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Synthesis of dihalo bi- and terpyridines by regioselective Suzuki–Miyaura cross-coupling reactions

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ABSTRACT

This paper describes an efficient and regioselective synthetic route leading to new dihalobi- and terpyridines. We developed a strategy based on regioselective sequence of Suzuki–Miyaura cross-coupling reactions between bromopyridyl boronic acids and dihalopyridines and dihalobipyridines. The study of the influence of the nature and the position of the halogen atoms leads to prepare bromoiododerivatives to obtain good selectivities.

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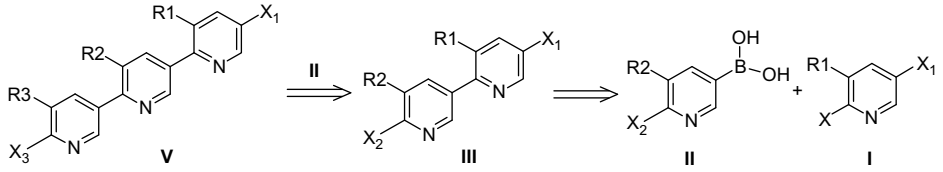
1. Introduction

Oligopyridines, like [2,2′]-bipyridines and [2,2′:6′,2″]-terpyridines, are widely used as ligands able to attach various metal atoms and the resulting metal complex have chemical, electrochemical, and optical properties.[1] From a synthetic point of view, two general strategies can be used to prepare these oligopyridines, either by non-catalyzed heterocycle syntheses such as aza diels–alder,[2] condensation,[3] pyrolysis,[4] and cycloaddition methodologies[5] or by cross-coupling reactions.[6] In modern organic chemistry, cross-coupling reactions have been developed to prepare a number of different oligopyridines. In general, these oligopyridines are only linked together by a C–C bond on C2,[7] except some natural oligopyridines, in particularly nemertelline. The synthesis of this quaterpyridine was reported,[8] but faced with synthetic difficulties, Bouillon[9] developed an efficient two-step rapid synthesis of nemertelline based on two successive Suzuki–Miyaura cross-coupling reactions between halopyridylboronic species and dihalopyridines.

Our laboratory is specialized in the preparation of boronic species[10] and in the study of their ability to be good coupling partners.[11] Thus, we have recently reported[12] a convergent and highly flexible synthesis of new halo-oligopyridines by using Suzuki–Miyaura cross-coupling reactions in a regioselective strategy named Garlanding. In this paper, we extend this strategy to the coupling reaction of halopyridylboronic species with dihalopyridines. We have studied in-depth roles played by the nature and the position of the halogen atom in order to obtain regioselectively new unsymmetric dihalo-oligopyridines **III** and **V** (Scheme 1). In the literature, only few examples of dihalobipyridines **III** were described[13] but nothing exist about the dihaloterpyridines **V**.



Scheme 1. Retrosynthetic aspect.

2. Results and discussion

The synthetic aspect consists in a regioselective sequence of Suzuki–Miyaura cross-coupling between halopyridylboronic acids **II** and dihalopyridines **I**. We used the bromo-3-pyridylboronic acid

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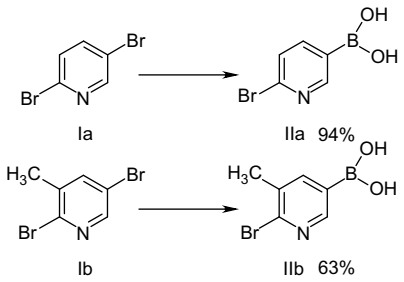
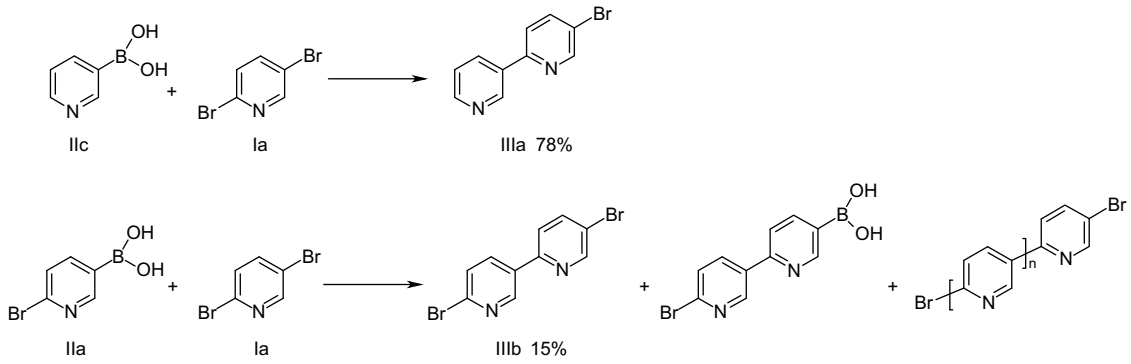


