

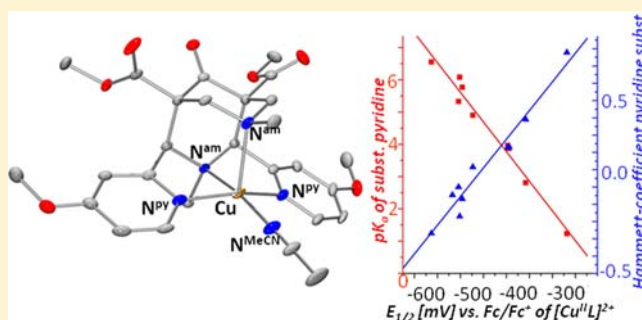
Tuning of the Properties of Transition-Metal Bispidine Complexes by Variation of the Basicity of the Aromatic Donor Groups

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Supporting Information

ABSTRACT: Bispidines (3,7-diazabicyclo[3.3.1]nonanes) as very rigid and highly preorganized ligands find broad application in the field of coordination chemistry, and the redox potentials of their transition-metal complexes are of importance in oxidation reactions by high-valent iron complexes, aziridination catalyzed by copper complexes, and imaging by ^{64}Cu positron emission tomography tracers. Here, we show that the redox potentials and stability constants of the copper(II) complexes of 15 tetradentate bispidines can be varied by substitution of the pyridine rings (variation of the redox potential over ca. 450 mV and of the complex stability over approximately 10 log units). It is also shown that these variations are predictable by the $\text{p}K_{\text{a}}$ values of the pyridine groups as well as by the Hammett parameters of the substituents, and the density functional theory based energy decomposition analysis also allows one to accurately predict the redox potentials and concomitant complex stability. It is shown that the main contribution emerges from the electrostatic interaction energy, and the partial charges of the pyridine donor groups therefore also correlate with the redox potentials.



INTRODUCTION

A large variety of tetra-, penta-, and hexadentate bispidine ligands (3,7-diazabicyclo[3.3.1]nonanes) and their transition-metal coordination chemistry have been reported.^{1–3} Important features of the adamantane-derived bispidine backbone are their rigidity and the well-defined cavity size and shape, which establish, together with subtle differences of the electronic properties of the donor groups, the thermodynamic and electronic properties and reactivities of the transition-metal complexes.^{4–7} An important observation was therefore that small modifications at the backbone may enforce well-defined structural changes [e.g., the stabilization of various and specific “Jahn–Teller isomers” of tetragonal copper(II) complexes]⁸ with predictable variations of the thermodynamic properties (complex stabilities and redox potentials, e.g., with two isomeric forms of a pentadentate bispidine)^{9,10} and reactivities (e.g., the stability and reactivity of the ferryl complexes of the two isomers of the pentadentate bispidine ligand).¹¹ The tuning of redox potentials of these complexes has been shown to be of importance in various applications of bispidine coordination chemistry, i.e., iron-based oxidation catalysis,^{12,13} copper-based aziridination catalysis,^{14–16} and selective stabilization of copper(II) complexes.^{2,10,17} The somewhat unexpected linear correlation between the redox potentials and complex stabilities of copper(II) complexes in general¹⁸ has been shown to lead to acceptable results (but separate correlations) for the two series of bispidine complexes of the type discussed here and “second generation” bispidines with aliphatic substituents at the bispidine scaffold.^{2,10}

A specific and important application for copper(II) complexes of high stability is positron emission tomography (PET), which has developed into one of the most important diagnostic tools in oncology,^{19,20} and ^{64}Cu , in particular, because of advantages in the decay scheme, half-life, and $^{64}\text{Cu}/^{67}\text{Cu}$ matched pair, is being studied with increasing interest.^{21–25} Bispidine ligands have been used successfully in this area,²⁶ and the main advantages are the efficient and often high-yielding modular ligand synthesis, variability of the donor set, high copper(II) complex stability and fast complexation kinetics, and various possibilities for coupling of the ligands to biomolecules. We have been interested in further improving the copper(II) complex stability (i.e., reduce the redox potential) without changing the structural properties of the ligand cavity. Here, we therefore describe a series of new tetradentate bispidine ligands with various para-substituted pyridine groups and the thorough analysis of their copper(II) complexes. Analogous penta- and hexadentate ligands with even higher stabilities may be prepared, and their application as chelators in PET will be reported elsewhere.

Because of the well-defined correlation of the redox potentials and copper(II) complex stabilities, it is of interest that there is a range of relatively simple and partially well-developed and promising methods to predict the redox potentials. Apart from various rather expensive quantum-chemical methods, schemes based on purely structural

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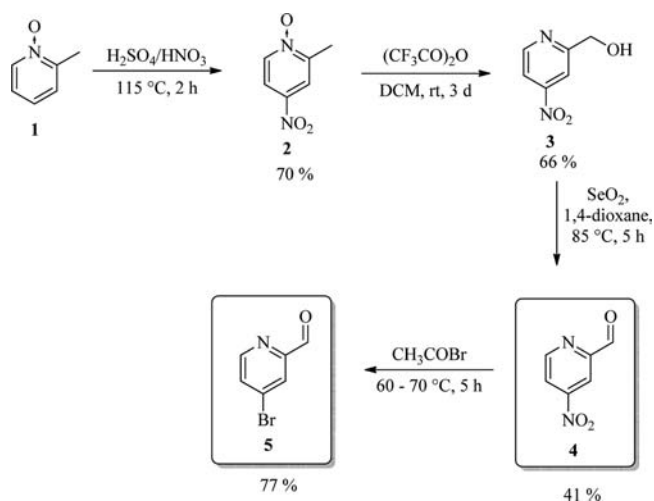
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aspects,^{27–29} ligand (and metal-ion)-based electrochemical parameters have been reported,³⁰ and other highly parametrized schemes, considering most of the decisive factors (steric strain, solvation, entropy, and electronics), have been proposed.³¹ Because of the rigid structure of the bispidine ligands and a fairly constant backbone that does not influence solvation much, the redox potentials of the copper(II) complexes described here are expected to be well-correlated with the basicity of the substituted pyridine groups. Therefore, the redox potentials of the newly synthesized 4'-substituted tetradentate bispidine ligand copper(II) complexes as well as some previously reported copper(II) compounds of substituted tetradentate bispidine ligands are compared with the pK_a values of the corresponding pyridine groups. Because electronic changes at the ligand atoms lead to predictable changes of the ligand-field and electron paramagnetic resonance (EPR) spectra, these have also been studied and analyzed by ligand-field models. Moreover, energy decomposition analyses (EDA)³² were performed on the various 4'-substituted bispidine copper(II) complexes, and the electrostatic part of the total energy and Mulliken charges are compared to the redox potentials. We conclude that we are now able to predict and tune the thermodynamic properties within the interesting series of bispidine coordination compounds, and this enables a true rational design of new compounds in this area based on simple and efficient methods.

RESULTS

Ligand and Copper(II) Complex Syntheses. The 4-substituted picolinaldehydes required for the bispidine syntheses are not commercially available and were accessible in three- to four-step sequences. The 4-nitro- and 4-bromopicolinaldehydes (**4** and **5**, respectively) were synthesized with slight changes with respect to a literature-known procedure (Scheme 1).³³ Picoline-*N*-oxide (**1**) was nitrated in

Scheme 1. Synthesis of 4-Nitro and 4-Prompicolinaldehyde (4 and 5, Respectively)



position 4 using concentrated sulfuric acid and fuming nitric acid to afford 4-nitropicoline-*N*-oxide (**2**).^{34,35} A Boekelheide rearrangement using trifluoroacetic anhydride leads to the corresponding alcohol **3**,^{33,36–39} which was oxidized with selenium dioxide to **4** (for general conditions for the selenium dioxide reaction, see 40–43; for related procedures using

manganese dioxide instead of selenium dioxide, see also refs 33 and 44). The latter product was also converted by acetyl bromide in one step to **5**, as reported previously.³³

The 4-chloro compound **9** was obtained in three steps (Scheme 2). At first, picolinic acid **6** was chlorinated in position 4 with thionyl chloride, and the in situ formed 4-chloropyridine-2-formyl chloride was esterified with methanol to afford methyl 4-chloropyridine-2-carboxylate (**7**; conditions slightly changed from those in the literature^{45–47}), which was reduced with sodium borohydride to the alcohol **8**.^{48,49} This benzylic alcohol was oxidized with selenium dioxide to the aldehyde **9**, as discussed above.

The methoxy, ethoxy, and thiomethoxy substituents as well as the dimethylamino and pyrrolidino groups were introduced by a nucleophilic ipso substitution according to known methods (Scheme 3). Therefore, either (4-nitropyridin-2-yl)methanol (**3**) or (4-chloropyridin-2-yl)methanol (**8**) as the precursor was reacted with the sodium salt of methanol, ethanol, or thiomethanol or the hydrochlorides of dimethylamine or pyrrolidine as the starting materials to afford the substituted pyridine alcohols **10**, **11**, **12**,⁵⁰ **13**,^{44,51} or **14**, which were oxidized by selenium dioxide to the aldehydes **15**, **16**, **17**, **18**⁴⁴ or **19**⁵² in moderate to good yields (for related syntheses of substituted pyridine methanols via ipso substitution of the pyridine-*N*-oxide precursors, see also refs 34 and 44).

The methyl group for an example of a bispidine with an aliphatic para substituent was introduced in the pyridinyl moiety as follows: 2,4-lutidine (**20**) was treated with hydrogen peroxide to yield the *N*-oxide **21** (according to a published procedure^{35,53,54}), which was transformed to the alcohol **22** in a Boekelheide rearrangement, and this was afterward oxidized with selenium dioxide to the aldehyde **23** (Scheme 4).

As the only nonpyridinyl compound of this series, methyl 2-pyrazinecarboxylate (**24**) was directly reduced to the aldehyde **25** with lithium–aluminum hydride (Scheme 5).⁵⁵

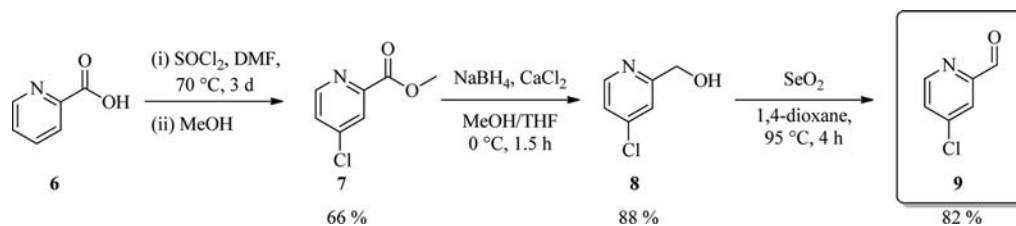
The other starting materials, 6-methoxypicolinaldehyde (**26**), 3-methylpicolinaldehyde (**27**), and 3,5-dibromopicolinaldehyde (**28**), are commercially available.

The tetradentate bispidine ligands are formed by two subsequent double Mannich reactions.⁵⁶ Therefore, dimethyl acetonedicarboxylate is reacted with methylamine and the corresponding 4-substituted picolinaldehyde (or pyrazinealdehyde). The resulting piperidones **P1–P11**, obtained as the enol tautomer (Figure 1; in solution, a complex syn/anti mixture related to the aromatic moieties of the keto/enol tautomers is observed),⁵⁷ were isolated and then reacted with formaldehyde and methylamine to the bispidones **B1–B11** (see Table 1 and Figure 2).⁵⁸

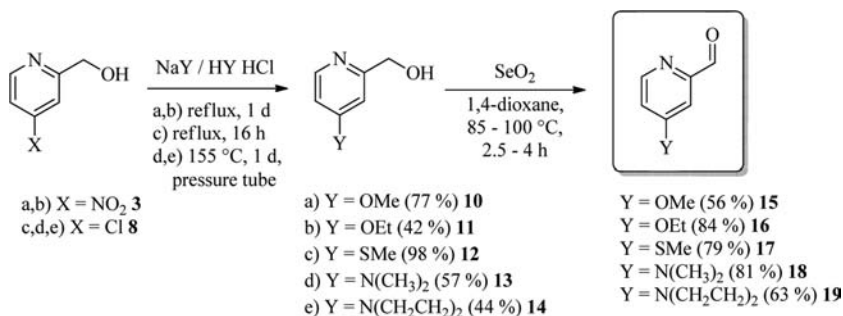
In most cases, the bispidones are isolated in the endo/endo configuration (syn isomer) concerning the aromatic 2,4-substituents, i.e., the configuration required for complexation of transition-metal ions, because this structure constitutes the thermodynamically favored isomer.^{9,59} However, for the (*p*-NO₂)- and (*p*-Br)bispidones **B1** and **B3**, both diastereomers (endo/endo or syn and endo/exo or anti isomer) were obtained as analytically pure samples by fractional crystallization. Attempts to gain the pyrazine-based as well as the *m,m*-dibromo-based bispidones **B10** and **B11** in the desired syn configuration failed (for related problems with hexadentate bispidines, see ref 60).

Because of the possibility for retro-Mannich reactions, the carbonyl group at position C⁹ of the bispidone backbone is responsible for the conversion of *syn*-bispidones to *anti*-

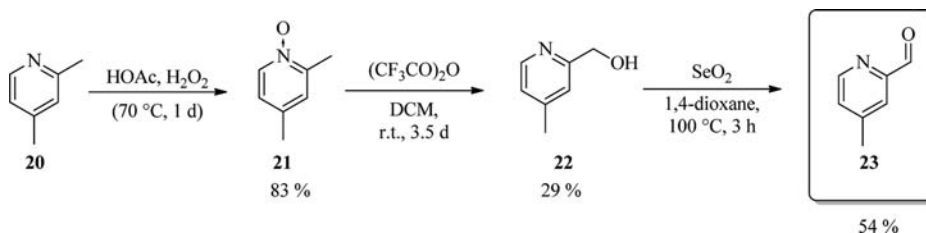
Scheme 2. Synthesis of 4-Chloropicolinaldehyde (9)



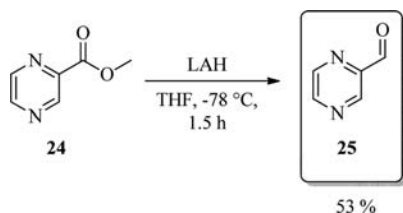
Scheme 3. General Synthesis of 4-Methoxy-, 4-Ethoxy-, 4-(Thiomethoxy)-, 4-(Dimethylamino)-, and 4-Pyrrolidinopicolinaldehyde (15–19, Respectively)



Scheme 4. Synthesis of 4-Methylpicolinaldehyde (23)



Scheme 5. Synthesis of Pyrazinecarbaldehyde (25)



bispidonates and vice versa and complete decomposition of the ligand. This can be prevented by reduction of the ketone to an alcohol. This was also expected to lead to a decrease of the redox potential of the corresponding copper(II) complexes and therefore an increase of their copper(II) complex stabilities. To further quantify the latter aspect, the *p*-Cl and *p*-MeO derivatives **B2** and **B5**, as well as the unsubstituted parent ligand **B12**,^{61–64} were also stereoselectively reduced to their secondary alcohol derivatives (Scheme 6).⁶³

With these new ligands at hand, complexation reactions with copper(II) perchlorate hexahydrate were made. In the cases of **B1–B5**, **B7**, and **B8**, the resulting complexes were isolated prior to their investigation; i.e., the ligand was reacted with copper(II) perchlorate in acetonitrile at ambient temperature overnight (Table 2). Isolation of the complexes was achieved by ether diffusion. In some cases, insufficient amounts of ligand obtained from the multistep synthetic route complicated attempts to isolate the complexes [i.e., with (*p*-EtO)₂N₂py₂

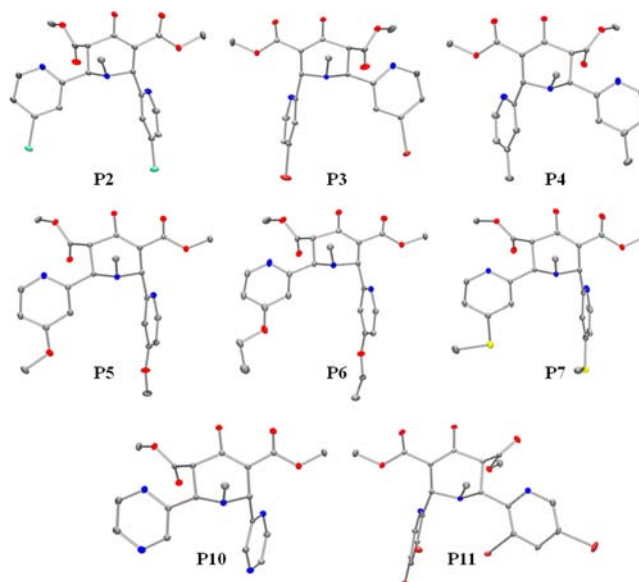
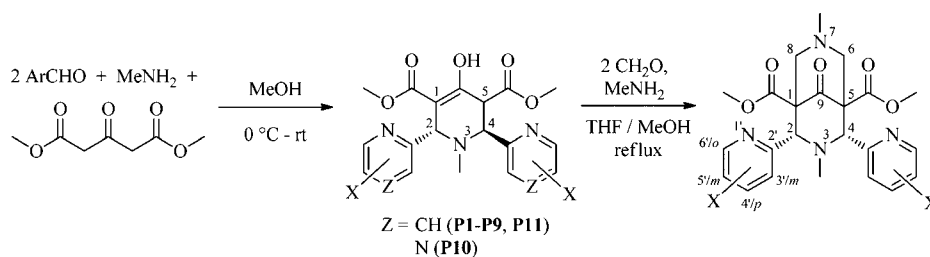


Figure 1. Experimental structures of the substituted piperidones **P2–P7**, **P10**, and **P11**. Ellipsoids are shown at the 30% probability level; cocrySTALLIZED solvent molecules and hydrogen atoms are omitted for clarity.

(**B6**) and (*m*-Me)₂N₂py₂ (**B9**)]. In these cases, the corresponding copper(II) complexes were prepared in situ by mixing the

Table 1. Synthesis of the Substituted Tetradentate Bispidones (the Desired *syn*-Bispidone Is Depicted) via the Isolated Piperidones^a



substituent X (aldehyde)		piperidone		bispidone			
(<i>p</i> -NO ₂)py	4	P1	18.0%	<i>syn</i> -B1	8.2%	<i>anti</i> -B1	42.2%
(<i>p</i> -Cl)py	9	P2	81.8%	B2	57.0%		
(<i>p</i> -Br)py	5	P3	55.2%	<i>syn</i> -B3	13.2%	<i>anti</i> -B3	55.2%
(<i>p</i> -Me)py	23	P4	42.5%	B4	48.3%		
(<i>p</i> -MeO)py	15	P5	51.3%	B5	54.8%		
(<i>p</i> -EtO)py	16	P6	45.9%	B6	9.2%		
(<i>p</i> -MeS)py	17	P7	67.6%	B7	31.4%		
(<i>o</i> -MeO)py ^{c)}	26	P8	67.2%	B8	36.2%		
(<i>m</i> / <i>3'</i> -Me)py ^{c)}	27	P9	54.6%	B9	46.8%		
pyr	25	P10	27.8%	<i>anti</i> -B10	36.4%		
(<i>m,m</i> / <i>3',S'</i> -di-Br)py ^{c)}	28	P11	62.4%	<i>anti</i> -B11	49.7%		

^aNonoptimized yields obtained by crystallization of the products.

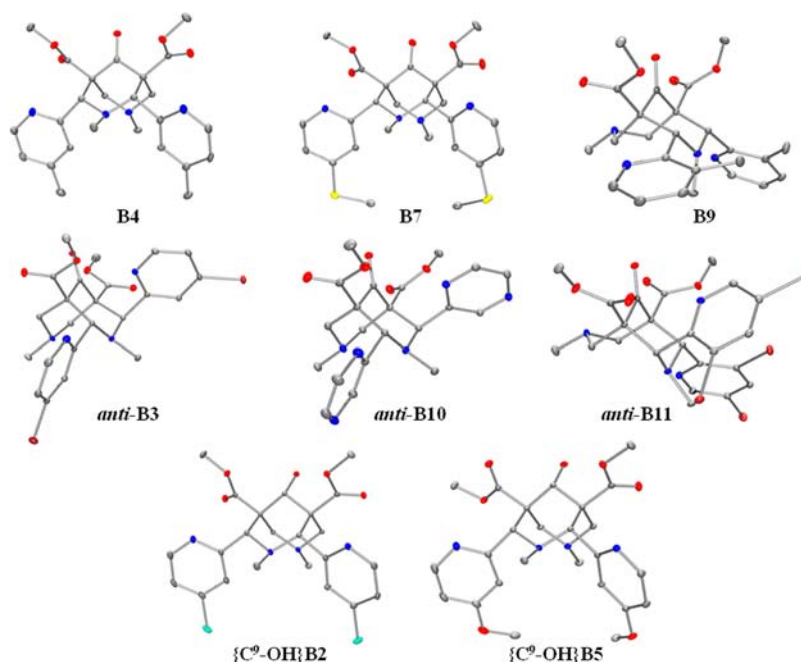


Figure 2. Experimental structures of the bispidones: *syn*-bispidones B4, B7, and B9; *anti*-bispidones B3, B10, and B11; C⁹-reduced *syn*-bispidones {C⁹-OH}B2 and {C⁹-OH}B5. Ellipsoids are shown at the 30% probability level; cocrystallized solvent molecules and hydrogen atoms are omitted for clarity.

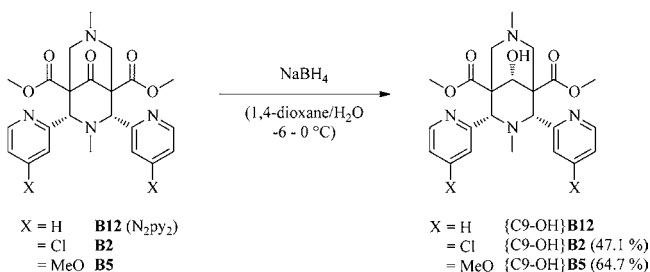
ligand and dry copper(II) perchlorate⁶⁵ in a ratio of 6:5 in acetonitrile.

Crystal Structures. As reported above, the piperidones crystallize in their enol form because of the stabilizing hydrogen bond formed by the enol hydroxy group and a carbonyl oxygen atom of one adjacent ester group. This results in an envelope conformation of the six-membered piperidone ring. The methyl group of N³ (numbering adopted from the corresponding bispidones; see Table 1) of each compound is located in the axial position. The steric hindrance caused by the pyridinyl

moieties and the N³ methyl group is minimized by adopting an *anti* configuration with respect to the pyridine rings. Each of the piperidone structures presented shows that the pyridine moiety closest to the enol double bond at C² (see Table 1 for numbering) is located in the axial position [and, therefore, the pyridine group at C⁴ is located in the equatorial position, which seems to be a prerequisite for the most stable form (Figure 1)].

