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Reductive Couplings of 2-Halopyridines without External Ligand: Phosphine-Free Nickel-Catalyzed Synthesis of Symmetrical and Unsymmetrical 2,2′-Bipyridines

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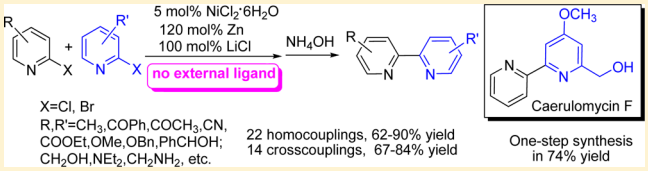
Supporting Information

ABSTRACT: An unexpectedly facile synthetic approach for symmetrical and unsymmetrical 2,2′-bipyridines through the Ni-catalyzed reductive couplings of 2-halopyridines was developed. The couplings were efficiently catalyzed by 5 mol % of $NiCl_2·6H_2O$ without the use of external ligands. A variety of 2,2′-bipyridines including caerulomycin F have been efficiently synthesized.



2,2′-Bipyridines represent a family of most widely used bidentate ligands due to their exceptional coordination chemistry. They have been extensively used as versatile building blocks in the fields of analytical, photo-, supra-, nano-, and macromolecular chemistry.[1] In organic chemistry, 2,2′-bipyridines can function as effective ligands for transition-metal-catalyzed coupling reactions,[2] and meanwhile, their chiral homologues are still a central class of chiral ligands for asymmetric transformations.[1b,3] In addition, these structural units can also be found in natural products such as caerulomycins and collismycins.[4] Hence, there is a great demand for efficient synthetic methods to access various 2,2′-bipyridine derivatives.

Transition-metal-catalyzed coupling reactions have found application in the synthesis of various biaryl compounds including arylpyridines and bipyridines; however, the preparation of 2,2′-bipyridines by these coupling reactions is usually considered to be most difficult relative to 2,3′- or 2,4′-bipyridines.[1d,5] This is due to two main problems associated with 2,2′-bipyridine-forming cross-coupling reactions: (a) the coordination ability of 2,2′-bipyridines can have an inhibition effect on the catalytic cycle[1d,5] and (b) the preparation of the 2-pyridyl organometallics can be problematic. To circumvent the difficulty with the 2-pyridyl organometallic preparation, Ni-catalyzed direct couplings of 2-halopyridines in the presence of reducing agents provide an alternative.[6] To date, the synthesis of 2,2′-bipyridines by this coupling has been mostly limited to those by homocoupling.[1c,6] Moreover, these homocouplings require a large amount of catalyst metal and ligands to offset the adverse effect of 2,2′-bipyridines on the catalytic cycle. For example, the previously reported Ni-mediated homocouplings of 2-halopyridines required stoichiometric $NiCl_2$ or $Ni(OAc)_2$ and 4 equiv of triphenylphosphine.[7] An improved and most commonly used procedure for this coupling still required 30 mol % of $NiBr_2(PPh_3)_2$, and 100 mol % of Et_4NI.[8] The large amounts of triphenylphosphine necessarily used in the above-mentioned methods usually require subsequent separation by chromatography, which extremely limits their industrial application.

We report herein a simple and efficient protocol for the synthesis of symmetrical and unsymmetrical 2,2′-bipyridines through Ni-catalyzed reductive couplings of 2-halopyridines. The most prominent advantage of this protocol is that the couplings are facilely catalyzed by 5 mol % of $NiCl_2·6H_2O$ without the use of external ligands. This finding is in sharp contrast to the general impression that the syntheses of 2,2′-bipyridines by Ni-catalyzed coupling reactions are usually difficult due to their adverse effects on the catalytic cycle. Importantly, in these cases the in situ formed 2,2′-bipyridines did not inhibit the catalytic cycle; instead, their nickel complexes actually catalyzed the couplings.

Our research is inspired by the fact that $Ni(bpy)X_2$ can efficiently catalyze the couplings of 2-halopyridines.[9] We thus surmise that the Ni-catalyzed reductive couplings of 2-halopyridines can also be catalyzed by the in situ formed Ni–bpy complex and can proceed autocatalytically if the excessive bipyridine continuously generated in the reaction can be removed timely. During our previous synthesis of 2,2′-bipyridine derivatives through a Negishi cross-coupling, we found that the product bipyridines could precipitate from the reaction mixture in the form of zinc complexes.[4a,10] This observation leads us to realize the possibility of achieving the above-mentioned coupling by using zinc as a reducing agent, in which the adverse binding of the excessive 2,2′-bipyridine with nickel can be prevented by forming a complex with simultaneously formed ZnX_2 [Scheme 1 (I)].[11] To test this premise, we chose the reductive homocoupling of 2-bromopyridine (**1a**) as the model reaction. After a series of optimization experiments (see the table in the Supporting Information), it was found that without any external ligands 2-bromopyridine could homocouple in a 83% yield under the

