Trans-ruthenium(II) complexes for photoactivated cChemotherapy: from design to anticancer activity

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Chapter 2

Simple and efficient method for amination of polypyridine N-oxides

Abstract: Herein we report a simple synthetic route towards both known and novel aminated polypyridyl ligands. The use of tosyl chloride in combination with potassium phthalimide followed by hydrolysis allows for chemo-selective ortho-amination of (poly)pyridyl mono-N-oxides with good to excellent yield. The reactions are scalable and reproducible while using inexpensive, commercially available reagents.

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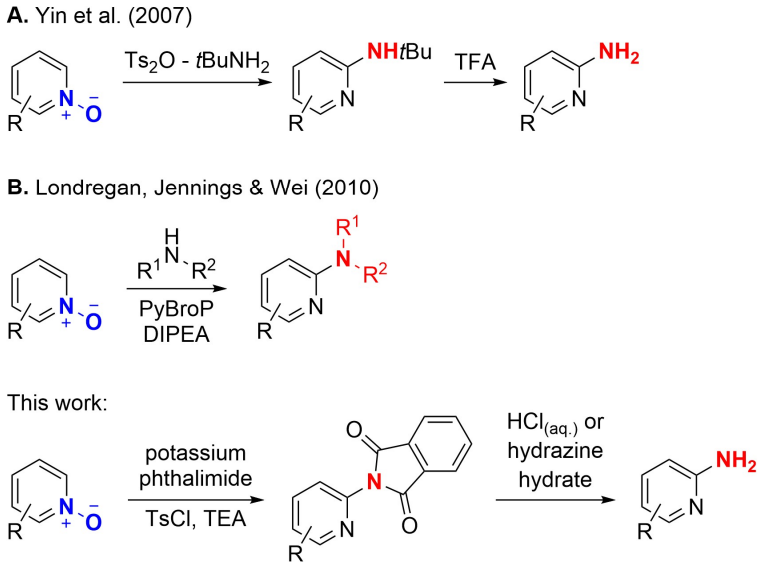
2.1 Introduction

Nitrogen heterocycles form an important class of chemicals used in a wide variety of scientific disciplines such as medicinal chemistry, photochemistry, or catalysis.[1] Polypyridyl derivatives, in particular, are in high demand as they form the core of many functional molecules. Therefore, the development of simple and efficient functionalization methods remains of high interest in chemistry. Among the wide range of preparative reactions available for the functionalization of polypyridine compounds, amination reactions are of particular interest, as amine-functionalized polypyridyl compounds have shown fascinating applications in drug discovery or catalysis. Fier *et al.* discussed the importance of 2-aminopyridines as pharmacophores and gave an excellent overview of their preparation using conventional methods such as the Chichibabin reaction.[2] More recently, Chen and Li demonstrated the application of 2-aminopyridines in the synthesis of various imidazo[1,2-*a*]pyridines as key intermediates in the synthesis of e.g. aldehyde dehydrogenase inhibitors.[3,4]

Although great progress has been made towards the direct C–H activation of N-heterocycles, the reported procedures are generally limited by a poor regioselectivity, a narrow functional-group tolerance, and/or the use of harsh conditions and special equipment (*e.g.*, for reactions in liquid ammonia).[5] The challenges of selective functionalization mainly arise from the electron deficiency of N-heterocycles and their tendency to coordinate to metal ions. Conversely, pyridines and quinolines can be more easily functionalized *ortho* to the nitrogen atom of the heterocycle from their corresponding *N*-oxides, which have enhanced electrophilic character of the C2 carbon.[6] The conversion of pyridine *N*-oxides into their 2-amino-pyridyl analogues was already reported in the 1960's by Abramovitch.[7] As reported by Yin *et al,* these reactions typically utilize an N-O activator such as acetic anhydride (Ac_2O), tosyl anhydride (Ts_2O) or tosyl chloride (TsCl), to make the *ortho*-C2 more reactive towards an amine-based nucleophile (Scheme 2.1A).[8] However, competing side-reactions between the two reagents are relatively common, which significantly lowers preparative yields, and complicates both the product isolation and the general applicability of this method notably at multi-gram scales.[8] One way to minimize the formation of side-products is to use phosphonium salts as activating agent, such as bromo-tris(1-pyrrolidinyl)phosphonium hexafluoridophosphate (PyBroP), which are less reactive towards nucleophilic amines (Scheme 2.1B).[9] Despite all efforts made to improve the selective amination of pyridines, these methods are still focused on single pyridines.[10,11] For example, the preparation of [2,2'-bipyridine]-6,6'-diamine, which is widely used in synthesis of polypyridine ligands, has only been reported using harsh reaction conditions and/or multi-step synthesis routes.[12–14] To our knowledge, amination procedures of polypyridine *N*-oxides using mild conditions and without extensive isolation have not been reported yet (Scheme 2.1C).

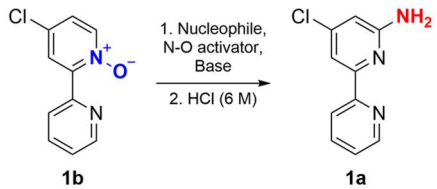


Scheme 2.1 Current methods towards 2-aminopyridines.

2.2 Results and Discussion

To investigate the synthesis of 4-chloro-2,2'-bipyridine-6-amine **1a** from the corresponding *N*-oxide **1b**, we screened a selection of previously reported reagents (Scheme 2.1 & Table 2.1). The procedure described by Yin was chosen as a starting point, since it reported good yields for mono-aminated products starting from 4-chloro-pyridine-1-oxide and 2,2'-bipyridine-1-oxide (between 71 and 81%) using Ts_2O and *tert*-butyl amine (NH_2tBu).[8] Unfortunately, application of these conditions on **1b** resulted in a low yield (Table 2.1, entry 1), also when the reaction was performed at a larger scale (entry 2). This is likely related to a side reaction between Ts_2O and NH_2tBu, as we observed significant amounts of the resulting *N*-(*t*Bu)-tosylamide. The use of PyBroP as a milder activator resulted in less side-products but not in increased yields (Table 2.1 entry 3 & 4). Therefore, we investigated the use of other amine sources as nucleophiles.

Table 2.1 Screening of reaction conditions for *ortho*-amination of 4-chloro-[2,2'-bipyridine]-1-oxide.

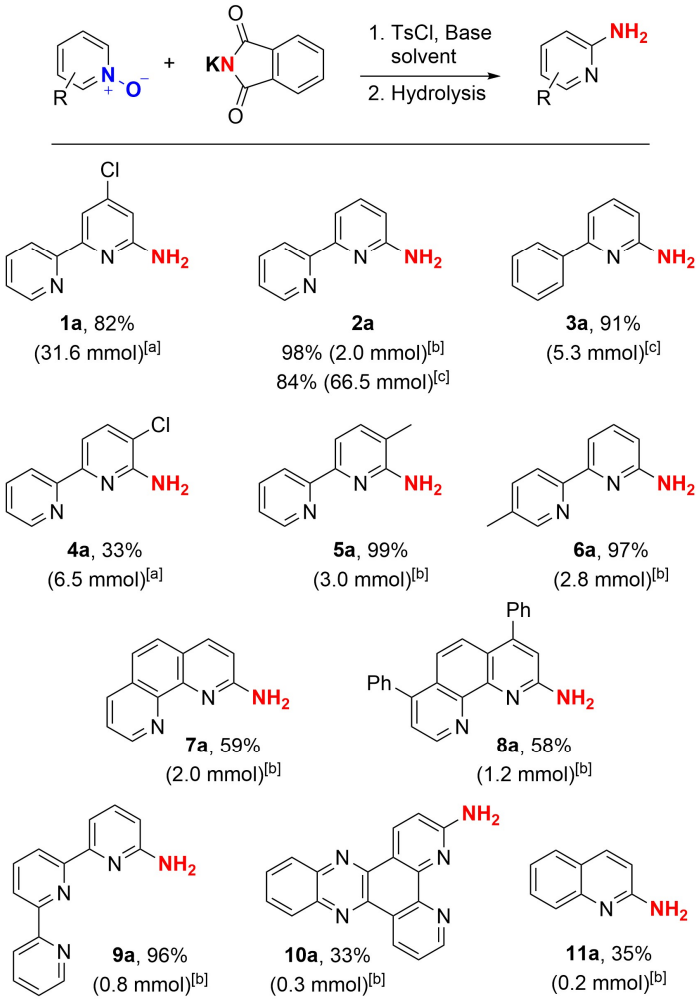


1b 1a

Entry[a]	Nucleophile (eq.)		N-O activator (eq.)		Base (eq)		Conc. (M)	Scale [b] (mmol)	Yield (%)[c]
1	NH_2tBu	6.0	Ts_2O	2.5	-	-	0.20	0.73	23
2	NH_2tBu	6.0	Ts_2O	2.5	-	-	0.20	3.15	16
3	NH_2tBu	1.3	PyBroP	3.0	DIPEA	3.75	0.25	1.00	26
4	NH_2tBu	1.8	PyBroP	2.5	DIPEA	3.75	0.25	12.10	5
5	Saccharin	1.2	TsCl	1.2	DIPEA	2.0	0.32	0.48	40
6	HMDS	4.0	TsCl	1.2	DIPEA	2.0	0.32	0.48	18
7	PHT	1.2	TsCl	1.2	DIPEA	2.0	0.32	0.48	94
8	PHT	1.2	TsCl	1.2	DIPEA	2.0	0.32	38.50	82

[a] All reactions were performed in dichloromethane (DCM) at RT. Entries 1-2 were performed in trifluorotoluene ($PhCF_3$). [b] Scale represents the amount of starting *N*-oxide. [c] Isolated yield. DIPEA = diisopropylethylamine.