The bispidones crystallize either in a chair–chair conformation [observed for *syn*-B4; *syn*-B7 and *anti*-B3; *anti*-B10, *syn*-{C⁹-OH}B2 and *syn*-{C⁹-OH}B5] or in a boat–chair

Scheme 6. Stereoselective Reduction of the Bispidones B12, B2, and B5 to the Bispidoles {C⁹OH}B12, {C⁹OH}B2, and {C⁹OH}B5



conformation (observed for *syn*-**B9** and *anti*-**B11**) with N⁷ as part of the ring with boat conformation (Figure 2). Neglecting heteroatoms, the chair–chair conformation of such a condensed bicyclic system represents the energetically favored structure. In a chair–chair conformation, the pyridinyl groups can adopt the favored equatorial position with respect to the six-membered N³ ring, and the N⁷ methyl group is able to point away from the sterically crowded cavity of the rigid bispidine backbone. Therefore, the lone-pair repulsion, emerging from N³ and N⁷, plays a minor role for the lowest-energy conformation. However, lone-pair repulsion is the reason for a rotation of the pyridinyl groups; i.e., the pyridine nitrogen atoms are pointing out of the cavity. The boat–chair conformation of *syn*-**B9** and *anti*-**B11** is a result of the specific substitution pattern. In *syn*-**B9**, the methyl groups at the 3'/meta position of the pyridine moieties force N³ into an almost trigonal-planar geometry. Therefore, the electron density of N³ is directly pointing into the cavity, and lone-pair repulsion of N³ and N⁷ becomes vitally important (this phenomenon is known as the hockey-sticks effect).^{1,66,67} This is avoided by adopting a boat–chair conformation. Similar effects apply for *anti*-**B11**.

Unfortunately, some bispidones only crystallized as the undesired anti isomers. There is no clear evidence that strains and stresses in the (hypothetical) *syn* isomer occur (e.g., in the pyrazine derivate **B10**). It might be that solubility effects are responsible. Crystallizations of the bispidones are preferably carried out in methanol as the solvent. Therefore, isomerization via a retro-Mannich reaction is still possible, and the thermodynamically more stable *syn* isomer may convert to the less stable but also less soluble anti isomer. Slow crystallization may then shift the equilibrium toward the anti isomer.

The copper(II) complexes of these tetradentate bispidine ligands are characterized by a tetragonal (square-pyramidal or elongated octahedral) coordination geometry (see Figure 3 and Table 3). The square plane is represented by the donors N³, N^{py1}, and N^{py2} and an equatorially coordinated acetonitrile (complexation reactions were carried out in acetonitrile at ambient temperature). N⁷ is the axial donor, and the Cu–N⁷ axis displays the expected pseudo-Jahn–Teller elongation, typical for Cu^{II} (d⁹). In some cases a perchlorate counterion is axially coordinated and completes the coordination sphere of Cu^{II} to distorted octahedral. An exception of this typical Cu^{II} tetradentate bispidine coordination geometry is the complex resulting from ligand **B8** (*o*-MeO substitution). In this case, a water molecule instead of acetonitrile is equatorially coordinated. This presumably is the result of two strong hydrogen bonds formed with the ortho-substituted pyridine methoxy groups. In addition, even with dry solvents (commercially available absolute acetonitrile), traces of water suffice to form the hydrate of the ligands at position C⁹ upon complexation. It is not obvious in which case the hydrate or keto form crystallizes, and similar to the coordination of a sixth ligand trans to N⁷, this might be fortuitous and based on crystal lattice effects.

Table 2. Synthesis of the Copper(II) Complexes of the Substituted Tetradentate Bispidine Ligands

X	Y	yield (%)
<i>p</i> -NO ₂	O/(OH) ₂	88.0
<i>p</i> -Cl		82.3
<i>p</i> -Br		85.5
<i>p</i> -Me		24.5
<i>p</i> -MeO		73.7
<i>p</i> -EtO		in situ ^a
<i>p</i> -MeS		91.0
<i>o</i> -MeO		48.0
<i>m</i> -Me		in situ ^a
H		73.0
<i>p</i> -MeO	Y = H, OH	91.5
<i>p</i> -Cl		88.5
H		91.5

^aThe complexes were not isolated prior to measurements; see the Experimental Section for details.

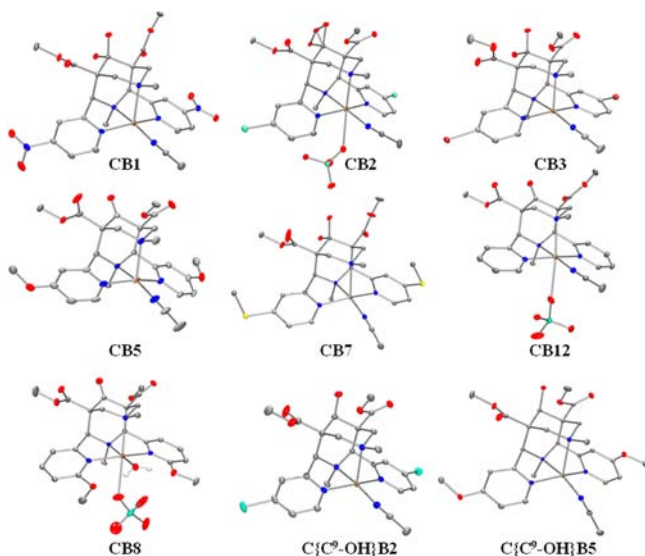


Figure 3. Experimental structures of the copper(II) complexes with the (substituted) bispidine ligands **B1–B3**, **B5**, **B7**, **B8**, **B12**, $\{C^9OH\}$ **B2**, and $\{C^9OH\}$ **B5**. Ellipsoids are shown at the 30% probability level; cocrystallized solvent molecules, counterions, and hydrogen atoms (except for the equatorially coordinated water molecule in $[Cu(\mathbf{B8})\text{-OH}_2]^{2+}$) are omitted for clarity.

Electronic and EPR Spectra. The UV/vis spectra of the copper(II) complexes with the newly synthesized bispidine ligands were measured at 25 °C in acetonitrile. To ensure the formation of identical forms of the ligand coordinated with respect to the hydrate and keto forms at position C^9 , the complexes under study were prepared in situ by taking the advantage of the fast exchange velocity of Cu^{II} . The ligand and dry copper(II) perchlorate were mixed in absolute acetonitrile and stirred for 30 min in a sealed vial. An immediate color change of the solution to blue/green indicated fast complex formation. The UV/vis spectra of the copper(II) complexes of the nine new ligands as well as of the bispidone with unsubstituted pyridine groups and the three C^9 -reduced ligands are given as Supporting Information, and the transitions are reported in Table 4. Except for $[Cu(\mathbf{B8})(\text{NCCCH}_3)]^{2+}$, the UV/vis spectra show qualitatively identical transitions: the rather

sharp band observed at around 630 nm ($\approx 15800 \text{ cm}^{-1}$) is attributed to the $d_{xy} \rightarrow d_{x^2-y^2}$ ($b_{2g} \rightarrow b_{1g}$) transition. A second, broader band observed at 900–1000 nm ($\approx 11000\text{--}10000 \text{ cm}^{-1}$) can be assigned to the $d_z^2 \rightarrow d_{x^2-y^2}$ ($a_{1g} \rightarrow b_{1g}$) transition. The coordination geometries of these copper(II) complexes in solution and the solid state are qualitatively identical, and this emerges from comparative measurements of the parameters in TiO_2 of the copper(II) complexes of the *p*-Br, *p*-MeO, and *p*-MeS ligands of **B3**, **B5**, and **B7** (see the Supporting Information).

The marginal spectroscopic variations are not surprising because the bispidine scaffold is very rigid.⁵ In the case of the para-substituted bispidine copper(II) complexes, the $N^3 \cdots N^7$ distance (see Table 3), a measure of the bispidine cavity size, varies by only about 0.04 Å (2.903–2.944 Å) in comparison to approximately 0.07 Å (2.866–2.940 Å) for the metal-free ligands (for syn isomers crystallizing in the chair–chair conformation). The distances of the in-plane pyridine donors py^1 and py^2 in these complexes range from 3.89 to 3.96 Å (a variation of only 0.07 Å; see Table 3). The experimental structural analysis reveals that with regard to the Cu^{II} -donor distances the main variability is observed for the Cu– N^7 bond length (Jahn–Teller axis) that ranges from 2.236 to 2.353 Å, a variation of 0.117 Å [for comparison: Cu– N^3 = 2.008–2.023 Å, variation of 0.015 Å; Cu– $\text{NCCCH}_3(\text{L})$ = 1.957–1.977 Å, variation of 0.020 Å; Cu– $\text{N}(\text{py})$ = 1.973–2.014 Å, variation of 0.041 Å].⁶⁸ Variation of the Cu– N^7 bond leads to differences in the perturbation of the d_z^2 orbital of the metal center and therefore has a significant influence on the $d_z^2 \rightarrow d_{x^2-y^2}$ ($a_{1g} \rightarrow b_{1g}$) transition. However, crystal structure analyses also reveal that the Cu– N^7 distance largely is modulated by coordination of perchlorate, and this does not necessarily translate to the situation observed in solution. The transition assigned to $d_{xy} \rightarrow d_{x^2-y^2}$ ($b_{2g} \rightarrow b_{1g}$) primarily arises from perturbation of the “in-plane” donors, and small differences of the bonding parameters do not seem to lead to a significant shift in the dd transition.

EPR spectra of the complexes based on **B2**, **B3**, **B5**, and **B7** have been recorded and simulated, and the corresponding parameters and spectra are given in the Supporting Information. As expected, the spin Hamiltonian parameters are very similar, and as for the electronic spectra, this is largely

Table 3. Selected Bond Lengths (Å) and Angles (deg) of the Molecular Cations of the Copper(II) Complexes

	CB1 (<i>p</i> -NO ₂)	CB2 (<i>p</i> -Cl)	CB3 (<i>p</i> -Br)	CB5 (<i>p</i> -MeO) ^a	CB7 (<i>p</i> -MeS)	CB8 (<i>o</i> -MeO)	CB12 (N ₂ py ₂)	C{C ⁹ OH} B2	C{C ⁹ OH} B5
Cu– N^3	2.008(3)	2.023(2)	2.011(3)	2.011(4)/2.004(4)	2.015(2)	1.993(3)	2.022(2)	2.023(2)	2.014(2)
Cu– N^7	2.274(3)	2.324(2)	2.253(3)	2.236(4)/2.253(4)	2.244(2)	2.340(3)	2.353(2)	2.241(2)	2.236(2)
Cu–N(py)	1.987(3)/ 2.001(3)	2.004(2)/ 1.995(2)	2.008(3)/ 2.013(3)	1.973(4)/2.001(5) / 1.989(4)/1.981(5)	1.984(2)/ 2.005(2)	2.066(3)/ 2.075(3)	2.003(2)/ 1.994(2)	2.012(2)/ 2.014(2)	1.986(2)/ 1.996(2)
Cu–L	1.968(3) ^b	1.977(3) ^b	1.957(3) ^b	1.965(4) ^b /1.960(5) ^b	1.964(2) ^b	1.932(3) ^c	1.972(2) ^b	1.971(2) ^b	1.966(2) ^b
Cu–O(ClO ₃)		2.610(3)				2.582(4)	2.757(2)		
$N^3 \cdots N^7$	2.923(4)	2.939(3)	2.921(4)	2.91(2)/2.91(2)	2.903(2)	2.917(4)	2.917(3)	2.944(2)	2.908(2)
$N(\text{py}1) \cdots N(\text{py}2)$	3.917	3.942(4)	3.963(4)	3.89(2)/3.90(2)	3.914(2)	4.084(4)	3.946(3)	3.961(2)	3.905(2)
N^3 –Cu– N^7	85.9(1)	84.79(8)	86.2(1)	86.3(2)/85.9(2)	85.79(6)	84.2(1)	83.26(7)	87.14(7)	86.19(5)
N^3 –Cu–N(py)	81.8(1)/ 82.2(1)	82.34(9)/ 81.88(9)	82.0(1)/ 82.1(1)	82.0(2)/81.6(2) / 81.6(2)/81.5(2)	82.13(7)/ 81.65(7)	82.3(1)/ 81.2(1)	81.67(8)/ 82.56(8)	81.89(7)/ 81.24(7)	81.96(6)/ 81.63(6)
N^3 –Cu–L	173.8(1) ^b	178.68(9) ^b	172.2(1) ^b	169.9(2) ^b /170.5(2) ^b	169.35(7) ^b	177.3(1) ^c	176.47(9) ^b	172.01(8) ^b	168.38(6) ^b
$N(\text{py}1)$ –Cu– $N(\text{py}2)$	158.4(1)	160.67(9)	160.50(1)	157.5(2)/156.5(2)	157.71(7)	161.0(1)	161.79(9)	159.31(7)	157.53(6)
N^7 –Cu–L	100.4(1) ^b	96.51(9) ^b	101.6(1) ^b	103.8(2) ^b /103.56(2) ^b	104.84(7) ^b	94.0(1) ^c	100.01(8) ^b	100.84(7) ^b	105.34(6) ^b
N^7 –Cu–O(ClO ₃)		173.31(8)				178.0(1)	175.26(7)		

^aTwo independent molecules. ^bL = NCCCH_3 . ^cL = H_2O .

Table 4. pK_a Values of Substituted Pyridines, Hammett Coefficients¹⁰⁹ of the Substituents, and Electrochemical Potentials and dd Transitions of the Copper(II) Bispidine Complexes

entry	substituent at pyridine	pK_a of the substituted pyridine ^a	Hammett's σ coefficient	$E_{1/2}$ (vs Fc/Fc ⁺ in ACN) ^b	dd transitions; λ/nm ($\epsilon/[L\text{ cm}^{-1}\text{ mol}^{-1}]$)
1	H (pyridine)	5.33	0	-504 (-442)	626 (77), 901 (15)
2	<i>p</i> -NO ₂	1.23	0.778	-269	630 (80), 955 (15)
3	<i>p</i> -Cl	3.97	0.227	-397 (-319)	630 (115), 957 (21)
4	<i>p</i> -Br	3.87	0.232	-394 (-330)	630 (120), 957 (21)
5	<i>p</i> -Me	6.08	-0.170	-502 (-471)	625 (106), 912 (20)
6	<i>p</i> -MeO	6.55	-0.268	-563 (-471)	629 (116), 912 (21)
7	<i>p</i> -EtO		-0.250	- (-508.0)	629 (82), 885 (15)
8	<i>p</i> -MeS		-0.047	-518 (-452)	630 (126), 920 (19)
9	<i>o</i> -MeO	3.28		-250 (-271)	698 (64), 962 (30)
10	<i>m</i> -MeO ^c	4.90	0.115	-473 ^c	627 (127), 929 (27)
11	<i>o</i> -Me ^d	6.03		-184 ^d	614 (sh), 699, 1010
12	<i>m</i> -Me (3'-Me)	5.77	-0.069	- (-484.0)	638 (72)
13	<i>m</i> -Me (5'-Me) ^c	5.77	-0.069	-496 ^c	624 (122), 920 (25)
14	<i>o</i> -Br ^c	0.81		-30 ^c	660 (52), 1091 (30)
15	<i>m</i> -Br (5'-Br) ^c	2.81	0.391	-358 ^c	633 (129), 970 (30)
16	H {C ⁹ OH}	5.33	0	-475 (-474)	626 (80), 912 (15)
17	<i>p</i> -Cl {C ⁹ OH}	3.97	0.227	-385 (-371)	628 (84), 954 (15)
18	<i>p</i> -MeO {C ⁹ OH}	6.55	-0.268	-564 (-548)	628 (83), 900 (16)

^aAverage values of literature-known protonation constants (see the Supporting Information for a detailed list). ^bValues in parentheses are measurements with in situ prepared complexes [6:5 ligand/copper(II) perchlorate in acetonitrile]; see the Experimental Section for details. ^cValues taken from ref 15; the counterions of these complexes are tetrafluoroborates instead of perchlorates. ^dValues taken from ref 14 and 110; the counterions of these complexes are tetrafluoroborates instead of perchlorates.

due to the rigidity of the bispidine backbone and, consequently, very similar structural properties.

Electrochemistry. Two different series of cyclic voltammograms (CVs) were measured at ambient temperature and in acetonitrile as the solvent (see the Supporting Information for details): (i) the isolated complexes were dissolved prior to measurement and, due to insufficient amounts of some of the ligands, (ii) all of the complexes under study were prepared in situ and directly subjected to CV measurements. Interestingly, upon comparison of the potentials of the isolated and in situ prepared copper(II) complexes of identical, C⁹-unreduced ligands, a significant shift in the redox potentials was observed (see Table 4). There are two possible explanations for this phenomenon. (i) Traces of water in the acetonitrile solution may lead to ligand exchange (OH₂ vs NCMe), and this would be expected to lead to significant shifts in the redox potentials. The expectation would be that in situ prepared complexes have water bound equatorially to the Cu^{II} center instead of an acetonitrile molecule. However, ligand exchange is expected to be relatively fast, and no time-dependent shift was observed in either of the spectra. (ii) The keto/hydrate equilibrium at C⁹ of the complexes might be another reason for the observed shift. Several crystal structures of various transition-metal bispidine complexes have been reported in either the keto or hydrate form (see above); when using methanol as the solvent, crystal structures of the C⁹ methyl acetal were also observed.¹ With (Cu^{II}-B2), we are now able to present the first example of a copper(II) bispidine complex with both forms in the lattice, indicating that the energies of these structures are very similar (see Figure 3). While the hydrate form predominates in the crystallized complexes because of the long isolation procedures, the keto form might prevail in the in situ prepared complexes, and this would be the case if the formation of hydrate is a slow process. If that were the case, the complexes of the C⁹-reduced derivatives ({C⁹OH}L) should not show major discrepancies in the redox potentials of the isolated and in situ prepared

complexes. Indeed, comparative studies with the *p*-MeO- and *p*-Cl-substituted as well as the parent unsubstituted ligand in its unreduced and C⁹-reduced forms show that the redox potentials are the same within an error of 10 mV (see Table 4). Therefore, we conclude that the in situ determined redox potentials are from the keto forms.⁶⁹

Within the series of para-substituted bispidines, the redox potential of the resulting copper(II) complex can be tuned in a range of 300 mV from the derivative with the least stable complex, [Cu^{II}(*p*-NO₂)N₂py₂](ClO₄)₂ (CB1) with $E_{1/2} = -269$ mV, to that with the most stable complex, [Cu^{II}(*p*-MeO)N₂py₂](ClO₄)₂ (CB5) with $E_{1/2} = -563$ mV.

DISCUSSION

It is known that the redox potentials of Cu^{II/I} couples in general are linearly correlated to the thermodynamic stability of the corresponding copper(II) complex, with a more negative potential resulting in a more stable copper(II) complex,⁷⁰ and nice correlations have been found for the pyridine-based¹⁰ and second-generation bispidine complexes.² It therefore appears that methods to predict the redox potentials can lead to a rational design of ligands with specific and high stability constants. This is of importance for various applications, in particular also for PET imaging with ⁶⁴Cu-labeled antibodies or nanoparticles, where the bispidine ligands have advantages because of their easy functionalization and fast complex formation and also because of their possibilities to modify the complex charge.

The influence of different substituents on the basicity of pyridine is well-studied. There are mainly two effects triggering the basicity of the pyridine ring, the inductive (I) and mesomeric (M) effects. The former depends on the electronegativity of the substituent: a more electronegative substituent decreases the basicity of pyridine. This effect decreases with the distance to the nitrogen donor from the ortho and meta to para position. The latter effect is caused by substituents with

conjugated lone pairs. Because of the need for conjugation to the nitrogen donor, the effect is large with ortho and para substitution. The same trend is valid for groups influencing the basicity by hyperconjugation, which is of minor importance but is still observed for alkyl substituents. All three effects interact with each other. However, with halides, the $-I$ effect predominates. Thus, independent from the substitution position, halides decrease the basicity of the pyridine ring ($\text{Cl} > \text{Br}$). Introduction of a methyl group enhances the basicity of the pyridine with the greatest effect in the para position followed by the ortho position. A methoxy group in the para position greatly enhances the basicity of pyridine because of a strong $+M$ effect that prevails over the $-I$ effect. Introduced at the ortho or meta position, the methoxy group causes a decrease of the basicity (stronger influence of the $-I$ effect and a less important contribution of the $+M$ effect because of the lower stability of the o -quinoid in comparison to the p -quinoid resonance structure).^{71,72}

There are many examples in the literature that deal with a systematic study of substitution effects of pyridine moieties as a simple ligand or as part of a more complex ligand system on the pyridine-to-metal bond strength,^{71,73–86} and there have also been reports of correlations of Hammett parameters with electrochemical data.⁷³ The correlation of the Hammett coefficients with the half-wave potentials of substituted metal complexes is not limited to a substitution of aromatic donor moieties.^{87,88} A linear relationship was reported of the Hammett coefficients and half-wave potentials of the cobalt(III) complexes of apically substituted hexaaza-cage ligands, which can be explained by either a through-space Coulombic mechanism or an interaction through the ligand's σ framework.⁸⁹

Figure 4 shows the correlation of the experimentally observed redox potentials of the substituted bispidine copper(II) complexes with literature-known basicities of the under-

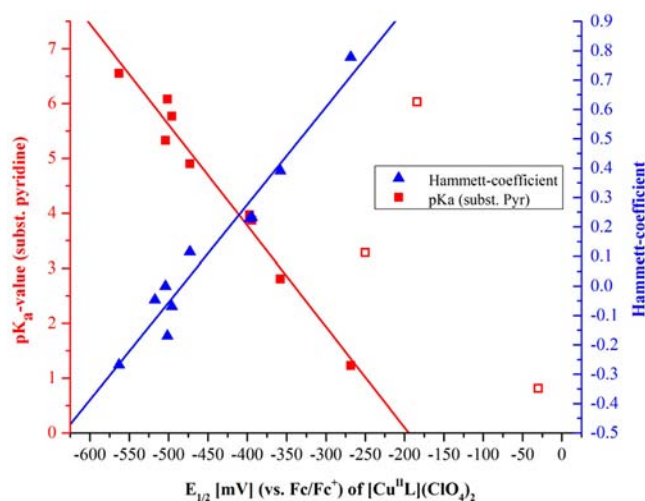


Figure 4. Correlation of the pK_a values (red squares) and Hammett's σ coefficients (blue triangles) of the underlying substituted pyridines with the redox potentials of the corresponding substituted bispidine copper(II) complexes (redox potentials from Table 4, hydrate form/isolated complexes, C^9 -reduced ligands not included; for correlation with pK_a values, entries 1–6, 9–11, and 13–15; for correlation with Hammett coefficients, entries 1–6, 8, 10, 13, and 15). Red hollow squares indicate ortho-substituted bispidine copper(II) complexes that were excluded from the linear fit.¹¹¹

lying substituted pyridine groups as well as with the Hammett coefficients of the substituents (see Table 4 for the corresponding data). There is an acceptable linear correlation; i.e., the basicity of the substituted pyridine can be used to predict the redox power and thermodynamic stability of tetradentate bispidine ligands. Note that this is primarily based on the constant and rigid ligand structure, and structural variations such as those observed with sterically hindered bispidine ligands with ortho-substituted pyridines do not fall into this correlation and were therefore not included in the fit shown in Figure 4 (note that for the same reason Hammett coefficients for ortho substitution are not established) and would need corrections for steric effects.^{28,29,90} Hammett coefficients, which were introduced to evaluate the influence of substituents at the benzene ring on the reaction rate of side-chain reactions (e.g., the hydrolysis of benzoic esters),^{91,92} are linearly correlated to the basicity of substituted pyridines and can therefore also be used to estimate the stability of even more complex, multisubstituted bispidine ligands.^{93,94} On the basis of these observations, we predict a very low redox potential for a tetradentate bispidine with para-substituted N,N -dimethylaminopyridine (DMAP) groups ($p\text{-Me}_2\text{N}$) N_2py_2 , with a pK_a value of DMAP of 9.47 (see the Supporting Information) and the corresponding Hammett coefficient of $\sigma_{\text{para}} = -0.6$. Using these correlations, a redox potential ($E_{1/2}$) of -710 or -664 mV, respectively, lower than all others, can be expected.