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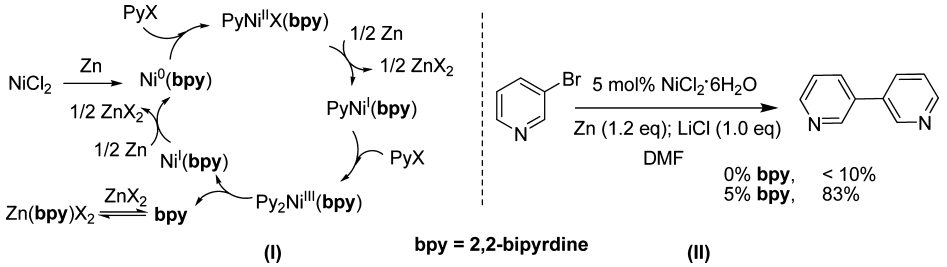
Scheme 1. Effect of 2,2′-Bipyridine in Ni-Catalyzed Reductive Coupling of Halopyridine

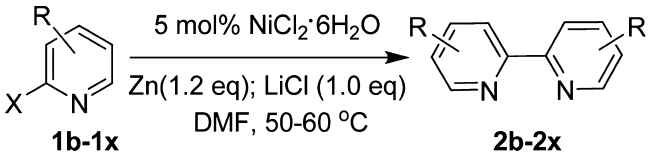


catalysis of 5 mol % of $NiCl_2·6H_2O$ in DMF using Zn−LiCl[12] as a reducing agent. 2-Chloropyridine could also be coupled well under these optimized conditions. It is worth mentioning that the dilution of the reaction mixture with toluene would result in the precipitation of zinc complex of 2,2′-bipyridine, indicating the formation of the zinc complex during the reaction as proposed in Scheme 1 (I). Meanwhile, the product could also be isolated through zinc complex precipitate in a 74% yield.

The above results confirmed our initial hypothesis: this reductive coupling could be catalyzed by the in situ formed Ni−bpy complex and proceeded smoothly in the absence of external ligands.[13] To further confirm that this coupling was catalyzed by the in situ formed Ni−bpy complex, a control experiment using 3-bromopyridine was performed [Scheme 1 (II)]. It clearly indicated that $NiCl_2$ could hardly catalyze the coupling in the absence of 2,2′-bipyridine; instead, the addition of external 2,2′-bipyridine promoted the reaction in 83% yield. Interestingly, it is generally believed that the preparation of 2,2′-bipyridines through the coupling reaction is usually more difficult relative to those of 3,3′-bipyridines,[1a,5] our findings lead to the opposite conclusion: the present reductive coupling of 2-halopyridines can proceed facilely without the external ligands, leading to 2,2′-bipyridine, conversely, the coupling of 3-bromopyridines to 3,3′-bipyrdine cannot take place under the same conditions.

At this point, the Ni-catalyzed reductive coupling of 2-halopyridines that used to require a large amount of catalyst metal and ligands to offset the product-inhibition effect turned out to be a remarkably facile reaction under the present conditions. We suppose that Zn−LiCl played an important role in this coupling by means of (a) the appropriate reducing activity; and (b) the synergic complexing of Zn^{2+} with the continuously producing 2,2′-bipyridine that keeps the concentration of 2,2′-bipyridine around nickel suitable for the efficient catalysis [Scheme 1, (I)]. To the best of our knowledge, the above coupling represents the first example of external-ligand-free Ni-catalyzed reductive coupling of 2- halopyridines with low catalyst loading. It also represents a very simple, practical, and highly efficient protocol to prepare 2,2′-bipyridines. This reaction was thus further explored with the results being summarized in Table 1. It was found that a variety of 2-bromo- and 2-chloropyridines could be readily homocoupled to furnish the corresponding 2,2′-bipyridines in moderate to high yields. Overall, the reaction showed a remarkable tolerance toward different functional groups such as ketone (entries 13 and 14), ester (entries 6 and 7), cyano (entries 8, 9, 19), amide (entry 12), benzyl ether, or alcohol (entries 11, 15−17). In addition, 2-chloroquinoline or quinoxaline could also be coupled (entries 20 and 21). Even more interesting is the fact that 2-bromo-5-chloropyridine was selectively coupled to give 5,5′-dichloro-

Table 1. Ni-Catalyzed Reductive Homocouplings of 2-Halopyridines[a]



