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Diastereoselective Self-Assembly of Double-Stranded Helicates from Tröger's Base Derivatives

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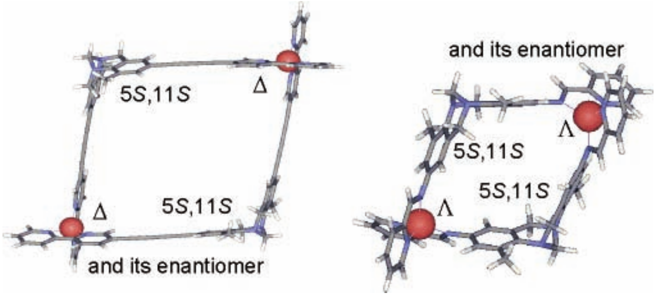
ABSTRACT



Several ligands based on the rigid, V-shaped structure of Tröger's base bearing 2,2′-bipyridine and 2-pyridylmethanimine moieties have been synthesized. These ligands undergo diastereoselective self-assembly to dinuclear double-stranded D_{2d}-symmetric helicates upon coordination to copper(I) and silver(I) ions as elucidated by NMR techniques and ESI mass spectrometric methods.

Tröger's base was first synthesized in 1887 by Julius Tröger.[1] C_2-symmetric chirality is induced into this molecule because an inversion of the two stereogenic nitrogen centers is structurally hindered due to the bridged bicyclic architecture of the compound. Its V-shaped structure and rigid conformation make it an almost ideal building block to introduce curvature into concave molecules which has led to an increased interest in the formation and application of a variety of new analogues of Tröger's base in the past years.[2] Usually, these derivatives are formed by condensation of a substituted aniline and formaldehyde under strongly acidic conditions.

A few years ago, Wärnmark[3] succeeded in the synthesis of dihalosubstituted analogues which are valuable precursors for the construction of larger architectures with extended V-shaped cores.[4]

Although Tröger's base scaffold has been widely used for the design of various macrocyclic receptors,[2] there is only one example for its incorporation into a series of metallo-macrocycles so far.[5] Recently, we were able to show that bis(bipyridyl) ligands derived from substituted 1,1′-binaphthyl (BINOL) units undergo diastereoselective self-assembly processes to form dinuclear helicates upon coordination to suitable transition metal ions.[6,7] Thus, we were wondering

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[1] Tröger, J. *J. Prakt. Chem.* **1887**, *36*, 225.

[2] (a) Demeunynck, M.; Tatibouet, A. Recent Developments in Tröger's Base Chemistry. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Cilchrist, T. L., Eds.; Pergamon: Oxford, UK, 1999; pp 1−20. (b) Valik, M.; Strongin, R. M.; Kral, V. *Supramol. Chem.* **2005**, *17*, 347.

[3] (a) Jensen, J.; Warnmark, K. *Synthesis* **2001**, 1873. (b) Hansson, A.; Jensen, J.; Wendt, O. F.; Waernmark, K. *Eur. J. Org.* **2003**, 3179.

[4] (a) Kiehne, U.; Lützen, A. *Synthesis* **2004**, 1687. (b) Hof, F.; Schar, M.; Scofield, D. M.; Fischer, F.; Diederich, F.; Sergeyev, S. *Helv. Chim. Acta* **2005**, *88*, 2333.

[5] Khoshbin, M. S.; Ovchinnikov, M. V.; Mirkin, C. A.; Golen, J. A.; Rheingold, A. L. *Inorg. Chem.* **2006**, *45*, 2603.

[6] (a) Lützen, A.; Hapke, M.; Griep-Raming, J.; Haase, D.; Saak, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2086; *Angew. Chem.* **2002**, *114*, 2190. (b) Schalley, C. A.; Lützen, A.; Albrecht, M. *Chem.−Eur. J.* **2004**, *10*, 1072.

[7] Diastereoselective self-assembly of helicates has also been reported by others: (a) Zarges, W.; Hall, J.; Lehn, J. M.; Bolm, C. *Helv. Chim. Acta* **1991**, *74*, 1843. (b) Albrecht, M.; Kotila, S. *Angew. Chem., Int. Ed.* **1995**, *34*, 2134; *Angew. Chem.* **1995**, *107*, 2285. (c) Prabaharan, R.; Fletcher, N. C.; Nieuwenhuyzen, N. *J. Chem. Soc., Dalton Trans.* **2002**, 602.

