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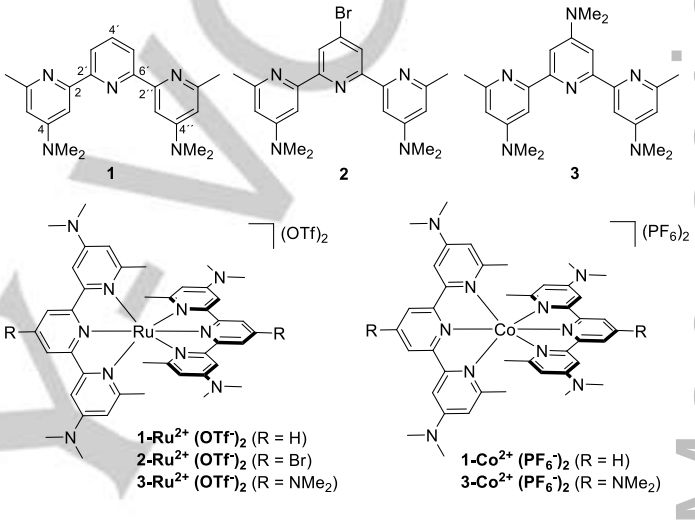
Full Paper

Efficient Syntheses of New Super Lewis Basic Tris(dialkylamino)-Substituted Terpyridines and Comparison of Their Methyl Cation Affinities

Merlin Kleoff,[a] Simon Suhr,[b] Biprajit Sarkar,[b] Reinhold Zimmer,[a] Hans-Ulrich Reissig,*[a] Marta Marin-Luna,[c] and Hendrik Zipse[c]

Abstract: Syntheses of very electron-rich dialkylamino-substituted 2,2´:6´,2´´-terpyridines (TPYs) were adapted to moderate scale preparation without tedious purification of intermediates. The key 4´-bromo-6,6´´-dimethyl-2,2´:6´,2´´-terpyridine-4,4´´-diyl bisnonaflate is now available in gram quantities. Its nucleophilic aromatic substitution with dimethylamine provided mixtures of 4´-bromo-substituted 4,4´´-bis(dimethylamino)-TPY and the tris(dimethylamino)-TPY. The bromo compound was used in a Buchwald-Hartwig amination to provide the tris(dimethylamino)-TPY in excellent yield. The 4´-bromo substituent was reductively removed to furnish the bis(dimethylamino)-TPY. The same sequence of reactions with pyrrolidine as nucleophile leads to the hitherto unknown pyrrolidino-TPYs. Calculations at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level predict very high methyl cation affinities for compounds of this type, with the 4,4´,4´´-tri(pyrrolidin-1-yl)-TPY being the most Lewis basic TPY synthesized to date. The efficiently prepared electron-rich TPYs should be excellent ligands for many applications.



Scheme 1. Electron-rich terpyridine derivatives **1**-**3** and ruthenium(II) and cobalt(II) complexes of these TPY ligands.

Introduction

In a preliminary report, we disclosed a novel approach to a unique class of dialkylamino-substituted 2,2´:6´,2´´-terpyridines **1**-**3** with very strong electron-donating groups in 4,4´´- or 4,4´,4´´-positions,[1] that can be regarded as hybrids of terpyridines (TPYs) and 4-*N*,*N*-dimethylaminopyridine (DMAP) (Scheme 1).[2] We expected these new TPYs to be strong Lewis bases and accordingly very methyl cation affinities (MCAs) were calculated for **1** and **3**.[1]

Later, ruthenium(II) complexes of **1**-**3**[3] and cobalt(II) complexes of **1** and **3**[4] were synthesized and structurally characterized. The electrochemical measurements of the Ru(II) complexes show that the incorporation of two or three dimethylamino groups on TPY ligands leads to a strong negative shift of the oxidation potential by almost 1 V. A newly developed OTTLE cell allowed the characterization of four reduction steps in these complexes, revealing that the two final steps lead to an unprecedented bond activation at the ruthenium center.[3] The cobalt complexes of **1** and **3** were also characterized and compared with related compounds bearing other TPY ligands of varying electron-density.[4] The complex **3**-Co(II) shows a very negative potential and is a highly efficient catalyst for the hydrogen evolution by electroreduction of protons.[5] Surprisingly, the unique TPY ligands also showed interesting properties in an entirely different field. It was found that compound **1** interacts rather selectively with G-quadruplexes and shows helicase inhibitory properties.[6] All these experimental observations from coordination chemistry, catalysis and bioorganic chemistry confirm the MCA calculations and reveal that electron-rich TPYs such as **1**-**3** are exceptional ligands. It is evident that they are also attractive ligands for other applications and deserve further investigation, particularly with respect to their synthetic accessibility.

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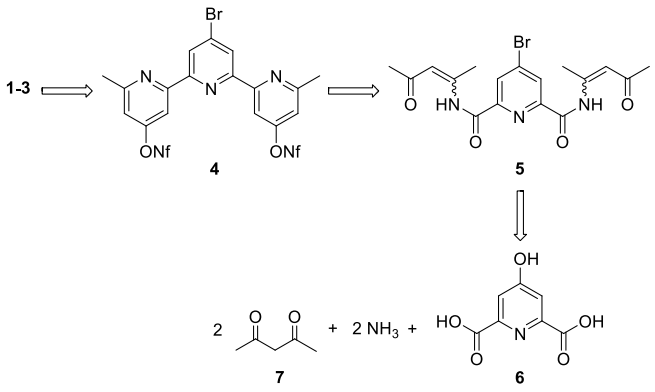
Due to the demand for these TPYs we re-synthesized **1**-**3** and thereby optimized the procedures for moderate up-scaling. The route to the compounds relies on TPY derivative **4** bearing three leaving groups (Scheme 2), allowing aromatic nucleophilic substitutions or palladium-catalyzed reactions for the introduction of new substituents. As precursor of **4** serves bis-β-ketoenamide **5** that is readily available from chelidamic acid **6**, ammonia and acetylacetone **7**.



