Basicity and Solvatochromism of Concave Pyridines with Extended π-Systems in Protic and Nonprotic Solvents[‡]

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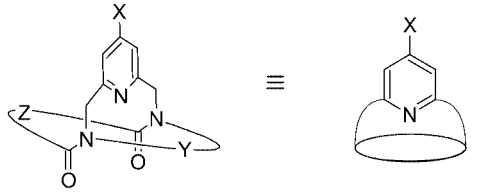
Arylalkyne substituents have been connected to the 4-positions of concave pyridines to give substituted concave pyridines **3**, which possess absorption maxima above 300 nm in their UV spectra. Their protonation and their interaction with polar solvents have been studied. Firstly, with strong acids, protonation occurs, and relative basicities ($\log K_{ass}$) have been determined. Substitution at the remote aryl ring influences the basicity of the pyridine, and Hammett plots show a linear relation between $\log K_{ass}$ and the electron density of the remote aryl ring. Secondly, concave pyridines **3** are capable of "sensing" hydrogen bonds between their pyridine nitrogen atom and an alcohol. Shifts of the absorption maxima to longer wavelengths are observed when *certain quantities* of alcohol are added.

Introduction

The intensive study of supramolecular processes[1−3] in recent decades has produced deep insights into molecular recognition processes. One potential application of this knowledge is in the construction of chemical sensors.[4−6] The two key features of a sensor molecule are: (i) the recognition process, and (ii) the production of a signal. In particular, sensors that produce optical signals are very useful, because they can be applied for the detection of very tiny amounts of analytes and, through the use of a (fluorescence) microscope, structural details of surfaces can be investigated visually. If, for instance, different OH groups − on cellulose or silica gel, to name some materials − are to be analysed, the formation of a hydrogen bond between the OH groups of the analyte and a hydrogen bond acceptor could be used for recognition.

In order to construct a selective sensor for different OH groups on these surfaces, the hydrogen bond recognition site has to bind the OH groups differently, and it also has to be connected with a reporter group that produces the optical signal.

Concave pyridines **1** are known to interact differently with varying OH groups. These bis(macrocyclic) pyridines



1

Y = $CH_2(CH_2OCH_2)_3CH_2$

Z = $C_{10}H_{20}$

1	X
a	I
b	H
c	OMe
d	NEt_2

Scheme 1

1 (Scheme 1) are a class of concave reagents that mimic the nature of enzymes[7] in the incorporation of a functional group in a concave environment.[8] By use of concave pyridines **1** as catalysts, alcohols can be acylated by ketenes[9] with remarkable selectivities. The selective recognition of a specific OH group of an alcohol,[10,11] including carbohydrates,[12,13] by the concave pyridine is governed by the shielding of the pyridine nitrogen atom.

The synthesis of concave pyridines **1** is well established:[14,15,16] the bis(macrocyclic) concave pyridines are accessible from pyridine-2,6-dialdehydes through two subsequent macrocyclizations. The chains Y and Z and the substituent X in the 4-position can be widely varied, and by use of halo-substituted concave pyridines **1**, even an arylalkyne-substituted concave pyridine − **3a** − has been synthesized by Sonogashira coupling with the terminal arylalkyne **2a**.[17]

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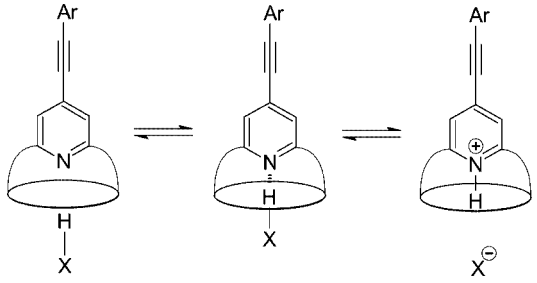
The introduction of the additional conjugated π-system in **3a** results in a long-wave absorption band in the UV/Vis spectrum, which may be used to gain deeper insight into the mechanism of the catalysis discussed above.[17,18] In this work we describe the synthesis of a family of arylalkyne-substituted concave pyridines **3a**−**f** and study the protonation of and hydrogen bond formation by the pyridine nitrogen atoms in **3**.

Results and Discussion

The successful[17] coupling of the iodo-substituted bimacrocyclic concave pyridine **1a** with phenylacetylene opens a general route to arylalkynyl-substituted concave pyridines **3** (Scheme 2). The iodo-bis(macrocycle) **1a** was therefore coupled with several arylalkynes **2**[19−22] to give new 4-substituted concave pyridines **3**. For comparison, the 4-iodopyridine-2,6-dicarboxylate **4**[17,23] was also coupled with different arylalkynes **2**, resulting in the formation of 4-substituted pyridinediesters **5**. Most of the terminal acetylenes **2** had to be synthesized; a Sonogashira reaction was also used for this purpose.[24,25] Palladium-catalysed coupling of trimethylsilylacetylene and the respective iodoarene gave the terminal arylethynes **2** in good yields after deprotection with a base.

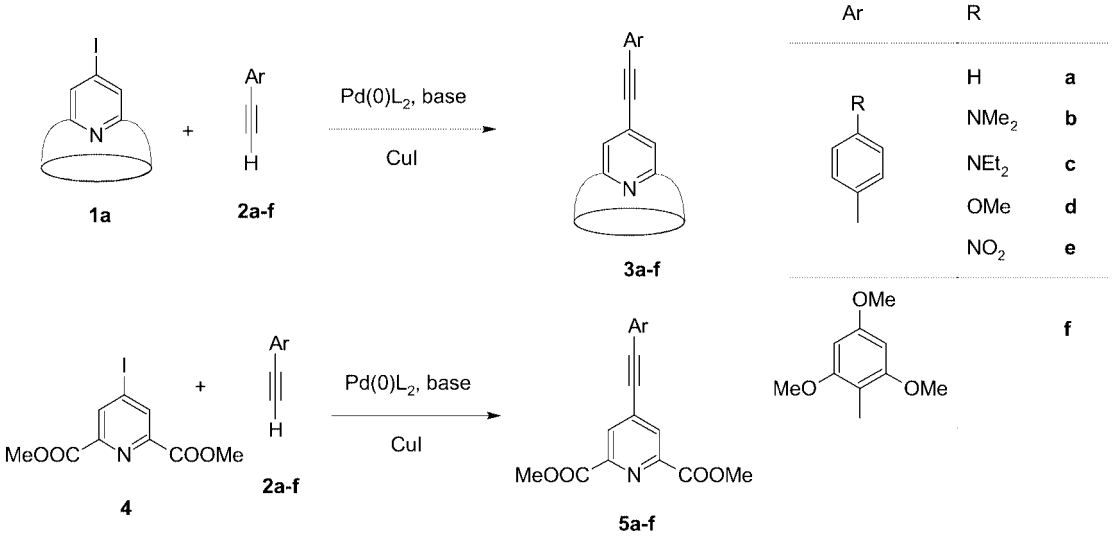
The new concave pyridines **3** and all diesters **5** were characterized spectroscopically, although some of the esters **5** had already been described in the literature, some of them, though, with only marginal characterization.[24,25] Because of the amide bridgeheads, the new 4-substituted concave pyridines **3** exist as mixtures of conformers, as does the starting material **1a**.[14,17]