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if this phenomena is a unique feature of this lead structure or if it is more general and would also allow the use of other C_2-symmetric building blocks and the use of other spacer units between the stereogenic element and the chelating metal binding site and still lead to the diastereoselective formation of metallo supramolecular assemblies. Therefore, we synthesized ligands **1**−**4** (Figure 1), bearing either 2,2′-bipyridine or 2-pyridylmethanimine units, which have proven to be powerful coordination sites in several self-assembled metal complexes of helical shape before,[8] that are linked by certain spacers of different length to the rigid core of Tröger's base.

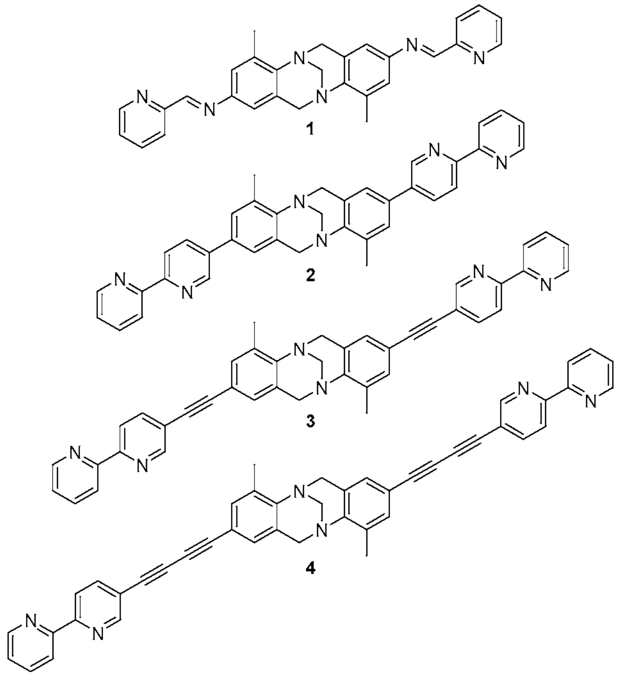
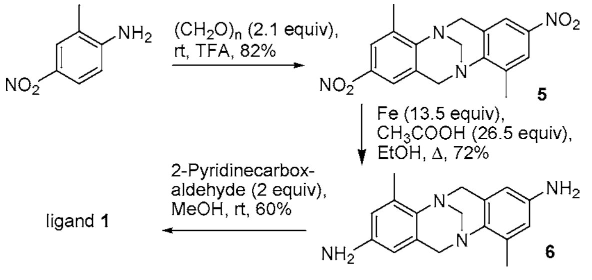


Figure 1. Ligands **1**−**4** bearing 2,2′-bipyridine or 2-pyridylmethanimine moieties as metal chelating units.

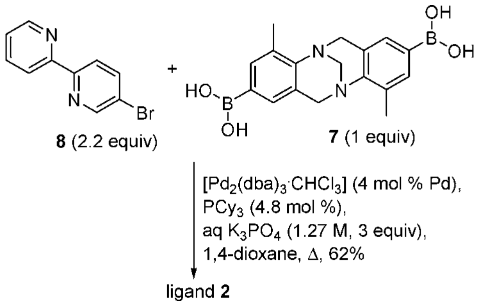
Ligand **1** was prepared in three steps starting from 2-methyl-4-nitro aniline, involving a condensation step for the synthesis of 2,8-dinitro derivative **5** of Tröger's base, followed by a reduction yielding the diamino-substituted compound **6**, which was used as a precursor for the preparation of diimine **1** (Scheme 1).

Scheme 1. Synthesis of Ligand **1**



Ligands **2**−**4** were synthesized using symmetrically functionalized derivatives of Tröger's base and different 5-substituted 2,2′-bipyridines in transition-metal-catalyzed cross-coupling reactions as the key steps in the reaction sequences. Ligand **2** was prepared in a 2-fold Suzuki cross-coupling of **7** and 5-bromo-2,2′-bipyridine (**8**) following a protocol published recently by Fu and co-workers (Scheme 2).[9]

Scheme 2. Synthesis of Ligand **2**



Ligands **3** and **4** bearing ethynyl and butadiynyl spacers were prepared in a 2-fold Sonogashira[10] or a 2-fold Cadiot−Chodkiewicz reaction[11] starting from either a diiodo or a diethynyl derivative of Tröger's base, respectively (Scheme 3). Whereas the Sonogashira reaction proceeded smoothly giving rise to **3** in excellent yield, the synthesis of **4** turned out to be more complicated mainly due to the formation of large amounts of homocoupling product of 5-bromoethynyl-2,2′-bipyridine (**11**). Thus, the purification of **4** proved to be very challenging. Nevertheless, we finally isolated at least a reasonable amount of **4** from the complicated reaction mixture.

