Palladium-Catalyzed Synthesis of Nonsymmetrically Functionalized Bipyridines, Poly(bipyridines) and Terpyridines

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Palladium-catalyzed coupling reactions were employed to prepare nonsymmetric, densely functionalized bipyridines and oligo(bipyridines), featuring sensitive functionalities like alcohol, ester and aldehyde groups. Stille coupling between halo(poly)pyridine and the proper (poly)pyridyltin derivative afforded in good yields nonsymmetric, derivatized oligo(bipyridines), amenable to further synthetic modifications. The methodology was used also to synthesize highly functionalized terpyridines. A series of Suzuki and Stille palladium-promoted coupling reactions allowed us to obtain in good yields terpyridines bearing two different and differently functionalizable groups, valuable building blocks for the construction of complex supramolecular frameworks.

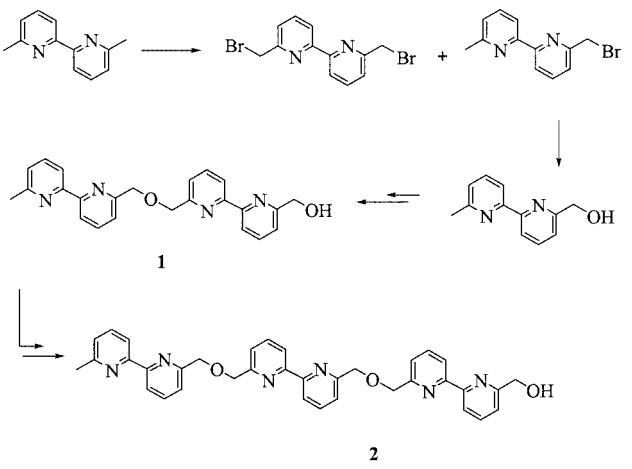
Introduction

Nitrogen heterocycles are commonly employed in the construction of supramolecular frameworks endowed with novel photo-, electrochemical or catalytic properties.[1] In this field oligo(bipyridines) and terpyridines have found widespread use as building blocks in the assembling of new supramolecular structures[2] that have been employed in polymer and dendrimer chemistry,[3] and as chiral ligands in asymmetric catalysis.[4]

In this context it became more and more important to develop efficient, high-yield synthetic strategies toward these ligands. Several methods for the preparation of symmetrically substituted 2,2′-bipyridines are available,[5] the most used being the Kronhke procedure[6] and the nickel-promoted coupling of halopyridines.[7] On the contrary, the synthesis of nonsymmetric oligopyridines and terpyridines is much less straightforward, and until a few years ago only a few examples were known.[8] The advent of palladium-promoted Suzuki[9] and Stille[10] couplings has offered new opportunities to build biaryl systems and recently examples of Stille,[11] Suzuki,.[12]and Negishi[13] cross-coupling reactions between halopyridines or pyridyl triflates and pyridyl-based organometallic reagents have been reported. However, these procedures were generally limited to the preparation of methyl- or alkyl-substituted bipyridines. To take full advantage of these modern methodologies, we investigated the use of tin derivatives and boronic acids for the synthesis of nonsymmetrically substituted, highly functionalized bipyridines, poly(bipyridines), and terpyridines. Here we wish to report the results of this study.

Results

To validate the possibility of exploiting palladium chemistry as a tool for the construction of poly(bipyridine) frameworks, we decided at first to improve the synthesis of the nonsymmetric, poly(bipyridine) alcohols **1** and **2** (Scheme 1).[14]



Scheme 1. Synthesis of poly(bipyridines) **1** and **2**

These molecules have been prepared by reaction of 6,6′-dimethyl-2,2′-bipyridine[7] with *N*-bromosuccinimide to give both the di- (37% yield) and the monobromo (35% yield) derivative. The monobromo derivative was hy-

