CTF synthesis (Figure 1). This paper reports the synthetic methods towards N-heterocycles that were developed with a view to their practical use in multigram synthesis. Once the N-heterocycles are assembled into CTFs, a variety of frameworks are obtained which differ in their pore sizes and denticity of the coordination sites. Eventually, the enlarged spectrum of building blocks will enhance the diversity of engineered CTF materials and foster their further application.

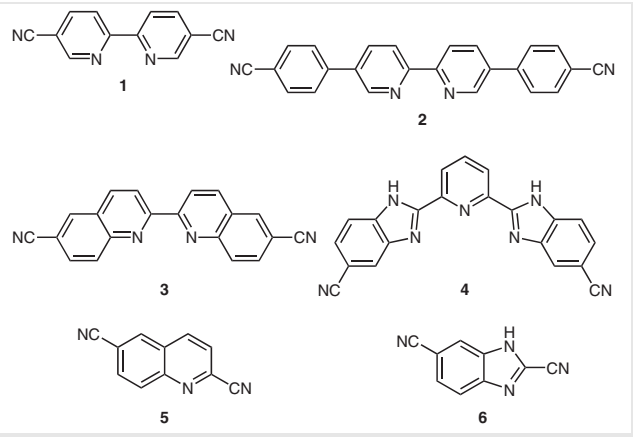
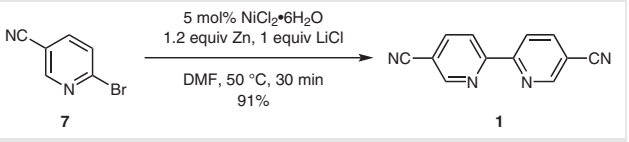



**Figure 1** The set of synthesized nitrile-functionalized N-heterocycles

2,2′-Bipyridine is the most simple member of the polypyridine ligand family, and therefore perhaps the most employed one.[2] 2,2′-Bipyridine-5,5′-dicarbonitrile (**1**) is a commonly used building block in CTF synthesis[23,24,27] and is commercially available, but at very high prices (e.g., € 500/g at Sigma-Aldrich[28]). Hence, an efficient synthesis of bipyridine **1** was of interest to us. Early synthetic methods include the dehydration of 2,2′-bipyridine-5,5′-dicarboxamide as described by Baxter and Connor and by Janiak et al.[29,30] However, a twofold sublimation was found necessary to obtain the product in satisfactory purity, resulting in a diminished yield of 43%. Besides, three additional reaction steps are required starting from commercially available and affordable 5,5′-dimethyl-2,2′-bipyridine to obtain 2,2′-bipyridine-5,5′-dicarboxamide.[31] An elegant and more direct approach was reported by Duan and co-workers, which proceeded through the reductive homocoupling of 2-bromo-5-cyanopyridine under nickel catalysis.[32] Contrary to common coupling methods that require large amounts of ligand, the authors took advantage of the in situ formed Ni–bpy complex, which was effective for the coupling in the absence of external ligand. The latter is of interest as it might avoid a tedious purification step.

Following Duan's procedure, we synthesized bipyridine **1** using 2-bromo-5-cyanopyridine (**7**) in a reductive coupling with 5 mol% $NiCl_2{\cdot}6H_2O$ in the presence of activated zinc dust at 60 °C. Full conversion was already obtained within 30 min as evidenced by LC-MS analysis. After the workup by extraction with chloroform and precipitation, bipyridine **1** was isolated in 93% yield as a pure product according to $^1$H NMR analysis. Unfortunately, we faced difficulties on reproducing this result on a regular basis when the described conditions were applied. In some of our attempts decyanation of the product was observed as a side reaction, affording major portions of 2,2′-bipyridine-5-carbonitrile (Figure S1 in the Supporting Information). Efforts to suppress this capricious side reaction by altering the amounts of nickel precatalyst, zinc, or LiCl were unsuccessful. Instead, the temperature of the exothermic reaction was found to play a key role in the reaction outcome. The side product formation was avoided and full conversion towards bipyridine **1** was achieved in a consistent manner by maintaining the temperature at 50 °C instead of the prescribed 60 °C as well as preventing temperature overshoot by using a temperature controller (Scheme 1). Using 2-chloro-5-cyanopyridine in the optimized homocoupling was also possible, but resulted in a more sluggish reaction, reaching 83% conversion after 18 h, which can be ascribed to the lower reactivity of the chloropyridine.




