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SYNTHESIS OF 2,4-DIBROMOPYRIDINE AND 4,4'-DIBROMO-2,2'-BIPYRIDINE. EFFICIENT USAGE IN SELECTIVE BROMINE-SUBSTITUTION UNDER PALLADIUM-CATALYSIS

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Abstract–We report an efficient method for preparing 2,4-dibromopyridine and 4,4'-dibromo-2,2'-bipyridine from the corresponding nitroazine *N*-oxide in one step via a tandem nucleophilic substitution–*N*-oxide reduction process. The one step preparation of 4,4'-dihalo-2,2'-bipyridines from dihalopyridines via a Stille reaction is also described. 4,4'-Dibromo-2,2'-bipyridine undergoes selective mono- or disubstitution processes under palladium catalysis. This short synthetic procedure is an efficient and reliable process for preparing conjugated pyridine and 2,2'-bipyridine building blocks for applications in coordination chemistry and materials science.

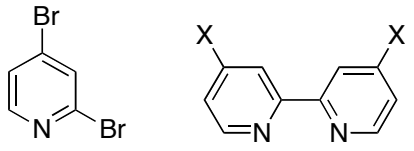
INTRODUCTION

There has been an extensive effort to develop synthetic methods for azines, specially pyridines and 2,2'-bipyridines, due to their presence as substructures in many natural products and pharmaceuticals, and also as ligands for transition metals.[1] The renewed interest in this chemistry has been driven, to a great extent, by their ability to act as chelating agents for almost all kinds of metal ions and the wide range of applications rising from their involvement in supramolecular chemistry[2] and in materials science.[3] However, synthetic access to functionalized derivatives is still difficult, and reliable preparative protocols are therefore highly desirable. Disubstituted 2,2'-bipyridines have been prepared by connecting two pyridine precursors at C-2 with the help of palladium or nickel transition metal complexes and some protocols have proven to be quite successful for the preparation of symmetrically and non–symmetrically substituted derivatives.[4, 5]

However, most of the reported disubstituted pyridine building blocks are 2,6- or 2,5-derivatives, whereas 2,4-derivatives are scarce, because 2,4-dihalopyridines are not readily available.[6]

The growing interest in this field and our interest in the synthesis of complex pyridine-containing

molecules[7] led us to focus on the development of expeditious methods for the preparation of suitable pyridine precursors for use in transition-metal catalyzed-processes, namely 2,4-dibromopyridine (**1**)[8] and 4,4'-dihalo-2,2'-bipyridine (**2**).[9]

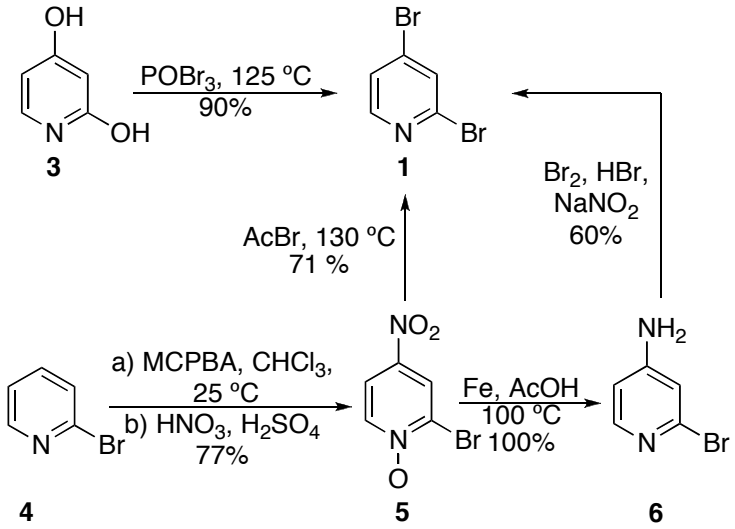


1 **2a** X = Br
2b X = Cl

Figure 1

RESULTS AND DISCUSSION

For the synthesis of 2,4-dibromopyridine two commercially available starting materials appeared to be the most appropriate, 2,4-dihydroxypyridine (**3**) and 2-bromopyridine (**4**) (Scheme 1)



