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Sulfur–Sulfur-Based Ligands Derived from D-Sugars: Synthesis of Pd^{II} Complexes, Application in Palladium-Catalyzed Allylic Alkylation for the Synthesis of Both Members of Enantiomer Pairs, and Structural Studies

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A divergent synthetic approach for the synthesis of optically pure bis(thioglycosides) of type **I** is reported. A common chiral intermediate with up to eight free hydroxy groups is obtained in only two steps, and from this common intermediate a large number of ligands can be synthesized. A strategy resembling positional scanning enabled the rapid discovery of an efficient catalyst for the palladium-catalyzed asymmetric allylation of malonate. Both enantiomers of the allylated product could be obtained in up to 90 % *ee* values through the use of natural D-sugars as catalyst precursors, thanks to the structural similarity of α-D-arabinose and β-L-galactose. Treatment of several C_2-symmetric bis(thioglycosides) with $[PdCl_2(CH_3CN)_2]$ always resulted in single diastereomeric Pd^{II} complexes. Dynamic NMR studies of various Pd^{II} complexes have shown that there is efficient stereochemical control over the sulfur configuration upon coordination to the palladium, as a consequence of the *exo*-anomeric effect. An explanatory model for the observed enantioselectivity based on NMR studies is discussed.

Introduction

The enormous efforts made in the area of enantioselective asymmetric synthesis[1] have resulted in the accrual of structurally diverse ligands. Nevertheless, the difficulty inherent in predicting the structural requirements of a ligand for generation of an efficient catalyst explains the need for new ligands that combine easy synthesis and high effectiveness.[2] An early analysis in this field, directed toward the restriction of diastereomeric transition states, resulted in the use of C_2 symmetry for successful ligand design.[3] However, the *trans* effect, resulting from the use of heterodonor ligands with different donor–acceptor properties of the chelating atoms, has recently demonstrated itself to be an effective means of control over the stereochemical restrictions needed for high enantioselectivity.[4]

In the case of allylic substitution – one of the most thoroughly studied chiral transformations (Figure 1) – some successful ligands including P–N[5] and P–S donors are

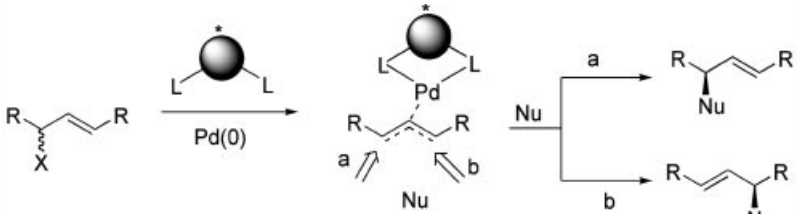

Figure 1. Palladium-catalysed allylic substitution.

products of the second approach,[6] while classical C_2-symmetrical diphosphane ligands such as binap and chiraphos are less successful.[7]

As part of our continuing interest in the synthesis and utilization of chiral sulfur compounds,[8] and in a clear analogy to the diphosphane ligands containing chiral phosphorus atoms,[9] we recently became interested in the use

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of C_2-symmetric bis(thioethers) in asymmetric catalysis[10] (Figure 2).

Figure 2. Structural similarities between metal complexes of bis(thioethers) and *P*-chiral diphosphanes.

A literature search shows that, although the coordinating ability of thioethers as donors in transition metal complexes is known,[11] only a few dithioethers have been used in allylic substitution (Figure 3).[12] Furthermore, with the exception of two examples, the enantioselectivity achieved with S–S donor ligands has been disappointedly low.[12a,13]

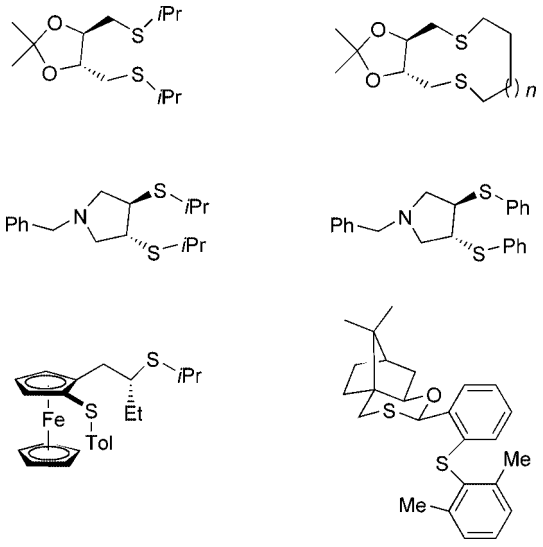


Figure 3. Some representative S/S ligands used in palladium-catalyzed asymmetric allylation.[12,13]

The sulfur atom becomes stereogenic upon coordination to the metal, and while the close proximity of the newly created chiral center to the coordination sphere of the transition metal may be beneficial, the low inversion barrier of the sulfur–metal bond may account for the low enantioselectivity observed.[14] Actually, ligands that allow efficient control – either sterically or stereoelectronically – over the sulfur–metal inversion have provided good enantioselectivities.[15] On the other hand, carbohydrates, which are amongst the cheapest and most abundant chiral starting materials, have a range of structural characteristics that make them very appealing as ligands in asymmetric catalysis.[16] Notably, carbohydrates possess various hydroxy groups in different orientations, allowing easy tuning of steric, electronic, and three-dimensional structures of carbohydrate-based ligands,[17] making them an ideal platform for molecular diversity. Conceptually, though, the utilization of carbohydrates in asymmetric synthesis is severely limited when both enantiomers are needed, as L-sugars are exceedingly expensive. While this problem has been elegantly solved by RajanBabu in the case of homodonor C_1-symmetric P–P ligands,[18] up to now there has been no solution in the case of C_2-symmetric sugar-based ligands. In order to address these problems, we report on the synthesis of S–S ligands derived from carbohydrates, a study of their Pd^{II} complexes, and their applications in palladium-catalyzed allylic alkylations. The reported design is based on a combinatorial-like approach, with three points of diversity: the linker, the sugar residue, and the protecting groups (Figure 3).[19] The sugar residue was intended to provide a cheap and well defined chiral environment, while control over the sulfur configuration was expected due to stereoelectronic factors acting at the anomeric center. The design was validated by the discovery of an efficient palladium-catalyzed asymmetric alkylation of 1,3-diphenylpropenyl acetate with dimethyl malonate. The diastereocontrol over the sulfur atom upon coordination to the palladium has been studied, and a new stereocontrol bias of the sulfur chirality based on the *exo*-anomeric effect has been discovered, and an explanation is discussed. On the other hand, the high structural diversity of natural D-sugars allows the synthesis of both enantiomers of the allylic alkylation product through the use of bis(thioglycosides) belonging to the D-series. The origin of the enantioselectivity is also discussed with the aid of NMR and X-ray studies.

Results and Discussion

Synthetic Design

The goals of the synthetic design were assessment of the efficiency of bis(thioglycosides) of type **I** as chiral ligands for palladium-catalyzed asymmetric alkylation and rapid optimization of their structures for better enantioselectivity. Accordingly, a parallel synthesis of ligands coupled with a positional scanning optimization strategy, similar to that pioneered by Hoveyda[20] and Jacobsen,[21] seemed the most promising. This strategy consists of the optimization of a single diversity element while the others are kept constant until an optimal catalyst is found. Of all the diversity points allowed by **I** we decided to vary only three of them:[22] the first one is the spacer between the two sulfur atoms, the second is the sugar itself, while the third one is the hydroxy protecting groups (Figure 4). Four variables were assigned for each of the diversity points, thus giving a maximum of 64 possible bis(thioglycosides). Accordingly, the spacers used in this study were propane-1,3-dithiol (*a*), ethane-1,2-dithiol (*b*), benzene-1,2-dithiol (*c*), and 1,2-benzenebis(methanethiol) (*d*). The selection of the spacers was directed towards the optimization of both the size (5, 6, or 7) and the conformation of the intermediate palladacycle. The four selected sugars were simply taken from the cheapest commercially available monosaccharides: glucose (*e*), mannose (*f*), galactose (*g*), and a glucosamine derivative (*h*). For the protecting groups (*i*–*l*) we chose either an ester or an ether function, with different steric and electronic characters.

