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2,2'-homocoupled azine *N,N'*-dioxides or azine *N*-oxides: CDC or S_NAr controlled chemoselectivity

Abadh Kishor Jha[a] and Nidhi Jain[a]*

Abstract: An unprecedented $Cu(OAc)_2$ and Li*t*OBu mediated homocoupling of azine *N*-oxides to yield 2,2'-azine *N,N'*-dioxides is reported. This is the first instance where copper has been used to catalyze the homodimerization reaction, especially with *N*-oxides of 2-phenyl pyridine. In the absence of catalytic copper, the reaction follows an alternative pathway, and instead of dioxide yields the 2,2'-azine *N*-monoxides. This protocol works efficiently with a range of *N*-heterocyclic oxides of pyridine, 2-phenyl pyridine, quinoline, and *N*-aryl-1,2,3-triazole. It is scalable, offers high regioselectivity, and gives the products in moderate to high yields. The observed chemoselectivity between copper-assisted and copper-free protocols is routed through an oxidative cross-dehydrogenative coupling (CDC), and nucleophilic aromatic substitution of hydrogen (S_NAr) respectively.

Introduction

Bipyridines, biquinolines, biisoquinolines and bitriazoles constitute an important class of biheterocycles with numerous applications in drug discovery,[1] and functional materials.[2] Not only the biheterocycles, but their *N*-oxides as well as *N,N'*-dioxides are important synthetic intermediates, often used as organocatalysts[3] and ligands[4] in metal-catalyzed reactions (Figure 1).

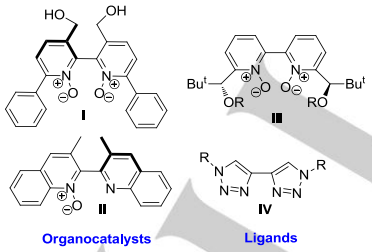
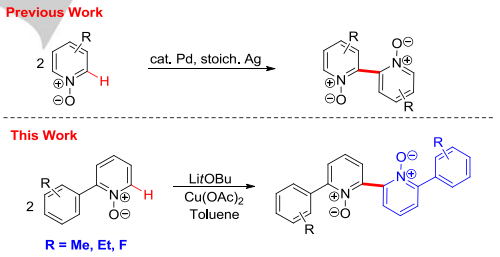


Figure 1. Synthetically useful heterocyclic *N,N'*-dioxides and *N*-oxides.

The general synthetic approach to access these biheterocycles relies on palladium or nickel catalyzed cross-coupling reactions of halogenated *N*-heterocycles with the heteroaryl organometallic reagents, which are activated site selectively by transmetallating groups like SnR_3, ZnX, BR_2, MgX, or SiR_3.[5] Of late, strategies involving direct C-H activation through transition-metal catalyzed oxidative cross-coupling between two hetero(arenes)[6] have lifted the limitation of working with pre-functionalized substrates, and have also been accomplished with heterocyclic *N*-oxides as the starting material.[7] As shown in Scheme 1, Kuang *et al* reported the first oxidative CH/CH direct coupling of azine *N*-oxides using a Pd-Ag system.[8] The strategy allowed an access to homocoupled pyridine *N*-oxides and 1,2,3-triazole *N*-oxides, in addition to the hetero- linked *N,N'*-dioxide products. This was followed by the work of Zhu and Liu who reported a similar Pd-Ag mediated homodimerization of azine *N*-oxides.[9] However, to the best of our knowledge, homocoupling of *N*-oxides with a copper catalyst still does not exist. Cognizant of the importance of these molecules, and driven by our interest in developing copper as a cheap catalyst for C-H functionalizations,[10] we initiated the work on homocoupling reactions.



Scheme 1. Synthesis of symmetrical azine *N, N'*-dioxides.

A literature search on homocoupled 2,2'-azine *N*-oxides revealed that they have been synthesized starting from azine *N*-oxides via a) palladium catalyzed coupling with halogenated azine (Scheme 2a),[11] b) coupling with 2-pyridyllithium prepared from 2-bromopyridine and *tert*-butyl lithium at -78 °C (Scheme 2b),[12] and c) coupling with another molecule of azine *N*-oxide in the presence of an organocatalyst (Scheme 2c).[13] However, each of these reactions suffered from limitations of pre-functionalized substrate, or expensive Pd catalyst, or drastic reaction conditions.

In view of above literature, and in continuation of our on-going interest in chemistry of azine *N*-oxides,[10(a)] we embarked upon a $Cu(OAc)_2$ and Li*t*OBu promoted oxidative homocoupling to synthesize 2,2'-azine *N,N'*-dioxides in moderate to good yields. Interestingly, in absence of catalytic copper, the reaction furnished 2,2'-azine *N*-monoxides selectively. The observed chemo-selectivity under the two sets of conditions has been rationalized based on the CDC and S_NAr pathways.

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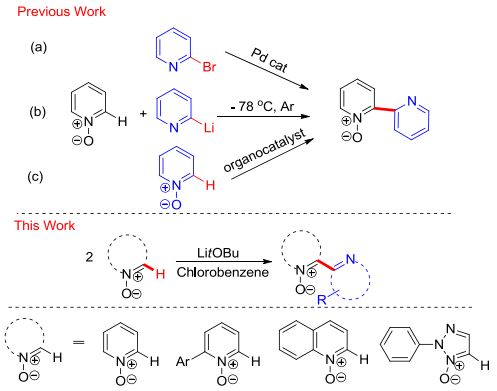
†Electronic Supplementary Information (ESI) available: copies of ^1H NMR, ^{13}C NMR and X-ray crystallographic data for compounds **2b** & **3d**.

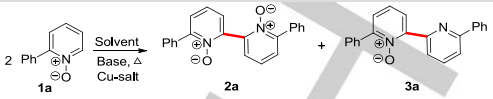


Scheme 2. Synthesis of azine *N*-oxides through different methods.