3 **1** **4** **5** **6**

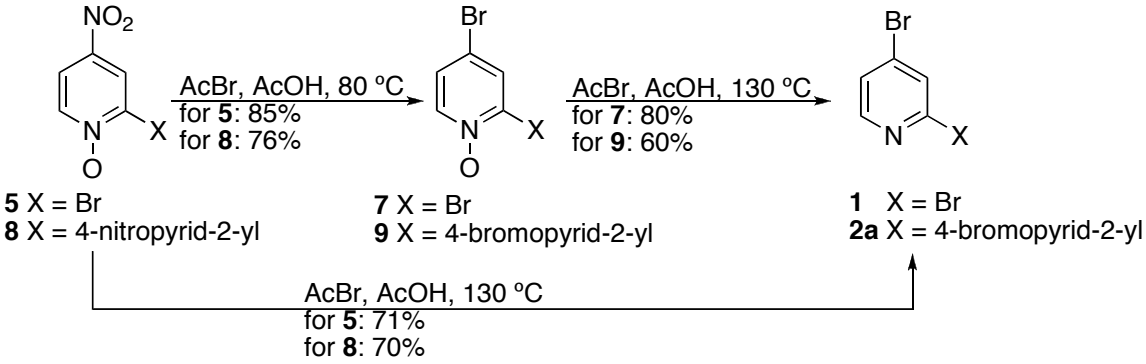
Scheme 1

Firstly, we optimized the method reported by den Hertog and prepared 2,4-dibromopyridine (**1**) in 90 % yield by treatment of 2,4-dihydroxypyridine with phosphorus oxybromide at 125 °C.[8a, 10] Alternatively, diazotation of amine **6** followed by bromine substitution provided 2,4-dibromopyridine in 46 % yield in four steps from easily accessible starting material 2-bromopyridine.[6b] Although these protocols gave quite satisfactory results, more practical and scalable routes to 2,4-dibromopyridine (**1**) would be very advantageous.

We have developed an alternative procedure for preparing larger quantities of dibromopyridine derivatives **1** and **2** starting from the appropriate pyridine *N*-oxide. Treatment of 2-bromo-4-nitropyridine *N*-oxide (**5**) with acetyl bromide yielded different products depending on the reaction temperature, either 2,4-dibromopyridine *N*-oxide (**7**) or 2,4-dibromopyridine (**1**). Thus, when the reaction between pyridine

N-oxide **5** and acetyl bromide was run at 80 ºC dibromopyridine *N*-oxide **7** was obtained in 85% yield. Most conveniently, keeping the temperature at 130 ºC throughout the reaction, the target 2,4-dibromopyridine (**1**) was prepared in 55% yield from 2-bromopyridine in three steps (Scheme 2).

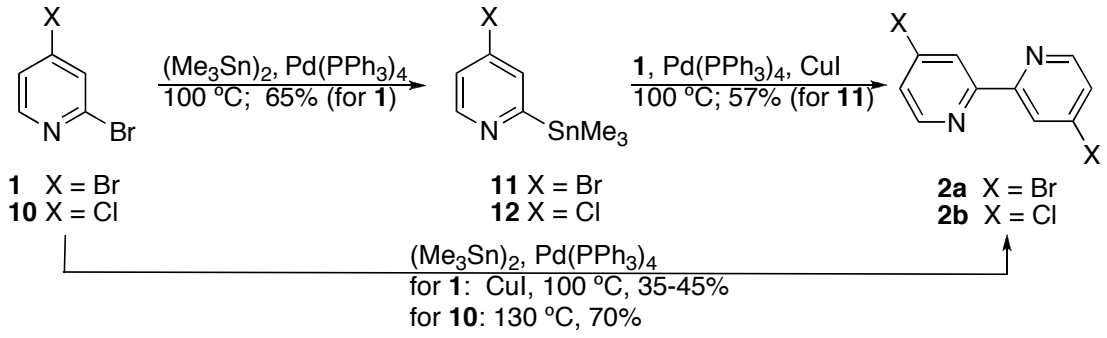
2,4-Dibromopyridine (**1**) undergoes efficient regioselective palladium-catalyzed cross-coupling reactions affording 4-bromo-2-carbon-susbstituted pyridines, which have proven to be quite difficult to prepare using other methods.[7c]