While using bis(trimethylsilyl)amine (HMDS) (Table 2.1, entry 6) did not result in an increased yield, Gabriel-type reagents saccharin (Table 2.1, entry 5) and phthalimide (PHT; Table 2.1, entry 7) provided a major breakthrough. Although saccharin and phthalimide are chemically relatively similar, the reaction yields dramatically increased from 40% with saccharin to 94% when phthalimide was used as nucleophile. Moreover, the latter reaction conditions allowed for 80–fold upscaling (Table 2.1, entry 8) without major reduction of the yield or formation of side-products, illustrating the excellent potential of this methodology. After establishing a working procedure (Method A), we applied it to a variety of polyaryl *N*-oxides (Scheme 2.2).



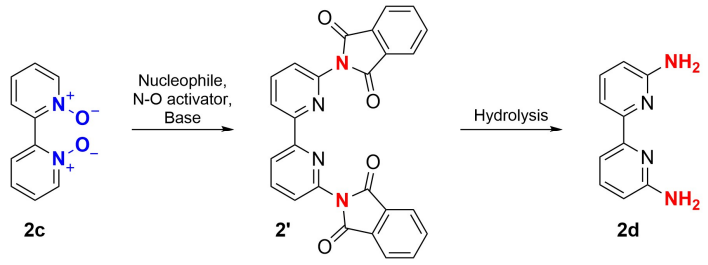
Scheme 2.2 Scope of mono-amination of polyaryl *N*-oxide. [a] PHT (1.2 eq), TsCl (1.2 eq) DIPEA (2.0 eq) in DCM (0.4 M) at RT for 24 h; hydrolysis with HCl (6.0 M) at 80 °C for 6 h (Method A). [b] KPHT (2.0 eq), TsCl (2.0 eq), TEA (2.0 eq) in DCM (0.2 M) at RT for 24 h; hydrolysis with hydrazine hydrate (5.0

eq) at 80 °C for 6 h (Method B). [c] KPHT (2.5 eq), TsCl (2.5 eq), TEA (2.5 eq) in ACN (0.05 M); hydrolysis with hydrazine hydrate (5.0 eq) at 80 °C for 24 h (Method C). Yields refer to the isolated product in percentage and amount in parentheses.

Interestingly, changing the position of the chloro substituent from para to meta relative to the *N*-oxide (**1a** and **4a**), resulted in a lower yield of 33%. Since complete consumption of the corresponding starting *N*-oxide towards **4a** was observed, we hypothesize that the lower yield might be due to isolation challenges. To circumvent the need of acid neutralization after hydrolysis of the phthalimide intermediate, hydrazine hydrate was used instead of hydrochloric acid. Additionally, the use of potassium phthalimide (KPHT) omits the need for deprotonation of the nucleophile, reducing the amount of base needed in the reaction (Method B). This leads to an overall higher concentration of the reaction mixture and facilitates unambiguous product isolation. With these conditions we were able to obtain various aminated products in good to excellent yields, including derivatives of methyl-2,2'-bipyridine (**5a**, **6a**), phenanthroline (**7a**, **8a**, **10a**), terpyridine (**9a**) and quinoline (**11a**). Changing the solvent to acetonitrile to ensure solubilization of the reagents when more equivalents were used (Method C), enabled the synthesis of **2a** and **3a** in excellent yield, on a notably large scale for **2a** (>11 g). For this reaction, most polar aprotic solvents could be used as long as *i)* there was no reactivity towards the reagents (e.g., DMF and DMSO did not work well), and *ii)* the solubility of the substrate and reagent were sufficient.

To further study the scope of this reaction, we decided to investigate the possibility of conducting two aminations in the same molecule. For this study 2,2'-bipyridine-1,1'-dioxide **2c** was chosen as a substrate, with the aim to synthesize the corresponding diamino product **2d** (Table 2.2). Since double amination of a substrate comes with new challenges, related to reactivity and solubility, an additional optimization study was performed (Table 2.2, Table S1).

Table 2.2 Optimization of reaction conditions towards the synthesis of [2,2'-bipyridine]-6,6'-diamine.



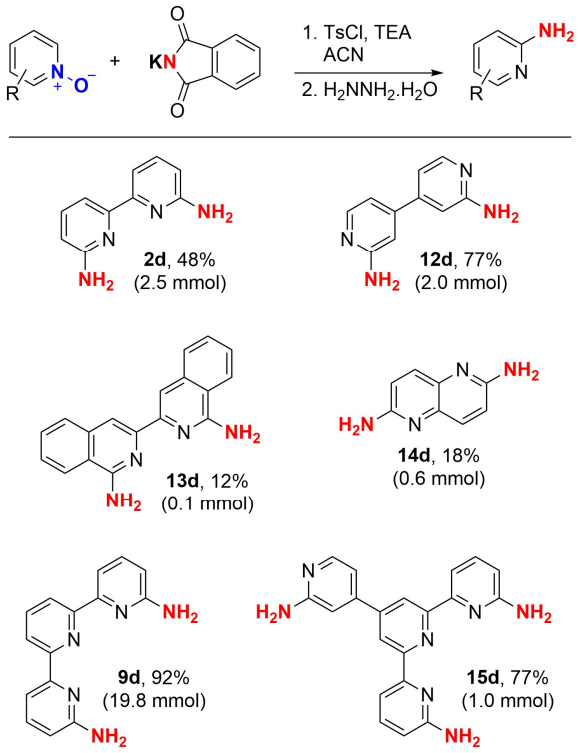
Entry[a]	Nucleophile (eq.)		N-O activator[b] (eq.)	Base (eq)		Solvent	Yield (%)
1	PHT	2.5	2.5	DIPEA	5.0	ACN	34
2	PHT	2.5	2.5	DBU	5.0	ACN	0
3	PHT	2.5	2.5	Pyridine	5.0	ACN	0
4	PHT	2.5	2.5	DIPEA	5.0	PhCN	14
5	PHT	2.5	2.5	DIPEA	5.0	Acetone	20
6	PHT	3.0	3.0	TEA	6.0	ACN	39
7	KPHT	3.0	3.0	DIPEA	6.0	ACN	40
8	PHT	3.0	3.0	DIPEA	6.0	ACN	35[c]
9	KPHT	5.0	5.0	K_2CO_3	10.0	ACN[d]	42
10	PHT	5.0	5.0	Cs_2CO_3	10.0	ACN[d]	22
11	KPHT	5.0	5.0	TEA	5.0	ACN[d]	51
12	KPHT	5.0	5.0	TEA	5.0	ACN[d]	>99[e]

[a] All reactions were conducted in one-pot with 100 mg (0.53 mmol) of **2c** at 0.1 M in a sealed glass tubes at RT for 48 h, followed by hydrolysis with HCl (6 M) at 80 °C for 6 h. The final mixtures were analyzed using quantitative ^{1}H-NMR, using 1,3,5-trimethoxybenzene as internal standard.[15] [b] TsCl was used as N-O activator during all reactions. [c] The first reaction step was performed at 50 °C. [d] The reaction was performed at 0.05 M. [e] Hydrazine hydrate (5 eq.) was used for the hydrolysis.