Results and Discussion

We chose to start the work with 2–phenyl pyridine *N*-oxide (**1a**), since no prior literature on its homocoupling through a dual C-H activation strategy existed. **1a** was heated at 120 °C in presence of Li*t*OBu (3 equiv.) and copper iodide (20 mol%) in chlorobenzene as the solvent. After allowing the reaction to continue for 72 h, we were delighted to see the formation of 6,6'–diphenyl-[2,2'-bipyridine] 1,1'-dioxide (**2a**) in 70% yield (Table 1, Entry 1). The finding was encouraging since the previous report on Pd catalyzed homocoupling was unsuccessful with 2–phenyl pyridine *N*-oxide as the substrate.[8] Replacing chlorobenzene with toluene, and reducing the amount of Li*t*OBu to 2.5 equiv. led to an increase in the yield of **2a** to 83% (Table 1, Entry 2). The yield increased further to 97% when $Cu(OAc)_2$ was used as the catalyst (Table 1, Entry 3). Further optimizations by reducing the amount of $Cu(OAc)_2$ to 10 mol%, or reducing the reaction time to 50 h, or carrying out the reaction in absence of Li*t*OBu resulted in a drastic drop in the product yield (Table 1, Entry 3). Notably, the reaction did not take place under nitrogen atmosphere (Table 1, Entry 4). Hence, the best conditions to synthesize homocoupled 2–phenyl pyridine *N,N'*-dioxide were found to be with $Cu(OAc)_2$ (20 mol%) and Li*t*OBu (2.5 equiv.) in toluene at 120 °C for 72 h. Interestingly, when we examined the reaction in absence of copper salt; a new product, 6,6'–diphenyl-[2,2'-bipyridine] 1-oxide (**3a**) was exclusively formed in 18% yield after 24 h (Table 1, Entry 5). To improve the yield, optimization of reaction with respect to solvent, base, temperature, and time was carried out (Table 1, Entries 6-15). Solvents such as *o*-xylene, *m*-xylene and chlorobenzene were screened, and chlorobenzene was found to give the highest yield of **3a** (Table 1, Entries 6-8). Replacement of Li*t*OBu with other bases such as K_2CO_3, Cs_2CO_3, K*t*OBu and Na*t*OBu affected the reaction negatively, and no product formation was seen (Table 1, Entries 9-12). Also, reducing the amount of Li*t*OBu to 2.5 and 2.0 equivalents dropped the yield to 40 and 25% respectively, suggesting that base had an important role in the reaction (Table 1, Entry 8). Variation in temperature and time was carried out next. Raising the temperature to 100 and 120 °C increased the yield to 85 and 91% respectively, while increasing it further to 130 °C dropped the yield (Table 1, Entries 13-15). Lowering the reaction time to 15 h decreased the yield to 70% while increasing it to 44 h did not help in improving the yield (Table 1, Entry 14). Thus, the best reaction conditions to synthesize homocoupled 2–phenyl pyridine *N*-oxide were found to be using 3.0 equiv. of Li*t*OBu in chlorobenzene at 120 °C for 24 h.

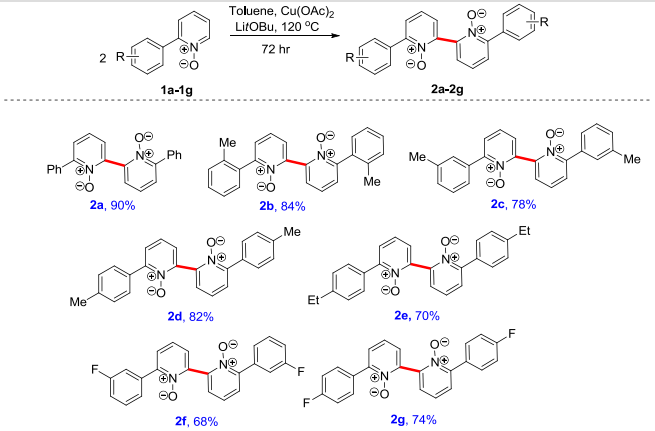
Table 1. Optimization of reaction conditions for homocoupling of 2-phenyl pyridine *N*-oxide.[a]



Entry	Solvent	Base	Temp. (° C)	Catalyst	Yield (%)	
					2a	**3a**
1	PhCl	Li*t*OBu	120	CuI	70	0
2	Toluene	Li*t*OBu	120	CuI	78,83[b]	0
3	Toluene	Li*t*OBu	120	$Cu(OAc)_2$	97,72[c], 10[d],20[e]	0
4	Toluene	Li*t*OBu	120	$Cu(OAc)_2$	0[f]	0
5	Toluene	Li*t*OBu	90	-	0	18
6	*o*-Xylene	Li*t*OBu	90	-	0	21
7	*m*-Xylene	Li*t*OBu	90	-	0	39
8	PhCl	Li*t*OBu	90	-	0	44,40 25[
9	PhCl	K_2CO_3	90	-	0	-
10	PhCl	Cs_2CO_3	90	-	0	-
11	PhCl	K*t*OBu	90	-	0	-
12	PhCl	Na*t*OBu	90	-	0	-
13	PhCl	Li*t*OBu	100	-	0	85
14	PhCl	Li*t*OBu	120	-	0	91,70 82[i],8
15	PhCl	Li*t*OBu	130	-	0	80

[a] Reaction conditions: **1a** (1.0 equiv., 0.06 mmol), Li*t*OBu (3.0 equiv., 14.41 mmol) and catalyst (0.2 equiv.) taken in a solvent and heated for 72 h in a sealed tube; Yields are based on % conversions as determined by HPLC, [b] Li*t*OBu (2.5 equiv.), [c] $Cu(OAc)_2$ (0.1 equiv.), [d] Time 50 h, [e] No base, [f] Reaction done under N_2 atmosphere [g] Li*t*OBu (2.0 equiv.), [h] Time 15 h, [i] Time 44 h; For entry 5 to 15, reaction time was 24 h and reaction was done in absence of catalyst.