As explained in the Introduction, the arylalkyne residue was attached to the concave pyridine with the goal of allowing photometric investigation of the formation of hydrogen bonds between the pyridine nitrogen atom and the OH groups of alcohols. There is, however, a competing reaction between pyridines and acidic hydrogen atoms: protonation, which also results in changes in the UV spectra. The stepwise transfer of a hydrogen atom from an alcohol to a pyridine is shown in Scheme 3.



Scheme 3

In order to be able to distinguish between the UV changes caused by protonation and those produced by the formation of hydrogen bonds, the protonation of all pyridines **3** and **5** had been investigated first. Trifluoroacetic acid was chosen for this purpose, as a relatively strong acid, soluble in dichloromethane and causing no significant absorption in the UV, and the UV changes observed during titrations of the pyridines with this acid were recorded. Figure 1 shows the protonation of **3a** by trifluoroacetic acid as an example, and Tables 1 and 2 list the absorption maxima and absorption coefficients for all pyridines **3** and **5** in protonated and unprotonated forms. The observation of clear isosbestic points argues for the existence of only two species in these titrations of the pyridines **3** and **5** with a strong acid. For reaction partners with less acidic hydrogen atoms, a third kind of UV spectrum, different from the neutral base and different from the protonated species, is to be expected (see below).



Scheme 2

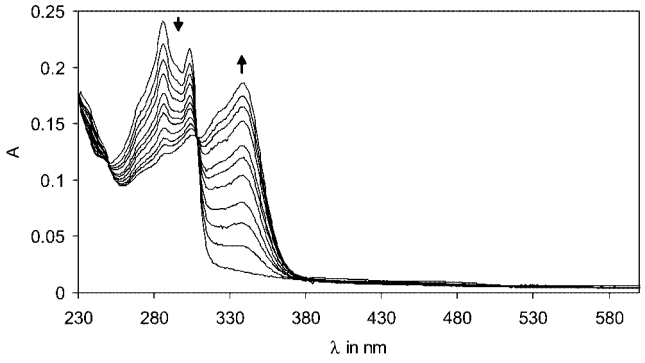


Figure 1. UV spectra from the titration of the concave phenylethynyl pyridine **3a** with trifluoroacetic acid in dry dichloromethane (concentration of **3a**: $4.95 \cdot 10^{-6}$ mol·L^{-1}); trifluoroacetic acid was added stepwise but not constantly with the same amount; the final concentration was $3.2 \cdot 10^{-4}$ mol·L^{-1}

The basicities of all new arylalkynyl-substituted pyridines **3** and **5** were quantified by photometric titrations. Both classes **3** and **5** were investigated in dichloromethane, while the basicities of the concave pyridines **3** were also determined in methanol. The analogous experiments in methanol could not be interpreted for the diesters **5**, due to their reduced basicities. Even for the concave pyridines **3**, the titrations in methanol should not be overinterpreted. When trifluoroacetic acid was added to the methanol solutions of **3**, the first droplets of acid were buffered, resulting in no change in absorption at the beginning of the titration. With larger amounts of acid added, a normal titration curve could be observed. Although all solvents were purified thoroughly, we cannot rule out that impurities may be responsible for this "buffer effect". These titration data have therefore been analysed in two ways: with and without correction for the buffer capacity {see Equation (1) (from ref.[18] ignoring buffer capacity) and Equation (2) (considering buffer capacity B). A = absorption, HA = trifluoroacetic acid, S = pyridine substrate, K_{ass} = [S·HA]/[S][HA], index 0 = total initial concentration, B = buffer capacity, determined empirically from the titration curve}. Two sets of data therefore exist for the titrations in methanol, but both suggest the same conclusions (see Figure 2).

Table 2. Maxima of absorption of dimethyl phenylethynylpyridine-2,6-dicarboxylates **5a**−**f** in dichloromethane. The extinction coefficients are given in 1000 cm^2·mol^{-1}

	λ_{max} [nm]	ε_{max}	logK_{ass}
5a[a]	298	38500	0.81
	313	40000	
5b	387.5	47000	2.41
5c	396	59600	3.57
5d	332.5	46100	1.24
5e	313.5	48700	0.69
5f	357	46300	2.06

[a] Two maxima have been found.

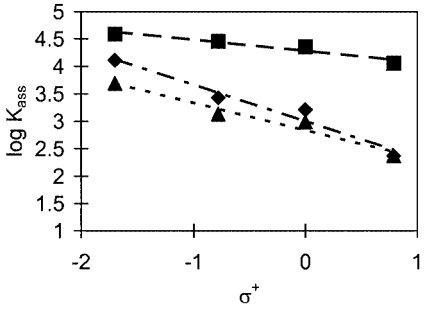


Figure 2. Hammett plot of the relative basicities (logK_{ass}) of the concave pyridines **3a**, **3b**, **3d**, and **3e** in dichloromethane (black square) and in methanol (black diamond and black triangel), versus the substituents' σ^+ constants; because methanol is protonable itself and buffers the added trifluoroacetic acid, the titrations in methanol result in two sets of log K_{ass} values depending on the formula used for their calculation [Equation (1), ignoring buffer capacity: black diamond, and Equation (2), considering buffer capacity: black triangel)

$$A = (A_S + A_{SHA} \cdot K_{ass} \cdot [HA]_0)/(1 + K_{ass} \cdot [HA]_0) \quad (1)$$

$$A = \{A_S + A_{SHA} \cdot K_{ass} \cdot ([HA]_0 - B)\}/\{1 + K_{ass} \cdot ([HA]_0 - B)\} \quad (2)$$

Relative basicities (logK_{ass}) were calculated by use of these equations; all logK_{ass} results are listed in Tables 1 and