Scheme 2. Synthesis of halopyridylboronic acids **IIa** and **IIb**. Reagents and conditions: (1) *n*-BuLi, 1.25 equiv, THF, −78 °C, 1 h; (2) $B(OiPr)_3$, 1.25 equiv, THF, −78 °C, 1 h then rt; (3) hydrolysis.

a regioselective halogen–lithium exchange, from dibromopyridine **Ia**. We applied this methodology to prepare the new boronic acid **IIb** from dibromomethylpyridine **Ib** (Scheme 2).

2,5-Dihalopyridines **Ia** and **Ib** represent both our starting materials and can be used to synthesize the corresponding halopyridylboronic acids **IIa** and/or **IIb**, and used as partners to couple with the latter acids to give dihalobipyridines **III**. And then, these dihalopyridines could be engaged in a second Suzuki–Miyaura cross-coupling reaction to couple with halopyridylboronic acids **IIa** or **IIb** leading to dihaloterpyridines **V**. The regioselective control of the formation of the pyridine–pyridine linkage requires an efficient and flexible strategy leading to a selective coupling with the desired halogen. In general, results of regioselective couplings are predictable in the case of numerous polyhaloheteroaromatics,[14] and, for example, the 2,5-dibromopyridine is described as a substrate allowing a regioselectivity, thanks to the electrophilic character of the C(2) position which is only substituted.[8a,15]



Scheme 3. Synthesis of halopyridinylboronic acids **IIIa** and **IIIb**.

IIa and the 6-bromo-5-methyl-3-pyridylboronic acid **IIb**,[10] which were not commercially available at the beginning of our study. We have previously described the synthesis of **IIa**, its preparation requires the reaction of an organolithium intermediate, generated by

Table 1
Synthesis of bipyridines **IIIb–e**

Substrates	Boronic acids	Products	Yields (%)
Ia	**IIa**	**IIIb**	15
Ib	**IIa**	**IIIc**	9
Ia	**IIb**	**IIId**	9
Ib	**IIb**	**IIIe**	15

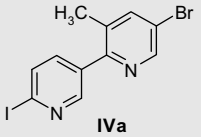
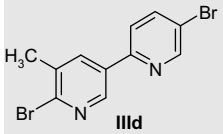
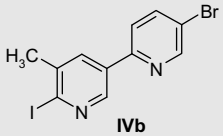
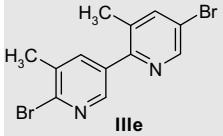
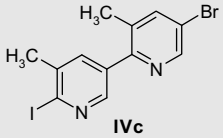
Reagents and conditions: Bromopyridylboronic acids **IIa** or **IIb** 1.25 equiv, dibromopyridines **Ia–b** 1 equiv, Na_2CO_3aq 2.5 equiv, $Pd(PPh_3)_4$ 0.05 equiv, 1,4-dioxane, reflux, 18 h.

Table 2
Synthesis of dibromobipyridines **IIIb–e**

Substrates	Boronic acids	Products	Yields (%)
Ic	**IIa**	**IIIb**	73
Id	**IIa**	**IIIc**	86
Ic	**IIb**	**IIId**	73
Id	**IIb**	**IIIe**	77

Reagents and conditions: Bromopyridylboronic acids **IIa** or **IIb** 1.25 equiv, bromoiodopyridines **Ic–d** 1 equiv, Na_2CO_3aq 2.5 equiv, $Pd(PPh_3)_4$ 0.05 equiv, 1,4-dioxane, reflux, 18 h.