To facilitate the synthesis of our focused library we chose a divergent approach, because of its facility to generate a large number of ligands from a common intermediate.[23] The key step throughout the approach is a Lewis acid-based

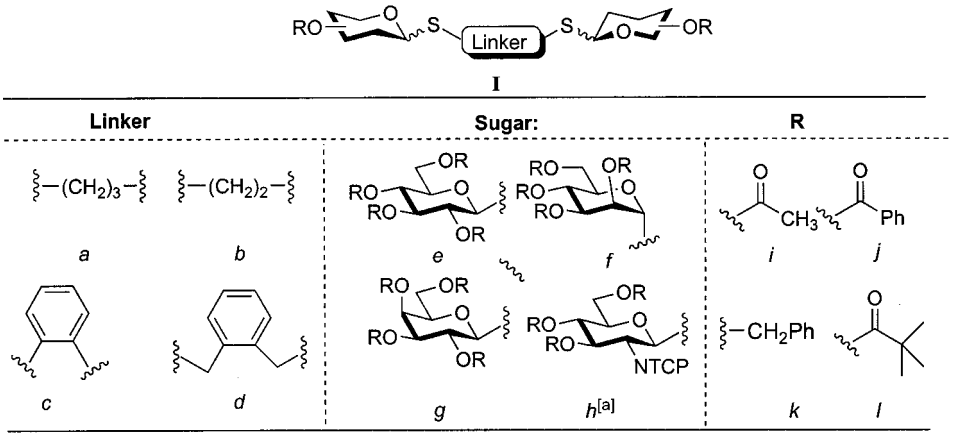
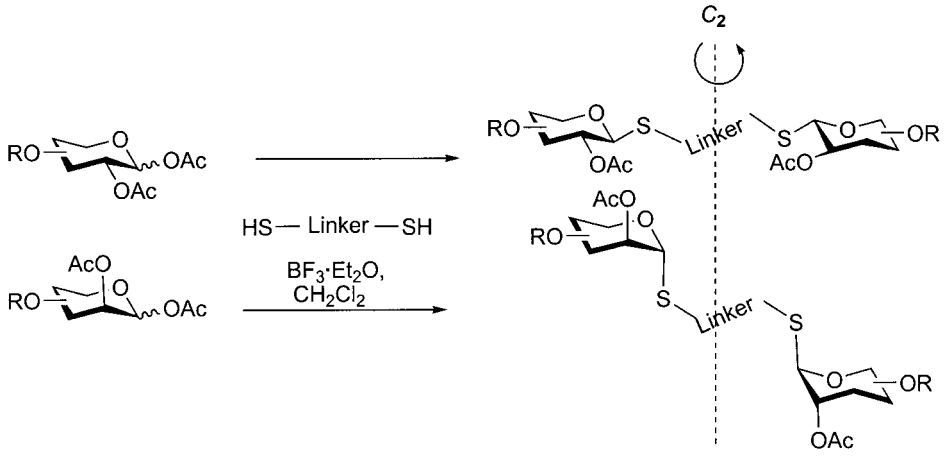


Figure 4. Ligand design. [a] TCP: tetrachlorophthalimide.



Scheme 1. Synthesis of C_2-symmetric bis(thioglycosides).

thioglycosidation with anomeric acetates as glycosyl donors (Scheme 1).[24] Condensation of a bis(thiol) linker with an anomeric glycosyl acetate in the presence of $BF_3{\cdot}Et_2O$ as catalyst afforded the 1,2-*trans*-linked C_2-symmetric bis(thioglycosides). In a simple, generally high-yielding step, the core of the ligand is built up. The desired C_2-symmetric bis(thioglycoside) was obtained with complete stereocontrol over the anomeric position regardless of the stereochemistry of the starting anomeric acetate, as a consequence of the anchimeric assistance of the participating group at C-2 (Scheme 1).

First Generation of Ligands – Optimization of the Spacer

Of the three possible beginnings allowed by our design we chose the optimization of the linker first. Accordingly, the fixed sugar and the protecting group were glucose and acetate. Condensation of 1 molar equiv. of a dithiol (*a–d*, Figure 3) with two molar equiv. of glucose pentaacetate in dichloromethane at room temperature in the presence of 4 molar equiv. of boron trifluoride afforded four bis(thioglycosides) **2**–**5** in excellent isolated yields (75–90%) (Figure 5). The four products were crystalline, allowing their easy purification either by recrystallization or by column chromatography. Compounds **2**–**5** are C_2-symmetric, as demonstrated by their ^{1}H NMR and ^{13}C NMR spectra.

Subsequently, the obtained ligands **2**–**5** were used in the allylation of dimethyl malonate by treatment with 10 mol% of ligand in combination with 1.5 mol-% of $[Pd(allyl)Cl]_2$ in the presence of BSA and KOAc. The obtained results are given in Table 1; as can be seen, bis(thioglycosides) are good ligands for the allylic alkylation catalyzed by Pd^0, as the product is always obtained in good isolated yield. With regard to the enantioselectivity, the three-carbon spacer, corresponding to a six-membered chelate, gave the quasi-racemic product **7** (4% *ee*; Table 1, Entry 1). The ligand **3** with a two-carbon spacer, corresponding to a five-membered chelate, afforded the product with a promising 64% *ee* in favor of isomer (*S*)-**7**. The bis(thioglycoside) **4**, derived from benzene-1,2-dithiol, designed to rigidify the chelate complex intermediate, afforded the product with a disappointing *ee* value of 24% (Table 1, Entry 3), probably as consequence of unfavorable steric hindrance. Surprisingly, ligand **5** with the *o*-phenylenebis(methylthio) spacer, designed to

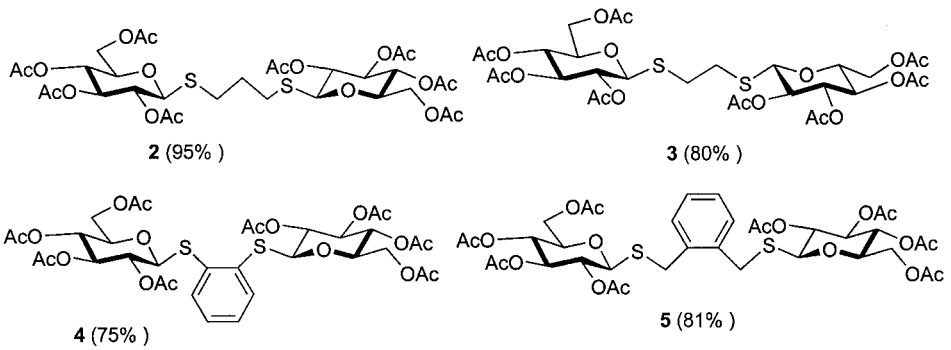
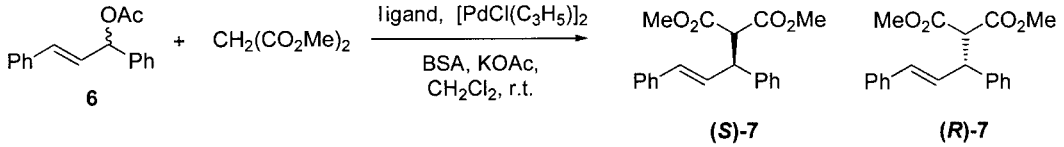


Figure 5. Structures of the bis(thioglycosides) used to optimize the spacer.