1b-1x 2b-2x

entry	1(X, R)	product	yield(%)[b]
1	**1b** (Br, 3-Me)	**2b**	80
2	**1c** (Br, 4-Me)	**2c**	81 (82)[c]
3	**1d** (Br, 5-Me)	**2d**	81 (80)[c]
4	**1d** (Cl, 5-Me)	**2d**	79
5	**1e** (Br, 6-Me)	**2e**	78
6	**1f** (Br, 5-MeOOC)	**2f**	77
7	**1f** (Cl, 5-MeOOC)	**2f**	74
8	**1g** (Br, 5-NC)	**2g**	90
9	**1h** (Br, 6-NC)	**2h**	83
10	**1i** (Br, 5-MeO)	**2i**	82
11	**1j** (Br, 5-BnO)	**2j**	78
12	**1k** (Br, 5-PhNHCO)	**2k**	81
13	**1l** (Br, 5-PhCO)	**2l**	67
14	**1m** (Br, 5-MeCO)	**2m**	62
15	**1n** (Br, 5-PhCHOH)	**2n**	77
16	**1n** (Cl, 5-PhCHOH)	**2n**	75
17	**1o** (Br, 6-PhCHOH)	**2o**	65
18	**1p** (Br, 5-Cl)	**2p**	68
19	**1q** (Cl, 5-$NCCH_2$)	**2q**	78
20	**1r** (2-chloroquinoline)	**2r**	72
21	**1s** (2-chloroquinoxaline)	**2s**	65

[a]$NiCl_2·6H_2O$ (0.5 mmol), Zn (12 mmol), LiCl (10 mmol), and 2-halopyridine (10 mmol), 50−60 °C, 3 h. [b]Isolated yields. [c]The yield in parentheses was obtained on a 100 mmol scale

2,2′-bipyridine (entry 18). This tolerance to chlorine in such couplings has been observed for the first time and allows the products containing a chlorine handle that can readily be derivatized to yield other functional bipyridines. Furthermore, the present procedure proved to be very easy to scale-up. We carried out the couplings of **1c** and **1d** on a 100 mmol scale; the yields were almost identical to those obtained on a small scale (entries 2 and 3).

To further extend the scope of this facile synthetic approach for 2,2′-bipyridines, we went on to explore the reductive cross-couplings of two different 2-halopyridines. Our preliminary experiments indicated that the homocouplings of 2-halopyridine or 2-halopicoline proceeded faster than those of the 2-halopyridines with a functional group such as OMe, NEt_2, NHAc, CH_2OH, CH_2NH_2, etc., and the couplings of the equivalent of the two different 2-halopyridines usually resulted in predominantly homocoupling products. In addition,

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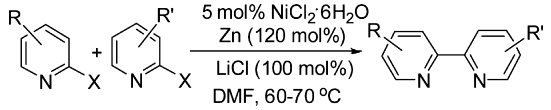
attempts to take advantage of the different reactivity of C−Cl/C−Br (such as the coupling between 2-chloropyridine with 2-bromo-6-methoxypyridine) to increase the selectivity of the cross-couplings gave rise to disappointing results. After a series of trials, we found that 2-halopyridine or 2-halopicoline could be selectively cross-coupled with another functionalized 2-halopyridine in a 2.5:1 ratio. Moreover, the dropwise addition of the solution of two 2-halopyridines in DMF over a period of 3 h helped to increase the yields of the cross-coupling products. Under the above-optimized conditions, the cross-couplings between two different 2-halopyridines were conducted, and the results are illustrated in Table 2. It can be seen that although

Table 2. Ni-Catalyzed Reductive Cross-Couplings of Two Different 2-Halopyridines[a,b]



entry	R	R′	product	yield[c] (%)
1	H	6-CN	**3a**	81
2	H	6-OMe	**3b**	85
3	6-Me	6-OMe	**3c**	75
4	5-Me	6-OMe	**3d**	73
5	5-Me	6-NEt_2	**3e**	84
6	H	6-CH_2OH	**3f**	75
7	H	6-$CH(OCH_2)_2$	**3g**[d]	80
8	6-Me	5-OMe	**3h**	68
9	H	5-NHAc	**3i**	72
10	H	5-OBn	**3j**	82
11[e]	H	5-CH(OH)Ph	**3k**	67
12[e]	H	5-CH_2NHPh	**3l**	68
13[f]	H	5-CH_2CN	**3m**	78
14[f]	H	5-CH_2NH_2	**3n**	73

[a]$NiCl_2·6H_2O$ (0.15 mmol), Zn (12.6 mmol), LiCl (10.5 mmol), 2-halopyridine (picoline) (7.5 mmol), functionalized 2-halopyridine (3 mmol), 60−70 °C, 6 h. [b]X = Br unless otherwise noted. [c]Isolated yields. [d]**3g** was isolated as 2,2′-bipyridine-6-carbaldehyde. [e]The mole ratio of 2-bromopyridine to the other pyridine was 4.0:1. [f]X = Cl.

these cross-couplings resulted in the homocoupling products of 2-halopyridine or 2-halopicoline as the side products, which could be separated by chromatography, the yields of cross-coupling products were moderate to high. A variety of common functional groups such as OMe, OBn, NEt_2, NHAc, CN, $CH(OR)_2$, CH_2OH, CH_2NH_2, and CH_2CN could facilitate the selective cross-couplings, demonstrating the generality of the reaction. Since 2,2′-bipyridines have been extensively used as versatile building blocks in various fields, the efficient preparation of the 2,2′-bipyridines bearing an easily derivatized functional group is highly desired, for they can be easily linked to a target molecule. Utilizing the present cross-coupling, this type of 2,2′-bipyridines such as **3f**, **3g**, **3k**, **3l**, or **3n** could be conveniently prepared in a one-pot manner. The application of this cross-coupling was finally highlighted in the one-step synthesis of natural product, caerulomycin F (Scheme 2).[14] Notably, caerulomycin F can be facilely transformed into caerulomycins E and A in a one-pot manner using the reported procedure.[4a]