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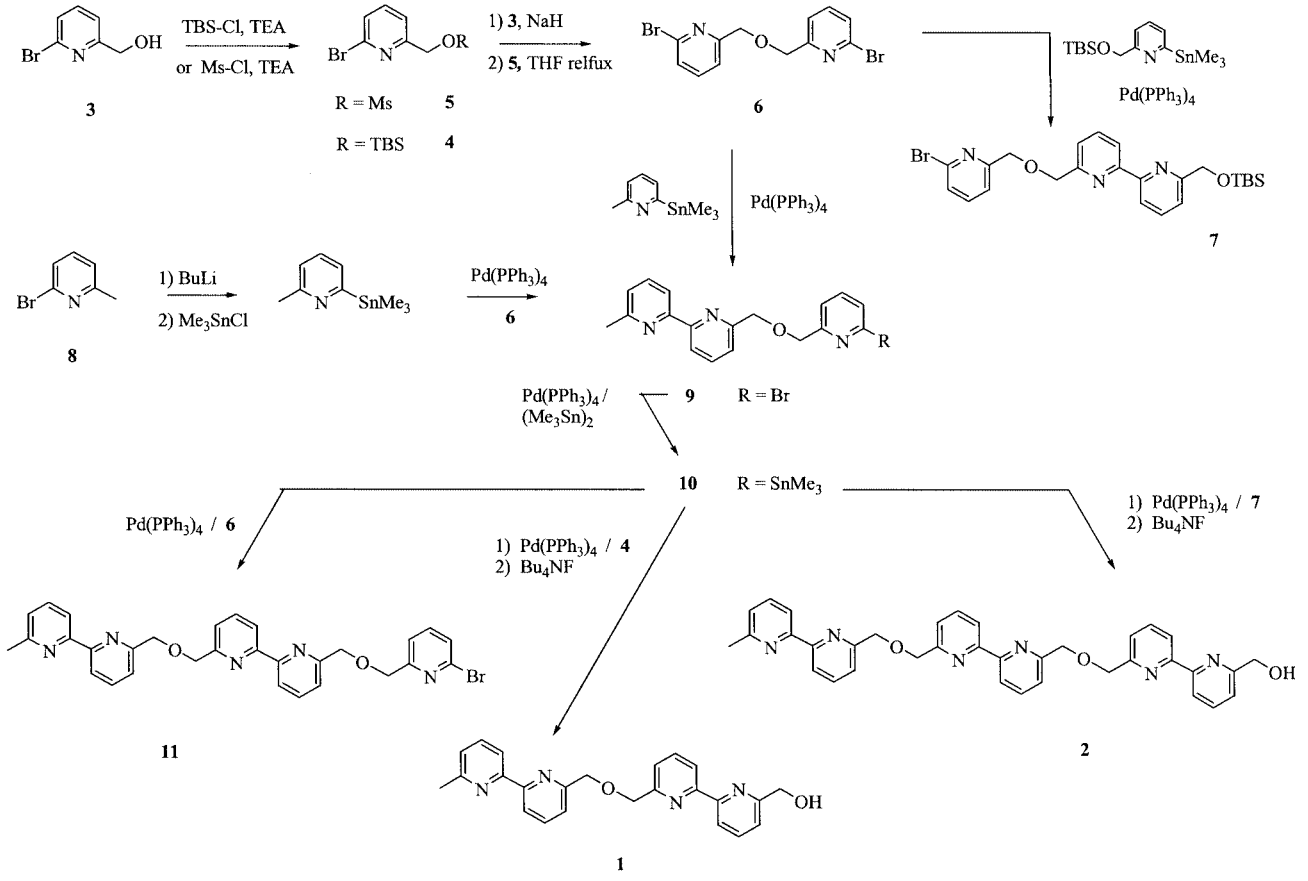
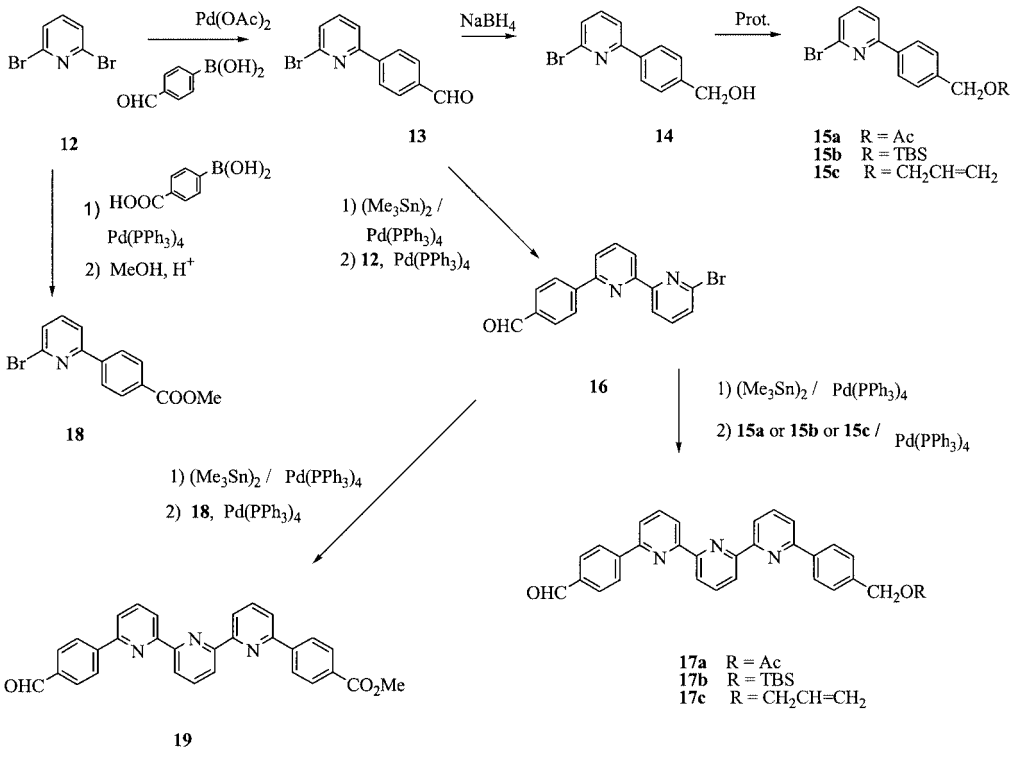
drolyzed to 6-(hydroxymethyl)-6′-methyl-2,2′-bipyridine and its sodium salt reacted with 6,6′-bis(bromomethyl)-2,2′-bipyridine to give, after K_2CO_3-promoted hydrolysis, the bis(bipyridine) alcohol **1** in 19.6% overall yield (Scheme 1). An iterative procedure allowed to prepare the tris(bipyridine) alcohol **2** in 7.5% overall yield starting from the commercially available 2-bromopicoline.[15]

A more efficient synthesis has now been performed (Scheme 2). Thus, the commercially available 2,6-dibromopyridine was transformed by lithiation with *n*-butyllithium, treatment with *N*,*N*-dimethylformamide (DMF), and in situ reduction with $NaBH_4$, into 2-bromo-6-(hydroxymethyl)pyridine (**3**), isolated in 98%yield by a single purification through a short plug of silica gel. Alcohol **3** was either protected as *tert*-butyldimethylsilyl ether **4** (96% yield), or converted into its mesylate **5** (95% yield). Reaction of the latter with the sodium alkoxide of **3** gave **6** in 93% yield after flash chromatographic purification (Scheme 2). Lithiation of the former followed by treatment with Me_3SnCl afforded the corresponding trimethylstannyl derivative that was coupled with **6** in THF (tetrahydrofuran) in the presence of 10% of $Pd(PPh_3)_4$; the expected product **7** was isolated after chromatographic purification in 65% yield. Similarly, the cross coupling reaction of **6** with 6-methyl-2-(trimethylstannyl)pyridine, obtained in 95% yield by lithiation of 2-bromopicoline (**8**) and treatment with Me_3SnCl, afforded adduct **9** in 66% yield. This was further converted into the corresponding trimethylstannyl derivative **10** in 87% yield by the $Pd(PPh_3)_4$-catalyzed reaction with Me_6Sn_2 in DMF for 12 h.[16]