Table 1. Pd-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (**6**) with dimethyl malonate in the presence of ligands **2**–**5**.[a]



Entry	Ligand	Time (h)	Yield (%) [b]	Enantiomeric ratio [(*S*)-**7**/(*R*)-**7**][c,d]
1	**2**	237	76	52:48
2	**3**	20	97	82:18
3	**4**	68	9	62:38
4	**5**	6	98	31:69

[a] All reactions were conducted in CH_2Cl_2 in the presence of 10 mol-% of the ligand and 1.5 mol-% of $[PdCl(C_3H_5)]_2$. [b] Isolated yields. [c] Determined by HPLC on a chiral column (Chiralpack-AD). [d] (*R*) or (*S*) configurations based on specific rotation values.

alleviate the steric hindrance, afforded the opposite isomer (*R*)-**7** as the major product, albeit in a low *ee* (Table 1, Entry 4).

Second Generation of Ligands – Optimization of the Sugar

Ethane-1,2-dithiol was thus chosen as best linker and was then kept constant, together with the acetate as protecting group, for the synthesis of the second generation of ligands intended to optimize the nature of the sugar residue (Figure 6). The parallel synthesis of the three ligands **8**–**10** incorporating ethane-1,2-diyl bridges was accomplished as previously, in good chemical yield (Figure 6).

The results of the allylic alkylation of **6** in the presence of ligands **3**, **8**, **9**, and **10** are summarized in Table 2. The best ligands were **3** and **8**, derived from glucose and galactose, respectively. Ligand **8** gave the (*S*)-**7** enantiomer in the same *ee* as obtained with **3**, but in a shorter reaction time (Table 2, Entry 2). In the case of the glucosamine derivative **9**, containing a bulky tetrachlorophthalimido (TCP) group, neither the chemical yield (14%) nor the enantioselectivity (20% *ee*) were suitable (Table 2, Entry 3). In the case of the interesting mannose-based bis(thioglycoside) **10** with an α-linkage at the anomeric position, the yield was acceptable (79%), but the enantioselectivity was disappointing (18% *ee*; Table 2, Entry 4).

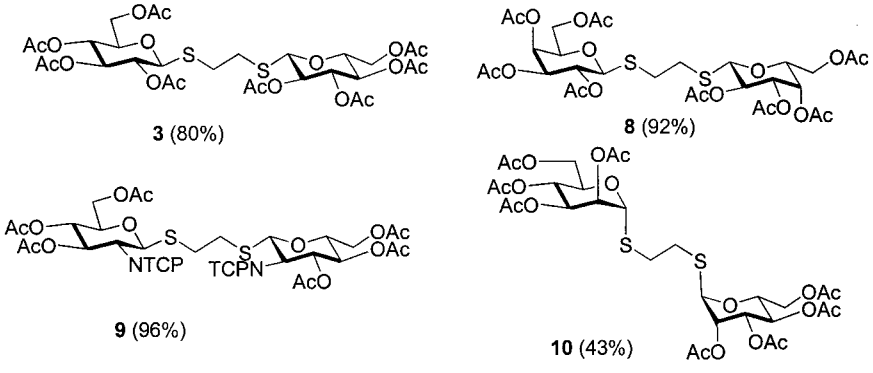
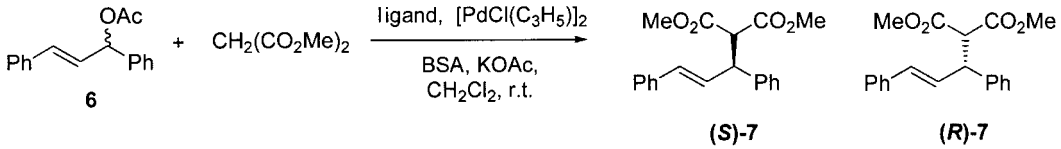


Figure 6. Structures of the bis(thioglycosides) used to optimize the sugar backbone.

Table 2. Pd-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (**6**) with dimethyl malonate in the presence of ligands **3** and **8**–**10**.[a]



Entry	Ligand	Time (h)	Yield (%) [b]	Enantiomeric ratio [(*S*)-**7**/(*R*)-**7**] [c,d]
1	**3**	20	97	82:18
2	**8**	17	98	81:19
3	**9**	48	14	60:40
4	**10**	20	79	59:41

[a] All reactions were conducted in CH_2Cl_2 in the presence of 10 mol-% of the ligand and 1.5 mol-% of $[PdCl(C_3H_5)]_2$. [b] Isolated yields. [c] Determined by HPLC on chiral column (Chiralpack-AD). [d] (*R*) or (*S*) configurations based on specific rotation values.

From the second generation of ligands it can thus be concluded that the best sugar residues are glucose and galactose, in combination with ethane-1,2-dithiol as linker. These parameters were thus fixed in order to optimize the last diversity point.

Third Generation of Ligands – Optimization of the Protecting Group

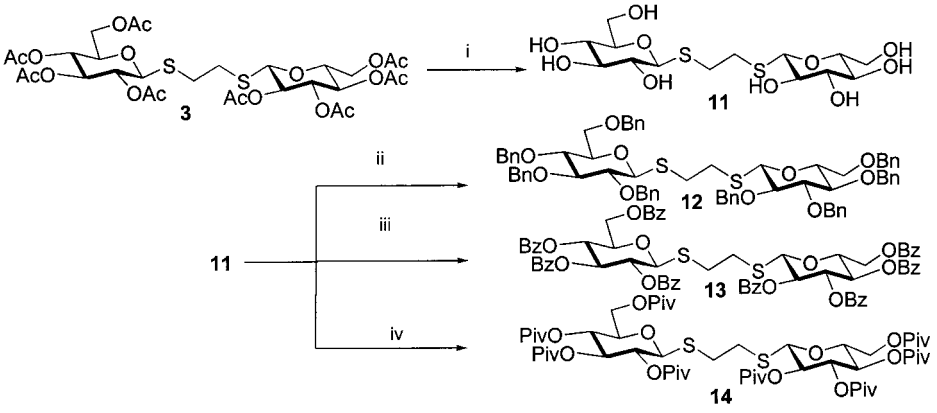
A simple Zemplén deacetylation of **3** gave the deprotected compound **11** in quantitative yield (Scheme 2). The octaol **11**, which constitutes an interesting intermediate for the synthesis of water-soluble catalysts, was used for a divergent approach with ligands **12**, **13**, and **14**.[25]

Treatment of **11** with sodium hydride and benzyl bromide in DMF afforded ligand **12** in 70% yield, whereas acylation of **11** with benzoyl chloride or with pivaloyl chloride was carried out in pyridine with a catalytic amount of DMAP to afford ligands **13** and **14** (Scheme 2) in 82% and 75% yields, respectively. The results of the catalytic reaction with the above ligands are collected in Table 3.