**Scheme 1** Optimized synthesis of 2,2′-bipyridine-5,5′-dicarbonitrile (**1**)

In addition to the optimized synthesis of bipyridine **1**, five new N-heterocyclic ligands were synthesized. The new ligand that we targeted first was the extended bipyridine congener, 5,5′-bis(4-cyanophenyl)-2,2′-bipyridine (**2**). Using elongated bipyridine building blocks in the CTF synthesis could give rise to mesopores, which facilitate the mass transport in the catalysis process. For the synthesis of bipyridine **2** an approach in which the 2,2′-bipyridine core is brominated and subsequently elongated through a cross-coupling reaction was considered as the most straightforward route. To selectively brominate the bipyridine core at the C5 and C5′ positions, 2,2′-bipyridine (**8**) was first converted into its dihydrobromide salt **9** using aqueous HBr as shown in previous reports (Scheme 2).[33,34] Next, bipyridine salt **9** was heated in neat bromine in a sealed tube at 170 °C for 72 h. The crude product contained mono- and dibromobipyridines **10**/**11** in an average ratio of 3:4. Crystallization from DMF/ethanol provided pure dibromo derivative **11** in a yield of 46% calculated from bipyridine **8**. The partially reacted residue could be recycled in the next run of the reaction. Prolonging the reaction time to 7 days did not result in appreciably higher yields (48%) of dibromobipyridine **11**, whereas increasing the temperature or the number of bromine equivalents led to polybrominated derivatives, which could not be separated from dibromobipyridine **11** by crystallization. Finally, the extension of bipyridine **11** was successfully effected by Suzuki–Miyaura cross-coupling with



4-cyanophenylboronic acid (**12**) under $Pd(PPh_3)_4$ catalysis and afforded 5,5′-bis(4-cyanophenyl)-2,2′-bipyridine (**2**) in 92% yield. The structure of bipyridine **2** was unambiguously established by single-crystal X-ray analysis (Figure 2).

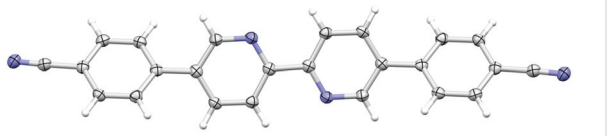
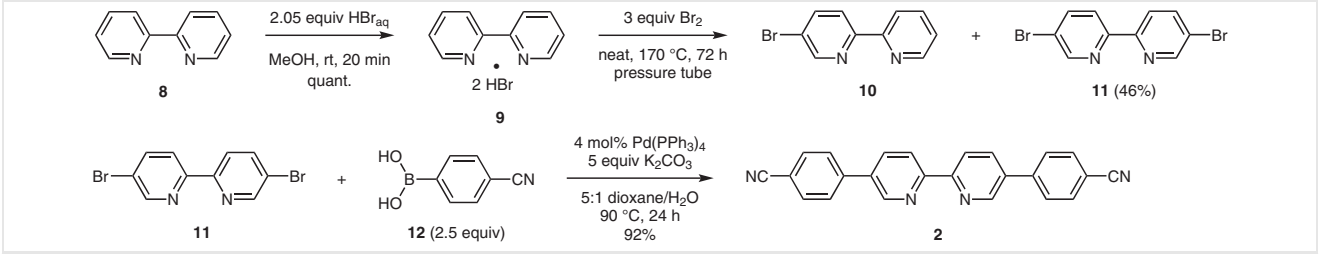


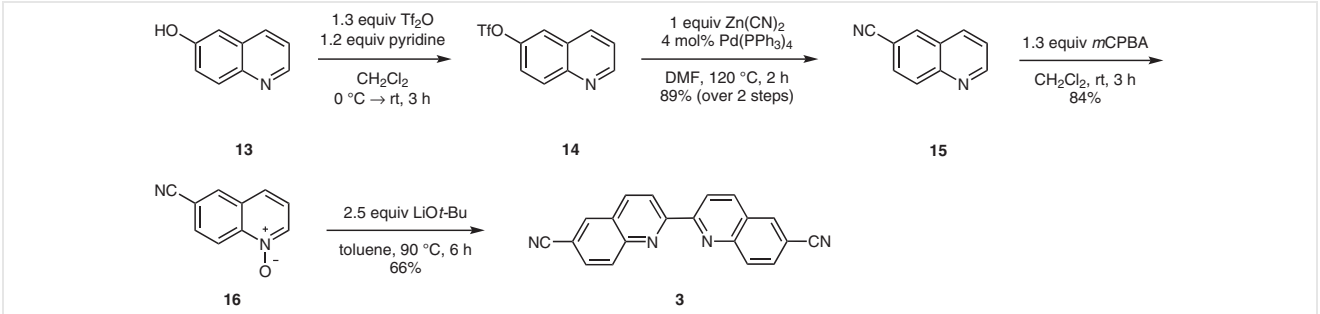
**Figure 2** Molecular X-ray structure of bipyridine **2**; thermal displacement ellipsoids are drawn at the 50% probability level