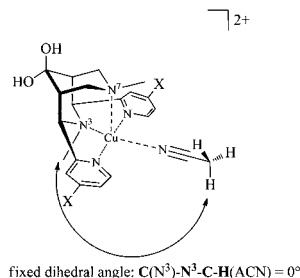
The ligand-field splitting of a transition-metal complex depends on the metal center, the donor atoms, and the coordination geometry, and with similar geometries, it is approximately inversely proportional to the sixth power of the metal–donor distance; i.e., with a given and known structure, the spectra may be predicted based on the ligand-field properties of the donor groups.⁹⁵ To do this, we have used a known parametrization for the ligand-field modeling, using the angular overlap model approach (AOM),^{96–99} in order to find a set of parameters that could also be used to predict the redox potentials and complex stabilities.

Although some trends are observable (e_{σ} strength: $p\text{-MeO} > p\text{-Br} > p\text{-NO}_2$), the obtained data, especially when ortho- and meta-substituted groups are included, do not lead to a consistent picture with respect to the strength of inductive and mesomeric effects and their dependencies on the position of substitution. Altogether, as expected (see spectroscopy and, in particular, Table 4), the spectroscopic parameters are too similar and the structural variations are too small to lead to any acceptable correlation (see the Supporting Information).

An interesting and promising possibility to screen the metal–ligand bonding in these systems is EDA,^{32,100} because in a series of structurally related complexes, this can give valuable insight in metal–donor-bonding energy differences contributing to the complex stabilities. Because modification of the electron density at the pyridine nitrogen atom, emerging from the para substituents, the total bonding energy E_{total} and, in particular, the electrostatic energy E_{elstat} should be correlated with the observed redox potentials. This could provide another tool to predict the electrochemical properties and stability constants of copper(II) complexes of novel bispidine ligands. The calculations were performed with a slightly simplified bispidine scaffold to minimize the computational cost and in their hydrate form. In addition to the experimentally studied complexes, others with potentially interesting substituted bispidine ligands were also computed (Table 5 and the Supporting Information).

Table 5. EDA of Substituted Bispidine copper(II) Complexes; Energies in [kcal/mol]^a

substituent X	E_{total}	E_{Pauli}	E_{elstat}	E_{orb}
H	-507.76	180.95	-337.19	-351.52
NO ₂	-481.45	179.28	-307.95	-352.77
Cl	-501.32	181.60	-329.16	-353.04
Br	-501.92	181.79	-327.76	-355.94
Me	-515.11	182.03	-343.43	-353.71
MeO	-521.75	183.39	-351.24	-353.91
EtO	-524.92	183.61	-353.73	-354.80
MeS	-518.92	183.94	-343.84	-359.02
pyrazine*	-551.44	146.14	-333.19	-364.39
F	-500.01	180.75	-328.69	-352.08
CHO	-495.08	180.09	-321.51	-353.66
COOCH ₃	-505.43	181.59	-332.00	-355.01
SO ₃ CH ₃	-495.28	180.06	-319.96	-355.39
N(CH ₃) ₂	-538.35	186.80	-366.89	-358.26
pyrrolidino	-543.07	187.24	-370.11	-360.21
pyrrolo	-517.09	184.54	-341.02	-360.62
Ph	-519.65	181.59	-340.64	-360.59



^aThe asterisk indicates a pyrazine instead of a substituted pyridine moiety.

As expected, the main variation is due to the electrostatic energy E_{elstat} (see Table 5), and correlations of the total and electrostatic energies (E_{total} and E_{elstat}) with the observed redox potentials are shown in Figure 5. With the exception of the

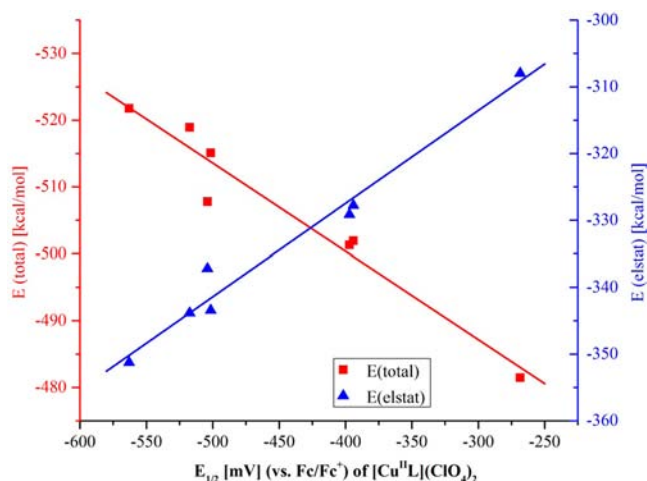


Figure 5. Correlation of the calculated (EDA) electrostatic and total bonding energies (E_{elstat} and E_{total}) of the simplified substituted bispidine copper(II) complexes with the experimentally observed redox potentials of the substituted bispidine copper(II) complexes (redox potentials from Table 4; hydrate form/isolated complexes, C⁹-reduced ligands not included; entries 1–6 and 8).¹¹²

pyrazine derivative (see Table 5), which has a slightly more negative orbital interaction (E_{orb}) and a significantly lower Pauli repulsion (E_{Pauli}), which probably is due to differences in the aromaticity (modification of the nitrogen-donor orbitals), the two correlations are both of very similar quality and accurate enough to predict the redox potentials (and complex stabilities). Therefore, Mulliken charges might also be used

for correlations with redox potentials (see the Supporting Information for correlations of Mulliken charges with E_{elstat} of EDA). The correlations shown in Figure 5 may be used to compute properties of the copper(II) complexes with unknown ligands. As shown in the section on Hammett's σ coefficients above, the copper(II) complex of the *p*-dimethylamino-substituted bispidine is expected to lead to an $E_{1/2}$ of -664 mV. The estimation by EDA using either the correlation of E_{elstat} or E_{total} with the redox potentials supports this prediction with a computed $E_{1/2}$ of -683 or -688 mV, respectively. As expected, the more rigid "closed" pyrrolidino derivative gives rise to an even more negative redox potential $E_{1/2}$ of -705 mV (E_{elstat} correlation) and -724 mV (E_{total} correlation). This is in agreement with the higher basicity of *p*-pyrrolidinopyridine compared to *p*-DMAP.

The correlation of the copper(II) complex stabilities, including all experimentally observed potentials and stability constants (red squares), experimentally observed potentials, and correlated stability constants (blue crosses) as well as computed potentials and correlated stabilities (shown for the *p*-DMAP analogue, black cross) is shown in Figure 6. The methoxy derivative **B5** with an observed potential of -563 mV is estimated to lead to the highest copper(II) formation constant known for a tetradentate bispidine-based ligand ($\log K = 16$ in comparison with the $\log K$ value of 15 for the unsubstituted parent complex emerging from the correlation), and the corresponding *p*-DMAP complex, which has not been prepared so far, should have a copper(II) stability constant of $\log K = 18$ (see the Supporting Information for a detailed list of predicted $\log K$ values).

CONCLUSION

A total of 11 new, substituted, tetradentate (*syn*-)bispidine ligands and their copper(II) complexes are reported. The copper(II) complexes are square-pyramidal or have elongated octahedral geometries with N³, py¹, py², and acetonitrile in

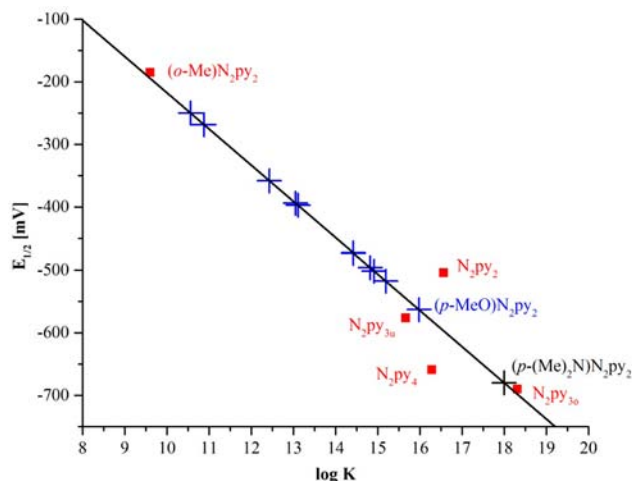


Figure 6. Correlation of the $\text{Cu}^{\text{II/I}}$ redox potential of the substituted bispidine complexes to the formation constants of the corresponding copper(II) complex (red squares: experimentally derived formation constants).¹⁰ The linear fit follows the equation: $y = -57.83176x + 360.98494$; $R^2 = 0.8707$. See the Supporting Information for a detailed list of estimated stability constants.

equatorial positions and N^7 (and ClO_4^-) in the axial positions. Because of the rigid backbone of the bispidines, there are no significant differences in the donor– Cu^{II} bond distances, except for the weak $\text{Cu}^{\text{II}}-\text{N}^7$ bond, which is long in six-coordinate structures and short in five-coordinate structures. Further evidence for these structural characteristics emerges from the electronic spectra: the complexes of the para-substituted ligands have a rather symmetric transition at 630 nm (unresolved transitions from d_{xy} , d_{xz} and d_{yz}) and the d_z^2 -based transition at 850–1000 nm (see Table 4 and the Supporting Information).

Cyclic voltammetry reveals reversible redox potentials that vary widely depending on the electronic nature of the pyridine substituent. These potentials are linearly correlated to the copper(II) complex stabilities: the more negative the redox potential, the more stable the complex. Importantly, there is also a linear correlation of the redox potentials with the pK_a values of the substituted pyridine groups and with the Hammett coefficients of the substituents, and this allows for the prediction of bispidine derivatives with high copper(II) complex stabilities. EDA calculations were used as a further tool to develop new tetradentate bispidine ligands. The total binding energy E_{total} as well as the electrostatic interaction E_{elstat} have been shown to correlate, as expected, linearly with the redox potentials and therefore with the copper(II) complex stabilities; as is also expected, E_{elstat} depends on the charge distribution (Mulliken charges on the pyridine nitrogen atom). Therefore, with EDA, further promising copper(II) chelators were predicted. On the basis of both the Hammett coefficients and EDA, we predict the *p*-dimethylamino-substituted tetradentate bispidine as a very promising ligand for very stable copper(II) complexes.

Because these methods are not limited to tetradentate bispidines and to copper(II) chemistry, we now have a simple and efficient method for the rational design of new bispidine-based ligands for use in various areas, from medicinal chemistry and bioinorganic model systems to oxidation and aziridination catalysis.

EXPERIMENTAL SECTION

Materials and Methods. All reactions in dry solvents were carried out under an inert atmosphere of argon or nitrogen applying standard Schlenk techniques. All glassware was heated and dried under vacuum prior to use. Chemicals were purchased from Sigma-Aldrich Chemie GmbH (Taufkirchen, Germany), ABCR GmbH & Co. KG (Karlsruhe, Germany), and Merck KGaA (Darmstadt, Germany) and were of the highest available purity. Dry solvents were used as delivered without further purification.

NMR spectra were recorded on a Bruker DRX 200, a Bruker Avance II 400, or a Bruker Avance III 600 spectrometer. The latter spectrometer was equipped with a direct detection cryoprobe for maximum sensitivity in the detection of ^{13}C , ^1H and ^{13}C NMR chemical shifts are referenced to the signals of the solvent (CDCl_3 and $\text{DMSO}-d_6$). NMR assignments of the new piperidones and bispidones are based on the known parent compounds.^{9,62,63,101,102}

UV/vis spectra were recorded on a Jasco V-570 UV/vis/near-IR spectrophotometer. Solution spectra were measured from in situ prepared complexes at ambient temperature in acetonitrile as the solvent. For solid-state UV/vis spectra, the isolated complexes were triturated with titanium(IV) oxide.

EPR measurements were performed on a Bruker ELEXSYS-E-500 instrument at 110 K, using methanol as the solvent. The spin-Hamiltonian parameters were obtained by simulation of the spectra with XSope.^{103,104}

Electrochemical measurements were performed on a CH Instruments CHI660D electrochemical workstation, equipped with a CH Instruments Picoamp Booster and Faraday Cage, with a three-electrode setup consisting of a glassy-carbon working electrode, a platinum wire auxiliary electrode, and an Ag/AgNO_3 reference electrode [0.01 M Ag^+ ; 0.1 M $(\text{Bu}_4\text{N})(\text{BF}_4)$ in MeCN]. The solutions were thoroughly degassed, and a slight argon stream was set above the solution during the measurement; a scan rate of 100 mV s^{-1} was used.

Mass spectra were recorded on Finnigan MAT8230 and Joel JMS-700 spectrometers. **Elemental analyses** were performed on a CHN-O-vario EL by the “Mikroanalytische Labor”, Department of Organic Chemistry, University of Heidelberg.

X-ray Crystallography. Data were collected on a Bruker AXS SMART 1000 CCD diffractometer (Mo $K\alpha$ radiation, sealed tube, and graphite monochromator) or an Agilent Technologies Supernova-E CCD diffractometer (Mo or Cu $K\alpha$ radiation, microfocus tube, and multilayer mirror optics); see the Supporting Information for details on the crystal structure determination.

Computational Methods Used. Ligand-field calculations were done with CAMMAG,¹⁰⁵ using a published setup^{95,96,105} and fitted parameters for the substituted pyridine groups.⁹⁷

For quantum-chemical calculations, the complexes were optimized by Gaussian 09¹⁰⁶ (B3LYP, TZVP) with a dihedral constraint (see Table 5 and the Supporting Information for a detailed list of the bond lengths and angles of the calculated structures). The methyl group of the equatorially coordinated acetonitrile was fixed to avoid rotation, which caused serious problems during optimization. EDA was performed to obtain the total bonding energy with various bispidine ligands, Cu^{II} , and acetonitrile as fragments; EDA was performed with ADF.^{107,108}

Syntheses. **4-Nitropicoline-N-oxide (2; $\text{C}_6\text{H}_6\text{N}_2\text{O}_3$, $M_W = 154.12 \text{ g mol}^{-1}$).** Picoline-N-oxide (**1**; 27.3 g, 0.25 mol, 1.0 equiv) was dissolved in sulfuric acid (122.6 g, 1.25 mol, 5.0 equiv) at 0 °C, and fuming nitric acid (78.8 g, 1.25 mol, 5.0 equiv) was added dropwise at 0 °C over 30 min. The reaction mixture was stirred for 2 h at 115 °C. After cooling, the reaction mixture was poured onto 400 mL of crushed ice. This slurry was neutralized by the portionwise addition of K_2CO_3 and filtered. The solid was washed with chloroform ($3 \times 50 \text{ mL}$), the phases were separated, and the aqueous phase was extracted with chloroform ($3 \times 100 \text{ mL}$). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to afford a yellow solid as the pure product in a yield of 73.1% (28.15 g, 182.7 mmol). ^1H NMR (200 MHz, CDCl_3): δ 2.57 (s, 3H, CH_3), 8.00 (dd, $^3J_{\text{H,H}} = 7.08 \text{ Hz}$, $^4J_{\text{H,H}} = 3.07 \text{ Hz}$, 1H, H^5), 8.14 (d, $^4J_{\text{H,H}} = 2.99 \text{ Hz}$, 1H, H^3), 8.32 (d,

$^3J_{\text{H,H}} = 7.08$ Hz, 1H, H^6). ^{13}C NMR (50 MHz, CDCl_3): δ 18.01, 118.05, 120.62, 140.01, 141.59, 150.59. HR-EI (positive mode, $[\text{M}]^+$). Calcd: m/z 154.0378. Obsd: m/z 154.0386. Elem anal (report 31055, $[\text{M}]$). Calcd: C, 46.76; H, 3.92; N, 18.18. Obsd: C, 46.62; H, 3.90; N, 18.06.

(4-Nitropyridin-2-yl)methanol (**3**; $\text{C}_6\text{H}_6\text{N}_2\text{O}_3$, $M_w = 154.12$ g mol^{-1}). **2** (5.00 g, 32.6 mmol, 1.0 equiv) was dissolved in 140 mL of dichloromethane (DCM), and trifluoroacetic anhydride (20.44 g, 13.54 mL, 97.32 mmol, 3.0 equiv) dissolved in 30 mL of DCM was added dropwise to the solution. After complete addition, the reaction mixture was stirred for 3 days at ambient temperature. Then the solution was concentrated in vacuo, and 100 mL of methanol and 50 mL of a saturated K_2CO_3 solution were added to the residue and vigorously stirred for 4 h at ambient temperature, whereupon a white solid formed. Methanol was removed in vacuo, and the resulting aqueous solution was extracted with DCM (3×200 mL). The combined organic phases were washed with brine (3×200 mL), dried over MgSO_4 , filtered, and concentrated to afford a yellow solid in a yield of 65.8% (3.29 g, 21.4 mmol). ^1H NMR (400 MHz, CDCl_3): δ 4.94 (s, 2H, CH_2OH), 7.94 (dd, $^3J_{\text{H,H}} = 5.40$ Hz, $^4J_{\text{H,H}} = 1.88$ Hz, 1H, H^5), 8.11 (d, $^4J_{\text{H,H}} = 1.51$ Hz, 1H, H^3), 8.85 (d, $^3J_{\text{H,H}} = 5.40$ Hz, 1H, H^6). ^{13}C NMR (100 MHz, CDCl_3): δ 64.36 (CH_2OH), 113.13 (C3), 114.86 (C5), 150.95 (C4), 154.37 (C6), 163.49 (C2).

4-Nitropicolinaldehyde (**4**; $\text{C}_6\text{H}_4\text{N}_2\text{O}_3$, $M_w = 152.11$ g mol^{-1}). **3** (6.98 g, 45.29 mmol, 2.0 equiv) and selenium dioxide (2.51 g, 22.65 mmol, 1.0 equiv) were dissolved in 100 mL of 1,4-dioxane and heated to 85 °C for 5 h. After the reaction mixture cooled, it was filtered through Celite 545 and concentrated in vacuo. The crude product was purified by Kugelrohr distillation (0.65 mbar, 165 °C) to afford a clear orange, viscous oil as the pure product in a yield of 41.4% (2.85 g, 18.74 mmol). ^1H NMR (200 MHz, CDCl_3): δ 8.27 (dd, $^3J_{\text{H,H}} = 5.25$ Hz, $^4J_{\text{H,H}} = 2.18$ Hz, 1H, H^5), 8.64 (dd, $^4J_{\text{H,H}} = 2.22$ Hz, $^5J_{\text{H,H}} = 0.68$ Hz, 1H, H^3), 9.12 (dd, $^3J_{\text{H,H}} = 5.29$ Hz, $^5J_{\text{H,H}} = 0.60$ Hz, 1H, H^6), 10.19 (s, 1H, CHO). ^{13}C NMR (50 MHz, CDCl_3): δ 114.21, 119.84, 152.51, 154.77, 155.26, 191.00. HR-EI (positive mode, $[\text{M}]^+$). Calcd: m/z 152.0222. Obsd: m/z 152.0207. HR-EI (positive mode, $[\text{M} - \text{CO}]^+$). Calcd: m/z 124.0273. Obsd: m/z 124.0284. Elem anal (report 30422, $[\text{M}]$). Calcd: C, 47.38; H, 2.65; N, 18.42. Obsd: C, 47.23; H, 2.86; N, 18.22.

4-Bromopicolinaldehyde (**5**; $\text{C}_6\text{H}_4\text{BrNO}$, $M_w = 186.01$ g mol^{-1}). In a flame-dried two-necked flask with condenser, acetyl bromide (30 mL) was rapidly added to **4** (1.83 g, 12.0 mmol) under an atmosphere of argon. The red solution was stirred at 60–70 °C for 15 h. A red solid formed. The suspension was poured onto crushed ice and slowly basified with Na_2CO_3 to pH = 8 by frequently adding ice to the mixture. This aqueous solution (200 mL) was extracted with diethyl ether (3×120 mL). The combined organic phases were dried over Na_2SO_4 , filtered, and concentrated to afford an orange oil as the fairly pure product in a yield of 77.7% (1.74 g, 9.35 mmol), which was directly used in the next step. ^1H NMR (200 MHz, CDCl_3): δ 7.70 (dd, $^3J_{\text{H,H}} = 5.21$ Hz, $^4J_{\text{H,H}} = 1.96$ Hz, 1H, H^5), 8.12 (dd, $^4J_{\text{H,H}} = 1.96$ Hz, $^5J_{\text{H,H}} = 0.68$ Hz, H^3), 8.61 (dd, $^3J_{\text{H,H}} = 5.21$ Hz, $^5J_{\text{H,H}} = 0.60$ Hz, H^6), 10.05 (s, 1H, CHO). ^{13}C NMR (50 MHz, CDCl_3): δ 125.13, 130.93, 134.18, 150.87, 153.61, 192.04. HR-EI (positive mode, $[\text{M}]^+$). Calcd: m/z 184.9476. Obsd: m/z 184.9488. HR-EI (positive mode, $[\text{M} - \text{CO}]^+$). Calcd: m/z 156.9527. Obsd: m/z 156.9504.