As can be seen, the modification of the electronic character of the protecting group from an ester function to an ether one improves the reaction rate but does not improve the *ee*. On the other hand, the modification of the steric hindrance of the protecting group has a beneficial effect on the enantioselectivity. Accordingly, the exchange of an acetate group for a benzoyl group does not induce a significant increase in the asymmetric induction (Table 3, Entry 3), but the asymmetric induction improves substantially in the case of the per-pivaloylated ligand **14**, affording an interesting 86% *ee* (Table 3, Entry 4). It is worth mentioning that this is one of the best results obtained with a C_2-symmetric S–S ligand. Selected representatives from the 64 theoretical, C_2-symmetric bis(thioglycosides) of structure **I** have thus been demonstrated to be good catalysts of the allylation of malonate – and their structures optimized – in only ten reaction steps.

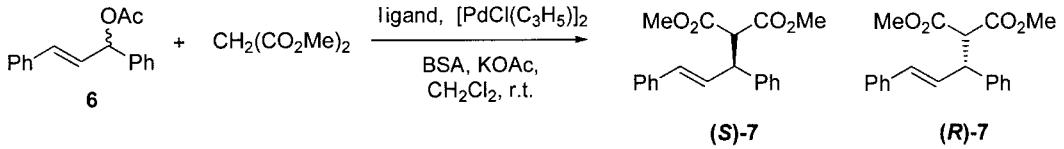
With the ligand structure optimized, the influence of the solvent and the temperature were studied; the results are collected in Table 4. A change of solvent from dichloromethane to diethyl ether provoked drops in both yield and *ee* (Table 4, Entry 2). In contrast, the use of acetonitrile allowed (*S*)-**7** to be obtained with the same *ee* as in dichloromethane but in a shorter reaction time (Table 4, Entries 1 and 3). Decreasing the temperature had a beneficial effect on the enantioselectivity, permitting the synthesis of (*S*)-**7** in 90% *ee* (Table 4, Entry 5).

The positional scanning strategy followed for the ligand optimization does not allow detection of cooperative effects of the tested variables. In order to determine that we had



Scheme 2. Synthesis of bis(thioglycosides) used to optimize the protecting group. i) MeONa, MeOH (quant.). ii) NaH, BnBr, DMF (70%). iii) BzCl, pyridine, DMAP (82%). iv) PivCl, pyridine, DMAP (75%).

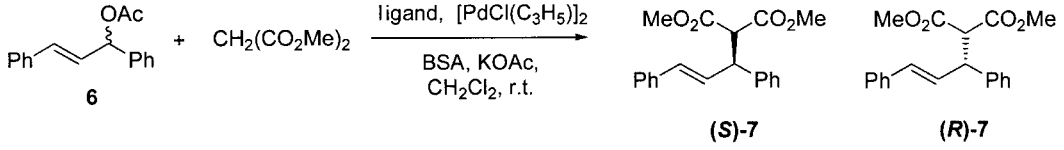
Table 3. Pd-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (**6**) with dimethyl malonate in the presence of ligands **3** and **12**–**14**.[a]



Entry	Ligand	Time (h)	Yield (%)[b]	Enantiomeric ratio [(*S*)-**7**/(*R*)-**7**][c,d]
1	**3**	20	97	82:18
2	**12**	17	98	71:29
3	**13**	24	63	83:17
4	**14**	17	83	93:7

[a] All reactions were conducted in CH_2Cl_2 in the presence of 10 mol-% of the ligand and 1.5 mol-% of $[PdCl(C_3H_5)]_2$. [b] Isolated yields. [c] Determined by HPLC on a chiral column (Chiralpack-AD). [d] (*R*) or (*S*) configurations based on specific rotation.

Table 4. Optimization of the Pd-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate (**6**) with dimethyl malonate in the presence of ligand **14**.[a]



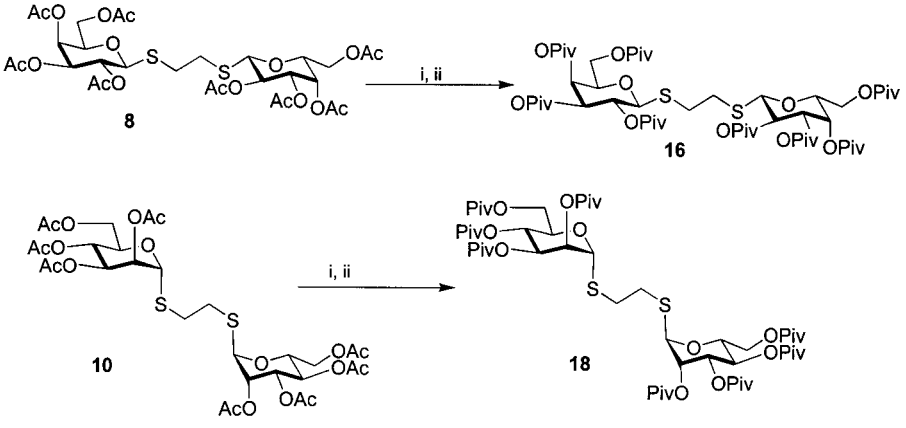
Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	Enantiomeric ratio [(*S*)-**7**/(*R*)-**7**][c,d]
1	CH_2Cl_2	25	17	97	93:7
2	Et_2O	25	24	39	83:17
3	CH_3CN	25	4	98	93:7
4	CH_3CN	0	36	72	95:5

[a] All reactions were conducted in the presence of 10 mol-% of **14** and 1.5 mol-% of $[PdCl(C_3H_5)]_2$. [b] Isolated yields. [c] Determined by HPLC on a chiral column (Chiralpack-AD). [d] (*R*) or (*S*) configurations based on specific rotation.

actually determined the (or one of the) optimal ligand(s), we synthesized ligands **16** and **18**, predicted to afford good and low selectivities, respectively (Scheme 3).

Zemplén deacetylation of ligands **8** and **10**, followed by treatment with pivaloyl chloride in pyridine in the presence of DMAP as catalyst, afforded the per-pivaloylated ligands **16** and **18** in good yields. As expected, the allylic alkylation of **6** in dichloromethane at room temp. in the presence of the aforementioned ligands afforded compound (*S*)-**7** in 88% and 28% *ee* values, respectively.

One of the major drawbacks in the use of carbohydrates as chiral auxiliaries or chiral ligands is the difficulty inherent in generating both enantiomers for a given process. Accordingly, while D-glucose is the cheapest chiral molecule in the market (€ 1.20 per mol), the price of L-glucose is prohibitive (€ 8690 per mol), ruling out its application as ligand



Scheme 3. Synthesis of bis(thioglycosides) **16** and **18**. i) MeONa, MeOH (75%). ii) PivCl, pyridine, DMAP (68%).