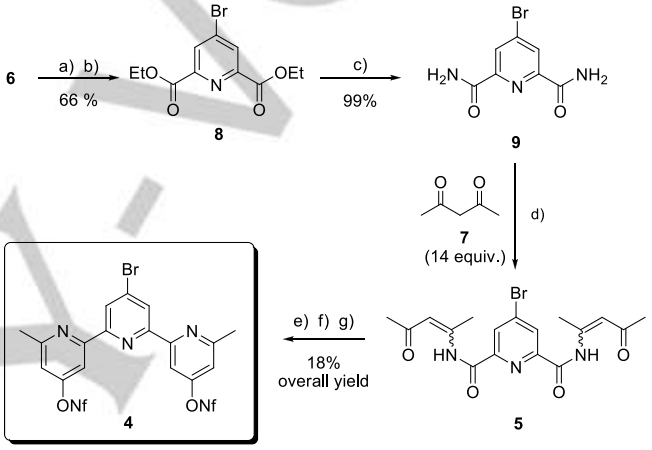
Scheme 2. Approach to TPYs **1**-**3** via bisnonaflate **4** and compound **5** with chelidamic acid **6**, ammonia and acetylacetone **7** as precursors. NfO = nonafluorobutanesulfonate

This approach is based on a cyclocondensation reaction developed by our group, which allowed the preparation of a series of 4-hydroxy-substituted pyridine, bipyridine or terpyridine derivatives.[7,8] The required β-ketoenamides are accessible by *N*-acylation of the corresponding β-ketoenamines that are available from 1,3-diketones such as acetylacetone and ammonia.[9] Alternatively, the β-ketoenamides were directly obtained from 1,3-diketones and acid-catalyzed reaction with the corresponding carboxylic acid amides.[10] Due to the polar character of several intermediates on the way to **1**-**3** thorough purification by chromatography is very tedious.

In this full account, we describe efficient protocols for the syntheses of **1**-**3**, that minimize the number of purification steps. We also report the preparation of hitherto unknown pyrrolidino congeners of **1**-**3** starting from key intermediate **4**. The resulting new TPYs should be even more electron-rich due to the known higher electron-donating ability of a pyrrolidino group compared to a dimethylamino group.[11] The synthetic efforts are accompanied by MCA calculations of the new TPYs to compare their Lewis basicity with related compounds.

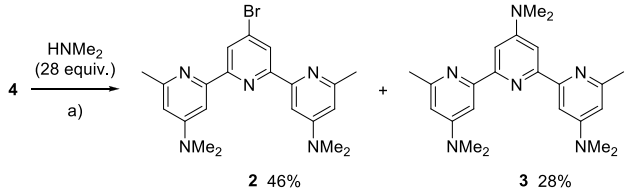
Results and Discussion

The reactions leading to key bisnonaflate **4** are illustrated in Scheme 2. Chelidamic acid **6** was converted into its carboxylic acid dibromide by treatment with phosphorus pentabromide, simultaneously transforming the 4-hydroxy group into a bromo substituent. An in situ esterification with ethanol furnished compound **8** in 66% yield. By using gaseous ammonia in hot methanol,[12] we could improve the yield of transformation of **8** into 4-bromo diamide **9** to 99%; this compound is now easily available in gram quantities. The bis-β-ketoenamide **5** was obtained by heating of bisamide **9** with an excess of acetylacetone **7** in the presence of catalytic amounts of *p*-toluenesulfonic acid for 16 h. Purification and isolation of **5** was possible, giving the compound in 44% yield in 3 g scale after tedious chromatography; however, the overall efficiency is higher and the protocol simpler, if the crude reaction mixture containing **5** is directly converted into the less polar *O*-nonaflated TPY **4**. Treatment with an excess of trimethylsilyl trifluoromethanesulfonate and Hünig base promoted the twofold cyclocondensation reaction to form the pyridine rings. Subsequent *O*- and *C*-desilylation[13] with trifluoroacetic acid, deprotonation with sodium hydride and treatment with nonafluorobutanesulfonyl fluoride gave the desired key compound bisnonaflate **4** in 18% overall yield (2.5 g) after chromatography. The yield for the last steps was higher if pure **5** was used (30%), nevertheless the procedure as illustrated is easier to perform and still satisfying, considering the complexity of this multi-step transformation.



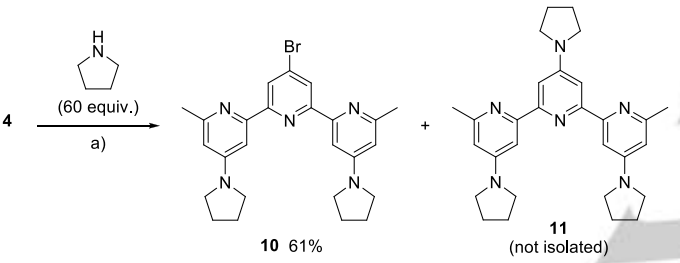
Scheme 3. Conversion of chelidamic acid **6** into 4-bromo diamide **9** followed by its reaction with acetylacetone **7** to bis-β-ketoenamide **5**, cyclocondensation and subsequent *O*-nonaflation to bisnonaflate **4**. Conditions: a) PBr_5 (2.5 equiv.), neat, 90 °C, 16 h; b) EtOH, $CHCl_3$, r.t., 1 h; c) MeOH, gaseous ammonia, 65 °C, 1.5 h; d) *p*-toluenesulfonic acid (0.3 equiv.), toluene, 110 °C, 16 h; e) trimethylsilyl trifluoromethanesulfonate (10 equiv.), *N*,*N*-diisopropylethylamine (8 equiv.), 1,2-dichloroethane, 80 °C, 72 h; f) trifluoroacetic acid (1.3 equiv.), r.t., 30 min; g) sodium hydride (12 equiv.), nonafluorobutanesulfonyl fluoride (5 equiv.), THF, r.t., 16 h.