Table 1. Maxima of absorption of unsubstituted 4-(phenylethynyl)pyridine[26] (**9**) (in cyclohexane) and concave phenylethynylpyridines **3a**−**f** (unprotonated and protonated) in dichloromethane and methanol; the wavelengths are given in nm; the extinction coefficients are given in 1000 cm^2·mol^{-1} (n. d.: not determinable)

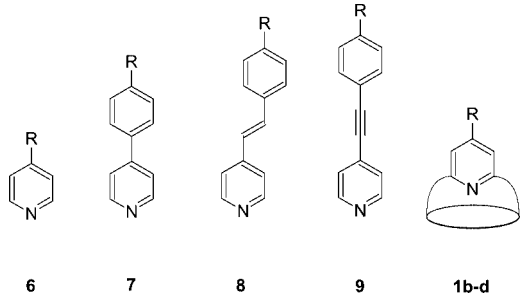
	CH_2Cl_2 *unprotonated*				*protonated*			MeOH *unprotonated*				*protonated*				
	λ_{max1}	ε_{max1}	λ_{max2}	ε_{max2}	λ_{max}	ε_{max}	**logK_{ass}**	λ_{max1}	ε_{max1}	λ_{max2}	ε_{max2}	λ_{max}	ε_{max}	**logK_{ass} with B**	**logK_{ass} without B**	buffer capacity B
9	281	27500	298.8	25000												
3a	286	37100	303.5	33600	338.5	28500	**4.36**	284.5	43400	301	39400	*305*/ 331.5	*27400*/ 31100	**3.21**	**2.99**	$5.18 \cdot 10^{-4}$
3b	360	48300	–	–	457.5	53800	**4.59**	359	47200	–	–	441.5	46500	**4.11**	**3.69**	$1.56 \cdot 10^{-4}$
3d	303	34700	318.5	33900	371.5	39700	**4.46**	304.5	44800	313.5	44500	362	38400	**3.43**	**3.13**	$4.66 \cdot 10^{-4}$
3e	315	44100	–	–	*320*/ 337	*49300*/ 46700	**4.06**	308.5	44200	–	–	317	50100	**2.37**	**2.37**	0
3f	325	24600	339	24000	406	36200	**4.39**	331	30200	–	–	396.5	35300	**3.53**	**n. d.**	$14.4 \cdot 10^{-4}$

2. In all cases, the amino-substituted compounds **3b**, **5b**, and **5c** are the most basic pyridines, while the nitro-substituted pyridines **3e** and **5e** possess the smallest basicities. Although only the remote phenyl ring is substituted, the substituents at this aryl ring do have an influence on the basicity of the pyridine nitrogen atom.

The influence of substitution at the 4-position of a pyridine ring on its basicity is well documented in the literature,[26−28] and Hammett ρ values have been calculated for several classes of substituted pyridines. Table 3 compares these literature or derived ρ values for the protonation of the pyridines **6**−**9** (Scheme 4) with the ρ values calculated from the logK_{ass} values of the concave pyridines **1** and **3**. Although only a few data points could be determined for **3**, the Hammett plots fit nicely, arguing for protonation only of the pyridine nitrogen atom (see Figure 2).

Table 3. Comparison of the ρ-values for the protonation of concave phenylethynyl pyridines **3** with the ρ-values for the protonation of 4-substituted pyridines **6**, 4-aryl pyridines **7**, 4-styryl pyridines **8**, 4-phenylethynyl pyridines **9**, and concave pyridines **1b**−**d**. The ρ values for **6**,[26] **7**,[27] **8**,[28] and **9**[28] were taken from the literature, the ρ value for **1**[29] was determined by use of σ^+ [30,31] values

Pyridine	Solvent	ρ
Pyridines **6**	H_2O	−5.71±0.30
4-Arylpyridines **7**	H_2O/EtOH (98:2)	−0.97±0.03
4-Styrylpyridines **8**	H_2O/EtOH (98:2)	−0.85±0.07
4-(Phenylethynyl)pyridines **9**	H_2O/EtOH (98:2)	−0.44±0.04
Concave pyridines **1b**−**d**	EtOH	−2.10±0.18
Concave sensors **3**	MeOH	−0.66±0.10
Concave sensors **3**	$CHCl_2$	−0.20±0.04



Scheme 4

With the UV spectra for protonated and unprotonated concave pyridines **3** now known, additional experiments in the presence of acidic molecules could then be carried out to determine whether compounds **3** could be used to study the formation of hydrogen bonds. When the UV spectra of the unprotonated concave pyridines **3** and **5** were compared in different solvents (e.g., dichloromethane and methanol), solvatochromism was observed for the concave pyridines **3**. Relatively broad maxima were observed for most of the concave pyridines **3**, with the sharpest signal being shown by the parent phenylethynyl-substituted bimacrocycle **3a**.

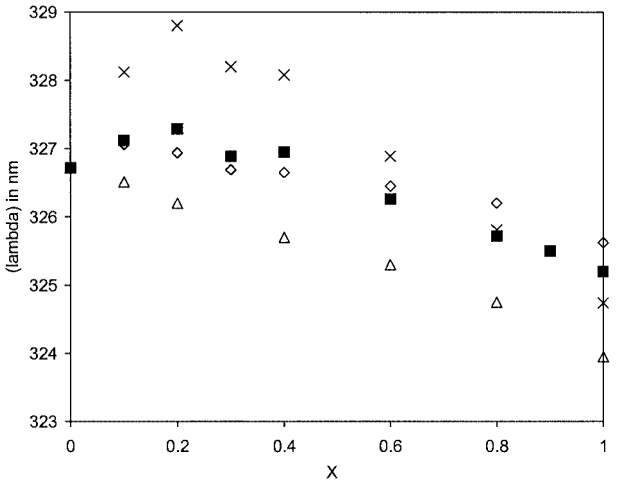


Figure 3. Absorption maxima of the concave pyridine **3a** (12.3 μM) in dichloromethane ($X = 0$) with gradual addition of different solvents ($X = 0 \rightarrow X = 1$): acetonitrile: open triangle, methanol: black square, 2-propanol: open diamond, trifluoroethanol: ×

Figure 3 shows the shifts of the absorption maximum at 327 nm for **3a** in mixtures of different solvents.

The addition of a more polar solvent to a dichloromethane solution of **3a** always has an influence on the position of the absorption maximum. Thus, the change in solvent polarity from 0 to 100% of acetonitrile in a dichloromethane/acetonitrile mixture results in a linear shift from 326.8 nm to 324.0 nm. When alcohols are mixed with dichloromethane, the absorption maxima also change with increasing content of the alcohol, but not in a linear way. Also, with alcohols that are more polar than dichloromethane, the final absorption wavelength at $X = 1$ is smaller in neat alcohol than in neat dichloromethane ($X = 0$). When only a small amount of alcohol is added (e.g., $X = 0.2$), however, the wavelengths of the absorption maxima are even larger than in neat dichloromethane.

