Exceptional Manganese(II) Stability and Manganese(II)/Zinc(II) Selectivity with Rigid Polydentate Ligands

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Supporting Information

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Dedicated to Professor Holger Braunschweig on the occasion of his 60th birthday

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1. Preparative work

All chemicals were purchased from Merck (Sigma Aldrich Chemie GmbH), Tokyo Chemical Industry Co. Ltd., Fisher Scientific GmbH and abcr GmbH. Analytical grade solvents were used without further purification and all reactions were carried out in air if not mentioned otherwise.

NMR spectra were recorded on a Bruker Avance I 200, a Bruker Avance II 400 or a Bruker Avance III 600. NMR chemical shifts are referenced on the solvents and two-dimensional correlation spectra were used to assign the signals. Mass spectra were recorded on a Bruker ApexQe FT-ICR instrument. X-ray data was collected on an Agilent Supernova dual CCD diffractometer (Mo-Kα and Cu-Kα). The plots of the solids state structures were performed using the programs POV-ray and ORTEP.¹⁻² Ultra-Performance Liquid Chromatography was performed on a Waters UPLC-SQD2 instrument (solvents: A: H₂O (0.1% TFA), B: MeCN; gradient 0-7 min 10-100% B, ionization method: APCI pos.). Elemental Analyses were performed on a CHN-O-vario EL by the micro analytical lab, Heidelberg University. UV/vis spectra were recorded with a Jasco V-570 UV-vis-NIR spectrometer in water with the thermostat JASCO ETC505T set at 20 °C and Quartz cuvettes with a length of 1 cm were used for the measurements or on a PerkinElmer Lambda 19 spectrometer (200-700 nm) at different time intervals.
**Ligand syntheses**

Bispidines 1a and 1b, and di(2-pyridyl)methyl chloride were synthesized according to literature procedure.

**Figure S1.** Final reaction step of the synthesis of the new ligands $L^1$ & $L^2$.

*General Procedure for the ligand syntheses:* To a suspension of 1 (a or b) (1.0 equiv.) in MeCN (20 ml/mmol) was added 1.0 – 4.0 equiv. of base, 1.0 equiv. of di(2-pyridyl)methyl chloride and the resulting slurry refluxed for 30 min or 16 h. After cooling to room temperature, the solvent was removed under reduced pressure and 50 ml of water and DCM were added to dissolve the solids. The layers were separated, and the aqueous layer extracted with DCM (3x50 ml). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and the solvent removed in vacuo. The crude ligands were purified by crystallization or columns chromatography.

$L^1$ was synthesized from 2.07 g of 1a (2.84 mmol), 602 mg of Na$_2$CO$_3$ and 579 mg of di(2-pyridyl)methyl chloride. Additionally, catalytic amounts of NaI (approx. 15 mg) were added to the reaction mixture. The reaction was stirred for 16 h. Ligand $L^1$ was recrystallized from hot MeOH, yielding the pure compound as light yellow solid (412 mg, 970 µmol, 31%).

$L^1$.5 MeOH: $^1$H-NMR (600 MHz, 295 K, CDCl$_3$): $\delta$ = 8.53 (d, $J$ = 4.3 Hz, 2H, $H_{dip}$), 8.38 (s, 1H, $H_{py3}$), 8.37 (d, $J$ = 4.6 Hz, 2H, $H_{py}$), 7.87 (m, 2H, $H_{py}$), 7.77 (d, $J$ = 7.8 Hz, 2H, $H_{py}$), 7.62 (t, $J$ = 7.2 Hz, 2H, $H_{dip}$), 7.48 (td, $J$ = 7.7, 1.2 Hz, 2H, $H_{dip}$), 7.37 (td, $J$ = 7.6, 1.3 Hz, 1H, $H_{py3}$), 7.14-7.09 (m, 2H, $H_{dip}$), 7.02 (m, 2H, $H_{py}$), 6.96 (m, 1H, $H_{py3}$), 6.77 (d, $J$ = 7.3 Hz, 1H, $H_{py3}$), 5.28 (s, 1H, $CH_{dip}$), 4.70-4.68 (m, 2H, $CH_{py}$), 4.65 (s, 1H, CHOH), 3.62 (s, 2H, $CH_{2,py}$), 3.54 (s, 6H, $CO_{2}Me$), 2.87 (m, 4H, $CH_{2,eq/ax}$) ppm; $^{13}$C-NMR (151 MHz, 295 K, CDCl$_3$): $\delta$ = 172.67, 159.55, 158.48, 149.16, 148.99, 148.56, 136.31, 135.82, 135.54, 124.95, 124.57, 124.38, 122.56, 122.51, 121.55, 71.96.
Synthesis of $L^2$ was achieved by using 356 mg of $1c$ (650 µmol), 635 mg of Cs$_2$CO$_3$ (1.95 mmol, 3.0 equiv.) and 133 mg of di(2-pyridyl)methyl chloride (650 µmol) after 30 min reaction time. The sodium salt was obtained as colorless solid in 48% yield (223 mg, 311 µmol), after flash column chromatography (C$_{18}$-SiO$_2$, 100% H$_2$O (0.1 % HCO$_2$H) → 70% MeOH).

$L^2$·Na·3.5 H$_2$O: $^1$H-NMR (400 MHz, 295 K, CD$_3$OD): $\delta = 8.92$ (bs, 2H, H$_{py}$), 8.37 (bs, 2H, H$_{py}$), 7.77 - 7.62 (m, 3H, H$_{dipy,pa}$), 7.52 (d, $J = 7.4$ Hz, 3H, H$_{dipy,pa}$), 7.39 (s, 1H, H$_{py}$), 7.33 - 7.27 (m, 2H, H$_{dipy}$), 7.22 (t, $J = 7.6$ Hz, 3H, H$_{dipy,py}$), 7.02 (bs, 2H, H$_{py}$), 6.27 (d, $J = 7.0$ Hz, 1H, H$_{pa}$), 4.84 (s, 1H, CH$_{dipy}$), 4.50 (s, 1H, CH$_{pa}$), 4.40 (s, 2H, CH$_{py}$), 3.49 (m, 8H, CO$_2$Me/CH$_2$,pa), 2.97 (d, $J = 12.0$ Hz, 2H, CH$_{2,ax/eq}$), 2.61 (d, $J = 11.4$ Hz, 2H, CH$_{2,ax/eq}$) ppm; $^{13}$C-NMR (151 MHz, 295 K, CD$_3$OD): $\delta = 192.10$, 191.09, 172.77, 154.90, 151.51, 141.87, 139.89, 138.70, 125.25, 124.54, 124.23, 123.83, 122.58, 73.95, 58.32, 52.57 ppm; ESI-HRMS (pos. DCM/MeOH), m/z for C$_{39}$H$_{38}$N$_7$O$_7^+$ (M+H$^+$) calcd. 716.2827, exp. 716.2860; elemental analysis, calcd. C 58.50, H 5.41, N 12.24, exp. C 58.26, H 5.31, N 12.20.