For the introduction of the dialkylamino group, compound **4** was treated with a tetrahydrofuran solution of dimethylamine (Scheme 4). In all attempts, the desired threefold aromatic nucleophilic substitution was incomplete and mixtures of bromo compound **2** and the desired tris(dimethylamino)-substituted compound **3** were isolated. The application of microwave conditions remarkably shortened the reaction time from two days to three hours, but it did not improve the ratio of **3** to **2**. At higher reaction temperatures we observed decomposition of the compounds. Attempts to convert compound **2** into **3** by treating it again with dimethylamine were not successful. Apparently, the two dimethylamino groups of **2** prohibit the third nucleophilic substitution at C-4´ due to their strong electron-donating effect.



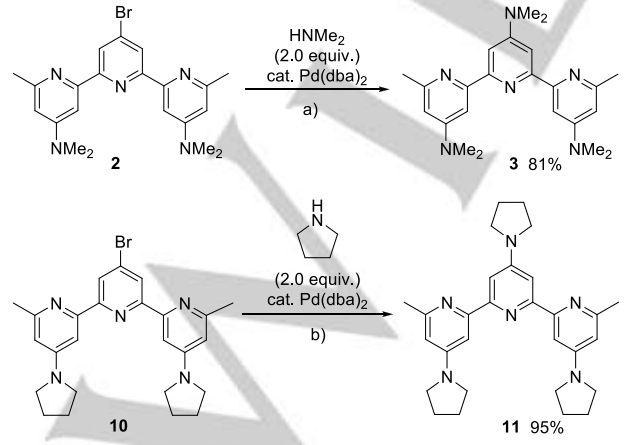
Scheme 4. Aromatic nucleophilic substitution of bisnonaflate **4** with dimethylamine providing a mixture of bromo-substituted TPY **2** and tris(dimethylamino)-substituted TPY **3**. Conditions: a) THF, pressure tube, microwave, 110 °C, 3 h.

The analogous direct synthesis of tri(pyrrolidino)-substituted TPY **11** from bisnonaflate **4** was not successful (Scheme 5). Treatment of **4** with pyrrolidine under similar conditions as above gave a mixture containing the desired compound **11**, but its purification and isolation was not possible due to inseparable side-products. After chromatography, only the bromo compound **10** was cleanly obtained in 61% yield.



Scheme 5. Nucleophilic aromatic substitution of bisnonaflate **4** with pyrrolidine affording bromo-substituted TPY **10**. Conditions: a) neat, pressure tube, microwave, 120 °C, 1 h.

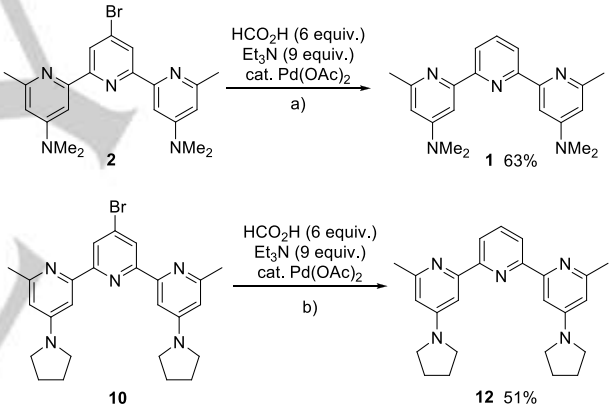
Having 4´-bromo-substituted terpyridines **2** and **10** available in substantial quantities, we also examined their suitability in Buchwald-Hartwig amination reactions.[14] Gratifyingly, under conditions applied by Johansson to 4´-chloro TPY,[15] compounds **2** and **10** were excellent substrates for this palladium-catalyzed reaction affording the tris(dialkylamino)-substituted TPYs **3** and **11** in very good yields (Scheme 6).



Scheme 6. Buchwald-Hartwig aminations of bromo-substituted TPYs **2** and **10** providing tris(dialkylamino)-substituted TPYs **3** and **11**. Conditions: a) $Pd(dba)_2$ (5 mol%), SPhos (10 mol%), NaO*t*Bu (2.1 equiv.), toluene/THF, 90 °C, 3 d; b) $Pd(dba)_2$ (5 mol%), SPhos (10 mol%), NaO*t*Bu (2.3 equiv.), toluene/THF, 100 °C, 16 h.

Although the Buchwald-Hartwig amination allowed the very efficient conversion of **2** and **10** - obtained as major products by the aromatic nucleophilic substitutions - into the desired tris(dialkylamino)-substituted TPYs **3** and **11**, a direct synthesis of these compounds should be possible by a threefold palladium-catalyzed reaction of 4´-bromo-substituted bisnonaflate **4** with the corresponding amines. Unfortunately, the amination of **4** under conditions as described above, but employing a larger excess of dimethylamine, did not deliver the expected TPY **3**. Traces of this compound and of the diamino-substituted product **2** could be detected in the crude reaction mixture, but their isolation was not possible. We did not attempt an optimization of this transformation by applications of alternative protocols.

Finally, syntheses of TPYs **1** and **12** were examined, that bear the dialkylamino substituents only at C-4 and C-4´´. Palladium-catalyzed reductions with formic acid as hydrogen source[16] were conducted with bromo compounds **2** and **10** furnishing the desired bis(dialkylamino)-substituted TPYs **1** and **12** in moderate yields. The conversion of **10** into **12** proceeded considerably slower, but no attempts were undertaken to optimize these transformations.