As the third bidentate N-ligand, we aimed for the synthesis of 2,2′-biquinoline-6,6′-dicarbonitrile (**3**), a dibenzo analogue of bipyridine **1**. Due to the fused rings, the ligand is a more sterically demanding ligand than bipyridine. The synthesis of biquinoline **3** started from quinolin-6-ol (**13**) as this reagent is widely available compared to 6-haloquinolines (Scheme 3). To replace the 6-hydroxy group by a nitrile functionality, it was activated as the triflate by treating quinoline **13** with triflic anhydride. After workup, crude triflate **14** was subjected to Pd-catalyzed cyanation using $Zn(CN)_2$ as the cyanide source. Pure quinoline-6-carbonitrile (**15**) was obtained after chromatographic purification in a yield of 89% over the two reaction steps. Next, quinoline **15** was transformed to the quinoline *N*-oxide derivative **16** with *m*CPBA to increase its reactivity and to facilitate the C2-homocoupling. A yield of 84% was obtained when *m*CPBA in dichloromethane was used in the oxidation of quinoline **15**, which is much higher than the yield reported for $H_2O_2$ in acetic acid (24% yield).[35] The C2-homocoupling of quinoline *N*-oxide **16** was carried out by a deoxygenative homocoupling reaction mediated by LiO*t*-Bu as described in the literature for other quinoline *N*-oxides.[36,37] Interestingly, instead of the expected biquinoline *N*-oxide, the homocoupling of *N*-oxide **16** afforded directly and almost exclusively deoxygenated 2,2′-biquinoline-6,6′-dicarbonitrile (**3**) as coupling product. Only traces of the biquinoline *N*-oxide were observed in the crude product on LC-MS analysis.

By synthesizing 2,2′-(pyridine-2,6-diyl)bis(1*H*-benzimidazole-5-carbonitrile) (**4**), we aimed to include a tridentate building block in our collection. Building block **4** was prepared by the condensation of 3,4-diaminobenzonitrile (**17**) and pyridine-2,6-dicarbaldehyde (**18**) in the presence of *p*-benzoquinone as the oxidant and was isolated by precipitation in a yield of 53% (Scheme 4). Tridentate coordination sites can also be generated in situ during the synthesis of the CTF. For instance, the cyclotrimerization of 2-cyanopyridyl moieties results in the formation of terpyridyl coordination sites within the framework. With 6-cyanoquinoline *N*-oxide (**16**) available, selective cyanation of the *N*-oxide at the C2 position would yield quinoline-2,6-dicarbonitrile (**5**), which holds such 2-cyanopyridyl moiety.[35] In this regard, *N*-oxide **16** was reacted with potassium cyanide and acetyl chloride as activating agent to afford quinoline **5** in a moderate yield of 58% (Scheme 5a).[38] For the same reason, the synthesis of 1*H*-benzimidazole-2,5-dicarbonitrile (**6**) was pursued. To this end, 3,4-diaminobenzonitrile (**17**) was treated with methyl 2,2,2-trichloroacetimidate in acetic acid to give 2-(trichloromethyl)benzimidazole **19** in 75% yield (Scheme 5b).[39] Subsequently, intermediate **19** was



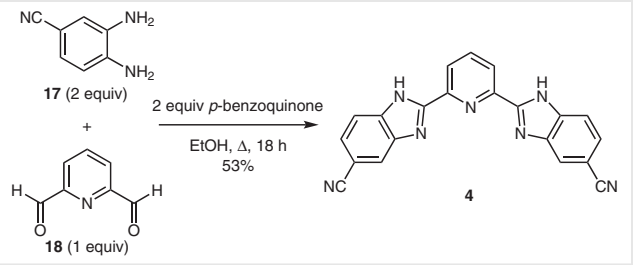

**Scheme 2** Synthesis of 5,5′-bis(4-cyanophenyl)-2,2′-bipyridine (**2**)




**Scheme 3** Synthesis of 2,2′-biquinoline-6,6′-dicarbonitrile (**3**)

reacted with an aqueous ammonia solution to obtain benzimidazole **6** in 89% yield.



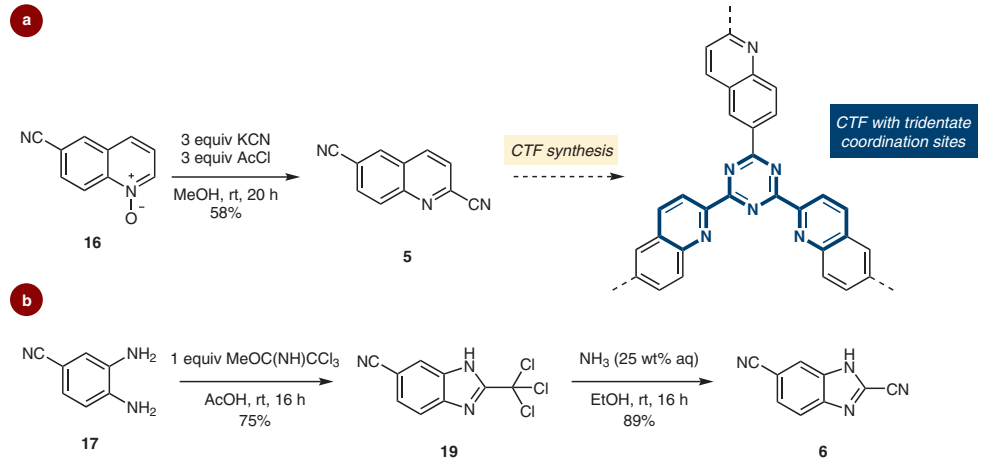

**Scheme 4** Synthesis of 2,2′-(pyridine-2,6-diyl)bis(1*H*-benzimidazole-5-carbonitrile) (**4**)

In summary, six nitrile-functionalized N-heterocyclic ligands were synthesized. For this, straightforward synthetic routes were elaborated considering the practical use in multigram syntheses. The nitrile functionalities on the ligands make them valuable as building blocks for CTFs with metal-binding sites. The set of experimentally available building blocks is extended by the developed methods to synthesize new N-heterocycles with cyano groups. This will lead to more diversity in CTFs, on which will be reported in due course. Therefore, the new synthetized building blocks are accelerating the development of CTFs as platform materials for heterogeneous catalysis.

