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C_2-Symmetric bis-thioglycosides as new ligands for palladium-catalyzed allylic substitutions

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Abstract—A new divergent design for the synthesis of optically pure bis-thioglycoside type **I** is reported. In only two steps a common chiral intermediate with up to eight free alcohols: two primary and six secondary is obtained. From this common intermediate a large number of ligands can be synthesized. A positional scanning like strategy has permitted the rapid discovery of an efficient catalyst for the palladium-catalyzed asymmetric allylation of malonate. Dynamic NMR spectroscopy of a Pd(II) complex has shown that there is an efficient stereochemical control of the sulfur configuration upon coordination to the palladium.

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, even though the coordinating ability of thioether donors in transition metal complexes is known.[2] In the particular case of palladium-catalyzed asymmetric alkylation,[3] there are a number of catalysts that afford excellent enantioselectivities (>90%). Nevertheless, up to now the enantioselectivities obtained using chiral S–S donor ligands are disappointedly low.[4]

An inherent characteristic of thioether ligands is that upon coordination to the metal, the sulfur atom becomes stereogenic. While the close proximity of the chirality to the coordination sphere of the transition metal may be beneficial,[5] the low inversion barrier of the sulfur metal bond may be responsible for the poor results observed.[6] Keeping this in mind, we report in this work the synthesis of C_2-symmetric bis-thioglycosides, as new ligands for palladium-catalyzed asymmetric alkylation.[7] The sugar residue was intended to provide a well-defined chiral environment, while the control of the sulfur configuration was expected due to stereoelectronic factors acting at the anomeric center. On the other hand, the high structural diversity of the natural D-sugars may allow the synthesis of both enantiomers by allylic alkylation. Our modular synthetic approach is presented in Figure 1 and is based on a parallel synthesis of a family of bis-thioglycosides, having three diversity points: the linker, the sugar residue and the protective groups.[8] The design is directed towards the evaluation of bis-thioglycosides type **I** as chiral ligands for palladium-catalyzed asymmetric substitution (Eq. (1)) and to a rapid optimization of their structure for a better enantioselectivity. In this preliminary work four variables were assigned for each of the diversity points, leading thus to a maximum of 64 bis-thioglycosides. To facilitate the synthesis of our

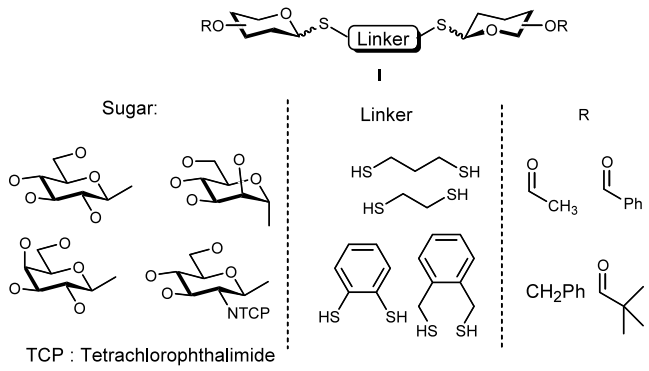

Figure 1. Ligands design.

Keywords: C_2-symmetric bis-thioglycosides; asymmetric catalysis; ligand design; parallel synthesis; carbohydrates.

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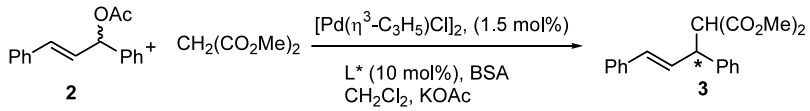
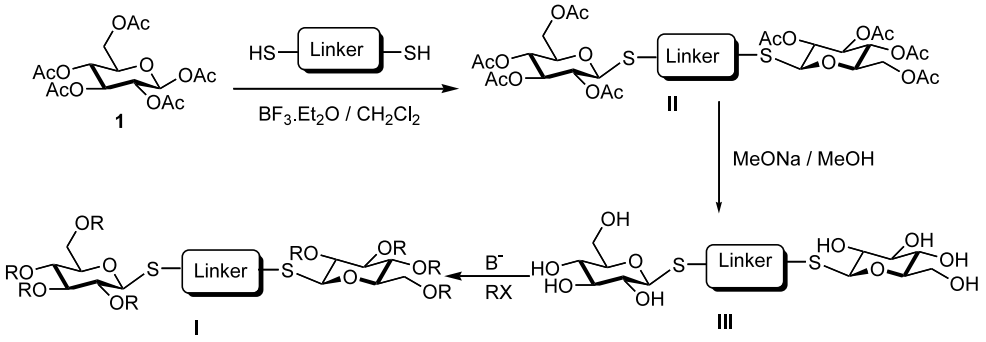