With the four racemic ligands in our hands, we then explored their coordination chemical behavior toward transition metal ions, i.e., their ability to form double-stranded helicates with suitable ions such as copper(I) and silver(I) ions (Cu^+ and Ag^+), which typically prefer a tetrahedral coordination geometry.

The complexation behavior of **1**−**4** was first investigated by ^{1}H NMR spectroscopic means.

Upon addition of the metal salts to solutions of our ligands, an immediate color change took place: in the case of Ag^+, the solution turned yellow, and in the case of Cu^+, a red brownish coloring was observed, both of them characteristic of silver(I) and copper(I) bis(bipyridine) and bis(2-pyridylmethanimine) complexes, respectively. The ^{1}H NMR spectra of **1** and its complexes are shown in Figure 2. Upon addition

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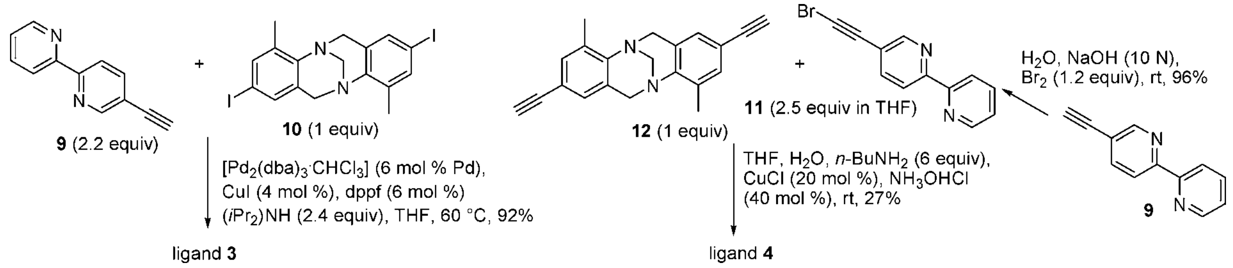
[8] (a) Albrecht, M. *Chem. Rev.* **2001**, *101*, 3457. (b) Piguet, C.; Bernardinelli, G.; Hopfgartner, G. *Chem. Rev.* **1997**, *97*, 2005. (c) Oleksi, A.; Blanco, A. G.; Boer, R.; Uson, I.; Aymami, J.; Rodger, A.; Hannon, M. J.; Coll, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1227; *Angew. Chem.* **2006**, *118*, 1249. (d) Childs, L. J.; Alcock, N. W.; Hannon, M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1079; *Angew. Chem.* **2001**, *114*, 4418.

[9] Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282; *Angew. Chem.* **2006**, *118*, 1304.

[10] Adapted procedure from ref 6a.

[11] Adapted from: Jiang, M. X.-W.; Rawat, M.; Wulff, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 5970.

Scheme 3. Synthesis of Ligands **3** and **4**



of Cu$^+$ in a 1:1 ratio, only broad signals are obtained indicating a very dynamic behavior on the NMR time scale of the complex (Figure 2a), as was found for the corresponding BINOL-derived ligands previously.[6] However, the addition of Ag$^+$ results in a well-resolved spectrum with only one set of sharp signals which are clearly shifted compared to Figure 2b. This is obvious not only for the pyridine and the imine protons but also for the bridgehead protons and the methyl substituent of the Tröger's base core, which are shifted downfield. Within **2**−**4**, the distance between the metal chelating units and the two stereogenic nitrogen atoms which bear the chiral information grows due to elongation of the spacer unit from a C−C single bond in **2** to a butadiynyl moiety in **4**. Figure 3 shows the ^{1}H NMR complexation behavior of **2**. Again (Figure 3c), the proton signals are clearly shifted upon addition of Ag$^+$, and only one set of signals appears.