Solvents and reagents were purchased from abcr, Acros, Fluorochem, Sigma-Aldrich, and TCI, and were used without further purification unless otherwise noted. DMF was dried over activated molecular sieves (4 Å) for at least 48 h. Dry $CH_2Cl_2$ and toluene were obtained using the MBRAUN SPS-800 solvent purification system. Zinc dust was activated before use by stirring with 1 M aq HCl solution, filtered, and subsequently washed with distilled water, EtOH, and $Et_2O$, and dried under vacuum. For TLC analysis of crude reaction mixtures or pure samples, glass-backed 0.25 mm Merck silica gel 60 $F_{254}$ TLC plates were used, and compounds were visualized by UV light (254 nm) or by a $KMnO_4$ stain. Column chromatography was performed using chromatographic silica gel (particle size 35–70 μM, pore diameter 6 nm). $^1H$ and $^{13}C$ NMR spectra were recorded at 400 and 100.6 MHz respectively, on a Bruker Avance III HD equipped with a $^1H$/BB z-gradient probe (BBO, 5 mm). All spectra were recorded at 25 °C and were processed using TopSpin 3.6.2. NMR spectra are referenced to the residual solvent peak ($CDCl_3$ $\delta_H$ = 7.26 and $\delta_C$ = 77.16; DMSO-$d_6$ $\delta_H$ = 2.50 and $\delta_C$ = 39.52). Peaks were assigned with the aid of 2D spectra (COSY, HSQC, HMBC). LC-MS analyses were performed on an Agilent 1200 Series HPLC system equipped with a Supelco Ascentis Express C18 column (3 cm × 4.6 mm, 2.7 μm fused-core particles, 90 Å), Phenomenex Guard column (SecurityGuard Standard) and a UV-DAD detector. The HPLC is coupled to an Agilent 1100 Series mass spectrometer with electrospray ionization (ESI, capillary voltage 4000 V, fragmentor voltage 70 V) and with a mass selective single quadrupole detector. Infrared spectra (FTIR) were recorded from samples in neat form with a Shimadzu IRAFFINITY-1S FTIR spectrophotometer with an ATR accessory. Melting points were determined using a Wagner & Munz Kofler Hot Bench (type WME, accuracy ±1 °C, range 50–260 °C). Elemental analyses were performed on 2.0–2.2 mg dried samples using a Thermo Scientific FLASH 2000 CHNS/O Analyzer.

### 2,2′-Bipyridine-5,5′-dicarbonitrile (1)

2,2′-Bipyridine-5,5′-dicarbonitrile (**1**) was synthesized via a modified procedure of Duan et al.[32] A flame-dried 250-mL flask was charged with 5 mol% $NiCl_2{\cdot}6H_2O$ (325 mg, 1.37 mmol) and placed under an argon atmosphere. Dry DMF (40 mL) was added and the resulting green solution was heated to 40 °C. The heating plate was provided with a temperature controller (IKA® ETS-D4 fuzzy) to prevent the temperature overshoot and to maintain the temperature below 50 °C. Close monitoring of the reaction temperature was important since the temperature was found to be the key factor in avoiding the decyanation side reaction. 2-Bromo-5-cyanopyridine (**7**; 5.00 g, 27.32 mmol), anhyd LiCl (1.16 g, 27.32 mmol, 1 equiv), and activated zinc dust (2.14 g, 32.79 mmol, 1.2 equiv) were consecutively added to the flask under a stream of argon. After raising the temperature to 50 °C, a grain of iodine and 2 drops of AcOH were added to the mixture, which was then stirred for about 30 min to complete the conversion. Subsequently, the mixture was cooled to 0 °C and the reaction was quenched by the addition of 1 M aq HCl (40 mL). The mixture was stirred for 30 min




**Scheme 5** Syntheses of building blocks which react to tridentate coordination sites during CTF synthesis: (a) quinoline-2,6-dicarbonitrile (**5**) and (b) 1*H*-benzimidazole-2,5-dicarbonitrile (**6**)

and then it was basified with aq ammonia (25 wt%) and the product was extracted with $CHCl_3$ (4 × 100 mL). The combined organic fractions were dried ($MgSO_4$) and filtered. The solution was concentrated with a rotatory evaporator to ca. 20 mL and was cooled in an ice bath to induce precipitation. The precipitated solid was collected by filtration, washed with cold EtOH and $Et_2O$, and dried under high vacuum. 2,2′-Bipyridine-5,5′-dicarbonitrile (**1**) was obtained as a fluffy beige powder; yield: 2.56 g (91%); mp >260 °C.