**Complex syntheses**

![Complexation of ligands $L^1$ and $L^2$ with different metaltriflates.](image)

**General procedure:** Metal triflate (1.0 equiv.) was dissolved in MeCN (1 ml/100 µmol) and was combined with a solution of the respective ligand (1.0 equiv.) in the same amount of MeCN. The mixture was stirred for 1 h at 50 °C. The solvent was removed in vacuo before, depending on the complex, MeCN or MeOH (1 ml) was added. After diffusion with diethyl ether the complex was obtained as crystals.
[MnⅢ(OTf)L1]OTf: The general procedure for the synthesis of complexes was followed using 49.5 mg (73.7 μmol) of L1 and 26.0 mg (73.7 μmol) of Mn(OTf)2. The complex was obtained in 73% yield (54.9 mg, 36.2 μmol) by diethyl ether diffusion into a solution in MeCN.

[Mn(OTf)L1]OTf: elemental analysis, calcd. C 46.88, H 3.64, N 9.57, found, C 46.84, H 3.74, N 9.56; ESI-HRMS (pos. H2O/MeOH), m/z calcd. for C39H39MnN7O6+ (M+OMe+, 100%), 757.2415, found, 757.2405, for C38H36ClMnN7O6+ (M+Cl+, 48%), 761.1925, found, 761.1919, for C38H37MnN7O82+ (M2+, 24%), 363.113, found, 363.116, for C39H36F3MnN7O8S+ (M+OTf+, 11%), 839.2082, found, 839.2081.

[ZnⅡL1]OTf2: The general procedure for the synthesis of complexes was followed using 25.8 mg (38.4 μmol) of L1 and 14.0 mg (38.4 μmol) of Zn(OTf)2. The complex was obtained in 37% yield (14.6 mg, 14.1 μmol) by diethyl ether diffusion into a solution in MeCN.

[ZnIL1]OTf: The general procedure for the synthesis of complexes was followed using 36.0 mg (50.3 μmol) of L2 and 17.8 mg (50.3 μmol) of Mn(OTf)2. The complex was obtained in 56% yield (25.8 mg, 28.1 μmol) by diethyl ether diffusion into a solution in MeOH.

[MnⅡL2]OTf·H2O·2 MeCN·0.5 HOTf: elemental analysis, calcd. C 50.05, H 4.11, N 10.26, found, C 50.07, H 4.10, N 10.25; ESI-HRMS (pos. MeOH), m/z calcd. for C39H36MnN7O7+ (M+, 100%), 769.2057, found, 769.2053.

[ZnⅡL2]OTf: The general procedure for the synthesis of complexes was followed using 36.0 mg (50.3 μmol) of L2 and 18.3 mg (50.3 μmol) of Zn(OTf)2. The complex was obtained in 43% yield (20.0 mg, 21.5 μmol) by diethyl ether diffusion into a solution in MeOH.

[ZnIL2]OTf·3 H2O·3.5 MeOH: elemental analysis, calcd. C 47.70, H 5.15, N 8.95, found, C 47.80, H 4.97, N 8.84; ESI-HRMS (pos. MeOH), m/z calcd. for C39H36N7O7Zn+ (M+), 778.1968, found,
778.1968; $^1$H-NMR (200 MHz, 300 K, CD$_3$OD): $\delta = 8.74$ (dd, $J = 4.9$, 1.2 Hz, 3H), 8.43 - 8.38 (m, 2H), 8.10 (dd, $J = 7.6$, 1.1 Hz, 1H), 7.96 (td, $J = 7.7$, 1.6 Hz, 2H), 7.82 (td, $J = 7.7$, 1.7 Hz, 2H), 7.76 $\{7.65$ (m, 3H), 7.54 (ddd, $J = 7.7$, 5.2, 1.3 Hz, 2H), 7.38 (dt, $J = 7.8$, 1.1 Hz, 2H), 7.29 (ddd, $J = 7.6$, 5.1, 1.1 Hz, 2H), 6.61 (dd, $J = 7.7$, 1.1 Hz, 1H), 4.97 (s, 2H), 4.88 (s, 1H), 3.62 (s, 5H), 3.35 (s, 4H) ppm.

2. Determination of ligand protonation and complex the stability constants

Solution preparation

Ligand concentrations were determined by adding an excess of ZnCl$_2$ solution to the ligand solution and titrating the metal excess with standardised Na$_2$H$_2$EDTA in urotropine buffer (pH 5.6 – 5.8) in the presence of Xylenol Orange as an indicator. The concentrations of the metal solutions were determined by complexometric titrations with standardised Na$_2$H$_2$EDTA.

Potentiometric titrations

Carbonate-free 0.1 M NaOH and 0.1 M HCl were prepared from Fisher Chemicals concentrates. Potentiometric titrations were performed in 0.15 M aqueous NaCl under nitrogen atmosphere and the temperature was controlled at 25±0.1 °C with a circulating water bath. The p[H] ($p[H] = -\log[H^+]$, concentration in molarity) was measured in each titration with a combined pH glass electrode (Metrohm) filled with 3 M KCl. The titrant addition was automated by use of a 702 SM titrino system (Metrohm). The electrode was calibrated in hydrogen ion concentration by titration of HCl with KOH in 0.1 M electrolyte solution. A plot of potential versus p[H] allows the determination of the electrode standard potential ($E^*$) and the slope factor (f). Continuous potentiometric titrations with 0.1 M NaOH were conducted on aqueous solutions containing 1.41 mM L$_1$ in 0.15 M NaCl ($V_0 = 5$ mL) with 2 minutes waiting time between successive points. The titrations of the metal (Zn$^{II}$, Ca$^{II}$ or Cu$^{II}$) complexes were performed with the same ligand solution containing 1 equivalent of the metal cation. For the Mn$^{II}$/L$_1$ system, direct titration was performed to assess the stability of the pre-complex MnL$_1^*$. Batch samples (0.5 mL) were prepared at 1:1 M:L ratios (~ 1.4 mM, 0.15 M NaCl). The samples were kept at 25°C until the equilibrium state was reached (2 days at pH 2.22 and ~ 5 hours at
pH 6.5). This was verified by monitoring the stabilization of the relaxivity and pH values in the samples over time.