Compound **10** was used as the starting material for the synthesis of an array of different structures. Coupling of **10** with pyridine **4** afforded, after desilylation with Bu_4NF, the bis(bipyridine) **1** in 57% yield over the two steps.[17] The overall yield for **1** was 30.6% which favorably compares with the 19.6% yield reported for the previous synthesis of this compound (Scheme 2). Similarly, the Pd^0-promoted reaction of **10** with bipyridine **7** followed by desilylation afforded the tris(bipyridine) alcohol **2** in 47% yield (two steps). In this case the overall yield of **2** starting form the commercially available 2,6-dibromopyridine was 26%, much higher than that of the previously reported preparation for this compound (7.5% yield).[14] Noteworthy, the tin derivative **10** was cross-coupled to **6** to afford in 50% yield the bis(bipyridine) adduct **11**, that presents a bromopyridine functionality amenable to iteration of the coupling procedure to yield functionalized tetrakis(bipyridines). Moreover, this strategy allows to circumvent the solubility problems associated to the handling of these poly(bipyiridine) moieties, that are poorly soluble in most organic and even chlorinated solvents, thus making really troublesome the purification, isolation, and further manipulation of these compounds. On the contrary, in the present strategy the poly(bipyridine) chain is built only in the very last step of the



Scheme 2. Synthesis of nonsymmetric, functionalized poly(bipyridines)



Scheme 3. Synthesis of nonsymmetric, functionalized terpyridines

synthesis, assembling two species readily soluble in many organic solvents.

To widen the scope of this chemistry, the synthesis of bipyridines and terpyridines bearing different and more versatile functional groups was then attempted. We were pleased to find that the use of Stille coupling allowed the preparation of nonsymmetrically substituted terpyridines containing alcohol, ester or aldehyde groups which are very difficult to prepare by other methods[18] (Scheme 3) and open access to a variety of derivatives.

Thus, the Suzuki reaction between 4-formyl-substituted phenylboronic acid and 2,6-dibromopyridine (**12**) (both commercially available) promoted by $Pd(OAc)_2$ and Ph_3P in toluene afforded the monocoupling product **13** in 55% yield after chromatographic purification. This intermediate was reduced to alcohol **14** (85% yield) by treatment with $NaBH_4$ and then protected either as acetate (**15a**), silyl (**15b**) or allyl (**15c**) ether, in 91, 88, and 80% yield, respectively.

Aldehyde **13** was also successfully transformed in the corresponding trimethylstannyl derivative by Pd^0-catalyzed reaction with Me_6Sn_2[16] and coupled a second time to **12** to give the bipyridine **16** in 63% yield, which was finally first converted into the tin derivative and then coupled to the *O*-protected (hydroxymethyl)pyridines **15a**−**c** to afford the corresponding, asymmetrically substituted terpyridines **17a**, **17b**, **17c** in 71, 65, and 57% yield, respectively (Scheme 3).

It is worth mentioning that it was also possible to couple the tin derivative of **16** with 2-bromo-6-(4-methoxycarbonylphenyl)pyridine (**18**)[19] to give in 48% yield terpyridine **19**, bearing two different and differently functionalizable groups, an ester and an aldehyde.

Conclusions

We have demonstrated that Stille cross coupling represents an efficient method to prepare asymmetrically functionalized bipyridines, poly(bipyridines), and terpyridines, that are valuable building blocks for the construction of complex supramolecular frameworks. The mild reaction conditions allow to synthesize densely functionalized molecules featuring sensitive functionalities like alcohol, aldehyde, and ester groups, amenable to further synthetic modifications. The methodology represents a useful tool for the synthesis of functionalized supramolecular structures and is currently exploited in our group for building enantiomerically pure double helicates, innovative β-turn mimics, and topologically relevant molecules.

Experimental Section

General: ^1H NMR spectra were recorded at 300 MHz in $CDCl_3$ unless otherwise stated, and were referenced to TMS (δ = 0.00 ppm). ^{13}C NMR spectra were recorded at 75 MHz and were referenced to $CDCl_3$ (δ = 77.0 ppm). IR spectra were recorded on thin films or as solutions in CH_2Cl_2. Compounds **1**,[20] **2**,[14b] **3**,[21] **4**[21] are known compounds; compound **8** is commercially available.

Synthesis of Compound 5: To a stirred solution of alcohol **3** (900 mg., 4.8 mmol) in dry THF under argon, at 0 °C, triethyl-

amine (0.87 mL, 6.23 mmol) and methanesulfonyl chloride (0.445 mL, 5.75 mmol) were added dropwise. The reaction mixture was stirred at room temperature for 12 h; then it was quenched with an NH_4Cl sat. sol., the organic phase was separated, the aqueous phase extracted twice with diethyl ether and the combined organic phases were dried with magnesium sulfate and concentrated under vacuum to give a very viscous oil. The crude product was used without further purification (1.21 g, yield 95%). ^{1}H NMR: δ = 3.12 (s, 3 H, *Me*), 5.28 (s, 2 H, CH_2OMs), 7.43 (d, $^3J_{H,H}$ = 12 Hz, 1 H), 7.48 (d, $^3J_{H,H}$ = 12. Hz, 1 H), 7.62 (t, $^3J_{H,H}$ = 12 Hz, 1 H) ppm. ^{13}C NMR: δ = 38.05, 72.5, 118.9, 120.9, 137.4, 158.2, 160.5 ppm. $C_7H_8BrNO_3S$ (266): calcd. C 31.59, H 3.03, Br 30.03, N 5.26, O 18.04, S 12.05; found C 31.61, H 3.07, Br 30.08, N 5.29, O 18.01, S 12.03.

Synthesis of Compound 6: A stirred 0.1 M solution of alcohol **3** (530 mg, 2.82 mmol) in dry tetrahydrofuran under argon was added to a suspension of NaH (50% dispersion in mineral oil, 162 mg, 3.38 mmol) in dry tetrahydrofuran. The reaction mixture was stirred at room temperature for 1 h. Mesylate **5** (750 mg, 2.82 mmol) was then added and the reaction mixture was refluxed overnight. The reaction mixture was then cooled, and residual sodium hydride quenched by addition of a small amount of methanol. The solvent was removed under vacuum. The crude product was purified by flash chromatography [dichloromethane/ethyl acetate (95:5) as eluent] to give the product (0.98 g, 93% yield). M.p. 153−155 °C. ^{1}H NMR: δ = 4.75 (s, 4 H, CH_2O), 7.41 (t, $^3J_{H,H}$ = 9 Hz, 1 H), 7.49 (d, $^3J_{H,H}$ = 12 Hz, 1 H), 7.59 (d, $^3J_{H,H}$ = 12 Hz, 1 H) ppm. ^{13}C NMR: δ = 74.5, 118.6, 120.3, 137.1, 158.0, 160.1 ppm. $C_{12}H_{10}Br_2N_2O$ (358): calcd. C 38.29, H 2.63, Br 46.32, N 8.12, O 4.64; found C 38.28, H 2.59, Br 46.38, N 8.15, O 4.60.

