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C_2-chiral dinucleating ligands with a 3,6-disubstituted pyridazine core

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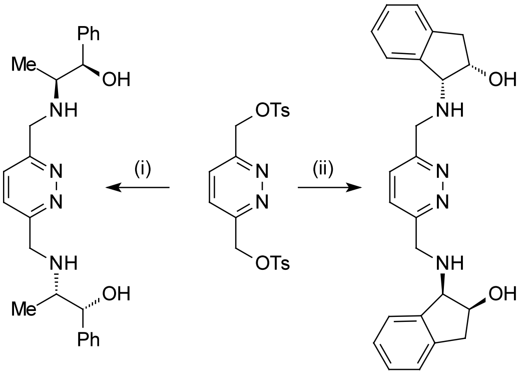
Abstract—Reaction of the 3,6-bis(tosyloxymethyl)pyridazine (**1**) with two equivalents of (1*R*-2*S*)-norephedrine or (1*S*-2*R*)-1-amino-2-indanol leads to the formation of C_2-chiral dinucleating ligands containing a 3,6-disubstituted pyridazine core flanked by aminoalcohol pendant arms, namely 3,6-bis((1*R*-2*S*)-(2-hydroxy-1-methyl-2-phenyl-ethyl)aminomethyl)pyridazine (**2**) and 3,6-bis((1*S*-2*R*)-(2-hydroxy-indan-1-yl)aminomethyl)pyridazine (**3**). As shown by spectrometric titration experiments as well as ESI/MS, ligands **2** and **3** bind copper(II) cations to form dinuclear complexes.

1. Introduction

Recent investigations in the field of Lewis acid catalysis have focused on the use of dinuclear metal complexes.[1–7] As a result of distinct synergistic effects occurring at the proximal metal centers, these complexes feature unique catalytic properties. While original studies dealt with mostly achiral systems,[1–3] a variety of asymmetric complexes have now emerged. An important aspect of this research concerns the preparation of chiral ligands designed to hold two metal cations in well defined positions. Examination of the literature indicates that the nature of the ligands so far investigated remains somewhat restricted. In addition, the use of large and flexible bifunctional chiral Schiff bases,[4] the binol ligands has received most of the attention and has been successfully incorporated in bimetallic catalysts.[5,6] In an effort to diversify the palette of chiral dinucleating ligands available,[7] we have engaged into the synthesis and coordination chemistry of C_2-chiral derivatives containing a 3,6-disubstituted pyridazine moiety as a central core. We note that, despite the widespread use of 3,6-disubstituted pyridazine ligands in the chemistry of dinuclear metal complexes,[8–13] only on one occasion has the preparation of chiral examples of such ligands been reported.[14]

2. Results and discussion

It occurred to us that, in order to avoid aggregation,[15] ligands able to present at least three basic sites to each metal center should be prepared. For this reason, the introduction of aminoalcohol pendant arms at the benzylic positions of a 3,6-dimethylpyridazine was selected as a synthetic target. 3,6-Bis(hydroxymethyl)pyridazine was prepared by following the published procedure[16] and was treated with *p*-toluenesulfonyl chloride to afford the bistosylate **1**. Following flash chromatography purification and rapid evaporation of the solvent, **1** was isolated in 85% yield. Compound **1** is stable when stored as a solid at −20°C but slowly decompose at room temperature.



2 **1** **3**

Scheme 1. (i) (1*R*-2*S*)-norephedrine, Na_2CO_3, MeCN; (ii) (1*S*-2*R*)-1-amino-2-indanol, Na_2CO_3, MeCN.

Keywords: dinucleating ligand; 3,6-pyridazine; C_2-chiral; copper complex.

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Compound **1** reacts smoothly with various aminoalcohols. Thus, treatment with two equivalents of (1*R*-2*S*)-norephedrine in the presence of Na_2CO_3 affords 3,6-bis((1*R*-2*S*)-(2-hydroxy-1-methyl-2-phenylethyl)-aminomethyl)pyridazine (**2**) in 88% yield after recrystallization from acetonitrile (Scheme 1). It is important to note that this substitution reaction is regioselective and that no *O*-substituted products or oligomers could be observed in the reaction mixture. The nature of **2** was confirmed by ^1H, ^{13}C NMR and FAB mass spectrometry which allowed the detection of the molecular peak. In a similar fashion, **1** reacts with (1*S*-2*R*)-1-amino-2-indanol to afford 3,6-bis((1*S*-2*R*)-(2-hydroxyindan-1-yl)aminomethyl)pyridazine (**3**) in a 76% yield (Scheme 1). As in the case of **2**, the identity of **3** has been confirmed by ^1H, ^{13}C NMR and FAB mass spectrometry.

