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High Yield Preparation of 4′-(4-Bromophenyl)-2,2′:6′,2″-terpyridine by a Condensation Reaction. Determination of the Stereochemistry of Two Complex By-products by a Combination of Molecular Mechanics and NMR Spectroscopy

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An improved high yield synthesis of 4′-(4-bromophenyl)-2,2′:6′,2″-terpyridine from 2-acetylpyridine (**1**) and 4-bromobenzaldehyde (**2**) has been developed, using a two-step aldol condensation. In this, the intermediate azachalcone **3** was isolated, then reacted with *N*-[2-oxo-2-(2-pyridyl)ethyl]pyridinium iodide, prepared from **1**, using ammonium acetate both as a base and as a ring closure agent. It could also be shown that one step aldol condensation of **1** and **2** gave low yields of the desired terpyridine due to facile formation of polycondensation products. Two of these, **8** and **10**, could be isolated in moderate yields from condensation reactions. The structure and relative configuration of these compounds were determined by a comparison of observed experimental NMR parameters with theoretical values, calculated by molecular mechanics.

Polypyridine complexes of ruthenium and osmium have been extensively studied during the last decades because of their potential as photosensitizers in artificial systems for harvesting solar energy. Complexes of bipyridine have been in focus due to their unique combination of chemical stability, and redox and excited state properties.[1] As part of our efforts to build artificial molecular mimics for the natural photosystem II, we are currently synthesizing bipyridine ligands for ruthenium, which permit the attachment of auxiliary electron donors and acceptors. In spite of the superiority of bipyridine over terpyridine complexes when it comes to excited-state and redox properties there are some major drawbacks of using the former. In order to optimize the performance of the photochemistry in a supramolecular assembly, where a long-lived charge-separated state is required to enable further chemical reactions, it is necessary to have control over the donor and acceptor distance. This is difficult to achieve in the chemistry of bipyridines, where isomers readily form. Terpyridines, on the other hand, lack other possibilities than to form well defined complexes which can easily be designed to be linear.[2] We have therefore turned our attention to suitably functionalized terpyridines. One attractive group of such synthones would be terpyridines substituted in the 4′-position by a functionalized aryl spacer. Examples are 4′-(4-bromophenyl)- and 4′-(4-methylphenyl)-2,2′:6′,2″-terpyridine (**5** and **6**).

A few synthetic routes are available for substituted terpyridines.[3] The compound **5** has been synthesized earlier[3e] by reacting 2-acetylpyridine (**1**), 4-bromobenzaldehyde (**2**) and ammonium acetate in acetamide at 180 °C. However, the yield was low, 20%. The terpyridine **6** has also been obtained in low yield by the same type of condensation reaction.[2a] Thus, there is room for improved synthetic methods and we decided to study the condensation between 2-acetylpyridine (**1**) and 4-bromobenzaldehyde (**2**).

It was found that the reaction between these two compounds gave a complex reaction mixture, probably explaining the low yields of terpyridines in the one pot synthetic procedures. Evidently, a series of equilibria is established and modifications of the condensation procedure permit isolation of either of the carbocyclic

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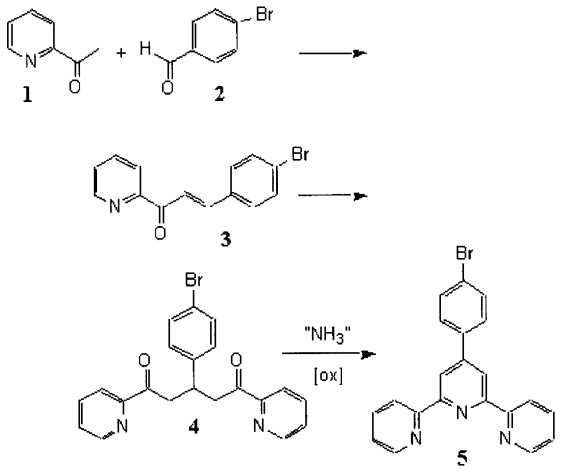
polycondensation products **8** and **10** in around 30% yield. Based on these results, improved conditions for the condensation could be developed, which lead to a threefold increase in the total yield of **5** from 20% to 63% based on the aldehyde **2**.

The relative configuration of compounds **8** and **10** could be determined by comparing experimental vicinal coupling constants and NOEs with those calculated from molecular mechanics minimized conformations.

Synthesis of the terpyridine **5**. Our strategy for improving the synthesis was to make **5** in three steps by aldol condensation of **1** and **2** (Scheme 1).



Scheme 1. Initial synthetic strategy for 4′(4-bromophenyl)-2,2′ : 6′,2″-terpyridine (**5**).