Scheme 7. Syntheses of TPYs **1** and **12** by palladium-catalyzed reduction of **2** and **10**. Conditions: a) $Pd(OAc)_2$ (20 mol%), 1,3-bis(diphenylphosphino)-propane (40 mol%), DMF, 90 °C, 6 h; b) $Pd(OAc)_2$ (20 mol%), 1,3-bis(diphenylphosphino)propane (40 mol%), DMF, 90 °C, 36 h.

Methyl cation affinities (MCAs) of the TPYs were calculated at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level of theory[17] and correspond to the reaction enthalpies (at 298.15 K and 1 atm, in kJ/mol) of the transformation shown in the equation 1.

$$\text{LB-CH}_3^{\oplus} \xrightarrow{\Delta H_{298}} \text{LB} + \text{CH}_3^{\oplus} \qquad (1)$$

MCA values of related pyridine and TPYs calculated with the same theoretical methods were reported previously[1,18] and a direct comparison can therefore be made to the pyrrolidino-substituted TPYs **11** and **12** (Scheme 8). MCA values of important reference compounds based on a single pyridine unit are those of 9-azajulolidine (TCAP, **15**, +602.7 kJ/mol), 4-pyrrolidinopyridine (PPY, **14**, +590.2) and 4-*N*,*N*-dimethylaminopyridine (DMAP, **13**, +581.2). TPYs such as **1** or **12** lacking a donor substituent at the central pyridine unit, have their most Lewis basic positions in the

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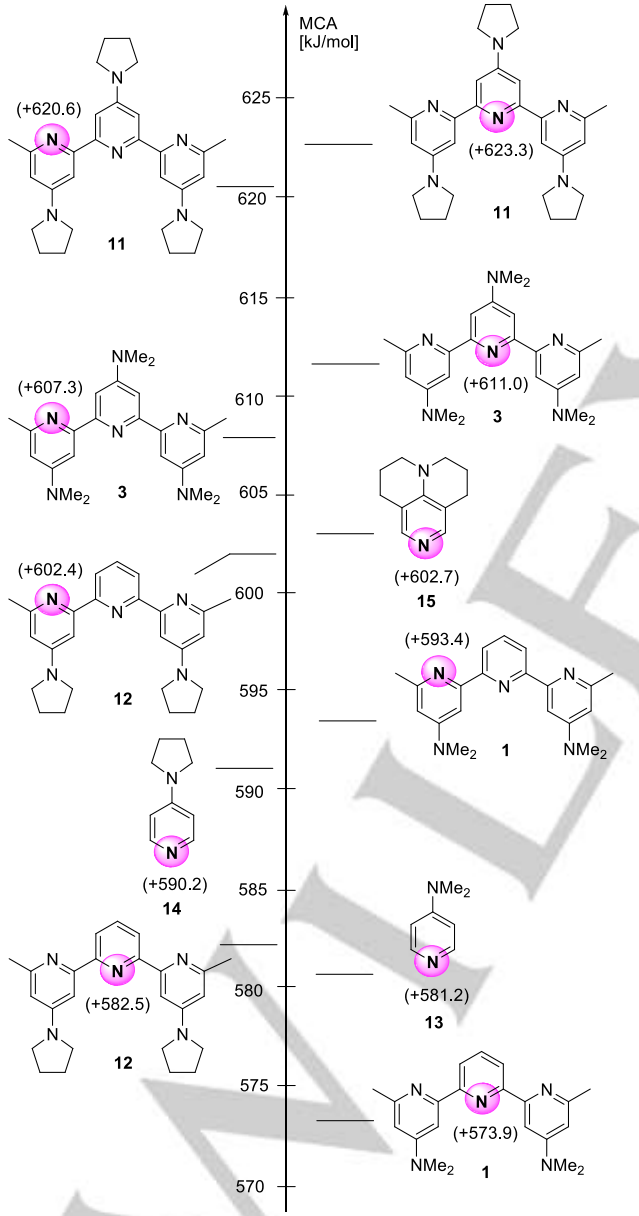
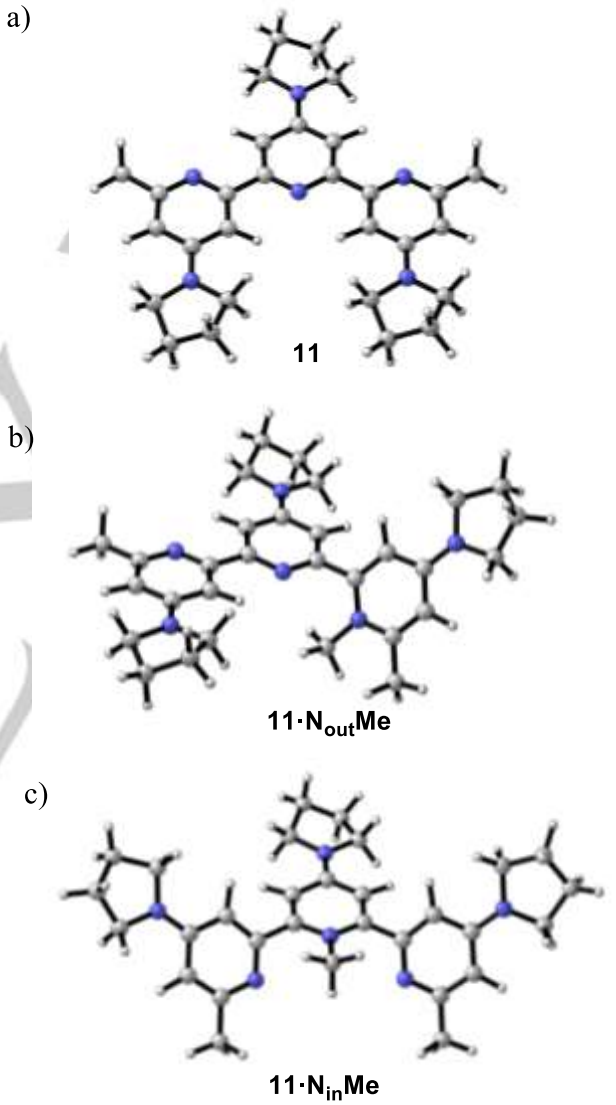
outer pyridine rings. As expected, the MCA value for the respective pyrrolidino-substituted system **12** (+602.4 kJ/mol) is higher than that for the dimethylamino-substituted system **1** (+593.4 kJ/mol). Adding donor-substituents to the central TPY ring as in compounds **3** or **11** leads to a general increase of Lewis basicity at all positions and makes the central pyridine ring more basic than its outer companions. The highest basicity is therefore found for the central pyridine ring in compound **11** (+623.3 kJ/mol), closely followed by the outer pyridine ring in the same compound (+620.6 kJ/mol). The basicity increase relative to the TPY **3** carrying dimethylamino-substituents amounts to 12.3 kJ/mol, which is slightly larger than the difference of 9.0 kJ/mol between PPY (**14**) and DMAP (**13**). With these improved donor substituents in place, the pyrrolidino-substituted compound **11** is the most Lewis basic TPY known to date.