Methyl 4-chloropicolinate (**7**; $\text{C}_7\text{H}_6\text{ClNO}_2$, $M_w = 171.58$ g mol^{-1}). Under an atmosphere of argon, thionyl chloride (75 mL, 122.3 g, 1.03 mol, approximately 10 equiv) was heated to 50 °C and *N,N*-dimethylformamide (2.50 mL, 2.36 g, 32.29 mmol, 0.17 equiv) was added carefully. The mixture was stirred for 10 min at 50 °C, whereupon picolinic acid (**6**; 24.00 g, 194.95 mmol, 1.0 equiv) was added portionwise to the reaction mixture. The color of the mixture changed from green to red. This mixture was stirred at 70 °C for 2 days. The formation of an orange precipitate was observed. After cooling to ambient temperature, 50 mL of toluene was added and the excess thionyl chloride was coevaporated in vacuo. The resulting precipitate was suspended in 150 mL of toluene, cooled to 0 °C, and treated dropwise with methanol (6.50 mL). A pale-yellow precipitate formed and was filtered and thoroughly washed with toluene (200

mL). This solid was dissolved in 200 mL of chloroform and washed with a saturated NaHCO_3 solution (3×250 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated. The pale-brown oil that crystallized was obtained as the fairly pure product in a yield of 66.3% (22.18 g, 129.27 mmol). ^1H NMR (400 MHz, CDCl_3): δ 4.03 (s, 3H, CH_3), 7.51 (dd, $^3J_{\text{H,H}} = 5.21$ Hz, $^4J_{\text{H,H}} = 1.82$ Hz, 1H, H^5), 8.15 (d, $^3J_{\text{H,H}} = 1.76$ Hz, 1H, H^3), 8.66 (d, $^3J_{\text{H,H}} = 5.27$ Hz, 1H, H^6). ^{13}C NMR (100 MHz, CDCl_3): δ 53.23, 125.68, 127.16, 145.50, 149.17, 150.60, 164.62. HR-EI (positive mode, $[\text{M}]^+$). Calcd: m/z 171.0087. Obsd: m/z 171.0080. HR-EI (positive mode, $[\text{M} - \text{COCH}_2]^+$). Calcd: m/z 113.0032. Obsd: m/z 113.0021. Elem anal (report 29274, $[\text{M}]$). Calcd: C, 49.00; H, 3.52; N, 8.16. Obsd: C, 49.00; H, 3.52; N, 8.16.

(4-Chloropyridin-2-yl)methanol (**8**; $\text{C}_6\text{H}_6\text{ClNO}$, $M_w = 143.57$ g mol^{-1}). In a flame-dried flask, finely crushed CaCl_2 (14.0 g, 126.2 mmol, approximately 4.0 equiv) and **7** (5.36 g, 31.2 mmol, 1.0 equiv) were suspended in a mixture of 30 mL of methanol and 18 mL of tetrahydrofuran (THF) and cooled to 0 °C. Then NaBH_4 (2.36 g, 62.5 mmol, 2.0 equiv) was added portionwise, and this suspension was vigorously stirred for 1.5 h at 0 °C. The reaction was quenched by the addition of 50 mL of aqua dest.; the suspension was stirred for another 2 h at ambient temperature and afterward extracted with ethyl acetate (3×150 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to afford a white-to-pale-yellow solid as the fairly pure product in a yield of 88.3% (3.96 g, 27.6 mmol). ^1H NMR (600 MHz, CDCl_3): δ 4.72 (s, 2H, CH_2OH), 7.18 (dd, $^3J_{\text{H,H}} = 5.35$ Hz, $^4J_{\text{H,H}} = 1.85$ Hz, 1H, H^5), 7.36 (br s, 1H, H^3), 8.38 (d, $^3J_{\text{H,H}} = 5.15$ Hz, 1H, H^6). ^{13}C NMR (150 MHz, CDCl_3): δ 64.01 (C6), 121.01 (C2), 122.65 (C4), 144.95 (C3), 149.36 (C5), 161.62 (C1). HR-EI (positive mode, $[\text{M}]^+$). Calcd: m/z 143.0138. Obsd: m/z 143.0101. HR-EI (positive mode, $[\text{M} - \text{H}]^+$). Calcd: m/z 142.0060. Obsd: m/z 142.0029. Elem anal (report 30863, $[\text{M}]$). Calcd: C, 50.19; H, 4.21; N, 9.76. Obsd: C, 50.64; H, 4.53; N, 9.82.

4-Chloropicolinaldehyde (**9**; $\text{C}_6\text{H}_4\text{ClNO}$, $M_w = 141.56$ g mol^{-1}). **8** (6.21 g, 43.3 mmol, 2.0 equiv) was dissolved in 100 mL of 1,4-dioxane. Then selenium dioxide (2.40 g, 21.6 mmol, 1.0 equiv) was added, and the resulting mixture was heated to 95 °C for 4 h. A brown precipitate formed and was filtered using Celite 545 and washed with 1,4-dioxane. The solution was concentrated in vacuum to afford a pale-yellow-to-brown solid as the fairly pure product in a yield of 82.2% (5.03 g, 35.53 mmol). Further purification could be done by distillation (0.4 mbar, 75 °C). ^1H NMR (600 MHz, CDCl_3): δ 7.54 (dd, $^3J_{\text{H,H}} = 5.25$ Hz, $^4J_{\text{H,H}} = 2.12$ Hz, 1H, H^5), 7.96 (dd, $^4J_{\text{H,H}} = 2.07$ Hz, $^5J_{\text{H,H}} = 0.56$ Hz, 1H, H^3), 8.70 (dd, $^3J_{\text{H,H}} = 5.25$ Hz, $^5J_{\text{H,H}} = 0.51$ Hz, 1H, H^6), 10.06 (s, 1H, CHO). ^{13}C NMR (150 MHz, CDCl_3): δ 122.06, 127.89, 145.68, 151.02, 153.88, 192.11.

(4-Methoxypyridin-2-yl)methanol (**10**; $\text{C}_7\text{H}_9\text{NO}_2$, $M_w = 139.15$ g mol^{-1}). **3** (12.13 g, 78.71 mmol, 1.0 equiv) was dissolved in 200 mL of methanol, and a methanolic solution of sodium methoxide (25 wt %, 64.26 g, 68.0 mL, 297.4 mmol, 3.8 equiv) was added dropwise at ambient temperature. The resulting solution was heated under reflux (80 °C) for 1 day. After the reaction mixture was allowed to cool to ambient temperature, the solution was neutralized using concentrated hydrochloric acid. The solid material was removed by filtration, the methanol was removed in vacuum, and the aqueous solution was extracted with DCM (4×250 mL), dried over Na_2SO_4 , filtered, and concentrated to afford a red-brown oily solid in a yield of 72.0% (7.88 g, 56.6 mmol). ^1H NMR (400 MHz, CDCl_3): δ 3.86 (s, 3H, OCH_3), 4.71 (s, 2H, CH_2OH), 6.73 (dd, $^3J_{\text{H,H}} = 5.77$ Hz, $^4J_{\text{H,H}} = 2.38$ Hz, 1H, H^5), 6.80 (d, $^4J_{\text{H,H}} = 2.38$ Hz, 1H, H^3), 8.36 (d, $^3J_{\text{H,H}} = 5.77$ Hz, 1H, H^6). ^{13}C NMR (100 MHz, CDCl_3): δ 55.17, 64.24, 105.78, 109.09, 149.63, 161.11, 166.31. Elem anal (report 29621, $[\text{M}]$). Calcd: C, 60.42; H, 6.52; N, 10.07. Obsd: C, 60.30; H, 6.62; N, 10.14.

(4-Ethoxypyridin-2-yl)methanol (**11**; $\text{C}_8\text{H}_{11}\text{NO}_2$, $M_w = 153.18$ g mol^{-1}). **3** (5.77 g, 37.4 mmol, 1.0 equiv) was dissolved in 100 mL of ethanol at ambient temperature, and 41.9 mL of an ethanolic solution of sodium ethoxide (21 wt %, 36.40 g, 112.32 mmol, 3.0 equiv) was added dropwise to the reaction mixture within 20 min. The red solution was refluxed for 1 day. After the reaction mixture was allowed to cool to ambient temperature, 50 mL of aqua dest. was added, and

the mixture was neutralized using concentrated hydrochloric acid. The ethanol was removed in vacuo, and another 100 mL of aqua dest. and 200 mL of DCM were added to the mixture and separated. The aqueous phase was further extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated. The dark-red oil was purified by Kugelrohr distillation (1.5 mbar, 170 °C) to afford a pale-yellow oil in a yield of 42.0% (2.41 g, 15.7 mmol) as the fairly pure product. ¹H NMR (200 MHz, CDCl₃): δ 1.44 (t, ³J_{H,H} = 7.04 Hz, 3H, OCH₂CH₃), 3.52 (s, 1H, CH₂OH), 4.10 (q, ³J_{H,H} = 7.00 Hz, 2H, OCH₂CH₃), 4.71 (s, 2H, CH₂OH), 6.72 (dd, ³J_{H,H} = 5.80 Hz, ⁴J_{H,H} = 2.47 Hz, 1H, H⁵), 6.78 (d, ⁴J_{H,H} = 1.88 Hz, 1H, H³), 8.34 (d, ³J_{H,H} = 5.80 Hz, 1H, H⁶). ¹³C NMR (50 MHz, CDCl₃): δ 14.42, 63.67, 64.14, 106.30, 109.53, 149.40, 160.94, 165.79. HR-EI (positive mode, M⁺). Calcd: *m/z* 153.0790. Obsd: *m/z* 153.0781. Elem anal (report 31992, [M + 1/2H₂O]). Calcd: C, 59.24; H, 7.46; N, 8.64. Obsd: C, 58.86; H, 7.22; N, 8.79.

[4-(Methylthio)pyridin-2-yl]methanol (**12**; C₇H₉NOS, M_w = 155.22 g mol⁻¹). **8** (3.21 g, 22.36 mmol, 1.0 equiv) and sodium thiomethoxide (2.35 g, 33.54 mmol, 1.5 equiv) were dissolved in 50 mL of ethanol and refluxed for 16 h. After cooling to ambient temperature, the excess of methylthiolate and most of the ethanol was removed in vacuum. The resulting yellow oil was portioned between 100 mL of DCM and 100 mL of aqua dest. The aqueous phase was further extracted with 100 mL of DCM. The combined organic phases were dried over Na₂SO₄, filtered, and concentrated in vacuo to afford a light-brown solid as the fairly pure product in a yield of 97.67% (3.39 g, 21.84 mmol). ¹H NMR (400 MHz, CDCl₃): δ 2.50 (s, 3H, SCH₃), 4.72 (s, 2H, CH₂OH), 7.02 (dd, ³J_{H,H} = 5.40 Hz, ⁴J_{H,H} = 1.76 Hz, 1H, H⁵), 7.07 (s, 1H, H³), 8.33 (d, ³J_{H,H} = 5.27 Hz, 1H, H⁶). ¹³C NMR (100 MHz, CDCl₃): δ 13.70 (SCH₃), 64.14 (CH₂OH), 116.13 (C3), 118.68 (C5), 147.76 (C4), 151.18 (C6), 158.79 (C2). HR-EI (positive mode, [M]⁺). Calcd: *m/z* 155.0405. Obsd: *m/z* 155.0413. HR-EI (positive mode, [M - H]⁺). Calcd: *m/z* 154.0327. Obsd: *m/z* 154.0349. Elem anal (report 30501, [M]). Calcd: C, 54.17; H, 5.84; N, 9.02. Obsd: C, 54.43; H, 5.93; N, 9.25.

[4-(Dimethylamino)pyridin-2-yl]methanol (**13**; C₈H₁₂N₂O, M_w = 152.19 g mol⁻¹). **8** (2.30 g, 16.02 mmol, 1.0 equiv), dimethylamine hydrochloride (6.53 g, 80.1 mmol, 5.0 equiv), and sodium hydroxide (3.00 g, 75.0 mmol, 4.68 equiv) were put into a pressure tube, 1 mL of aqua dest. was added, and the apparatus was sealed. The reaction mixture was stirred at 155 °C for 1 day. After cooling to ambient temperature, the reaction mixture was filtered, diluted with 50 mL of aqua dest., and extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting brown solid was recrystallized from hot acetone to afford brown crystals, which were washed with further cold acetone. The product was obtained in a yield of 57.0% (1.39 g, 9.13 mmol). ¹H NMR (200 MHz, CDCl₃): δ 3.02 (s, 6H, N(CH₃)₂), 4.65 (s, 2H, CH₂OH), 6.41–6.46 (m, 2H, H^{ar}), 8.15–8.20 (m, 1H, H^{ar}). ¹³C NMR (50 MHz, CDCl₃): δ 39.18 (2C, N(CH₃)₂), 64.41 (CH₂OH), 102.51 (C3), 105.75 (C5), 148.36 (C4), 154.89 (C6), 159.05 (C2).

[4-Pyrrolidinopyridin-2-yl]methanol (**14**; C₁₀H₁₄N₂O, M_w = 178.23 g mol⁻¹). **8** (1.77 g, 12.33 mmol, 1.0 equiv) and pyrrolidine (5.26 g, 6.17 mL, 73.98 mmol, 6.0 equiv) were heated to 155 °C for 1 day in a pressure tube. After the reaction mixture was allowed to cool to ambient temperature, it was concentrated under vacuum. The residue was taken up in 20 mL of DCM and 20 mL of aqua dest., and the phases were separated. The organic phase was washed with further aqua dest. (20 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting pale-brown solid was recrystallized from hot acetone to afford pale-brown crystals as the pure product in a yield of 43.6% (0.96 g, 5.38 mmol). ¹H NMR (200 MHz, CDCl₃): δ 2.02 (td, ³J_{H,H} = 6.55 Hz, ³J_{H,H} = 3.40 Hz, 4H, H^β), 3.25–3.35 (m, 4H, H^β), 4.62 (s, 2H, CH₂OH), 6.28 (dd, ³J_{H,H} = 5.80 Hz, ⁴J_{H,H} = 2.50 Hz, 1H, H⁵), 6.33 (d, ⁴J_{H,H} = 2.10 Hz, 1H, H³), 8.12 (d, ³J_{H,H} = 5.80 Hz, 1H, H⁶). ¹³C NMR (50 MHz, CDCl₃): δ 25.26, 46.97, 64.45, 102.98, 105.98, 148.25, 152.31, 159.25. HR-EI (positive mode, [M]⁺). Calcd: *m/z* 178.1106. Obsd: *m/z* 178.1125. HR-EI (positive mode, [M - H]⁺). Calcd: *m/z* 177.1028. Obsd: *m/z* 177.1043. Elem anal (report 32378,

[M]). Calcd: C, 67.39; H, 7.92; N, 15.72. Obsd: C, 67.36; H, 7.91; N, 15.36.

4-Methoxypicolinaldehyde (**15**; C₇H₇NO₂, M_w = 137.14 g mol⁻¹). **10** (19.03 g, 136.8 mmol, 2.0 equiv) and selenium dioxide (7.59 g, 68.38 mmol, 1.0 equiv) were dissolved in 300 mL of 1,4-dioxane and heated to 85 °C for 4 h. After cooling, the solution was filtered through Celite 545 and concentrated in vacuo. The resulting brown viscous oil was purified by distillation (1.4–1.5 mbar, 140 °C) to afford a yellow oil in a yield of 55.3% (10.37 g, 75.62 mmol). ¹H NMR (400 MHz, CDCl₃): δ 3.92 (s, 3H, OCH₃), 7.03 (dd, ³J_{H,H} = 5.65 Hz, ⁴J_{H,H} = 2.63 Hz, 1H, H⁵), 7.48 (d, ⁴J_{H,H} = 2.64 Hz, 1H, H³), 8.59 (d, ³J_{H,H} = 5.65 Hz, 1H, H⁶), 10.04 (s, 1H, CHO). ¹³C NMR (100 MHz, CDCl₃): δ 55.59, 106.69, 114.57, 151.22, 154.65, 166.54, 193.37. HR-EI (positive mode, [M]⁺). Calcd: *m/z* 137.0477. Obsd: *m/z* 137.0460. HR-EI (positive mode, [M - CO]⁺). Calcd: *m/z* 109.0528. Obsd: *m/z* 109.0526.

4-Ethoxypicolinaldehyde (**16**; C₈H₉NO₂, M_w = 151.16 g mol⁻¹). **11** (2.24 g, 14.62 mmol, 1.0 equiv) and selenium dioxide (0.81 g, 7.31 mmol, 0.5 equiv) were suspended in 20 mL of 1,4-dioxane and heated to 90 °C for 4 h. After cooling to ambient temperature, the solution was decanted from the solid material and concentrated in vacuo. The residue was purified by distillation (145 °C, 1.8 mbar) to afford a colorless oil in a yield of 84.1% (1.86 g, 12.30 mmol). ¹H NMR (600 MHz, CDCl₃): δ 1.47 (t, ³J_{H,H} = 7.01 Hz, 3H, OCH₂CH₃), 4.16 (q, ³J_{H,H} = 7.03 Hz, 3H, OCH₂CH₃), 7.01 (dd, ³J_{H,H} = 5.60 Hz, ⁴J_{H,H} = 2.57 Hz, 1H, H⁵), 7.46 (d, ⁴J_{H,H} = 2.52 Hz, 1H, H³), 8.58 (d, ³J_{H,H} = 5.65 Hz, 1H, H⁶), 10.04 (s, 1H, CHO). ¹³C NMR (150 MHz, CDCl₃): δ 14.35, 64.15, 107.13, 114.94, 151.22, 154.59, 165.87, 193.45.

4-(Methylthio)picolinaldehyde (**17**; C₇H₇NOS, M_w = 153.20 g mol⁻¹). **12** (3.54 g, 22.81 mmol, 1.0 equiv) and selenium dioxide (1.27 g, 11.41 mmol, 0.5 equiv) were suspended in 40 mL of 1,4-dioxane and heated to 100 °C for 2.5 h. After cooling, the solution was decanted from the solid material and concentrated. The resulting brown oil was purified by distillation (145 °C, 1.0 mbar) to afford a pale-brown oil as the pure product in a yield of 79.8% (2.79 g, 18.21 mmol). ¹H NMR (400 MHz, CDCl₃): δ 2.55 (s, 3H, SCH₃), 7.31 (dd, ³J_{H,H} = 5.33 Hz, ⁴J_{H,H} = 2.07 Hz, 1H, H⁵), 7.75 (d, ⁴J_{H,H} = 1.88 Hz, 1H, H³), 8.55 (d, ³J_{H,H} = 5.27 Hz, 1H, H⁶), 10.04 (s, 1H, CHO). ¹³C NMR (100 MHz, CDCl₃): δ 13.81, 117.20, 123.80, 149.24, 152.27, 152.45, 193.33. HR-EI (positive mode, [M]⁺). Calcd: *m/z* 153.0248. Obsd: *m/z* 153.0245. HR-EI (positive mode, [M - CO]⁺). Calcd: *m/z* 125.0299. Obsd: *m/z* 125.0318. Elem anal (report 30502, [M]). Calcd: C, 54.88; H, 4.61; N, 9.14. Obsd: C, 54.85; H, 4.63; N, 9.32.

4-(Dimethylamino)picolinaldehyde (**18**; C₈H₁₀N₂O, M_w = 150.18 g mol⁻¹). **13** (1.32 g, 8.67 mmol, 1.0 equiv) and selenium dioxide (0.48 g, 4.34 mmol, 0.5 equiv) were suspended in 15 mL of 1,4-dioxane and heated to 100 °C for 3 h. After cooling, the solution was decanted from the solid material and concentrated. The resulting oil was purified by Kugelrohr distillation (1.1 mbar, 185 °C) to afford a pale-yellow oil as the pure product in a yield of 80.6% (1.05 g, 6.99 mmol). ¹H NMR (200 MHz, CDCl₃): δ 3.05 (s, 6H, N(CH₃)₂), 6.64 (dd, ³J_{H,H} = 5.89 Hz, ⁴J_{H,H} = 2.82 Hz, 1H, H⁵), 7.16 (d, ⁴J_{H,H} = 2.82 Hz, 1H, H³), 8.36 (d, ³J_{H,H} = 5.89 Hz, 1H, H⁶), 9.97 (s, 1H, CHO). ¹³C NMR (50 MHz, CDCl₃): δ 39.20, 104.31, 109.84, 150.08, 153.05, 154.71, 194.62. HR-EI (positive mode, [M - CO]⁺). Calcd: *m/z* 122.0844. Obsd: *m/z* 122.0835. Elem anal (report 30359, [M + 1/2H₂O]). Calcd: C, 62.12; H, 6.84; N, 18.11. Obsd: C, 61.96; H, 7.06; N, 18.19.

4-Pyrrolidinopicolinaldehyde (**19**; C₁₀H₁₂N₂O, M_w = 176.22 g mol⁻¹). **14** (907.4 mg, 5.09 mmol, 1.0 equiv) and selenium dioxide (282.9 mg, 2.55 mmol, 0.5 equiv) were suspended in 15 mL of 1,4-dioxane and heated to 100 °C for 3 h. After cooling, the solution was decanted from the solid material and concentrated. The resulting oil was purified by Kugelrohr distillation (1.3 mbar, 230 °C) to afford a pale-yellow oil as the pure product in a yield of 62.5% (0.56 g, 3.18 mmol). ¹H NMR (400 MHz, CDCl₃): δ 2.07 (td, ³J_{H,H} = 6.53 Hz, ³J_{H,H} = 3.39 Hz, 4H, H^β), 3.38 (dt, ³J_{H,H} = 5.80 Hz, ³J_{H,H} = 3.70 Hz, 4H, H^β), 6.54 (dd, ³J_{H,H} = 5.77 Hz, ⁴J_{H,H} = 2.64 Hz, 1H, H⁵), 7.06 (d, ⁴J_{H,H} = 2.64 Hz, 1H, H³), 8.36 (d, ³J_{H,H} = 5.77 Hz, 1H, H⁶), 9.99 (s,

1H, CHO). ¹³C NMR (100 MHz, CDCl₃): δ 25.32, 47.24, 104.79, 110.27, 149.91, 152.20, 152.92, 194.76. HR-EI (positive mode, [M]⁺). Calcd: *m/z* 176.0950. Obsd: *m/z* 176.0937. HR-EI (positive mode, [M - H]⁺). Calcd: *m/z* 175.0871. Obsd: *m/z* 175.0885. HR-EI (positive mode, [M - CO]⁺). Calcd: *m/z* 148.1001. Obsd: *m/z* 148.1012. Elem anal (report 30488, [M]). Calcd: C, 68.16; H, 6.86; N, 15.90. Obsd: C, 68.02; H, 6.96; N, 15.91.