Reaction of **1** and **2** was expected to give the azachalcone **3** as the first intermediate. 1,4-addition of the enolate of **1** to **3** should then yield a 1,5-diketone **4** which could be ring closed in a straightforward manner with ammonium acetate or hydroxylamine hydrochloride. A very similar route employing 4-methylbenzaldehyde instead of **2** gave moderate yields of the corresponding terpyridine **6** (Fig. 1).

In the initial attempt to synthesize 4-bromo-2′-azachalcone (**3**), **1** was added to a basic solution of equimolar amounts of **2** in methanol. A complex reaction mixture was formed and the new condensation product **8** precipitated out of solution. The gross structure of this product was indicated by NMR spectroscopy which revealed that the 4-bromophenyl and 2-pyridyl moieties were present in a ratio of 2:3 instead of the expected 1:1 for **3** or 1:2 for **4**. A possible mode of formation of **8** is described

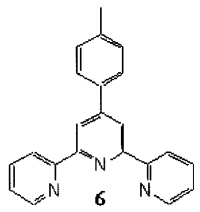
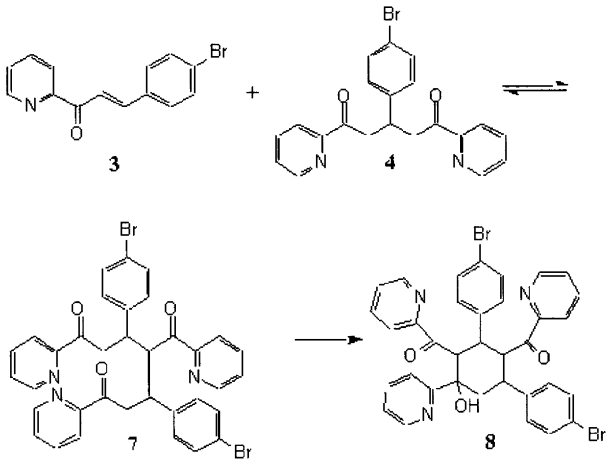


Fig. 1. 4′-(4-Methylphenyl)-2,2′:6′,2″-terpyridine (**6**).

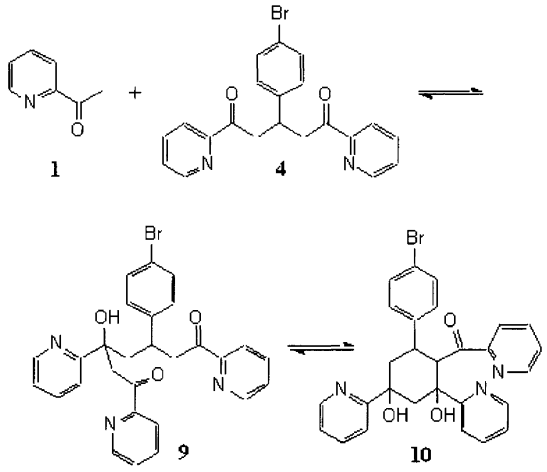


Scheme 2. Proposed formation of condensation product **8**.

in Scheme 2. Initially, **1** and **2** condense to form the azachalcone **3**, as intended. Under the reaction conditions, another equivalent of **1** is added to **3** to form **4**. Unfortunately, the reaction does not stop at this stage but **4** adds to **3** to give a symmetrical triketone **7** with the observed 2:3 ratio of aromatic moieties. From the NMR spectrum, it could be concluded that the final condensation product **8** is non-symmetrical, with five non-equivalent aromatic moieties, and it was therefore assumed that the product **8** was a self-condensation product of **7**. The exact structure of **8** will be addressed further below.

It was clear from the above result that more than one molecule of each reagent readily take part in the condensation. We therefore looked for conditions that would yield diketone **4** directly from condensation of two equivalents of **1** with one equivalent of **2**.[5] In order to avoid inclusion of more than one equivalent of **2**, an experiment was done where the aldehyde **2** was added slowly to the ketone **1**. However, instead of the desired product another new condensation product, **10**, was obtained. The ^{1}H NMR spectrum revealed a compound containing three pyridyl moieties for each bromophenyl. A reasonable mode of formation in this case is described in Scheme 3. An aldol condensation of **1** and the intermediate diketone **4** would give the diketo alcohol **9**. This could be ring closed in two different ways to give cyclohexane derivatives. The presence of an isolated methylene indicates that the product has the structure **10**. The exact structure of **10** will be discussed below.