This behaviour may be explained by two effects: (i) a change in solvent polarity influencing the whole molecule and resulting in a shift to shorter wavelengths, as can be observed with acetonitrile, and (ii) the formation of hydrogen bonds between alcohols and the pyridine. However, the higher polarity of alcohols than of dichloromethane also results in a general shift as observed with acetonitrile. The results in Figure 3 may be discussed and interpreted in the following way: there is potential for the formation of hydrogen bonds between the pyridine nitrogen atom and the alcohol, which results in a shift of the absorption maxima to longer wavelengths. This shift can already be observed at small mixture ratios X, because the formation of hydrogen bonds is strong in relation to solvation only.[1−3] When the percentage of alcohol is raised considerably, however, the overall solvation of the concave pyridine **3a** by the polar solvent also becomes recognizable and gradually gives rise to absorption maxima at shorter wavelengths, just as observed with the polar solvent acetonitrile, which, in contrast to the alcohols, can only solvate the whole molecule, and cannot form a hydrogen bond.

This assumption is supported by the fact that the shifts of the absorption maxima to longer wavelengths are larger for trifluoroethanol than for methanol or 2-propanol. Because of the fluoro substitution, trifluoroethanol is more acidic than methanol or 2-propanol[32] and should therefore form stronger hydrogen bonds.

Conclusion

Concave pyridines have been connected to arylalkyne substituents through their 4-positions to give substituted concave pyridines **3**, which possess absorption maxima above 300 nm in their UV spectra. Their protonation and their interactions with polar solvents were studied. Three different processes could be observed:

(i) Proton transfer from an acid to the pyridine nitrogen atom results in UV spectra with large shifts in their absorption maxima. The existence of isosbestic points suggests a simple protonation/deprotonation equilibrium, for which relative basicities ($\log K_{ass}$) were determined. Substitution at the remote aryl ring influences the basicity of the pyridine, and Hammett plots show a linear relationship between $\log K_{ass}$ and the electron density on the remote aryl ring.

(ii) Polar solvents may also shift the absorption maxima to longer wavelength, but the shift is considerably smaller than that observed by protonation.

(iii) When the polar solvent is able to form hydrogen bonds to the pyridine nitrogen atom, shifts to longer wavelengths were observed when a certain quantity of alcohol (10−30%) was added. The more acidic the alcohol, the larger the observed shift. Unfortunately, alcohols may also cause a shift to shorter wavelengths by polar solvation, which dominates when the percentage of alcohol is large.

Overall, concave pyridines **3** are capable of sensing hydrogen bonds between their pyridine nitrogen atom and an alcohol, but the sensitivity of the system is still low. The new concave pyridines **3** therefore require further improvement.

Experimental Section

General Remarks: The following chemicals were obtained commercially and were used without further purification: bis(triphenylphosphanyl)palladium(II) dichloride (Fluka), copper(I) iodide (Fluka), phenylacetylene (**2a**, Janssen). 29-Iodo-1,14,33-triaza-17,20,23-trioxatricyclo[12.11.7.1^{27,31}]tritriaconta-27(33),28,30-triene-2,13-dione (**1a**)[17] and dimethyl 4-iodopyridine-2,6-dicarboxylate (**4**)[17] were prepared by literature procedures. The terminal alkynes **2b**,[19] **2c**,[20] **2d**,[20] **2e**,[21] and **2f**[22] were prepared from the iodoarenes by Sonogashira coupling according to the cited literature. The synthesis of **3a** has already been described.[17] THF was dried by distillation from lithium aluminium hydride, and dry triethylamine was prepared by azeotropic distillation (only the dry middle fraction was used). The solvents for spectroscopic measurements were dried before use. Column chromatography was carried out on silica gel. ^{1}H NMR and ^{13}C spectra were recorded with Bruker AC 200, Bruker AM 300 or Bruker DRX 500 (200−500 MHz and 50−125 MHz, respectively) instruments. IR spectra were recorded with a Perkin−Elmer 1600 Series machine. MS spectra were recorded on a Finnegan MAT 8230 instrument. Elemental analyses were carried out with a VarioEl machine (Elementaranalysensysteme GmbH). UV spectra were recorded with Perkin−Elmer Lambda 14. The relative basicities were determined as described.[15,16,33]

General Procedure for the Sonogashira Couplings

The iodoarene (**1** or **3**, ca. 3.2 mmol), $Pd(PPh_3)_2Cl_2$ (0.06 mmol) and copper(I) iodide (0.33 mmol), dissolved in a mixture of dry THF (15 mL) and dry triethylamine (15 mL), were subjected to ultrasound treatment under argon atmosphere for 5 min. The terminal alkyne **2a**−**f** (3.9 mmol), dissolved in dry THF (5 mL), was added by syringe. The reaction mixture was stirred for 3.5 to 4 h at 40 to 60 °C. The solvents were removed in vacuo, and the residue was dissolved in chloroform (30 mL) and extracted four times with water (10 mL each). The organic layer was separated and dried, and the solvent was removed in vacuo. The residue was purified by chromatography.

Unless stated otherwise, the amounts of solvent were chosen as listed above.