The main problem to be solved for the di-amination reactions is the poor solubility of di-*N*-oxides in the organic aprotic solvents that were used for the mono-amination reactions. Polar solvents like DMF and DMSO were found to be unsuitable for this transformation, due to their reactivity towards TsCl.[16,17] Of the solvents investigated, acetonitrile seemed to be most suitable (entry 1, 4, 5). When other bases than TEA and DIPEA were used such as 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU; entry 2) or pyridine (entry 3), no product formation

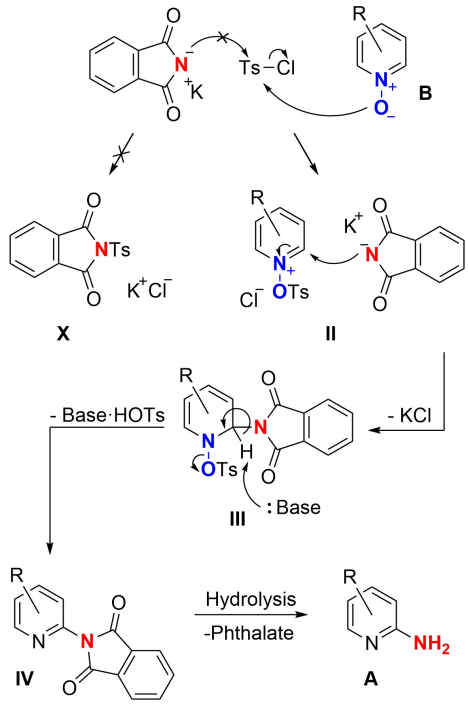
was observed. However, the use of K_2CO_3 (entry 9) or Cs_2CO_3 (entry 10) resulted in a decent yield. Performing the reaction under mild heating (50 °C) during the first step, did not lead to an increase in yield (entry 8).A significant increase of product formation was observed when a higher dilution and an excess of reagents was used (entry 1 *versus* 11). Subsequently, changing from HCl (entry 11) to hydrazine hydrate (entry 12) as hydrolysis agent increased the yield to quantitative. As we observed poor solubility of intermediate **2'** in both organic solvents and water, **2'** could be simply isolated before hydrolysis by filtration. Additionally, lowering the amount of hydrolysis reagent we managed to generate conditions in which the target product precipitated from the final reaction mixture, enabling its isolation and purification by simple filtration.

Altogether, the optimized procedure is very simple to perform and was applied on a series of polypyridyl substrates (Scheme 3). While it was optimized towards **2d**, this methodology also allowed for the preparation of its *para* isomer **12d** with a good yield. Additionally, this procedure also allowed for the synthesis of biisoquinoline **13d** and naphthyridine **14d** albeit with a lower yield. Strikingly, the reaction conditions allow for the synthesis towards terpyridine derivative **9d** with an excellent yield at a 20 mmol scale. This is particularly interesting since the synthesis of this compound has only been reported using liquid ammonia under high pressure.[18] As demonstrated by the preparation of compound **15d**, the procedure allows for multiple amination reactions within a substrate.



Scheme 2.3 Scope of double amination of polypyridyl di-*N*-oxides. All reactions were performed at room temperature with KPHT (2.5 eq), TsCl (2.5 eq), TEA (2.5 eq) in ACN (0.05 M); hydrolysis with hydrazine hydrate (5.0 eq) at 80 °C for 24 hours (Method C). Yields refer to the isolated product in percentage and amount in parentheses.

The mechanism of the reaction is assumed to be similar to that discussed in previous reports (Scheme 2.4).[8] In short, a nucleophilic attack of starting *N*-oxide **B** towards TsCl results in the formation of pyridinium-tosylate **II**. The *N*-tosylate withdraws electron density from the pyridine and allows for a nucleophilic substitution by a phthalate anion on the C2 position of the pyridyl ring while between the activator and the nucleophile. This advantage is due to the use of TsCl as activator and KPHT as nucleophile, which releases tosylic acid (Scheme 2.4, **III**). The formed phthalate intermediate **IV** is then hydrolyzed to produce the target amine product **A**. The phthalate intermediate **2e** (**IV**, R = 2,2'-pyridyl) towards product **2a** has been characterized. The main difference of our conditions compared to previous work is the prevention of a side-reaction taking place, as side-product **X** can only form at elevated temperatures.[19]



Scheme 2.4 Proposed reaction mechanism.

2.3 Conclusion

In summary, we have developed an efficient and facile procedure for mono- and di-amination of (poly)pyridine *N*-oxides in an operationally simple manner with high selectivity and good to excellent yields. While the substrate examples reported here are primarily focused on the preparation of polyaminopyridyl building blocks for ligands to be used in coordination complexes, the scope might be extended to pharmaceutical compounds. Especially the possibility to prepare diaminopolypyridyl compounds with ease in a two-step procedure makes this a useful methodology. Further exploration of the substrate scope is currently ongoing. Several of the amino-bipyridines reported here have been used in other parts of this thesis, i.e. **2a** in Chapters 3, 4 and 5 while **1a**, **4a**, **5a** and **6a** have been used in Chapter 5.

2.4 Experimental

2.4.1 General

All reagents and solvents were purchased from commercial suppliers (Fluorochem, Sigma-Aldrich, BLDPharm, VWR, TCI) and used without further purification unless noted otherwise.

Anhydrous and oxygen-free solvents were obtained using common distillation, drying (activated 4 Å molecular sieves) and degassing (freeze-pump-thaw method) procedures. The reactions were carried under air at room temperature (RT) unless stated otherwise. The standard Schlenk technique was used for the reactions that were carried out under an inert atmosphere. TLCs were performed using either Supelco analytical silica gel on Al foils with fluorescence indicator 254 nm or Supelco analytical aluminium oxide 60 with fluorescence indicator 254 nm. Column chromatography was carried on silica gel (40-63 µm) or on activated neutral aluminium oxide (Brockmann Grade I) from VWR Chemicals and driven by pressurized air; the columns were packed using slurry method. NMR spectra were recorded on Bruker Avance 300, 400 or 500 MHz and the FIDs were treated with MestReNova software. The chemical shifts are given relative to the residual signal of the solvent ($CDCl_3$: δ (^{1}H) = 7.26 ppm, δ (^{13}C) = 77.16 ppm; DMSO-d_6: δ (^{1}H) = 2.50 ppm; δ (^{13}C) = 39.52 ppm; D_2O: δ (^{1}H) = 4.79 ppm), or relative to an external standard (TMS: δ (^{1}H) = 0 ppm, δ (^{13}C) = 0 ppm).[20] The mass spectra were recorded on Shimadzu LCMS-2020 (ESI-Q). All the *N*-oxides were prepared according to procedures modified from literature.

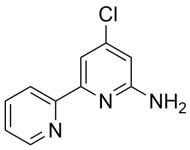
2.4.2 Amination procedures

Method A: Phthalimide (1.2 eq), DIPEA (2 eq) and the respective *N*-oxide (1 eq) were dissolved in DCM (0.4 M by *N*-oxide) and cooled to 0 °C. TsCl (1.2 eq) was added portionwise and the mixture was allowed to stir overnight at RT. Once the reaction was completed according to thin layer chromatography, the solvent was evaporated *in vacuo*. The remaining residue was redissolved in 6 M HCl and stirred at 80 °C for 6 h. The resulting solution was neutralized with a saturated aqueous solution of $NaHCO_3$, extracted with EtOAc or DCM and dried with $MgSO_4$. Activated charcoal (1 g per 2.5 mmol of N-O) was added and the mixture was refluxed for 20 min. Hot filtration and evaporation of the solvent yielded the target compound.

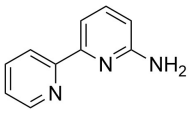
Method B: Potassium phthalimide (2 eq), TEA (2.0 eq), and the respective *N*-oxide (1 eq) were dissolved in DCM (0.2 M by *N*-oxide) and cooled to 0 °C. TsCl (2 eq) was added portionwise and the mixture was allowed to stir overnight at RT. Once the reaction was complete according to thin layer chromatography, the solvent was evaporated *in vacuo*. The remaining residue was redissolved in aq. 80% hydrazine hydrate solution (5 eq per N-O group, d = 1.02 g/ml), diluted with H_2O (0.2 M by *N*-oxide) and stirred at 80 °C for 6 h. After completion of the reaction, the mixture was extracted with $CHCl_3$. The combined organic phase was washed with 1 M NaOH, dried with $MgSO_4$ and filtered. Evaporation of the solvent yielded the target product.