It was obvious from TLC analyses of the reaction mixtures from the formation of **8** and **10** that quite a number of other products were formed as well. It seems unlikely that condensation between **1** and **2**, maintaining the products in solution, could give reasonable yields of **3** or **4**, and consequently, **5**. We therefore decided to screen for a solvent system that would allow isolation of the intermediate azachalcone **3**. It was found that a high isolated yield of **3** (ca. 80%) could be obtained simply by reacting **1** and **2** in 75% aqueous methanol. This is



Scheme 3. Proposed formation of condensation product **10**.

considerably higher than the yields reported earlier (39%).[6]

Unfortunately, the reaction between **3** and the sodium enolate of **1**, followed by cyclization with ammonium acetate, gave a very low yield of the terpyridine **5** (ca. 13% overall). However, by using instead pyridacyl pyridinium iodide (*N*-[2-oxo-2-(2-pyridyl)ethyl]pyridinium iodide) as nucleophile, **3** could be converted into the desired product **5** in 78% yield, thus achieving our initial goal.

Structure elucidation of condensation products **8** *and* **10**. From the ^{1}H NMR spectra, the number of aromatic moieties in the condensation products **8** and **10** could easily be worked out. The wide range of observed coupling constants in the aliphatic region indicated that new ring systems had been formed, most probably rigid six-membered rings. By DEPT and decoupling experiments, **8** was found to contain a CH_2–CH–CH–CH–CH unit and **10** one isolated CH_2 and a CH_2–CH–CH moiety. It was also clear by NMR that both products were diastereomerically pure since each of them showed only one set of peaks in the region of the spectra corresponding to the aliphatic protons. IR spectra indicated the presence of two carbonyls and one hydroxy group in **8** and one carbonyl and two hydroxy groups in **10**. Based on these observations it was possible to suggest structures for **8** and **10** (Fig. 2).

Structure verification by molecular mechanics and NMR spectroscopy. We have recently shown that the relative configuration of stereogenic centres in a flexible ring can be determined by calculating expected NMR observables from molecular mechanics minimized conformations and comparing these with the experimental values.[7]

The substituted cyclohexane **8** contains five stereogenic centres. This means that 16 possible diastereomeric forms of **8** could be generated. In order to determine the relative configuration of **8**, the theoretical vicinal coupling constants, derived from molecular mechanics calculations,

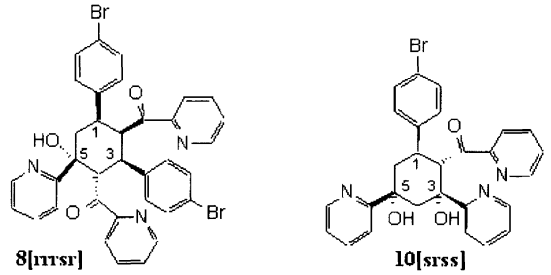


Fig. 2. The numbering of hydrogens and stereocentres, and the relative configuration of the substituents of compounds **8** and **10**.

for the protons of the cyclohexane ring were estimated for all these structures and compared with experimental results. Experimental and theoretical NOEs were also compared. The same procedure was used for the eight possible diastereomeric forms of **10**.

In order to locate all minima in the conformational space of **8** and **10**, a pseudo-systematic Monte Carlo search as implemented in the MACROMODEL program was used. This method, in combination with a geometry optimization method, will most likely find all minima of interest. The large size of the molecules examined forced us to restrict the conformational search to the substituents on the cyclohexane ring. This was made by choosing the torsional angles to hydroxy, pyridyl, and carbonyl groups. The initial torsional resolution was given a value of 2 (180°) for an sp^2–sp^2 bond, 3 (120°) for an sp^3–sp^3 bond, and 6 (60°) for an sp^2–sp^3 bond. The cyclohexyl ring was initialized in a chair conformation, assuming twist boat conformations to be unimportant for energetic reasons. No explicit change of the cyclohexane conformation was done in the search, but no restrictions were imposed in the minimization. Both possible chair conformations of each diastereomer were included in the search.

From the produced ensembles of conformers of **8** and **10**, vicinal proton coupling constants (^3J) were calculated. In the calculations the contribution from each conformer was taken from the Boltzmann distribution at a temperature of 300 K. A comparison between the different isomers by means of the RMS showed that the two structures, [*rrrsr*] and [*rrrss*], seemed most probable for **8** and the three structures, [*srss*], [*srrs*] and [*rsrs*], for **10**. The RMS error in the predictions were about 0.8 Hz in the case of **8** and about 0.6 Hz in the case of **10**. In the analyses of NOEs those isomers were studied that differ only in the configuration at the tertiary carbons in the cyclohexane ring, that is, in position 5 for compound **8** and in positions 3 and 5 for compound **10** (Fig. 2).