Scheme 2

These results prompted us to apply the same strategy to the synthesis of 4,4'-dibromo-2,2'-bipyridine (**2**), an important building block in supramolecular chemistry and coordination chemistry. Treatment of dinitro compound **8** with acetyl bromide in glacial acetic acid at 130 ºC led to dibromobipyridine **2a** in good yield in one-pot with the subsequent waste reduction. This global transformation can also be carried out stepwise in a 46% overall yield (Scheme 2).[11]

The efficiency of metal-catalyzed cross-coupling reactions for connecting unsaturated and saturated fragments is well documented, particularly for (aza)biaryl bond formation.[12] The Stille reaction has already proven to be a very attractive procedure to synthesize oligopyridines.[13] We therefore conceived an alternative approach to dihalobipyridines by position-selective Stille coupling of 2-bromo-4-halopyridines with 4-halo-2-stannylpyridines. The latter could in turn be prepared *in situ* by Pd-assisted cross-coupling of the same 2-bromo-4-halopyridine with hexaalkyldistannanes[14] (Scheme 3).



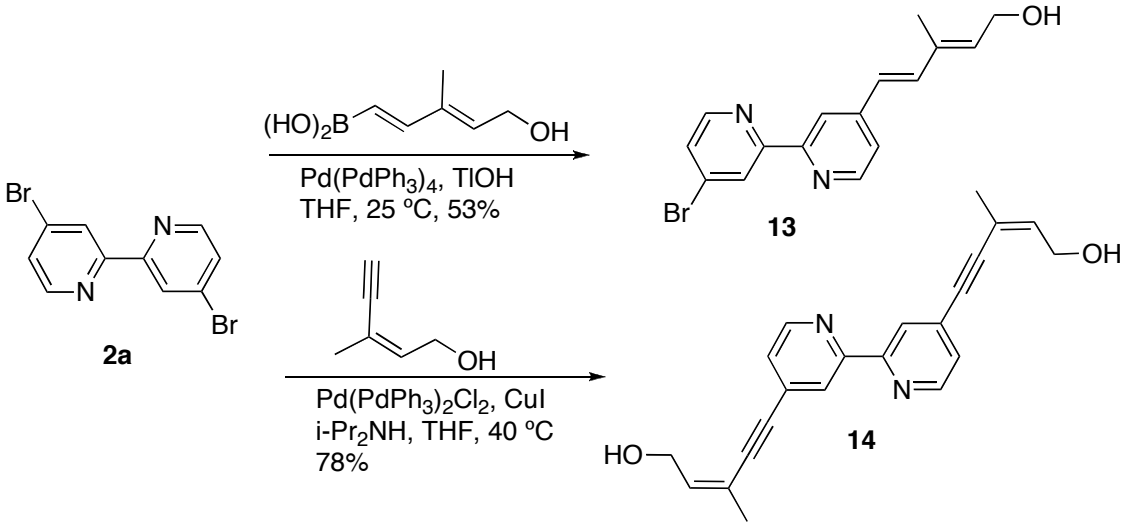
Scheme 3

Treatment of 2-bromo-4-chloropyridine (**10**) with hexamethyldistannane (60 mol%) and $Pd(PPh_3)_4$ (10