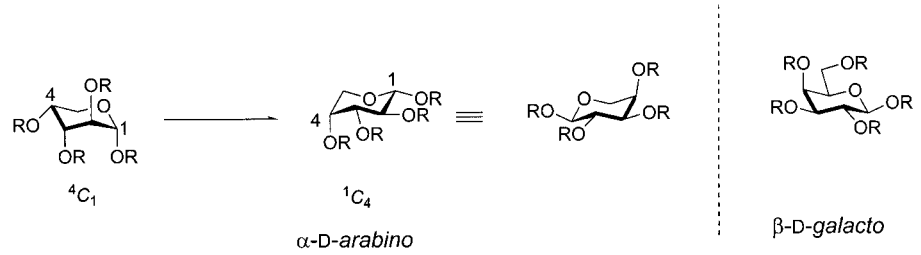
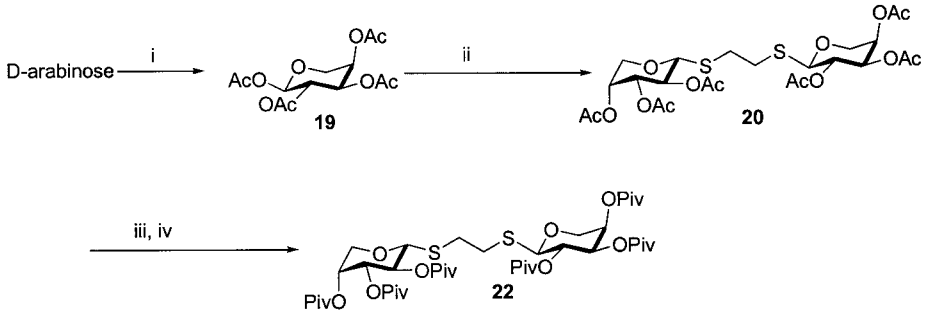
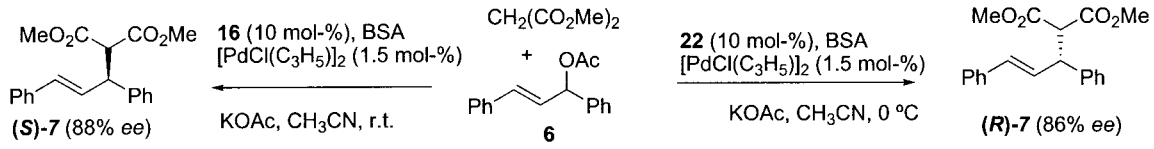


Figure 7. Structural relationship between α-D-arabinose and β-D-galactose.



Scheme 4. Synthesis of bis(thioglycoside) **22** derived from arabinopyranose. i) Ac_2O, AcONa. ii) $HSCH_2CH_2SH$, BF_3Et_2O, CH_2Cl_2. iii) MeONa, MeOH. iv) PivCl, pyridine, DMAP.



Scheme 5.

precursor even in catalytic amounts. In order to solve this problem, we made use of the similarity between some L-sugars and the stable conformations of others belonging to the D series. In this regard, it is worth mentioning that α-D-arabinose, a cheap commercially available D-pentopyranose existing mainly in the $^1C_4$ conformation, is almost a mirror image of β-D-galactose (Figure 7).[26]

We reasoned that a bis(thioglycoside) with an α-D-arabinopyranose unit as a sugar backbone, a 1,2-ethane linker, and a pivaloyl protecting group might act similarly to an enantiomer of ligand **16** and might thus provide (*R*)-**7** with good enantioselectivity. Acetylation of arabinose with acetic anhydride and sodium acetate afforded α-D-arabinose tetraacetate **19** in 64% yield. Thioglycosidation under standard conditions afforded C_2-symmetric bis(thioglycoside) **20** in 70% yield.[27] Zemplén deacetylation, followed by pivaloylation as before, afforded the desired per-*O*-pivaloylated ligand **22** (Scheme 4) in 63% yield.

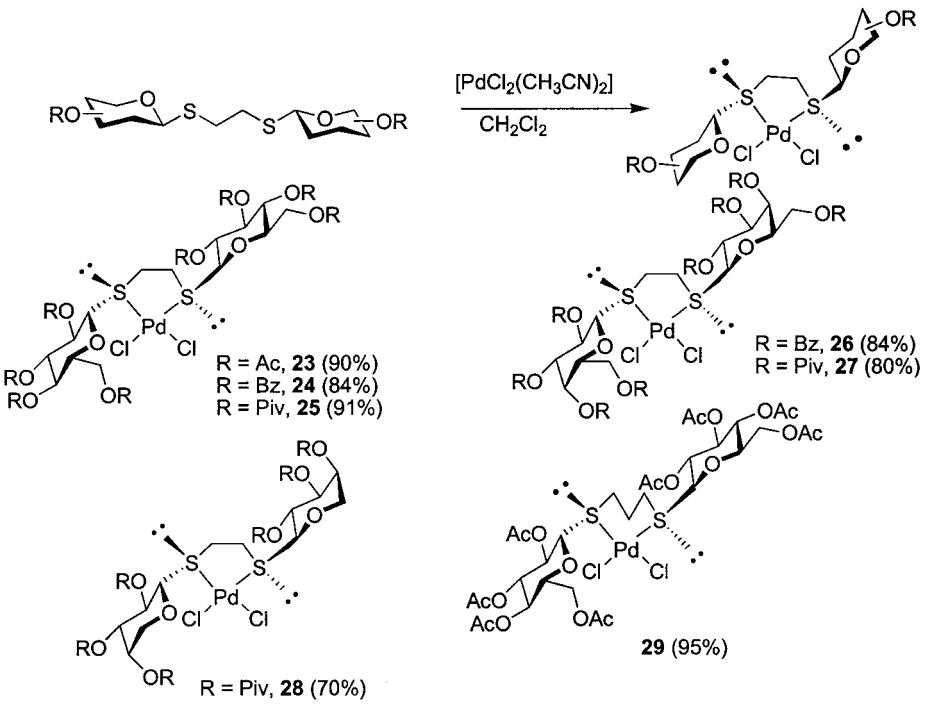
Allylic alkylation of **6** in the presence of ligand **22** afforded (*R*)-**7** in 77% *ee* in CH_2Cl_2 at r.t and in 86% *ee* in acetonitrile at 0 °C. Thus, even though they both belong to the D-series, ligands **16** and **22** behave as pseudoenantiomers in the Pd^0-catalyzed allylation of malonate (Scheme 5).

Mechanistic Considerations

The focus of this research was the question relating to control over the stereochemistry of the sulfur atom upon coordination to the metal. In order to address this query, various bis(thioglycosides) with different spacers, protecting groups, and sugar rings were treated with [$PdCl_2(CH_3CN)_2$] in CH_2Cl_2 (Scheme 6).

The reaction takes place smoothly, affording the Pd^{II} complexes as orange solids within 2–3 h and generally in high chemical yields. Upon coordination of $PdCl_2$ to the sulfur atoms, two stereogenic centers are created, and the product may exist as up to three diastereoisomers (one *syn* and two *anti*; Figure 8).

Nevertheless, in all cases the final Pd^{II} complex was obtained as a single diastereoisomer, regardless of the sugar ring, the protecting groups, and the size of the palladacycle. The formed isomer has C_2 symmetry as indicated by its ^1H NMR and ^{13}C NMR spectra, and all the prepared complexes showed similar spectroscopic behavior. Upon coordination to the palladium, the chemical shifts of protons H-2, H-3, and H-6,6′ do not change significantly, while proton H-5 and the protons α to the sulfur atom are deshielded by 0.1 ppm to 0.4 ppm. Significantly, the anomeric protons of



Scheme 6. Synthesis of bis(thioglycoside) palladium(II) complexes.

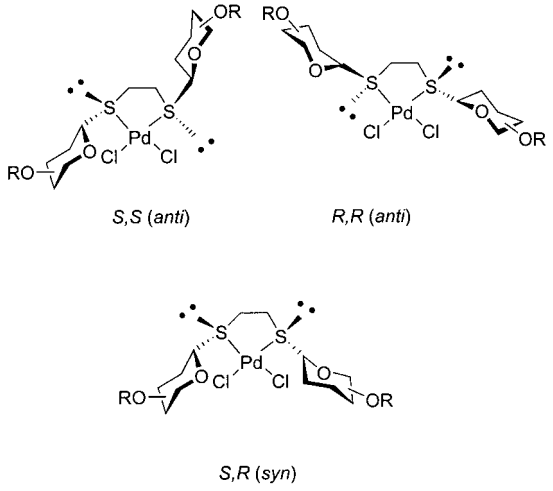


Figure 8. Possible diastereoisomers of bis(thioglycoside) Pd^{II} complexes.

the Pd^{II} complexes are highly deshielded, by 0.6 to 0.8 ppm in the case of the five-membered palladacycles (**23**–**28**) and by up to 1 ppm in the case of the six-membered palladacycle **29**. In the ^{13}C NMR spectra the most significant change corresponds to the deshielding of the carbon α to the sulfur atom by 3 to 4 ppm.