A Boltzmann-averaged calculation of NOEs was used and calculated values were plotted versus experimental values (Figs. 3 and 4) showing that the isolated products must indeed be **8** and **10**, as depicted in Fig. 2. The most important NOEs used in the determination of the relative configuration of the tertiary carbons are those from

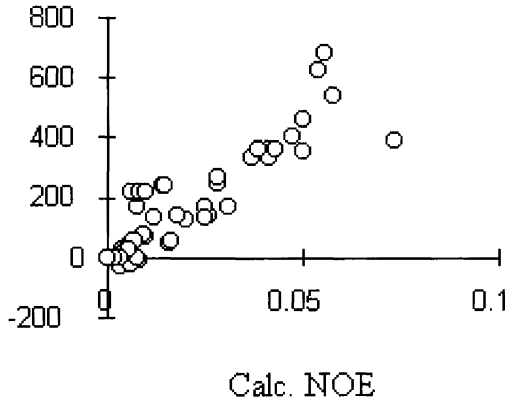


Fig. 3. Plot of experimental values of NOEs versus calculated values for isomer [*rrrsr*] of compound **8**. Correlation coefficient $r^2 = 0.86$ (experimental values given as the volume of the NOE peak).

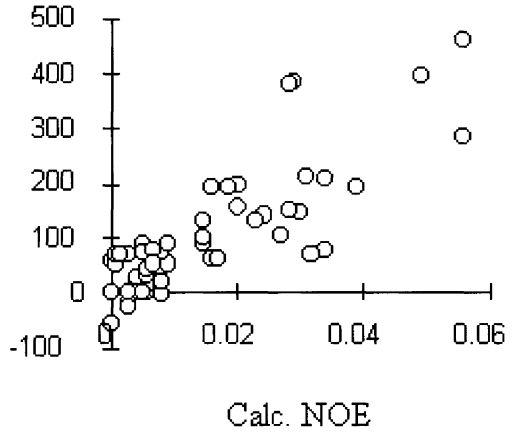


Fig. 4. Plot of experimental values of NOEs versus calculated values for isomer [*srss*] of compound **10**. Correlation coefficient $r^2 = 0.87$ (experimental values given as the volume of the NOE peak).

hydroxy groups and H_3 of the pyridyl groups attached to the tertiary carbons, to the aliphatic protons of the cyclohexane ring.

An interesting feature of compound **8** is that the acylpyridine substituent in the 2 position of the cyclohexyl ring is axial. This indicates that once the compound is formed it does not equilibrate before crystallizing. A possible explanation to this formation of a high energy diastereomer is that it is formed via the lowest energy conformer of **7**. This is the *meso* isomer which is calculated to be 4.5 kJ mol^{-1} lower in energy than the isomer leading to the all equatorial isomer of **8**. In this type of condensation reaction the energies of the transition states of different diastereomeric products might be expected to correlate with the energies of the respective products. Under this tentative assumption, the low energy isomer of **7** should be favored both thermodynamically and kinetically. Assuming the final ring closure step to be fast, being intramolecular, and irreversible due to crystallization, the formation of **8** [*rrrsr*] as depicted in Fig. 2 should be expected.

During the course of the preparation of 4′-(4-methylphenyl)-2,2′:6′,2″-terpyridine, **6**, mentioned before, we were able to isolate another polycondensation product, **11** (Fig. 5).

This was not examined as thoroughly as **8** and **10** but due to similarities to **8** the structure **11** could confidently be assigned to this new compound. The formation of **11** is accomplished by reaction conditions rather different from those used in the formation of **8** (for details see the Experimental section). This means that **11** could well be formed with the same configuration as **8** and then isomerize, since it does not precipitate during the reaction.

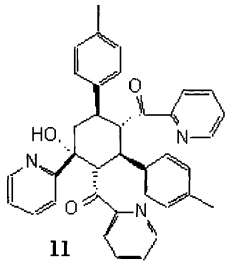
Conclusions

Our investigation shows that simple aldol condensation is not a good vehicle for the preparation of terpyridines from 2-acetylpyridine and aldehydes. Complicated reaction mixtures are formed as shown by TLC and the isolation of two of the by-products, **8** and **10**, from the reaction with 4-bromobenzaldehyde. However, if the intermediate azachalcone, in this case **3** , can be precipitated in decent yield out of the reaction mixture, the condensation between this and a Kröhnke-type nucleophile[8] followed by reaction with ammonium acetate can give the terpyridine in good yield.

Finally, our study also illustrates the power of the combination of NMR spectroscopy and molecular mechanics in determining relative stereochemistry in carbocyclic rings.