Experimental data were refined using the computer program Hyperquad 2008. All equilibrium constants are concentration quotients rather than activities and are defined as:

$$K_{HmMmLl} = \frac{[M_mL_lH_h]}{[M]^m[L]^l[H]^h}$$

The ionic product of water under the experimental conditions is $pK_w = 13.77$. Fixed values were used for $pK_w$, ligand acidity constants and total concentrations of metal, ligand and acid. All values and errors (one standard deviation) reported are at least the average of three independent experiments.

The protonation constants $\log K_{H1}$ of ligands $L^1$ and $L^2$, necessary to obtain thermodynamic stability constants for the metal complexes, were measured by potentiometric titrations. Low solubility of $L^1$ in the basic region (pH>9) prevented the determination of its first protonation constant; a lower limit for $\log K_{H1}$ was therefore estimated from the protonation constant determined for the $Ca^{II}$ complex ($CaL^1$; the first protonation constant determined for $CaL^1$, corresponding to a tertiary amine, was taken as a lower limit to estimate $\log K_{H1}$ of the ligand $L^1$ itself, which is not accessible for direct determination due to low solubility in basic solution. By analogy to other bispidine ligands, the first protonation constant for both $L^1$ and $L^2$ is attributed to one of the tertiary amine groups, while the other amine of the bispidine skeleton remains unprotonated in the chair-chair conformation of the ligand. Subsequent protonation steps occur at the nitrogen of the methyl-pyridine ($\log K_{H2}$ for $L^1$) and on the dipyridyl groups ($\log K_{H3}$ and $\log K_{H4}$ for $L^1$ and $\log K_{H2}$ and $\log K_{H3}$ for $L^2$), while the last protonation step corresponds to a pyridine directly linked to the diaza-adamantane scaffold for $L^1$. For $L^2$ this last protonation might alternatively involve the picolinate.

For $CuL^1$ and $MnL^2$ the stability is too high to be assessed by pH-potentiometry.
**Relaxometric measurements**

While pH-potentiometric titrations represent the most standard technique to assess the stability of metal complexes, for paramagnetic metals such as Mn$^{II}$, pH dependent proton relaxivity measurements can also allow for following complex formation and determining conditional complex stability constants. By using the ligand protonation constants, they can be then converted to thermodynamic stability constants. On these titration curves (Figures 2 a and c), complex formation is accompanied by a strong decrease of relaxivity from the Mn$^{II}$ aqua ion to the monohydrated (MnL$^1$) or non-hydrated (MnL$^2$) complex. For MnL$^1$, the small plateau between pH 2.4-2.8 corresponds to the formation of the protonated complex.

Longitudinal and transverse proton relaxivities, respectively, were measured in equilibrated MnL$^1$ and MnL$^2$ batch samples at $c_{MnL} = 1.4$ mM concentration between $c_{HCl} = 0.09$ M and pH 11 (MnL$^1$) and $c_{HCl} = 0.8$ M and pH 11 (MnL$^2$) at 25°C and 60 MHz on a Bruker Minispec relaxometer.

We have fitted the pH dependent relaxivities measured in batch samples of MnL$^1$ and MnL$^2$ to calculate thermodynamic stability constants (Table 2). The fit of the relaxivities vs. $H^+$ concentration to yield the stability constant was performed using Visualiseur/Optimiseur (F. Yerly, VISUALISEUR 2.3.5, Switzerland, 1999.; F. Yerly, OPTIMISEUR 2.3.5, Switzerland, 1999) running on a MATLAB 8.3.0 (R2014a) platform. Errors indicated represent one standard deviation. We note the excellent agreement for MnL$^1$ between the log$K_{MnL}$ values obtained by potentiometry and relaxometry; for MnL$^2$, the stability is too high and could be only assessed by relaxometric titration.

We note that oxidation of Mn$^{II}$ to Mn$^{III}$ in the batch samples can be excluded, based on the redox potentials, the UV-vis spectra, the ESI-MS data as well as the relaxation behavior (NMRD profiles) of the complexes, which are characteristic for Mn$^{II}$.

**$^1$H NMR measurements on ZnL$^2$**

$^1$H NMR spectra of a ZnL$^2$ solution ($c = 3.5$ mM) were recorded in D$_2$O between pH 1.6 and 11.62 at 600 MHz on a Bruker Avance Spectrometer using a 5mm BBFO probe.
**UV-vis measurements**

UV-Vis spectra of a ZnL\(^2\) solution (c = 50 \(\mu\)M) were recorded between pH 1.6 and 11.2 on a PerkinElmer Lambda 19 spectrometer (1 cm pathlength) at 25°C. Time-dependent UV-Vis spectra have been also recorded in batch samples of ZnL\(^1\) and MnL\(^1\) (c = 50 \(\mu\)M).

**NMRD profiles**

Proton NMRD profiles of MnL\(^1\) were recorded in an aqueous solution (c\(_{\text{MnL}}\) = 1.48 mM, pH 7.0) as well as in the presence of 0.6 mM human serum albumin (c\(_{\text{MnL}}\) = 1.57 mM; pH 7.0) at 25°C and 37 °C on a Stelar SMARTTracer Fast Field Cycling relaxometer (0.01-10 MHz) and a Bruker WP80 NMR electromagnet adapted to variable field measurements (20-80 MHz) and controlled by a SMARTTracer PC-NMR console. The temperature was monitored by a VTC91 temperature control unit and maintained by a gas flow. The temperature was determined by previous calibration with a Pt resistance temperature probe.

3. **X-ray crystal structure determinations**

Crystal data and details of the structure determinations are compiled in Table S1. Full shells of intensity data were collected at low temperature with an Agilent Technologies Supernova-E CCD diffractometer (Mo- or Cu-K\(\alpha\) radiation, microfocus X-ray tubes, multilayer mirror optics). Detector frames (typically w-, occasionally j-scans, scan width 0.5 or 1°) were integrated by profile fitting.\(^{15-17}\) Data were corrected for air and detector absorption, Lorentz and polarization effects\(^{16-17}\) and scaled essentially by application of appropriate spherical harmonic functions.\(^{16-18}\) Absorption by the crystal was treated with a semiempirical multiscan method (as part of the scaling procedure), and augmented by a spherical correction,\(^{16-18}\) or numerically (Gaussian grid).\(^{16-17,19-20}\) An illumination correction was performed as part of the numerical absorption correction.\(^{16-17}\)