2,4-Lutidine-N-oxide (21; C₇H₉NO, M_w = 123.15 g mol⁻¹). To 20 (10.80 g, 0.101 mol) was slowly added 30 mL of glacial acetic acid with stirring. Then 16 mL of an aqueous solution of hydrogen peroxide (30%) was added portionwise. This solution was stirred at 70 °C for 1 day. After the mixture was allowed to cool to ambient temperature, a small amount of Na₂SO₃ was added in order to destroy unreacted hydrogen peroxide and stirring was continued for 10 min. An aqueous solution of sodium hydroxide (20%) was added until pH = 12, and the solution was extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated. A colorless, smelly, and viscous oil was obtained as the pure product in a yield of 82.3% (10.24 g, 83.15 mmol). ¹H NMR (400 MHz, CDCl₃): δ 2.30 (s, 3H, CH₃), 2.48 (s, 3H, CH₃), 6.93 (dd, ³J_{H,H} = 6.50 Hz, ⁴J_{H,H} = 2.00 Hz, 1H, H⁵), 7.05 (br s, 1H, H³), 8.13 (d, ³J_{H,H} = 6.53 Hz, 1H, H⁶). ¹³C NMR (100 MHz, CDCl₃): δ 17.72, 20.18 (2C, CH₃), 124.28, 127.11, 136.97, 138.68, 148.20 (5C, C^{ar}). Elem anal (report 30781, [M + ¹/₅H₂O]). Calcd: C, 66.33; H, 7.47; N, 11.05. Obsd: C, 66.54; H, 7.69; N, 11.25.

(4-Methylpyridin-2-yl)methanol (22; C₇H₉NO, M_w = 123.15 g mol⁻¹). To 21 (9.88 g, 80.23 mmol, 1.0 equiv) dissolved in 200 mL of DCM was added dropwise trifluoroacetic anhydride (50.55 g, 33.45 mmol, 240.7 mmol, 3.0 equiv) dissolved in a further 50 mL of DCM. The red solution was stirred at ambient temperature for 3.5 days. Then trifluoroacetic anhydride and DCM were removed under vacuum, and 200 mL of methanol and 250 mL of a saturated K₂CO₃ solution were added to the residue. After stirring for 3 h, methanol was removed and the aqueous phase was extracted with DCM (3 × 200 mL). The combined organic phases were washed with brine (2 × 250 mL), dried over Na₂SO₄, filtered, and concentrated. A brown oil was obtained as the fairly pure product containing traces of educt in a yield of 29.3% (2.89 g, 23.5 mmol). ¹H NMR (200 MHz, CDCl₃): δ 2.36 (s, 3H, CH₃), 4.72 (s, 2H, CH₂OH), 7.03 (d, ³J_{H,H} = 5.12 Hz, 1H, H⁵), 7.07–7.09 (m, 1H, H³), 8.41 (d, ³J_{H,H} = 5.12 Hz, 1H, H⁶). ¹³C NMR (50 MHz, CDCl₃): δ 21.02, 64.05, 121.22, 123.39, 147.90, 148.18, 158.84. HR-EI (positive mode, M⁺). Calcd: *m/z* 123.0684. Obsd: *m/z* 123.0682. Elem anal (report 30855, [M + ¹/₃H₂O]). Calcd: C, 65.09; H, 7.54; N, 10.84. Obsd: C, 64.80; H, 7.56; N, 10.87.

4-Methylpicolinaldehyde (23; C₇H₇NO, M_w = 121.14 g mol⁻¹). 22 (2.68 g, 21.76 mmol, 1.0 equiv) and selenium dioxide (1.21 g, 10.9 mmol, 0.5 equiv) were suspended in 40 mL of 1,4-dioxane and heated to 100 °C for 3 h. After cooling to ambient temperature, the solution was decanted from the solid material and concentrated. The residue was purified by Kugelrohr-distillation (105 °C, 1.0 mbar) to afford a colorless oil in a yield of 54.2% (1.43 g, 11.80 mmol). ¹H NMR (200 MHz, CDCl₃): δ 2.43 (s, 3H, CH₃), 7.33 (ddd, ³J_{H,H} = 4.95 Hz, ⁴J_{H,H} = 1.75 Hz, ⁴J_{H,H} = 0.73 Hz, 1H, H⁵), 7.75–7.79 (m, 1H, H³), 8.62 (d, ³J_{H,H} = 4.95 Hz, 1H, H⁶), 10.05 (s, 1H, CHO). ¹³C NMR (50 MHz, CDCl₃): δ 20.98 (CH₃), 122.46, 128.68, 148.53, 149.92, 152.68 (5C, C^{ar}), 193.64 (CHO). HR-EI (positive mode, [M]⁺). Calcd: *m/z* 121.0528. Obsd: *m/z* 121.0554. HR-EI (positive mode, [M - CO]⁺). Calcd: *m/z* 93.0579. Obsd: *m/z* 93.0586. Elem anal (report 30861, [M + ¹/₅H₂O]). Calcd: C, 67.40; H, 5.98; N, 11.23. Obsd: C, 67.52; H, 5.95; N, 11.26.

Pyrazine-2-carboxaldehyde (25; C₅H₄N₂O, M_w = 108.10 g mol⁻¹). Methyl-2-pyrazinecarboxylate (24; 2.01 g, 14.55 mmol, 1.0 equiv) was dissolved in 40 mL of dry THF at -78 °C under an atmosphere of argon. To this solution was added 7.28 mL of a 1 M solution of lithium–aluminum hydride in THF over 20 min. The mixture was stirred at -78 °C for a further 1.5 h. Then 2 mL of glacial acid was added to the mixture at low temperature. The mixture was then stirred for 0.5 h, allowing it to warm to ambient temperature. The solvent was removed in vacuo, and the resulting residue was taken up in diluted hydrochloric acid (3 mL of concentrated HCl/12 mL of aqua dest.)

and extracted with chloroform (8 × 20 mL). The combined organic phases were washed with a saturated NaHCO₃ solution (1 × 50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford a dark-red oil as the fairly pure product in a yield of 53.4% (0.84 g, 7.77 mmol). This oil was used for the next step without further purification. ¹H NMR (600 MHz, CDCl₃): δ 8.78 (br s, 1H, H^{ar}), 8.82 (d, ³J_{H,H} = 2.22 Hz, 1H, H^{ar}), 9.19 (s, 1H, H^{ar}), 10.18 (s, 1H, CHO). ¹³C NMR (150 MHz, CDCl₃): δ 143.57, 144.89, 146.94, 148.54 (4C, C^{ar}), 192.47 (CHO). HR-EI (positive mode, [M]⁺). Calcd: *m/z* 108.0324. Obsd: *m/z* 108.0310.

Piperidone (p-NO₂)Npy₂P1 (C₂₀H₁₉N₅O₂, M_w = 473.39 g mol⁻¹). 4 (2.54 g, 16.70 mmol, 2.0 equiv) was dissolved in 10 mL of methanol at 0 °C, and then an aqueous solution of methylamine (40%, 0.65 g, 0.72 mL, 8.35 mmol, 1.0 equiv) and 26 (1.45 g, 1.21 mL, 8.35 mmol, 1.0 equiv) was added dropwise. After stirring at 0 °C for 10 min, the reaction mixture was allowed to stand at 0 °C for several days until a brown slimy precipitate formed. The solution was decanted, and a small amount of methanol was added to the precipitate, whereupon a yellow solid appeared. This yellow solid was filtered and washed with cold methanol to afford the pure product in a yield of 18.0% (0.71 g, 1.50 mmol). ¹H NMR (400 MHz, CDCl₃): δ 2.31 (s, 3H, NCH₃), 3.65 (s, 3H, COOCH₃), 3.82 (s, 3H, COOCH₃), 4.19 (d, ³J_{H,H} = 9.03 Hz, 1H, NCHCH), 4.69 (d, ³J_{H,H} = 9.16 Hz, 1H, NCHCH), 5.00 (s, 1H, NCH), 7.91 (dd, ³J_{H,H} = 5.40 Hz, ⁴J_{H,H} = 2.01 Hz, 1H, H^{ar}), 7.96–7.99 (m, 2H, H^{ar}), 8.35 (d, ⁴J_{H,H} = 1.88 Hz, 1H, H^{ar}), 8.81 (d, ³J_{H,H} = 5.40 Hz, 1H, H^{ar}), 8.93 (d, ³J_{H,H} = 5.40 Hz, 1H, H^{ar}), 12.51 (s, 1H, enol OH). ¹³C NMR (100 MHz, CDCl₃): δ 37.92, 45.01, 52.03, 52.98, 61.03, 64.60, 97.55, 115.04, 115.27, 115.54, 115.78, 150.96, 151.13, 154.46, 154.57, 161.56, 164.61, 166.84, 170.24, 171.36. HR-ESI (positive mode, [M + H]⁺). Calcd: *m/z* 474.12610. Obsd: *m/z* 474.12541. HR-ESI (positive mode, [M + Na]⁺). Calcd: *m/z* 496.10805. Obsd: *m/z* 496.10739. Elem anal (report 30780, [M]). Calcd: C, 50.74; H, 4.05; N, 14.79. Obsd: C, 50.76; H, 4.11; N, 14.74.

Piperidone (p-Cl)Npy₂P2 (C₂₀H₁₉Cl₂N₅O₂, M_w = 452.29 g mol⁻¹). 9 (5.05 g, 35.67 mmol, 2.0 equiv) was diluted in 30 mL of methanol, and an ethanolic solution of methylamine (8 M, 17.84 mmol, 2.23 mL, 1.0 equiv) was added at 0 °C. At this temperature, dimethylacetone dicarboxylate (3.11 g, 2.60 mL, 17.84 mmol, 1.0 equiv) was added dropwise to the solution and stirred for 10 min and furthermore for 2 h at ambient temperature. The resulting solution was stored at -6 °C. A white-to-pale-purple solid formed and was filtered, washed with cold methanol, and dried in vacuo to afford a pure product in a mixture of isomers in a yield of 81.8% (6.60 g, 14.6 mmol). Further crystallization from hot methanol affords a white crystalline solid as a single isomer. ¹H NMR (600 MHz, CDCl₃): δ 2.24 (s, 3H, NCH₃), 3.64 (s, 3H, COOCH₃), 3.76 (s, 3H, COOCH₃), 4.19 (d, ³J_{H,H} = 9.69 Hz, 1H, NCHCH), 4.47 (d, ³J_{H,H} = 9.69 Hz, 1H, NCHCH), 4.83 (s, 1H, NCH), 7.16 (dd, ³J_{H,H} = 5.25 Hz, ⁴J_{H,H} = 1.61 Hz, 1H, H^{ar}), 7.24 (dd, ³J_{H,H} = 5.30 Hz, ⁴J_{H,H} = 1.56 Hz, 1H, H^{ar}), 7.27 (m, 1H, H^{ar}), 7.56 (d, ⁴J_{H,H} = 1.41 Hz, 1H, H^{ar}), 8.38 (d, ³J_{H,H} = 5.35 Hz, 1H, H^{ar}), 8.54 (d, ³J_{H,H} = 5.25 Hz, 1H, H^{ar}), 12.48 (s, 1H, enol OH). ¹³C NMR (150 MHz, CDCl₃): δ 37.65, 44.73, 51.92, 52.66, 60.36, 64.60, 97.53, 122.74, 123.08, 123.17, 123.64, 144.47, 144.59, 149.46, 150.02, 159.74, 162.42, 167.19, 170.67, 171.64. HR-ESI (positive mode, [M + H]⁺). Calcd: *m/z* 452.07800. Obsd: *m/z* 452.07770. HR-ESI (positive mode, [M + Na]⁺). Calcd: *m/z* 474.05995. Obsd: *m/z* 474.05994. HR-ESI (positive mode, [M + K]⁺). Calcd: *m/z* 490.03388. Obsd: *m/z* 490.03395. Elem anal (report 30807, [M]). Calcd: C, 53.11; H, 4.23; N, 9.29. Obsd: C, 53.29; H, 4.25; N, 9.44.

Piperidone (p-Br)Npy₂P3 (C₂₀H₁₉Br₂N₅O₂, M_w = 541.19 g mol⁻¹). To 5 (1.57 g, 8.44 mmol, 2.0 equiv) dissolved in 10 mL of methanol was subsequently added an ethanolic solution of methylamine (8 M, 0.58 mL, 4.64 mmol, 1.1 equiv) followed by dimethylacetone dicarboxylate (0.74 g, 0.62 mL, 4.22 mmol, 1.0 equiv). The solution was stirred at 0 °C for 1 h and at ambient temperature for another 1 h. The solution was concentrated to half of its volume and freed from minor particles by filtration into a hot flask. Crystallization took place immediately. A pale-yellow crystalline solid was obtained as the pure product in a yield of 55.2% (1.26 g, 2.33 mmol). ¹H NMR (400 MHz,

CDCl_3): δ 2.24 (s, 3H, NCH_3), 3.65 (s, 3H, COOCH_3), 3.77 (s, 3H, COOCH_3), 4.19 (d, $^3J_{\text{H,H}} = 9.54$ Hz, 1H, NCHCH), 4.47 (d, $^3J_{\text{H,H}} = 9.66$ Hz, 1H, NCHCH), 4.83 (s, 1H, NCH), 7.33 (dd, $^3J_{\text{H,H}} = 5.21$ Hz, $^4J_{\text{H,H}} = 1.44$ Hz, 1H, H^{ar}), 7.40 (dd, $^3J_{\text{H,H}} = 5.21$ Hz, $^4J_{\text{H,H}} = 1.44$ Hz, 1H, H^{ar}), 7.44 (d, $^4J_{\text{H,H}} = 0.75$ Hz, 1H, H^{ar}), 7.73 (d, $^4J_{\text{H,H}} = 1.25$ Hz, 1H, H^{ar}), 8.31 (d, $^3J_{\text{H,H}} = 5.27$ Hz, 1H, H^{ar}), 8.46 (d, $^3J_{\text{H,H}} = 5.27$ Hz, 1H, H^{ar}), 12.48 (s, 1H, enol OH). ^{13}C NMR (100 MHz, CDCl_3): δ 37.71, 44.86, 51.93, 52.69, 60.37, 64.58, 97.58, 125.74, 126.07, 126.23, 126.69, 133.26, 133.33, 149.35, 149.89, 159.62, 162.29, 167.16, 170.62, 171.63. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 541.97492. Obsd: m/z 541.97475. HR-ESI (positive mode, $[\text{M} + \text{Na}]^+$). Calcd: m/z 563.95687. Obsd: m/z 563.95700. HR-ESI (positive mode, $[\text{M} + \text{K}]^+$). Calcd: m/z 579.93081. Obsd: m/z 579.93092. Elem anal (report 30963, [M]). Calcd: C, 44.39; H, 3.54; N, 7.76. Obsd: C, 44.59; H, 3.62; N, 8.04.

Piperidone (p-Me)Npy₂P4 ($\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_5$, $M_w = 411.45$ g mol⁻¹). **23** (1.01 g, 8.34 mmol, 2.0 equiv) was dissolved in 10 mL of methanol at 0 °C, and an ethanolic solution of methylamine (8 M, 0.39 g, 0.52 mL, 4.17 mmol, 1.0 equiv) and dimethylacetone dicarboxylate (0.73 g, 0.61 mL, 4.17 mmol, 1.0 equiv) were added dropwise consecutively. The solution was stirred at 0 °C for 2 h and further on at ambient temperature overnight. The solvent was then allowed to evaporate slowly at ambient temperature. After 2 days, big colorless crystals were obtained as the pure product in a yield of 42.5% (723.0 mg, 1.77 mmol). ^1H NMR (400 MHz, CDCl_3): δ 2.22 (s, 3H, $\text{N}^3\text{CH}_3/\text{pyCH}_3$), 2.26 (s, 3H, $\text{N}^3\text{CH}_3/\text{pyCH}_3$), 2.40 (s, 3H, $\text{N}^3\text{CH}_3/\text{pyCH}_3$), 3.63 (s, 3H, COOCH_3), 3.73 (s, 3H, COOCH_3), 4.29 (d, $^3J_{\text{H,H}} = 9.91$ Hz, 1H, N^3CHCH), 4.44 (d, $^3J_{\text{H,H}} = 9.91$ Hz, 1H, N^3CHCH), 4.88 (s, 1H, N^3CH), 6.95 (d, $^3J_{\text{H,H}} = 5.02$ Hz, 1H, H^{ar}), 7.02 (s, 1H, H^{ar}), 7.05 (d, $^3J_{\text{H,H}} = 4.89$ Hz, 1H, H^{ar}), 7.34 (br s, 1H, H^{ar}), 8.34 (d, $^3J_{\text{H,H}} = 5.02$ Hz, 1H, H^{ar}), 8.53 (d, $^3J_{\text{H,H}} = 5.02$ Hz, 1H, H^{ar}), 12.48 (s, 1H, enol OH). ^{13}C NMR (100 MHz, CDCl_3): δ 20.90, 21.34, 37.71, 45.40, 51.84, 52.47, 60.47, 64.73, 98.02, 123.33, 123.63, 123.70, 124.34, 147.53, 148.36, 148.98, 157.76, 159.82, 167.55, 169.14, 171.28, 171.88. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 412.18725. Obsd: m/z 412.18665. HR-ESI (positive mode, $[\text{M} + \text{Na}]^+$). Calcd: m/z 434.16919. Obsd: m/z 434.16880. HR-ESI (positive mode, $[\text{M} + \text{K}]^+$). Calcd: m/z 450.14313. Obsd: m/z 450.14274. Elem anal (report 30952, [M]). Calcd: C, 64.22; H, 6.12; N, 10.21. Obsd: C, 64.16; H, 6.16; N, 10.14.

Piperidone (p-MeO)Npy₂P5 ($\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_7$, $M_w = 443.45$ g mol⁻¹). **15** (10.27 g, 74.89 mmol, 2.0 equiv) was diluted in 50 mL of methanol and cooled to 0 °C. Then an ethanolic solution of methylamine (8 M, 4.68 mL, 37.45 mmol, 1.0 equiv) and dimethylacetone dicarboxylate (6.52 g, 5.46 mL, 37.45 mmol, 1.0 equiv) was added dropwise. This solution was stirred at 0 °C for 10 min and at ambient temperature overnight. The solution was concentrated to approximately 40 mL and another 40 mL of diethyl ether was added. This solution was stored at -6 °C for several days. The colorless crystals were filtered and further washed with cold methanol. This procedure was repeated with the reaction mixture for several times to increase the yield. The pure product was obtained as colorless-to-white crystals (to white powder) in a yield of 51.3% (8.52 g, 19.2 mmol). ^1H NMR (400 MHz, CDCl_3): δ 2.22 (s, 3H, N^3CH_3), 3.64 (s, 3H, COOCH_3), 3.73 (s, 3H, COOCH_3), 3.79 (s, 3H, pyOCH_3), 3.91 (s, 3H, pyOCH_3), 4.22 (d, $^3J_{\text{H,H}} = 9.54$ Hz, 1H, N^3CHCH), 4.42 (d, $^3J_{\text{H,H}} = 9.54$ Hz, 1H, N^3CHCH), 4.92 (br s, 1H, N^3CH), 6.68 (dd, $^3J_{\text{H,H}} = 5.65$ Hz, $^4J_{\text{H,H}} = 2.51$ Hz, 1H, H^{ar}), 6.75–6.79 (m, 2H, H^{ar}), 7.13 (d, $^4J_{\text{H,H}} = 2.01$ Hz, 1H, H^{ar}), 8.31 (d, $^3J_{\text{H,H}} = 5.65$ Hz, 1H, H^{ar}), 8.46 (d, $^3J_{\text{H,H}} = 5.77$ Hz, 1H, H^{ar}), 12.44 (s, 1H, enol OH). ^{13}C NMR (100 MHz, CDCl_3): δ 37.95, 46.37, 51.91, 52.55, 55.14, 55.39, 61.26, 66.81, 108.73, 108.80, 108.93, 109.22, 109.63, 149.96 (2C), 159.92, 161.51, 166.13, 167.39, 167.41, 171.30, 171.68. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 444.17708. Obsd: m/z 444.17660. Elem anal (report 30891, [M]). Calcd: C, 59.59; H, 5.68; N, 9.48. Obsd: C, 59.48; H, 5.69; N, 9.41.

Piperidone (p-EtO)Npy₂P6 ($\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_7$, $M_w = 471.50$ g mol⁻¹). **16** (1.77 g, 11.71 mmol, 2.0 equiv) was dissolved in 20 mL of methanol at 0 °C, and an ethanolic solution of methylamine (8 M, 0.55 g, 0.73 mL, 5.86 mmol, 1.0 equiv) and dimethylacetone

dicarboxylate (1.02 g, 0.85 mL, 5.86 mmol, 1.0 equiv) were added dropwise consecutively. The mixture was stirred at 0 °C for 2 h and afterward at ambient temperature overnight. The product was crystallized by slow evaporation of the solvent at ambient temperature, filtered, washed with further cold methanol, and dried under vacuum. A white, crystalline solid was obtained as the pure product in a yield of 45.9% (1.27 g, 2.69 mmol). ^1H NMR (400 MHz, CDCl_3): δ 1.39 (t, $^3J_{\text{H,H}} = 6.90$ Hz, 3H, $\text{pyOCH}_2\text{CH}_3$), 1.45 (t, $^3J_{\text{H,H}} = 7.15$ Hz, 3H, $\text{pyOCH}_2\text{CH}_3$), 2.21 (s, 3H, N^3CH_3), 3.64 (s, 3H, COOCH_3), 3.74 (s, 3H, COOCH_3), 3.98–4.19 (m, 4H, $\text{pyOCH}_2\text{CH}_3$), 4.21 (d, $^3J_{\text{H,H}} = 9.54$ Hz, 1H, N^3CHCH), 4.41 (d, $^3J_{\text{H,H}} = 9.54$ Hz, 1H, N^3CHCH), 4.88 (br s, 1H, N^3CH), 6.65 (d, $^3J_{\text{H,H}} = 5.65$ Hz, 1H, H^{ar}), 6.70–6.78 (m, 2H, H^{ar}), 7.08 (s, 1H, H^{ar}), 8.30 (d, $^3J_{\text{H,H}} = 5.65$ Hz, 1H, H^{ar}), 8.43–8.47 (m, 1H, H^{ar}), 12.43 (s, 1H, enol OH). ^{13}C NMR (100 MHz, CDCl_3): δ 14.40, 14.49, 37.96, 46.42, 51.87, 52.51, 61.21, 63.48, 63.66, 98.50, 109.13, 109.21, 109.50, 149.96, 150.46, 155.73, 157.22, 159.91, 163.28, 165.44, 167.35, 169.09, 171.26, 171.76. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 472.20838. Obsd: m/z 472.20791. HR-ESI (positive mode, $[\text{M} + \text{Na}]^+$). Calcd: m/z 494.19032. Obsd: m/z 494.19015. Elem anal (report 30808, [M]). Calcd: C, 61.14; H, 6.20; N, 8.91. Obsd: C, 61.17; H, 6.16; N, 8.92.