While the C_2 symmetry points to the formation of an *anti* structure, this may be either a single isomer or a mixture of both *anti* diastereoisomers in fast equilibrium. In order to assess the stereochemical ratio in solution, a dynamic NMR study was carried out on the five-membered palladacycles **23** and **25** (see Supporting Information). In neither case was any other isomer detected throughout the temperatures range tested (+50 °C to –80 °C), confirming the formation of a single *anti* diastereomer. Similar results were obtained with the six-membered paladacycle **29**, indicating generality in the stereochemical outcome of the formation of the bis-(thioglycoside)-Pd^{II} complexes. Taking account of the low inversion barrier of the S–Met bond (15–20 kcal mol^{-1}) and of the fact that a priori there is no sterochemical bias controlling the sulfur stereochemistry, the formation of a single bis(thioglycoside) Pd^{II} complex was unexpected.

X-ray analysis of complex **25** shed light on the origin of the stereochemical outcome of the reaction.[28] Compound **25** has an overall C_2 symmetry with the sugars in a pseudoaxial orientation, while the sulfur atoms both have (*S*) absolute configurations. Interestingly, the bulky $Pd(Cl_2)$ group is *anti* to the C2 and to the C2′ carbons (carbohydrate numbering) of the pyranose rings. Moreover, the ethylene group, which is *gauche* to the endocyclic oxygens (O5 and O5′) and to the carbons α to the anomeric positions (C2 and C2′) of the pyranose rings, allows the location of the sulfur lone pairs *anti* to the C_1–$O_{endocyclic}$ bond (C1–O5 and C1′-O5′; Figure 9).

These data are indicative that the conformations of both pyranose rings in the complex are those corresponding to the *exo*-anomeric effect.[29] It is worth mentioning that in this conformation there is stabilization through hyperconjugative delocalization of the sulfur lone-pair density into the empty axial σ*CO orbital. Nonetheless, the conformation of the complex in the solid state may differ from that in solution, which is of interest for the reaction mechanism. On constructing molecular models of 1,2-*trans* diequatorial bis(thioglycoside) Pd^{II} complexes such as **25**, with both

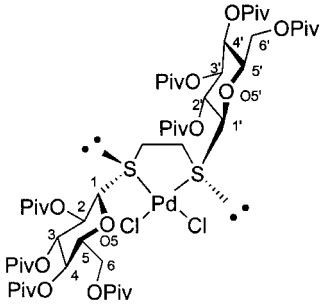


Figure 9. Numbering system for compound **25**.

sugars in the *exo*-anomeric conformation, we have noticed that the H-2 protons and the methylene bridge are in close proximity. Accordingly, in the crystal structure of **25**, the distance between H-2 and one of the diastereotopic methylene protons α to the sulfur atom (Pro-*R* proton) is around 2.3 Å, and this distance can therefore be used as an NMR marker to determine the 3D shape of the Pd^{II} complex **25** in solution by 2D NOESY experiments. Nevertheless, neither the usually used deuterated chloroform nor deuterated dichloromethane were suitable for such NMR experiment, as H-2 and H-4 have the same chemical shifts (δ = 5.1 ppm). Fortunately, after trying different solvents, we found [D_6]acetone to be the best. Accordingly, in this solvent, not only do all the pyranose protons have different chemical shifts, but there is also an increase in the nonequivalence of the diastereotopic protons vicinal to the chelated sulfur atom ($\Delta\nu$ = 150 Hz). A 2D NOESY of the complex **25** in [D_6]acetone shows NOE contacts between H1–H3, H1–H5, and H3–H5, characteristic of a $^4C_1$ conformation of the glucopyranose ring. Interestingly, a strong NOE contact between H-2 and only one of the diastereotopic methylene protons α to the sulfur atom has also been detected (see Supporting Information). This result indicates that the major conformation of complex **25** in solution is that in which both sugar rings adopt the *exo*-anomeric conformation.

In view of these results, and in order to explain the highly diastereoselective formation of the Pd^{II} complexes, it is necessary to determine the stable equilibrium conformation of the starting thioglycoside. The few conformational studies carried out on thiosaccharides have shown by means of NMR (NOE) and molecular mechanics calculations that the stable conformations of thiocellobiose at equilibrium are those reflecting the *exo*-anomeric effect.[30] Additionally, in studies on sulfinyl glycosides we and others have recently invoked the *exo*-anomeric conformation in thioglycosides in order to explain their reactivity towards electrophiles.[31,32] On the basis of these assumptions, we propose that the conformation of the starting bis(thioglycoside) is that consistent with the *exo*-anomeric effect (Figure 10). In this conformation, the Pro-*R* lp (lone pair) is in a 1,3-diaxial disposition with regard to H-2 and the O-5 lp. Accordingly, it is the Pro-*S* lp of the sulfur atom *anti* to the C1–O5 bond that is positioned for an n–σ* hyperconjugative delocalization invoked as the origin of the *exo*-anomeric effect. Taking into account that, upon complexation to the palladium atom, the bulkier group is no longer the CH_2R chain but the $PdCl_2$ group, only the pro-*S* lone pair coordination can produce a conformation that maintains the *exo*-anomeric effect (pathway B, Figure 10). It is worth remarking that in the final complex it is the former Pro-*R* lp that is located *anti* to the C1–O5 bond and can thus undergo an n–σ* hyperconjugative delocalization (Figure 10).

Interestingly enough, a CCDC search showed that four of the five crystal structures of Pd^{II} complexes of mixed ligands with a thioglucose moiety reported in the literature crystallize in the *exo*-anomeric conformation.[33] Since its discovery by Lemieux four decades ago, the *exo*-anomeric effect has been a permanent area of debate and controversy.[34,35] The recent discovery that oligosaccharides play a prominent role in significant biological events such as cell–cell adhesion, bacterial recognition, and viral infection has increased the interest in understanding the origin of the *exo*-anomeric effect. The results reported here, which for the first time invoke the importance of the *exo*-anomeric

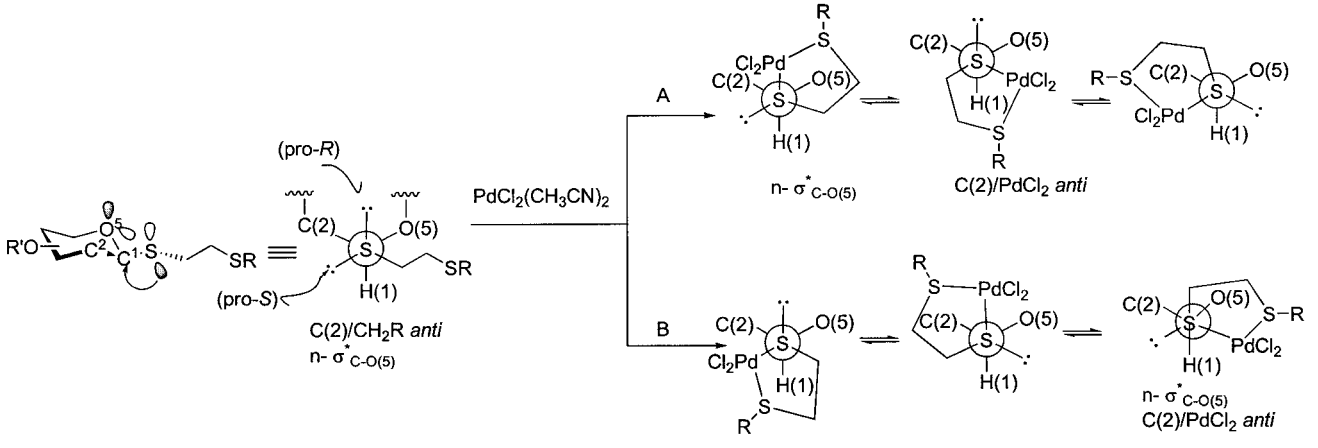


Figure 10. The role of the *exo*-anomeric effect in the stability of bis(thioglycoside) Pd^{II} complexes.

effect in the stability of sugar–metal complexes, are in full agreement with the n–σ* hyperconjugative delocalization hypothesis.