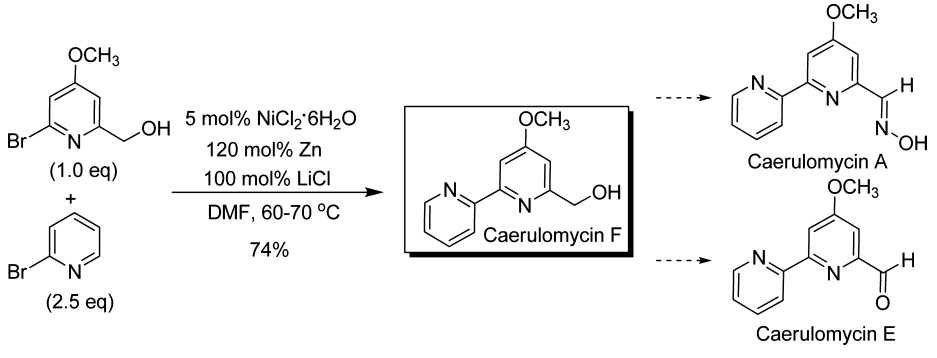
In summary, we have developed an unexpectedly facile synthetic approach for symmetrical and unsymmetrical 2,2′-bipyridines through the Ni-catalyzed reductive couplings of 2-halopyridines, which have previously been considered to be highly difficult due to the product-inhibition effect. Contrary to the common methods that need to use a large amount of catalyst metal and ligands to offset the adverse effect of 2,2′-bipyridine on the catalytic cycle, we took advantage of the in situ formed Ni−bpy complex to catalyze the coupling and performed the reaction with low catalyst loading in the absence of external ligands. Furthermore, the reaction pattern presented herein makes us realize that many of the couplings of 2-halopyridine and *N*-heterocyclic analogues can probably be performed in an external-ligand-free way. The further mechanism study and other external-ligand-free couplings of 2-halopyridines are being investigated in our laboratories.

EXPERIMENTAL SECTION

General Procedure for the Preparation of Symmetrical 2,2′-Bipyridines via Homocouplings of 2-Halopyridines. A 100 mL round-bottom flask was charged with $NiCl_2·6H_2O$ (0.12 g, 0.5 mmol) and DMF (20 mL). The resulting solution was stirred and heated to 40 °C, and then 2-halopyridine (10 mmol), anhydrous LiCl (0.43 g, 10 mmol), and zinc dust (0.78 g, 12 mmol) were added. When the temperature rose to 50 °C, a grain of iodine crystal and two drops of acetic acid were added to the mixture. An immediate rise in temperature and color change to black was caused, indicating the reaction was triggered (note 1). The mixture was stirred at 55−60 °C for 2−3 h until complete conversion of 2-halopyridine (monitored by TLC). To the cooled reaction mixture was added 1 N HCl aqueous solution (15 mL) to consume the remaining zinc dust. The resulting mixture was made alkaline with aqueous ammonia (25%) and taken up with CH_2Cl_2 (note 2). The organic layers were collected, dried over anhydrous Na_2CO_3, and concentrated. The crude material was purified by flash chromatography to give the desired product.

Note 1: The reaction is highly exothermic in the initiation stage and may cause a runaway when carried out on a large scale! In a 100 mmol scale experiment, only 10 mmol of 2-halopyridine was added to the

Scheme 2. One-Step Synthesis of Caerulomycin F



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flask to initiate the reaction. The remaining 2-halopyridine was dripped slowly into the reaction mixture at 50−60 °C. The reaction was then performed and post-treated as described above.

Note 2: The product could also be isolated through the zinc complex precipitate as follows: after the reaction was complete, the reaction mixture was diluted with 70−80 mL toluene, and stirred at room temperature for 2 h. The precipitate was collected by filtration, then dissolved with aqueous ammonia (25%), and extracted with CH_2Cl_2. The desired product was then isolated as described above.

General Procedure for the Preparation of Unsymmetrical 2,2′-Bipyridines via Cross-Couplings between Two Different 2-Halopyridines. A 100 mL round-bottom flask was charged with $NiCl_2{\cdot}6H_2O$ (0.04g, 0.15 mmol) and DMF (20 mL). The resulting solution was stirred and heated to 40 °C, and then 2-halopyridine or 2-halopicoline (2.5 mmol), functionalized 2-halopyridine (1 mmol), anhydrous LiCl (0.44g, 10.5 mmol), and zinc dust (0.82 g, 12.6 mmol) were added. When the temperature rose to 50 °C, a grain of iodine crystal and two drops of acetic acid were added to initiate the reaction. The solution of the remaining 2-halopyridine (2-halopicoline) (5 mmol) and functionalized 2-halopyridine (2 mmol) in 20 mL of DMF was added dropwise into the mixture at 60−70 °C over a period of 3 h. The resulting mixture was then stirred at 60−70 °C for an additional 3 h until complete conversion of 2-halopyridine (monitored by TLC). The product was isolated as described in the procedure for the homocouplings.