Despite repeated attempts, single crystals of **2** could not been obtained. In the case of **3**, however, slow cooling of an ethanol solution lead to the formation of single crystals that were subjected to an X-ray analysis. Compound **3** crystallizes in the orthorhombic space group $P2_{(1)}2_{(1)}2$ with two molecules per unit cell (Fig. 1). Examination of the structure confirms the proposed connectivity and in particular, the *N*-attachment of the aminoalcohol moiety. Molecules of **3** have a crystallographically imposed C_2 symmetry. The bond angles and bond lengths observed in the structure of the pyridazine core of **3** resemble those previously reported for related molecules such as bis(hydroxymethyl)pyridazine[17] or 3,6-dicarboxylic-pyridazine acid.[18] There are no unusual bond lengths and angles in the amino-indanol moieties that flank each side of the pyridazine ring.

With the preparation of binuclear complexes as a goal, it became important to investigate the ligative behavior of **2** and **3** toward a prototypical metal cation such as copper(II). Addition of $CuCl_2$ to a 10^{-4} M solution of **2** or **3** in EtOH resulted in the appearance of a charge transfer band at 365 nm. In both cases, absorption at that wavelength increased steadily until exactly two equivalents of metals had been added (Fig. 2). With further addition of Cu^{2+}, the absorbance at that wavelength remained constant thus indicating the nearly quantitative formation of the dinuclear complexes. In the case of **3**, the existence of dinuclear complexes could also be confirmed by ESI mass spectrometry of methanol solutions containing **3** and two equivalents of $Cu(OTf)_2$. The base peak, observed at 675 amu, results from the loss of two molecule of HOTf and one OTf^- anion from the parent complex $\mathbf{3}\cdot(CuOTf_2)_2$. Loss of an additional HOTf molecule results in a peak observed at 525 amu.

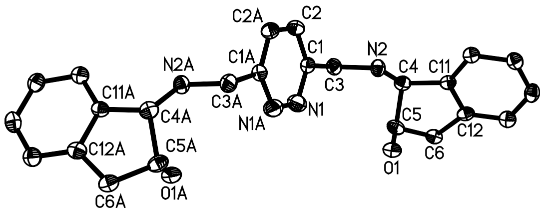

Figure 1. ORTEP view of **3** in the crystal (50% elipsoids). Selected bond length [Å] and angles [°]: O(1)–C(5) 1.432(5), N(1)–C(1) 1.325(5), N(1)–N(1A) 1.349(7), N(2)–C(4) 1.460(5), N(2)–C(3) 1.480(4), C(1)–C(2) 1.390(6), C(1)–C(3) 1.513(5), C(2)–C(2A) 1.384(8), C(4)–C(5) 1.561(5), C(5)–C(6) 1.538(5), C(1)–N(1)–N(1A) 120.0(2), C(4)–N(2)–C(3) 113.0(3), N(1)–C(1)–C(2) 122.4(4), N(1)–C(1)–C(3) 113.4(4), C(2)–C(1)–C(3) 124.1(4), C(2A)–C(2)–C(1) 117.6(2), N(2)–C(3)–C(1) 108.8(3), N(2)–C(4)–C(11) 113.2(3), N(2)–C(4)–C(5) 116.2(3), C(11)–C(4)–C(5) 101.6(3), O(1)–C(5)–C(6) 112.4(3), O(1)–C(5)–C(4) 104.9(3), C(6)–C(5)–C(4) 102.2(3), C(12)–C(6)–C(5) 103.2(3).

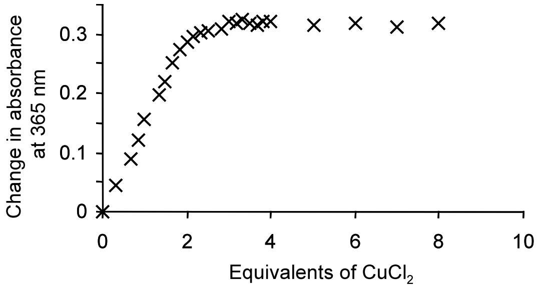

Figure 2. Spectrometric titration of **3** with $CuCl_2$ in EtOH. Change in absorbance variation at 365 nm as a function of the number of equivalents of $CuCl_2$ added.

3. Summary

In conclusion, we report the synthesis of simple chiral ligands of C_2 symmetry in which two copper(II) cations can be embedded. Current studies are focused on the use of these complexes in asymmetric catalysis.