Table 2. Homocoupling of 2-phenyl pyridine *N*-oxide derivatives in presence of copper catalyst.[a]



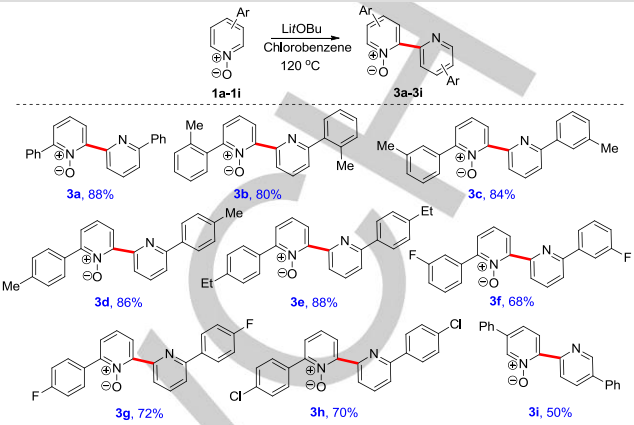
[a] Reaction conditions: Isolated yield, **1a-1g** (0.23 mmol, 1.0 equiv.), Li*t*OBu (0.69 mmol, 3.0 equiv.) taken in toluene solvent and heated at 120 °C in a sealed tube for 72 h.

With the optimized reaction condition in hand, the scope of copper catalyzed homocoupling for various derivatives of 2–phenyl pyridine *N*-oxide was explored, and the results are summarized in Table 2. Reaction with *ortho*-, *meta*-, and *para*-methyl substituted 2-phenylpyridine *N*-oxides gave the corresponding *N,N'*-dioxides (**2b-2d**) in 78-84% yields. With *para*-ethyl derivative, however, slightly lower yield of the corresponding product **2e** was obtained. Phenyl ring substituted with electron withdrawing fluoro- group gave the corresponding products **2f** and **2g** in 68 and 74% yields respectively. As a general observation, yield with *meta*-substituted derivatives (**2c** and **2f**) was lower compared to the *ortho*- and *para*-counterparts (**2b**, **2d**, **2g**). It is noteworthy to reiterate that there are no prior reports on synthesizing these molecules directly through dual CH activation.

During the reaction optimization studies (Table 1), we found that in absence of catalytic amount of copper acetate, the reaction furnished homocoupled 2-phenyl pyridine *N*-oxide (**3a**) as the only product instead of the dioxide **2a** which was formed under metal-catalyzed conditions. To confirm the generality of this observation, the reaction was explored with various derivatives of 2-phenyl pyridine *N*-oxide. As shown in Table 3, the desired products (**3a-3i**) were obtained in moderate to good yields. It was found that 2-phenylpyridine *N*-oxide substituted with electron donating methyl/ethyl group on phenyl ring gave higher yield of products (**3b-3e**) compared to those bearing electron withdrawing fluoro/chloro-substituents at similar positions (**3f-3h**). Notably, changing the position of phenyl substituent on pyridine *N*-oxide from 2- to 3-, dropped the yield of the corresponding product 3-phenyl pyridine *N*-oxide (**3i**) significantly to 50%.

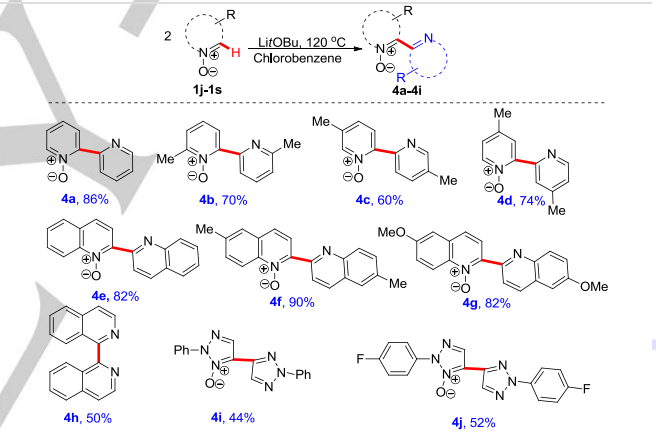
The scope of metal-free homocoupling was extended to other *N*-heterocyclic oxides (Table 4). Pyridine *N*-oxide (**1j**), and methyl substituted pyridine *N*-oxides were tried, and gave the

Table 3. Homocoupling of 2-phenyl pyridine *N*-oxide derivatives in absence of copper catalyst.[a]



[a] Reaction conditions: Isolated yield, **1a-1i** (0.53 mmol, 1.0 equiv.), Li*t*OBu (1.59 mmol, 3.0 equiv.) taken in chlorobenzene solvent and heated at 120 °C in a sealed tube for 24 h.

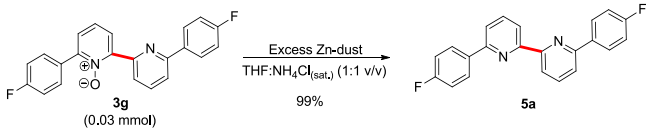
Table 4. Scope of other *N*-heterocyclic oxides in absence of copper catalyst.[a]



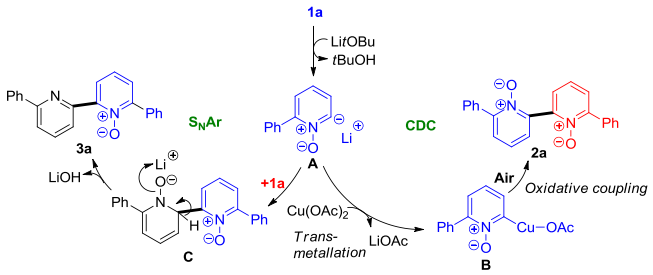
[a] Reaction conditions: Isolated yield, **1j-1s** (0.23 mmol, 1.0 equiv.), Li*t*OBu (0.69 mmol, 3.0 equiv.) taken in chlorobenzene solvent and heated at 120 °C in a sealed tube for 24 h.

corresponding 2,2'-homocoupled *N*-oxide products (**4a-4d**) in 60-86% yields. The lower yield with *meta*-substituted methyl derivative (**4c**, 60%) was in accordance to the earlier observation with *meta*-substituted phenyl pyridine *N*-oxide (**3i**, Table 2). The reaction was found to be equally facile with quinoline and substituted quinoline *N*-oxides, and gave the products (**4e-4g**) in 82-90% yields. Surprisingly, reaction with isoquinoline *N*-oxide resulted in complete deoxygenation of the product, and 1,1'-biisoquinoline (**4h**) was obtained in 50% yield. Notably, even *N*-aryl-1,2,3-triazole *N*-oxides sustained the reaction conditions, and the corresponding 5,5'-coupled triazole *N*-oxides (**4i, 4j**) were obtained albeit in lower yields. To establish synthetic utility of the developed protocol, the reaction was tested on a gram scale. We were pleased to find that reaction with 10.5 mmol of **1j** under the standard reaction conditions afforded [2.2'-bipyridine] 1-oxide (**4a**) in 86% yield (1.56 g).