Synthesis of Compound 7

Synthesis of 2-[(*tert*-Butyldimethylsilyl)oxymethyl]-6-(trimethylstannyl)pyridine: To a dry Et_2O solution of silyl derivative **4** (1.32 mmol, 0.4 g) at −78 °C under argon, a 1.5 M solution *n*-butyllithium in hexanes (1.36 mmol, 0.9 mL) was added dropwise within 30 min; the reaction mixture was stirred at −78 °C for 1 h, then a 1 M solution of Me_3SnCl in dry THF was added dropwise (1.4 mmol, 1.4 mL) and the reaction mixture was allowed to warm up to room temperature and was stirred overnight. The solvent was evaporated and the crude reaction mixture was rinsed with diethyl ether; the solid (LiCl) was filtered and the solvent removed under vacuum to give a pale yellow oil that was used in the next step without further purification (501 mg, yield > 98%). ^{1}H NMR: δ = 0.15 (s, 6 H, CH_3Si), 0.30 (s, 9 H, CH_3Sn), 0.95 (s, 9 H, Si*t*Bu), 4.85 (s, 2 H, CH_2O), 7.25−7.45 (m, 2 H), 7.50 (t, $^3J_{H,H}$ = 9 Hz, 1 H) ppm.

Synthesis of Compound 7 (Cross Coupling Procedure): To a degassed dry THF solution of 2-[(*tert*-butyldimethylsilyl)oxymethyl]-6-(trimethylstannyl)pyridine (250 mg, 0.65 mmol) and ether **6** (370 mg, 1 mmol), $Pd(PPh_3)_4$ (53 mg, 0.045 mmol) was added and the reaction mixture was heated to reflux for 15 h. The solvent was removed under vacuum and the product **7** was purified by flash chromatography on silica gel [dichloromethane/ethyl acetate (90:10) as eluent] to give a white solid (218 mg, 0.42 mmol, 65% yield). M.p. 135−138 °C ^{1}H NMR: δ = 0.11 (s, 6 H, CH_3Si), 0.95 (s, 9 H, Si*t*Bu), 4.75 (s, 2 H, OCH_2Py), 4.81 (s, 2 H, OCH_2BiPy), 4.90 (s, 2 H, CH_2OTBS), 7.39 (d, $^3J_{H,H}$ = 10 Hz, 1 H), 7.50−7.60 (m, 4 H), 7.80 (t, $^3J_{H,H}$ = 10 Hz, 2 H), 8.18 (d, $^3J_{H,H}$ = 10 Hz, 1 H), 8.22 (d, $^3J_{H,H}$ = 10 Hz, 1 H) ppm. ^{13}C NMR: δ = −0.1, 25.3, 73.3, 74.3, 78.5, 119.6, 120.2, 120.4, 120.6, 126.3, 126.7, 136.5, 137.3, 138.6, 153.3, 154.5, 154.7, 155.5, 157.8, 158.7 ppm. $C_{24}H_{30}BrN_3O_2Si$ (500): calcd. C 57.59, H 6.04, Br 15.96, N 8.40, O 6.39, Si 5.61; found C 57.54, H 6.06, Br 15.98, N 8.43, O 6.40, Si 5.63.

Synthesis of Compound 9

Synthesis of 6-Methyl-2-(trimethylstannyl)pyridine: To a dry Et_2O solution of 2-bromo-6-methylpyridine (1.6 mmol, 0.275 g) at −78 °C under argon, a 1.6 M solution of *n*-butyllithium in hexanes (1.6 mmol, 1 mL) was added dropwise within 30 min; the reaction mixture was stirred at −78 °C for 1 h, then a 1 M solution of Me_3SnCl in dry THF was added dropwise (1.7 mmol, 1.7 mL), and the reaction mixture was allowed to warm up to room temperature and was stirred overnight. The solvent was evaporated and the crude reaction mixture was rinsed with diethyl ether; the solid (LiCl) was filtered and the solvent removed under vacuum to give a pale yellow oil that was used in the next step without further purification (401 mg, yield > 98%). ^{1}H NMR: δ = 0.30 (s, 9 H, CH_3Sn), 2.55 (s, 3 H, Me), 6.80−7.45 (m, 3 H) ppm.

Synthesis of Compound 9 (Cross Coupling Procedure): To a degassed dry THF solution of 6-methyl-2-(trimethylstannyl)pyridine (160 mg, 0.5 mmol) and ether **6** (271 mg, 0.7 mmol), $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) was added and the reaction mixture was heated to reflux for 15 h. The solvent was removed under vacuum and the product **9** was purified by flash chromatography on silica gel [dichloromethane/ethyl acetate (90:10) as eluent] to give a white solid (122 mg, 66% yield). M.p. 164−166 °C ^{1}H NMR: δ = 2.60 (s, 3 H, *Me*), 4.80 (s, 2 H, OCH_2Py), 4.90 (s, 2 H, OCH_2BiPy), 7.19 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.39 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.55 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.50−7.60 (m, 2 H), 7.60 (t, $^3J_{H,H}$ = 8 Hz, 1 H), 7.80 (t, $^3J_{H,H}$ = 7 Hz, 2 H), 8.18 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 8.30 (d, $^3J_{H,H}$ = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 24.3, 74.4, 74.7, 119.6, 120.8, 121.4, 121.6, 122.3, 122.7, 136.8, 137.3, 138.2, 152.3, 153.5, 154.1, 154.5, 157.2, 158.8 ppm. $C_{18}H_{16}BrN_3O$ (370): calcd. C 58.39, H 4.36, Br 21.58, N 11.35, O 4.32; found C 58.34, H 4.36, Br 21.56, N 11.33, O 4.30.