4. Experimental

4.1. Synthesis

4.1.1. 3,6-Bis(tosyloxymethyl)pyridazine (1). A solution of *p*-toluenesulfonyl chloride (13.7 g, 72 mmol) in THF (30 mL) was added to a solution of 3,6-bis(hydroxymethyl)pyridazine (5 g, 36 mmol) and NaOH (4 g, 0.1 mol) in a mixture of water (20 mL) and THF (20 mL). After stirring at 25°C for 3 h, the solution was concentrated by partial evaporation of the solvent, which resulted in the precipitation of the product as a white solid. The product was isolated by filtration and was purified by flash chromatography (washed with dichloromethane and eluted with ethylacetate) to give **1** (13.7 g, 85% yield). Mp 118–120°C. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.46 (s, 6H), 5.36 (s, 4H), 7.36 (d, $^3J_{HH} = 8.4$ Hz, 4H), 7.65 (s, 2H), 7.83 (d, $^3J_{HH} = 8.4$ Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.8, 69.8, 126.2, 128.3, 130.3, 132.7, 145.7, 157.1. MS (+FAB): *m*/*z*: 449 [MH^+]. Elemental analysis: Anal. calcd for $C_{20}H_{20}N_2O_6S_2$: (448.5): C, 53.55; H, 4.45; N, 6.25; found: C, 53.56; H, 4.61; N, 6.27.

4.1.2. 3,6-Bis((1*R*-2*S*)-(2-hydroxy-1-methyl-2-phenylethyl)aminomethyl)pyridazine (2) and 3,6-bis((1*S*-2*R*)-(2-hydroxy-indan-1-yl)aminomethyl)pyridazine (3). Compounds **2** and **3** were prepared by reaction of **1** with two equivalents of (1*R*-2*S*)-norephedrine and (1*S*-2*R*)-1-amino-2-indanol, respectively, in the presence of four equivalents Na_2CO_3 in MeCN. The reactions were complete after 3 h and the products were purified by recrystallization from MeCN. **2**: 88% yield, mp 152–154°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, $^3J_{\mathrm{HH}}=$ 6.6 Hz, 6H), 3.03 (qd, $^3J_{\mathrm{HH}}=6.6$ Hz, $^3J_{\mathrm{HH}}=3.6$ Hz, 2H), 4.17 (d, $^2J_{\mathrm{HH}}=14.7$ Hz, 2H), 4.25 (d, $^2J_{\mathrm{HH}}=14.7$ Hz, 2H), 4.81 (d, $^3J_{\mathrm{HH}}=3.6$ Hz, 2H), 7.31 (m, 12H), 7.50 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.8, 51.0, 58.7, 73.8, 126.3, 126.7, 127.4, 128.3, 140.8, 160.7. MS (+FAB): *m*/*z*: 407 [MH^+]. **3**: 76% yield, mp 164–166°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.99 (dd, $^3J_{\mathrm{HH}}=3$ Hz, $^2J_{\mathrm{HH}}=13.5$ Hz, 2H), 3.07 (dd, $^3J_{\mathrm{HH}}=4.8$ Hz, $^2J_{\mathrm{HH}}=$ 13.5 Hz, 2H), 4.16 (d, $^3J_{\mathrm{HH}}=5.1$ Hz, 2H), 4.30 (d, $^2J_{\mathrm{HH}}=15$ Hz, 2H), 4.37 (d, $^2J_{\mathrm{HH}}=15$ Hz, 2H), 4.45 (m, 2H), 7.27 (m, 6H), 7.38 (m, 2H), 7.58 (s, 2H). ^{13}C NMR (pyridine-d_6, 75 MHz) δ 40.5, 52.0, 66.6, 72.0, 125.4, 125.5, 126.6, 126.7, 127.8, 141.7, 144.6, 162.0. MS (+FAB): *m*/*z*: 403 [MH^+]. Elemental analysis: Anal. calcd for $C_{24}H_{26}N_4O_2$: C, 71.62; H, 6.51; N, 13.91; found: C, 71.18; H, 6.53; N, 13.79.

4.2. Crystal and structure determination data for 3

A single crystal was selected, glued onto a glass fiber and mounted on the goniometer of a Siemens SMART-CCD diffractometer utilizing Mo Kα radiation ($\lambda=$ 0.71073 Å). 5906 reflections (2258 unique, $R_{\mathrm{int}}=0.0579$) were collected at $T=110$ K with 0.3°-wide ω-scans and with $1.08\leq\theta\leq28.28°$. The structure was solved by direct methods and refined by full-matrix least-squares against F_2 using the SHELXTL/PC (ver. 5.10) package. The refinement converged with residuals of $R_1=0.0893$, $wR_2=0.1991$ (all data) for 2258 unique reflections and 136 refined parameters. Other important crystallographic parameters are as follows: $C_{24}H_{26}N_4O_2$; $M=$ 402.49; orthorhombic space group $P2_{(1)}2_{(1)}2$; $a=37.790(9)$, $b=4.6788(11)$, $c=5.6130(13)$ Å; $V=$ 992.4(4) Å^3; $Z=2$; ρ_{calcd}1.347 Mg/m^3. The complete crystallographic data for the structural analysis of **3** have been deposited with the Cambridge Crystallographic Data Centre and allocated the CCDC No. 168202. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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