29-[4-(Dimethylamino)phenylethynyl]-1,14,33-triaza-17,20,23-trioxatricyclo[12.11.7.1^{27,31}]tritriaconta-27(33),28,30-triene-2,13-dione (3b): Compound **1a** (883 mg, 1.43 mmol), $Pd(PPh_3)_2Cl_2$ (24 mg, 34 μmol), and CuI (35 mg, 0.18 mmol) in THF (7.5 mL) and triethylamine (7.5 mL) were allowed to react with 4-(dimethylamino)ethynylbenzene (**2b**, 274 mg, 1.89 mmol) for 4 h at 60 °C according to the General Procedure, R_f (dichloromethane/ethanol, 10:1) = 0.35 (yellow fluorescence). Yield: 683 mg (75%). IR (KBr): $\tilde{\nu}$ = 2924 (m, aliph. CH), 2853 (m), 2198 (m, C≡C), 1642 (s, C=O), 1591 (s, arom. C=C), 1121 (m, C−O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90−2.55 (m, ca. 20 H, CH_2), 3.03 [s, 6 H, $N(CH_3)_2$], 3.20−4.00 (m, ca. 16 H, OCH_2), 4.60−5.30 (m, 4 H, $PyCH_2$), 6.68 (d, ^3J = 9.1 Hz, 2 H, Ar-2,6-*H*), 6.99 (d, ^4J = 1.25 Hz, 0.34 H, *ZE*, Py-*H*), 7.08 (s, 1.40 H, *ZZ*, Py-*H*), 7.24 (d, ^4J = 1.25 Hz, 0.26 H, *ZE*, Py-*H*), 7.45 (d, ^3J = 9.1 Hz, 2 H, Ar-3,5-*H*) ppm; ratio of conformers *ZZ*/*ZE*/*EE* <70:<30:not assignable. ^{13}C NMR (75 MHz, $CDCl_3$):[34] δ = 24.38 (t, CH_2CH_2C=O), 26.93−29.50 (many t, $CH_2CH_2CH_2$), 32.09 (t, CH_2C=O), 40.12 [q, $N(CH_3)_2$], 47.95 (t, NCH_2CH_2), 55.40 (t, NCH_2Py), 70.53−71.13 (many t, OCH_2), 85.46 (s, Ar-*C*≡C), 95.50 (s, Py-*C*≡C), 108.15 (s, Ar-*C*1), 111.68 (d, Ar-*C*3, Ar-*C*5), 119.46 (d, Py-*C*3, Py-*C*5), 128.58 (s, Py-*C*4), 132.13 (d, Ar-*C*2, Ar-*C*6), 150.70 (s, Ar-*C*4), 158.19 (s, Py-*C*2, Py-*C*6), 174.68 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 632 (71) [M$^+$], 602 (48), 290 (39), 250 (100). CI-MS (isobutane): *m*/*z* (%) = 633 (100) [M$^+$ +1], 69 (73). $C_{37}H_{52}N_4O_5$ (632.83): calcd. C 70.22, H 8.28, N 8.85. $C_{37}H_{52}N_4O_5 \cdot 0.2CH_3CH_2OH \cdot 0.3CH_2Cl_2$: calcd. C 67.83, H 8.12, N 8.38; found. C 67.98, H 8.21, N 7.99.

29-(4-Methoxyphenylethynyl)-1,14,33-triaza-17,20,23-trioxatricyclo[12.11.7.1^{27,31}]tritriaconta-27(33),28,30-triene-2,13-dione (3d): Compound **1a** (889 mg, 1.44 mmol), $Pd(PPh_3)_2Cl_2$ (24 mg, 34 μmol), and CuI (35 mg, 0.18 mmol) in THF (7.5 mL) and triethylamine (7.5 mL) were allowed to react with 4-methoxyethynylbenzene (**2d**, 258 mg, 1.95 mmol) for 4 h at 40 °C according to the General Procedure, R_f (dichloromethane/ethanol, 10:1) = 0.43 (yellow fluorescence). Yield: 692 mg (78%). IR (dissolved in dichloromethane): $\tilde{\nu}$ = 2926 (s, CH_2), 2209 (w, C≡C), 1646 (s, C=O), 1594 (s, arom. C=C), 1511 (s), 1251 (s, C−O), 834 (w, Ar-C-H) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90−2.55 (m, ca. 20 H, CH_2), 3.20−4.40 (m, ca. 19 H, OCH_3, OCH_2), 4.00−5.30 (m, 4 H, $PyCH_2$), 6.93 (d, ^3J = 9.0 Hz, 2 H, Ar-2,6-*H*), 7.01 (d, ^4J = 1.1 Hz, 0.32 H, *ZE*, Py-*H*), 7.11 (s, 1.42 H, *ZZ*, Py-*H*), 7.26 (d, ^4J = 1.1 Hz, 0.26 H, *ZE*, Py-*H*), 7.52 (d, ^3J = 9.0 Hz, 2 H, Ar-3,5-*H*)

ppm; ratio of conformers *ZZ*/*ZE*/*EE* <71:<39:not assignable. ^{13}C NMR (75 MHz, $CDCl_3$):[34] δ = 24.89 (t, *C*H_2*C*H_2C=O), 26.93−29.43 (many t, CH_2*C*$H_2$$CH_2$), 32.16 (t, *C*$H_2$C=O), 48.01 (t, N*C*$H_2$$CH_2$), 55.38 (q, O*C*$H_3$), 55.43 (t, N*C*$H_2$Py), 70.71−71.14 (many t, O*C*H_2), 85.80 (s, Ar-*C*≡C), 94.48 (s, Py-*C*≡C), 113.89 (s, Ar-*C*1), 114.20 (d, Ar-*C*3, Ar-*C*5), 119.25 (d, Py-*C*3, Py-*C*5), 128.43 (s, Py-*C*4), 133.06 (d, Ar-*C*2, Ar-*C*6), 158.42 (s, Py-*C*2, Py-*C*6), 160.45 (s, Ar-*C*4), 174.68 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 619 (100) [M$^+$], 523 (65), 489 (62), 237 (59), 69 (39). CI-MS (isobutane): *m*/*z* (%) = 620 (100) [M$^+$ +1], 279 (53), 99 (25). $C_{36}H_{49}N_3O_6$ (619.79): calcd. C 69.76, H 7.97, N 6.78. $C_{36}H_{49}N_3O_6$·CH_3CH_2OH·0.2CH_2Cl_2: calcd. C 67.19, H 8.18, N 6.15; found. C 67.06, H 8.51, N 6.09.