Table 3
Synthesis of bromoiodobipyridines **IVa–c**

Substrates	Products	Yields (%)
 **IIIc**	 **IVa**	74
 **IIId**	 **IVb**	89
 **IIIe**	 **IVc**	81

Reagents and conditions: acetyl chloride 2×2 equiv, sodium iodide 2×4 equiv, CH_3CN, reflux, 2×24 h.

This selectivity can be verified with 3-pyridylboronic acid **IIc**,[16] which gave the predicted bipyridine **IIIa** in high yield. The latter was previously described.[17] Unfortunately this selectivity was totally lost with the use of 6-bromo-3-pyridylboronic acid, in this case the reaction gave a mixture of bipyridine and oligopyridine derivatives from which the desired product **IIIb** was isolated in very low yield (Scheme 3).

Even if the alpha position of the pyridine ring is more sensitive to a cross-coupling reaction than the beta one, the formation of by-products was due to the low selectivity of the reaction. Faced with these selectivity difficulties of the reaction, we reinvestigated the cross-coupling according to the nature of the halogen and its position on the pyridine ring. Among halogens, it is known that iodine has a better reactivity than bromine or chloride or fluorine. That is why we tried to increase the selectivity of the reaction by using the 3-bromo-6-iodopyridine **Ic**.

Corcoran[18] first reported a method to exchange bromine by iodine in alpha position of the nitrogen atom of a pyridine to obtain 2-iodopyridines from 2-bromopyridines. Subsequently, Song[19] applied this method on 2,5-dibromopyridine and 2,5-dibromo-3-picoline and reported that the I–Br exchange occurred exclusively at the C(2) position. We applied this method to prepare 5-bromo-2-iodo-3-methylpyridine **Id**, and 2-iodo-5-bromopyridine **Ic** is commercially available. Then, we engaged **Ic** and **Id** in cross-coupling reactions with bromopyridylboronic acids **II**. Results were excellent leading to new dibromo-[2,3′]-bipyridines **III** with good yields. In turn, we applied a second I–Br exchange reaction based on the same method as mentioned above starting with these dibromobipyridines **III** to obtain 5-bromo-6′-iodobipyridines **IV**. Yields of this exchange remained excellent. These latter were then engaged in a Suzuki–Miyaura cross-coupling reaction to couple with bromopyridylboronic acids leading to very new dibromoterpyridines **V** with good yields.

All these results and details about the experimental conditions are summarized in Tables 1–4.

3. Conclusion

All these results illustrate the efficiency of our regioselective cross-coupling methodology, which allowed an easy access to new unknown bi- and terpyridines and, which could be applied to produce numerous oligopyridines in view of their valorization in various fields of chemistry.

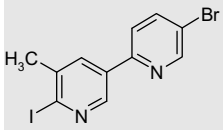
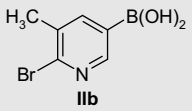
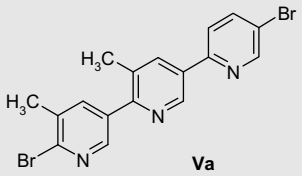
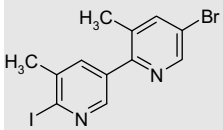
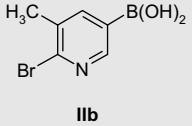
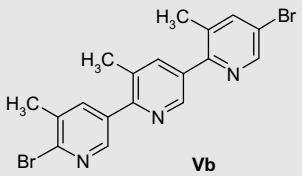
4. Experimental section

4.1. General procedure

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler heating bench. IR spectra were recorded on a Perkin–Elmer BX FTIR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard and coupling constants in hertz. Mass spectra were recorded on a JEOL JMS GCMate spectrometer at ionizing potential of 70 eV (EI) and with pfk as internal standard for high-resolution procedure, or were performed using a spectrometer LC–MS Waters alliance 2695 (ESI+). Chromatography was carried out on a column using flash silica gel 60 Merck (0.063–0.200 mm) as the stationary phase. Thin layer chromatography (TLC) was performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck) and spots were visualized using an ultraviolet-light lamp. Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

Starting materials were purchased from Aldrich, Acros Organics, and Alfa Aesar and used without purification.