Method C: Potassium phthalimide (2.5 eq per N-O group), TEA (2.5 eq per N-O group) and respective *N*-oxide (1 eq) were mixed with acetonitrile (0.05 M by *N*-oxide) in a round-bottom flask equipped with a $CaCl_2$ drying tube, followed by careful addition of solid TsCl

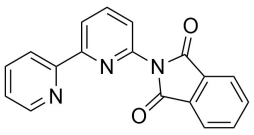
(2.5 eq per N-O group). The obtained mixture was stirred at RT for 24 h until thin layer chromatography indicated reaction completion. The resulting suspension was diluted twice with water, filtered, and the precipitate was washed with plenty of water. The obtained powder was air-dried, then mixed with aq. 80% hydrazine hydrate solution (5 eq per N-O group, d = 1.02 g/ml) diluted with H_2O (0.2 M by *N*-oxide), and the mixture was stirred at 80 °C for another 24 h. The resulting suspension was diluted twice with water, filtered, and the precipitate was washed with plenty of water. Drying *in vacuo* afforded the target product.



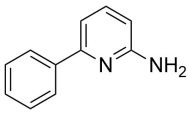
4-chloro-2,2'-bipyridin-6-amine, **1a**: Method A yielded the product as an off-white powder (6.50 g, 31.6 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.25 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.29 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 6.53 (d, *J* = 1.6 Hz, 1H), 4.60 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.84, 156.06, 153.33, 149.29, 146.08, 136.96, 124.02, 121.30, 112.29, 108.27. ESI-MS: exact m/z calculated for $[C_{10}H_8ClN_3 + H]^+$: 206.1, found: 206.2.



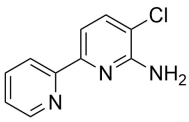
2,2'-bipyridin-6-amine, **2a**: Method B (341 mg, 2.0 mmol, 98%) and Method C (11.40 g, 66.5 mmol, 84%) yielded a light-yellow powder. TLC ($CHCl_3$/MeOH = 8/1: product R_f = 0.55; UV lamp). Analysis was consistent with previous reports.[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.30 – 8.23 (m, 1H), 7.78 (td, *J* = 7.8, 1.8 Hz, 1H), 7.70 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.58 (dd, *J* = 8.1, 7.5 Hz, 1H), 7.27 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 6.56 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.67 (s, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.01, 156.12, 154.27, 149.34, 138.98, 136.92, 123.58, 121.15, 111.70, 109.26. ESI-MS: exact m/z calculated for $[C_{10}H_9N_3 + H]^+$: 172.1, found: 172.0.



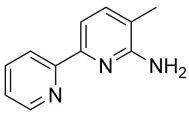
2,2'-bipyridin-6-phthalamide, **2e**: Prior to the hydrolysis step in method B, the target compound by precipitation from acetonitrile and H_2O as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 8.48 (dd, *J* = 7.9, 1.0 Hz, 1H), 8.42 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.06 – 7.95 (m, 3H), 7.87 – 7.75 (m, 3H), 7.46 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.32 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.88, 156.46, 155.34, 149.28, 145.67, 139.29, 137.17, 134.72, 132.00, 124.22, 124.10, 121.84, 121.81, 120.69. ESI-MS: exact m/z calculated for $[C_{18}H_{12}N_3O_2 + H]^+$: 302.1, found: 302.1.



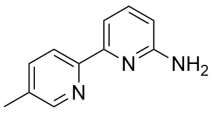
6-phenylpyridin-2-amine, **3a:** Method C yielded a light-yellow powder (0.91 g, 5.3 mmol, 91%). TLC ($CHCl_3$/MeOH = 12/1: product R_f = 0.63; UV lamp). Analysis was consistent with previous reports.[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.89 (m, 2H), 7.54 – 7.49 (m, 1H), 7.47 – 7.42 (m, 2H), 7.41 – 7.35 (m, 1H), 7.09 (dd, *J* = 7.5, 0.8 Hz, 1H), 6.48 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.66 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.15, 155.85, 139.33, 138.70, 128.79, 128.67, 126.90, 111.03, 107.34. ESI-MS: exact m/z calculated for $[C_{11}H_{10}N_2 + H]^+$: 171.1, found: 171.0; exact m/z calculated for $[C_{11}H_{10}N_2 + ACN + H]^+$: 212.1, found: 212.1.



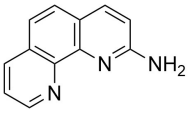
5-chloro-2,2'-bipyridin-6-amine, **4a**: Method A yielded the product as an off-white powder (1.34 g, 6.5 mmol, 33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.24 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.77 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.27 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 4.94 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.62, 154.18, 153.01, 149.25, 137.72, 136.90, 123.62, 121.03, 115.44, 112.51. ESI-MS: exact m/z calculated for $[C_{10}H_8ClN_3 + H]^+$: 206.1, found: 206.2.



5-methyl-2,2'-bipyridin-6-amine, **5a**: Method B yielded the product as a white powder (0.56 g, 3.0 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 8.24 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.24 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 4.48 (s, 2H), 2.19 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.74, 156.68, 152.49, 149.21, 138.77, 136.81, 123.11, 120.85, 117.29, 112.18, 17.20. ESI-MS: exact m/z calculated for $[C_{11}H_{11}N_3 + H]^+$: 186.1, found: 186.3.

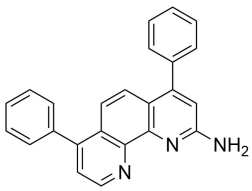


5'-methyl-2,2'-bipyridin-6-amine, **6a**: Method B yielded the product as a white powder (0.51 g, 2.8 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 2.2 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.67 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.60 – 7.52 (m, 2H), 6.52 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.52 (s, 2H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.08, 154.75, 153.90, 149.70, 138.70, 137.38, 133.09, 120.61, 111.38, 108.69, 18.44. ESI-MS: exact m/z calculated for $[C_{11}H_{11}N_3 + H]^+$: 186.1, found: 186.3

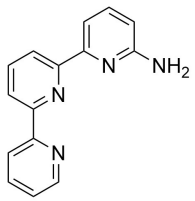


1,10-phenanthrolin-2-amine, **7a**: After performing method B, isolation by column chromatography (alumina, gradient from 0 to 10% MeOH in DCM with 0.5% triethylamine) yielded the product as an off-white powder (208 mg, 1.1 mmol, 59%). Analysis was consistent with previous reports.[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.97 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.56 – 7.49 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 5.13 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.89, 149.64, 145.83, 145.16, 138.20, 136.08, 129.35,

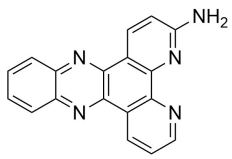
126.58, 122.90, 122.54, 122.00, 112.03. ESI-MS: exact m/z calculated for $[C_{12}H_9N_3 + H]^+$: 196.1, found: 196.2.



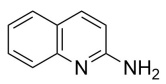
4,7-diphenyl-1,10-phenanthrolin-2-amine, **8a**: After performing method B, isolation by column chromatography (alumina, gradient from 0 to 10% MeOH in DCM with 0.5% triethylamine) yielded the product as a yellow powder (233 mg, 0.7 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, *J* = 4.5 Hz, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.57 (d, *J* = 9.3 Hz, 1H), 7.53 – 7.46 (m, 11H), 6.88 (s, 1H), 5.41 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.17, 150.88, 149.17, 148.44, 146.03, 145.36, 138.42, 138.24, 129.78, 129.52, 128.65, 128.54, 128.46, 127.20, 124.24, 123.15, 121.18, 119.61, 112.41. ESI-MS: exact m/z calculated for $[C_{24}H_{17}N_3 + H]^+$: 348.2, found: 348.2.



2,2':6',2''-terpyridin-6-amine, **9a**: Method B yielded the product as an off-white powder (192 mg, 0.8 mmol, 96%). Analysis was consistent with previous reports.[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.62 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.41 (dd, *J* = 7.8, 1.1 Hz, 1H), 8.35 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.98 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.92 (t, *J* = 7.8 Hz, 1H), 7.85 (td, *J* = 7.7, 1.8 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.32 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 6.57 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.51 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.08, 156.52, 155.74, 155.34, 154.84, 149.21, 138.68, 137.85, 136.97, 123.81, 121.36, 120.96, 120.75, 111.83, 109.05. ESI-MS: exact m/z calculated for $[C_{15}H_{12}N_4 + H]^+$: 249.1, found: 249.2

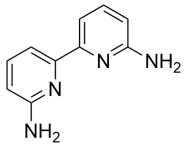


dipyrido[3,2-a:2',3'-c]phenazin-3-amine, **10a**: Method B yielded the product as a brown powder (93 mg, 0.3 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (dd, *J* = 8.1, 1.8 Hz, 1H), 9.33 (d, *J* = 8.7 Hz, 1H), 9.23 (dd, *J* = 4.5, 1.9 Hz, 1H), 8.32 – 8.25 (m, 2H), 7.90 – 7.81 (m, 2H), 7.74 (dd, *J* = 8.1, 4.5 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 5.29 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.02, 152.34, 148.40, 148.27, 142.77, 141.86, 141.71, 140.24, 135.86, 133.95, 130.47, 129.65, 129.58, 129.31, 127.89, 123.76, 119.98, 111.56. ESI-MS: exact m/z calculated for $[C_{18}H_{11}N_5 + H]^+$: 298.1, found: 298.1.

