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# Highly diastereoselective formation of $C_2$-symmetric bis-thioglycoside Pd(II) complexes: the role of the *exo* anomeric effect†

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**Treatment of several $C_2$ symmetric bis-thioglycosides with $Pd(CH_3CN)_2Cl_2$ always leads to a single diastereomeric Pd(II) complex as a consequence of the *exo*-anomeric effect.**

The development of new chiral ligands for metal-catalyzed asymmetric transformations is an important task in the field of enantioselective asymmetric synthesis.[1] Surprisingly, very few chiral dithioether ligands have been used,[2] even though the coordinating ability of thioether donors in transition metal complexes is known.[3] An inherent characteristic of thioether ligands is that upon coordination to the metal, the sulfur atom becomes stereogenic. While the close proximity of the chiral sulfur center to the coordination sphere of the transition metal may be beneficial,[4] the low inversion barrier of the sulfur metal bond may account for the scarce use of dithioethers in asymmetric catalysis.[5] Thus, any attempts to incorporate a thioether into a chiral ligand must firstly address stereocontrol at the sulfur atom. Such control may be accomplished by steric bias (Scheme 1), as recently reported by Evans in the synthesis of efficient catalysts based on chiral mixed S/P ligands.[6]

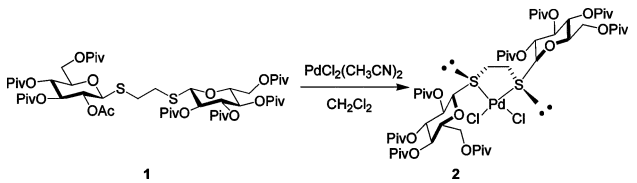
Nevertheless, in the case of bis-thioethers with no substituent at the carbon α to the sulfur atom (Fig. 1, R′ = H), such steric control is not possible. In the present work we report an effective stereochemical control which do not rely on steric factors, but is based on stereoelectronic effects.

Initially, we have noticed that bis-thioglycoside **1** used recently in Pd-catalyzed allylic alkylation, with dimethyl malonate as nucleophile, in up to 90% ee,[7] afforded the corresponding Pd(II) complex **2** in 91% yield upon treatment with $PdCl_2(CH_3CN)_2$ (Scheme 1).

While up to three diastereoisomers (one *syn* and two *anti*) are possible during the formation of the Pd(II) complex, only one isomer was obtained. In order to understand the high diastereoselectivity observed and to assess its generality, various bis-thioglycosides with different spacers, protective groups and sugar rings were used in the same reaction, Fig. 2. Both the five-membered palladacycles (**2–9**) and six-membered-palladacyle **10**, were obtained as a single isomer regardless of the sugar ring and the protective groups.

In all the cases studied the formed isomer has $C_2$ symmetry as indicated by the $^1H$ and $^{13}C$ NMR spectra. All the complexes presented a similar spectroscopic behaviour: a deshielding of the anomeric protons (0.6–1 ppm) and the carbon α to the sulfur atom (3–4 ppm) compared to the free ligand. While the $C_2$-symmetry is pointing to the formation of an *anti* structure, this may either be a single isomer or a mixture of both *anti* diastereoisomers in fast equilibrium. A dynamic NMR study was thus carried out on the complexes **2** and **3**, and no other isomer was detected throughout the temperature range tested (+50 to −80° C), confirming the formation of a single *anti* diastereoisomer. Similar results were obtained with the six-membered palladacycle **10**, indicating the generality in the stereochemical outcome of the formation of the bis-thioglycoside Pd(II) complexes. A literature survey shows that in most cases the Pd(II) complexes with an ethylene bridged dithioether are obtained as a mixture of *syn* and *anti* isomers, due to the low inversion barrier of the S–Met bond (15–20 kcal $mol^{-1}$).[5,8] Accordingly, the formation of a single bis-thioglycoside Pd(II) complex was unexpected, as there is no stereochemical bias controlling the sulfur stereochemistry.