mol%) in xylene at 130 °C for 20 h, afforded 4,4'-dichloro-2,2'-bipyridine (**2b**) in 70 % yield. The reaction was highly halogen-selective, since only traces of a side product, identified as 4,4"-dichloro-2,2':4',2"-terpyridine, were detected by ^{1}H-NMR analysis of the reaction mixture. However, under these conditions bipyridine **2a** was obtained in lower yield. Although position 2 should react faster as expected for a S_N2-like process, probably the temperature is too high to discriminate fully between both C—Br bonds and the preparation of the intermediate stannylpyridine **11** was required. Thus, position-selective reaction of 2,4-dibromopyridine with hexamethylbistannane (110 mol %) involved heating at 90ºC in toluene for 16 h in the presence of $Pd(PPh_3)_2Cl_2$ (10 mol%) and LiCl (30 mol%). The desired 2-stannylpyridine **11** was obtained in 62 % yield and the regioselectivity (C2:C4 coupling) was 10:0.5. The use of $Pd(PPh_3)_4$ in dioxane at 100 ºC for 8 h afforded the target compound **11** in 65% yield with a similar regioselectivity (10:0.7). Finally, the cross-coupling of pyridylstannane **11** and 2,4-dibromopyridine (**1**) using $Pd(PPh_3)_4$ (10 mol%) in the presence of CuI in dioxane at 100 ºC for 90 h gave 4,4'-dibromo-2,2'-bipyridine (**2a**) in 56% yield, along with small amounts of 2,4'-dibromo-4,2'-bipyridine and 4,4"-dibromo-2,4':2',2"-terpyridine.

Bipyridine **2a** turned out to be a useful starting material for producing highly conjugated systems under palladium-catalyzed cross-coupling reaction conditions. Under Suzuki (or Stille) conditions the monocoupled compound **13** was the major product (85% corrected yield), while under Sonogashira conditions the dicoupled product **14** was obtained in good yield (78% yield). (Scheme 4).

This methodology represents a useful procedure for preparing, symmetrically and non-symmetrically substituted bipyridines from 4,4'-dibromo-2,2'-bipyridine (**2a**).



Scheme 4

In summary, we have developed a practical synthetic route to 2,4-dibromopyridine and 4,4'-dibromo-2,2'-bipyridine from the corresponding nitroazine *N*-oxides via a tandem two-step sequence. The Stille coupling of 2-bromo-4-bromo(chloro)pyridine, either in one or two steps, constitutes a direct

route to 4,4'-dibromo(dichloro)-2,2'-bipyridine. Both azines proved to be valuable compounds in palladium-catalyzed cross-coupling processes to produce highly conjugated pyridines and bipyridines, architectural motifs with potential uses in coordination and materials chemistry.

EXPERIMENTAL

General: Reagents and solvents were purchased as reagent-grade and used without further purification unless otherwise stated. Solvents were dried according to published methods[15] and distilled before use. All reactions were performed in oven-dried or flame-dried glassware under an inert atmosphere of Ar unless otherwise stated. NMR spectra were recorded in a Bruker AMX400 (400.13 MHz and 100.61 MHz for proton and carbon respectively) spectrometer at 298 K with residual solvent peaks as internal reference and the chemical shifts are reported in δ [ppm], coupling constants *J* are given in [Hz] and expressed as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ^{13}C-multiplicities assigned with DEPT experiments and COSY, HMBC and HSQC methods were used to establish atom connectivities. Electronic impact ionization (EI) and fast atom bombardment (FAB) mass spectra were recorded on a VG-Autospec M instrument. Melting points (mp) were taken on a Stuart Scientific apparatus.

2,4-Dibromopyridine (**1**). **Method a**: 2,4-Dihydroxypyridine (**3**) (2.7 g, 24.3 mmol) and $POBr_3$ (23 g, 80.22 mmol) were heated in a Schlenk flask to 125 ºC for 4.5 h. After cooling to 25 ºC, the reaction mixture was carefully poured into water, neutralized with Na_2CO_3 and extracted with CH_2Cl_2. The combined extracts were dried and the solvent removed in vacuo. The residue was purified by flash chromatography (40:60, CH_2Cl_2/hexane) to give 5.24 g (90 % yield) of 2,4-dibromopyridine (**1**) as a white solid, mp 35-36 ºC (EtOH), (lit.,[8a] 38.0-38.5 ºC) and 698 mg (9%) of 2,3,4-tribromopyridine, mp 86 ºC (EtOH), (lit.,[8a] 84-85 ºC). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 5.3, 1.4 Hz, 1H), 7.71 (d, *J* = 1.4 Hz, 1H), 8.21 (d, *J* = 5.3 Hz, 1H). ^{13}C NMR (100.63 MHz, $CDCl_3$): δ 126.2 (CH, C^5), 130.9 (CH, C^3), 133.9 (C, C^4), 142.5 (C, C^2), 150.5 (CH, C^6). MS: *m/z* (%) 237 (M^+ ^{81}[Br]^{79}[Br], 75), 158 (97), 156 (100).