Experimental

General. All solvents and reagents were purchased from commercial sources and used as received, except for 2-acetylpyridine which was vacuum distilled prior to use and 4-methylbenzaldehyde which was dissolved in dichloromethane, washed with aqueous sodium carbonate, dried with sodium sulfate and evaporated. 2-Pyridacylpyridinium iodide was prepared according to a literature procedure.[8] ^1H NMR and ^{13}C NMR were recorded on a 400 MHz NMR (Bruker model AM 400) or a 500 MHz NMR (Bruker model Avance DMX 500)



11

Fig. 5. The structure of condensation product **11**.

instrument and processed using XWIN-NMR Version 1.0 on a Silicon Graphics Indy workstation. ^{1}H NMR chemical shifts are reported in δ (ppm) relative to Me_4Si as internal standard. ^{13}C NMR chemical shifts are given in δ values relative to the solvent peak ($CDCl_3$ 77.0 ppm). Total assignment of **8** and **10** was possible utilizing COSY for separate ring systems and NOESY for the connectivity between the cyclohexyl ring and the aromatics. Non-degassed samples were used in the 2D NMR experiments. Infrared (IR) spectra were obtained with a Perkin–Elmer FT-IR spectrometer 1725X.

Computational methods. Computer modelling was carried out with the MACROMODEL program (version 4.5) using a Silicon Graphics Indigo 2 workstation. The following parameters were used in the conformational search on the different isomers of **7**, **8** and **10**: force field: MM3*, minimization algorithm: truncated Newton–Raphson, derivative convergent criteria: 0.05 kJ $Å^{-1}$ mol^{-1}, permissible window above lowest energy conformation: 30 kJ mol^{-1}, number of Monte Carlo steps: 1000. The MM3* force field was modified to include updated parameters for the oxymethylpyridine moiety.[9] Vicinal proton coupling constants (^3J) were calculated within the MACROMODEL program (using the method of Altona *et al.*[10]) and were Boltzmann-averaged at 300 K. NOEs were calculated using a Microsoft Excel macro developed in house,[7a] and were Boltzmann-averaged at 300 K, with a simulated lattice relaxation of 0.1 s^{-1}.

4-Bromo-2'-azachalcone (**3**). 4-Bromobenzaldehyde (**2**, 3.70 g, 20.0 mmol) was dissolved in 45 ml methanol (99.5%) and 15 ml NaOH (1 M). 2-Acetylpyridine (**1**, 2.56 g, 21.1 mmol) was added and the reaction mixture was stirred for 30 min. The resulting precipitate was filtered off, dissolved in CH_2Cl_2 and washed once with water. The organic phase was dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was recrystallized from methanol to give **3** as a light yellow solid.[9] Yield 4.65 g (80.7%). ^{1}H NMR ($CDCl_3$): δ 8.77 (ddd, J=0.9, 1.7, 4.7 Hz, 1 H, H_{6Py}), 8.32 (d, J=16.0 Hz, 1 H, CH), 8.21 (ddd, J=0.9, 1.2, 7.8 Hz, 1 H, H_{3Py}), 7.91 (ddd, J=1.7, 7.5, 7.8 Hz, 1 H, H_{4Py}), 7.89 (d, J=16.0 Hz, 1 H, CH), 7.62 (m, 2 H, Ar), 7.52 (m, 2 H, Ar), 7.52 (ddd, J=1.2, 4.7, 7.5 Hz, 1 H, H_{5Py}). ^{13}C NMR ($CDCl_3$): δ 189.7, 154.5, 149.3, 143.6, 137.5, 134.5, 132.5, 130.6, 127.4, 125.2, 123.4, 121.9

4'-(4-Bromophenyl)-2,2':6',2''-terpyridine (**5**). 4-Bromo-2'-azachalcone (**3**, 0.58 g, 2.0 mmol), 2-pyridacylpyridinium iodide (0.62 g, 2.0 mmol), and ammonium acetate (4.0 g, 51 mmol) were dissolved in 4 ml of glacial acetic acid and refluxed for 7 h. The reaction mixture was kept at room temperature overnight and was then made alkaline with 7 ml NaOH (10 M). The reaction mixture was extracted with 5 × 20 ml of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and evaporated on aluminium oxide (activated, neutral). Flash chromatography (100 g of activated, neutral aluminium oxide, 8:2:1–3:6:2 hexanes–CH_2Cl_2–EtOAc) gave 604 mg (78%) of **5** as a light yellow solid.[5] ^{1}H NMR ($CDCl_3$): δ 8.72 (ddd, J=0.9, 1.8, 4.8 Hz, 2 H, H_6, $H_{6''}$), 8.69 (s, 2 H, $H_{3'}$, $H_{5'}$), 8.66 (ddd, J=0.9, 1.2, 8.0 Hz, 2 H, H_3, H3''), 7.87 (ddd, J=1.8, 7.5, 8.0 Hz, 2 H, H_4, $H_{4''}$), 7.77 (m, 2 H, Ar), 7.63 (m, 2 H, Ar), 7.35 (ddd, J=1.2, 4.8, 7.5 Hz, 2 H, H_5, $H_{5''}$). ^{13}C NMR ($CDCl_3$): δ 156.1, 156.0, 149.2, 149.1, 137.5, 137.0, 132.1, 128.9, 124.0, 123.5, 121.4, 118.6.