IR (neat): 2239 (C≡N), 1591, 1535, 1460, 1369, 1236, 1028, 947, 845, 733, 650, 550, 488 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.97 (dd, *J* = 2.0, 0.8 Hz, 2 H, H6/6′), 8.64 (dd, *J* = 8.3, 0.8 Hz, 2 H, H3/3′), 8.14 (dd, *J* = 8.3, 2.0 Hz, 2 H, H4/4′).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 157.0 (C2/2′), 152.1 (C6/6′), 140.5 (C4/4′), 121.7 (C3/3′), 116.5 (2 × C≡N), 110.7 (C5/5′).

MS (ESI): *m*/*z* (%) = 207 (100) $[M + H]^+$.

Anal. Calcd for $C_{12}H_6N_4$: C, 69.90; H, 2.93; N, 27.17. Found: C, 70.04; H, 3.04; N, 27.90.

The spectral data are in agreement with the literature.[40]

### 5,5′-Dibromo-2,2′-bipyridine (11)

The synthetic procedure for 5,5′-dibromo-2,2′-bipyridine (**11**) was based on the method reported by D'Souza et al.[34] A solution of 2,2′-bipyridine (**8**; 5.00 g, 3.20 mmol) in MeOH (30 mL) was treated with aq HBr solution (48 wt% in $H_2O$, 7.4 mL, 6.56 mmol, 2.05 equiv) at 0 °C in an ice bath. After the addition, the ice bath was removed and the mixture was stirred for another 20 min at rt. Subsequently, the solvent was removed under reduced pressure and the residue was thoroughly dried under high vacuum to obtain 2,2′-bipyridine hydrobromide salt (**9**) as a pale yellow powder; yield: 10.18 g (quant).

A 10-mL pressure resistant tube of Pyrex glass was charged with finely grounded 2,2′-bipyridine hydrobromide (**9**; 2.75 g, 8.65 mmol) and cooled to 0 °C. Subsequently, bromine (1.33 mL, 25.94 mmol, 3 equiv) was slowly added using a disposable plastic syringe with a long needle, making sure that the tip of the needle was digging into **9**. After screwing the cap tightly onto the pressure resistant tube, the temperature was raised to 170 °C and held for 72 h. After, the tube was cooled to 0 °C before opening it. (Caution! wear protective clothing and be aware that HBr gas can escape when loosening the cap.) The hard lump of crude product was crumbled with a spatula and transferred into a 500-mL flask containing $Na_2SO_3$ (3.0 g), NaOH (1 M, 50 mL), and $CHCl_3$ (150 mL). The mixture was stirred at rt until complete dissolution. The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$ (2 × 20 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by crystallization by first dissolution in DMF, followed by the addition of EtOH as the nonsolvent until tiny precipitates started to form. The solution was left overnight at rt and 5,5′-dibromo-2,2′-bipyridine (**11**) was obtained as thin, white needles; yield: 1.25 g (46%) based on the amount of 2,2′-bipyridine used; mp 229 °C.

IR (neat): 1454, 1356, 1086, 1007, 826, 725, 700, 637, 457 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 2.2 Hz, 2 H, H6/6′), 8.29 (d, *J* = 8.5 Hz, 2 H, H3/3′), 7.94 (dd, *J* = 8.5, 2.2 Hz, 2 H, H4/4′).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 153.8 (C2/2′), 150.4 (C6/6′), 139.8 (C4/4′), 122.4 (C3/3′), 121.6 (C5/5′).

MS (ESI): *m*/*z* (%) = 315 (100) $[M + H]^+$.

The spectral data are in agreement with the literature.[34]

### 5,5′-Bis(4-cyanophenyl)-2,2′-bipyridine (2)

5,5′-Dibromo-2,2′-bipyridine (**11**; 2.00 g, 6.4 mmol), 4-cyanoboronic acid (2.34 g, 15.9 mmol, 2.5 equiv), $Pd(PPh_3)_4$ (294 mg, 0.25 mmol, 4 mol%), and $K_2CO_3$ (4.40 g, 31.85 mmol, 5 equiv) were loaded into a two-neck flask (250 mL) equipped with a condenser and two rubber septa, and placed under an argon atmosphere. Degassed dioxane (100 mL) and degassed water (20 mL) were added, after which the yellow solution was heated to 90 °C for 24 h. After cooling to rt, the precipitate was collected by filtration and thoroughly washed with water, THF, and $CHCl_3$. After drying, 5,5′-bis(4-cyanophenyl)-2,2′-bipyridine (**2**) was obtained as an off-white powder; yield: 2.10 g (92%); mp >260 °C.

Crystals for analytical purposes were obtained by suspending bipyridine **2** (100 mg) in DMF (28 mL, 0.01 M) and heating the suspension to 120 °C until a clear solution was obtained (ca. 15 min). The solution was then allowed to cool very slowly to rt during which crystals were formed. The crystals were collected by filtration, rinsed with MeOH, and dried under high vacuum to afford bipyridine **2** as yellowish crystals (87 mg).