The structures were solved by the charge flip procedure (compound [Mn(OTf)L\(^1\)]OTf),\(^{21-23}\) by ab initio dual space methods (compound [MnL\(^2\)]OTf·0.2H\(_2\)O),\(^{24-25}\) by ab initio dual space methods involving difference Fourier syntheses (VLD procedure, compounds [ZnL\(^1\)](OTf)\(_2\)-MeCN and [ZnL\(^2\)]OTf)\(^{26-27}\) or by “modern” direct methods with dual-space recycling (compound L\(^1\)-x
MeOH)\(^{26, 28-29}\) and refined by full-matrix least squares methods based on \(F^2\) against all unique reflections.\(^{30-33}\) All non-hydrogen atoms were given anisotropic displacement parameters. Hydrogen atoms were generally input at calculated positions and refined with a riding model.\(^{34-37}\) When justified by the quality of the data the positions of some hydrogen atoms (typically hydroxyl and water hydrogens) were taken from difference Fourier syntheses and either refined (OH) or included in rigid groups (water). Split atom models were used to refine disordered groups, solvent molecules and triflate anions. When found necessary, suitable geometry and adp restraints or constraints were applied.\(^{34-38}\) Due to severe disorder and fractional occupancy, some of the electron density attributed to solvent of crystallization (methanol) was removed from the structure of \(L^1\cdot x\) MeOH with the BYPASS procedure,\(^{39-40}\) as implemented in PLATON (squeeze/hybrid).\(^{41}\) Partial structure factors from the solvent masks were included in the refinement as separate contributions to \(F_{\text{calc}}\). Crystals of \(L^1\cdot x\) MeOH were twinned; the structure was solved using only reflections with small overlap factors (typically < 0.4). Final refinement was carried out against all single and composite reflections involving both domains (refined twin fractions 0.59:0.41). Crystals of [MnL\(^2\)]OTf\(\cdot\)0.2H\(_2\)O were refined as inversion twins (refined twin fractions 0.58:0.42). CCDC 2054452, 2054455, 2054456, 2054457 and 2054463 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre's and FIZ Karlsruhe's joint Access Service via https://www.ccdc.cam.ac.uk/structures/?.
Figure S3. ORTEP plot of the complex cations in a) [Mn(OTf)L₁]OTf, b) [MnL₂]OTf·0.2H₂O, c) [ZnL₁](OTf)₂·MeCN and d) [ZnL₂]OTf; atoms are shown at 50% probability, hydrogen atoms are omitted for clarity.

Crystals suitable for x-ray crystallographic analysis of the Mn⁺⁺ and Zn⁺⁺ complexes were obtained by ether diffusion into a solution in MeCN (MnL₁) or methanolic solution. For [ZnL₁](OTf)₂·MeCN it appears that there is one dangling pyridine donor of the respective ligand, ultimately leading to a sixfold coordination of the respective Zn⁺⁺ metal center. On the other hand, in the case of [ZnL₂]OTf no dangling donor is observable. However, the metal donor distances in [ZnL₂]OTf to the pyridine donor Npy1 (d_M-Npy1 = 3.81 Å) and donor-donor distance between Npy1 and Npy2 (d_{Npy1-Npy2} = 5.25 Å) are highly elongated (see Fig. S4 for atom numbering). Furthermore, it appears that the metal center is sitting outside the bispidine cavity and thus being mainly coordinated by the stronger picolinate donor moiety at N3 and the dipyridyl residues and N7.
Figure S4. ORTEP plot of the x-ray structure of ligand L\textsuperscript{1} showing the desired chair-chair confirmation of the ligand; atoms are shown at 50% probability, hydrogen atoms and solvent molecules are omitted for clarity.

Crystals for the x-ray crystallographic structure determination of ligand L\textsuperscript{1} were obtained via ether diffusion into methanolic solution (Fig. S4). Despite of the voluminous dipyridylmethyl-moiety at the N7 nitrogen atom, the bispidine scaffold is in, for metal ion complexation, desirable chair-chair confirmation with the two pyridine donors at C2 and C4 in equatorial position. This leads to a highly preorganized structure of the free ligand.
Table S1. Crystallographic data of \([\text{Mn(OTf)} L^1]\text{OTf}, [\text{MnL}^2]\text{OTf} \cdot 0.2\text{H}_2\text{O}, [\text{ZnL}^1]\text{(OTf)}_2 \cdot \text{MeCN}, [\text{ZnL}^2]\text{OTf} \text{ and } L^1 \cdot x \text{ MeOH.}