29-(4-Nitrophenylethynyl)-1,14,33-triaza-17,20,23-trioxatricyclo[12.11.7.1^{27,31}]tritriaconta-27(33),28,30-triene-2,13-dione (3e): Compound **1a** (440 mg, 0.72 mmol), $Pd(PPh_3)_2Cl_2$ (12 mg, 17 μmol), and CuI (17 mg, 0.089 mmol) in THF (7.5 mL) and triethylamine (7.5 mL) were allowed to react with 4-nitroethynylbenzene (**2e**, 149 mg, 1.03 mmol) for 6 h at 60 °C according to the General Procedure, R_f (TLC, dichloromethane) = 0.06, in the purification step, the column was finally washed with dichloromethane/ethanol (1:1). Yield: 370 mg (81%). IR (dissolved in dichloromethane): ṽ = 2926 (s, CH_2), 1647 (s, C=O), 1599 (m, arom. C=C), 1519 (m), 1343 (s, C−O), 856 (m, Ar−C−H) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90−2.55 (m, ca. 20 H, CH_2), 3.20−4.40 (m, ca. 16 H, OCH_2), 4.00−5.30 (m, 4 H, PyCH_2), 7.06 (d, ^4J = 1.2 Hz, 0.38 H, *ZE*, Py-*H*), 7.16 (s, 1.18 H, *ZZ*, Py-*H*), 7.32 (d, ^4J = 1.2 Hz, 0.36 H, *ZE*, Py-*H*), 7.56 (s, 0.08 H, *EE*, Py-*H*), 7.73 (d, ^3J = 9.0 Hz, 2 H, Ar-3,5-*H*), 8.28 (d, ^3J = 9.0 Hz, 2 H, Ar-2,6-*H*) ppm; ratio of conformers *ZZ*/*ZE*/*EE* 59:37:4. ^{13}C NMR (75 MHz, $CDCl_3$):[34] δ = 24.87 (t, *C*H_2*C*H_2C=O), 26.90−29.46 (many t, CH_2*C*$H_2$$CH_2$), 32.12 (t, *C*$H_2$C=O), 48.11 (t, N*C*$H_2$$CH_2$), 55.48 (t, N*C*$H_2$Py), 70.60−72.62 (many t, O*C*H_2), 91.33 (s, Ar-*C*≡C), 108.54 (s, Py-*C*≡C), 112.83 (s, Ar-*C*1), 119.96 (d, Ar-*C*3, Ar-*C*5), 123.75 (d, Py-*C*3, Py-*C*5), 131.25 (s, Py-*C*4), 132.70 (d, Ar-*C*2, Ar-*C*6), 147.66 (s, Ar-*C*4), 158.89 (s, Py-*C*2, Py-*C*6), 174.65 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 634 (30) [M$^+$], 523 (100), 489 (70), 277 (53), 149 (70). CI-MS (isobutane): *m*/*z* (%) = 635 (61) [M$^+$ +1], 524 (63), 279 (70), 71 (100). HRMS ($C_{35}H_{46}N_4O_7$): calcd. 634.33667; found 634.33620; ($C_{34}{}^{13}CH_{46}N_4O_7$): calcd. 635.34003; found 635.34000. $C_{35}H_{46}N_4O_7$ (634.76): calcd. C 66.23, H 7.30, N 8.83. $C_{35}H_{46}N_4O_7$·0.2CH_2Cl_2 (668.74): calcd. C 63.58, H 7.05, N 8.38; found C 63.57, H 7.16, N 8.02.

29-(2,4,6-Trimethoxyphenylethynyl)-1,14,33-triaza-17,20,23-trioxatricyclo[12.11.7.1^{27,31}]tritriaconta-27(33),28,30-triene-2,13-dione (3f): Compound **1a** (980 mg, 1.59 mmol), $Pd(PPh_3)_2Cl_2$ (44.5 mg, 60.8 μmol), and CuI (36.7 mg, 0.193 mmol) in THF (7.5 mL) and triethylamine (7.5 mL) were allowed to react with 2,4,6-trimethoxyethynylbenzene (**2f**, 370 mg, 1.03 mmol) for 4 h at 60 °C according to the General Procedure, R_f (dichloromethane/ethanol, 10:1) = 0.45. The product contains notable amounts of starting material **1a**; the starting material signals are not listed below. Therefore, no correct elementary analysis could be obtained. Yield: 620 mg (max. 88%). IR (KBr): ṽ = 2926 (s, CH_2), 2854 (s, CH), 2203 (m, C≡C), 1645 (s, C=O), 1592 (s, arom. C=C), 1463 (s), 1340 (s), 1128 (s), 813 (m), 733 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90−2.55 (m, ca. 20 H, CH_2), 3.20−4.40 (m, ca. 25 H, OCH_3, OCH_2), 4.00−5.30 (m, 4 H, PyCH_2), 6.13 (s, 2 H, Py-*3*-H), 7.05 (d, ^4J = 1.2 Hz, 0.38 H, *ZE*, Py-*H*), 7.13 (s, 1.2 H, *ZZ*, Py-*H*), 7.30 (d, ^4J = 1.2 Hz, 0.32 H, *ZE*, Py-*H*), 7.47 (s, 0.11 H, *EE*, Py-*H*) ppm; ratio of conformers *ZZ*/*ZE*/*EE* 60:35:5. ^{13}C NMR (75 MHz, $CDCl_3$):[34] δ = 24.23 (t, *C*H_2*C*H_2C=O), 26.71−28.34 (many t, CH_2*C*$H_2$$CH_2$), 32.16 (t, *C*$H_2$C=O), 47.76 (t, N*C*$H_2$$CH_2$), 55.22 (q, Ar-4-O*C*$H_3$), 55.87 (q, Ar-2,6-O*C*$H_3$), 58.01 (t, N*C*$H_2$Py), 70.60−72.62 (many t, O*C*H_3), 87.94 (s, Ar-*C*≡C), 90.21 (d, Ar-*C*3, Ar-*C*5), 93.80 (s, Py-*C*≡C), 106.65 (s, Ar-*C*1), 119.66 (d, Py-*C*3, Py-*C*5), 133.71 (s, Py-*C*4), 157.85 (s, Py-*C*2, Py-*C*6), 159.04 (s, Ar-*C*4), 162.49 (s, Ar-*C*2, Ar-*C*6), 174.647 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 680 (100) [M$^+$], 650 (32), 297 (66). CI-MS (isobutane): *m*/*z* (%) = 681 (100) [M$^+$ +1], 490 (92).