Scheme 8. Computed methyl cation affinities (Boltzmann-averaged, in kJ/mol) of pyridine and TPY derivatives. Methylation occurs at the marked nitrogen atoms.

Interestingly, all neutral TPYs studied here preferentially orient the outer pyridine rings opposite to the central pyridine unit (Scheme 9a). Methylation of the outer or inner pyridine units then triggers a conformational reorientation such that the adjacent free pyridine ring unit points its ring nitrogen atom towards the methyl group hydrogen atoms (Scheme 9b and 9c). As already discussed for compound **3**[1] this cisoid arrangement reduces steric interactions with the attached methyl group and allows electrostatic attraction between the *N*-methyl group and the adjacent pyridine rings.



Scheme 9. Predicted conformations of **11** (a) and methylated derivatives **11·N$_{out}$Me** (b) and **11·N$_{in}$Me** (c).

Conclusion

Starting from chelidamic acid **6** the synthesis of bisnonaflate **4** was optimized by minimizing the purification efforts. This key intermediate is now easily available in gram quantities and it served as precursor of the dimethylamino-substituted TPYs **1**-**3** and the hitherto unknown pyrrolidino-substituted TPYs **10**-**12**. By nucleophilic aromatic substitution with dimethylamine or

pyrrolidine, bisnonaflate **4** provided only tris(dimethylamino)-substituted TPY **3** in moderate yield, whereas the pyrrolidino derivative TPY **11** was formed in negligible amounts. Major products of these reactions were TPYs **2** or **10** bearing untouched 4´-bromo substituents. Gratifyingly, Buchwald-Hartwig amination efficiently converted these compound into the desired tris(dialkylamino)-substituted TPYs **3** and **11** in excellent yields, making these target compounds available in good overall efficacy. Reductive removal of the 4´-bromo substituent of **2** or **10** led to the 4,4´´-bis(dialkylamino)-substituted TPYs **1** and **12**. All TPYs of this report bear methyl groups at 6- and 6´´-position that can also be used for subsequent functionalization.[8b] Introduction of additional donor sites should lead to an extension of the library of very electron-rich TYPs. For the new TPYs **11** and **12** very high methyl cation affinities were calculated reflecting the expected strong electron-donating effect of the pyrrolidino substituents. Compound **11** is the most Lewis basic TPY synthesized to date and hence it should be an unparalleled ligand for metal complexes with unique properties. The electron-rich terpyridine derivatives described here should be of interest for many applications in complex chemistry, catalysis and supramolecular chemistry.[19]

Experimental Section

General Methods: Reactions were generally performed under argon in flasks dried by heat gun. Solvents and reagents were added by syringes. Solvents were dried using standard procedures. Reagents were purchased and were used as received without further purification unless stated otherwise. Chelidamic acid **6** was purchased as monohydrate and was dried in vacuo (100 °C, $1x10^{-3}$ mbar, 16 h). Reactions under microwave irradiation were performed using a MONOWAVE 300 instrument (Anton Parr) with a maximum power of 850 W. Reactions were monitored by thin-layer chromatography (TLC). Products were purified by flash chromatography on silica gel (40-63 µm). Unless otherwise stated, yields refer to chromatographically homogeneous and spectroscopically pure materials (^{1}H-NMR spectroscopy). NMR spectra were recorded with JEOL (ECX 400, Eclipse 500) and Bruker (AV 700) instruments. Chemical shifts (δ) are listed in parts per million (ppm) and are reported relative to solvent residual signals: $CDCl_3$ (^{1}H NMR: δ = 7.26 ppm, ^{13}C: δ = 77.2 ppm), DMSO-d_6 (^{1}H: δ = 2.50 ppm, ^{13}C NMR: δ = 39.5 ppm). Integrals are in accordance with assignments; coupling constants are given in Hz. ^{13}C-NMR spectra are ^{1}H-decoupled. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), m_c (centered multiplet), dd (doublet of doublet), br s (broad singlet). HRMS analyses were performed with a Varian Ionspec QFT-7 instrument (ESI-FT ICRMS). Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