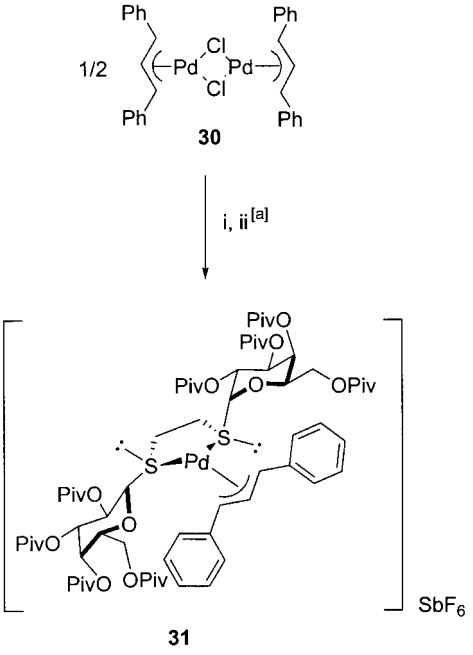
Possible Origin of the Enantioselectivity

The formation of the single isomeric Pd^{II} complexes of the bis(thioglycoside) ligands, while necessary, is not sufficient for achieving good enantioselectivity in the Pd^0 asymmetric allylation of malonate. Accordingly, ligands **2**, **8**, and **13** gave only moderately selective catalysts, even though their reactions with $[PdCl_2(CH_3CN)_2]$ afforded single Pd^{II} complexes. This result was anticipated, and can be explained in terms of the transition state intermediate in the allylic alkylation reaction. Mechanistic studies have shown that soft nucleophiles such as malonate anion directly attack one of the two terminal carbons of the allyl moiety from the face opposite the coordinated palladium atom,[36] so the site of the formation of the new asymmetric center is far from the chiral ligand, precluding high enantioselectivity. In recent years, however, different approaches to circumvent this obstacle have been designed, and a number of ligands did indeed afford high enantioselectivities (>90%). In the case of bidentate ligands, the mechanistic justifications for the observed selectivity are summarized in Figure 11.

These mechanistic justifications involve: *a*) the action of a pendant group to direct the nucleophilic attack on one of the allylic termini,[38] and *b*) the role, in the case of mixed ligands, of electronic interactions such as the *trans* effects to differentiate between both termini,[39] together with the operation of steric effects acting either at an early transition state (*c*), or at a late transition state (*d*).[40] In the case of C_2-symmetric ligands both mechanisms (*c*) and (*d*) have been advanced to account for the observed selectivity. Mechanism (*c*) is based on intramolecular steric effects and the attendant charge separation in the Pd–C bonds of the π-allyl termini. Mechanism (*d*), which assumes that the reaction has a late transition state, is based on the relative stabilities of the intermediate Pd(π)–olefin π complexes resulting from the addition of the nucleophile to the π-allyl complexes.

In enantioselective palladium-catalyzed allylic substitution reactions, analysis of ground state properties of intermediates has been successfully used to predict the sense, if not the absolute value, of the enantioselectivity.[41] In this connection, NMR methods have been widely used. The analysis of data from 1-D and 2-D homo and heteronuclear NMR experiments giving both scalar (*J*) and space correlation (NOE) information can provide a clear picture of the 3D shape of the intermediate Pd complexes in solution.

We undertook the detailed NMR study of the solution structure(s) of bis(thioglycoside) complex **31** – [Pd(η³-PhCHCHPh)-**16**]SbF_6 – in order to determine its dynamics and to understand the origin of the enantioselectivity. The complex **31** was prepared in quantitative yield according to Scheme 7. Its ^1H and ^{13}C NMR spectra show that complex **31** exists in solution as a single diastereoisomer. The molecule has lost its C_2 symmetry, and the sugar part resembles that of a disaccharide. In order to carry out further structural studies on the molecule, we first assigned all the protons of the chiral ligands and the allyl moiety by use of different NMR experiments (COSY, TOCSY, HETCOR). The use of 1D-TOCSY at different mixing times allowed us to identify the protons belonging to pyranoses *A* and *B* (Figure 12). With all the protons assigned, the 3D shapes



Scheme 7. Synthesis of Pd-allyl complex **31**. [a] (i) **16**, CH_2Cl_2, MeOH; (ii) $AgSbF_6$.

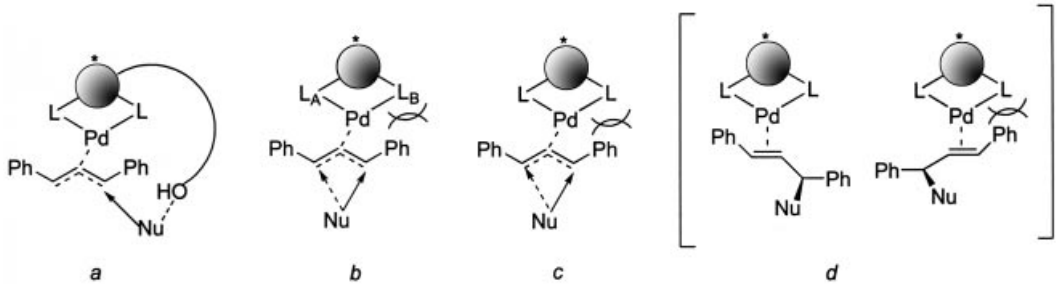


Figure 11. Models proposed to explain the enantioselectivity observed in the Pd^0-catalyzed allylic substitution.[37]

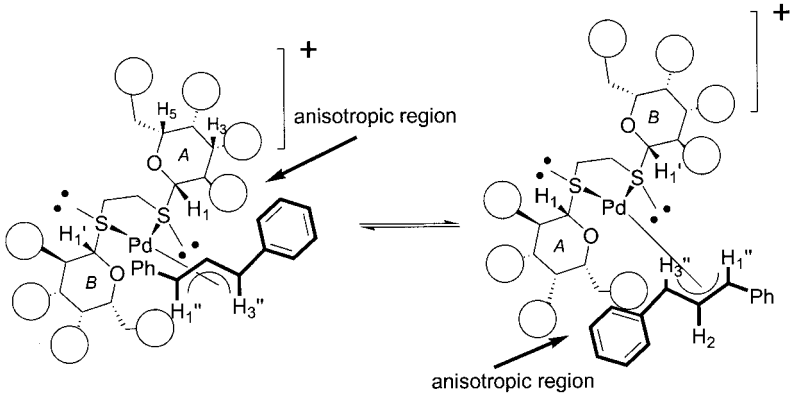
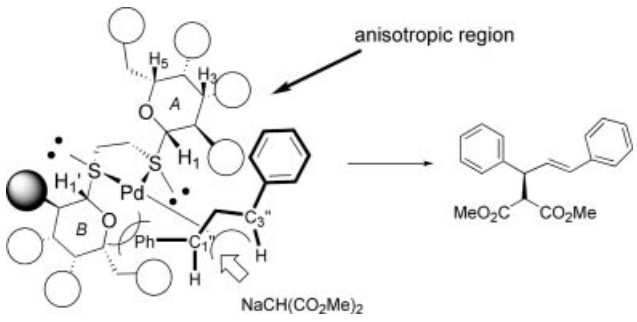