2,2′-Bipyridine (2a). The product was isolated as a white solid in 83% yield (647 mg): mp = 67−68.5 °C; R_f = 0.46 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 4.3 Hz, 2H), 8.33 (d, J = 8.0 Hz, 2H), 7.74−7.77 (m, 2H), 7.32−7.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 149.1, 135.8, 123.6, 121.0. Data was consistent with that reported in the literature.[8a]

3,3′-Dimethyl-2,2′-bipyridine (2b). The product was isolated as a colorless oil in 80% yield (736 mg): R_f = 0.32 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 4.6 Hz, 2H), 7.55 (d, J = 7.7 Hz, 2H), 7.20−7.15 (m, 2H), 2.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 146.5, 138.3, 131.5, 122.9, 18.4. Data was consistent with that reported in the literature.[15]

4,4′-Dimethyl-2,2′-bipyridine (2c). The product was isolated as a white solid in 81% yield (745 mg): mp = 169.5−170.5 °C; R_f = 0.40 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 5.0 Hz, 2H), 8.21 (s, 2H), 7.10 (d, J = 4.8 Hz, 2H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 148.9, 148.1, 124.6, 122.0, 21.1. Data was consistent with that reported in the literature.[15,16]

5,5′-Dimethyl-2,2′-bipyridine (2d). The product was isolated as a white solid in 81% yield (745 mg): mp = 119.8−121.2 °C; R_f = 0.52 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 2H), 8.19 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 149.5, 137.3, 132.9, 120.3, 18.3. Data was consistent with that reported in the literature.[17]

6,6′-Dimethyl-2,2′-bipyridine (2e). The product was isolated as a white solid in 78% yield (718 mg): mp = 88.6−90.4 °C; R_f = 0.55 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.8 Hz, 2H), 7.61 (t, J = 7.8 Hz, 2H), 7.08 (d, J = 7.6 Hz, 2H), 2.56 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 155.9, 137.0, 123.0, 118.1, 24.7. Data was consistent with that reported in the literature.[15,16]

Dimethyl 2,2′-Bipyridine-5,5′-dicarboxylate (2f). The product was isolated as a white solid in 77% yield (524 mg), mp = 260.6−261.9 °C; R_f = 0.28 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr) 1727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 2H), 8.52 (s, 2H), 8.39 (s, 2H), 3.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 158.3, 150.6, 138.1, 122.5, 121.3, 52.5. Data was consistent with that reported in the literature.[15,18]

2,2′-Bipyridine-5,5′-dicarbonitrile (2g). The product was isolated as a white solid in 90% yield (464 mg): mp = 267.6−268.8 °C; R_f = 0.46 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr): 2239; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, J = 1.3 Hz, 2H), 8.64 (d, J = 8.3 Hz, 2H), 8.14 (dd, J = 2.0 Hz, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 152.1, 140.4, 121.6, 116.4, 110.8. Data was consistent with that reported in the literature.[19]

2,2′-Bipyridine-6,6′-dicarbonitrile (2h). The product was isolated as a white solid in 83% yield (427 mg): mp = 264.5−265.9 °C; R_f = 0.22 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr): 2236; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 8.1 Hz, 2H), 8.02 (t, J = 7.8 Hz, 2H), 7.78 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 138.4, 133.4, 129.0, 124.6, 117.0. Data was consistent with that reported in the literature.[20]

5,5′-Dimethoxyl-2,2′-bipyridine (2i). The product was isolated as a white solid in 82% yield (443 mg): mp = 135−137.3 °C; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 2.7 Hz, 2H), 8.21 (d, J = 8.8 Hz, 2H), 7.25 (dd, J = 2.8 Hz, J = 8.8 Hz, 2H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 148.9, 136.5, 129.6, 121.0, 55.7. Data was consistent with that reported in the literature.[21]

5,5′-Bis(benzyloxy)-2,2′-bipyridine (2j). The product was isolated as a white solid in 78% yield (718 mg): mp = 195.2−197.4 °C; R_f = 0.15 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 2H), 8.17 (d, J = 8.4 Hz, 2H), 7.19−7.40 (m, 12H), 5.09 (s, 4H), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.8, 148.9, 137.2, 136.1, 128.7, 128.3, 127.6, 122.4, 121.1, 70.5; MS (ESI) $[M + H]^+$ (m/z, 369). Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 77.98; H, 5.74; N. 7.53.