Dimethyl 4-(Phenylethynyl)pyridine-2,6-dicarboxylate (5a): Dimethyl 4-iodopyridine-2,6-dicarboxylate (**4**, 1000 mg, 3.12 mmol), $Pd(PPh_3)_2Cl_2$ (40 mg, 0.06 mmol), and CuI (67 mg, 0.35 mmol) were allowed to react with phenylacetylene (**2a**, 380 mg, 3.73 mmol) for 3.5 h at 50 °C according to the General Procedure, R_f (pentane) = 0.05. Yield: 436 mg (48%, 84%[24]). m.p. 147 °C (153−154 °C[24]). IR (film): ṽ = 2214 (w, C≡C), 1752 (s, C=O), 1720 (s, C=O), 1602 (m, arom. C=C), 1442 (s), 1259 (s, C−O) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.04 (s, 6 H, OCH_3), 7.4−7.6 (m, 5 H, Ar-*H*), 8.37 (s, 2 H, Py-*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 53.18 (q, O*C*H_3), 85.29 (s, Ar-*C*≡C), 96.80 (s, Py-*C*≡C), 121.28 (s, Ar-*C*1), 128.53 (d, Ar-*C*4), 129.53 (d, Ar-*C*3, Ar-*C*5), 129.74 (d, Ar-*C*2, Ar-*C*6), 132.00 (d, Py-*C*3, Py-*C*5), 134.37 (s, Py-*C*4), 148.38 (s, Py-*C*2, Py-*C*6), 164.63 (s, *C*=O) ppm. EI-MS (70 eV), *m*/*z* (%) = 295 (12) [M$^+$], 237 (100), 205 (44), 177 (34). CI-MS (isobutane), *m*/*z* (%) = 296 (100) [M$^+$ +1]. HRMS ($C_{17}H_{13}NO_4$): calcd. 295.08447; found 295.08420; ($C_{16}{}^{13}CH_{13}NO_4$): calcd. 296.08780; found 296.08770. $C_{17}H_{13}NO_4$: (295.30): calcd. C 69.15, H 4.44, N 4.74. $C_{17}H_{13}NO_4$·0.25 CH_3OH (303.30): calcd. C 68.31, H 4.65, N 4.62; found C 68.35, H 4.42, N 4.66.

Dimethyl 4-[4-(Dimethylamino)phenylethynyl]pyridine-2,6-dicarboxylate (5b): Dimethyl 4-iodopyridine-2,6-dicarboxylate (**4**, 1000 mg, 3.12 mmol), $Pd(PPh_3)_2Cl_2$ (40 mg, 0.06 mmol) and CuI (65 mg, 0.34 mmol) were allowed to react with 4-(dimethylamino)-ethynylbenzene (**2b**, 538 mg, 3.71 mmol) for 3.5 h at 50 °C according to the General Procedure, R_f (diethyl ether) = 0.32. Yield: 1086 mg (quant., 48%[25]). m.p. 192 °C (215−216 °C[25]). IR (Film): ṽ = 2956 (w, CH_2), 2203 (m, C≡C), 1757 (s, C=O), 1715 (s, C=O), 1593 (s, arom. C=C), 1443 (s), 1244 (s, C−O), 975 (m, Ar−C−H), 814 (m, Ar−C−H) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.03 (s, 6 H, NCH_3), 4.03 (s, 6 H, OCH_3), 6.66 (d, ^3J = 9.0 Hz, 2 H, Ar-2,6-*H*), 7.45 (d, ^3J = 9.0 Hz, 2 H, Ar-3,5-*H*), 8.30 (s, 2 H, Py-*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 39.96 (q, N*C*H_3), 53.11 (q, O*C*H_3), 84.49 (s, Ar-*C*≡C), 99.64 (s, Py-*C*≡C), 107.44 (s, Py-*C*4), 111.58 (d, Ar-*C*3, Ar-*C*5), 129.03 (d, Ar-*C*2, Ar-*C*6), 133.49 (d, Py-*C*3, Py-*C*5), 135.39 (s, Ar-*C*1), 148.16 (s, Py-*C*2, Py-*C*6), 150.96 (s, Ar-*C*4), 164.87(s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 338 (100) [M$^+$], 220 (21). CI-MS (isobutane): *m*/*z* (%) = 339 (100) [M$^+$ +1]. HRMS ($C_{19}H_{18}N_2O_4$): calcd. 338.12665; found 338.12660; ($C_{18}{}^{13}CH_{18}N_2O_4$): calcd. 339.13000; found 339.12980. $C_{19}H_{18}N_2O_4$ (338.36): calcd. C 67.45, H 5.36, N 8.28. $C_{19}H_{18}N_2O_4$·CH_3OH (370.40): calcd. C 64.85, H 5.99, N 7.57; found C 64.91, H 5.41, N 7.91.

Dimethyl 4-[4-(Diethylamino)phenylethynyl]pyridine-2,6-dicarboxylate (5c): Dimethyl 4-iodopyridine-2,6-dicarboxylate (**4**, 1000 mg, 3.12 mmol), $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol), and CuI (61 mg, 0.31 mmol) were allowed to react with 4-(diethylamino)-ethynylbenzene (**2c**, 640 mg, 3.70 mmol) for 3.5 h at 60 °C according to the General Procedure, R_f (diethyl ether) = 0.49. Yield: 705 mg (62%). m.p. 119 °C. IR (KBr): ṽ = 2970 (m, CH_2), 2202 (m, C≡C), 1719 (s, C=O), 1591 (s, arom C=C), 1520 (s), 1372 (s), 1263 (s, C−O), 1204 (s, C−O), 781 (m, Ar−C−H) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7 Hz, 6 H, CH_2CH_3), 3.40 (q, ^3J = 7 Hz, 4 H, C$H_2$$CH_3$), 4.03 (s, 6 H, OC$H_3$), 6.64 (d, ^3J =

9 Hz, 2 H, Ar-2,6-*H*), 7.42 (d, ^3J = 9 Hz, 2 H, Ar-3,5-*H*), 8.67 (s, 2 H, Py-*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.46 (q, CH_2CH_3), 44.34 (t, NCH_2), 53.11 (q, OCH_3), 84.40 (s, Ar-*C*≡C), 100.01 (s, Py-*C*≡C), 106.43 (s, Py-*C*4), 111.07 (d, Ar-*C*3, Ar-*C*5), 128.98 (d, Ar-*C*2, Ar-*C*6), 133.79 (d, Py-*C*3, Py-*C*5), 135.53 (s, Ar-*C*1), 148.15 (s, Py-*C*2, Py-*C*6), 148.59 (s, Ar-*C*4), 164.92 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 366 (59) [M^+], 351 (100). CI-MS (isobutane): *m*/*z* (%) = 367 (100) [M^+ +1]. HRMS ($C_{21}H_{22}N_2O_4$): calcd. 366.15796; found 366.15780; ($C_{20}{}^{13}CH_{22}N_2O_4$) calcd. 367.16132; found 367.16102. $C_{21}H_{22}N_2O_4$ (366.41): calcd. C 68.84, H 6.05, N 7.64; found C 68.52, H 6.28, N 7.57.