| ID       | [Mn(OTf) L^1]OTf | [MnL^2]OTf·0.2H_2O | [ZnL^1](OTf)_2·MeCN | [ZnL^2]OTf | L^1·x MeOH |
|----------|-----------------|--------------------|---------------------|-------------|------------|
| Empirical formula | \(\text{C}_{40}\text{H}_{37}\text{F}_6\text{MnN}_7\text{O}_{11}\text{S}_2\) | \(\text{C}_{40}\text{H}_{36.46}\text{F}_3\text{MnN}_7\text{O}_{10.23}\text{S}_2\) | \(\text{C}_{40}\text{H}_{36}\text{F}_2\text{N}_8\text{O}_{11}\text{S}_2\text{Zn}\) | \(\text{C}_{40}\text{H}_{36}\text{F}_2\text{N}_8\text{O}_{10}\text{S}_2\text{Zn}\) | \(\text{C}_{40}\text{H}_{36}\text{F}_2\text{N}_8\text{O}_7\) |
| Formula weight [g·mol^{-1}] | 1024.82 | 922.90 | 1076.31 | 929.19 | 735.83 |
| Temperature [K] | 120(1) | 120(1) | 120(1) | 120(1) | 120(1) |
| \(\chi\)-radiation, wavelength [Å] | Mo \(K\alpha\), 0.71073 | Mo \(K\alpha\), 0.71073 | Mo \(K\alpha\), 0.71073 | Mo \(K\alpha\), 0.71073 | Cu \(K\alpha\), 1.54184 |
| Crystal system | monoclinic | orthorhombic | monoclinic | monoclinic | triclinic |
| Space group | \(P \ 2_1/c\) | \(P \ 2_12_12_1\) | \(P \ 2_1/n\) | \(P \ 2_1/n\) | \(P \ -1\) |
| \(a\) [Å] | 19.3925(3) | 15.1948(2) | 14.6954(3) | 10.32190(12) | 13.7472(6) |
| \(b\) [Å] | 12.60082(18) | 15.91390(10) | 13.7159(3) | 13.51880(16) | 17.3475(7) |
| \(c\) [Å] | 17.5375(2) | 16.27560(10) | 46.0787(11) | 28.8179(3) | 24.4303(10) |
| \(\alpha\) [°] | 90 | 90 | 90 | 90 | 72.376(4) |
| \(\beta\) [°] | 93.7106(12) | 90 | 98.128(2) | 95.8066(11) | 87.886(4) |
| \(\gamma\) [°] | 90 | 90 | 90 | 90 | 88.088(3) |
| \(V\) [Å³] | 4276.51(10) | 3935.58(6) | 9194.4(4) | 4000.61(8) | 5547.4(4) |
| \(Z\) | 4 | 4 | 8 | 4 | 6 |
| \(\rho_{\text{calc}}\) [g·cm^{-3}] | 1.592 | 1.558 | 1.555 | 1.543 | 1.322 |
| \(\mu\) [mm^{-1}] | 0.502 | 0.474 | 0.718 | 0.749 | 0.753 |
| Transmission factors max/min | 1.000/0.633 \(^{\text{a}}\) | 1.000/0.895 \(^{\text{b}}\) | 1.000/0.838 \(^{\text{b}}\) | 1.000/0.806 \(^{\text{a}}\) | 1.000/0.538 \(^{\text{b}}\) |
| \(F_{\text{000}}\) [e] | 2100 | 1901 | 4416 | 1912 | 2340 |
| \(2\theta\) range [°] | 4.2 .. 61.1 | 4.4 .. 68.4 | 4.6 .. 61.4 | 4.4 .. 68.4 | 5.4 .. 145.4 |
| Index ranges | -27 ≤ \(h\) ≤ 27, -17 ≤ \(k\) ≤ 18, -25 ≤ \(l\) ≤ 25 | -23 ≤ \(h\) ≤ 23, -24 ≤ \(k\) ≤ 24, -25 ≤ \(l\) ≤ 25 | -21 ≤ \(h\) ≤ 20, -19 ≤ \(k\) ≤ 19, -65 ≤ \(l\) ≤ 65 | -16 ≤ \(h\) ≤ 16, -21 ≤ \(k\) ≤ 21, -43 ≤ \(l\) ≤ 44 | -16 ≤ \(h\) ≤ 16, -20 ≤ \(k\) ≤ 21, -30 ≤ \(l\) ≤ 29 |
| Reflections, collected | 169182 | 177070 | 186986 | 140970 | 272244 |
| Reflections, unique | 13072 \([R_{\text{int}} = 0.0637]\) | 15915 \([R_{\text{int}} = 0.057]\) | 14131 \([R_{\text{int}} = 0.145]\) | 16048 \([R_{\text{int}} = 0.070]\) | 48051 \([R_{\text{int}} = 0.094]\) |
| Reflections, observed \([I ≥ 2\sigma(I)]\) | 11015 | 14153 | 10653 | 12444 | 24590 |
| Data / Restraints / Parameters | 13072 / 223 / 691 | 15915 / 72 / 587 | 14131 / 348 / 710 | 16048 / 407 / 635 | 48051 / 14 / 1447 |
|-------------------------------|-------------------|-----------------|-------------------|-------------------|------------------|
| Goodness-of-fit on $R^2$      | 1.055             | 1.026           | 1.192             | 1.024             | 1.049            |
| Final $R$ indices [I≥2σ(I)]   | $R(F) = 0.0562,$ | $R(F) = 0.0402,$| $R(F) = 0.0873,$ | $R(F) = 0.00431,$| $R(F) = 0.0825,$ |
|                               | $wR(F^2) = 0.1350$| $wR(F^2) = 0.0915$| $wR(F^2) = 0.1646$| $wR(F^2) = 0.0948$| $wR(F^2) = 0.2505$|
| $R$ indices (all data)        | $R(F) = 0.0674,$ | $R(F) = 0.0489,$| $R(F) = 0.1166,$ | $R(F) = 0.0640,$ | $R(F) = 0.1337,$ |
|                               | $wR(F^2) = 0.1413$| $wR(F^2) = 0.0953$| $wR(F^2) = 0.1743$| $wR(F^2) = 0.1035$| $wR(F^2) = 0.2658$|
| Largest diff peak and hole    | 0.747/-0.663      | 0.446/-0.398    | 1.333/-0.999      | 0.596/-0.440      | 1.036/-0.508     |
| [e-Å$^{-3}$]                  |                   |                 |                   |                   |                   |
| Deposition number CCDC        | 2054452           | 2054456         | 2054455           | 2054457           | 2054463          |

*a* numerical absorption correction.  
*b* semi-empirical absorption correction.
4. Cavity size calculation

Cavity size calculations were performed with MOMEC97. The energy minimum of each of the calculated curves was set to 0 kJ mol\(^{-1}\) (see Figure 2 in the main text). The energy given in these plots is the computed total strain energy, and it does not include metal-based energies, except for C–D–M bending: For each step in the computation of these curves all metal-ligand distances are fixed to specific values using Lagrange multipliers. Therefore, the energies of the metal-based stretching terms could be set to 0.0 kJ/mol. Moreover, the ligand-metal-ligand bending terms can be set to 0.0 when a points-on-a-sphere approach is used, and this generally and successfully is done in MOMEC. For the asymmetric variation of the cavity size (variation of the averaged bond distances), there are two approaches available in MOMEC, i.e. “sum constraints” or the technique used here: the individual metal-ligand distances for all points in the computed curves were obtained by individual, asymmetric variations of all seven M–D bonds (linear interpolation between the longest (Zn\(^{II}\)–D) and the shortest (Co\(^{III}\)–D) bond distances (these two points were obtained by a full structure optimization of the corresponding Zn\(^{II}\) and Co\(^{III}\) complexes) and linear extrapolations to obtain the calculated distance for each M–D bond for the corresponding sum and average metal-ligand bond distances. Therefore, the strain energy of the ligand as a function of the average metal-donor distance (M–D)\(_{\text{av}}\) was obtained by simultaneous individual asymmetric variation of all metal-donor distances. For full coordination of all donors of the ligands the minimum is reached at approx. 2.65 Å (M–D)\(_{\text{av}}\) for \(L^1\) and at 2.50 Å (M–D)\(_{\text{av}}\) for \(L^2\), respectively. The ideal size of Mn\(^{II}\) is derived from the crystal structures of both Mn\(^{II}\) complexes (\(M\text{–D})_{\text{Mn}} = 2.43\) Å), the one for Zn\(^{II}\) from the crystal structure of \([\text{ZnL}^1](\text{OTf})_2\) (Figures 2, S3). In both cases, the complexation of Mn\(^{II}\) leads to marginal loss of steric energy (approx. 1 – 3 kJ mol\(^{-1}\)), whereas the loss in steric energy accompanied with the complexation of Zn\(^{II}\), with approx. 45 – 55 kJ mol\(^{-1}\), is high and implies low stability, which is in full agreement with the experimentally determined complex stability constants, see below.