Further, the synthesized biheteroaryl *N*-oxides could be transformed to the corresponding biheteroaryls by carrying out reduction with Zn-dust. As shown in Scheme 3, treatment of 6,6'-bis(4-fluorophenyl)-[2,2'-bipyridine] 1-oxide (**3g)** with an excess of Zn-dust in THF:$NH_4Cl_{(sat.)}$ for 2 h yielded the deoxygenated product, 6,6'-bis(4-fluorophenyl)-[2,2'-bipyridine] (**5a**) in quantitative yield.



Scheme 3. Deprotection of 6,6'-bis(4-fluorophenyl)-[2,2'-bipyridine] 1-oxide.



Scheme 4. Plausible mechanism(s) for homocoupling of heterocyclic *N*-oxides.

Based on our observations and previous literature,[14] a plausible mechanism for homocoupling of *N*-heterocyclic oxides with and without copper salt is given in Scheme 4. We noticed that the copper acetate catalyzed coupling did not proceed under nitrogen atmosphere (Table 1, Entry 4), while it had no influence when the reaction was carried out under metal-free conditions (Table 1, Entry 14). This indicated that air was necessary only under copper catalyzed conditions, and that the reaction probably followed an oxidative cross-dehydrogenative coupling (CDC) pathway. In light of this, we propose that the reaction is initiated by deprotonation of the C2-H by Lit*O*Bu to generate the lithium salt of azine *N*-oxide (**A**). This is followed by trans-metallation with $Cu(OAc)_2$ to give an intermediate **B**, which undergoes oxidative coupling in presence of air to yield the homocoupled 2,2'-azine *N,N'*-dioxide. In absence of copper acetate, the reaction follows an alternate nucleophilic aromatic substitution pathway (S_NAr), where intermediate **A** attacks another molecule of azine *N*-oxide to yield an intermediate **C** which undergoes loss of LiOH to produce the homocoupled 2,2'-azine *N*-oxide.

Conclusions

In conclusion, we demonstrate for the first time a $Cu(OAc)_2$ - Lit*O*Bu mediated oxidative CDC of 2-phenyl pyridine *N*-oxides to yield the 2,2'-homocoupled *N,N'*-dioxides. In contrast, under copper-free conditions, the homocoupling is routed through an S_NAr pathway, and yields azine *N*-oxides instead of the *N,N'*-dioxides. The coupled products are obtained in moderate to good yields with high regio- and chemo-selectivity. The reactions are highly efficient, and work with a variety of heterocyclic *N*-oxides. The methodology is scalable, and provides a practical access to symmetrical biheterocyclic frameworks. The observed chemo-selectivity in the reaction is speculated to arise out of the two mechanistic pathways that might be invoked under copper-catalyzed and copper-free conditions.

Experimental Section

All the chemicals were purchased from commercial sources and used as received. The products were purified by flash column chromatography on silica gel using 230-400 mesh. ^1H and ^{13}C NMR spectra were measured on a Bruker DPX-300 MHz spectrometer (^1H 300 MHz, ^{13}C 75MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given in δ (ppm) relative to TMS, the coupling constants (*J)* are given in Hz**.** High-resolution mass spectra were recorded with a Q-TOF instrument, using electrospray ionization (ESI) as the ionization method.

General experimental procedure for preparation of *N*-Oxides:

A solution of nitrogenous compound (7.8 mmol) in dichloromethane was taken in 100 ml round bottom flask. To this solution, 70% mCPBA (1.0 equiv.) was added portion wise at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The progress of reaction was monitored through TLC. The reaction mixture was diluted with dichloromethane, 4.0 equiv. of K_2CO_3 was added, and the contents were stirred for another 10 minutes. The desired product was purified on flash column chromatography using methanol-dichloromethane solvent.

General experimental procedure for homocoupling of 2-phenyl pyridine *N*-oxide derivatives in presence of copper catalyst (2a-2g):

2-phenyl pyridine *N*-oxide derivatives (0.23 mmol, 1.0 equiv.), Lit*O*Bu (0.69 mmol, 3.0 equiv.) and $Cu(OAc)_2$ (0.2 equiv.) were taken in sealed tube in 2 ml toluene solvent. The contents were heated at 120 °C for 72 hours. The solvent was evaporated on rotary evaporator. The desired product was purified through flash column chromatography using dichloromethane and methanol solvent.

General experimental procedure for homocoupling of azine/azole *N*-oxide derivatives in absence of copper catalyst (3a-3i & 4a-4j):

Azine/azole *N*-oxides (0.53 mmol, 1.0 equiv.) and Lit*O*Bu (1.59 mmol, 3.0 equiv.) were taken in sealed tube in 2 ml chlorobenzene solvent. The contents were heated at 120 ˚C for 24 hours. The solvent was evaporated on rotary evaporator. The desired product was purified through flash column chromatography using ethyl acetate-hexane solvent.

Experimental procedure for deoxygenation of 2-(4-fluorophenyl)pyridine 1-oxide (3g):

Compound **1g** (0.03 mmol) was dissolved in THF: $NH_4Cl_{(aq.)}$ (0.03 M) (1:1 v/v). An excess of zinc dust was added to this solution, and it was stirred at 70 °C for 2 hours. The reaction was filtered over celite, and the solvent was evaporated on rotary evaporator at low pressure to get the pure desired product (**5a**).

6,6'–diphenyl-[2,2'-bipyridine] 1, 1'-dioxide (2a): Light yellowish amorphous solid, melting point = 154-156 ˚C, 179 mg, 90%; IR: (υ_{max}/cm^{-1}) = 1249 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 5.1 Hz, 4H), 7.60 (d, *J* = 6.9 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.37-7.44 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 143.7, 139.3, 132.5, 129.6, 128.1, 127.7, 127.0, 124.8, 114.1; HRMS ESI: $[M+H]^+$, Calculated for $C_{22}H_{17}N_2O_2$ 341.1285; found 341.1283.