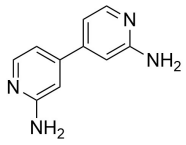


Quinoline-2-amine, **11a**: Method B yielded an off-white powder (34 mg, 0.24 mmol, 35%). Analysis was consistent with previous reports.[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.8, 0.8 Hz, 1H), 7.67 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.63 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.56 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.27 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 4.94 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.93,

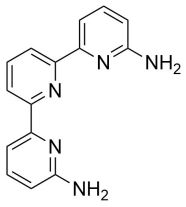
147.31, 138.46, 130.07, 127.67, 125.81, 123.66, 122.97, 111.85. ESI-MS: exact m/z calculated for $[C_9H_8N_2 + H]^+$: 145.1, found: 145.2.



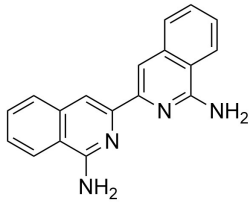
2,2'-bipyridine-6,6'-diamine, **2d**: Method C yielded a light-yellow crystals (0.47 g, 2.5 mmol, 48%). Analysis was consistent with previous reports.[26] TLC ($CHCl_3$/MeOH = 8/1: product R_f = 0.63; UV lamp). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.48 – 7.38 (m, 4H), 6.43 (dd, *J* = 7.8, 1.3 Hz, 2H), 5.88 (s, 4H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$) δ 159.04, 154.11, 137.58, 108.67, 108.11. ESI-MS: exact m/z calculated for $[C_{10}H_{10}N_4 + H]^+$: 187.1, found: 187.2.



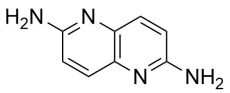
4,4'-bipyridine-2,2'-diamine, **12d**: Method C yielded a light-beige powder (0.38 g, 2.0 mmol, 77%). Analysis was consistent with previous reports.[27] ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.97 (dd, *J* = 5.3, 0.7 Hz, 2H), 6.68 (dd, *J* = 5.3, 1.6 Hz, 2H), 6.64 (dd, *J* = 1.7, 0.8 Hz, 2H), 6.05 (s, 4H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-*d*$_6$) δ 160.50, 148.68, 146.71, 109.50, 104.80. ESI-MS: exact m/z calculated for $[C_{10}H_{10}N_4 + ACN + H]^+$: 228.1, found: 228.1.



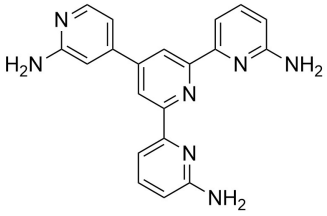
2,2':6',2''-terpyridine-6,6''-diamine, **9d**: Method C yielded a white powder (5.21 g, 19.8 mmol, 92%). TLC ($CHCl_3$/MeOH = 2/1: product R_f = 0.75; UV lamp). ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.23 (d, *J* = 7.8 Hz, 2H), 7.97 (t, *J* = 7.8 Hz, 1H), 7.72 (dd, *J* = 7.4, 0.9 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 6.53 (dd, *J* = 8.1, 0.9 Hz, 2H), 6.05 (s, 4H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-*d*$_6$) δ 159.34, 155.23, 153.48, 137.96, 137.59, 119.66, 108.89, 108.79. ESI-MS: exact m/z calculated for $[C_{15}H_{13}N_5 + H]^+$: 264.1, found: 264.2; exact m/z calculated for $[2C_{15}H_{13}N_5 + Na]^+$: 549.2, found: 549.2.



[3,3'-bis-isoquinoline]-1,1'-diamine, **13d**: Method C with isolation by column chromatography (silica, gradient from 10% to 50% MeOH in $CHCl_3$ with 0.2% TEA) yielded a yellow powder (0.04 g, 0.14 mmol, 12%). TLC ($CHCl_3$/MeOH = 8/1: product R_f = 0.10; UV lamp). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.73 – 8.17 (m, 6H), 8.02 (d, *J* = 5.5 Hz, 2H), 7.98 – 7.81 (m, 4H), 7.79 – 7.61 (m, 2H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 155.87, 137.34, 132.97, 127.84, 125.07, 117.52, 107.38. ESI-MS: exact m/z calculated for $[C_{18}H_{14}N_4+H]^+$: 287.1; found: 287.2.

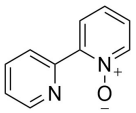


1,5-naphthyridine-2,6-diamine, **14d**: Method C yielded a brown powder (0.09 g, 0.6 mmol, 18%). TLC ($CHCl_3$/MeOH = 1/1: product R_f = 0.68; UV lamp). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 6.06 (s, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ 155.35, 137.66, 134.74, 114.42. ESI-MS: exact m/z calculated for $[C_8H_8N_4 + H]^+$: 161.1, found: 161.1.

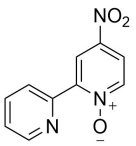


4'-(2-aminopyridin-4-yl)-[2,2':6',2''-terpyridine]-6,6''-diamine, **15d**: Method C yielded a yellow powder (0.36 g, 1.01 mmol, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 2H), 8.09 (d, J = 5.3 Hz, 1H), 7.77 (dd, J = 7.4, 0.9 Hz, 2H), 7.63 – 7.54 (m, 2H), 6.93 – 6.77 (m, 2H), 6.56 (dd, J = 8.2, 0.8 Hz, 2H), 6.21 (s, 2H), 6.13 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.64, 159.45, 156.22, 153.10, 149.04, 147.68, 146.57, 138.05, 116.95, 109.68, 109.16, 109.12, 105.20. ESI-MS: exact m/z calculated for $[C_{20}H_{17}N_7+H]^+$: 356.2; found: 356.2.

2.4.3 Precursor synthesis

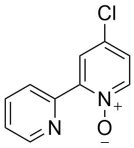


2,2'-bipyridine-1-oxide, **2b**: A solution of 2,2'-bipyridine (10.00 g, 63.4 mmol, 1 eq) in TFA (43 ml) was stirred at 0 °C for 10 min. Then the aqueous H_2O_2 (6.0 ml, 35%, d = 1.13 g/ml, 69.7 mmol, 1.1 eq) was added dropwise to the mixture over 15 min at 0 °C followed by stirring at RT for 24 h. After reaction completion, TFA was distilled out under vacuum and the remaining crude was poured in ice and neutralized with 6 M NaOH. The resulting solution was extracted with $CHCl_3$ (4 x 50 mL), the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford final product as white powder (10.73 g, 62.3 mmol, 98%). TLC (Hexane/EtOAc = 4/1: starting material R_f = 0.35, product R_f = 0.08; $CHCl_3$/MeOH = 4/1: product R_f = 0.65; UV lamp). Analysis was consistent with previous reports.[28,29] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (dt, J = 8.0, 1.1 Hz, 1H), 8.72 (ddd, J = 4.9, 1.9, 1.0 Hz, 1H), 8.31 (dd, J = 6.6, 1.3 Hz, 1H), 8.17 (dd, J = 8.1, 2.2 Hz, 1H), 7.83 (td, J = 7.8, 1.8 Hz, 1H), 7.40 – 7.31 (m, 2H), 7.26 (td, J = 7.0, 2.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.68, 149.44, 147.40, 140.82, 136.47, 128.04, 125.91, 125.68, 125.40, 124.43. ESI-MS: exact m/z calculated for $[C_{10}H_8N_2O - e]^+$: 172.1, found: 172.1

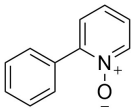


4-nitro-2,2'-bipyridine-1-oxide, **1c**: A mixture of 2,2'-bipyridine 1-oxide **2b** (34.40 g, 0.2 mol, 1 eq) and KNO_3 (152.00 g, 1.5 mol, 7.5 eq) in concentrated H_2SO_4 (267 ml) was stirred at 80 °C. After 45 h, the mixture was allowed to cool to RT, poured onto ice and neutralized with 6 M NaOH to pH = 9. The formed precipitate was collected by filtration, washed with cold water and dried *in vacuo*. The resulting crude was redissolved in DCM, filtered and concentrated *in vacuo*. Recrystallization from DCM/hexane (2/1) at -20 °C overnight yielded the product as a yellow crystalline solid (11.10 g, 51.1 mmol, 26%). Analysis was consistent with previous

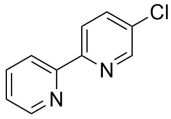
reports.[30,31] ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (dd, *J* = 3.4, 0.5 Hz, 1H), 8.82 (ddd, *J* = 4.7, 1.8, 1.0 Hz, 1H), 8.77 (dt, *J* = 8.1, 1.1 Hz, 1H), 8.58 (dd, *J* = 7.2, 0.5 Hz, 1H), 8.23 (dd, *J* = 7.2, 3.4 Hz, 1H), 8.02 (ddd, *J* = 8.1, 7.6, 1.8 Hz, 1H), 7.58 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 149.85, 147.52, 146.84, 142.44, 142.19, 136.93, 125.48, 124.65, 121.60, 119.86. ESI-MS: exact m/z calculated for $[C_{10}H_7N_3O_3 + H]^+$: 218.1, found: 218.2.