5. DFT calculations

All DFT calculations were performed using the Gaussian 16 suite of programs. The geometries were optimized using the B3LYP-D3 functional with LACVP basis set comprising the LanL2DZ-Los Alamos effective core potential for Mn and a 6-31g(d) basis set for the other atoms.
This functional has been employed by us and others earlier to predict the correct spin state energetics of several mononuclear metal complexes. Frequency calculation on the optimized structures was undertaken to confirm the minima on the potential-energy surface (PES).

To understand the interaction between the metal and ligand, energy decomposition analyses (EDA) have been performed for the complexes choosing metal and ligand as fragments and the results are presented in Table 1. The nature of the interactions between metal and ligand has been analysed by means of energy decomposition analysis, implemented in the ADF\textsuperscript{50} program package based on the methods of Morokuma\textsuperscript{51} and Ziegler\textsuperscript{52} at level of B3LYP-D3/TZ2P with ZORA. The instantaneous interaction energy between the two fragments has been calculated using the following equation, $\Delta E_{\text{int}} = \Delta E_{\text{elstat}} + \Delta E_{\text{pauli}} + \Delta E_{\text{orb}}$ and the percentage covalency have been calculated using $\left[\frac{\Delta E_{\text{orb}}}{\Delta E_{\text{elstat}} + \Delta E_{\text{orb}}}\right] \times 100$.

The computed bonding energy differences between the Mn\textsuperscript{II} and Zn\textsuperscript{II} complexes with L\textsuperscript{1} and L\textsuperscript{2} in favor for Mn\textsuperscript{II} are 300 kJ/mol and 340 kJ/mol, respectively. Note that for a comparison with complex stabilities, these energies need to be corrected by the desolvation of the metal aqua ions, which differ by around 200 kJ/mol for Mn\textsuperscript{II} and Zn\textsuperscript{II}. Note also that solvation of the complexes and fragments was not considered. With assumed $\Delta(\Delta G)$ values of approx. 50 kJ/mol and 90 kJ/mol for the L\textsuperscript{1} and L\textsuperscript{2} based systems, respectively, this amounts to $\Delta(\log K)$ values of around 10 and 15, respectively. Taking into consideration the approximations used and the intrinsic problems of DFT to describe metal ligand bonds, these predictions are well supporting the observed stability constants discussed in the main manuscript, i.e. the Mn\textsuperscript{II} selectivity is of the order of 10 orders of magnitude, with L\textsuperscript{2} being more selective than L\textsuperscript{1}.

### Table S2. Energy decomposition analysis (in kcal mol\textsuperscript{-1}) of [Mn(OTf)L\textsuperscript{1}]OTf, [MnL\textsuperscript{2}]OTf·H\textsubscript{2}O, [ZnL\textsuperscript{1}](OTf)\textsubscript{2}·MeCN and [ZnL\textsuperscript{2}]OTf complexes at B3LYP-D3/TZ2P level using ligand and Metal as fragments.

|        | Pauli repulsion $\Delta E_{\text{pauli}}$ | Electrostatic interaction $\Delta E_{\text{elstat}}$ | Total steric interaction | Orbital interactions $\Delta E_{\text{orb}}$ | Total bonding energy $\Delta E_{\text{int}}$ | % Electrostatic | % Covalency |
|--------|------------------------------------------|------------------------------------------------------|--------------------------|---------------------------------------------|---------------------------------------------|----------------|-------------|
| [Mn(OTf)L\textsuperscript{1}]$^+$ | 763.71                                   | -441.19                                               | 322.52                   | -504.97                                     | -182.45                                     | 46.63          | 53.37       |
| [ZnL\textsuperscript{1}](OTf)$^+$ | 493.19                                   | -356.05                                               | 137.14                   | -246.4                                      | -109.26                                     | 59.10          | 40.90       |
| [MnL\textsuperscript{2}]$^+$ | 560.12                                   | -321.31                                               | 238.81                   | -454.9                                      | -216.09                                     | 41.39          | 58.61       |
| [ZnL\textsuperscript{2}]$^+$ | 391.35                                   | -296.01                                               | 95.34                    | -228.8                                      | -133.46                                     | 56.40          | 43.60       |
**Table S3.** Selected bond distances [Å] and angles [°] in the DFT optimized structure and crystal structure of [Mn(OTf)L]$^1$OTf, [MnL]$^2$OTf-H$_2$O, [ZnL]$^1$[OTf]$_2$·MeCN and [ZnL]$^2$OTf.

|                  | [Mn(OTf)L]$^1$OTf | [MnL]$^2$OTf-H$_2$O | [ZnL]$^1$[OTf]$_2$·MeCN | [ZnL]$^2$OTf |
|------------------|-------------------|----------------------|--------------------------|--------------|
| **Distance[Å]**  | DFT               | X-Ray                | DFT                      | X-Ray        | DFT               | X-Ray          | DFT               | X-Ray          |
| M-N3             | 2.546             | 2.4527(17)           | 2.691                    | 2.3593(15)   | 2.258             | 2.155(3)       | 2.771             | 2.7449(11)    |
| M-N7             | 2.459             | 2.4079(16)           | 2.457                    | 2.5523(15)   | 2.210             | 2.208(3)       | 2.438             | 2.4791(11)    |
| M-Npy1           | 3.066             | 3.037(2)             | 2.404                    | 2.3635(18)   | 2.230             | 2.134(3)       | 3.291             | 3.8058(14)    |
| M-Npy2           | 2.322             | 2.2937(19)           | 2.633                    | 2.9098(22)   | 2.552             | 2.534(3)       | 2.241             | 2.1601(12)    |
| M-D(N3)          | 2.334             | 2.2728(18)           | 2.298                    | 2.2412(17)   | 2.173             | 2.149(3)       | 2.088             | 2.1363(12)    |
| M-Ndpy1          | 2.297             | 2.2520(18)           | 2.480                    | 2.4233(17)   | 3.157             | 3.374(4)       | 2.258             | 2.1643(12)    |
| M-Ndpy2          | 2.322             | 2.5487(17)           | 2.395                    | 2.3775(18)   | 2.152             | 2.059(3)       | 2.353             | 2.2300(12)    |
| M-O$_x$          | 2.193             | 2.3804(16)           | 2.096                    | 2.2018(14)   | -                 | -              | 2.088             | 2.1244(10)    |
| **Angle [°]**    |                   |                      |                          |              |                   |                |                   |               |
| N3-M-N7          | 71.91             | 72.42(5)             | 71.90                    | 73.37(5)     | 83.29             | 83.26(11)      | 68.89             | 65.69(3)      |
| Npy1-Mn-Npy2     | 128.94            | 130.92(6)            | 127.43                   | 129.37(5)    | 143.97            | 149.46(11)     | 122.26             | 120.67(4)     |