Table 4
Synthesis of dibromoterpyridines **Va–b**

Substrates	Boronic acid	Products	Yields (%)
 **IVb**	 **IIb**	 **Va**	66
 **IVc**	 **IIb**	 **Vb**	75

Reagents and conditions: 2-bromo-3-methyl-5-pyridylboronic acid **IIb** 1.25 equiv, bromoiodobipyridines **IVb–c** 1 equiv, Na_2CO_3aq 2.5 equiv, $Pd(PPh_3)_4$ 0.05 equiv, 1,4-dioxane, reflux, 18 h.

4.2. General procedure for the synthesis of 2-bromo-3-methyl-5-pyridyl boronic acid IIb

To a stirred solution of 2,5-dibromo-3-methylpyridine (20 g, 79.7 mmol) under nitrogen in dried tetrahydrofuran, cooled to −78 °C, was added *n*-BuLi (2.5 M) (39.8 mL, 99.6 mmol, 1.25 equiv). After 50 min of stirring at this temperature was added triisopropylborate (23 mL, 99.2 mmol, 1.25 equiv). The resulting mixture was allowed to react at this temperature for 50 min and then warmed to room temperature over a course of 1 h. The mixture was quenched by slow addition of 4% aqueous NaOH solution (200 mL). The resulting aqueous layer was collected and acidified down to pH=3–4 by dropwise addition of 3 N HCl. Product was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated to obtain **IIb** (11 g, 64%) as a pale yellow solid after washing with ether. Mp 204 °C; IR (KBr): 3362, 1568, 1417, 1316, 1265, 1167, 1128, 1055, 830, 761, 691. ^{1}H NMR (DMSO): δ 8.44 (s, 1H), 8.41 (s, 2H), 7.99 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (DMSO): δ 152.7, 146.1, 144.8, 133.5, C-5 not observed, 21.3. HRMS (EI) *m*/*z* calcd: 215.7680, found: 215.8510. Anal. Calcd for $C_6H_7N0_2BBr$: C, 33.39; H, 3.27; N, 6.49. Found: C, 33.28; H, 3.32; N, 6.36.

4.3. General procedure for the halogen–halogen exchange

A mixture of 2,5-dibromopyridines, sodium iodide (4 equiv), and acetyl chloride (2 equiv) in acetonitrile was refluxed for 24 h. It was carefully quenched with water and treated with saturated aqueous solution of $NaHCO_3$ until pH=8. Product was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. The residue was subjected to above reaction condition again and worked up as above. Organic extract was washed with saturated aqueous solution of $NaHSO_3$, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate: 9:1) to afford halo-bipyridines.

4.3.1. 5-Bromo-6′-iodo-3-methyl-[2,3′]bipyridine ***IVa***

Beige solid, mp 134 °C. IR (KBr): 3048, 1575, 1438, 1417, 1377, 1352, 1104, 1077, 1005, 859, 761, 669, 555. ^{1}H NMR ($CDCl_3$): δ 8.60 (d, *J*=2.92, 1H), 8.53 (d, *J*=1.96, 1H), 8.07 (d, *J*=2.92, 1H), 7.83 (d, *J*=8.80, 1H), 7.78 (d, *J*=1.96, 1H), 7.52 (dd, *J*=2.92, 8.80), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 152.8, 150.7, 148.6, 141.1, 138.0, 134.7, 134.5, 132.9, 120.0, 117.6, 19.8. HRMS (EI) *m*/*z* calcd: 373.8915, found: 373.8914. Anal. Calcd for $C_{11}H_8N_2BrI$: C, 35.23; H, 2.15; N, 7.47. Found: C, 35.29; H, 1.87; N, 7.33.

4.3.2. 5-Bromo-6′-iodo-5′-methyl-[2,3′]bipyridine ***IVb***

White solid, mp 185 °C. IR (KBr): 1567, 1450, 1386, 1352, 1236, 1095, 1039, 1000, 831, 669, 573. ^{1}H NMR ($CDCl_3$): δ 8.75 (d, *J*=2.92, 1H), 8.69 (d, *J*=2.92, 1H), 8.07 (d, *J*=2.92, 1H), 7.91 (dd, *J*=2.92, 8.80, 1H), 7.64 (d, *J*=8.80, 1H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 152.2, 151.2, 145.6, 139.6, 139.4, 134.7, 133.3, 126.1, 121.5, 120.4, 26.2. HRMS (EI) *m*/*z* calcd: 373.89154, found: 373.89219. Anal. Calcd for $C_{11}H_8N_2BrI$: C, 35.23; H, 2.15; N, 7.47. Found: C, 35.11; H, 1.89; N, 6.97.