Piperidone (p-MeS)Npy₂P7 ($\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_5\text{S}_2$, $M_w = 475.58$ g mol⁻¹). **17** (2.65 g, 17.30 mmol, 2.0 equiv) was dissolved in 30 mL of methanol at 0 °C, and an ethanolic solution of methylamine (8 M, 1.08 mL, 8.65 mmol, 1.0 equiv) and dimethylacetone dicarboxylate (1.51 g, 1.26 mL, 8.65 mmol, 1.0 equiv) were added dropwise consecutively. The solution was stirred for 1.5 h at 0 °C. During that time, a precipitate formed. The suspension was stirred for another 3.5 h at ambient temperature. Afterward, the mixture was stored at -6 °C overnight to complete precipitation. Then the white solid was filtered, washed with cold methanol, and dried under vacuum to afford the product in a yield of 67.6% (2.78 g, 5.85 mmol). Crystals could be obtained by recrystallization from hot methanol. ^1H NMR (400 MHz, CDCl_3): δ 2.21 (s, 3H, N^3CH_3), 2.42 (s, 3H, pySCH_3), 2.53 (s, 3H, pySCH_3), 3.64 (s, 3H, COOCH_3), 3.72 (s, 3H, COOCH_3), 4.21 (d, $^3J_{\text{H,H}} = 9.41$ Hz, 1H, N^3CHCH), 4.40 (d, $^3J_{\text{H,H}} = 9.54$ Hz, 1H, N^3CHCH), 4.86 (s, 1H, N^3CH), 6.94 (dd, $^3J_{\text{H,H}} = 5.33$ Hz, $^4J_{\text{H,H}} = 1.82$ Hz, 1H, H^{ar}), 7.01–7.05 (m, 2H, H^{ar}), 7.37 (d, $^4J_{\text{H,H}} = 1.13$ Hz, 1H, H^{ar}), 8.28 (d, $^3J_{\text{H,H}} = 5.27$ Hz, 1H, H^{ar}), 8.41 (d, $^3J_{\text{H,H}} = 5.40$ Hz, 1H, H^{ar}), 12.44 (s, 1H, enol OH). ^{13}C NMR (100 MHz, CDCl_3): δ 13.63, 13.72, 37.85, 45.80, 51.88, 52.53, 60.92, 66.62, 98.17, 118.61, 118.70, 119.37, 119.44, 148.10, 150.71, 157.65, 159.65, 159.71, 167.20, 168.98, 171.01, 171.69. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 476.13139. Obsd: m/z 476.13116. Elem anal (report 30806, [M]). Calcd: C, 55.56; H, 5.30; N, 8.84. Obsd: C, 55.92; H, 5.34; N, 8.93.

Piperidone (o-MeO)Npy₂P8 ($\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_7$, $M_w = 443.45$ g mol⁻¹). **26** (0.97 g, 7.07 mmol, 2.0 equiv) was dissolved in 10 mL of methanol at 0 °C, and then an ethanolic solution of methylamine (8 M, 0.44 mL, 3.54 mmol, 1.0 equiv) and dimethylacetone dicarboxylate (0.62 g, 0.52 mL, 3.54 mmol, 1.0 equiv) were added dropwise. The solution was stirred at 0 °C for 1 h and at ambient temperature for another 2.5 h. Then 20 mL of diethyl ether was added to the solution, and crystallization was performed at -6 °C. After storage for 3 months at -6 °C, a colorless solid crystallized and was filtered and washed with cold methanol. The mother liquor was concentrated to afford further white solid. The clean product was obtained in a yield of 67.2% (1.06 g, 2.38 mmol). ^1H NMR (600 MHz, CDCl_3): δ 2.24 (s, 3H, N^3CH_3), 3.66 (s, 3H, COOCH_3), 3.70 (s, 3H, COOCH_3), 3.89 (s, 3H, pyOCH_3), 3.91 (s, 3H, pyOCH_3), 4.25 (d, $^3J_{\text{H,H}} = 9.99$ Hz, 1H, N^3CHCH), 4.69 (d, $^3J_{\text{H,H}} = 9.99$ Hz, 1H, N^3CHCH), 4.72 (s, N^3CH), 6.59 (d, $^3J_{\text{H,H}} = 8.17$ Hz, 1H, H^{ar}), 6.63 (d, $^3J_{\text{H,H}} = 8.07$ Hz, 1H, H^{ar}), 6.89 (d, $^3J_{\text{H,H}} = 7.37$ Hz, 1H, H^{ar}), 7.17 (d, $^3J_{\text{H,H}} = 7.27$ Hz, 1H, H^{ar}), 7.49 (t, $^3J_{\text{H,H}} = 7.72$ Hz, 1H, H^{ar}), 7.59 (t, $^3J_{\text{H,H}} = 7.67$ Hz, 1H, H^{ar}), 12.44 (s, 1H, enol OH). ^{13}C NMR (150 MHz, CDCl_3): δ 37.41, 44.44, 51.60, 52.19, 53.30, 53.42, 60.02, 64.24, 98.61, 108.68, 109.27, 115.51, 116.25, 138.65, 138.84, 155.88, 158.66, 163.09, 163.22, 166.57, 171.06, 172.29. Elem anal (report 31192, [M]). Calcd: C, 59.59; H, 5.68; N, 9.48. Obsd: C, 59.36; H, 5.61; N, 9.40.

Piperidone (m/3'-Me)Npy₂P9 ($\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_5$, $M_w = 411.45$ g mol⁻¹). **27** (2.23 g, 18.41 mmol, 2.0 equiv) was dissolved in 15 mL of

methanol and cooled to 0 °C. Then an aqueous solution of methylamine (40%, 1.04 g, 1.38 mL, 11.05 mmol, 1.2 equiv) and dimethylacetone dicarboxylate (1.60 g, 1.34 mL, 9.21 mmol, 1.0 equiv) were added to the solution dropwise. The solution was stirred at 0 °C for 2 h, whereupon a precipitate formed, and furthermore at ambient temperature overnight. The white solid was filtered, washed with cold methanol, and dried on air. The pure product was obtained in a yield of 54.6% (2.07 g, 5.03 mmol). ¹H NMR (200 MHz, CDCl₃): δ 1.50 (s, 3H, N³CH₃/pyCH₃), 2.24 (s, 3H, N³CH₃/pyCH₃), 2.46 (s, 3H, N³CH₃/pyCH₃), 3.57 (s, 3H, COOCH₃), 3.64 (s, 3H, COOCH₃), 4.72 (m, 1H, CH), 4.77 (s, 1H, CH), 4.82 (br s, 1H, CH), 7.02 (dd, ³J_{H,H} = 7.64 Hz, ³J_{H,H} = 4.74 Hz, 1H, H^{5'}), 7.12 (dd, ³J_{H,H} = 7.45 Hz, ³J_{H,H} = 4.67 Hz, 1H, H^{5'}), 7.27 (ddd, ³J_{H,H} = 7.55 Hz, ⁴J_{H,H} = 1.65 Hz, ⁴J_{H,H} = 0.69 Hz, 1H, H^{4'}), 7.49 (ddd, ³J_{H,H} = 7.55 Hz, ⁴J_{H,H} = 1.61 Hz, ⁴J_{H,H} = 0.69 Hz, 1H, H^{4'}), 8.30–8.35 (m, 1H, H^{6'}), 8.45 (dd, ³J_{H,H} = 4.80 Hz, ⁴J_{H,H} = 1.39 Hz, 1H, H^{6'}), 12.50 (s, 1H, enol OH). ¹³C NMR (50 MHz, CDCl₃): δ 16.46, 18.37, 36.56, 41.52, 51.49, 52.11, 56.03, 62.09, 96.52, 121.97, 122.27, 132.66, 133.56, 137.59, 138.10, 145.35, 145.67, 155.50, 158.73, 167.83, 170.95, 172.10. Elem anal (report IPMB-MM455, [M]). Calcd: C, 64.22; H, 6.12; N, 10.21. Obsd: C, 64.20; H, 6.33; N, 10.17.

Piperidone NPyr₂P10 (C₁₈H₁₉N₅O₅, M_w = 385.37 g mol⁻¹). **25** (25; 0.91 g, 8.42 mmol, 2.0 equiv) was dissolved in 10 mL of methanol at 0 °C, and then an ethanolic solution of methylamine (8 M, 0.48 g, 0.63 mL, 5.05 mmol, 1.2 equiv) followed by dimethylacetone dicarboxylate (0.73 g, 0.61 mL, 4.21 mmol, 1.0 equiv) were added to the solution and stirred at 0 °C for 2 h and afterward at ambient temperature overnight. A yellow crystalline solid was obtained as the pure product by slow evaporation of the solvent at ambient temperature in a yield of 27.8% (0.45 g, 1.17 mmol). ¹H NMR (600 MHz, CDCl₃): δ 2.28 (s, 3H, N³CH₃), 3.64 (s, 3H, COOCH₃), 3.74 (s, 3H, COOCH₃), 4.21 (d, ³J_{H,H} = 8.78 Hz, 1H, N³CHCH), 4.68 (br s, 1H, N³CHCH), 4.89 (s, 1H, N³CH), 8.46 (s, 1H, H^{ar}), 8.47 (s, 1H, H^{ar}), 8.52 (s, 1H, H^{ar}), 8.54 (s, 1H, H^{ar}), 8.59 (s, 1H, H^{ar}), 8.87 (s, 1H, H^{ar}), 12.52 (s, 1H, enol OH). ¹³C NMR (150 MHz, CDCl₃): δ 37.54 (NCH₃), 43.82, 51.96, 52.78, 58.71, 62.82, 96.98, 143.26 (2C), 143.35, 143.62, 145.22, 145.63, 153.29, 156.19, 166.86, 170.15, 171.42. HR-ESI (positive mode, [M + H]⁺). Calcd: m/z 386.14644. Obsd: m/z 386.14582. HR-ESI (positive mode, [M + Na]⁺). Calcd: m/z 408.12839. Obsd: m/z 408.12777. HR-ESI (positive mode, [M + K]⁺). Calcd: m/z 424.10233. Obsd: m/z 424.10173. Elem anal (report 30951, [M]). Calcd: C, 56.10; H, 4.97; N, 18.17. Obsd: C, 56.09; H, 5.04; N, 18.12.

Piperidone (m,m-di-Br)Npy₂P11 (C₂₀H₁₇Br₂N₃O₅, M_w = 698.98 g mol⁻¹). **28** (1.04 g, 3.93 mmol, 2.0 equiv) was dissolved in 5 mL of methanol at 0 °C, and an ethanolic solution of methylamine (33 wt %, 0.22 g, 0.29 mL, 2.36 mmol, 1.2 equiv) and dimethylacetone dicarboxylate (0.34 g, 0.28 mL, 1.97 mmol, 1.0 equiv) were added dropwise subsequently to the solution, which was then stirred for 2 h at 0 °C and another 4 h at ambient temperature. A white solid precipitated. The resulting solid was removed by filtration, washed with a small amount of cold methanol, and dried on air. The pure product was obtained in a yield of 62.4% (0.86 g, 1.23 mmol). ¹H NMR (enol form; 200 MHz, CDCl₃): δ 2.25 (s, 3H, N³CH₃), 3.61 (s, 3H, COOCH₃), 3.67 (s, 3H, COOCH₃), 4.62 (d, ³J_{H,H} = 11.24 Hz, 1H, N³CHCH), 5.07 (br s, 1H, N³CH), 5.24 (d, ³J_{H,H} = 11.24 Hz, N³CHCH), 7.93 (d, ⁴J_{H,H} = 2.02 Hz, 1H, H^{ar}), 8.07 (d, ⁴J_{H,H} = 2.02 Hz, 1H, H^{ar}), 8.52–8.56 (m, 1H, H^{ar}), 8.61 (d, ⁴J_{H,H} = 2.02 Hz, 1H, H^{ar}), 12.50 (s, 1H, enol OH). ¹³C NMR (keto and enol forms; 50 MHz, CDCl₃): δ 30.40, 36.49, 41.44, 51.88, 52.19, 52.52, 54.95, 57.05, 62.47, 66.72, 96.15, 118.99, 119.91, 120.10, 123.01, 123.52, 123.58, 142.21, 143.14, 143.22, 147.76, 147.95, 147.98, 148.16, 153.15, 167.49, 168.38, 169.82, 171.40, 200.39. HR-ESI (positive mode, [M + H]⁺). Calcd: m/z 699.79390. Obsd: m/z 699.79389. Elem anal (report IPMB_MM405, [M]). Calcd: C, 34.37; H, 2.45; N, 6.01. Obsd: C, 34.56; H, 2.83; N, 6.01.

Bispidone (p-NO₂)N₂py₂B1 (C₂₃H₂₄N₆O₉, M_w = 528.47 g mol⁻¹). Piperidone **P1** (0.64 g, 1.35 mmol, 1.0 equiv) was suspended in 10 mL of THF and heated to 50 °C. At this temperature, an aqueous solution of formaldehyde (37%, 0.22 g, 0.20 mL, 2.70 mmol, 2.0 equiv) and an aqueous solution of methylamine (40%, 0.13 g, 0.14 mL, 1.62 mmol,

1.2 equiv) were added dropwise to the suspension consecutively, and the mixture was refluxed for 1 h. After cooling to ambient temperature, the solvent was removed in vacuo. The resulting foam was taken up in hot methanol. A yellow solid formed. For further precipitation, the suspension was stored at 6 °C overnight. The solid material was filtered and washed with a small amount of cold methanol. The solid material consists of a fine powdery white solid and a more crystalline yellow solid, which could be separated manually. The former white solid turned out to be *syn*-bispidone (endo/endo isomer) and was obtained in a yield of 8.2% (0.06 g, 0.11 mmol); the yellow solid turned out to be *anti*-bispidone (endo/exo isomer) and was obtained in a yield of 42.2% (0.30 g, 0.57 mmol). **syn-B1**. ¹H NMR (400 MHz, CDCl₃): δ 2.10 (s, 3H, N³CH₃), 2.33 (s, 3H, N⁷CH₃), 2.59 (d, ²J_{H,H} = 12.55 Hz, 2H, CH_{ax}H_{eq}), 2.81 (d, ²J_{H,H} = 12.80 Hz, 2H, CH_{ax}H_{eq}), 3.85 (s, 6H, COOCH₃), 5.04 (s, 2H, NCH), 8.01 (dd, ³J_{H,H} = 5.33 Hz, ⁴J_{H,H} = 2.07 Hz, 2H, H^{5'}), 8.84 (d, ³J_{H,H} = 5.27 Hz, 2H, H^{6'}), 8.94 (d, ⁴J_{H,H} = 1.63 Hz, 2H, H^{3'}). ¹³C NMR (100 MHz, CDCl₃): δ 43.62, 44.23, 52.82, 60.74, 61.72, 73.03, 115.77, 116.23, 151.60, 154.86, 162.85, 167.68, 201.79. **anti-B1**. ¹H NMR (400 MHz, CDCl₃): δ 2.06 (s, 3H, N³CH₃), 2.28 (s, 3H, N⁷CH₃), 2.77 (d, ²J_{H,H} = 12.27 Hz, 1H, N⁷CH_{ax}H_{eq}), 2.92 (dd, ²J_{H,H} = 12.60 Hz, ⁴J_{H,H} = 1.6 Hz, 1H, N⁷CH_{ax}H_{eq}), 3.17 (d, ²J_{H,H} = 11.04 Hz, 1H, N⁷CH_{ax}H_{eq}), 3.58 (s, 3H, COOCH₃), 3.69 (dd, ²J_{H,H} = 11.04 Hz, ⁴J_{H,H} = 1.51 Hz, 1H, N⁷CH_{ax}H_{eq}), 3.88 (s, 3H, COOCH₃), 5.05 (br s, 1H, N³CH), 5.21 (br s, 1H, N³CH), 7.92 (dd, ³J_{H,H} = 5.14 Hz, ⁴J_{H,H} = 2.20 Hz, 1H, H^{5'}), 7.93 (dd, ³J_{H,H} = 5.14 Hz, ⁴J_{H,H} = 2.26 Hz, 1H, H^{5'}), 8.07 (d, ⁴J_{H,H} = 1.88 Hz, 1H, H^{3'}), 8.69 (br s, 1H, H^{3'}), 8.79 (d, ³J_{H,H} = 5.40 Hz, 1H, H^{6'}), 8.88 (d, ³J_{H,H} = 5.27 Hz, 1H, H^{6'}). ¹³C NMR (100 MHz, CDCl₃): δ 40.33, 44.05, 52.55, 52.82, 61.71, 61.76, 61.88, 65.67, 70.12, 72.51, 114.47, 115.21, 115.90, 116.88, 150.46, 151.12, 153.94, 154.40, 161.03, 162.37, 168.62, 168.86, 200.77. HR-ESI (positive mode, [M + H]⁺). Calcd: m/z 529.16830. Obsd: m/z 529.16749. HR-ESI (positive mode, [M + MeOH + H]⁺). Calcd: m/z 561.19452. Obsd: m/z 561.19372. Elem anal (report 29622, [M]). Calcd: C, 52.27; H, 4.58; N, 15.90. Obsd: C, 52.37; H, 4.70; N, 15.62.

Bispidone (p-Cl)N₂py₂B2 (C₂₃H₂₄Cl₂N₄O₅, M_w = 507.37 g mol⁻¹). Piperidone **P2** (2.00 g, 4.42 mmol, 1.0 equiv) was suspended in 30 mL of methanol and heated to 50 °C. At this temperature, an aqueous solution of methylamine (40%, 0.34 g, 0.38 mL, 4.42 mmol, 1.0 equiv) and an aqueous solution of formaldehyde (37%, 0.72 g, 0.66 mL, 8.84 mmol, 2.0 equiv) were added to the suspension and heated to reflux for 3 h. The newly formed suspension was allowed to stand at ambient temperature overnight and filtered. The solid was washed with cold methanol to afford a white crystalline solid as the pure product in a yield of 57.0% (1.28 g, 2.52 mmol). ¹H NMR (400 MHz, CDCl₃): δ 2.08 (s, 3H, N³CH₃), 2.30 (s, 3H, N⁷CH₃), 2.53 (d, ²J_{H,H} = 12.30 Hz, 2H, CH_{ax}H_{eq}), 2.90 (d, ²J_{H,H} = 12.80 Hz, 2H, CH_{ax}H_{eq}), 3.83 (s, 6H, COOCH₃), 4.78 (s, 2H, NCH), 7.27 (dd, ³J_{H,H} = 5.27 Hz, ⁴J_{H,H} = 2.01 Hz, 2H, H^{5'}), 8.10 (d, ⁴J_{H,H} = 1.88 Hz, 2H, H^{3'}), 8.42 (d, ³J_{H,H} = 5.27 Hz, 2H, H^{6'}). ¹³C NMR (100 MHz, CDCl₃): δ 43.46, 44.24, 52.61, 60.74, 61.86, 73.31, 123.57, 123.77, 144.95, 150.14, 160.71, 168.11, 202.72. HR-ESI (positive mode, [M + H]⁺). Calcd: m/z 507.12020. Obsd: m/z 507.11987. Elem anal (report 29806, [M]). Calcd: C, 54.45; H, 4.77; N, 11.04. Obsd: C, 54.30; H, 4.74; N, 10.93.

Bispidone (p-Br)N₂py₂B3 (C₂₃H₂₄Br₂N₄O₅, M_w = 596.27 g mol⁻¹). Piperidone **P3** (0.94 g, 1.74 mmol, 1.0 equiv) was dissolved in 10 mL of THF and heated to 50 °C, whereupon 0.16 mL of an aqueous solution of methylamine (40%, 0.14 g, 1.74 mmol, 1.0 equiv) followed by 0.26 mL of an aqueous solution of formaldehyde (37%, 0.28 g, 3.48 mmol, 2.0 equiv) were added. The suspension was heated to reflux for 1 h. After the mixture was allowed to cool to ambient temperature, the solvent was removed in vacuo. The residue was taken up in hot methanol, whereupon a white solid crystallized. The suspension was allowed to stand at -6 °C for further crystallization. The white solid was filtered and washed with methanol. The solution was furthermore concentrated, whereupon yellow crystals formed. The white solid (first crystallization), which turned out to be *syn*-bispidone (endo/endo isomer), was obtained in a yield of 13.2% (0.14 g, 0.23 mmol). The yellow needles (second crystallization), which turned out to be *anti*-bispidone (endo/exo isomer), were obtained in a yield of 55.2% (0.57

g, 0.96 mmol). *syn-B3*. $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.07 (s, 3H, N^3CH_3), 2.30 (s, 3H, N^7CH_3), 2.51 (d, 2H, $^2J_{\text{H,H}} = 12.13$ Hz, 1H, $\text{N}^7\text{CH}_2\text{H}_{\text{eq}}$), 2.88 (d, $^2J_{\text{H,H}} = 12.88$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 3.81 (s, 6H, COOCH_3), 4.76 (s, 2H, N^3CH), 7.42 (dd, $^3J_{\text{H,H}} = 5.31$ Hz, $^4J_{\text{H,H}} = 1.89$ Hz, 2H, H^{S}), 8.27 (d, $^4J_{\text{H,H}} = 1.64$ Hz, 2H, H^{S}), 8.32 (d, $^3J_{\text{H,H}} = 5.31$ Hz, 2H, H^{S}). $^{13}\text{C NMR}$ (50 MHz, CDCl_3): δ 43.43, 44.07, 52.54, 60.70, 61.90, 73.26, 126.45, 126.95, 133.59, 149.98, 160.58, 168.04, 202.58. *anti-B3*. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.05 (s, 3H, N^3CH_3), 2.28 (s, 3H, N^7CH_3), 2.76 (br d, $^2J_{\text{H,H}} = 12.05$ Hz, $\text{N}^7\text{CH}_2\text{H}_{\text{eq}}$), 3.08 (d, $^2J_{\text{H,H}} = 10.92$, $\text{N}^7\text{CH}_2\text{H}_{\text{eq}}$), 3.49 (br s, 1H, $\text{N}^7\text{CH}_2\text{H}_{\text{eq}}$), 3.54 (s, 3H, COOCH_3), 3.65 (d, $^2J_{\text{H,H}} = 10.79$ Hz, $\text{N}^7\text{CH}_2\text{H}_{\text{eq}}$), 3.85 (s, 3H, COOCH_3), 4.79 (s, 1H, N^3CH), 5.07 (s, 1H, N^3CH), 7.33–7.37 (m, 2H, H^{S}), 7.48 (s, 1H, H^{S}), 8.04 (br s, 1H, H^{S}), 8.30 (d, $^3J_{\text{H,H}} = 5.27$ Hz, 1H, H^{S}), 8.38 (d, $^3J_{\text{H,H}} = 5.27$ Hz, 1H, H^{S}). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 40.22, 44.08, 52.28, 52.64, 61.38, 62.06, 65.90, 69.76, 69.79, 72.39, 125.24, 125.96, 126.48, 127.47, 132.86, 133.16, 149.00, 149.66, 158.73, 160.05, 169.08, 169.36, 201.41. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 597.01712. Obsd: m/z 597.01684. HR-ESI (positive mode, $[\text{M} + \text{MeOH} + \text{H}]^+$). Calcd: m/z 629.04334. Obsd: m/z 629.04301. Elem anal (report 30487, [M]). Calcd: C, 46.33; H, 4.06; N, 9.40. Obsd: C, 46.54; H, 4.20; N, 9.35.