Condensation product **8**. 4-Bromobenzaldehyde (**2**, 36.7 g, 0.198 mol) dissolved in 50 ml of methanol was added to 120 ml methanol saturated with NaOH, whereupon the mixture was cooled to 5 °C. 2-Acetylpyridine (**1**, 24.0 g, 0.198 mol) was added dropwise over 15 min and the reaction mixture was stirred for 5 h at 10 °C. A further 5 g (0.04 mol) of **1** was added and the reaction mixture was stirred for 1 h at 20 °C. The precipitate formed was collected by filtration, washed with water and recrystallized from acetonitrile. Yield 12 g (26%). IR (KBr): ν_{max} 3377, 1691, 1680. ^{1}H NMR ($CDCl_3$): δ 8.50 (ddd, 1 H, J=1.0, 1.7, 4.8 Hz, 1 H, H_{6Py4}), 8.23 (ddd, J=1.0, 1.8, 4.8 Hz, 1 H, H_{6Py6}), 8.19 (ddd, J=0.9,1.7, 4.7 Hz, 1 H, H_{6Py2}), 7.88 (app dt, J=1.0, 8.0 Hz, 1 H, H_{3Py6}), 7.66 (ddd, J=1.0, 1.3, 7.9 Hz, 1 H, H_{3Py2}), 7.53 (ddd, J=1.8, 7.5, 8.0 Hz, 2 H, H_{4Py6}, H_{4Py2}), 7.48 (ddd, J=1.7, 7.3, 7.9 Hz, 1 H, H_{4Py4}), 7.43 (ddd, J=0.9, 1.4, 7.8 Hz, 1 H, H_{3Py4}), 7.20 (m, 2 H, $Ar_{3.1}$), 7.19 (ddd, J=1.4, 4.8, 7.3 Hz, 1 H, H_{5Py4}), 7.16 (m, 4 H, Ar_1), 7.15 (ddd, J=1.2, 4.8, 7.5 Hz, 1 H, H_{5Py2}), 6.95 (m, 2 H, $Ar_{3.2}$), 6.90 (ddd, J=1.1, 4.8, 7.5 Hz, 1 H, H_{5Py6}), 6.27 (d, J=12.6 Hz, 1 H, H_4), 5.55 (app t, J=5.1 Hz, 1 H, H_2), 4.46 (dd, J=5.0, 12.0 Hz, 1 H, H_3), 4.16 (ddd, J=3.4, 5.1, 13.1 Hz, 1 H, H_1), 3.52 (app td, J=1.9, 13.1 Hz, 1 H, H_{61}), 1.98 (ddd, J=1.4, 3.3, 13.0 Hz, 1 H, H_{62}). ^{13}C NMR ($CDCl_3$): δ 205.1, 203.1, 162.1, 154.0, 153.7, 148.1, 148.0, 146.9, 141.0, 139.8, 136.2, 136.1, 130.8, 130.7, 130.3, 129.6, 126.1, 126.1, 121.9, 121.7, 121.2, 121.0, 120.0, 119.9, 75.5, 48.4, 47.7, 44.8, 40.7, 37.9. An analytical sample was prepared by recrystallization from toluene followed by recrystallization from acetonitrile. Anal. Calcd. for $C_{35}H_{27}Br_2N_3O_3$: C, 60.28; H, 3.90; Br, 22.91; N, 6.03. Found: C, 60.05; H, 3.88; Br, 22.63; N, 6.01.

Condensation product **10**. 2-Acetylpyridine (**1**, 1.35 g, 11.2 mmol) was dissolved in 20 ml ethanol (99.5%) together with 1 ml saturated NaOH in water. The solution was cooled to 5 °C, after which 4-bromobenzaldehyde (**2**, 0.94 g, 5.1 mmol), dissolved in 15 ml ethanol (99.5%), was added dropwise over a period of 2 h. The reaction mixture was stirred for 30 min, poured into 40 ml of water, and the water phase was extracted with 3 × 40 ml of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. The yellow, oily residue was dissolved in ethanol, and water was added to form a precipitate. This was dissolved in