**Table S4.** Selected bond distances [Å] and angles [°] in the DFT optimized structure and crystal structure of [ZnL]$^2$OTf.

|                  | Zn-Py1 elongated | Zn-Py2 elongated | Zn-N3 elongated | Zn-N7 elongated |
|------------------|-----------------|-----------------|-----------------|-----------------|
| **Distance[Å]**  | X-Ray           | DFT             | DFT             | DFT             | DFT             |
| M-N3             | 2.7449(11)      | 2.771           | 2.773           | 3.083           | 2.744           |
| M-N7             | 2.4791(11)      | 2.438           | 2.432           | 2.425           | 3.256           |
| M-Npy1           | 3.8058(14)      | 3.291           | 2.244           | 2.525           | 2.791           |
| M-Npy2           | 2.1601(12)      | 2.241           | 3.270           | 2.703           | 2.478           |
| M-D(N3)          | 2.1363(12)      | 2.088           | 2.201           | 2.128           | 2.140           |
| M-Ndpy1          | 2.1643(12)      | 2.258           | 2.355           | 2.421           | 2.409           |
| M-Ndpy2          | 2.2300(12)      | 2.353           | 2.261           | 2.363           | 2.635           |
| M-O$_x$          | 2.1244(10)      | 2.088           | 2.087           | 2.088           | 2.098           |
| **Angle [°]**    |                 |                 |                 |                 |                 |
| N3-M-N7          | 65.69(3)        | 68.89           | 69.06           | 63.68           | 68.89           |
| Npy1-Mn-Npy2     | 120.67(4)       | 122.26          | 122.32          | 111.71          | 122.26          |
| comp rel energy  | --              | 0.0             | 0.9             | 6.8             | 8.0             |

kJ/mol
Figure S5. DFT optimized (blue) and X-ray (red) structure overlay of a) [Mn(OTf)L¹]OTf, b) [MnL²]OTf·0.2 H₂O, c) [ZnL¹](OTf)·MeCN and d) [ZnL²]OTf. Hydrogen atoms are omitted for clarity.
6. NMR spectroscopy

**Figure S6.** $^1$H-NMR spectrum (600 MHz, 295 K, CDCl$_3$) of ligand L$^1$.

**Figure S7.** $^{13}$C-NMR spectrum (151 MHz, 295 K, CDCl$_3$) of ligand L$^1$. 
Figure S8. $^1$H-NMR spectrum (400 MHz, 295 K, CD$_3$OD) of ligand L$_2$.

Figure S9. $^{13}$C-NMR spectrum (151 MHz, 295 K, CD$_3$OD) of ligand L$_2$. 
Figure S10. $^1$H-NMR spectrum (300 MHz, 300 K, CD$_3$CN) of [ZnL$^1$](OTf)$_2$.

Figure S11. $^1$H-NMR spectrum (300 MHz, 300 K, CD$_2$OD) of ligand [ZnL$^2$]OTf.
7. Potentiometric data

Figure S12. Potentiometric titration curves for L₁ in the absence and in the presence of metal ions. \( c(L^1) = c(M) = 1.4 \) mM; 0.15 M NaCl, 25 °C. For the MnL₁ system, the blue points correspond to individual batch samples while the violet curve was obtained by direct potentiometric titration (pre-complex formation).

Figure S13. Potentiometric titration curves for L₂ in the absence and in the presence of metal ions. \( c(L^2) = c(M) = 1.4 \) mM; 0.15 M NaCl, 25 °C. The blue points correspond to individual batch samples.
Figure S14. pH-dependent variation in a selected region of the $^1$H NMR spectra of ZnL$_2$ a) and chemical shift difference between the two methylene protons as a function of pH b). The separation of the two proton signals is a direct consequence of the decreased flexibility of the bispidine skeleton following complex formation.
Figure S15. Species distribution curves calculated for ZnL\(^2\) (1 mM concentration) and pH-dependent variation of the maximum UV-Vis absorbance at 259 nm \((l = 1\) cm\) in a 50 μM ZnL\(^2\) solution (Δ).

Figure S16. Illustration of complex formation for ZnL\(^1\) and MnL\(^1\) complexes. The UV-Vis spectra have been recorded after mixing the metal and the ligand, at \(c_{\text{ML}} = 0.05\) mM, as a function of time.
Assessment of the nature of the precomplex MnL*

We have performed the following experiment to assess the transformation of the precomplex into the final product. We have mixed equimolar quantities of Mn$^{2+}$ and L$^1$ (1.5 mM) in a weakly buffered solution (at pH 4.2, in N-methyl piperazine) and monitored the pH change over time (Figure S18). We note an immediate pH drop after the preparation of the sample, corresponding to the formation of the protonated precomplex (at this pH, the precomplex exists in di- and mainly tri-protonated forms). Then a slower pH decrease follows until the sample reaches equilibrium at pH 3.8. This clearly shows that the transformation of the precomplex is accompanied by the release of protons.

In a second experiment, the same buffer (identical concentration and starting pH) is titrated with and HCl solution until the same final pH is reached and the proton consumption is measured until this point. This corresponds to ~3 equivalent protons (with respect to 1 equivalent ligand), which is in accordance with the transformation of a tri-protonated precomplex to a non-protonated MnL$^1$ complex. We note that similar experiments have been...
carried out previously to assess the protonation state of the intermediate formed during GdDOTA complex formation.\textsuperscript{53}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure_s18.png}
\caption{Variation of pH in a weakly buffered solution (N-methyl piperazine) after mixing equimolar quantities of Mn\textsuperscript{2+} and L\textsuperscript{1} (1.5 mM).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure_s19.png}
\caption{Nuclear Magnetic Relaxation Dispersion profiles of MnL\textsuperscript{1} in water (c_{MnL1} = 1.48 mM) at 25\degree C and 37\degree C, and in the presence of physiological, 0.6 mM concentration of human serum albumin (HSA, 25 \degree C, c_{MnL1} = 1.57 mM). pH 7.4}
\end{figure}
**Assessment of the kinetic inertness of MnL**

Concerning dissociation kinetics, which is an important parameter for safe in vivo use of Mn$^{2+}$ complexes, it has been assessed in Cu$^{2+}$ trans-metalation experiments for MnL$^1$. Transmetalation studies represent the most common way to study dissociation kinetics of Mn$^{2+}$ complexes.\textsuperscript{54-55}

For the trans-metaling agent, both Cu$^{2+}$ and Zn$^{2+}$ are commonly used, here, we selected Cu$^{2+}$ due to its capacity to replace Mn$^{2+}$.