Method b: Acetyl bromide (2.4 mL, 31.96 mmol) was added to a solution of 2-bromo-4-nitropyridine *N*-Oxide (**5**)[16] (0.5 g, 2.3 mmol) in AcOH (4 mL) and the reaction mixture was heated to 130 ºC for 16 h. Then, it was carefully poured into ice, basified with Na_2CO_3 to pH=9 and extracted with CH_2Cl_2. The combined organic phase was separated, dried and the solvent removed under reduced pressure. The residue was purified to give 2,4-dibromopyridine (**1**) (0.39 g, 71 % yield).

4,4'-Dibromo-2,2'-bipyridine (2a). Method a: following method b for the preparation of 2,4-dibromopyridine (**1**), acetyl bromide (6.4 mL, 86 mmol) and 4,4'-dinitro-2,2'-bipyridine *N,N*'-dioxide (**10**)[9a] (0.43 g, 1.55 mmol) in AcOH (11 mL) at 130 ºC for 10 h gave 4,4'-dibromo-2,2'-bipyridine (**2a**) (0.34 g, 70%) as a white solid after purification by silica gel column chromatography (96:4,

hexane/EtOAc). Mp 139-140 ºC (lit.,[9a] 141-142 ºC) (hexane). ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 5.2, 1.8 Hz, 2H), 8.46 (d, *J* = 5.2 Hz, 2H), 8.60 (d, *J* = 1.8 Hz, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 124.8 (CH), 127.4 (CH), 134.0 (C), 149.8 (CH), 156.0 (C).

Method b: **4-bromo-2-trimethylstannylpyridine (11):** In a dry Schlenk flask, $Pd(PPh_3)_2Cl_2$ (0.075 g, 0.105 mmol), LiCl (0.015 g, 0.3 mmol) and toluene (5 mL) were placed and purged with argon. Then Me_6Sn_2 (1.2 mL of a solution 0.97 M in toluene, 1.15 mmol) was added followed by 2,4-dibromopyridine (**1a**) (0.250 g, 1.05 mmol). The reaction mixture was stirred at 90 ºC for 16 h, then washed with aqueous saturated KF and extracted with CH_2Cl_2. The combined organic layer was separated, dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification by distillation afforded 4-bromo-2-trimethylstannylpyridine (**12a**) (220 mg, 65%) along with a compound identified as 2-bromo-4-trimethylstannylpyridine in a 20:1 ratio. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ 0.36 (s, $^2J_{119Sn-H}$ = 56.2 Hz, $^2J_{117Sn-H}$ = 53.7 Hz, 9H), 7.33 (dd, *J* = 5.4, 2.1 Hz, 1H), 7.61 (d, *J* =2.0 Hz, $^3J_{119Sn-H}$ = 22.3 Hz, $^3J_{117Sn-H}$ = 18.4 Hz, 1H), 8.53 (d, *J* = 5.4 Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ -9.8 (CH_3), 89.8 (C), 125.3 (CH), 131.8 (C), 134.0 (CH), 150.8 (CH). MS (FAB^+) *m/z* (%): 322 ($[M+1]^+$, 6). HRMS (FAB^+) calcd. for $C_8H_{13}NBrSn$ 319.9244, found 319.9247. **2-Bromo-4-trimethylstannylpyridine**: ^{1}H-NMR (400.16 MHz, $CDCl_3$): δ 0.35 (s, $^2J_{Sn-H}$ = 55.4 Hz, 9H), 7.32 (d, *J* = 4.5 Hz, $^3J_{Sn-H}$ = 37.8 Hz, 1H), 7.56 (bs, $^3J_{Sn-H}$ = 39.6 Hz, 1H), 8.26 (d, *J* = 4.5 Hz, 1H). MS (FAB^+) *m/z* (%): 322 ($[M+1]^+$, 43).