Synthesis of Trimethylstannyl Derivative 10: To a degassed, dry DMF solution of compound **9** (185 mg, 0.5 mmol), hexamethyldistannane (327 mg, 1 mmol) was added dropwise. $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) was added and the reaction mixture was heated at 120 °C for 15 h. The solvent was evaporated under vacuum and the crude reaction mixture purified by chromatography through a very short column on neutral alumina [dichloromethane/hexanes (70:30) as eluent] to give the product as a very viscous oil (197 mg, 87% yield). ^{1}H NMR: δ = 0.30 (s, 9 H, CH_3Sn), 2.62 (s, 3 H, *Me*), 4.80 (s, 2 H, OCH_2Py), 4.82 (s, 2 H, OCH_2BiPy), 7.10 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.30 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.35 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.50 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.51 (t, $^3J_{H,H}$ = 8 Hz, 1 H), 7.60 (t, $^3J_{H,H}$ = 8 Hz, 1 H), 7.82 (t, $^3J_{H,H}$ = 8 Hz, 2 H), 8.15 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 8.30 (d, $^3J_{H,H}$ = 8 Hz, 1 H) ppm.

Synthesis of Compound 11: To a degassed dry DMF solution of trimethylstannyl derivative **10** (197 mg, 0.435 mmol) and ether **6** (236 mg, 0.6 mmol), $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) was added and the reaction mixture was heated at 120 °C for 15 h. The solvent was removed under vacuum and the product **11** was purified by flash chromatography on silica gel [dichloromethane/ethyl acetate (30:70) as eluent] to give a white solid (122 mg, 50% yield). M.p. 184−186 °C (dec). ^{1}H NMR: δ = 2.60 (s, 3 H, *Me*), 4.80 (s, 2 H, OCH_2Py), 4.83 (s, 2 H, OCH_2BiPyMe), 4.90 (s, 4 H, OCH_2BiPy), 7.18 (d, $^3J_{H,H}$ = 9 Hz, 1 H), 7.38 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.40−7.55 (m, 5 H), 7.60 (t, $^3J_{H,H}$ = 8 Hz, 2 H), 7.80 (m, 3 H), 8.20 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 8.30 (m, 2 H) ppm. ^{13}C NMR: δ = 23.7, 73.8, 74.1, 74.3, 74.7, 118.6, 119.1, 119.3, 119.7, 120.3, 120.8, 121.2, 121.6, 122.6, 122.9, 136.8, 137.3, 137.5, 137.8, 138.2, 152.3, 152.8,

153.5, 154.1, 154.5, 154.9, 157.2, 158.3, 158.9, 159.6 ppm. $C_{30}H_{26}BrN_5O_2$ (568): calcd. C 63.38, H 4.61, Br 14.06, N 12.32, O 5.63; found C 63.41, H 4.58, Br 14.11, N 12.31, O 5.59.

Synthesis of Compound 1: To a degassed dry DMF solution of trimethylstannyl derivative **10** (150 mg, 0.33 mmol) and silyl derivative **4** (100 mg, 0.33 mmol), $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) was added and the reaction mixture was heated at 120 °C for 15 h. The solvent was removed under vacuum, the crude reaction mixture was dissolved in THF, Bu_4NF (140 mg, 0.5 mmol) was added and the solution was stirred at room temperature for 30 min; then the solvent was evaporated under reduced pressure and the product **1** was purified by flash chromatography on silica gel [chloroform/methanol (95:5) as eluent] to give a white solid (75 mg, 57% yield). The product shows spectral characteristics identical to those reported in the literature.[20] M.p. 172−174 °C (ref.[20] 178 °C).

Synthesis of Compound 2: To a degassed dry DMF solution of trimethylstannyl derivative **10** (150 mg, 0.33 mmol) and compound **7** (171 mg, 0.3 mmol), $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) was added and the reaction mixture was heated at 120 °C for 15 h. The solvent was removed under vacuum, the crude reaction mixture was dissolved in THF, Bu_4NF (140 mg, 0.5 mmol) was added and the solution was stirred at room temperature for 30 min; then the solvent was evaporated under reduced pressure and the product **2** was purified by flash chromatography on neutral alumina (Brockman type II) [dichloromethane/methanol (80:20) as eluent] to give a white solid (84 mg, 47% yield). The product shows spectral characteristics identical to those reported in the literature.[14b] M.p. 182−184 °C (ref.[14b] 186 °C).

Synthesis of Aldehyde 13: To a degassed solution of 2,6-dibromopyridine (**12**) (1.5 g, 6.3 mmol) in 100 mL of dry toluene, $Pd(OAc)_2$ (210 mg, 0.95 mmol) and triphenylphosphane (500 mg, 1.9 mmol) were added. After 10 min of stirring at room temperature, a 2 M Na_2CO_3 solution (19 mL, 38 mmol) and the commercially available 4-(formylphenyl)boronic acid (950 mg, 6.3 mmol) were added. The reaction mixture was stirred at 90 °C for 20 h. The solvent was evaporated and the crude reaction mixture purified by flash chromatography on silica gel (dichloromethane as eluent) to give product **13** as a white solid (908 mg, 55% yield). M.p. 111−115 °C. IR: $\tilde{\nu}$ = 1703.8 cm^{-1}. ^1H NMR: δ = 7.49 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.69 (t, $^3J_{H,H}$ = 8 Hz, 1 H), 7.80 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 8.00 (d, $^3J_{H,H}$ = 10 Hz, 2 H), 8.30 (d, $^3J_{H,H}$ = 10 Hz, 2 H), 10.05 (s, CHO, 1 H) ppm. ^{13}C NMR: δ = 119.9, 127.5, 128.2, 130.3, 137.5, 139.3, 142.0, 142.8, 157.1, 191.9 ppm. $C_{12}H_8BrNO$ (262): calcd. C 55.02, H 3.08, Br 30.49, N 5.34, O 6.13; found C 55.02, H 3.04, Br 30.51, N 5.30, O 6.13.