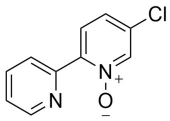
4-chloro-2,2'-bipyridine-1-oxide, **1b**: Acetyl chloride (54.2 ml, d = 1.10 g/ml, 0.8 mol, 15 eq) was dropwise added to solid 4-nitro-2,2'-bipyridine-1-oxide **1c** (11.00 g, 50.6 mmol, 1 eq) and stirred at 50 °C. After 1 h, excess acetyl chloride was removed under vacuum. To the residue ice water (100 ml) was added and the mixture was neutralized with aqueous saturated Na_2CO_3 solution. The resulting mixture was extracted with $CHCl_3$ (5 x 100 ml) and the combined organic phase was dried over $MgSO_4$. After filtration and evaporation of the solvent, the crude was recrystallized from acetone yielding the product as a faint yellow solid (10.32 g, 49.9 mmol, 99%). Analysis was consistent with previous reports.[31,32] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (dt, *J* = 8.1, 1.1 Hz, 1H), 8.72 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 8.27 – 8.17 (m, 2H), 7.83 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 7.37 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.23 (dd, *J* = 7.0, 3.1 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.56, 148.53, 147.92, 141.55, 136.59, 132.02, 127.78, 125.60, 125.49, 124.91. ESI-MS: exact m/z calculated for $[C_{10}H_7ClN_2O+ H]^+$: 207.0, found: 207.4.



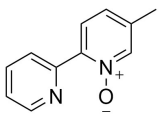
2-phenylpyridine-1-oxide, **3b**: *m*-CPBA (11.83 g (77%), 52.8 mmol, 1.4 eq) was added as a solid to a solution of 2-phenylpyridine (5.5 ml, d = 1.09 g/ml, 37.7 mmol, 1 eq) in DCM (189 ml) and the resulting mixture was stirred for 24 h at RT. Upon reaction completion the organic phase was washed with 1 M NaOH (3 x 50 ml), dried over Na_2SO_4 and concentrated *in vacuo* to afford final product as white powder (5.87 g, 34.3 mmol, 91%). TLC (Hexane/EtOAc = 4/1: starting material R_f = 0.66, product R_f = 0; $CHCl_3$/MeOH = 8/1: product R_f = 0.64; UV lamp). Analysis was consistent with previous report.[33] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (ddd, *J* = 6.5, 1.3, 0.6 Hz, 1H), 7.85 – 7.77 (m, 2H), 7.53 – 7.41 (m, 4H), 7.34 (td, *J* = 7.7, 1.3 Hz, 1H), 7.25 (ddd, *J* = 7.5, 6.5, 2.1 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.58, 140.72, 132.57, 129.87, 129.45, 128.48, 127.64, 126.46, 124.71. ESI-MS: exact m/z calculated for $[C_{11}H_9NO + H]^+$: 172.1, found: 172.0.



5-chloro-2,2'-bipyridine, **4c**: 2-tributylstannylpyridine (8.1 ml, d = 1.14 g/ml, 25.0 mmol, 1 eq) was added to a solution of 2-bromo-5-chloropyridine (5.29 g, 27.5 mmol, 1.1 eq) in anhydrous toluene (83 ml) and degassed by bubbling N_2 through the mixture. After 1 h, $Pd(PPh_3)_4$ (2.89 g, 2.50 mmol, 0.1 eq) was added and the reaction mixture was refluxed for 3 days under N_2 atmosphere. The reaction mixture was cooled to RT, filtered to remove any solids and concentrated *in vacuo*. Aqueous 1 M HCl (100 ml) was added to the residue, which was washed with DCM (100 ml) and neutralized with solid $NaHCO_3$. The product was extracted from the aqueous phase with DCM (3 x 100 ml). The combined organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude by column chromatography on alumina (petroleum ether/EtOAc = 98/2) provided the product as an off-white solid (3.98 g, 21.0 mmol, 83 %). TLC (alumina, petroleum ether/EtOAc = 98/2: product R_f = 0.51; UV lamp). Analysis was consistent with previous reports.[34,35] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 – 8.63 (m, 1H), 8.61 (dd, *J* = 2.5, 0.7 Hz, 1H), 8.39 – 8.36 (m, 1H), 8.36 – 8.33 (m, 1H), 7.84 – 7.75 (m, 2H), 7.30 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.25, 154.44, 149.35, 148.13, 137.11, 136.74, 132.37, 124.05, 121.96, 121.13. ESI-MS: exact m/z calculated for $[C_{10}H_7ClN_2 + H]^+$: 191.0, found: 191.2.

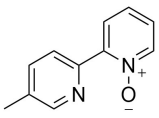


5-chloro-2,2'-bipyridine-1-oxide, **4b**: A solution of 5-chloro-2,2'-bipyridine **4c** (3.80 g, 19.9 mmol, 1 eq) in TFA (15 ml) was cooled to 0°C and hydrogen peroxide (35 % aq., 2.6 ml, d = 1.11 g/ml, 30 mmol, 1.5 eq) was added dropwise. After the addition, the reaction mixture was allowed to stir overnight at RT. Excess TFA was removed by vacuum distillation and the remaining residue was poured onto ice. The mixture was neutralized with 6 M NaOH (aq.) and extracted with $CHCl_3$ (6 x 50 ml). The combined organic phase was dried with $MgSO_4$ and filtered. Evaporation of the solvent yield the product as a white crystalline solid (3.90 g, 18.9 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (dt, *J* = 8.1, 1.1 Hz, 1H), 8.71 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.35 (dd, *J* = 2.0, 0.5 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.83 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 7.39 – 7.31 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.57, 148.82, 146.13, 139.86, 136.54, 132.60, 127.87, 126.87, 125.45, 124.65. ESI-MS: exact m/z calculated for $[C_{10}H_7ClN_2O + H]^+$: 207.0, found: 207.2.

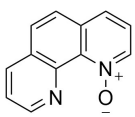


5-methyl-2,2'-bipyridine-1-oxide, **5b**: A solution of 5-methyl-2,2'-bipyridine (1.70 g, 10 mmol, 1 eq) in TFA (7.7 ml) was cooled to 0 °C and H_2O_2 (35 % aq., 1.3 ml; d = 1.11 g/ml, 15 mmol, 1.5 eq) was added dropwise. After the addition, the reaction mixture was allowed to stir overnight at RT. Excess TFA was removed by vacuum distillation and the remaining residue was poured onto ice. The mixture was neutralized with 6 M NaOH (aq.) and extracted with $CHCl_3$ (6 x 50 ml). The combined organic phase was dried with $MgSO_4$, filtered and concentrated *in vacuo*. Isolation by column chromatography (silica, acetone/hexane = 2/5 with 0.5 % of

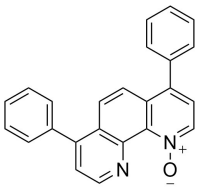
triethylamine) yielded the product as an off-white crystalline solid (0.64 g, 3.4 mmol, 34%). TLC (Silica; acetone/hexane = 2/5: product R_f = 0.5; UV lamp). Analysis was consistent with previous reports.[31] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (dt, *J* = 8.1, 1.1 Hz, 1H), 8.66 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 8.13 (dt, *J* = 1.7, 0.8 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.80 – 7.73 (m, 1H), 7.30 – 7.26 (m, 1H), 7.14 (ddd, *J* = 8.3, 1.8, 0.9 Hz, 1H), 2.30 (t, *J* = 0.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.80, 149.32, 144.67, 140.40, 136.26, 136.08, 127.30, 127.22, 125.41, 124.04, 18.12. ESI-MS: exact m/z calculated for $[C_{11}H_{10}N_2O+H]^+$: 187.1, found: 186.9.