N^5,$N^{5\prime}$-Diphenyl-2,2′-bipyridine-5,5′-dicarboxamide (2k). The product was isolated as a white solid in 81% yield (798 mg): mp > 300 °C; R_f = 0.22 (petroleum ether/ethyl acetate =3:1); IR (cm^{-1}, KBr) 1669; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 2H), 8.92 (d, J = 2.2 Hz, 2H), 8.33 (dd, J = 2.4 Hz, J = 8.2 Hz, 2H), 7.74−7.69 (m, 6H), 7.36 (t, J = 7.7 Hz, 4H), 7.12 (t, J = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.4, 153.2, 149.8, 139.5 139.1, 130.5, 129.2, 124.6, 120.9 (one carbon missing due to overlap). Data was consistent with that reported in the literature.[22]

2,2′-Bipyridine-5,5′-diylbis(phenylmethanone) (2l). The product was isolated as a white solid in 67% yield (610 mg): mp = 211.2−212.9 °C; R_f = 0.28 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 1648; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 2H), 7.79 (d, J = 7.2 Hz, 4H), 7.68 (d, J = 7.3 Hz, 4H), 7.65 (m, 2H), 7.53 (t, J = 7.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 145.2, 141.5, 135.5, 134.4, 133.9, 129.8, 129.0, 126.9, 125.9. Data was consistent with that reported in the literature.[16]

1,1′-(2,2′-Bipyridine-5,5′-diyl)diethanone (2m). The product was isolated as a pale yellow solid in 62% yield (372 mg): mp = 210−211 °C; R_f = 0.60 (petroleum ether/ethyl acetate =3:1); IR (cm^{-1}, KBr) 1684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, J = 1.6 Hz, 2H), 8.61 (d, J = 8.3 Hz, 2H), 8.38 (dd, J = 8.3 Hz, J = 2.2 Hz, 2H), 2.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 158.2, 149.7, 136.7, 132.4, 121.7, 26.9. Data was consistent with that reported in the literature.[23]

2,2′-Bipyridine-5,5′-diylbis(phenylmethanol) (2n). The product was isolated as a white solid in 77% yield (708 mg): mp = 175.2−177 °C, R_f = 0.35 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr): 3297, 1599; ^{1}H NMR (400 MHz, CD_3COCD_3) δ 8.65 (d, J = 1.5 Hz, 2H), 8.27 (d, J = 8.2 Hz, 2H), 7.83 (dd, J = 1.9 Hz, J = 8.2 Hz, 2H), 7.41 (d, J = 7.4 Hz, 4H), 7.33 (d, J = 7.4 Hz, 4H), 7.25 (m, 2H), 6.10 (d, J = 3.4 Hz, 2H), 5.83 (br s 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.4, 147.9, 145.3, 141.6, 135.4, 128.8, 127.5, 126.7, 120.5, 72.6; MS (ESI) $[M + H]^+$ (m/z, 369). Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.47; H, 5.72; N, 7.53.

2,2′-Bipyridine-6,6′-diylbis(phenylmethanol) (2o). The product was isolated as a white solid in 65% yield (598 mg): mp = 66−68 °C; R_f = 0.25 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr) 3114, 1594; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 2.8 Hz, 2H,), 7.65 (t, J = 6.0 Hz, 2H), 7.40 (d, J = 5.8 Hz, 4H), 7.36 (t, J = 6.0 Hz, 4H), 7.32−7.29 (m, 2H), 7.23 (t, J = 4.6 Hz, 2H), 5.79 (s, 2H), 5.19 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 147.8, 143.2, 136.8, 128.6, 127.8, 127.1,122.4, 121.3, 75.0. Data was consistent with that reported in the literature.[24]

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5,5′-Dichloro-2,2′-bipyridine (2p). The product was isolated as a white solid in 68% yield (383 mg): mp = 207−208 °C; R_f = 0.56 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 2.2 Hz, 2H), 8.34 (d, J = 8.5 Hz, 2H), 7.75 (dd, J = 2.5 Hz, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 147.1, 135.7, 131.5, 120.8. Data was consistent with that reported in the literature.[25]

2,2′-Bipyridine-5,5′-diacetonitrile (2q). The product was isolated as a yellow solid in 78% yield (456 mg): mp = 215.9−217.8 °C, R_f = 0.15 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr) 2255; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 2H), 8.59 (d, J = 7.2 Hz, 2H), 7.95 (d, J = 7.9 Hz, 2H) 3.88 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 148.5, 136.6, 128.9, 121.4, 116.7, 29.7. Data was consistent with that reported in the literature.[26]

2,2′-Biquinoline (2r). The product was isolated as a white solid in 72% yield (461 mg): mp =193−195 °C; R_f = 0.66 (petroleum ether/ethyl acetate = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 8.6 Hz, 2H), 8.28 (d, J = 8.6 Hz, 2H), 8.20 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.1 Hz, 2H), 7.70 (t, J = 7.2 Hz, 2H), 7.52 (t, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.5, 136.8, 130.2, 127.7, 127.1, 125.8, 122.4, 121.6. Data was consistent with that reported in the literature.[17]