Synthesis of Alcohol 14: A solution of aldehyde **13** (300 mg, 1.14 mmol) in 12 mL of ethanol was cooled to 0 °C; $NaBH_4$ (17.3 mg, 0.45 mmol) was added and the reaction mixture was stirred for 10 min. A few drops of water were added, the ethanol was evaporated, dichloromethane was added and the organic phase was separated; the aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phases were dried with magnesium sulfate and concentrated under vacuum. The product was purified by flash chromatography on silica gel [dichloromethane/ethyl acetate (60:40) as eluent] to give a white solid (295 mg, 98% yield). M.p. 128−131 °C. ^1H NMR: δ = 4.80 (s, 2 H, CH_2OH), 7.40 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.45 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.60 (t, $^3J_{H,H}$ = 7 Hz, 1 H), 7.60 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 8.00 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H) ppm. ^{13}C NMR: δ = 64.5, 118.9, 126.3, 127.2, 127.3, 130.5, 139.1, 142.2, 142.7, 158.0 ppm. $C_{12}H_8BrNO$ (264): calcd. C 55.02; H 3.08; Br 30.49; N 5.34; O 6.13; found C 55.02; H 3.04; Br 30.51; N 5.30; O 6.13.

Synthesis of *O*-Acetyl Derivative 15a: Alcohol **14** (1.1 g., 4.1 mmol) was dissolved in 4 mL of pyridine and the solution was cooled to 0 °C. Acetic anhydride (7 mL) was added and the reaction mixture was stirred at room temperature for 20 h. Water and dichloromethane were added, the two phases separated, the aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phases were dried with magnesium sulfate and concentrated under vacuum. The product was purified by flash chromatography on silica gel [dichloromethane/ethyl acetate (90:10) as eluent] to give a white solid (1.1 g, 91% yield). M.p. 68−69 °C. IR: $\tilde{\nu}$ = 1738 cm^{-1}. ^1H NMR: δ = 2.15 (s, 3 H, *Ac*), 5.18 (s, 2 H, CH_2OAc), 7.40 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H), 7.45 (d, $^3J_{H,H}$ = 9.5 Hz, 2 H), 7.55 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H), 7.65 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H), 8.00 (d, $^3J_{H,H}$ = 9.5 Hz, 2 H) ppm. ^{13}C NMR: δ = 21.2, 65.9, 119.1, 126.6, 127.3, 128.7, 137.5, 139.1, 142.2, 142.5, 158.1, 170.9 ppm. $C_{14}H_{12}BrNO_2$ (306): calcd. C 54.92, H 3.95, Br 26.10, N 4.58, O 10.45; found C 54.89, H 3.98, Br 26.08, N 4.55, O 10.50.

Synthesis of *O*-Silyl Derivative 15b: Alcohol **14** (1.37 g, 5.2 mmol) was dissolved in 25 mL of DMF and the solution was cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (0.78 g, 5.2 mmol) and triethylamine (0.79 mL, 5.7 mmol) were added and the reaction mixture was stirred at room temperature for 20 h. Water and diethyl ether were added, the two phases separated, the aqueous phase was extracted twice with diethyl ether and the combined organic phases were dried with magnesium sulfate and concentrated under vacuum. The product was purified by flash chromatography on silica gel (dichloromethane as eluent) to give a white solid (1.59 g, 88% yield). M.p. 62−65 °C. ^1H NMR: δ = 0.15 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, *t*BuSi), 4.78 (s, 2 H, CH_2OSi), 7.40 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.45 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 7.55 (t, $^3J_{H,H}$ = 7 Hz, 1 H), 7.62 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.95 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H) ppm. ^{13}C NMR: δ = 0.1, 25.8, 64.6, 118.6, 126.2, 126.4, 126.4, 136.5, 138.6, 142.0, 142.7, 158.5 ppm. $C_{18}H_{24}BrNOSi$ (378): calcd. C 57.14, H 6.39, Br 21.12, N 3.70, O 4.23, Si 7.42; found C 57.10, H 6.37, Br 21.15, N 3.69, O 4.23, Si 7.46.

Synthesis of *O*-Allyl Derivative 15c: A stirred 0.1 M solution of alcohol **14** (258 mg, 0.98 mmol) in dry tetrahydrofuran under argon was added to a suspension of NaH (50% dispersion in mineral oil, 52 mg, 1.08 mmol) in dry tetrahydrofuran (3 mL). The reaction mixture was stirred at 0 °C for 30 min. Allyl bromide (296 mg, 2.42 mmol) was then added and the reaction mixture was stirred at room temperature overnight. The residual sodium hydride was quenched by addition of a small amount of methanol and the solvent was removed under vacuum. The product was purified by flash chromatography on silica gel [dichloromethane/ethyl acetate (98:2) as eluent] to give a white solid (241 mg, 81% yield). M.p. 51−53 °C. ^1H NMR: δ = 4.15 (d, $^3J_{H,H}$ = 5 Hz, 2 H, $OCH_2CH{=}CH_2$), 4.60 (s, 2 H, OCH_2Ar), 5.33 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, $OCH_2CH{=}CH_2$), 5.39 (d, $^3J_{H,H}$ = 15 Hz, 1 H, $OCH_2CH{=}CH_2$), 6.03 (ddt, $^3J_{H,H}$ = 8.5, $^3J_{H,H}$ = 15, $^3J_{H,H}$ = 5 Hz, 1 H, $OCH_2CH{=}CH_2$), 7.33 (d, $^3J_{H,H}$ = 9 Hz, 1 H), 7.46 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H), 7.65 (t, $^3J_{H,H}$ = 9 Hz, 1 H), 7.70 (d, $^3J_{H,H}$ = 9 Hz, 1 H), 8.00 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H) ppm. ^{13}C NMR: δ = 71.3, 71.8, 117.4, 119.0, 126.4, 127.1, 127.8, 134.0, 137.7, 139.1, 140.5, 142.0, 160.0 ppm. $C_{15}H_{14}BrNO$ (304): calcd. C 59.23, H 4.64, Br 26.27, N 4.60, O 5.26; found C 59.26, H 4.65, Br 26.25, N 4.56, O 5.28.