Diethyl 4-bromopyridine-2,6-dicarboxylate (8): This compound was prepared by a slight modifications of the published procedure.[1] At 0 °C phosphorus tribromide (11.3 mL, 119 mmol, 3.1 equiv.) was added dropwise to a vigorously stirred solution of bromine (4.90 mL, 95.6 mmol, 2.5 equiv.) in hexanes (80 mL). The cooling bath was removed and the mixture was stirred for 1 h. After the yellow solid had precipitated, the solution was removed *via* syringe and the solid was washed with hexanes (3 × 20 mL). To this solid was added compound **6** (7.00 g, 38.2 mmol, 1 equiv.) in one portion as solid and this mixture was heated to 90 °C for 16 h. After cooling to room temperature, the mixture was diluted with $CHCl_3$ (100 mL) and EtOH (50 mL) was added slowly with water bath cooling. The resulting mixture was stirred at room temperature for 1 h and subsequently concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (100 mL) and neutralized with sat. aqueous solution of $NaHCO_3$ (200 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (4 × 200 mL). The combined organic layers were dried (Na_2SO_4), filtrated and concentrated under reduced pressure. Column chromatography (SiO_2, hexanes/EtOAc 6:1) afforded **8** (7.61 g, 66%) as a colorless solid. R_f = 0.29 (SiO_2; hexanes/EtOAc 6:1).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, J = 7.1 Hz, 6 H, CH_2CH_3), 4.49 (q, J = 7.1 Hz, 4 H, CH_2CH_3), 8.42 (s, 2 H, 3-H) ppm. The data agree with those of the literature.[1]

4-Bromopyridine-2,6-dicarboxamide (9): This compound was prepared by a slight modification of the published procedure.[1] A suspension of diester **8** (7.50 g, 24.8 mmol, equiv.) in 25% aqueous NH_3 solution (600 mL) was stirred at 35 °C for 1 h. After cooling to 0 °C for 1 h, the precipitate was filtrated off, washed with water (100 mL), CH_2Cl_2 (0 °C cold, 100 mL) and Et_2O (0 °C cold, 100 mL). Drying of the precipitate under reduced pressure afforded **9** (5.00 g, 83%) as a colorless solid. R_f = 0.30 (SiO_2; CH_2Cl_2/MeOH 10:1).
^{1}H NMR (400 MHz, DMSO-d6): δ = 7.86 (s, 2 H, NH), 8.30 (s, 2 H, 3-H), 8.91 (s, 2 H, NH) ppm. The data agree with those of the literature.[1]
Alternative Procedure: diester **8** (2.00 g, 6.60 mmol) was dissolved in methanol (3 mL) and the mixture was heated to 65 °C. Gaseous ammonia was slowly bubbled through the solution and the mixture was stirred for 3 h. After 1.5 h additional methanol (1.5 mL) was added. Removal of the solvent afforded the desired bisamide **9** (1.60 g, 99%) as solid that was used without further purification.

4´-Bromo-6,6´´-dimethyl-2,2´:6´,2´´-terpyridine-4,4´´-diyl bisnonaflate (4): To a suspension of **9** (4.50 g, 18.4 mmol, 1 equiv.) in toluene (300 mL) were added pentane-2,4-dione (**7**) (26.4 mL, 258 mmol, 14 equiv.) and *p*-toluenesulfonic acid (1.16 g, 6.09 mmol, 0.33 equiv.). Using a Dean-Stark-apparatus, the suspension was heated to reflux for 16 h resulting in a black solution. After cooling to room temperature, the mixture was concentrated under reduced pressure. The remaining residue was dissolved in CH_2Cl_2 (300 mL) and washed with sat. aqueous $NaHCO_3$ solution (300 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with brine (400 mL), dried (Na_2SO_4), filtrated, concentrated under reduced pressure and thoroughly dried in vacuo to provide crude **5** as brown solid.
Without purification, crude **5** was dissolved in 1,2-dichloroethane (700 mL). *N*,*N*-Diisopropylethylamine (25.8 mL, 147 mmol, 8 equiv.) and trimethylsilyl trifluoromethanesulfonate (33.4 mL, 184 mmol, 10 equiv.) were slowly added and the brown mixture was heated to reflux for 3 d. After cooling to room temperature, the mixture was exposed to air and stirred for 10 min at room temperature. Then, trifluoroacetic acid (1.85 mL, 24.0 mmol, 1.3 equiv.) was added and the mixture was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure and thoroughly dried. The residue was suspended in EtOAc (200 mL) and sonicated for 30 min at room temperature. The remaining precipitate was brought to a plug on Celite® (ca. 3 cm), washed with EtOAc (3 × 20 mL)* and then dissolved in MeOH (5 × 30 mL). The methanolic filtrate was concentrated under reduced pressure and dried. The brown residue was dissolved in THF (80 mL). At 0 °C, sodium hydride (60% in mineral oil, 11.1 g, 276 mmol, 15 equiv.) was added as solid in portions. After stirring for 10 min at 0 °C, nonafluorobutanesulfonyl fluoride (16.6 mL, 92.2 mmol, 5 equiv.) was slowly added and the mixture was stirred at room temperature for 16 h. At 0 °C sat. aqueous NH_4Cl solution (50 mL)** was added dropwise. The mixture was stirred for 10 min at 0 °C, then diluted with EtOAc (200 mL) and water (200 mL). The aqueous layer was separated and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (300 mL) and concentrated under reduced pressure. The residue was dissolved in THF (50 mL) and loaded on silica gel. Column chromatography (SiO_2; hexanes/EtOAc 1:0 to 15:1) afforded **4** (3.05 g, 18% over 4 steps) as a colorless solid. R_f = 0.80 (SiO_2; hexanes/EtOAc 10:1).
* *This washing of the precipitate can take many hours; vacuum filtration is recommended; using substantially more EtOAc than noted can significantly diminish the yield*. ** *The quench with sat. aqueous NH_4Cl solution can lead to a highly exothermic reaction with the excess of sodium hydride and should be done very cautiously*.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.72 (s, 6 H, Me), 7.16 (d, J = 2.3 Hz, 2 H, 5-H), 8.27 (d, J = 2.3 Hz, 2 H, 3-H), 8.72 (s, 2 H, 3´-H) ppm; the spectrum of this sample shows minor impurities.