Stille coupling: $Pd(PPh_3)_4$ (0.4 g, 0.035 mmol), CuI (135 mg, 705 mmol), 4-bromo-2-trimethylstannylpyridine (**12a**) (0.11 g, 0.35 mmol) and 2,4-dibromopyridine (**1a**) (90 mg, 0.4 mmol) were heated in degassed THF (4 mL) at 100 ºC for 96 h under argon. The reaction mixture was allowed to cool to 25 ºC, the solvent evaporated and the residue was taken up in CH_2Cl_2. Then a 30% NH_4OH (1 mL) and EDTA (0.18 g) were added and the mixture stirred at 40 ºC for 1 h. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried, the solvent removed and the residue purified by chromatography in alumina grade III (10:90 CH_2Cl_2/hexane) to give 4,4'-dibromo-2,2'-bipyridine (**2a**) (63 mg, 57 %). **2,4'-Dibromo-4,2'-bipyridine**: ^{1}H-NMR (400.16 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.83 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.94 (d, *J* = 1.6 Hz, 1H), 8.10 (d, *J* = 1.2 Hz, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.56 (d, *J* = 5.2 Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 120.1 (CH), 124.5 (CH), 125.6 (CH), 127.5 (CH), 134.0 (C), 143.2 (C), 147.8 (C), 150.7 (C), 150.8 (C), 154.3 (C). MS (EI^+) *m/z* (%): 317 ($[M+1]^+$ ^{81}[Br], 6), 316 ($[M]^+$ ^{81}[Br], 53), 315 ($[M+1]^+$ ^{79}[Br] ^{81}[Br], 13), 314 ($[M]^+$ ^{79}[Br] ^{81}[Br], 96), 313 ($[M+1]^+$ ^{79}[Br], 7), 312 ($[M]^+$ ^{79}[Br], 54). HRMS (EI^+) calcd. for $C_{10}H_6N_2Br_2$ 311.8898, found 311.8891. **4,4''-Dibromo-2,4':2',2''-terpyridine**: ^{1}H-NMR (400.16 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.54 (dd, *J* = 5.2, 1.8 Hz, 1H), 8.01 (dd, *J* = 5.1, 1.4 Hz, 1H), 8.13 (d, *J* = 1.8 Hz, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 8.59 (d, *J* = 5.2 Hz, 1H), 8.70 (d, *J* = 1.6 Hz, 1H), 8.81 (d, *J* = 5.1 Hz, 1H), 8.94 (d, *J* = 1.4 Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$):

δ 118.6 (C), 121.8 (C), 124.5 (CH), 124.8 (CH), 127.1 (CH), 133.9 (C), 134.1 (C), 146.3 (C), 149.8 (CH), 150.0 (CH), 150.7 (CH), 156.0 (C). MS (EI^+) *m/z* (%): 392 ($[M+1]^+$ ^{81}[Br], 8), 393 ($[M]^+$ ^{81}[Br], 51), 392 ($[M+1]^+$ ^{79}[Br] ^{81}[Br], 19), 391 ($[M]^+$ ^{79}[Br] ^{81}[Br], 100), 389 ($[M+1]^+$ ^{79}[Br], 10), 389 ($[M]^+$ ^{79}[Br], 49). HRMS (EI^+) calcd. for $C_{15}H_9N_3Br_2$ 388.9163, found 388.9156.

4,4'-Dichloro-2,2'-bipyridine (2b). To a mixture of $Pd(PPh_3)_4$ (0.320 g, 0.25 mmol), 2-bromo-4-chloropyridine (**1b**)[17] (0.480 g, 2.5 mmol) in xylene (12.5 mL) under argon, Me_6Sn_2 (276 μL, 1.3 mmol) was added. The reaction mixture was stirred at 130 ºC for 20 h. Then the solvent was removed under reduced pressure and the residue purified by flash chromatography (silica gel, 96:4 hexane/EtOAc) to give 4,4'-dichloro-2,2'-bipyridine (**2b**) (196 mg, 70 % yield) as a white solid. Mp 132 ºC (hexane) (lit.,[9b] 129 ºC).

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