IR (neat): 2230 (C≡N), 1607, 1587, 1537, 1456, 1366, 1314, 1277, 1225, 1180, 1130, 1115, 1065, 1030, 999, 931, 862, 847, 827, 746, 638, 563, 525, 471, 409 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.95 (d, *J* = 2.3 Hz, 2 H, H6/6′), 8.59 (d, *J* = 8.3 Hz, 2 H, H3/3′), 8.07 (dd, *J* = 8.3, 2.3 Hz, 2 H, H4/4′), 7.76–7.83 (m, 8 H, 8 × $CH_{phenyl}$).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 155.6 (C2/2′), 147.9 (C6/6′), 142.2 (2 × $C_q$Py), 135.6 (C4/4′), 135.0 (C5/5′), 133.1 (2 × $CH_{phenyl}$), 127.9 (2 × $CH_{phenyl}$), 121.5 (C3/3′), 118.7 (2 × C≡N), 112.2 (2 × $C_q$C≡N),

MS (ESI): *m*/*z* (%) = 359 (100) $[M + H]^+$.

Anal. Calcd for $C_{24}H_{14}N_4$: C, 80.43; H, 3.94; N, 15.63. Found: C, 79.32; H, 3.88; N, 15.96.

### Quinoline-6-carbonitrile (15)

An oven-dried, 250-mL two-neck flask equipped with a dropping funnel was charged with quinolin-6-ol (**13**; 4.00 g, 27.56 mmol) in dry $CH_2Cl_2$ (110 mL) and pyridine (2.67 mL, 33.07 mmol, 1.2 equiv) and placed under an argon atmosphere. The brown suspension was cooled to 0 °C in an ice bath before a solution of triflic anhydride (10.0 g, 35.44 mmol, 1.3 equiv) in dry $CH_2Cl_2$ (30 mL) was added dropwise. The resulting black solution was allowed to warm to rt and stirred for 2 h. At the end of the reaction (monitored by TLC), the mixture was quenched with 1.0 M aq HCl (20 mL) and washed with sat. $NaHCO_3$ and brine. The aqueous phase was extracted with $CH_2Cl_2$ (2 × 30 mL). The combined organic fractions were dried (anhyd $MgSO_4$) and the solvent was removed under reduced pressure. Crude quinolin-6-yl trifluoromethanesulfonate (**14**) was obtained as a brown viscous liquid; crude yield: 7.64 g (quant).

To a 250-mL flask containing crude triflate **14** was added $Zn(CN)_2$ (3.24 g, 27.56 mmol, 1 equiv) and $Pd(PPh_3)_4$ (1.27 g, 1.10 mmol, 4 mol%). The flask was fitted with a reflux condenser and rubber septum and placed under argon atmosphere by vacuum-argon cycles (3×). Degassed DMF (90 mL) was added and the solution was heated to 120 °C for 2 h. Afterward, the solvent was partially removed by vacuum distillation until 20 mL of solution remained. Sat. aq $NaHCO_3$ (20 mL) was added and the mixture was stirred for 10 min. The product was then extracted from the mixture with EtOAc (3 × 100 mL), the combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Purification of the crude product

via column chromatography (silica gel, PE/EtOAc 55:45) afforded quinoline-6-carbonitrile (**15**) as a white powder; yield: 3.79 g (89% over 2 steps); mp 143 °C; $R_f$ = 0.40 (silica gel; hexane/EtOAc, 55:45).

IR (neat): 2224 (C≡N), 1620, 1591, 1570, 1495, 1452, 1429, 1358, 1317, 1153, 1115, 912, 833, 797, 554, 476 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.06 (dd, *J* = 4.3, 1.7 Hz, 1 H, H2), 8.21–8.24 (m, 2 H, H4, H5), 8.20 (d, *J* = 8.9 Hz, 1 H, H8), 7.86 (dd, *J* = 8.7, 1.8 Hz, 1 H, H7), 7.54 (dd, *J* = 8.3, 4.2 Hz, 1 H, H3).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 153.3 (C2), 149.2 (C8a), 136.4 (C4), 134.1 (C5), 131.2 (C8), 130.2 (C7), 127.6 (C4a), 122.7 (C3), 118.5 (C≡N), 110.5 (C6).

MS (ESI): *m*/*z* (%) = 155 (100) $[M + H]^+$.

The spectral data are in agreement with the literature.[41]

### 6-Cyanoquinoline *N*-Oxide (16)

A 100-mL flask was charged with a solution of quinoline-6-carbonitrile (**15**; 1.50 g, 9.73 mmol) in $CH_2Cl_2$ (50 mL) and cooled to 0 °C in an ice bath. *m*CPBA (70 wt%, 3.12 g, 12.65 mmol, 1.3 equiv) was added portionwise over 15 min. The mixture was allowed to warm to rt and stirred for 3 h until complete conversion. Next, 1 M NaOH (40 mL) was added to the flask and the organic phase was separated and washed again with 1 M NaOH (15 mL). The combined aqueous fractions were extracted with *i*-PrOH/$CHCl_3$ (1:4; 3 × 10 mL). The combined organic fractions were dried ($MgSO_4$) and filtered and the solvent was evaporated under reduced pressure. 6-Cyanoquinoline *N*-oxide (**16**) was obtained as a pale yellow powder; yield: 1.40 g (84%); mp 209 °C.