4´-Bromo-6,6´´-dimethyl-4,4´´-bis(dimethylamino)-2,2´:6´,2´´-terpyridine (2) and 6,6´´-Dimethyl-4,4´,4´´-tris(dimethylamino)-2,2´:6´,2´´-terpyridine (3): A solution of bisnonaflate **4** (1.00 g, 1.07 mmol, 1 equiv.) in dimethylamine (2 M in THF; 15.0 mL, 29.9 mmol, 28 equiv.) was stirred in a microwave vessel at 100 °C under irradiation for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (80 mL) and 1 M aqueous NaOH solution (80 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtrated and concentrated under reduced pressure. Column chromatography (basic Al_2O_3, activity grade I; CH_2Cl_2/EtOAc 15:1 to 4:1, then CH_2Cl_2/MeOH 10:1) afforded **2** (0.209 g, 46%) and **3** (0.118 g, 28%) as colorless solids.

Data of **2**: R_f = 0.63-0.45 (neutral Al_2O_3, activity grade I; CH_2Cl_2/EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (s, 6 H, 6-Me), 3.09 (s, 12 H, NMe), 6.43 (d, J = 2.5 Hz, 2 H, 5-H), 7.73 (d, J = 2.5 Hz, 2 H, 3-H), 8.58 (s, 2 H, 3´-H) ppm. The data agree with those of the literature.[1]

Data of **3**: R_f = 0.32 (neutral Al_2O_3, activity grade I; CH_2Cl_2/MeOH 25:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.57 (s, 6 H, 6-Me), 3.10 (s, 12 H, 4-NMe), 3.20 (s, 6 H, 4´-NMe), 6.41 (d, J = 2.5 Hz, 2 H, 5-H), 7.73 (s, 2 H, 3´-H), 7.78 (d, J = 2.5 Hz, 2 H, 3-H) ppm. The data agree with those of the literature.[1]

4´-Bromo-6,6´´-dimethyl-4,4´´-di(pyrrolidin-1-yl)-2,2´:6´,2´´-terpyridine (10): According to the reaction leading to **2** and **3**, a solution of bisnonaflate **4** (0.200 g, 0.214 mmol, 1 equiv.) in pyrrolidine (1.06 mL, 12.8 mmol, 60 equiv.) was stirred in a microwave vessel at 120 °C under irradiation for 1 h. Work-up and column chromatography (basic Al_2O_3, activity grade I; CH_2Cl_2/EtOAc 5:1 to 1:1) afforded **10** (0.062 g, 61%) as colorless crystals.

R_f = 0.21 (neutral Al_2O_3, activity grade I, CH_2Cl_2/EtOAc 4:1). M.p. >200 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02–2.08 (m, 8 H, 4-NCH$_2$CH_2), 2.54 (s, 6 H, 6-Me), 3.39–3.45 (m, 8 H, 4-NCH_2CH$_2$), 6.31 (d, J = 2.3 Hz, 2 H, 5-H), 7.55 (d, J = 2.3 Hz, 2 H, 3-H), 8.56 (s, 2 H, 3´-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (q, 6-Me), 25.5 (t, 4-NCH$_2$CH_2), 47.2 (t, 4-NCH$_2$CH_2), 102.8, 106.5, 124.1 (3 d, C-3´, C-5), 134.8, 153.2, 154.5, 157.1, 157.8 (5 s, C-2, C-2´, C-4, C-4´, C-6) ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{29}BrN_5$ $[M+H]^+$: 478.1601, found 478.1618.

Synthesis of 6,6´´-Dimethyl-4,4´,4´´-tris(dimethylamino)-2,2´:6´,2´´-terpyridine (3) by Buchwald-Hartwig Amination: To a solution of **2** (0.190 g, 0.446 mmol, 1 equiv.), NaO*t*Bu (0.090 g, 0.936 mmol, 2.1 equiv.), $Pd(dba)_2$ (12.8 mg, 22.0 µmol, 0.05 equiv.) and 2-dicyclohexylphosphino-2´,6´-dimethoxybiphenyl (18.3 mg, 45.0 µmol, 0.1 equiv.) in toluene (5 mL) dimethylamine (2 M in THF, 446 µL, 0.891 mmol, 2 equiv.) was added. The resulting red mixture was stirred at 90 °C for 3 d in an ACE pressure tube. After cooling to room temperature, the mixture was quenched by the addition of 2 M aqueous NaOH solution (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtrated and concentrated under reduced pressure. Recrystallization of the resulting solid from hot $CHCl_3$/Et_2O afforded **3** (0.141 g, 81%) as colorless crystals.

Synthesis of 6,6´´-Dimethyl-4,4´,4´´-tri(pyrrolidin-1-yl)-2,2´:6´,2´´-terpyridine (11) by Buchwald-Hartwig Amination: According to the Buchwald-Hartwig amination of **2**, to a solution of **10** (15 mg, 31 µmol, 1 equiv.), NaO*t*Bu (6.9 mg, 72 µmol, 2.3 equiv.), $Pd(dba)_2$ (0.9 mg, 1.6 µmol, 0.05 equiv.) and 2-dicyclohexylphosphino-2´,6´-dimethoxybiphenyl (1.3 mg, 3.1 µmol, 0.1 equiv.) in toluene (1 mL) was added a solution of pyrrolidine (5.1 µL, 4.4 mg, 63 µmol, 2.0 equiv., dissolved in 0.1 mL of toluene). The resulting mixture was stirred at 100 °C for 16 h. Work-up and recrystallization from hot $CHCl_3$/Et_2O afforded **11** (14 mg, 95%) as colorless crystals.