acetonitrile and reprecipitated by partitioning between water and light petroleum, forming a white solid. This was collected by filtration and dried. Yield: 0.63 g (32%). IR (KBr): ν_{max} 3479, 3319, 1692 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.53 (ddd, J=1.0, 1.8, 4.8 Hz, 1 H, H_{6Py5}), 8.47 (ddd, J=0.9, 1.7, 4.8 Hz, 1 H, H_{6Py2}), 8.27 (ddd, J=0.9, 1.7, 4.8 Hz, 1 H, H_{6Py3}), 7.77 (app dt, J=1.1, 8.0 Hz, 1 H, H_{3Py5}), 7.70 (ddd, J=1.8, 7.3, 8.0 Hz, 1 H, H_{4Py5}), 7.58 (app dt, J=1.1, 8.0 Hz, 1 H, H_{3Py3}), 7.49 (ddd, J=1.7, 7.4, 7.9 Hz, 1 H, H_{4Py2}), 7.42 (ddd, J=1.8, 7.5, 8.0 Hz, 1 H, $H4_{Py3}$), 7.40 (ddd, J=0.9, 1.4, 7.9 Hz, 1 H, $H3_{Py2}$), 7.23 (m, 2 H, $Ar_{1.1}$), 7.21 (ddd, J=1.4, 4.8, 7.4 Hz, 1 H, H_{5Py2}), 7.16 (m, 2 H, $Ar_{1.2}$), 7.15 (ddd, J= 1.2, 4.8, 7.4 Hz, 1 H, H_{5Py5}), 6.87 (ddd, J=1.2, 4.8, 7.4 Hz, 1 H, H_{5Py3}), 6.50 (br s, 1 H, H_{OH3}), 6.23 (s, 1 H, H_{OH5}), 5.47 (d, J=12.2 Hz, 1 H, H_2), 4.09 (app td, J= 3.4, 12.6 Hz, 1 H, H_1), 3.10 (dd, J=1.3, 14.3 Hz, 1 H, H_{41}), 2.68 (app t, J=13.3 Hz, 1 H, H_{61}), 2.09 (ddd, J= 2.3, 3.5, 13.6 Hz, 1 H, H_{62}), 2.02 (dd, J=2.3, 14.4 Hz, 1 H, H_{42}). ^{13}C NMR ($CDCl_3$): δ 204.7, 165.2, 162.9, 153.9, 148.4, 148.3, 148.0, 141.9, 137.3, 136.8, 131.5, 130.5, 126.8, 122.4, 122.3, 120.6, 120.5, 119.8, 60.7, 54.1, 46.9, 46.7, 39.9. An analytical sample was prepared by recrystallization from acetonitrile. Anal. Calcd. for $C_{25}H_{24}BrN_3O_3$: C, 63.40; H, 4.56; Br, 15.06; N, 7.92. Found: C, 63.26; H, 4.42; Br, 14.88; N, 7.81.

4-Methyl-2'-azachalcone. To a solution of 4-methylbenzaldehyde (18.1 g, 150 mmol) in methanol (120 ml) saturated with NaOH, at 4 °C, was added dropwise 2-acetylpyridine (18.1 g, 150 mmol) over 75 min. After additional stirring for 3 h the reaction mixture was poured on to ice–water. The resulting precipitate was collected by filtration and recrystallized from methanol to give 4-methyl-2'-azachalcone as yellow crystals. Yield 16.4 g (49%). ^1H NMR ($CDCl_3$): δ 8.74 (ddd, J=0.9, 1.7, 4.8 Hz, 1 H, H_6), 8.26 (d, J=16.0 Hz, 1 H, CH), 8.19 (ddd, J=0.9, 1.2, 7.8 Hz, 1 H, H_3), 7.93 (d, J= 16.0 Hz, 1 H, CH), 7.87 (ddd, J=1.7, 7.6, 7.8 Hz, 1 H, H_4), 7.64 (m, 2 H, Ar), 7.48 (ddd, J=1.2, 4.8, 7.6 Hz, 1 H, H_5), 7.22 (m, 2 H, Ar), 2.39 (s, 3 H, Me).