IR (neat): 2228 (C≡N), 1691, 1680, 1571, 1366, 1306, 1271, 1246, 1198, 1184, 849, 831, 787, 731, 523, 517, 492 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.87 (d, *J* = 9.1 Hz, 1 H, H8), 8.61 (d, *J* = 6.2 Hz, 1 H, H2), 8.28 (s, 1 H, H5), 7.90 (d, *J* = 9.1 Hz, 1 H, H4), 7.77 (d, *J* = 8.5 Hz, 1 H, H7), 7.44 (dd, *J* = 8.5, 6.2 Hz, 1 H, H3).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 142.9 (C8a), 137.8 (C2), 134.2 (C5), 131.1 (C4), 130.2 (C4a), 125.3 (C7), 123.2 (C3), 121.9 (C8), 117.6 (C≡N), 113.3 (C6).

MS (ESI): *m*/*z* (%) = 171 (100) $[M + H]^+$.

### 2,2′-Biquinoline-6,6′-dicarbonitrile (3)

A flame-dried 250 mL flask was charged with 6-cyanoquinoline *N*-oxide (**16**; 2.00 g, 11.75 mmol) and anhyd toluene (60 mL), placed under $N_2$ atmosphere and heated to 90 °C. Li*O*t-Bu (1.0 M in THF, 29.4 mL, 2.5 equiv) was slowly added dropwise to the solution. After stirring for 6 h, toluene was evaporated, and the residue was stirred in $CHCl_3$ (80 mL) and water (40 mL). The precipitated brown solid was collected by filtration and washed with $CHCl_3$. The yellow-brown sticky residue was resuspended in $CHCl_3$ (20 mL), collected again by filtration, and dried under high vacuum. 2,2′-Biquinoline-6,6′-dicarbonitrile (**3**) was obtained as a yellow-brown powder; yield: 1.18 g (66%); mp >260 °C.

IR (neat): 2230 (C≡N), 1628, 1551, 1425, 1142, 1086, 901, 820, 597, 513, 419 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.28 (d, *J* = 1.8 Hz, 2 H, H5/5′), 8.18 (d, *J* = 8.9 Hz, 2 H, H8/8′), 7.83 (d, *J* = 8.9, 1.8 Hz, 2 H, H7/7′), 7.74 (d, *J* = 9.2 Hz, 2 H, H4/4′), 6.85 (d, *J* = 9.2 Hz, 2 H, H3/3′).

$^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): δ =161.7 (C2/2′), 141.4 (C8a/8a′), 133.4 (C5/5′), 130.7 (C7/7′), 130.0 (C4/4′), 119.6 (C4a/4a′), 119.5 (2 × C≡N), 119.4 (C8/8′), 116.0 (C6/6′), 102.1 (C2/2′).

MS (ESI): *m*/*z* (%) = 307 (100) $[M + H]^+$.

Anal. Calcd for $C_{20}H_{10}N_4$: C, 78.42; H, 3.29; N, 18.29. Found: C, 79.39; H, 3.26; N, 18.99.

### 2,2′-(Pyridine-2,6-diyl)bis(1*H*-benzimidazole-5-carbonitrile) (4)

3,4-Diaminobenzonitrile (**17**; 1.87 g, 14.06 mmol, 2 equiv) and pyridine-2,6-dicarbaldehyde (**18**; 0.95 g, 7.03 mmol, 1 equiv) were dissolved in EtOH (100 mL). The solution was stirred for 20 min at rt, and then *p*-benzoquinone (1.52 g, 14.06 mmol, 2 equiv) was added and the flask was equipped with a reflux condenser to heat the solution at reflux temperature for 18 h. Once complete conversion of the reagents was reached (determined by $^1H$ NMR), the mixture was cooled to rt. The formed precipitate was collected by filtration and thoroughly washed sequentially with cold EtOH and $Et_2O$. The filtrate was concentrated and stored at rt. A precipitate formed again, which was collected by filtration and washed. The combined precipitates were dried under high vacuum. The title compound **4** was obtained as a purple-grey powder; yield: 1.35 g (53%); mp >260 °C.

IR (neat): 3161 (N–H), 2222 (C≡N), 1620, 1599, 1445, 1416, 1312, 1236, 995, 947, 809, 735, 692 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 13.48 (br s, 2 H, 2 × NH), 8.46 (d, *J* = 7.8 Hz, 2 H, H3/5), 8.32 (s, 2 H, H4′/4″), 8.25 (t, *J* = 7.8 Hz, 1 H, H4), 7.93 (d, *J* = 8.4 Hz, 2 H, H7′/7″), 7.70 (d, *J* = 8.4 Hz, 2 H, H6′/6″).

$^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): δ = 153.1 (C2′/2″), 147.0 (C2/6), 139.6 (C4), 126.4 (C6′/6″), 122.8 (C3/5), 121.7 (C4′/4″), 119.8 (2 × C≡N), 116.4 (C7′/7″), 104.8 (C5′/5″).

MS (ESI): *m*/*z* (%) = 384 (100) $[M + Na]^+$.

Anal. Calcd for $C_{21}H_{11}N_7$: C, 69.80; H, 3.07; N, 27.13. Found: C, 69.06; H, 3.21; N, 27.41.