2,2′-Biquinoxaline (2s). The product was isolated as a pale yellow solid in 65% yield (445 mg): mp 224−225 °C; R_f = 0.55 (petroleum ether/ethyl acetate = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 2H), 8.28 (m, 2H), 8.23 (m, 2H), 7.87 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 144.3, 142.8, 141.7, 130.9, 130.6, 130.0, 129.4. Data was consistent with that reported in the literature.[27]

2,2′-Bipyridine-6-carbonitrile (3a). The product was isolated as a white solid in 81% yield (670 mg): mp = 125−126 °C; R_f = 0.66 (petroleum ether/ethyl acetate = 3:1); IR (cm^{-1}, KBr) 2234; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 8.1 Hz, 2H), 8.47 (d, J = 8.0 Hz, 1H), 7.96 (t, J = 7.9 Hz, 1H), 7.87 (m, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 154.0, 149.3, 137.9, 137.2, 133.2, 128.1, 124.8, 124.2, 121.6, 117.4. Data was consistent with that reported in the literature.[28]

6-Methoxy-2,2′-bipyridine (3b). The product was isolated as a colorless oil in 85% yield (474 mg): R_f = 0.67 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.77 (m, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.25 (m, 1H), 6.77 (d, J = 8.1 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 156.0, 153.3, 149.0, 139.4, 136.9, 123.5, 121.1, 113.8, 111.1, 53.2. Data was consistent with that reported in the literature.[29]

6-Methoxy-6′-methyl-2,2′-bipyridine (3c). The product was isolated as a white solid in 75% yield (450 mg): mp = 56−57 °C; R_f = 0.89 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 7.8 Hz, 1H), 8.04 (d, J = 7.4 Hz, 1H), 7.67 (m, 2H), 7.13 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 4.0 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 157.8, 155.5, 153.8, 139.3, 136.9, 123.1, 118.0, 113.7, 110.8, 53.2, 24.6. Data was consistent with that reported in the literature.[29]

6′-Methoxy-5-methyl-2,2′-bipyridine (3d). The product was isolated as a white solid in 73% yield (438 mg): mp = 45−46 °C; R_f = 0.62 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.27 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 7.4 Hz, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.56 (dd, J = 8.1 Hz, J = 1.4 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 4.02 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 155.9, 149.3, 138.9, 123.0, 122.4, 121.7, 120.9, 118.1, 117.4, 55.6, 24.6. Data was consistent with that reported in the literature.[30]

***N,N*-Diethyl-5′-methyl-2,2′-bipyridin-6-amine (3e).** The product was isolated as a light yellow oil in 84% yield (607 mg): R_f = 0.24 (petroleum ether/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (m, 1H), 8.27 (J = 8.1 Hz, 1H), 7.60 (d, J = 7.3 Hz, 1H), 7.53 (m, 2H), 6.47 (d, J = 8.3 Hz, 1H), 3.58 (q, J = 7.0 Hz, 4H), 2.34 (s, 3H), 1.22 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 154.9, 154.1, 149.1, 137.9, 137.1, 132.5, 120.4, 107.8, 105.5, 42.6, 18.2, 13.0; MS (ESI) $[M + H]^+$ (m/z, 242). Anal. Calcd for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.62; H, 7.97; N, 17.38.

2,2′-Bipyridin-6-ylmethanol (3f). The product was isolated as a light yellow oil in 75% yield (419 mg): R_f = 0.26 (petroleum ether/ethyl acetate = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (m, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.82 (m, 2H), 7.32 (m, 1H), 7.27 (d, J = 7.4 Hz, 1H), 4.84 (s, 2H), 3.11 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 155.7, 154.9, 149.2, 137.0, 123.9, 122.3, 121.1, 120.5, 119.7, 64.2. Data was consistent with that reported in the literature.[31]

2,2′-Bipyridin-6-carbaldehyde (3g). The product was isolated as a pale yellow solid in 80% yield (442 mg): mp = 166−167 °C; R_f = 0.14 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 1698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.66 (m, 1H), 8.49 (d, J = 8.0 Hz, 1H), 8.41 (dd, J = 0.7 Hz, J = 7.9 Hz, 1H), 7.86 (t, J = 7.8 Hz, 1H), 7.81 (dd, J = 1.8 Hz, J = 8.2 Hz, 1H), 7.56 (m, 1H), 7.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 156.7, 155.9, 149.1, 137.7, 136.9, 123.8, 121.5, 121.3, 120.5, 104.0. Data was consistent with that reported in the literature.[10]

4-Methoxy-6′-methyl-2,2′-bipyridine (3h). The product was isolated as a pale yellow solid in 68% yield (408 mg): mp = 45−46 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 5.6 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 2.5 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.15 (d, J = 7.6 Hz; 1H), 6.81 (m, 1H), 3.92 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 153.6, 153.5, 149.5, 139.3, 137.3, 133.1, 120.5, 113.3, 110.6, 53.2, 18.3; MS (ESI) $[M + H]^+$ (m/z, 201). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.02; H, 6.08; N, 13.92.