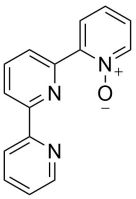
5'-methyl-2,2'-bipyridine-1-oxide, **6b**: A solution of 5-methyl-2,2'-bipyridine (1.70 g, 10 mmol, 1 eq) in TFA (7.7 ml) was cooled to 0 °C and H_2O_2 (35 % aq., 1.3 ml, d = 1.11 g/ml, 15 mmol, 1.5 eq) was added dropwise. After the addition, the reaction mixture was allowed to stir overnight at RT. Excess TFA was removed by vacuum distillation and the remaining residue was poured onto ice. The mixture was neutralized with 6 M NaOH (aq.) and extracted with $CHCl_3$ (6 x 50 ml). The combined organic phase was dried with $MgSO_4$, filtered and concentrated *in vacuo*. Isolation by column chromatography (silica, acetone/hexane = 2/5 with 0.5 % of triethylamine) yielded the product as an off-white crystalline solid (0.55 g, 3.0 mmol, 30%). TLC (Silica; acetone/hexane = 2/5: product R_f = 0.45; UV lamp). Analysis was consistent with previous reports.[31] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 8.2, 0.8 Hz, 1H), 8.51 (dt, *J* = 2.3, 0.8 Hz, 1H), 8.26 (dd, *J* = 6.5, 1.4 Hz, 1H), 8.13 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.60 (ddd, *J* = 8.2, 2.3, 0.8 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.21 (ddd, *J* = 7.5, 6.5, 2.2 Hz, 1H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.93, 147.50, 146.99, 140.71, 136.71, 134.31, 127.66, 125.76, 124.97, 18.51. ESI-MS: exact m/z calculated for $[C_{11}H_{10}N_2O+H]^+$: 187.1, found: 187.0.



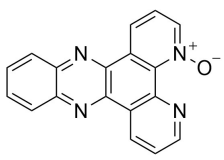
1,10-phenanthroline-1-oxide, **7b**: A solution of 1,10-phenanthroline (510 mg, 2.8 mmol, 1 eq) in TFA (2.1 ml) was cooled to 0 °C and H_2O_2 (35% aq., 0.4 ml, d = 1.11 g/ml, 4.2 mmol, 1.5 eq) was added dropwise. After the addition, the reaction mixture was allowed to stir overnight at RT. The resulting mixture was poured onto ice and neutralized with 6 M NaOH (aq.) to pH 9. The mixture extracted with $CHCl_3$ (4 x 50 ml) and the combined organic phase was dried with $MgSO_4$, filtered. Evaporation of the solvent *in vacuo* yielded the product as an off-white crystalline solid (427 mg, 2.2 mmol, 77%). Analysis was consistent with previous reports.[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (dd, *J* = 4.3, 1.9 Hz, 1H), 8.70 (dd, *J* = 6.3, 1.2 Hz, 1H), 8.19 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.69 (dd, *J* = 8.6, 1.7 Hz, 2H), 7.62 (dd, *J* = 8.1, 4.4 Hz, 1H), 7.41 (dd, *J* = 8.1, 6.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.05, 142.69, 140.83, 138.41, 135.91, 133.34, 129.10, 128.95, 126.55, 124.53, 123.20, 122.89. ESI-MS: exact m/z calculated for $[C_{12}H_8N_2O+H]^+$: 197.1, found: 197.1.



4,7-diphenyl-1,10-phenanthroline-1-oxide, **8b**: A solution of 4,7-diphenyl-1,10-phenanthroline (501 mg, 1.5 mmol, 1 eq) in TFA (1.2 ml) was cooled to 0 °C and H_2O_2 (35% aq., 0.2 ml, d = 1.11 g/ml, 2.2 mmol, 1.5 eq) was added dropwise. After the addition, the reaction mixture was allowed to stir overnight at RT. The resulting mixture was poured onto ice and neutralized with 6 M NaOH (aq.) to pH 9. The mixture extracted with $CHCl_3$ (4 x 50 ml) and the combined organic phase was dried with $MgSO_4$ and filtered. Evaporation of the solvent *in vacuo* yielded the product as a yellow crystalline solid (519 mg, 1.5 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, *J* = 4.5 Hz, 1H), 8.79 (d, *J* = 6.5 Hz, 1H), 7.84 (d, *J* = 9.5 Hz, 1H), 7.74 (d, *J* = 9.5 Hz, 1H), 7.59 (d, *J* = 4.5 Hz, 1H), 7.55 – 7.44 (m, 10H), 7.42 (d, *J* = 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.12, 148.17, 143.36, 140.07, 138.71, 137.88, 137.54, 136.96, 130.82, 129.88, 129.84, 128.93, 128.82, 128.76, 128.68, 126.96, 126.53, 124.36, 123.93, 123.72. ESI-MS: exact m/z calculated for $[C_{24}H_{16}N_2O+ H]^+$: 349.1, found: 349.6

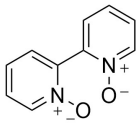


2,2':6',2''-terpyridine-1-oxide, **9b**: To a solution of 2,2':6',2''-terpyridine (517 mg, 2.1 mmol, 1 eq) in DCM (21 ml) was slowly added *m*-CPBA (526 mg (77%), 2.4 mmol, 1.1 eq). After the addition, the reaction mixture was allowed to stir overnight at RT. The resulting mixture was quenched with Na_2CO_3 (20 ml, sat. aq.) and extracted with DCM (3 x 50 mL). The combined organic phase was dried with $MgSO_4$, filtered and concentrated *in vacuo.* Isolation by column chromatography (silica, acetone/hexane = 1/1 with 0.5 % of triethylamine) yielded the product as a white solid (297 mg, 1.2 mmol, 54%). Analysis was consistent with previous reports.[37] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.70 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.51 – 8.46 (m, 2H), 8.38 (ddd, *J* = 8.0, 2.2, 0.6 Hz, 1H), 8.34 (ddd, *J* = 6.5, 1.3, 0.6 Hz, 1H), 7.97 (t, *J* = 7.9 Hz, 1H), 7.83 (ddd, *J* = 8.0, 7.4, 1.8 Hz, 1H), 7.40 (ddd, *J* = 8.0, 7.4, 1.3 Hz, 1H), 7.35 – 7.27 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.98, 155.80, 149.35, 148.88, 147.61, 140.93, 137.49, 137.02, 128.15, 125.76, 125.58, 125.30, 124.03, 121.76, 121.20. ESI-MS: exact m/z calculated for $[C_{15}H_{12}N_3O+ H]^+$: 250.1, found: 250.1.

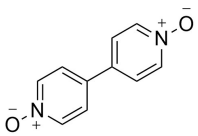


dipyrido[3,2-a:2',3'-c]phenazine-4-oxide, **10b**: A solution of dipyrido[3,2-a:2',3'-c]phenazine (300 mg, 1.1 mmol, 1 eq) in TFA (0.8 ml) was cooled to 0 °C and H_2O_2 (35% aq., 0.14 ml, d = 1.11 g/ml, 1.6 mmol, 1.5 eq) was added dropwise. After the addition, the reaction mixture was allowed to stir overnight at RT. The resulting mixture was poured onto ice and neutralized with 6 M NaOH (aq.) to pH 9. The mixture extracted with $CHCl_3$ (6 x 50 ml) and the combined organic phase was dried with $MgSO_4$ and filtered. Evaporation of the solvent *in vacuo* yielded the product as a red powder (154 mg, 0.5 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (dd, *J* = 8.1, 1.9 Hz, 1H), 9.33 (dd, *J* = 4.4, 1.9 Hz, 1H), 9.24 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.79 (dd, *J* = 6.4, 1.3 Hz, 1H), 8.35 – 8.28 (m, 2H), 7.98 – 7.89

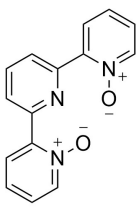
(m, 2H), 7.79 (dd, *J* = 8.1, 4.4 Hz, 1H), 7.60 (dd, *J* = 8.2, 6.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 151.51, 144.81, 143.91, 143.22, 142.79, 141.04, 139.73, 133.57, 132.50, 131.57, 131.24, 129.80, 129.68, 127.38, 126.00, 124.30, 124.00, 121.87. ESI-MS: exact m/z calculated for $[C_{18}H_{10}N_4O+ H]^+$: 299.1, found: 299.2.