*Note*: peak broadening due to rapid benzimidazole tautomerism does not allow all the expected $^{13}C$ signals (C3a′, C3a″, C7a′ and C7a″) in the acquired $^{13}C$ NMR spectrum to be obtained.

### Quinoline-2,6-dicarbonitrile (5)

6-Cyanoquinoline *N*-oxide (**16**; 1 g, 5.88 mmol) was added to a suspension of KCN (1.15 g, 17.64 mmol, 3 equiv) in MeOH (20 mL). The flask was placed under a flow of $N_2$ gas, which flushed the liberated HCN through two consecutive gas washing bottles containing 1 M KOH solution and 1 M $Na_2S_2O_3$ solution. Acetyl chloride (1.25 mL, 17.64 mmol, 3 equiv) was added dropwise over 5 min, after which the suspension was stirred for 20 h at rt. During the course of the reaction, a color change from yellow to light pink was observed. Upon addition of water (30 mL), a pale pink precipitate was formed. The precipitate was collected by filtration, washed with water and $Et_2O$, and subsequently dried under high vacuum. Quinoline-2,6-dicarbonitrile (**5**) was crystallized from MeOH as pale pink needles; yield: 606 mg (58%); mp 225 °C.

IR (neat): 2232 (C≡N), 1585, 1483, 1396, 1329, 1306, 1215, 917, 843, 833, 472 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.5 Hz, 1 H, H4), 8.32 (d, *J* = 1.7 Hz, 1 H, H5), 8.30 (d, *J* = 8.8 Hz, 1 H, H8), 7.99 (dd, *J* = 8.8, 1.7 Hz, 1 H, H7), 7.84 (d, *J* = 8.5 Hz, 1 H, H3).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 148.8 (C8a), 138.1 (C4), 136.5 (C2), 133.9 (C5), 131.7 (C7), 131.7 (C8), 127.8 (C4a), 124.9 (C3), 117.6 (C10≡N), 116.7 (C9≡N), 113.3 (C6).

MS (ESI): *m*/*z* (%) = 180 (100) $[M + H]^+$.

Anal. Calcd for $C_{11}H_5N_3$: C, 73.74; H, 2.81; N, 23.45. Found: C, 74.10; H, 2.86; N, 24.21.

**2-(Trichloromethyl)-1*H*-benzimidazole-5-carbonitrile (19)**

Methyl 2,2,2-trichloroacetimidate (620 μL, 5 mmol) was added dropwise to 3,4-diaminobenzonitrile (**17**; 666 mg, 5 mmol, 1 equiv) in AcOH (10 mL) at rt. After stirring for 16 h, water (20 mL) was added and the suspension was stirred for a further 5 min. The precipitate was collected by filtration and washed with water, after which it was dried under high vacuum to afford 2-(trichloromethyl)-1*H*-benzimidazole-5-carbonitrile (**19**) as a grey-white powder; yield: 1.04 g (75%).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.29 (s, 1 H), 7.82 (d, $J_{AB}$ = 8.4 Hz, 1 H), 7.74 (d, $J_{AB}$ = 8.4 Hz, 1 H).

$^{13}$C NMR (100.6 MHz, DMSO-$d_6$): δ = 153.5, 127.3, 119.4, 105.8, 88.1.

Note: peak broadening due to rapid benzimidazole tautomerism does not allow all the expected $^{13}$C signals in the acquired $^{13}$C NMR spectrum to be obtained.

**1*H*-Benzimidazole-2,5-dicarbonitrile (6)**

To a solution of 2-(trichloromethyl)-1*H*-benzimidazole-5-carbonitrile (**19**; 1.042 g, 4 mmol) in EtOH (70 mL) was added aq ammonia solution (25 wt%; 150 mL). The mixture was stirred at rt for 16 h, after which the solvent was evaporated under reduced pressure (*Caution*! use a rotavapor in a fume hood). The solid residue was dispersed in 50 mL water, sonicated for 5 min, filtered, and washed with water. The residue was dried under high vacuum to afford 1*H*-benzimidazole-2,5-dicarbonitrile (**6**) as a white-grey powder; yield: 0.599 g (89%); mp >260 °C.

IR (neat): 3115 (N–H), 2241 (C≡N), 1620, 1431, 1410, 1317, 1271, 1221, 1001, 823 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.40 (s, 1 H, H4), 7.90 (d, $J_{AB}$ = 8.5 Hz, 1 H, H7), 7.79 (d, $J_{AB}$ = 8.5 Hz, 1 H, H6).

$^{13}$C NMR (100.6 MHz, DMSO-$d_6$): δ = 139.3 (C3a), 138.5 (C7a), 127.7 (C6), 127.5 (C2), 123.4 (C4), 119.1 (C≡N$_{benz}$), 117.1 (C7), 111.9 (C≡N$_{im\text{-}id}$), 106.8 (C5).

MS (ESI): *m*/*z* (%) = 186 (100) [M + Na]$^+$, 169 (26) [M + H]$^+$.

Anal. Calcd for $C_9H_4N_4$: C, 64.28; H, 2.40; N, 33.32. Found: C, 63.91; H, 2.51; N, 34.11.

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## Supporting Information

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