4.3.3. 5-Bromo-6′-iodo-3,5′-dimethyl-[2,3′]bipyridine ***IVc***

Pale yellow solid, mp 128 °C. IR (KBr): 2959, 1582, 1442, 1378, 1110, 1067, 1041, 891, 761, 658, 561. ^{1}H NMR ($CDCl_3$): δ 8.58 (d, *J*=1.96, 1H), 8.31 (d, *J*=1.96, 1H), 7.77 (d, *J*=1.96, 1H), 7.62 (d, *J*=1.96, 1H), 2.46 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 152.9, 148.5, 147.4, 141.1, 139.1, 137.1, 134.7, 133.0, 125.0, 119.9, 26.2, 19.8. HRMS (EI) *m*/*z* calcd: 387.90719, found: 387.9079. Anal. Calcd for $C_{12}H_{10}N_2BrI$: C, 37.05; H, 2.59; N, 7.20. Found: C, 37.39; H, 2.30; N, 7.36.

4.4. General procedure for cross-coupling reactions

A mixture of bromopyridinylboronic acid (1.2 equiv), dihalopyridines (1 equiv), tetrakis(triphenylphosphine) palladium(0) (5 mol%), and aqueous Na_2CO_3 (2.5 equiv) in 1,4-dioxane was heated at 80 °C for 1 h then under reflux until the complete consumption of aryl halide (TLC). The reaction mixture was concentrated and extracted with ethyl acetate. Organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate: 9:1) to afford dihalo-oligopyridines.

4.4.1. 5-Bromo-[2,3′]bipyridine ***IIIa***

White solid, mp 70 °C. Same experimental data described in the literature.

4.4.2. 5,6′-Dibromo-[2,3′]bipyridine ***IIIb***

Yellow solid, mp 194 °C. IR (KBr): 3010, 1575, 1461, 1376, 1090, 1005, 823, 698, 620. ^{1}H NMR ($CDCl_3$): δ 8.92 (d, *J*=1.96, 1H), 8.76 (d, *J*=1.96, 1H), 8.18 (dd, *J*=1.96, 8.80, 1H), 7.92 (dd, *J*=1.96, 8.80, 1H), 7.64 (d, *J*=8.80, 1H), 7.69 (d, *J*=8.80, 1H). ^{13}C NMR ($CDCl_3$): δ 152.1, 151.3, 148.3, 143.0, 139.6, 136.6, 133.1, 128.2, 121.3, 120.5. HRMS (EI) *m*/*z* calcd: 311.88969, found: 311.88916. Anal. Calcd for $C_{10}H_6N_2Br_2$: C, 38.25; H, 1.93; N, 8.92. Found: C, 38.73; H, 1.41; N, 8.49.

4.4.3. 5,6′-Dibromo-3-methyl-[2,3′]bipyridine ***IIIc***

Yellow solid, mp 150 °C. IR (KBr): 3056, 1578, 1557, 1418, 1354, 1107, 1093, 1008, 862, 762, 671, 555. ^{1}H NMR ($CDCl_3$): δ 8.60 (d, *J*=1.96, 1H), 8.54 (d, *J*=1.96, 1H), 7.79 (d, *J*=1.96, 1H), 7.74 (dd, *J*=1.96, 8.80, 1H), 7.59 (d, *J*=8.80, 1H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 152.6, 150.0, 148.5, 141.9, 141.1, 138.9, 134.4, 133.0, 127.7, 120.0, 19.8. HRMS (EI) *m*/*z* calcd: 325.90534, found: 325.90623. Anal. Calcd for $C_{11}H_8N_2Br_2$: C, 40.28; H, 2.46; N, 8.54. Found: C, 40.58; H, 2.33; N, 7.62.