2,2'-bipyridine-1,1'-dioxide, **2c**: 2,2'-bipyridine (5.10 g, 32.3 mmol, 1 eq) was firstly dissolved in EtOAc (160 ml) at RT and then solid *m*-CPBA (17.35 g (77%), 77.0 mmol, 2.4 eq) was slowly added inside. The obtained mixture was stirred for 24 h at RT until reaction completion. The resulting suspension was stirred at 80 °C for 30 min followed by hot filtration of white precipitate. The solid on a filter was washed with EtOAc (30 ml) and pentane (30 ml), dried under air flow for 10 min and then transferred to round-bottomed flask. Drying *in vacuo* afforded target compound as white powder (5.60 g, 29.8 mmol, 92%). Analysis was consistent with previous reports.[11,12] ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 – 8.32 (m, 2H), 7.73 – 7.67 (m, 2H), 7.40 – 7.31 (m, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 141.98, 140.42, 130.07, 128.92, 127.52. ^1H NMR (500 MHz, D_2O) δ 8.51 – 8.45 (m, 2H), 7.85 (ddd, *J* = 8.4, 7.4, 1.2 Hz, 2H), 7.76 (dtd, *J* = 6.9, 3.6, 2.1 Hz, 4H). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O) δ 141.86, 139.79, 131.56, 128.94, 128.53. ESI-MS: exact m/z calculated for $[C_{10}H_8N_2O_2 + H]^+$: 189.1, found: 189.1.

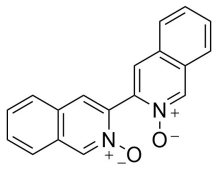


4,4'-bipyridine-1,1'-dioxide, **12c**: To a solution of 4,4'-bipyridine (1.00 g, 6.4 mmol, 1 eq) in glacial acetic acid (8 ml) was dropwise added H_2O_2 (0.9 ml (35%), d = 1.13 g/ml, 19.2 mmol, 3 eq) and the mixture was heated to 80 °C. After 7.5 h, another 3 equivalents of hydrogen peroxide were added and the reaction was refluxed for 18 h. Once completed, the mixture was concentrated *in vacuo*. Crystallization from H_2O/acetone = 1/20 yielded the product as a white crystalline solid (1.07 g, 5.7 mmol, 89%). Analysis was consistent with previous reports.[13] ^1H NMR (300 MHz, D_2O) δ 8.40 – 8.35 (m, 4H), 7.94 – 7.89 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, D_2O) δ 139.44, 138.04, 124.76. ESI-MS: exact m/z calculated for $[C_{10}H_8N_2O_2 + H]^+$: 189.1, found: 189.2.

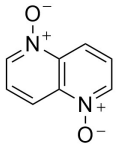


2,2':6',2''-terpyridine-1,1''-dioxide, **9c**: 2,2':6',2''-terpyridine (5.00 g, 20.8 mmol, 1 eq) and *m*-CPBA (11.62 g (70%), 47.1 mmol, 2.3 eq) were dissolved in DCM (214 ml) and stirred at RT for 24 h. The resulting suspension was quenched with saturated aqueous Na_2CO_3 (40 ml) and concentrated *in vacuo*. The obtained residue was then crushed to powder and refluxed for 15 min in $CHCl_3$ (250 ml) with a few spoons of anhydrous Na_2SO_4. The precipitate was then filtered, washed with hot $CHCl_3$ (2 x 250 ml) and the filtrate was concentrated *in vacuo* to afford target product as white powder (5.50 g, 20.7 mmol, 100%). Analysis was consistent with previous reports.[14] TLC ($CHCl_3$/MeOH = 8/1: product R_f = 0.51; UV lamp). ^1H NMR (500 MHz, $CDCl_3$) δ 8.94 (d, *J* = 8.0 Hz, 2H), 8.33 (ddd, *J* = 6.5, 1.3, 0.6 Hz,

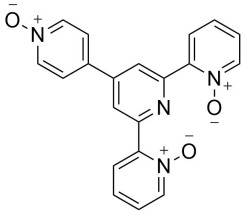
2H), 8.19 (ddd, *J* = 8.0, 2.2, 0.6 Hz, 2H), 7.97 (t, *J* = 8.0 Hz, 1H), 7.37 (ddd, *J* = 8.0, 7.5, 1.3 Hz, 2H), 7.29 (ddd, *J* = 7.5, 6.5, 2.2 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 149.51, 147.31, 140.88, 136.78, 128.09, 126.20, 125.76, 125.50. ESI-MS: exact m/z calculated for $[C_{15}H_{11}N_3O_2 + H]^+$: 266.1, found: 266.1.



[3,3'-biisoquinoline] 2,2'-dioxide, **13c**: 3,3'-biisoquinoline (0.50 g, 1.95 mmol, 1 eq) and *m*-CPBA (1.20 g (70%), 4.88 mmol, 2.5 eq) were dissolved in ACN (20 mL) and stirred at RT for 24 h. Upon reaction completion the mixture was quenched with saturated aqueous Na_2CO_3 (10 mL) and concentrated *in vacuo*. The obtained residue was then crushed to powder and refluxed for 15 min in ACN (150 mL) with a few spoons of anhydrous Na_2SO_4. The precipitate was then filtered, washed with hot ACN (2 x 50 mL) and the filtrate was concentrated in vacuo to afford target product as light-yellow powder (0.35 g, 1.21 mmol, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 2H), 8.29 (s, 2H), 7.98 (ddd, *J* = 10.7, 8.1, 1.2 Hz, 4H), 7.74 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 2H), 7.68 (ddd, *J* = 8.2, 7.0, 1.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 140.83, 135.21, 129.85, 128.64, 127.51, 126.98, 126.58, 124.65. ESI-MS: exact m/z calculated for $[C_{18}H_{12}N_2O_2+H]^+$: 289.1; found: 289.1; exact m/z calculated for $[2\cdot C_{18}H_{12}N_2O_2+Na]^+$: 599.2; found: 599.3.



1,5-naphthyridine-1,5-dioxide, **14c**: 1,5-naphthyridine (2.00 g, 14.6 mmol, 1 eq) and *m*-CPBA (7.58 g (77%), 33.8 mmol, 2.3 eq) were mixed in DCM (146 ml) and stirred at RT for 24 h. The resulting suspension was quenched with saturated aqueous Na_2CO_3 (20 ml) and concentrated *in vacuo*. The obtained residue was then crushed to powder and refluxed for 15 min in $CHCl_3$ (500 ml) with a few spoons of anhydrous Na_2SO_4. The precipitate was then filtered, washed with hot $CHCl_3$ (2 x 500 ml) and the filtrate was concentrated in vacuo to afford target product as light-yellow crystals (1.38 g, 8.3 mmol, 57%). ^{1}H NMR (500 MHz, D_2O) δ 8.87 (d, *J* = 6.2 Hz, 2H), 8.77 – 8.67 (m, 2H), 7.93 (dd, *J* = 9.1, 6.1 Hz, 2H). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (dt, *J* = 6.2, 0.6 Hz, 2H), 8.29 (dt, *J* = 8.8, 0.5 Hz, 2H), 7.69 (dd, *J* = 8.8, 6.0 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 137.45, 124.89, 116.11. ESI-MS: exact m/z calculated for $[C_8H_6N_2O_2$ + MeOH + $H]^+$: 195.1, found: 195.1.



4'-(1-oxidopyridin-4-yl)-[2,2':6',2''-terpyridine] 1,1''-dioxide, **15c**: 4'-(pyridin-4-yl)-2,2':6',2''-terpyridine (0.50 g, 1.61 mmol, 1 eq) and *m*-CPBA (1.39 g (70%), 5.64 mmol, 3.5 eq) were dissolved in ACN (16 mL) and stirred at RT for 24 h. Upon reaction completion the mixture was quenched with saturated aqueous Na_2CO_3 (10 mL) and concentrated *in vacuo*. The obtained residue was then crushed to powder and refluxed for 15 min in $CHCl_3$ (150 mL) with a few spoons of anhydrous Na_2SO_4. The precipitate was then filtered, washed with hot $CHCl_3$ (2 x 50 mL) and the filtrate was

concentrated in vacuo to afford target product as light-yellow powder (0.47 g, 1.31 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 2H), 8.40 – 8.33 (m, 2H), 8.31 – 8.25 (m, 4H), 7.78 – 7.72 (m, 2H), 7.43 (td, *J* = 7.8, 1.3 Hz, 2H), 7.35 (ddd, *J* = 7.5, 6.4, 2.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.47, 146.62, 144.19, 141.00, 139.82, 135.16, 128.15, 126.11, 125.96, 124.45, 123.03. ESI-MS: exact m/z calculated for $[C_{20}H_{14}N_4O_3+H]^+$: 359.1; found: 359.2; exact m/z calculated for $[C_{20}H_{14}N_4O_3+Na]^+$: 381.1; found: 381.1.

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