(1)

focused library, we chose a divergent approach in order to synthesize a large number of ligands from a common intermediate.[9] This approach is typified in Scheme 1 using D-glucose as the sugar residue. Condensation of the bis-thiol linker with β-D-glucose pentaacetate **1** in methylene chloride, catalyzed with $BF_3{\cdot}Et_2O$, afforded the 1,2-*trans* linked C_2-symmetric bis-thioglycoside **II**, generally in excellent yield, and with complete stereocontrol of the anomeric position (Scheme 1).[10] Zemplen deacetylation leads to a common octaalcohol **III** intermediate, which can lead to various ligands by homo or orthogonal protections of the free alcohols. In order to optimize the ligand structure for the enantioselective palladium-catalyzed allylic substitution of 1,3-diphenyl propenyl acetate **2** (Eq. (1)), we choose a positional scanning-like strategy by screening one diversity element while holding the others constant.[11]

Consequently, in the first step we fixed the sugar residue to glucose, the protective group to acetate, and we changed the linker. The results achieved with the four ligands **L1**–**L4** for the allylation of dimethyl malonate are given in Figure 2. A 10% mol of the ligand in combination with 1.5 mol% of [Pd (allyl)Cl]$_2$ in the presence of BSA and KOAc gave the best chemical yields and was used in all the runs. From this first generation of ligands it can be seen that the three carbon spacer leading to a six-membered chelate gave the product with good yield but quasi-racemic (4% ee). The two carbon spacer leading to a five-membered chelate afforded the product with a good yield and a promising 64% ee in favor of the (*S*)-**3** isomer. Surprisingly bis-thioglycoside **L-3** and **L-4** with 1,2-benzenedithiol and 1,2-benzyldithiol linkers, designed to rigidify the chelate complex intermediates with various cone angles, afforded the product with low ee's (38 and 24%, respectively). 1,2-Ethanedithiol was thus chosen as best linker and fixed, together with acetate as protective group, for the synthesis of the second generation of ligands directed to optimize the nature of the sugar residue. As can be seen from Figure 2, neither the glucosamine based ligand **L-6** with a bulky tetrachlorophthalimido (TCP) group, nor the mannose-based bis-thioglycoside **L-7** with an α-anomeric linkage,



Scheme 1. General scheme for the synthesis of C_2-symmetric bis-thioglycosides.

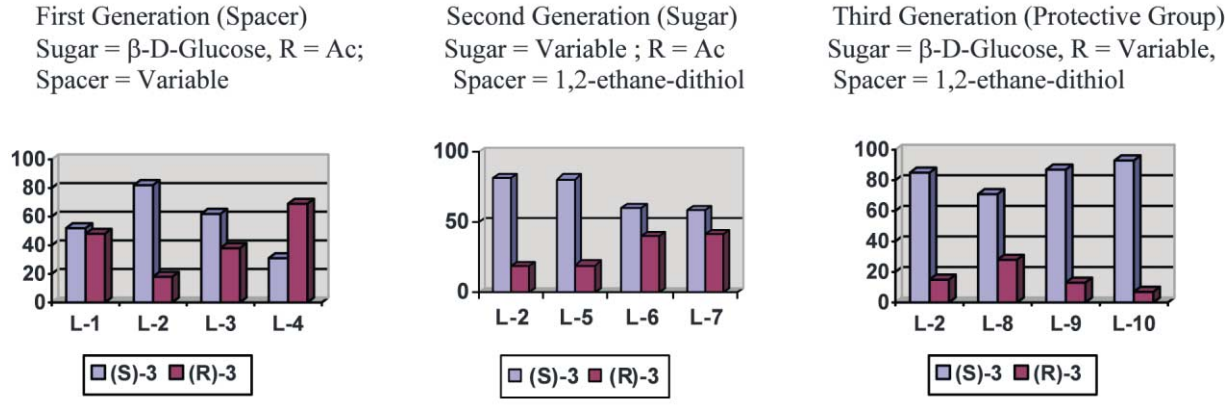
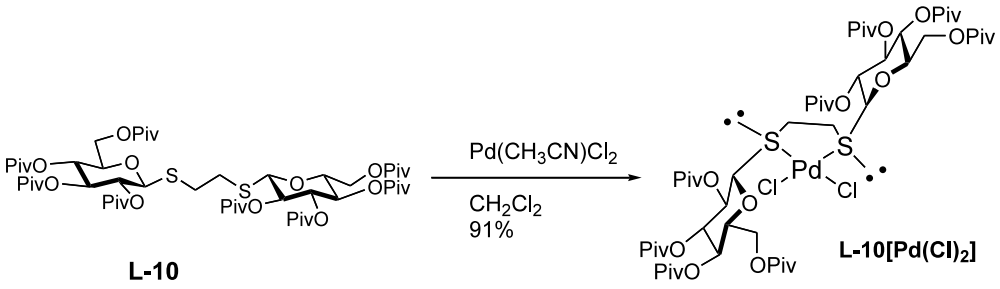