Synthesis of Aldehyde 16: To a solution of aldehyde **13** (116 mg, 0.44 mmol) in 6 mL of dry, degassed dimethoxyethane (DME) hexamethyldistannane (288 mg, 0.88 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.044 mmol) were added and the reaction mixture was refluxed for 18 h. The solvent was evaporated, the crude mixture was rinsed with diethyl ether, filtered and the solvent removed under vacuum

to give the crude trimethylstannyl derivative that was used without further purification. To a solution of the tin derivative in dry, degassed DME (7 mL) 2,6-dibromopyridine (83 mg, 0.35 mmol) and $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) were added. The reaction mixture was stirred at 90 °C for 20 h. The solvent was evaporated and the crude reaction mixture purified by flash chromatography on silica gel [dichloromethane/ethyl acetate (90:10) as eluent] to give product **16** as white solid (75 mg, 63% yield). M.p. 169−173 °C. IR: $\tilde{\nu}$ = 1688.4 cm^{-1}. ^1H NMR: δ = 7.54 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.72 (t, $^3J_{H,H}$ = 8 Hz, 1 H), 7.80 (t, $^3J_{H,H}$ = 7 Hz, 1 H), 7.86 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.93 (d, $^3J_{H,H}$ = 10 Hz, 2 H), 8.27 (d, $^3J_{H,H}$ = 10 Hz, 2 H), 8.40 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 8.60 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 10.15 (s, CHO, 1 H) ppm. ^{13}C NMR: δ = 119.9, 120.8, 121.5, 127.5, 128.2, 130.1, 136.5, 138.0, 139.2, 141.5, 144.7, 154.5, 155.0, 157.1, 193.1 ppm. $C_{17}H_{11}BrN_2O$ (339): calcd. C 60.19, H 3.27, Br 23.56, N 8.26, O 4.72; found C 60.20, H 3.25, Br 23.58, N 8.24, O 4.73.

Synthesis of Compounds 17 (Cross Coupling Procedure): To a solution of aldehyde **16** (240 mg, 0.74 mmol) in 7 mL of dry, degassed DME hexamethyldistannane (460 mg, 2.2 mmol) and $Pd(PPh_3)_4$ (84 mg, 0.074 mmol) were added and the reaction mixture was refluxed for 18 h. The solvent was evaporated, the crude mixture was rinsed with diethyl ether, filtered and the solvent removed under vacuum to give the crude trimethylstannyl derivative that was used without further purification. To a solution of the tin derivative in dry, degassed DME (8 mL) compound **15a** (or **15b** or **15c**) (0.65 mmol) and $Pd(PPh_3)_4$ (63 mg, 0.055 mmol) were added. The reaction mixture was stirred at 90 °C for 20 h. The solvent was evaporated and the crude reaction mixture purified by flash chromatography on silica gel.

Product 17a: Dichloromethane/ethyl acetate (90:10) as eluent. White solid (224 mg, 71% yield). M.p. 218−221 °C. IR: $\tilde{\nu}$ = 1735.1, 1693.3 cm^{-1}. ^1H NMR: δ = 2.18 (s, 3 H, *Ac*), 5.22 (s, 2 H, CH_2OAc), 7.53 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 7.78 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H), 7.90 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.90−8.10 (m, 6 H), 8.20 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 8.40 (d, $^3J_{H,H}$ = 9 Hz, 2 H), 8.60 (d, $^3J_{H,H}$ = 7 Hz, 1 H),.8.70 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 8.72 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 10.12 (s, CHO, 1 H) ppm. ^{13}C NMR: δ = 21.2, 66.1, 119.7, 120.5, 120.6, 121.1, 121.4, 121.6, 127.3, 127.6, 128.7, 130.3, 136.6, 136.9, 137.0, 137.8, 138.1, 139.5, 145.1, 155.0, 155.2, 155.2, 156.0, 156.1, 156.2, 171.0, 192.1 ppm. $C_{31}H_{23}N_3O_3$ (485): calcd. C 76.69, H 4.77, N 8.65, O 9.89; found C 76.72, H 4.76, N 8.62, O 9.90.

Product 17b: Dichloromethane/ethyl acetate (99:1) as eluent. White solid (236 mg, 65% yield). M.p. 212−215 °C. IR: $\tilde{\nu}$ = 1696.8 cm^{-1}. ^1H NMR: δ = 0.06 (s, 6 H, SiMe_2), 0.90 (s, 9 H, *t*BuSi), 4.90 (s, 2 H, CH_2OSi), 7.53 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 7.78 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H), 7.90 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 7.92 (t, $^3J_{H,H}$ = 7 Hz, 1 H), 7.90−8.10 (m, 4 H), 8.20 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 8.38 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H), 8.60 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 8.68 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 8.72 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 8.74 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 10.11 (s, 1 H, CHO) ppm. ^{13}C NMR: δ = 0.1, 18.2, 64.8, 119.2, 120.2, 120.5, 120.9, 121.2, 121.5, 126.4, 126.8, 127.5, 130.2, 136.5, 137.6, 137.7, 137.8, 138.0, 142.5, 144.9, 154.3, 154.3, 154.9, 155.1, 156.3, 156.4, 171.0, 192.1 ppm. $C_{35}H_{35}N_3O_2Si$ (558): calcd. C 75.37, H 6.32, N 7.53, O 5.74, Si 5.04; found C 75.32, H 6.29, N 7.56, O 5.75, Si 5.08.