The trans-metalation is followed at different pH values (2.3-3.5) by measurements of the transverse relaxivity in the presence of a large excess (10-40 fold) of Cu$^{2+}$ in order to ensure pseudo-first order conditions. The time-dependent variation of the relaxation rates, under any of the experimental conditions, can be described by the sum of two mono-exponential terms, which likely reflects that MnL$^1$ has two different isomers with different dissociation rates (see one example at pH 3.15 in the figure below):

\[
T_2 = A(0) - (a_1 \times e^{-k_{obs1}t} + a_2 \times e^{-k_{obs2}t})
\]

**Figure. S20** Variation of $r_2$ as a function of time during trans-metalation of MnL$^1$ by Cu$^{2+}$. 60 MHz, 25°C, $c_{MnL} = 1.6$ mM. \(\Delta : c_{Cu2+} = 16\) mM ; \(\Delta : c_{Cu2+} = 32\) mM ; \(\Delta : c_{Cu2+} = 48\) mM ; \(\Delta : c_{Cu2+} = 64\) mM. Curves represent the fit.
Thus, two observed rate constants, $k_{\text{obs}}$, are calculated for each pH and Cu$^{2+}$ concentration. We note that the proportion of the two terms is identical for all experimental conditions which comforts the hypothesis that they originate from isomers, although we do not have at this point further confirmation on this.

When the $k_{\text{obs}}$ are plotted against the Cu$^{2+}$ concentration, we observe a linear dependency, while they are completely independent of pH as shown below:

\[ k_{\text{obs}} = k_0 + k_{\text{Cu}} \cdot [\text{Cu}^{2+}] \]

**Figure. S21.** Variation of $k_{\text{obs}}$ as a function of the concentration of Cu$^{2+}$. □ : pH 2,30 ; × : pH 2,50 ; Δ : pH 2,70 ; ○ : pH 3,15 ○ : pH 3,53. $c_{\text{MnL}} = 1,6$ mM, 25°C. a) and b) represent the series of the two $k_{\text{obs}}$ values calculated for each experiment, likely corresponding to two isomers.

The $k_{\text{obs}}$ data were fitted to the following equation to calculate the rate constant characterizing the metal-assisted dissociation, $k_{\text{Cu}}$, and the rate constant $k_0$, characterizing the spontaneous dissociation:
\[ k_{\text{obs}} = k_0 + k_{\text{Cu}^{2+}} [\text{Cu}^{2+}] \]

The pH invariance indicates that the proton-assisted dissociation pathway is negligible, a phenomenon which is unique for a Mn\(^{2+}\) complex.

The fit of the two curves gives \( k_{\text{Cu}} \) of 0.024±0.005 s\(^{-1}\)Ms\(^{-1}\) for one isomer and 0.075±0.008 s\(^{-1}\)Ms\(^{-1}\) for the other, while the \( k_0 \) values are ill-defined, as obtained with large errors. This is not surprising given that the experiments are done far from physiological pH and Cu\(^{2+}\) concentration (it is not possible to work at low Cu\(^{2+}\) concentration and pH 7.4), therefore decided to fix them to zero.

Then, we can estimate the dissociation half-life for physiological conditions (\( c_{\text{Cu}}=10^6 \) M, pH 7.4). This gives \( t_{1/2} = 334 \) days and 106 days, respectively, for the two isomers. These are extraordinarily high values, to be compared to 54 hours for the macrocyclic MnPC2A-EA chelate under similar conditions, which is considered as one of the most inert monohydrated Mn\(^{2+}\) complexes.\(^{56}\)

Nevertheless, we cannot exclude that under physiological conditions the role of spontaneous dissociation becomes important and thus the dissociation half-life is reduced.
8. Mass Spectrometry

Figure S22. High resolution ESI-mass spectrum (H$_2$O/MeOH) of [Mn(OTf)L$_1$]OTf.

Figure S23. Zoom-In of the main peak at m/z = 757.2416 in the HR-ESI-MS (H$_2$O/MeOH) of [Mn(OTf)L$_1$]OTf.
**Figure S24.** Zoom-in of the m/z = ½ area in the HR-ESI-MS of [Mn(OTf)L\(^1\)]OTf.

**Figure S25.** High resolution ESI-mass spectrum (H\(_2\)O/MeOH) of [MnL\(^2\)]OTf.
**Figure. S26.** Zoom-In of the m/z = ½ area in the HR-ESI-MS of [Mn(OTf)L₁]OTf. Insert shows the main peak clearly being a species of +1 charge most probably resembling a fragment of the ligand.

HR-ESI mass spectra of the MnL₁ (Figures S22 – S 24) and MnL₂ complexes (Figures S25, S26) show distinct signals matching the respective Mn²⁺ species. The zoom-in at the m/z = ½ m/z areas with respect to the signal of the Mn²⁺-bispidine complexes (Figures S24, S26) clearly show no sign of the corresponding Mn³⁺ complexes, supporting the evidence from the NMRD data and the cyclic voltammograms that there is no air oxidation of the Mn²⁺ complexes (see main text).

9. Redox chemistry

The NMRD and ESI-MS data (see above) indicate that air oxidation of the Mn²⁺ complexes to the corresponding Mn³⁺ complexes does not occur. We also report here the cyclic voltammogram of Mn²⁺L₂ in MeCN (see Figure S27) with a redox potential of 840 mV vs. Fc/Fc⁺. This appears to be too high for the oxidation with O₂, with the corresponding potentials in H₂O to O₂²⁻ (-0.12) and H₂O (0.41), and to H₂O in MeCN (1.21, all vs. Fc/Fc⁺).
Figure. S27. Cyclic voltammogram of [MnL₂]OTf (MeCN, 0.1 M (tBu₄N)(PF₆) vs. Fc/Fc⁺). The electrochemical measurements were conducted on a CH Instruments CHI660D electrochemical workstation, equipped with a CH Instruments Picoamp Booster and Faraday Cage. A three-electrode setup consisting of a platinum wire auxiliary electrode, an Ag/AgCl reference electrode (3 M NaCl) and a glassy-carbon working electrode was used (scan rate 0.1V/s); the potential is referenced against the potential of ferrocene as an external standard (E₁/₂(Fc/Fc⁺) = 0.55 V).

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