6,6'-di-o-tolyl-[2,2'-bipyridine] 1, 1'-dioxide (2b): Light yellowish amorphous solid, melting point = 184-185 ˚C, 167 mg, 84%; IR: (υ_{max}/cm^{-1}) = 1245 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 4.5 Hz, 2H), 7.33 (bs, 5H), 7.27 (s, 7H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 143.4, 138.4, 133.1, 130.0, 129.4, 129.3, 128.0, 127.2, 125.7, 123.7, 19.7; DEPT 135 NMR (75 MHz, $CDCl_3$) δ 130.0, 129.4, 129.3, 128.0, 127.2, 125.7, 123.7, 19.7; HRMS ESI: $[M+H]^+$, Calculated for $C_{24}H_{21}N_2O_2$ 369.1598; found 369.1610.

6,6'-di-m-tolyl-[2,2'-bipyridine] 1, 1'-dioxide (2c): Light brown amorphous solid, melting point = 160-164 ˚C, 155 mg, 78%; IR: (υ_{max}/cm^{-1}) = 1247 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.75 (s, 2H), 7.62 (t, *J* = 10.2 Hz, 4H), 7.55 (d, *J* = 5.7 Hz, 2H), 7.37 (t, *J* = 6.6 Hz, 4H), 7.29 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 143.6, 137.7, 132.4, 130.3, 130.1, 128.0, 127.5, 126.9, 126.6, 124.4, 21.4; HRMS ESI: $[M+H]^+$, Calculated for $C_{24}H_{21}N_2O_2$ 369.1598; found 369.1591.

6,6'-di-*p*-tolyl-[2,2'-bipyridine] 1, 1'-dioxide (2d): Light brown amorphous solid, melting point = 209-210 ˚C, 163 mg, 82%; IR: (υ_{max}/cm^{-1}) = 1244 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 5.1 Hz, 4H), 7.51-7.56(m, 4H), 7.26 (bs, 6H), 2.39 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 143.8, 139.7, 129.6, 129.5, 128.7, 127.3, 126.6, 124.6, 21.4; HRMS ESI: $[M+Na]^+$, Calculated for $C_{24}H_{20}N_2NaO_2$ 391.1417; found 391.1414.

6,6'-bis(4-ethylphenyl)-[2,2'-bipyridine] 1, 1'-dioxide (2e): Light brown viscous liquid, 139 mg, 70%; IR: (υ_{max}/cm^{-1}) = 1232 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J'* = 2.1 Hz, *J"* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 4H), 7.40 (dd, *J'* = 2.1 Hz, *J"* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 4H), 6.95 (t, *J* = 7.8 Hz, 2H), 2.70 (q, *J* = 7.5 Hz, 4H), 1.26 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 146.2, 135.7, 130.4, 129.3, 127.6, 126.8, 125.2, 113.1, 28.7, 15.3, DEPT 135 NMR (75 MHz, $CDCl_3$) δ 135.7, 129.3, 127.6, 126.8, 125.2, 28.8, 15.3; HRMS ESI: $[M+H]^+$, Calculated for $C_{26}H_{25}N_2O_2$ 397.1911; found 397.1908.

6,6'-bis(3-fluorophenyl)-[2,2'-bipyridine] 1, 1'-dioxide (2f): Colorless viscous liquid, 135 mg, 68%; IR: (υ_{max}/cm^{-1}) = 1248 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 10.2 Hz, 2H), 7.54-7.60 (m, 6H), 7.39-7.49 (m, 4H), 7.11-7.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3 (d, $^1J_{CF}$ = 244.2 Hz), 148.5, 143.8, 134.2, 129.6 (d, $^3J_{CF}$ = 8.2 Hz), 127.6, 127.3, 125.3, 124.5, 116.8 (d, $^2J_{CF}$ = 23.7 Hz), 116.7, 116.5; HRMS ESI: $[M+Na]^+$, Calculated for $C_{22}H_{14}F_2N_2NaO_2$ 399.0916; found 399.0946.

6,6'-bis(4-fluorophenyl)-[2,2'-bipyridine] 1,1'-dioxide (2g): Colorless viscous liquid, 147 mg, 74%; IR: (υ_{max}/cm^{-1}) = 1249 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.86-7.90 (m, 4H), 7.54 (t, *J* = 8.1 Hz, 4H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.14 (t, *J* = 8.7 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (d, $^1J_{CF}$ = 248.7 Hz), 148.82, 143.9, 131.7 (d, $^3J_{CF}$ = 8.4 Hz), 128.4, 127.4, 126.8, 124.6, 115.1 (d, $^2J_{CF}$ = 21.6 Hz); HRMS ESI: $[M+Na]^+$, Calculated for $C_{22}H_{14}F_2N_2NaO_2$ 399.0916; found 399.0912.

6,6'–diphenyl-[2,2'-bipyridine] 1-oxide (3a): Light yellowish amorphous solid, melting point = 129-130 ˚C, 178 mg, 94%; IR: (υ_{max}/cm^{-1}) = 1256 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.82 (d, *J* = 5.4 Hz, 1H), 8.27 (bs, 1H), 8.07 (bs, 2H), 7.78 (bs, 4H), 7.40-7.46 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 150.2, 149.9, 148.2, 139.1, 136.8, 133.4, 129.5, 129.4, 129.1, 128.8, 128.2, 127.1, 126.9, 126.8, 125.2, 124.2, 120.7; HRMS ESI: $[M+H]^+$, Calculated for $C_{22}H_{17}N_2O$ 325.1335; found 325.1323.