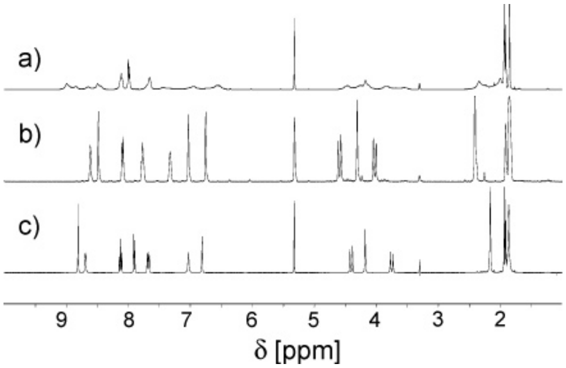


Figure 2. ^{1}H NMR complexation studies of **1** in CD$_2$Cl$_2$/CD$_3$CN (3:1). (a) **1** + [Cu(CH$_3$CN)$_4$]BF$_4$ (1:1). (b) **1**. (c) **1** + [Ag(CH$_3$CN)$_2$]BF$_4$ (1:1).

The spectrum of the Cu$^+$ complex (Figure 3a) also shows relatively broad signals; nevertheless, the signals are much sharper than in the case of the 2-pyridylmethanimine ligand **1**. Complexation studies of ligands **3** and **4** provided similar results (^{1}H NMR spectra can be found in the Supporting Information).

Several conclusions can be drawn from these spectra: (i) The shift of the signals upon metal ion addition indicates successful formation of metal complexes. (ii) The appearance of sharp signals for the silver(I) and most of the copper(I) complexes refers to the formation of discrete dinuclear helicates and excludes the formation of oligomeric or polymeric species. This could also be proven by ESI-MS experiments because only signals of the dinuclear silver and copper species and some fragments resulting from them could be detected, which is shown representatively for the dinuclear copper complex of ligand **1** in Figure 4 (see Supporting Information for ESI-MS data of all other complexes). (iii) The number of signals of the free ligands is equal to the

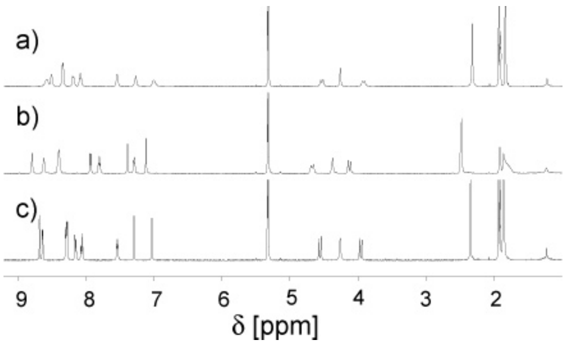


Figure 3. ^{1}H NMR complexation studies of **2** in CD$_2$Cl$_2$/CD$_3$CN (3:1). (a) **2** + [Cu(CH$_3$CN)$_4$]BF$_4$ (1:1). (b) **2**. (c) **2** + [Ag(CH$_3$CN)$_2$]BF$_4$ (1:1).

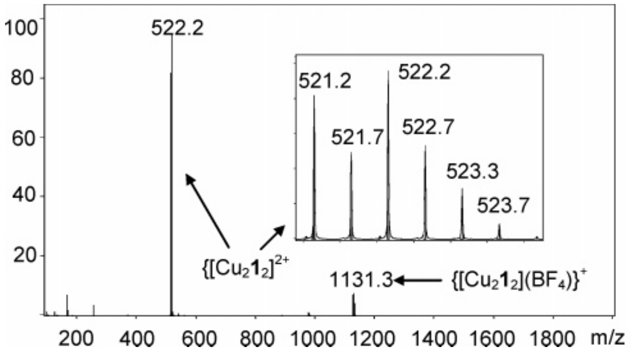


Figure 4. Positive ESI-MS of a solution of [Cu$_2$(**1**)$_2$](BF$_4$)$_2$ in CH$_2$Cl$_2$.

number of signals of their silver(I) (and copper(I)) complexes. This is only possible if the ligands retain their symmetry in the aggregates. This, however, is only feasible when the newly formed chiral metal centers have the same configuration (Δ,Δ or Λ,Λ), thus excluding the formation of Δ,Λ- or Λ,Δ-configured "*meso*"-helicates. For the same reason, we can exclude the formation of heteroleptic complexes—meaning the incorporation of differently configured ligands within one assembly—because one would (at least) expect the double amount of signals in this case. Thus, only homoleptic complexes with equally configured ligands are formed. Because Δ,Δ- or Λ,Λ-configured helicates of these chiral ligands are diastereomers, however, it is at least very unlikely that all of the proton signals of the Δ,Δ- or Λ,Λ-configured helicates should be isochronic by coincidence; therefore, one can conclude that the self-assembly processes are indeed completely diastereoselective yielding racemic pairs of dinuclear complexes, each having two metal centers with the same configuration.