R_f = 0.36-0.24 (neutral Al_2O_3, activity grade I; CH_2Cl_2/MeOH 25:1). M.p. >215 °C (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.98–2.07 (m, 12 H, 4-NCH$_2$CH_2), 2.53 (s, 6 H, 6-Me), 3.37–3.47 (m, 8 H, 4-NCH_2CH$_2$), 3.52–3.57 (m, 4 H, 4´-NCH_2CH$_2$), 6.27 (d, J = 2.3 Hz, 2 H, 5-H), 7.52 (s, 2 H, 3´-H), 7.61 (d, J = 2.3 Hz, 2 H, 3-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.0 (q, 6-Me), 25.5 (t, 4-NCH$_2$CH_2), 47.1,* 47.5 (2 t, 4,4´´-NCH$_2$CH$_2$), 102.7, 104.2, 105.8 (3 d, C-3, C-3´, C-5), 153.1, 153.8, 156.2, 157.1, 157.6 (5 s, C-2, C-2´, C-4, C-4´,C-6) ppm; *signal with higher intensity. HRMS (ESI-TOF): calcd. for $C_{29}H_{36}N_6$: 469.3080 $[M+H]^+$; found m/z = 469.3094.

6,6´´-Dimethyl-4,4´´-bis(dimethylamino)-2,2´:6´,2´´-terpyridine (1): To a solution of **2** (0.100 g, 0.235 mmol, 1 equiv.), $Pd(OAc)_2$ (10.5 mg, 47.0 µmol, 0.2 equiv.) and 1,3-bis(diphenylphosphino)propane (39.0 mg, 94.0 µmol, 0.4 equiv.) in DMF (5 mL) were added Et_3N (0.293 mL, 0.211 mmol, 9 equiv.) and HCO_2H (64.8 mg, 53.1 µL, 141 µmol, 6 equiv.). The mixture was stirred at 90 °C for 6 h. After cooling to room temperature, 0.5 M aqueous NaOH solution (15 mL) was slowly added and the resulting suspension was stirred for 15 min at room temperature. The precipitate was filtered off, dissolved in MeOH (3 × 10 mL) and the methanolic filtrate was concentrated under reduced pressure. Recrystallization from hot $CHCl_3$/Et_2O afforded **2** (51 mg, 63%) as colorless crystals.

R_f = 0.43-0.18 (neutral Al_2O_3, activity grade I; CH_2Cl_2/MeOH 50:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (s, 6 H, 6-Me), 3.06 (s, 12 H, NCH_3), 6.41 (d, J = 2.4 Hz, 2 H, 5-H), 7.76 (d, J = 2.4 Hz, 2 H, 3-H), 7.87 (t, J = 7.8 Hz, 1 H, 4´-H), 8.39 (d, J = 7.8 Hz, 2 H, 3'-H) ppm. The data agree with those of the literature.[1]

6,6´´-Dimethyl-4,4´´-di(pyrrolidin-1-yl)-2,2´:6´,2´´-terpyridine (12): To a solution of **10** (14 mg, 29 µmol, 1 equiv.), $Pd(OAc)_2$ (1.3 mg, 5.8 µmol, 0.2 equiv.) and bis(diphenylphosphino)propane (4.8 mg, 12 µmol, 0.4 equiv.) in DMF (0.4 mL) were added Et_3N (36 µL, 0.27 mmol, 9 equiv.) and HCO_2H (8.3 mg, 6.8 µL, 0.18 mmol, 6 equiv.). The mixture was stirred at 90 °C for 36 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (15 mL) and washed with 1 M aqueous NaOH solution (2 × 10 mL) and the combined aqueous layers were extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtrated and concentrated under reduced pressure. Column chromatography (basic Al_2O_3, activity grade I; CH_2Cl_2/EtOAc/MeOH 10:1:0 to 10:3:0 to 10:1:0.1) afforded **12** (6.1 mg, 51%) as a colorless solid.

R_f = 0.54-0.27 (neutral Al_2O_3, activity grade I; CH_2Cl_2/MeOH 100:3). M.p. >155 °C (decomp.). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 2.04–2.08 (m, 8 H, 4-NCH$_2$CH_2), 2.56 (s, 6 H, 6-Me), 3.44 (s, 8 H, 4-NCH_2CH$_2$), 6.31 (d, J = 2.2 Hz, 2 H, 5-H), 7.61 (s, 2 H, 3-H), 7.88 (s, 1 H, 4´-H), 8.38 (d, J = 7.7 Hz, 2 H, 3´-H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ = 24.9 (q, 6-Me), 25.5 (t, NCH$_2$CH$_2$), 47.2 (t, NCH$_2$CH$_2$), 102.3 (d, C-3), 106.1 (d, C-5), 121.3 (d, C-3´), 137.9 (d, C-4´), 153.6, 155.8, 156.0 (3 s, C-2, C-2´, C-4), 158.0 (s, C-6) ppm. HRMS (ESI-TOF): calcd. for $C_{25}H_{29}N_5$ $[M+H]^+$: 400.2501; found 400.2506.

Copies of NMR spectra of all compounds and details concerning the computations can be found in the Supporting Information.

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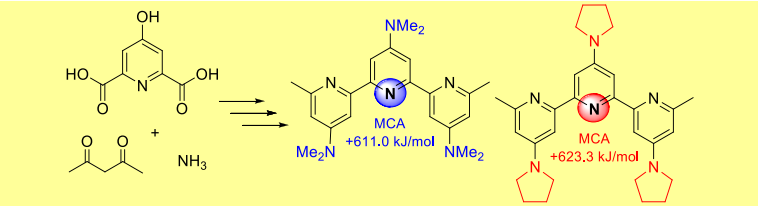

Super! The access to very electron-rich terpyridines was further developed making the new tri(pyrrolidino)-substituted derivatives available. Calculated methyl cation affinities (MAC) reveal that these compounds are the strongest Lewis basic terpyridines synthesized to date and thus should be unique donor ligands.

M. Kleoff, S. Suhr, B. Sarkar, R. Zimmer, H.-U. Reissig, M. Marin-Luna, H. Zipse*

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Efficient Syntheses of New Super Lewis Basic Tris(dialkylamino)-Substituted Terpyridines and Comparison of Their Methyl Cation Affinities