6,6'-di-*o*-tolyl-[2,2'-bipyridine] 1-oxide (3b): Brick red crystalline solid, melting point = 147-149 ˚C, 152 mg, 80%; IR: (υ_{max}/cm^{-1}) = 1259 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.91 (d, *J* = 7.8 Hz, 1H), 8.28 (d, *J* = 6.0 Hz, 1H), 7.84 (t, *J* = 7.5 Hz, 1H), 7.46 (bs, 2H), 7.31-7.37 (m, 9H), 2.46 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 151.5, 149.4, 147.9, 140.2, 137.8, 136.4, 135.9, 133.7, 130.9, 130.0, 129.8, 129.3, 128.4, 127.3, 127.0, 126.0, 125.9, 124.7, 124.5, 123.6, 20.6, 19.6; HRMS ESI: $[M+H]^+$, Calculated for $C_{24}H_{21}N_2O$ 353.1648; found 353.1660.

6,6'-di-m-tolyl-[2,2'-bipyridine] 1-oxide (3c): colourless crystalline solid, melting point = 120-121 ˚C, 160 mg, 84%; IR: (υ_{max}/cm^{-1}) = 1257 (R_3N^+-O^-); ^{1}HNMR (300 MHz, CDCl3) δ 8.80 (d, J = 7.5 Hz, 1H), 8.28 (t, J = 6.0 Hz, 1H), 7.82-7.90 (m, 3H), 7.77 (d, J = 7.8 Hz, 1H), 7.64 (s, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.36-7.43 (m, 4H), 7.26 (s, 2H), 2.46 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 150.4, 149.9, 148.2, 139.1, 138.4, 137.8, 136.7, 133.3, 130.1, 130.0, 129.8, 128.6, 128.2, 127.6, 127.1, 126.8, 126.5, 125.2, 124.1, 124.0, 120.8, 21.6, 21.4; HRMS ESI: $[M+H]^+$, Calculated for $C_{24}H_{21}N_2O$ 353.1648; found 353.1649.

6,6'-di-*p*-tolyl-[2,2'-bipyridine] 1-oxide (3d): Colourless amorphous solid, melting point = 172-174 ˚C, 164 mg, 86%; IR: (υ_{max}/cm^{-1}) = 1252 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.79 (d, *J* = 7.5 Hz, 1H), 8.26 (d, *J* = 3.6 Hz, 1H), 7.99 (d, *J* = 6.9 Hz, 2H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.70-7.76 (m, 3H), 7.41 (s, 2H), 7.30 (d, *J* = 7.2 Hz, 4H), 2.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 150.2, 149.9, 148.2, 139.4, 139.1, 136.7, 136.4, 130.4, 129.5, 129.4, 128.9, 126.9, 126.7, 126.6, 125.1, 123.9, 120.4; HRMS ESI: $[M+H]^+$, Calculated for $C_{24}H_{21}N_2O$ 353.1648; found 353.1648.

6,6'-bis(4-ethylphenyl)-[2,2'-bipyridine] 1-oxide (3e): colourless amorphous solid, melting point = 154-155 ˚C, 168 mg, 88%; IR: (υ_{max}/cm^{-1}) = 1238 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.80 (t, *J* = 4.5 Hz, 1H), 8.27 (q, *J* = 3.6 Hz, 1H), 8.00 (t, *J* = 5.4 Hz, 2H), 7.81-7.87 (m, 1H), 7.72-7.75 (m, 3H), 7.40-7.43 (m, 2H), 7.33 (d, *J* = 6.0 Hz, 4H), 2.72 (t, *J* = 2.1 Hz, 4H), 1.26-1.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 150.2, 149.9, 148.2, 145.7, 145.4, 136.7, 136.7, 130.6, 129.5, 128.3, 127.7, 126.9, 126.9, 126.6, 125.1, 123.9, 120.4, 28.8, 28.7, 15.5, 15.5; HRMS ESI: $[M+H]^+$, Calculated for $C_{26}H_{25}N_2O$ 381.1961; found 381.1961.

6,6'-bis(3-fluorophenyl)-[2,2'-bipyridine] 1-oxide (3f): Colourless amorphous solid, melting point = 174-176 ˚C, 130 mg, 68%; IR: (υ_{max}/cm^{-1}) = 1240 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.84 (d, *J* = 7.2 Hz, 1H), 8.31 (bs, 1H), 7.85 (q, *J* = 9.3 Hz, 4H), 7.54-7.62 (m, 2H), 7.47 (d, *J* = 4.2 Hz, 4H), 7.16 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (d, $^1J_{CF}$ = 241.3 Hz), 162.4 (d, $^1J_{CF}$ = 244.5 Hz), 155.3 (d, $^4J_{CF}$ = 2.8 Hz), 149.8, 148.9, 148.1, 141.3, 141.2, 137.0, 135.1, 135.0, 130.2 (d, $^3J_{CF}$ = 8.1 Hz), 129.8 (d, $^3J_{CF}$ = 8.2 Hz), 127.5, 126.9, 125.2 (d, $^4J_{CF}$ = 3.5 Hz), 124.7, 122.3 (d, $^4J_{CF}$ = 2.6 Hz), 120.8, 116.7 (d, $^2J_{CF}$ = 23.6 Hz), 116.3, 116.0 (d, $^2J_{CF}$ = 21.2 Hz), 114.0, 113.7; HRMS ESI: $[M+H]^+$, Calculated for $C_{22}H_{15}F_2N_2O$ 361.1147; found 361.1142.

6,6'-bis(4-fluorophenyl)-[2,2'-bipyridine] 1-oxide (3g): Colourless amorphous solid, melting point = 184-185 ºC, 137 mg, 72%; IR: (υ_{max}/cm^{-1}) = 1256 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.77 (d, *J* = 7.5 Hz, 1H), 8.26 (t, *J* = 4.5 Hz, 1H), 8.06-8.10 (m, 2H), 7.74-7.89 (m, 4H), 7.44 (d, *J* = 4.5 Hz, 2H), 7.18 (t, *J* = 8.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (d, $^1J_{CF}$ = 247.1 Hz), 163.2 (d, $^1J_{CF}$ = 248.1 Hz), 155.8, 149.9, 149.2, 148.2, 136.9, 135.2 (d, $^4J_{CF}$ = 3.4 Hz), 131.6 (d, $^3J_{CF}$ = 8.3 Hz), 129.5 (d, $^4J_{CF}$ = 3.8 Hz), 128.7 (d, $^3J_{CF}$ = 8.2 Hz), 127.1, 126.7,

125.1, 124.0, 120.4, 115.6 (d, $^2J_{CF}$ = 21.4 Hz), 115.3 (d, $^2J_{CF}$ = 21.7 Hz); HRMS ESI: $[M+H]^+$, Calculated for $C_{22}H_{15}F_2N_2O$ 361.1147; found 361.1165.