Dimethyl 4-(4-Methoxyphenylethynyl)pyridine-2,6-dicarboxylate (5d): Dimethyl 4-iodopyridine-2,6-dicarboxylate (**4**, 1003 mg, 3.12 mmol), $Pd(PPh_3)_2Cl_2$ (41 mg, 0.058 mmol), and CuI (68 mg, 0.36 mmol) were allowed to react with 4-methoxyethynylbenzene (**2d**, 538 mg, 4.08 mmol) for 4 h at 60 °C according to the General Procedure, (diethyl ether) = 0.38. Yield: 669 mg (66%). m.p. 140−141 °C. IR (film): ṽ = 2956 (w, aliph. C-H), 2211 (m, C≡C), 1750 (s, C=O), 1719 (s, C=O), 1592 (s, arom. C=C), 1442 (s), 1253 (s, C−O) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, Ar-4-OCH_3), 4.04 (s, 6 H, COOCH_3), 6.93 (d, ^3J = 9.0 Hz, 2 H, Ar-3,5-*H*), 7.53 (d, ^3J = 9.0 Hz, 2 H, Ar-2,6-*H*), 8.34 (s, 2 H, Py-*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 53.26 (q, COOCH_3), 55.34 (q, Ar-OCH_3), 84.54 (s, Ar-*C*≡C), 97.48 (s, Py-*C*≡C), 113.25 (s, Py-*C*4), 114.24 (d, Ar-*C*3, Ar-*C*5), 129.40 (d, Ar-*C*2, Ar-*C*6), 133.75 (d, Py-*C*3, Py-*C*5), 134.84 (s, Ar-*C*1), 148.26 (s, Py-*C*2, Py-*C*6), 160.78 (s, Ar-*C*4), 164.76 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 325 (81) [M^+], 267 (100), 235 (37), 207 (46). CI-MS (isobutane): *m*/*z* (%) = 326 (100) [M^+ +1]. HRMS ($C_{18}H_{15}NO_5$): calcd. 325.09503; found 325.09490; ($C_{17}{}^{13}CH_{15}NO_5$): calcd. 326.09839; found 326.09840. $C_{18}H_{15}NO_5$ (325.31): calcd. C 66.46, H 4.65, N 4.31; found C 66.17, H 4.75, N 4.25.

Dimethyl 4-(4-Nitrophenylethynyl)pyridine-2,6-dicarboxylate (5e): Dimethyl 4-iodopyridine-2,6-dicarboxylate (**4**, 1000 mg, 3.12 mmol), $Pd(PPh_3)_2Cl_2$ (43 mg, 0.061 mmol), and CuI (66 mg, 0.35 mmol) were allowed to react with 4-nitroethynylbenzene (**2e**, 576 mg, 3.97 mmol) for 3.5 h at 40−60 °C according to the General Procedure, R_f (dichloromethane) = 0.5. Yield: 670 mg (63%). m.p. 162 °C. IR (Film): ṽ = 2222 (w, C≡C), 1720 (s, C=O), 1601 (s, arom. C=C), 1523 (s), 1343 (s, C−O), 856 (m, Ar−C−H) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.06 (s, 6 H, OCH_3), 7.76 (d, ^3J = 8.7 Hz, Ar-2,6-*H*), 8.29 (d, ^3J = 8.7 Hz, Ar-3,5-*H*), 8.41 (s, 2 H, Py-*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 53.27 (q, OCH_3), 89.35 (s, Ar-*C*≡C), 93.75 (s, Py-*C*≡C), 123.73 (d, Ar-*C*3, Ar-*C*5), 127.86 (s, Py-*C*4), 129.55 (d, Ar-*C*2, Ar-*C*6), 132.81 (d, Py-*C*3, Py-*C*5), 133.08 (s, Ar-*C*1), 147.92 (s, Ar-*C*4), 148.61 (s, Py-*C*2, Py-*C*6), 164.39 (s, *C*=O) ppm. EI-MS (70 eV): *m*/*z* (%) = 340 (2.8) [M^+], 282 (100). CI-MS (isobutane): *m*/*z* (%) = 341 (100) [M^+ +1]. $C_{17}H_{12}N_2O_6$ (340.29): calcd. C 60.00, H 3.55, N 8.23. $C_{17}H_{12}N_2O_6$·0.2 CH_2Cl_2 (357.29): calcd. C 57.82, H 3.50, N 7.84; found C 58.05, H 3.64, N 7.68.

Dimethyl 4-(2,4,6-Trimethoxyphenylethynyl)pyridine-2,6-dicarboxylate (5f): Dimethyl 4-iodopyridine-2,6-dicarboxylate (**4**, 521 mg, 1.62 mmol), $Pd(PPh_3)_2Cl_2$ (26 mg, 0.037 mmol), and CuI (31 mg, 0.16 mmol) in THF (7.5 mL) and triethylamine (7.5 mL) were allowed to react with 2,4,6-trimethoxyethynylbenzene (**2f**, 400 mg, 2.08 mmol) for 4 h at 60 °C according to the General Procedure, R_f (diethyl ether) = 0.26. Yield: 460 mg (74%). m.p. 236 °C. IR (Film): ṽ = 2950 (w, CH_3), 2206 (s, C≡C), 1750 (s, C=O), 1716 (s), 1592 (s, arom. C=C), 1442 (m), 1336 (s, OCH_3), 1130 (s), 810 (w, Ar-C-H), 780 (w, Ar-C-H) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, Ar-4-OCH_3), 3.92 (s, 6 H, Ar-2,6-OCH_3), 4.03 (s, 6 H, COOCH_3), 6.13 (s, 2 H, Ar-*H*), 8.38 (s, 2 H, Py-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.26 (q, COOCH_3), 55.53 (q, Ar-C4-OCH_3), 56.10 (q, Ar-C2,C6-OCH_3), 90.40 (d, Ar-*C*3, Ar-*C*5), 91.38 (s, Py-*C*≡C), 92.78 (s, Ar-*C*≡C), 129.48 (d, s, Py-*C*3, Py-*C*5, Py-*C*4), 135.67 (s, Ar-*C*1), 148.10 (s, Py-*C*2, Py-*C*6), 163.01 (s, *C*=O), 163.21 (s, Ar-*C*4), 165.01 (s, Ar-*C*2, Ar-*C*6) ppm. EI-MS (70 eV): *m*/*z* (%) = 385 (100) [M^+], 327 (60). CI-MS (isobutane): *m*/*z* (%) = 386 (100) [M^+ +1], 117 (86). HRMS ($C_{20}H_{19}NO_7$): calcd. 385.11615; found 385.11600; ($C_{19}{}^{13}CH_{19}NO_7$): calcd. 386.11951; found 386.11950. $C_{20}H_{19}NO_7$ (385.37): calcd. C 62.36, H 4.97, N 3.63. $C_{20}H_{19}NO_7$·0.5 CH_3OH[34] (401.39): calcd. C 61.34, H 5.27, N 3.49; found C 61.53, H 5.01, N 3.53.

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