4'-(4-Methylphenyl)-2,2':6',2''-terpyridine (**6**). To a slurry of NaH (0.79 g, 32 mmol) in 5 ml dry THF under argon was added 2-acetylpyridine (3.5 g, 29 mmol) via a cannula. This was rinsed with another 10 ml THF. After 30 min of stirring, 4-methyl-2'-azachalcone (6.0 g, 29 mmol) dissolved in 15 ml THF was added. The mixture was stirred for 1 h and thereafter split into two halves and placed in the freezer overnight. The following day, ammonium acetate (1.7 g, 22 mmol) was added to one of the halves followed by 20 ml acetic acid. The THF was distilled off for 1.5 h and the mixture was refluxed for further 1.5 h. After evaporation, 50 ml water were added and the water phase was made basic with sodium carbonate. The mixture was extracted with 5 × 50 ml CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and evaporated. Flash chromatography (30 g of activated, neutral aluminium oxide, toluene) followed by recrystallization from hexanes–CH_2Cl_2 gave 4'-(4-methylphenyl)-2,2':6',2''-terpyridine as a light yellow solid[3] (1.25 g, 26.7%). ^1H NMR ($CDCl_3$): δ 8.74 (s, 2 H, H3', H5'), 8.73 (ddd, J=0.9, 1.8, 4.7 Hz, 2 H, H6, H6''), 8.68 (ddd, J=0.9, 1.2, 8.0 Hz, 1 H, H3, H3''), 7.87 (ddd, J=1.8, 7.4, 8.0 Hz, 2 H, H4, H4''), 7.82 (m, 2 H), 7.34 (ddd, J=1.2, 4.8, 7.4 Hz, 2 H, H5, H5''), 7.31 (m, 2 H), 2.43 (s, 3 H, Me).^{13}C NMR ($CDCl_3$): δ 156.8, 156.3, 150.6, 149.5, 139.5, 137.3, 135.9, 130.1, 127.6, 124.2, 121.8, 119.0, 21.7.

Condensation product **11**. To a slurry of NaH (3.46 g, 79 mmol) in 10 ml dry THF under argon was added 2-acetylpyridine (8.74 g, 72 mmol) via a cannula. This was rinsed with another 10 ml THF. After 30 min of stirring, 4-methyl-2'-azachalcone (16.1 g, 72 mmol) dissolved in 40 ml THF was added. The mixture was stirred for 1 h and thereafter split into two halves and put in the freezer overnight. The following day, ammonium acetate (2.78 g, 36 mmol) was added to one of the halves followed by 50 ml acetic acid. The THF was distilled off for 1 h and the mixture was cooled to room temperature. 50 ml water were added and the water phase was made alkaline with sodium carbonate. The mixture was extracted with 5 × 50 ml CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and evaporated with activated, neutral aluminium oxide. Flash chromatography (30 g of activated, neutral aluminium oxide, 54:36:10 hexanes–diethyl ether–CH_2Cl_2) gave very pure 4'-(4-methylphenyl)-2,2':6',2''-terpyridine, which crystallized in lower part of the column. The column was washed with CH_2Cl_2 and after evaporation the terpyridine was recrystallized from ethyl acetate–hexanes (1:1). A white residue was filtered off during the recrystallization and was recrystallized from ethyl acetate, yielding 0.28 g (1.4%) of **11**. ^1H NMR ($CDCl_3$): δ 8.54 (ddd, J=0.9, 1.8, 4.9 Hz, 1 H), 8.45 (ddd, J=1.0, 1.5, 4.8 Hz, 1 H), 8.34 (ddd, 1 H, J=0.9, 1.8, 4.9 Hz, 1 H), 7.66 (app dt, J=1.1, 8.0 Hz, 1 H), 7.49 (app td, J=1.8, 7.6, 1 H), 7.43 (app td, J=1.8, 7.6, 1 H), 7.36 (app td, J=1.4, 6.6, 8.4, 1 H), 7.32 (app dt, J=0.9, 7.8 Hz, 1 H), 7.31 (app dt, J=1.2, 8.1 Hz, 1 H), 7.23 (m, 2 H), 7.19 (ddd, J= 1.3, 4.8, 7.4 Hz, 1 H), 7.11 (ddd, J=1.7, 4.7, 7.0 Hz, 1 H), 7.03 (br s, 2 H), 6.92 (ddd, 1 H, J=1.2, 4.9, 7.3 Hz, 1 H), 6.83 (m, 2 H), 6.48 (m, 2 H), 6.02 (s, 1 H), 5.57 (d, J=12.2 Hz, 1 H), 5.37 (app t, J=10.7 Hz, 1 H), 4.14 (app t, J=11.6 Hz, 1 H), 4.01 (app td, J=3.4, 12.0 Hz, 1 H), 2.70 (app t, J=13.4 Hz, 1 H), 2.16 (dd, J=3.7, 13.7 Hz, 1 H), 2.10 (s, 3 H), 1.9 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 206.5, 205.0, 164.5, 153.8, 153.4, 148.0, 147.9, 139.7, 136.4, 136.1, 135.6, 135.6, 135.5, 135.5, 129.2, 128.6, 128.1, 127.9, 126.1, 125.7, 121.9, 121.7, 121.5, 119.8, 77.3, 47.0, 46.5, 43.2, 20.8, 20.6. MS: m/z (relative intensity) 567.2 (M^+, 0.3).

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