N-(2,2′-Bipyridin-4-yl)acetamide (3i). The product was isolated as a pale yellow solid in 72% yield (460 mg): mp = 178−179 °C; R_f = 0.60 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 1675; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.52 (s, 1H), 8.95 (d, J = 1.3 Hz, 1H), 8.68 (t, J = 7.0 Hz, 1H), 8.33 (dd, J = 1.5 Hz, J = 6.7 Hz, 1H), 8.24 (d, J = 10.8 Hz, 1H), 8.01 (m, 1H), 7.90 (m, 1H), 7.46 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 154.7, 149.9, 148.1, 146.1, 142.5, 130.8, 126.8, 114.3, 111.5, 104.8, 24.9. Data was consistent with that reported in the literature.[32]

5-(Benzyloxy)-2,2′-bipyridine (3j). The product was isolated as a pale yellow solid in 82% yield (644 mg): mp = 84−85 °C; R_f = 0.45 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 4.8 Hz, 2H), 8.36 (d, J = 7.7 Hz, 2H), 7.81 (m, 2H), 7.26 (m, 1H), 7.17 (m, 2H), 6.74 (m, 1H), 6.65 (d, J = 7.7 Hz, 2H), 4.41 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 154.9, 149.1, 147.7, 143.2, 139.9, 137.1, 135.3, 128.7, 127.8, 126.6, 123.8, 121.4, 121.1, 73.7; MS (ESI) $[M + H]^+$ (m/z, 263). Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.88; H, 5.40; N, 10.65.

2,2′-Bipyridin-5-yl(phenyl)methanol (3k). The product was isolated as a pale yellow solid in 67% yield (527 mg): mp = 97−98 °C; R_f = 0.38 (petroleum ether/ethyl acetate = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (m, 2H), 8.38 (m, 2H), 7.82 (m, 2H), 7.65 (dd, J = 1.5 Hz, J = 7.7 Hz, 1H); 7.31 (m, 5H), 6.32 (s, 1H), 2.90 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 155.3, 149.2, 137.6, 137.0, 128.8, 128.4, 127.6, 123.8, 123.0, 122.0, 121.7, 121.0, 120.4, 70.4; MS (ESI) $[M + H]^+$ (m/z, 263). Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.81; H, 5.41; N, 10.66.

***N*-(2,2′-Bipyridin-5-ylmethyl)aniline (3l).** The product was isolated as a pale yellow solid in 68% yield (506 mg): mp = 77−78 °C; R_f = 0.15 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 2H), 8.37 (t, J = 7.8 Hz, 2H), 7.80 (m, 2H), 7.20 (m, 1H), 7.18 (m, 2H), 6.74 (t, J = 7.3 Hz, 1H), 6.66 (d, J = 7.9 Hz, 2H), 4.42 (s, 2H), 4.09 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 155.4, 149.2, 148.5, 147.7, 136.9, 136.1, 135.1, 129.4, 123.7, 121.1, 121.0, 118.1, 113.1, 45.8; MS (ESI) $[M + H]^+$ (m/z, 262). Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08 Found: C, 78.06; H, 5.72; N, 16.02.

2-(2,2′-Bipyridin-5-yl)acetonitrile (3m). The product was isolated as a pale yellow solid in 78% yield (456 mg): mp = 87−88 °C; R_f = 0.18 (petroleum ether/ethyl acetate = 5:1); IR (cm^{-1}, KBr) 2249; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (m, 2H), 8.42 (dd, J = 2.0 Hz, J = 8.2 Hz, 2H), 7.83 (m, 2H), 7.34 (m, 1H), 3.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 155.9, 153.6, 148.9, 147.8, 139.33,

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139.32, 124.5, 121.7, 113.9, 110.8, 21.2; MS (ESI) $[M + H]^+$ (m/z, 196). Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.80; H, 4.68; N, 21.47.

2,2′-Bipyridin-5-ylmethanamine (3n). The product was isolated as a pale yellow solid in 75% yield (405 mg): mp = 68−69 °C; R_f = 0.10 (petroleum ether/ethyl acetate = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.54 (s, 1H), 8.27 (dd, J = 2.0 Hz, J = 8.0 Hz, 2H), 7.78 (m, 2H), 7.30 (m, 1H), 4.70 (s, 2H), 3.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 155.1, 149.1, 147.9, 137.1, 136.7, 135.8, 123.8, 121.3, 121.1, 62.3. Data was consistent with that reported in the literature.[31]

Caerulomycin F. The product was isolated as a pale yellow solid in 74% yield (480 mg): mp = 63−64 °C; R_f = 0.10 (petroleum ether/ethyl acetate = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 4.6 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.88−7.79 (m, 1H), 7.33−7.30 (m, 1H), 6.77 (d, J = 2.0 Hz, 1H), 4.77 (s, 2H), 4.14 (br s, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 160.9, 156.5, 155.5, 148.9, 136.9, 123.9, 121.3, 106.6, 105.3, 64.3, 55.3. Data was consistent with that reported in the literature.[14]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General information, optimization experiments, and copies of ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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