4.4.4. 5,6′-Dibromo-5′-methyl-[2,3′]bipyridine ***IIId***

Yellow solid, mp 169 °C. IR (KBr): 3057, 2949, 1566, 1450, 1393, 1353, 1096, 1049, 1002, 916, 836, 677, 507. ^{1}H NMR ($CDCl_3$): δ 8.76 (d, *J*=2.92, 1H), 8.72 (d, *J*=2.92, 1H), 8.16 (d, *J*=1.96, 1H), 7.92 (dd, *J*=2.92, 8.8, 1H), 7.64 (d, *J*=8.80, 1H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 152.1, 151.2, 145.5, 145.2, 139.6, 136.8, 135.3, 133.2, 121.8, 120.4, 22.0. HRMS (EI) *m*/*z* calcd: 325.90534, found: 325.90487. Anal. Calcd for $C_{11}H_8N_2Br_2$: C, 40.28; H, 2.46; N, 8.54. Found: C, 40.31; H, 2.13; N, 7.61.

4.4.5. 5,6′-Dibromo-3,5′-dimethyl-[2,3′]bipyridine ***IIIe***

Pale yellow solid, mp 130 °C. IR (KBr): 2953, 1588, 1447, 1393, 1378, 1114, 1071, 1053, 887, 760, 663, 562. ^{1}H NMR ($CDCl_3$): δ 8.60 (d, *J*=1.96, 1H), 8.35 (d, *J*=2.92, 1H), 7.78 (d, *J*=1.96, 1H), 7.72 (d, *J*=1.92, 1H), 2.46 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 152.8, 148.5, 147.0, 144.5, 141.1, 139.2, 135.0, 134.5, 133.0, 119.9, 22.0, 19.8. HRMS (EI) *m*/*z* calcd: 339.92099, found: 339.92068. Anal. Calcd for $C_{12}H_{10}N_2Br_2$: C, 42.14; H, 2.95; N, 8.19. Found: C, 42.34; H, 2.41; N, 8.03.

4.4.6. 5,6″-Dibromo-5′,5″-dimethyl-[2,3′,6′,3″]terpyridine ***Va***

Pale yellow solid, mp 204 °C. IR (KBr): 2920, 1573, 1450, 1382, 1096, 1049, 1002, 912, 829, 771, 692, 522. ^{1}H NMR ($CDCl_3$): δ 9.06 (d, *J*=1.96, 1H), 8.79 (d, *J*=1.96, 1H), 8.42 (d, *J*=1.96, 1H), 8.26 (d, *J*=1.96, 1H), 7.94 (dd, *J*=1.96, 8.8, 1H), 7.80 (d, *J*=1.96, 1H), 7.71 (d, *J*=8.80, 1H), 2.48 (s, 3H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 154.7, 152.6, 151.2, 147.2, 145.5, 144.4, 139.6, 139.3, 137.0, 135.1, 135.0, 132.9, 131.4, 121.6, 120.3, 22.0, 20.0. HRMS (EI) *m*/*z* calcd: 430.96319, found: 430.96112. Anal. Calcd for $C_{17}H_{13}N_3Br_2$: C, 48.72; H, 3.13; N, 10.03. Found: C, 48.31; H, 2.84; N, 9.31.

4.4.7. 5,6″-Dibromo-3,5′,5″-trimethyl-[2,3′,6′,3″]terpyridine ***Vb***

Pale yellow solid, mp 141 °C. IR (KBr): 2953, 1585, 1456, 1398, 1385, 1113, 1079, 1047, 887, 773, 653, 528. ^{1}H NMR ($CDCl_3$): δ 8.69 (d, *J*=1.96, 1H), 8.62 (d, *J*=1.96, 1H), 8.42 (d, *J*=1.96, 1H), 7.79–7.81 (m, 3H), 2.48 (s, 3H), 2.46 (s, 3H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 153.9, 153.5, 148.5, 147.3, 147.2, 144.3, 141.0, 139.4, 139.3, 135.2, 134.9,

134.5, 133.1, 131.0, 119.8, 22.0, 20.0, 19.9. HRMS (EI) *m*/*z* calcd: 430.96319, found: 430.96112. Anal. Calcd for $C_{18}H_{15}N_3Br_2$: C, 49.91; H, 3.49; N, 9.70. Found: C, 49.69; H, 3.46; N, 9.49.

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