Figure 2. Ligand optimization by variation of the: (i) linker (first generation), (ii) sugar residue (second generation) and (iii) protective group (third generation). First generation: linker = 1,3-propane-dithiol (**L-1**), 1,2-ethane-dithiol (**L-2**), 1,2-benzyl-dithiol (**L-3**), 1,2-benzene-dithiol (**L-4**). Second generation, sugar = β-D-galactose (**L-5**), 2-tetrachlorophtalimido-β-D-glucose (**L-6**), α-D-mannose (**L-7**). Third generation, protective group = benzyl (**L-8**), benzoate (**L-9**), pivaloate (**L-10**).



Scheme 2.

are effective ligands, while the use of the ligand **L-5** with a β-galactose residue permits the synthesis of the final product (*S*)-**3** with 62% ee. Thus, from the second generation of ligands it can be concluded that the best sugar residue is either glucose or galactose, in combination with 1,2-ethane-dithiol as linker. These parameters were thus fixed in order to optimize the last diversity point. A simple Zemplén deacetylation of **L-2** leads to the corresponding octaalcohol as intermediate which was protected by means of benzyl chloride, benzoyl chloride, or pivaloyl chloride leading to the corresponding ligands **L8**–**L10**. **L-8**, with eight benzyl ethers, afforded (*S*)-**3** with poor selectivity (38% ee), even though the reaction rate was faster. Interestingly, replacement of acetate into benzoate, leads to a small enhancement of the enantioselectivity (72% ee), and the use of pivaloate allows the obtention of (*S*)-**3** with an excellent 86% ee at room temperature (rt) and 90% ee at 0°C. Thus, preparing and evaluating only 10 ligands from the 64 theoretical combination, the structure of the C_2-symmetric bis-thioglycoside ligand of type **I** has been optimized.

At the onset of this research was the question of the control of the configuration of the sulfur atom upon coordination to the metal. Palladium(II) complex of the **L-10** was synthesized in 91% yield by reaction with $Pd(CH_3CN)_2Cl_2$ in methylene chloride at rt (Scheme 2), and its solution dynamics determined. ^1H NMR studies **L-10**[$Pd(Cl)_2$] in CD_2Cl_2 from −80 to +50°C show that a single isomer with C_2 symmetry exists in solution, pinpointing a strong stereoelectronic bias exerted by the sugar residue on the sulfur atom. Thus, the high enantioselectivity obtained can be accounted for at least in part, by a well defined chiral pocket made possible by the coordination of a single diastereotopic *L*p of the thioglycoside to the metal.

In conclusion, we have reported a simple, modular and efficient synthetic design for the synthesis of optically pure C_2-symmetric bis-thioglycosides. This, associated with a positional scanning like strategy, allows the discovery of a new type of ligand for the palladium-catalyzed allylic alkylation and a quick optimization of its structure. The simplicity of the design predicts the utilization of the new ligands in other meta-catalyzed asymmetric transformations, while the hydrophilicity of the octaalcohol intermediates predisposes their utilization as chiral ligands for catalysis in water. These aspects are presently being actively investigated in our laboratory.

Acknowledgements

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