To get better insight into the high diastereoselection observed, suitable crystals of compound **2** were obtained and its structure was determined by X-ray analysis, Fig. 3.‡ The compound has an overal $C_2$ symmetry with the sugars in a pseudo-axial orientation. Both sulfur atoms have an *S* absolute configuration, and the Pd–S as well as the Pd–Cl bond lengths are in the same range as the known Pd(II) complexes.




**Scheme 1**

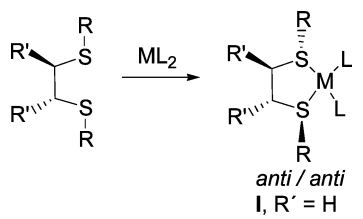



**Fig. 1**

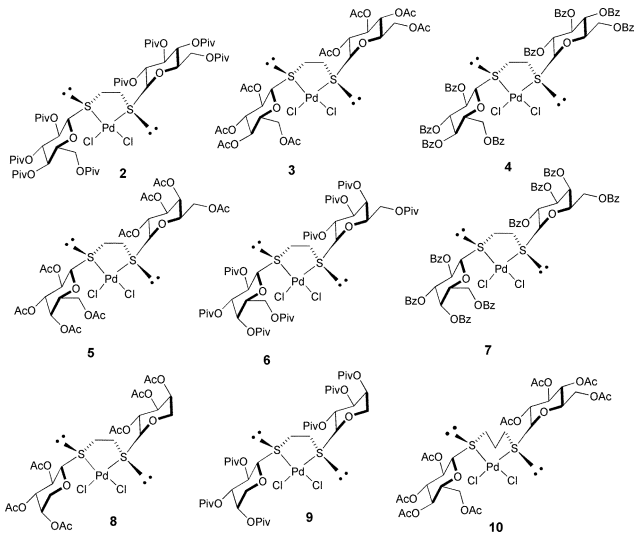



**Fig. 2**

† Electronic supplementary information (ESI) available: $^1H$, $^{13}C$, 2D COSY DQF and 2D NOESY NMR spectra. See http://www.rsc.org/suppdata/cc/b3/b313798h/

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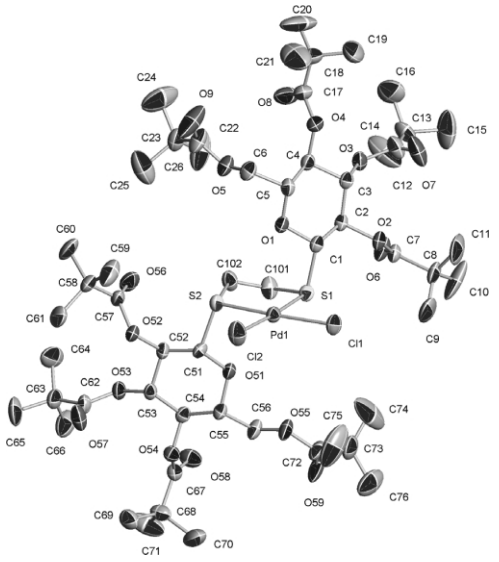
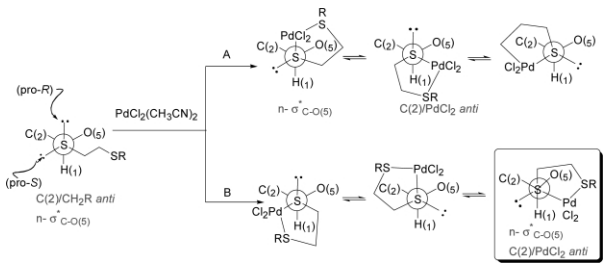