Bispidone (p-Me)N₂py₂B4 ($\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_5$, $M_w = 466.53$ g mol $^{-1}$). Piperidone P4 (620.7 mg, 1.51 mmol, 1.0 equiv) was suspended in 15 mL of THF and heated to 50 °C, whereupon 0.13 mL of an aqueous solution of methylamine (40%, 0.12 g, 1.51 mmol, 1.0 equiv) and then 0.23 mL of an aqueous solution of formaldehyde (37%, 0.25 g, 3.02 mmol, 2.0 equiv) were added. The suspension was heated to reflux for 1 h. After the mixture was allowed to cool to ambient temperature, the solvent was removed under vacuum. Methanol was added to the resulting white foam. The solution was allowed to stand at –6 °C for crystallization. The white solid was filtered and washed with cold methanol. A white crystalline solid was obtained as the pure product in a yield of 48.3% (0.34 g, 0.73 mmol). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.02 (s, 3H, N^3CH_3), 2.29 (s, 3H, N^7CH_3), 2.45 (s, 6H, pyCH_3), 2.55 (d, $^2J_{\text{H,H}} = 12.05$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 3.06 (d, $^2J_{\text{H,H}} = 11.92$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 3.81 (s, 6H, COOCH_3), 4.66 (s, 2H, CH), 7.04 (d, $^3J_{\text{H,H}} = 4.89$ Hz, 2H, H^{S}), 7.85 (s, 2H, H^{S}), 8.36 (d, $^3J_{\text{H,H}} = 5.02$ Hz, 2H, H^{S}). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 21.49, 43.14, 44.36, 52.43, 60.66, 62.20, 73.91, 123.99, 124.28, 147.32, 148.92, 158.61, 168.62, 203.57. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 467.22945. Obsd: m/z 467.22914. HR-ESI (positive mode, $[\text{M} + \text{MeOH} + \text{H}]^+$). Calcd: m/z 499.25566. Obsd: m/z 499.25526. Elem anal (report 30486, [M]). Calcd: C, 64.36; H, 6.48; N, 12.01. Obsd: C, 64.58; H, 6.54; N, 12.14.

Bispidone (p-MeO)N₂py₂B5 ($\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_7$, $M_w = 498.53$ g mol $^{-1}$). Piperidone P5 (3.00 g, 6.77 mmol, 1.0 equiv) was suspended in 40 mL of methanol and heated to 50 °C. Then an aqueous solution of methylamine (40%, 0.53 g, 0.59 mL, 6.77 mL, 1.0 equiv) and an aqueous solution of formaldehyde (37%, 1.10 g, 1.01 mL, 13.54 mmol, 2.0 equiv) were added, and the suspension was heated to reflux for 3 h. The solution was concentrated to one-third of its original volume and stored at –6 °C for several days. The precipitate formed was filtered and washed with cold methanol. This procedure can be repeated with the mother liquor to increase the yield. The pure product was obtained as a white solid in a yield of 54.8% (1.85 g, 3.71 mmol). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.07 (s, 3H, N^3CH_3), 2.28 (s, 3H, N^7CH_3), 2.50 (d, $^2J_{\text{H,H}} = 12.17$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 3.00 (d, $^2J_{\text{H,H}} = 12.55$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 3.83 (s, 6H, COOCH_3), 3.92 (s, 6H, pyOCH_3), 4.71 (s, 2H, N^3CH), 6.75 (dd, $^3J_{\text{H,H}} = 5.77$ Hz, $^4J_{\text{H,H}} = 2.63$ Hz, 2H, H^{S}), 7.69 (d, $^4J_{\text{H,H}} = 2.51$ Hz, 2H, H^{S}), 8.32 (d, $^3J_{\text{H,H}} = 5.65$ Hz, 2H, H^{S}). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 43.36, 44.49, 52.48, 54.99, 60.93, 61.91, 73.53, 108.96, 109.41, 150.43, 160.70, 166.23, 168.52, 203.57. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 499.21927. Obsd: m/z 499.21893. HR-ESI (positive mode, $[\text{M} + \text{Na}]^+$). Calcd: m/z 521.20122. Obsd: m/z 521.20113. HR-ESI (positive mode, $[\text{M} + \text{MeOH} + \text{H}]^+$). Calcd: m/z 531.24549. Obsd: m/z 531.24493. Elem anal (report 29809, [M]). Calcd: C, 60.23; H, 6.07; N, 11.24. Obsd: C, 60.44; H, 6.00; N, 11.26.

Bispidone (p-EtO)N₂py₂B6 ($\text{C}_{27}\text{H}_{34}\text{N}_4\text{O}_7$, $M_w = 526.58$ g mol $^{-1}$). Piperidone P6 (0.82 g, 1.74 mmol, 1.0 equiv) was suspended in 10 mL

of THF and heated to 50 °C. At this temperature, an aqueous solution of methylamine (40%, 0.16 g, 0.18 mL, 2.09 mmol, 1.2 equiv) and an aqueous solution of formaldehyde (37%, 0.28 g, 0.26 mL, 3.48 mmol, 2.0 equiv) were added dropwise to the mixture consecutively. The mixture was refluxed for 1 h and then concentrated in vacuo after cooling to ambient temperature. The residue was taken up in methanol and precipitated by slow evaporation of the solvent. The resulting white solid was filtered and washed with a small amount of cold methanol (product is fairly soluble in methanol) to afford the pure product in a yield of 9.2% (83.7 mg, 0.16 mmol). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.49 (t, $^3J_{\text{H,H}} = 6.96$ Hz, 6H, OCH_2CH_3), 2.06 (s, 3H, N^3CH_3), 2.27 (s, 3H, N^7CH_3), 2.51 (d, $^2J_{\text{H,H}} = 11.92$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 3.02 (d, $^2J_{\text{H,H}} = 11.42$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 3.81 (s, 6H, COOCH_3), 4.15 (m, 4H, $\text{pyOCH}_2\text{CH}_3$), 4.68 (s, 2H, N^3CH), 6.72 (dd, $^3J_{\text{H,H}} = 5.65$ Hz, $^4J_{\text{H,H}} = 2.38$ Hz, 2H, H^{S}), 7.65 (br s, 2H, H^{S}), 8.29 (d, $^3J_{\text{H,H}} = 5.65$ Hz, 2H, H^{S}). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 14.54 (2C, OCH_2CH_3), 43.27 (N^3CH_3), 44.54 (N^7CH_3), 52.47 (2C, COOCH_3), 60.85 (2C, $\text{C}^{6/8}\text{H}_2$), 61.94, 63.38 (OCH_2CH_3), 73.49 (2C, $\text{C}^{2/4}\text{H}$), 109.63 (4C, $\text{C}^{4/16}$), 150.33 (2C, C^3), 160.62, 165.54, 168.53, 203.57. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 527.25057. Obsd: m/z 527.24987. HR-ESI (positive mode, $[\text{M} + \text{Na}]^+$). Calcd: m/z 549.23252. Obsd: m/z 549.23210. Elem anal (report IPMB23, [M]). Calcd: C, 61.58; H, 6.51; N, 10.64. Obsd: C, 61.18; H, 6.56; N, 10.55.

Bispidone (p-MeS)N₂py₂B7 ($\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_5\text{S}_2$, $M_w = 530.66$ g mol $^{-1}$). Piperidone P7 (1.74 g, 3.66 mmol, 1.0 equiv) was suspended in THF and heated to 50 °C. At this temperature, an aqueous solution of methylamine (40%, 0.28 g, 0.31 mL, 3.66 mmol, 1.0 equiv) and an aqueous solution of formaldehyde (37%, 0.59 g, 0.54 mL, 7.32 mmol, 2.0 equiv) were added consecutively to the suspension and heated to reflux for 1 h. After allowed to cool to ambient temperature, the solvent was removed under vacuum, and the resulting residue was taken up in ethanol. A solid was obtained by slow evaporation of the solvent at ambient temperature and was recrystallized from hot methanol to afford a white solid as the pure product in a yield of 31.4% (0.61 g, 1.15 mmol). $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 2.08 (s, 3H, N^3CH_3), 2.26 (s, 3H, N^7CH_3), 2.49 (d, $^2J_{\text{H,H}} = 12.01$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 2.58 (s, 6H, pySCH_3), 2.89 (d, $^2J_{\text{H,H}} = 11.91$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 3.83 (s, 6H, COOCH_3), 4.74 (s, 2H, N^3CH), 7.02 (d, $^3J_{\text{H,H}} = 5.25$ Hz, H^{S}), 8.01 (s, 2H, H^{S}), 8.29 (d, $^3J_{\text{H,H}} = 5.35$ Hz, 2H, H^{S}). $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 13.68, 43.38, 44.49, 52.54, 60.83, 61.82, 73.25, 118.94, 119.16, 148.61, 150.74, 158.65, 168.39, 203.38. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 531.17359. Obsd: m/z 531.17355. HR-ESI (positive mode, $[\text{M} + \text{MeOH} + \text{H}]^+$). Calcd: m/z 563.19980. Obsd: m/z 563.19977. Elem anal (report 30544, [M]). Calcd: C, 56.58; H, 5.70; N, 10.56. Obsd: C, 56.65; H, 5.75; N, 10.59.

Bispidone (o-MeO)N₂py₂B8 ($\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_7$, $M_w = 498.53$ g mol $^{-1}$). Piperidone P8 (336.0 mg, 0.76 mmol, 1.0 equiv) was suspended in 5 mL of THF and heated to 50 °C. At this temperature, an aqueous solution of methylamine (40%, 0.07 g, 0.08 mL, 0.91 mmol, 1.2 equiv) and an aqueous solution formaldehyde (37%, 0.12 g, 0.11 mL, 1.52 mmol, 2.0 equiv) were added. The mixture was refluxed for 2 h. The solvent was removed in vacuo, and the resulting white foam was taken up in methanol. Slow evaporation of the solvent afforded a white crystalline solid in a yield of 36.1% (0.137 g, 0.274 mmol). $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 2.14 (2s, 6H, $\text{N}^{3/7}\text{CH}_3$), 2.52 (d, $^2J_{\text{H,H}} = 11.71$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 2.90 (d, $^2J_{\text{H,H}} = 10.29$ Hz, 2H, $\text{CH}_{\text{ax}}\text{H}_{\text{eq}}$), 3.83 (s, 6H, $\text{COOCH}_3/\text{pyOCH}_3$), 3.85 (s, 6H, $\text{COOCH}_3/\text{pyOCH}_3$), 4.67 (s, 2H, N^3CH), 6.64 (dd, $^3J_{\text{H,H}} = 7.20$ Hz, $^4J_{\text{H,H}} = 1.40$ Hz, 2H, H^{S}), 7.64 (br s, 2H, H^{S}), 7.66 (t, $^3J_{\text{H,H}} = 7.27$ Hz, 2H, H^{S}). $^{13}\text{C NMR}$ (150 MHz, CDCl_3): δ 43.46, 44.25, 52.26, 53.11, 60.73, 61.99, 72.72, 109.65, 116.05, 138.73, 156.85, 163.37, 168.80, 204.46. HR-ESI (positive mode, $[\text{M} + \text{H}]^+$). Calcd: m/z 499.21927. Obsd: m/z 499.21845. HR-ESI (positive mode, $[\text{M} + \text{MeOH} + \text{H}]^+$). Calcd: m/z 531.24549. Obsd: m/z 531.24416. Elem anal (report 31250, $[\text{M} + \frac{1}{3}\text{H}_2\text{O}]$). Calcd: C, 59.51; H, 6.13; N, 11.10. Obsd: C, 59.60; H, 6.13; N, 10.98.

Bispidone (m/3'-Me)N₂py₂B9 ($\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_5$, $M_w = 466.53$ g mol $^{-1}$). Piperidone P9 (1.03 g, 2.50 mmol, 1.0 equiv) was suspended in THF

and heated to 50 °C. At this temperature, an aqueous solution of methylamine (40%, 0.19 g, 0.21 mL, 2.50 mmol, 1.0 equiv) and an aqueous solution of formaldehyde (37%, 0.41 g, 0.38 mL, 5.00 mmol, 2.0 equiv) were added consecutively. The mixture was heated to reflux for 2 h. After allowed to cool to ambient temperature, the solvent was removed in vacuo. The residue was recrystallized from hot methanol twice to afford the pure product in a yield of 46.8% (0.55 g, 1.17 mmol). ¹H NMR (200 MHz, CDCl₃): δ 2.05 (s, 3H, N³CH₃), 2.47 (s, 6H, pyCH₃), 2.49 (N⁷CH₃), 3.57 (s, 6H, COOCH₃), 3.87 (d, ²J_{H,H} = 12.63 Hz, 2H, N⁷CH_{ax}H_{eq}), 4.25 (d, ²J_{H,H} = 12.63 Hz, 2H, N⁷CH_{ax}H_{eq}), 4.85 (s, 2H, N³CH), 7.08 (dd, ³J_{H,H} = 7.58 Hz, ³J_{H,H} = 4.67 Hz, 2H, H⁵), 7.45 (br d, ³J_{H,H} = 7.20 Hz, 2H, H⁴), 8.34 (br d, ³J_{H,H} = 3.66 Hz, 2H, H⁶). ¹³C NMR (50 MHz, CDCl₃): δ 18.94 (2C, C^{ar}CH₃), 35.50 (N³CH₃), 45.62 (N⁷CH₃), 51.99 (2C, COOCH₃), 60.00 (2C, CH₂), 65.74 (2C, C^{1/5}), 69.39 (2C, CH), 122.56 (2C, C^{ar}), 133.40 (2C, C^{ar}), 138.07 (2C, C^{ar}), 146.18 (2C, C^{ar}), 155.71 (2C, C^{ar}), 170.80 (2C, COOCH₃), 205.09 (C⁹O). HR-ESI (positive mode, [M + H]⁺). Calcd: m/z 467.22945. Obsd: m/z 467.22895. HR-ESI (positive mode, [M + MeOH + H]⁺). Calcd: m/z 499.25566. Obsd: m/z 499.25513. Elem anal (report IPMB_Mimo456b, [M]). Calcd: C, 64.36; H, 6.48; N, 12.01. Obsd: C, 64.33; H, 6.57; N, 11.93.

Bispidone N₂pyr₂anti-B10 (C₂₁H₂₄N₆O₅; M_w = 440.45 g mol⁻¹). Piperidone **P10** (0.34 g, 0.88 mmol, 1.0 equiv) was suspended in 5 mL of THF and heated to 60 °C, and then an aqueous solution of methylamine (40%, 0.08 g, 0.09 mL, 1.06 mmol, 1.2 equiv) and an aqueous solution of formaldehyde (37%, 0.14 g, 0.13 mL, 1.76 mmol, 2.0 equiv) were added dropwise to the suspension consecutively. The mixture was heated to reflux for 3 h. After cooling to ambient temperature, the solvent was removed in vacuo, and the resulting residue was recrystallized from ethyl acetate to afford yellow crystals as the pure anti-bispidone in a yield of 36.4% (0.14 g, 0.32 mmol). ¹H NMR (600 MHz, CDCl₃): δ 2.09 (s, 3H, N³CH₃), 2.26 (s, 3H, N⁷CH₃), 2.93 (d, ²J_{H,H} = 11.91 Hz, 1H, N⁷CH_{ax}H_{eq}), 3.17 (d, ²J_{H,H} = 10.80 Hz, 1H, N⁷CH_{ax}H_{eq}), 3.27 (d, ²J_{H,H} = 11.50 Hz, 1H, N⁷CH_{ax}H_{eq}), 3.54 (s, 3H, COOCH₃), 3.63 (d, ²J_{H,H} = 10.80 Hz, N⁷CH_{ax}H_{eq}), 3.82 (s, 3H, COOCH₃), 4.98 (br s, 1H, N³CH), 5.20 (br s, 1H, N³CH), 8.45 (d, ³J_{H,H} = 2.60 Hz, 2H, H^{ar}), 8.46 (d, ³J_{H,H} = 2.65 Hz, 2H, H^{ar}), 8.49 (m, 1H, H^{ar}), 8.54 (m, 1H, H^{ar}), 8.63 (m, 1H, H^{ar}), 8.88 (br s, 1H, H^{ar}). ¹³C NMR (150 MHz, CDCl₃): δ 39.96, 44.25, 52.37, 52.74, 60.84, 61.24, 62.07, 65.80, 67.76, 69.62, 142.88, 142.93, 143.53, 143.58, 144.90, 146.08, 153.26, 153.56, 169.06, 169.20, 201.24. HR-ESI (positive mode, [M + H]⁺). Calcd: m/z 441.18864. Obsd: m/z 441.18798. HR-ESI (positive mode, [M + Na]⁺). Calcd: m/z 463.17059. Obsd: m/z 463.16998.

Bispidone (m,m-di-Br)N₂py₂anti-B11 (C₂₃H₂₂Br₄N₄O₅; M_w = 754.06 g mol⁻¹). Piperidone **P11** (1.08 g, 1.55 mmol, 1.0 equiv) was dissolved in 10 mL of methanol and heated to 50 °C. At this temperature, an aqueous solution of methylamine (40%, 0.12 g, 0.13 mL, 1.55 mmol, 1.0 equiv) and an aqueous solution of formaldehyde (37%, 0.25 g, 0.23 mL, 3.10 mmol, 2.0 equiv) were added to the mixture. The reaction mixture was stirred at reflux for 1 h. After cooling to ambient temperature, the solution was slowly concentrated by evaporation of the solvent at ambient temperature. A yellow crystalline solid was obtained, filtered, and washed with cold methanol to afford the pure anti-bispidone in a yield of 49.7% (0.58 g, 0.77 mmol). ¹H NMR (200 MHz, CDCl₃): δ 2.20 (s, 3H, N³CH₃), 2.45 (s, 3H, N⁷CH₃), 3.47 (m, 2H, N⁷CH), 3.61 (d, ²J_{H,H} = 12.00 Hz, 1H, N⁷CH), 3.65 (s, 3H, COOCH₃), 3.66 (s, 3H, COOCH₃), 4.44 (d, ²J_{H,H} = 11.62 Hz, N⁷CH), 5.08 (s, 1H, N³CH), 5.98 (s, 1H, N³CH), 7.96 (d, ⁴J_{H,H} = 2.02 Hz, 1H, H^{ar}), 8.06 (d, ⁴J_{H,H} = 2.02 Hz, 1H, H^{ar}), 8.54 (d, ⁴J_{H,H} = 2.02 Hz, 1H, H^{ar}), 8.55 (d, ⁴J_{H,H} = 2.02 Hz, 1H, H^{ar}). ¹³C NMR (50 MHz, CDCl₃): δ 38.45, 45.14, 52.23, 52.38, 60.25, 60.45, 60.54, 63.57, 66.99, 68.99, 118.51, 119.61, 122.24, 124.06, 142.09, 142.71, 147.39, 148.70, 154.46, 154.66, 170.16, 170.47, 199.20. HR-ESI (positive mode, [M + H]⁺). Calcd: m/z 754.83610. Obsd: m/z 754.83380. Elem anal (report IPMB-MM457, [M]). Calcd: C, 36.63; H, 2.94; N, 7.43. Obsd: C, 36.75; H, 3.28; N, 7.37.

Bispidone {C⁹OH}B2 (C₂₃H₂₆Cl₂N₄O₅; M_w = 509.38 g mol⁻¹). Bispidone **B2** (0.44 g, 0.87 mmol, 1.0 equiv) was suspended in 35 mL of a 2:1 mixture of 1,4-dioxane/water and cooled to -6 °C. At this

temperature, sodium borohydride (16.7 mg, 0.44 mmol, 0.5 equiv) dissolved in a further 10 mL of a 2:1 mixture of 1,4-dioxane/water was slowly added dropwise to the suspension. The reaction mixture was stirred for 1 h at -6 °C and at ambient temperature for 18 h. Then the pH was adjusted to 2 by slowly adding concentrated sulfuric acid and stirring of the mixture was continued for 2 h at ambient temperature. Afterward, the pH of the mixture was adjusted to 12 by slowly adding an aqueous solution of sodium hydroxide (20 wt %) and stirring of the mixture was continued for another 2 h at ambient temperature. The solvent was removed in vacuo, and the resulting white residue was taken up in methanol for crystallization. If this procedure failed, the crude product was purified as follows: the aqueous phase was extracted with DCM (3 × 50 mL), the combined organic phases were dried over Na₂SO₄, filtered, and concentrated, and the resulting residue was recrystallized from hot methanol. A white crystalline solid was obtained as the pure product in a yield of 47.1% (0.21 g, 0.41 mmol) by slow evaporation of the solvent. ¹H NMR (200 MHz, CDCl₃): δ 1.93 (s, 3H, N³CH₃), 2.26 (s, 3H, N⁷CH₃), 2.36 (d, ²J_{H,H} = 12.25 Hz, 2H, CH_{ax}H_{eq}), 2.49 (d, ²J_{H,H} = 12.51 Hz, 2H, CH_{ax}H_{eq}), 3.67 (s, 6H, COOCH₃), 4.13 (s, 2H, N³CH), 4.78 (d, ³J_{H,H} = 5.56 Hz, 1H, C⁹HOH), 7.23 (dd, ³J_{H,H} = 5.31 Hz, ⁴J_{H,H} = 2.15 Hz, 2H, H⁵), 7.94 (d, ⁴J_{H,H} = 1.77 Hz, 2H, H^{3'}), 8.38 (d, ³J_{H,H} = 5.31 Hz, 2H, H^{6'}). ¹³C NMR (50 MHz, CDCl₃): δ 43.93, 45.58, 50.58, 52.16, 52.70, 71.74, 74.38, 123.25, 123.41, 144.70, 149.40, 161.99, 172.15. HR-ESI (positive mode, [M + H]⁺). Calcd: m/z 509.13585. Obsd: m/z 509.13533. Elem anal (report 32466, [M]). Calcd: C, 54.23; H, 5.14; N, 11.00. Obsd: C, 54.31; H, 5.42; N, 10.93.