The question resulting from that is which enantiomer of Tröger's bases gives rise to which configuration of the metal centers within the assemblies. Unfortunately, we have not been able to obtain crystals suitable for X-ray analysis of our aggregates, yet. However, to elucidate the stereochemistry, ROESY NMR experiments can also be used because they allow an assignment of the relative orientation of the metal chelating unit and the Tröger's base core. Thus, these experiments were carried out with the silver(I) complexes of **1**−**3** (see Supporting Information) and revealed that in aggregates of **1** a (5*S*,11*S*)-configuration of Tröger's base causes a (Λ,Λ)-configuration and a (5*R*,11*R*)-configuration causes a (Δ,Δ)-configuration of the metal centers, respectively. The opposite assignment can be made for **3**: (5*S*,11*S*)-configured Tröger's bases lead to a (Δ,Δ)-configuration of the metal centers. The butadiynyl spacer of **4** is too long to allow the assignment of the relative configuration; however, the very similar chemical shifts of the helicates of **3** and **4** suggest a similar orientation and therefore configuration of the relevant groups. Unfortunately, a twist of the aromatic rings of the Tröger's base and the bipyridine core via the C−C single bond in **2** does not allow a definite assignment of the metal centers (see also Supporting Information); therefore, the (Δ,Δ)-configuration for complexes of (5*S*,11*S*)-**2** as in the cases of the other bis(bipyridine)-based ligands **3** and **4** is likely from the modeling studies[12] (Figure 5) but needs to be confirmed in due course.

In conclusion, we have synthesized racemic ligands **1**−**4** and demonstrated that they form homoleptic D_{2d}-symmetric dinuclear double-stranded helicates upon coordination to Ag^+ and Cu^+ in diastereoselective self-assembly processes. The configuration of the newly formed chiral metal centers is completely controlled by the configuration of the Tröger's base, even when ligands with elongated spacer units such as **3** or even **4** are used that set the stereogenic centers of the Tröger's base and the metal centers up to 14.3 Å apart from each other. We are currently extending the studies in terms of introducing both a more flexible spacer and different metal chelating units as well as using different metal ions to form triple-stranded helicates.

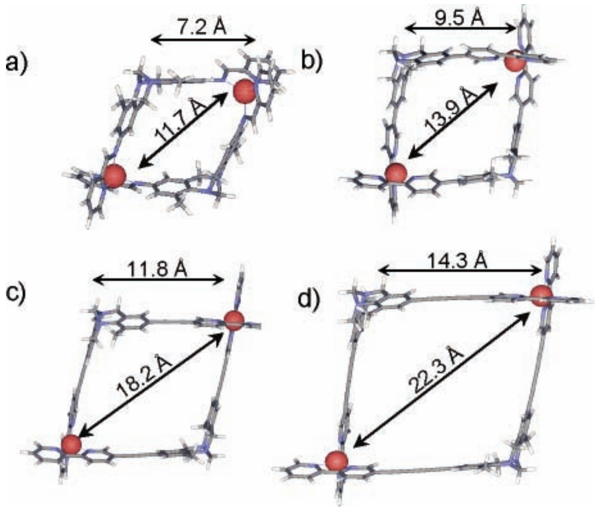


Figure 5. PM3-TM minimized structures of the dinuclear helicates formed in diastereoselective self-assembly processes of (5*S*,11*S*)-configurated ligands **1**−**4** (revealed by ROESY NMR experiments for **1** and **3**, proposed for **2** and **4**): (a) (Λ,Λ)-$[Cu_2\{(5S,11S)\text{-}(\mathbf{1})\}_2]^{2+}$, (b) (Δ,Δ)-$[Cu_2\{(5S,11S)\text{-}(\mathbf{2})\}_2]^{2+}$, (c) (Δ,Δ)-$[Cu_2\{(5S,11S)\text{-}(\mathbf{3})\}_2]^{2+}$, (d) (Δ,Δ)-$[Cu_2\{(5S,11S)\text{-}(\mathbf{4})\}_2]^{2+}$.

Acknowledgment. We are grateful to the DFG (SPP 1118) for financial support.

Supporting Information Available: Synthetic procedures and characterization data for **1**−**6** and **11** and NMR and ESI-MS data for the complexes of **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] For the PM3-method, see: Bosque, R.; Maseras, F. *J. Comput. Chem.* **2000**, *21*, 562 and references cited therein.