6,6'-bis(4-chlorophenyl)-[2,2'-bipyridine] 1-oxide (3h): Colourless amorphous solid, melting point = 189-190 ˚C, 134 mg, 70%; IR: (υ_{max}/cm^{-1}) = 1253 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.78 (d, *J* = 5.7 Hz, 1H), 8.26 (bs, 1H), 8.03 (d, *J* = 5.4 Hz, 2H), 7.86 (d, *J* = 5.7 Hz, 1H), 7.76 (bs, 3H), 7.46 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 149.9, 149.1, 148.2, 137.4, 137.0, 135.4, 135.3, 131.6, 130.9, 128.9, 128.5, 128.1, 127.3, 126.7, 125.2, 124.3, 120.5; HRMS ESI: $[M+H]^+$, Calculated for $C_{22}H_{15}Cl_2N_2O$ 393.0556; found 393.0552.

5,5'-diphenyl-[2,2'-bipyridine] 1-oxide (3i): Light yellowish crystalline solid, melting point = 159-162 ˚C, 95 mg, 50%; IR: (υ_{max}/cm^{-1}) = 1260 (R_3N^+-O^-);^{1}HNMR (300 MHz, CDCl3) δ 9.12 (d, *J* = 8.4 Hz, 1H), 8.98 (d, *J* = 1.8 Hz, 1H), 8.61 (d, *J* = 1.5 Hz, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 8.05 (dd, *J'* = 2.4 Hz, *J"* = 8.4 Hz, 1H), 7.59-7.68 (m, 5H), 7.42-7.54 (m, 6H); ^{13}C NMR (75 MHz, CDCl3) δ 148.1, 147.7, 145.4, 139.1, 138.8, 137.3, 136.9, 135.0, 134.5, 129.3, 129.3, 129.1, 128.4, 127.5, 127.1, 126.9, 125.3, 124.5; HRMS ESI: $[M+H]^+$, Calculated for $C_{22}H_{17}N_2O$ 325.1335; found 325.1326.

[2.2'-bipyridine] 1-oxide (4a): Dark brown viscous liquid, 156 mg, 86%; IR: (υ_{max}/cm^{-1}) = 1245 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.99 (d, *J* = 6.0 Hz, 1H), 8.72 (bs, 1H), 8.33 (d, *J* = 6.3 Hz, 1H), 8.18 (d, *J* = 9.9 Hz, 1H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.35-7.40 (m, 2H), 7.29 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 149.3, 147.3, 140.6, 136.2, 127.8, 125.6, 125.4, 125.2, 124.2; HRMS ESI: $[M+H]^+$, Calculated for $C_{10}H_9N_2O$ 173.0709; found 173.0710.

6,6'–dimethyl-[2, 2'-bipyridine] 1-oxide (4b): Dark brown amorphous solid, melting point = 174-175 ˚C, 128 mg, 70%; IR: (υ_{max}/cm^{-1}) = 1252 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.8 Hz, 1H), 7.95-7.98 (m, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.22-7.25 (m, 2H), 7.17 (d, *J* = 7.5 Hz, 1H), 2.60 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 149.7, 149.6, 147.6, 136.1, 125.5, 125.5, 124.7, 123.4, 122.3, 24.5, 18.3; HRMS ESI: $[M+Na]^+$, Calculated for $C_{12}H_{12}N_2NaO$ 223.0842; found 223.0850.

5,5'–dimethyl-[2, 2'-bipyridine] 1-oxide (4c): Dark brown amorphous solid, melting point = 113-114 ˚C, 110 mg, 60%; IR: (υ_{max}/cm^{-1}) = 1268 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.81 (d, *J* = 8.4 Hz, 1H), 8.53 (s, 1H), 8.16 (s, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.60-7.64 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 2.40 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 147.1, 144.8, 140.3, 136.6, 135.6, 133.9, 127.2, 126.9, 124.8, 18.4, 18.0; HRMS ESI: $[M+Na]^+$, Calculated for $C_{12}H_{12}N_2NaO$ 223.0842; found 223.0841.

4,4'–dimethyl-[2, 2'-bipyridine] 1-oxide (4d): Dark brown viscous liquid, 136 mg, 74%; IR: (υ_{max}/cm^{-1}) = 1243 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.57 (d, *J* = 4.8 Hz, 1H), 8.20 (q, *J* = 6.6 Hz, 1H), 7.93 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 4.2 Hz, 1H), 7.05-7.08 (m, 1H), 2.44 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 149.0, 147.4, 146.5, 139.9, 137.3, 128.2, 126.4, 126.0, 125.2, 21.2, 20.3; HRMS ESI: $[M+H]^+$, Calculated for $C_{12}H_{13}N_2O$ 201.1022; found 201.1016.

[2,2'-biquinoline] 1-oxide (4e): Dark brown amorphous solid, melting point = 152-154 ˚C, 154 mg, 82%; IR: (υ_{max}/cm^{-1}) = 1253 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.88-8.96 (m, 2H), 8.29 (d, *J* = 8.7 Hz, 2H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.82 (d, *J* = 9.6 Hz, 2H), 7.72-7.77 (m, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.61 (q, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 148.1, 143.8, 142.3, 135.6, 130.4, 130.3, 129.8, 129.5, 128.9, 128.1, 128.0, 127.5, 127.4, 125.2, 123.7, 122.8, 120.2; HRMS ESI: $[M+H]^+$, Calculated for $C_{18}H_{13}N_2O$ 273.1022; found 273.1020.