**Fig. 3** ORTEP plot for **2**.

Interestingly, the dihedral angle Pd–S1–C1–C2 = 177°, and Pd–S2–C51–C52 = 174.06°, indicates that the bulky Pd($Cl_2$) group is *anti* to the C2 and to the C52 carbons of the pyranose rings. Moreover, the ethylene group is *gauche* to the endocyclic oxygens (O1 and O51) and to carbons α to the anomeric positions (C2 and C52) of the pyranose rings. Consequently, the sulfur lone pairs are thus located *anti* to the $C_{anomeric}$–$O_{endocyclic}$ bond (C1–O1 and C51–O51). All together, this data indicates that the conformation of both pyranose rings in the complex is that of the *exo*-anomeric effect.[9] This conformation allows a stabilization by an hyperconjugative delocalisation of the sulfur lone-pairs density into the empty axial σ*CO orbitals. The formation of the five-membered ring palladacycle, with both sugars under the *exo*-anomeric conformation, brings the H-2 proton in close proximity to the methylene bridge. Accordingly, in the crystal structure of **2**, H2···H10A is 2.346 Å and H52–H10C is 2.238 Å. A 2D NOESY of the complex **2** in acetone-$d_6$ shows a strong NOE between H-2 and one of the diastereotopic methylene protons α to the sulfur atom. Therefore, it can be concluded that in solution, compound **2** also adopts the conformation with both sugar rings under the *exo*-anomeric effect.

This data indicates that it is the *exo*-anomeric effect which is responsible for the formation of a single isomer in the thioglycoside Pd(II) complexes. Accordingly, in the Newman projection of the starting bis-thioglycoside in the conformation stabilized by the *exo* anomeric effect, it can be seen that only the coordination of pro *S* lone pair to the Pd can lead to a conformation which maintains the *exo*-anomeric effect (Scheme 2).

Interestingly enough we have noticed that four of the five Pd(II) complexes of mixed ligands with a thioglucose moiety reported in the literature crystallize in the *exo*-anomeric conformation.[10] Typically, in the mixed ligand which does not crystallize under the




**Scheme 2**

*exo*-anomeric conformation, the C–S bond length is larger (1.822 Å), and the S–$C_{anomeric}$–$O_{endocyclic}$ angle is shorter (104.04°), than the other four complexes, which are in the same range as **2** [S–$C_{anomeric}$ bond (1.817, 1.791 Å), S–$C_{anomeric}$–$O_{endocyclic}$ angle (108.11 and 110.33°)]. While the *exo*-anomeric effect has been usually used to explain the relative stability of mutual orientations of the neighbouring saccharide units in oligo- and polysaccharides, its origin is still controversial.[11] The results reported here, which invokes for the first time the importance of the *exo*-anomeric effect in the stability of sugar–metal complexes, are in full agreement with the n–σ* hyperconjugative delocalisation hypothesis.

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## Notes and references

‡ *Crystal data* for compound **2**: $C_{54}H_{90}Cl_2O_{18}PdS_2$, $M_r$ = 1268.68, yellow prism (0.34 × 0.09 × 0.07 mm) from hexane–ethyl acetate, monoclinic, space group $P2_1$ (no. 4), $a$ = 15.4657(14), $b$ = 12.6196(11), $c$ = 19.2645(17) Å, $\beta$ = 108.956(2)°, $V$ = 3556.0(5) Å$^3$, $Z$ = 2, $D_c$ = 1.185 Mg m$^{-3}$, $\lambda$(Mo-Kα) = 0.71073 Å, $\mu$ = 0.452 mm$^{-1}$, $T$ = 298(2) K. X-Ray diffraction data were collected on a Bruker SMART diffractometer APEX, graphite-monochromated Mo-Kα radiation, and a Kryoflex low-temperature device. Data reduction up to $\theta$ = 30° by program the SAINT, corrections for absorption with the program SADABS, 32756 reflections measured, 16009 independent, $R_{int}$ = 0.073. Structure solution with direct methods, structure refinement on $F^2$ using the program SHELXL97. Final refinement with 16009 data, 1 restraint, and 694 parameters gave $R1$ = 0.0738, $wR2$ = 0.1314 [$I > 2\sigma(I)$], and $R1$ = 0.1801, $wR2$ = 0.1707 (all data) ($S$ = 0.953). Flack parameter $x$ = −0.03(3). CCDC 198203. See http://www.rsc.org/suppdata/cc/b3/b313798h/ for crystallographic data in CIF or other electronic format.

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