Bispidone {C⁹OH}B5 (C₂₅H₃₂N₄O₇; M_w = 500.54 g mol⁻¹). Bispidone **B5** (0.75 g, 1.5 mmol, 1.0 equiv) was suspended in 70 mL of a 3:1 mixture of 1,4-dioxane/water and cooled to -6 °C. At this temperature, sodium borohydride (28.4 mg, 0.75 mmol, 0.5 equiv) dissolved in a further 10 mL of a 3:1 mixture of 1,4-dioxane/water was slowly added dropwise to the suspension. The reaction mixture was stirred for 1 h at -6 °C and at 0 °C overnight. Then the pH was adjusted to 1–2 by slowly adding concentrated sulfuric acid and stirring of the mixture was continued for 1 h at ambient temperature. Afterward, the pH of the mixture was adjusted to 12 by slowly adding an aqueous solution of sodium hydroxide (20 wt %) and stirring of the mixture was continued for another 2 h at ambient temperature. The solvent was removed in vacuo, and the resulting white residue was taken up in 50 mL of water. The aqueous phase was extracted with DCM (4 × 50 mL), and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated in vacuo. A white crystalline solid was obtained as the pure product in a yield of 64.7% (485.0 mg, 0.97 mmol). ¹H NMR (200 MHz, CDCl₃): δ 1.93 (s, 3H, N³CH₃), 2.25 (s, 3H, N⁷CH₃), 2.36 (d, ²J_{H,H} = 12.26 Hz, 2H, CH_{ax}H_{eq}), 2.59 (d, ²J_{H,H} = 12.25 Hz, 2H, CH_{ax}H_{eq}), 3.67 (s, 6H, COOCH₃), 3.89 (s, 6H, pyOCH₃), 4.08 (s, 2H, N³CH), 4.78 (d, ³J_{H,H} = 5.56 Hz, 1H, C⁹HOH), 6.72 (dd, ³J_{H,H} = 5.68 Hz, ⁴J_{H,H} = 2.65 Hz, 2H, H⁵), 7.53 (d, ⁴J_{H,H} = 2.53 Hz, 2H, H^{3'}), 8.28 (d, ³J_{H,H} = 5.81 Hz, 2H, H^{6'}). ¹³C NMR (50 MHz, CDCl₃): δ 43.76, 45.82, 50.72, 52.04, 52.69, 54.84, 72.04, 74.58, 108.47, 109.16, 149.66, 162.05, 166.09, 172.44. HR-ESI (positive mode, [M + H]⁺). Calcd: m/z 501.23492. Obsd: m/z 501.23432. Elem anal (report 32193, [M]). Calcd: C, 59.99; H, 6.44; N, 11.19. Obsd: C, 59.97; H, 6.57; N, 11.19.

General Procedure for the Complexation of Tetradentate Bispidines with Cu²⁺. A total of 0.2 mmol of the bispidine was suspended in 2.5 mL of acetonitrile at ambient temperature, and Cu(ClO₄)₂·6H₂O dissolved in 2.5 mL of acetonitrile was added to the suspension. The appearance of a dark-blue solution indicated immediate complexation. The solution was stirred for 2 h or overnight at ambient temperature, respectively. Crystallization was performed by ether diffusion at ambient temperature. The crystals were filtered, washed with a small amount of cold acetonitrile, and dried in air.

[Cu^{II}B1(NCCH₃)](ClO₄)₂ (C₂₅H₃₂Cl₂CuN₇O₁₇; M_w = 831.97 g mol⁻¹). The synthesis was performed according to the general procedure with 0.2 mmol of ligand (105.7 mg, 1.0 equiv) and 0.2 mmol of Cu(ClO₄)₂·6H₂O (74.11 mg, 1.0 equiv) in a total volume of 3.5 mL of acetonitrile. Dark-blue crystals were obtained in a yield of 88.0% (146.7 mg, 0.176 mmol). FAB (positive mode, [B1 + Cu^{II} + H₂O]⁺).

Calcd: m/z 609.1. Obsd: m/z 608.9. FAB (positive mode, $[\mathbf{B1} + \text{Cu}^{\text{II}} + \text{H}_2\text{O} + \text{ClO}_4^-]^+$). Calcd: m/z 708.1. Obsd: m/z 707.9. Elem anal (report 32380, $[\mathbf{B1} + \text{Cu}(\text{ClO}_4)_2 + \text{CH}_3\text{CN} + 2\text{H}_2\text{O}]$). Calcd: C, 34.59; H, 3.60; N, 11.30. Obsd: C, 34.72; H, 3.83; N, 11.29. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 630 (80), 955 (15). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -268.5 \text{ mV}$ (vs Fc/Fc^+).

$[\text{Cu}^{\text{II}}\mathbf{B2}(\text{NCCH}_3)](\text{ClO}_4)_2 (\text{C}_{25}\text{H}_{27}\text{Cl}_4\text{CuN}_5\text{O}_{13}; M_W = 810.87 \text{ g mol}^{-1})$. The synthesis was performed according to the general procedure with 0.3 mmol of ligand (152.21 mg, 1.0 equiv) and 0.3 mmol of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (111.16 mg, 1.0 equiv) in a total volume of 6 mL of acetonitrile. Blue crystals were obtained in a yield of 82.3% (200.7 mg, 0.247 mmol). HR-FAB (positive mode, $[\mathbf{B2} + \text{Cu}^{\text{I}} + \text{H}_2\text{O}]^+$). Calcd: m/z 587.0525. Obsd: m/z 587.0549. HR-FAB (positive mode, $[\mathbf{B2} + \text{Cu}^{\text{II}} + \text{ClO}_4^- + \text{H}_2\text{O}]^+$). Calcd: m/z 686.0011. Obsd: m/z 686.0025. Elem anal (report 31095, $[\mathbf{B2} + \text{Cu}(\text{ClO}_4)_2 + 2\text{CH}_3\text{CN} + \text{H}_2\text{O}]$). Calcd: C, 37.28; H, 3.71; N, 9.66. Obsd: C, 37.21; H, 3.74; N, 9.70. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 630 (115), 957 (21). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -397.0 \text{ mV}$ (vs Fc/Fc^+).

$[\text{Cu}^{\text{II}}\mathbf{B3}(\text{NCCH}_3)](\text{ClO}_4)_2 (\text{C}_{25}\text{H}_{27}\text{Br}_2\text{Cl}_2\text{CuN}_5\text{O}_{13}; M_W = 899.77 \text{ g mol}^{-1})$. The synthesis was performed according to the general procedure with 0.2 mmol of ligand (119.25 mg, 1.0 equiv) and 0.2 mmol of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (74.11 mg, 1.0 equiv) in a total volume of 5 mL of acetonitrile. Dark-blue crystals were obtained in a yield of 85.5% (154.2 mg, 0.171 mmol). HR-FAB (positive mode, $[\mathbf{B3} + \text{Cu}^{\text{II}} + \text{H}_2\text{O}]$). Calcd: m/z 676.9495. Obsd: m/z 676.9462. HR-FAB (positive mode, $[\mathbf{B3} + \text{Cu}^{\text{II}} + \text{ClO}_4^-]^+$). Calcd: m/z 757.8874. Obsd: m/z 757.8820. Elem anal (report 31193, $[\mathbf{B3} + \text{Cu}(\text{ClO}_4)_2 + \text{CH}_3\text{CN} + \text{H}_2\text{O}]$). Calcd: C, 32.72; H, 3.18; N, 7.63. Obsd: C, 32.67; H, 3.34; N, 7.91. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 630 (120), 957 (21). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -394.0 \text{ mV}$ (vs Fc/Fc^+).

$[\text{Cu}^{\text{II}}\mathbf{B4}(\text{NCCH}_3)](\text{ClO}_4)_2 (\text{C}_{27}\text{H}_{33}\text{Cl}_2\text{CuN}_5\text{O}_{13}; M_W = 770.03 \text{ g mol}^{-1})$. The synthesis was performed according to the general procedure with 0.2 mmol of ligand (93.31 mg, 1.0 equiv) and 0.2 mmol of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (74.11 mg, 1.0 equiv) in a total volume of 5 mL of acetonitrile. Dark-blue crystals were obtained in a yield of 24.5% (38.1 mg, 0.049 mmol). HR-FAB ($[\mathbf{B4} + \text{Cu}^{\text{I}} + \text{H}_2\text{O}]$). Calcd: m/z 547.1618. Obsd: m/z 547.1585. HR-FAB ($[\mathbf{B4} + \text{Cu}^{\text{I}}]$). Calcd: m/z 529.1512. Obsd: m/z 529.1500. Elem anal (report 31094, $[\mathbf{B4} + \text{Cu}(\text{ClO}_4)_2 + \text{CH}_3\text{CN}]$). Calcd: C, 42.11; H, 4.32; N, 9.09. Obsd: C, 41.56; H, 4.64; N, 9.79. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 625 (106), 912 (20). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -501.5 \text{ mV}$ (vs Fc/Fc^+).

$[\text{Cu}^{\text{II}}\mathbf{B5}(\text{NCCH}_3)](\text{ClO}_4)_2 (\text{C}_{27}\text{H}_{33}\text{Cl}_2\text{CuN}_5\text{O}_{15}; M_W = 802.03 \text{ g mol}^{-1})$. The synthesis was performed according to the general procedure with 0.3 mmol of ligand (149.6 mg, 1.0 equiv) and 0.3 mmol of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (111.16 mg, 1.0 equiv) in a total volume of 5 mL of acetonitrile. Blue crystals were obtained in a yield of 73.7% (177.3 mg, 0.221 mmol). FAB (positive mode, $[\mathbf{B5} + \text{Cu}^{\text{I}} + \text{H}_2\text{O}]^+$). Calcd: m/z 579.2. Obsd: m/z 579.0. FAB (positive mode, $[\mathbf{B5} + \text{Cu}^{\text{II}} + \text{ClO}_4^- + \text{H}_2\text{O}]^+$). Calcd: m/z 678.1. Obsd: m/z 677.9. Elem anal (report 31072, $[\mathbf{B5} + \text{Cu}(\text{ClO}_4)_2 + \text{CH}_3\text{CN} + \text{H}_2\text{O}]$). Calcd: C, 39.55; H, 4.30; N, 8.54. Obsd: C, 39.42; H, 4.30; N, 8.50. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 629 (116), 912 (21). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -563.0 \text{ mV}$ (vs Fc/Fc^+).

$[\text{Cu}^{\text{II}}\mathbf{B7}(\text{NCCH}_3)](\text{ClO}_4)_2 (\text{C}_{27}\text{H}_{35}\text{Cl}_2\text{CuN}_5\text{O}_{14}\text{S}_2; M_W = 852.17 \text{ g mol}^{-1})$. The synthesis was performed according to the general procedure with 0.2 mmol of ligand (106.13 mg, 1.0 equiv) and 0.2 mmol of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (74.11 mg, 1.0 equiv) in a total volume of 6 mL of acetonitrile. Dark-blue crystals were obtained in a yield of 91.0% (151.8 mg, 0.182 mmol). HR-ESI (positive mode, $[\mathbf{B7} + \text{Cu}^{\text{II}} + \text{ClO}_4^- + \text{MeOH}]^+$). Calcd: m/z 724.07009. Obsd: m/z 724.09040. HR-FAB (positive mode, $[\mathbf{B7} + \text{Cu}^{\text{I}} + \text{H}_2\text{O}]^+$). Calcd: m/z 611.1059. Obsd: m/z 611.1094. Elem anal (report 31073, $[\mathbf{B7} + \text{Cu}(\text{ClO}_4)_2 + 2\text{CH}_3\text{CN} + \text{H}_2\text{O}]$). Calcd: C, 38.99; H, 4.29; N, 9.41. Obsd: C, 39.12; H, 4.31; N, 9.42. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 630 (126), 920 (19). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -517.5 \text{ mV}$ (vs Fc/Fc^+).

$[\text{Cu}^{\text{II}}\mathbf{B8}(\text{NCCH}_3)](\text{ClO}_4)_2 (\text{C}_{27}\text{H}_{33}\text{Cl}_2\text{CuN}_5\text{O}_{15}; M_W = 802.03 \text{ g mol}^{-1})$. The synthesis was performed according to the general procedure with 0.2 mmol of ligand (100.0 mg, 1.0 equiv) and 0.2 mmol of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (74.11 mg, 1.0 equiv) in a total volume of 5.0 mL

of acetonitrile. Blue crystals were obtained as the pure product in a yield of 48.0% (75.0 mg, 0.096 mmol). HR-FAB (positive mode, $[\mathbf{B8} + \text{Cu}^{\text{I}}]^+$). Calcd: m/z 561.1411. Obsd: m/z 561.1400. HR-FAB (positive mode, $[\mathbf{B8} + \text{Cu}^{\text{I}} + \text{H}_2\text{O}]^+$). Calcd: m/z 579.1516. Obsd: m/z 579.1497. Elem anal (report 33067, $[\mathbf{B8} + \text{Cu}(\text{ClO}_4)_2 + \text{H}_2\text{O}]$). Calcd: C, 38.55; H, 4.14; N, 7.19. Obsd: C, 38.41; H, 4.20; N, 7.12. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 698 (64), 962 (30). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -250.0 \text{ mV}$ (vs Fc/Fc^+).

$[\text{Cu}^{\text{II}}\mathbf{B12}(\text{NCCH}_3)](\text{ClO}_4)_2 (\text{C}_{25}\text{H}_{29}\text{Cl}_2\text{CuN}_5\text{O}_{13}; M_W = 741.98 \text{ g mol}^{-1})$. The synthesis was performed according to the general procedure with 0.2 mmol of ligand (87.7 mg, 1.0 equiv) and 0.2 mmol of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (74.11 mg, 1.0 equiv) in a total volume of 4.0 mL of acetonitrile. Blue crystals were obtained in a yield of 73.0% (108.0 mg, 0.146 mmol). HR-FAB (positive mode, $[\mathbf{B12} + \text{Cu}^{\text{I}}]^+$). Calcd: m/z 501.1200. Obsd: m/z 501.1202. HR-FAB (positive mode, $[\mathbf{B12} + \text{Cu}^{\text{I}} + \text{H}_2\text{O}]^+$). Calcd: m/z 519.1305. Obsd: m/z 519.1349. Elem anal (report 32467, $[\mathbf{B12} + \text{Cu}(\text{ClO}_4)_2 + \text{CH}_3\text{CN} + \text{H}_2\text{O}]$). Calcd: C, 39.51; H, 4.11; N, 9.22. Obsd: C, 39.88; H, 4.14; N, 9.61. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 626 (77), 901 (15). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -410.0 \text{ mV}$ (vs Fc/Fc^+) proposed keto form/ -504.0 mV (vs Fc/Fc^+) proposed hydrate form.

$[\text{Cu}^{\text{II}}\{\text{C}^{\text{O}}\text{OH}\}\mathbf{B12}(\text{NCCH}_3)](\text{ClO}_4)_2 (\text{C}_{25}\text{H}_{31}\text{Cl}_2\text{CuN}_5\text{O}_{13}; M_W = 743.99 \text{ g mol}^{-1})$. The synthesis was performed according to the general procedure with 0.2 mmol of ligand (88.1 mg, 1.0 equiv) and 0.2 mmol of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (74.11 mg, 1.0 equiv) in a total volume of 3.5 mL of acetonitrile. Dark-blue crystals were obtained in a yield of 91.5% (136.1 mg, 0.183 mmol). FAB (positive mode, $[\{\text{C}^{\text{O}}\text{OH}\}\mathbf{B12} + \text{Cu}^{\text{I}}]^+$). Calcd: m/z 503.1. Obsd: m/z 503.0. FAB (positive mode, $[\{\text{C}^{\text{O}}\text{OH}\}\mathbf{B12} + \text{Cu}^{\text{I}} + \text{ClO}_4^-]^+$). Calcd: m/z 602.1. Obsd: m/z 601.9. Elem anal (report 32381, $[\{\text{C}^{\text{O}}\text{OH}\}\mathbf{B12} + \text{Cu}(\text{ClO}_4)_2 + 2\text{H}_2\text{O}]$). Calcd: C, 37.38; H, 4.36; N, 7.58. Obsd: C, 37.74; H, 4.36; N, 7.66. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 626 (80), 912 (15). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -475.0 \text{ mV}$ (vs Fc/Fc^+).

$[\text{Cu}^{\text{II}}\{\text{C}^{\text{O}}\text{OH}\}\mathbf{B2}(\text{NCCH}_3)](\text{ClO}_4)_2 (\text{C}_{25}\text{H}_{29}\text{Cl}_4\text{CuN}_5\text{O}_{13}; M_W = 812.88 \text{ g mol}^{-1})$. The synthesis was performed according to the general procedure with 0.056 mmol of ligand (28.4 mg, 1.0 equiv) and 0.056 mmol of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (20.75 mg, 1.0 equiv) in a total volume of 3.0 mL of acetonitrile. Dark-blue crystals were obtained in a yield of 98.2% (44.6 mg, 0.055 mmol). FAB (positive mode, $[\{\text{C}^{\text{O}}\text{OH}\}\mathbf{B2} + \text{Cu}^{\text{I}}]^+$). Calcd: m/z 571.1. Obsd: m/z 570.9. FAB (positive mode, $[\{\text{C}^{\text{O}}\text{OH}\}\mathbf{B2} + \text{Cu}^{\text{II}} + \text{ClO}_4^-]^+$). Calcd: m/z 670.0. Obsd: m/z 669.8. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 628 (84), 954 (15). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -384.5 \text{ mV}$ (vs Fc/Fc^+).

$[\text{Cu}^{\text{II}}\{\text{C}^{\text{O}}\text{OH}\}\mathbf{B5}(\text{NCCH}_3)](\text{ClO}_4)_2 (\text{C}_{27}\text{H}_{35}\text{Cl}_2\text{CuN}_5\text{O}_{15}; M_W = 804.04 \text{ g mol}^{-1})$. The synthesis was performed according to the general procedure with 0.2 mmol of ligand (100.1 mg, 1.0 equiv) and 0.2 mmol of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (74.11 mg, 1.0 equiv) in a total volume of 3.5 mL of acetonitrile. Dark-blue crystals were obtained in a yield of 88.5% (142.1 mg, 0.177 mmol). HR-ESI (positive mode, $[\{\text{C}^{\text{O}}\text{OH}\}\mathbf{B5} + \text{Cu}^{\text{II}} + \text{MeO}^-]^+$). Calcd: m/z 594.17509. Obsd: m/z 594.17489. Elem anal (report 32379, $[\{\text{C}^{\text{O}}\text{OH}\}\mathbf{B5} + \text{Cu}(\text{ClO}_4)_2 + 2\text{H}_2\text{O}]$). Calcd: C, 37.58; H, 4.54; N, 7.01. Obsd: C, 37.51; H, 4.46; N, 6.97. UV/vis $[\text{CH}_3\text{CN}, \text{rt}; \lambda, \text{nm} (\epsilon, \text{L cm}^{-1} \text{mol}^{-1})$]: 628 (83), 900 (16). CV ($\text{CH}_3\text{CN}, \text{rt}$): $E_{1/2} = -563.5 \text{ mV}$ (vs Fc/Fc^+).

General in Situ Preparation of the Copper(II) Complexes with Tetradentate Bispidines. Commercially available $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ was dried in vacuo for 1 day and was considered dry. A stock solution of Cu^{II} was prepared by dissolving 131.23 mg (0.5 mmol) of $\text{Cu}(\text{ClO}_4)_2$ in 100 mL of absolute acetonitrile. Then 1 mL of the Cu^{II} stock solution (5 μmol) was added to 6 μmol of the (substituted) N_2py_2 ligand (approximately 3–4 mg, depending on the substituent); i.e., Cu^{II} and ligand are dissolved in a ratio of 5:6. An immediate dissolution of the ligand and a pale-blue color of the solution indicate complex formation. The solution was stirred for 30 min at ambient temperature. Then UV/vis spectra and CV measurements were subsequently undertaken using the same solution for both experiments.

■ ASSOCIATED CONTENT

■ Supporting Information

UV/vis/near-IR and EPR spectra as well as CVs of the reported copper(II) complexes, a list of pK_a values of substituted pyridine groups, details of the AOM calculations, structural data of the DFT calculations, details of the EDA analyses, Mulliken charges, details of the crystallographic work (CCDC 921801–921825 contains the supplementary crystallographic data; these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif), and all relevant NMR and mass spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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positive mode for piperidone corresponding to **18** ($[M + H]^+$). Calcd: m/z 470.2. Obsd: m/z 470.1. ESI positive mode for **19** ($[M + H]^+$). Calcd: m/z 522.3. Obsd: m/z 522.2.], but crystallization/isolation of pure products out of the brown mother liquor was not achieved.

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(69) Note that there is some ambiguity in terms of the redox potentials published previously with respect to the keto–hydrate equilibrium. On the basis of the interpretation adopted here, the hydrate and C^9 -reduced forms have similar redox potentials while that of the keto form is, as expected, significantly more positive.

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(98) The calculations were only performed on these copper(II) complexes not showing an axially coordinated coligand in the experimental structure.

(99) $e_\sigma(\text{pyridine})$ was varied to fit to the lowest-energy dd transition at about 10000–11000 cm^{-1} . Together with the observed bond length in the complex under study, a normalized e_σ parameter was obtained, reflecting the donor strength of the substituted pyridine group.

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(111) The linear correlation of the pK_a value of the substituted pyridines and the redox potential of the corresponding copper(II) complexes follows the equation $y = -0.01839x - 3.57837$; $R^2 = 0.96934$; the linear correlation of the Hammett coefficient of the

substituents and the redox potential of the copper(II) complexes follows the equation $y = 0.00332x + 1.60334$; $R^2 = 0.94536$.

(112) The linear correlation of the calculated electrostatic energy (E_{elstat}) and the redox potential of the corresponding copper(II) complexes follows the equation $y = 0.1393x - 271.76983$; $R^2 = 0.9666$; the linear correlation of the calculated total bonding energy (E_{total}) and the redox potential of the copper(II) complexes follows the equation $y = 0.13196x - 447.59138$; $R^2 = 0.93564$.