6,6'-dimethyl-[2,2'-biquinoline] 1-oxide (4f): Yellowish crystalline solid, melting point = 170-172 ˚C, 170 mg, 90%; IR: (υ_{max}/cm^{-1}) = 1257 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.89 (d, *J* = 8.7 Hz, 1H), 8.75 (d, *J* = 8.7 Hz, 1H), 8.20 (t, *J* = 9.3 Hz, 2H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.62 (s, 2H), 7.58 (d, *J* = 2.7 Hz, 1H), 7.55 (bs, 1H), 2.54 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 146.6, 143.2, 140.6, 139.1, 137.4, 134.9, 132.6, 131.8, 130.3, 129.4, 128.1, 127.0, 126.4, 125.0, 123.6, 122.9, 119.9, 21.7, 21.4; HRMS ESI: $[M+Na]^+$, Calculated for $C_{20}H_{16}N_2NaO$ 323.1155; found 323.1148.

6,6'-dimethoxy-[2,2'-biquinoline] 1-oxide (4g): Yellowish crystalline solid, melting point = 202-204 ˚C, 156 mg, 82%; IR: (υ_{max}/cm^{-1}) = 1263 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.96 (d, *J* = 8.7 Hz, 1H), 8.79 (d, *J* = 9.6 Hz, 1H), 8.28 (d, *J* = 8.7 Hz, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 9 Hz, 1H), 7.37-7.42 (m, 2H), 7.13-7.14 (m, 2H), 3.96 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 158.5, 148.9, 144.2, 142.3, 137.7, 134.2, 131.6, 131.2, 129.2, 124.5, 124.1, 123.2, 122.4, 122.4, 121.9, 106.0, 104.8, 55.7, 55.6; HRMS ESI: $[M+H]^+$, Calculated for $C_{20}H_{17}N_2O_3$ 333.1234; found 333.1247.

1,1'-biisoquinoline (4h): Dark brown liquid, 88 mg, 50%; IR: (υ_{max}/cm^{-1}) = 1262 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.71 (d, *J* = 5.7 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 5.4 Hz, 1H), 7.67-7.76 (m, 2H), 7.44-7.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 141.9, 136.8, 130.4, 127.8, 127.6, 127.1, 126.9, 121.1; DEPT 135 NMR (75 MHz, $CDCl_3$) δ 141.9, 130.3, 127.5, 127.1, 126.9, 121.0; HRMS ESI: $[M+Na]^+$, Calculated for $C_{18}H_{12}N_2Na$ 279.0893; found 279.0901.

2,2'-diphenyl-2H,2'H-[4,4'-bi(1,2,3-triazole)] 3-oxide (4i): Light brown crystalline solid, melting point = 97-100 ˚C, 83 mg, 44%; IR: (υ_{max}/cm^{-1}) = 1224 (R_3N^+-O^-); ^{1}HNMR (300 MHz, CDCl3) δ 7.79 (s, 1H), 7.55-7.57 (m, 4H), 7.46 (d, J = 8.4 Hz, 3H), 7.29-7.35 (m, 3H), 7.02-7.06 (m, 1H), 6.47 (s, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 149.7, 138.9, 136.2, 130.2, 129.5, 129.2, 128.9, 124.4, 122.7, 121.2, 121.1, 117.9; Elemental analysis (Calculated): C, 63.15; H, 3.97; N, 27.62; Found: C, 71.65; H, 8.18; N, 11.29.

2,2'-bis(4-fluorophenyl-2H,2'H-[4,4'-bi(1,2,3-triazole)] 3-oxide (4j): Light brown crystalline solid, melting point = 107-109 ˚C, 99 mg, 52%; IR: (υ_{max}/cm^{-1}) = 1221 (R_3N^+-O^-); ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.51-7.56 (m, 2H), 7.39-7.43 (m, 2H), 7.29 (s, 1H), 7.23 (s, 1H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, $^1J_{CF}$ = 248.8 Hz), 158.7 (d, $^1J_{CF}$ = 240.7 Hz), 150.9, 149.6, 134.9 (d, $^4J_{CF}$ = 2.6 Hz), 132.1 (d, $^4J_{CF}$ = 3.1 Hz), 126.7 (d, $^3J_{CF}$ = 8.8 Hz), 120.0 (d, $^3J_{CF}$ = 7.9 Hz), 117.2 (d, $^2J_{CF}$ = 22.9 Hz), 115.9 (d, $^2J_{CF}$ = 22.6 Hz); Elemental analysis (Calculated): C, 56.47; H, 2.96; N, 24.70; Found: C, 63.64; H, 5.82; N, 13.40.

6,6'-bis(4-fluorophenyl)-2,2'-bipyridine (5a): colourless crystalline solid, melting point = 154-155 ˚C, 9 mg, 99 %; ^{1}HNMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.8 Hz, 1H), 8.16 (q, *J* = 3.3 Hz, 2H), 7.91 (t, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.17-7.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (d, $^1J_{CF}$ = 249.5 Hz), 155.8, 155.3, 137.7, 135.5 (d, $^4J_{CF}$ = 3.1 Hz), 128.7 (d, $^3J_{CF}$ = 8.2 Hz), 119.9, 119.4, 115.6 (d, $^2J_{CF}$ = 21.4 Hz); DEPT 135 NMR (75 MHz, $CDCl_3$) δ 137.7, 128.74 (d, $^3J_{CF}$ = 8.3 Hz), 120.0, 119.4, 115.6 (d, $^2J_{CF}$ = 21.4 Hz); HRMS ESI: $[M+H]^+$, Calculated for $C_{22}H_{15}F_2N_2$ 345.1198; found 345.1198.

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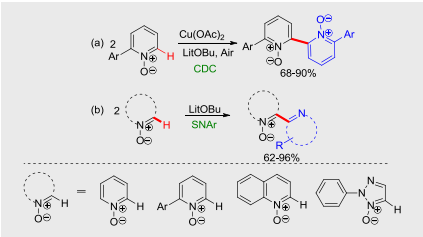
FULL PAPER

An unprecedented copper acetate-catalyzed and copper-free homocoupling of 2-phenyl pyridine *N*-oxides to yield *N,N'*-dioxides or *N*-monoxides in the presence of Li*t*OBu is reported. The chemoselectivity is governed through an oxidative CDC and S_NAr pathways respectively.



CDC vs S_NAr

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2,2'-homocoupled azine *N,N'*-dioxides or azine *N*-oxides: CDC or S_NAr controlled chemoselectivity

CDC vs S_NAr controlled homocoupling of heterocyclic *N*-oxides.