Product 17c: Dichloromethane/ethyl acetate (90:10) as eluent. White solid (178 mg, 57% yield). M.p. 202−207 °C. IR: $\tilde{\nu}$ = 1694.8 cm^{-1}. ^1H NMR: δ = 4.12 (d, $^3J_{H,H}$ = 3.5 Hz, 2 H, OCH_2CH=CH_2), 4.70 (s, 2 H, OCH_2Ar), 5.30 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, OCH$_2$CH=CH_2), 5.37 (d, $^3J_{H,H}$ = 17 Hz, 1 H, OCH$_2$CH=CH_2), 6.05 (ddt, $^3J_{H,H}$ = 8.5, $^3J_{H,H}$ = 17, $^3J_{H,H}$ = 3.5 Hz, 1 H, OCH$_2$*CH*=CH$_2$), 7.53 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 7.80 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H), 7.91 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.94 (t, $^3J_{H,H}$ = 8 Hz, 1 H), 7.90−8.10 (m, 4 H), 8.22 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 8.38 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 8.60 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 8.71 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 8.73 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 8.74 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 10.10 (s, 1 H, CHO) ppm. ^{13}C NMR: δ = 71.3, 71.9, 117.3, 119.5, 120.5, 120.6, 121.1, 121.3, 121.6, 127.1, 127.6, 128.2, 130.3, 134.8, 136.6, 137.7, 137.9, 138.0, 139.5, 145.0, 155.0, 155.1, 155.2, 156.0, 156.1, 156.2, 192.2 ppm. $C_{32}H_{25}N_3O_3$ (483): calcd. C 79.48, H 5.21, N 8.69, O 6.62; found C 76.51, H 5.19, N 8.72, O 6.58.

Synthesis of Ester 18: To a degassed solution of 2,6-dibromopyridine (**12**) (1.43 g, 6.03 mmol) in 100 mL of acetonitrile, (4-carboxyphenyl)boronic acid (1 g, 6.03 mmol) and $Pd(PPh_3)_4$ (346 mg, 0.3 mmol) were added. After 10 min of stirring at room temperature, a 2 M Na_2CO_3 solution (6 mL, 12 mmol) was added and the reaction mixture was stirred at 100 °C for 20 h. The solvent was evaporated; to the crude reaction mixture 1 M NaOH was added (until pH basic), the aqueous phase was extracted with CH_2Cl_2, then acidified with HCl (until pH neutral) and finally extracted three times with ethyl acetate/methanol (95:5). The organic phase was dried with magnesium sulfate and the solvents were evaporated under vacuum. The crude reaction product was dissolved in methanol (15 mL) and refluxed for 20 h in the presence of a catalytic amount of *p*-toluenesulfonic acid. Product **18** was purified by flash chromatography on silica gel [hexanes/ethyl acetate (50:50) as eluent] to give a white solid (876 mg, 51% yield). M.p. 151−153 °C. IR: $\tilde{\nu}$ = 1721.4 cm^{-1}. ^1H NMR: δ = 3.90 (s, 3 H, OMe), 7.41 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 7.60 (t, $^3J_{H,H}$ = 8 Hz, 1 H), 7.70 (d, $^3J_{H,H}$ = 8 Hz, 1 H), 8.05 (d, $^3J_{H,H}$ = 10 Hz, 2 H), 8.12 (d, $^3J_{H,H}$ = 10 Hz, 2 H) ppm. ^{13}C NMR: δ = 55.4, 119.8, 127.3, 128.2, 130.6, 137.5, 139.3, 142.0, 142.9, 156.7, 170.5 ppm. $C_{13}H_{10}BrNO_2$ (292): calcd. C 53.45, H 3.45, Br 27.35, N 4.79, O 10.95; found C 53.46, H 3.41, Br 27.38, N 4.82, O 10.93.

Synthesis of Terpyridine 19: To a solution of aldehyde **16** (240 mg, 0.74 mmol) in 7 mL of dry, degassed DME hexamethyldistannane (314 mg, 1.5 mmol) and $Pd(PPh_3)_4$ (84 mg, 0.074 mmol) were added and the reaction mixture was refluxed for 18 h. The solvent was evaporated, the crude mixture was rinsed with diethyl ether, filtered and the solvent removed under vacuum to give the crude trimethylstannyl derivative that was used without further purification. To a solution of the tin derivative in dry, degassed DME (10 mL) compound **18** (244 mg, 0.65 mmol) and $Pd(PPh_3)_4$ (63 mg, 0.055 mmol) were added. The reaction mixture was stirred at 90 °C for 20 h. The solvent was evaporated and the crude reaction mixture purified by flash chromatography on silica gel [dichloromethane/ethyl acetate (98:2) as eluent] to give a white solid (147 mg, 48% yield). M.p. 135−137 °C. IR: $\tilde{\nu}$ = 1705.1, 1691 cm^{-1}. ^1H NMR (CF_3COOD): δ = 4.26 (s, 3 H, *OMe*), 8.21 (d, $^3J_{H,H}$ = 7 Hz, 2 H), 8.23 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H), 8.33 (d, $^3J_{H,H}$ = 6 Hz, 1 H), 8.36 (d, $^3J_{H,H}$ = 6 Hz, 2 H), 8.49−8.60 (m, 4 H), 8.65 (t, $^3J_{H,H}$ = 8 Hz, 1 H), 8.71 (d, $^3J_{H,H}$ = 7 Hz, 2 H), 8.80 (t, $^3J_{H,H}$ = 7 Hz, 2 H), 8.90 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 8.93 (d, $^3J_{H,H}$ = 7 Hz, 1 H), 10.18 (s, CHO, 1 H) ppm. ^{13}C NMR (CF_3COOD): δ = 55.4, 126.1, 126.5, 128.4, 128.6, 129.6, 129.8, 130.7, 131.4, 133.1, 133.5, 135.6, 136.7, 138.4, 140.3, 143.5, 149.1, 149.2, 149.8, 150.2, 150.5, 150.6, 155.6, 155.8, 170.0, 198.1 ppm. $C_{30}H_{21}N_3O_3$ (471): calcd. C 76.42, H 4.49, N 8.91, O 10.18; found C 76.43, H 4.51, N 8.89, O 10.17.

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[18] For a recent, efficient synthesis of terpyrdines see ref.[13c] where a variety of terpyridines, bipyridines and phenanthrolines have been synthesized by Negishi coupling. However, the methodology is limited to the preparation of aryl/alkyl derivatives compatible with the preparation and use of organozinc halides. For the preparation of methoxyaryl-substituted oligopyridines by employing Stille coupling reactions see also: M. Benaglia, F. Ponzini, C. R. Woods, J. S. Siegel, *Org. Lett.* **2001**, *3*, 967−969.
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