Figure 12. Dynamics of the Pd-allyl complex **31**.

and the dynamics of the molecule were determined by 2D NOESY experiment. From $^3J_{H1'',H2''}$ (12 Hz), which indicates the *anti* disposition of H1′′ and H2′′, and from the strong NOE contact between H1′′/H3′′, we conclude that the allyl moiety of the complex has a *syn /syn* geometry. Both the coupling constant around the pyranose ring ($^3J_{H1,H2}$ = $^3J_{H2,H3}$ = 10 Hz) and the NOE contact (between H1, H3, and H5) are indicative of $^4C_1$ conformations of the sugars. Surprisingly, while one of the anomeric protons is at 4.2 ppm, the other one is at higher field (δ =2.1 ppm), an unusual chemical shift for an acetallic proton. We explain this as a consequence of the anisotropy due to the proximity of an aromatic ring. Additionally, both protons H-3 and H-5 of the same spin system are shielded by 0.60 ppm and 0.75 ppm respectively. These data indicate that the whole α-face of one of the sugars is facing one of the aromatic rings of the allyl moiety. The 2D-NOESY spectrum (0.8 s) at room temperature shows interesting dynamics of the molecule. There are various NOE contacts with positive signs indicative of a chemical exchange.

These positive NOEs are between H1/H1′, H2/H2′, H3/H3′, H4/H4′, H5/5′, and H6a,6b/H6′a,6′b. This indicates that at room temperature there is an equilibrium in which one pyranose ring interchanges into another. Taking into account that the studies on Pd^{II} complexes have shown that there is no sulfur inversion, the observed dynamics must be attributed to the dynamics of the allyl moiety. Accordingly, the allyl flip from a W to an M conformation interchanges the pyranose ring *A* into ring *B* and vice-versa (Figure 12). These dynamics are active at temperature as low as –50 °C but are blocked at –78 °C. In respect to the enantioselectivity of the process, the formation of (*S*)-**7** as the major enantiomer in the M conformation indicates that the nucleophilic attack is taking place at the allylic carbon distant from the anisotropic region: C1′′ (Scheme 8). Taking into account that the allyl moiety in the complex is most probably rotated,[42] the most significant nonbonding interactions in the π-allyl complex intermediate seem to be those between the phenyl ring at $C_{1''}$ and one or more protective groups, probably $C_{2'}$–OR. Although more data are needed in order to ascertain the exact origin of the enantioselectivity, the model presented in Scheme 8 is in accordance with the experimental results, relating the enantioselectivity with the steric hindrance of the protecting groups and not the nature of the pyranose ring. Therefore, the larger the substituent at the C_2–OH, the more significant is the $C_{2'}$–OR/phenyl ring nonbonding interaction, and the more favored is the attack at C1′′ affording (*S*)-**7** with high *ee*.



Scheme 8. Possible reaction pathway in the allylic alkylation of **6** in the presence of C_2-symmetric bis(thioglyosides) as ligands.

In conclusion, we report a simple, modular, and efficient synthetic approach for the synthesis of new homodonor sulfur–sulfur ligands, based on the use of carbohydrates as cheap starting materials. A strategy similar to positional scanning enabled the discovery of a new type of ligand for the palladium-catalyzed allylic alkylation and a quick optimization of its structure. X-ray analysis and dynamic NMR studies of various bis(thioglycoside)-Pd^{II} complexes demonstrated that there is efficient stereochemical control over the sulfur configuration upon coordination to the palladium both in solution and in the solid state. The high stereocontrol over the sulfur-metal stereochemistry is the result of n–σ* hyperconjugative delocalization, namely the *exo*-anomeric effect.

On the other hand, both enantiomers of the allylated product **7** have been obtained with the use of natural D-sugars as catalyst precursors, thanks to the structural similarity of α-D-arabinose and β-L-galactose. The synthetic simplicity of the ligands, associated with the high stereocontrol over the stereogenic sulfur atom, makes us optimistic about the behavior of the new ligands in other metal-cata-

lyzed asymmetric transformations. These aspects, as well those directed toward the determination of the exact mechanism of the reported system, are currently being actively investigated in our laboratory and will be reported in due courses.

Experimental Section

General Methods: All reactions were run under dry argon in oven-dried glassware and with freshly distilled and dried solvents. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. TLC was performed on silica gel GF254 (Merck) with detection by charring with phosphomolybdic acid/EtOH. For flash chromatography, silica gel (Merck, 230–400 mesh) was used. Columns were eluted with positive air pressure. Chromatographic eluents are given as volume to volume ratios (v/v). NMR spectra were recorded with Bruker AMX 500 (^{1}H, 500 MHz) and Bruker Avance DRX 500 (^{1}H, 500 MHz) spectrometers. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Routine spectra were referenced to the residual proton or carbon signals of the solvent. High-resolution mass spectra were recorded on a Kratos MS-80RFA 241-MC apparatus. Optical rotations were determined with a Perkin–Elmer 341 polarimeter.

1,2,3,4,5-Penta-*O*-acetyl-β-D-glucopyranose (**1**) and 1,2,3,4,5-penta-*O*-acetyl-β-D-galactopyranose were purchased from Aldrich, whilst 1,2,3,4,5-penta-*O*-acetyl-D-manopyranose, 1,2,3,4-tetra-*O*-acetyl-D-arabinoopyranose,[43,44] and 1,3,4,5-tetra-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-D-glucopyranose[45] were prepared according to published procedures.

General Procedure for the Synthesis of Peracetylated Bis(thioglycosides): $BF_3{\cdot}Et_2O$ (4 molar equiv.) was added at room temperature to a solution (0.5 M) of a peracetylated glycopyranose (1 molar equiv.) and the corresponding thiol (0.5 molar equiv.) in dichloromethane. Once the TLC analysis of a diluted aliquot of the reaction mixture showed the total consumption of the starting material, the mixture was diluted with dichloromethane and was washed successively with saturated aqueous sodium hydrogencarbonate ($NaHCO_3$) and brine. The organic layer was dried (Na_2SO_4) and concentrated, giving the desired compound almost pure. Analytically pure compound can be obtained either by column chromatography or by recrystallization.

1,3-Propanediyl Bis(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside) (2): White solid, recrystallized from CH_2Cl_2/hexanes (95%): m.p. 196–197 °C. $[a]_D^{20}$ = –29.2 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.18 (t, *J* = 9.4 Hz, 2 H), 5.04 (t, *J* = 9.8 Hz, 2 H), 4.99 (t, *J* = 9.7 Hz, 2 H), 4.46 (d, *J* = 10.0 Hz, 2 H), 4.21 (dd, *J* = 12.3, *J* = 4.8 Hz, 2 H), 4.11 (dd, *J* = 12.3, *J* = 1.8 Hz, 2 H), 3.70–3.67 (m, 2 H), 2.81–2.77 (m, 2 H), 2.72–2.67 (m, 2 H), 2.06 (s, 6 H), 2.03 (s, 6 H), 1.99 (s, 6 H), 1.98 (s, 6 H), 1.87 (t, *J* = 7.14 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 170.2, 169.4, 169.3, 83.6, 75.9, 73.8, 69.8, 68.3, 62.1, 29.8, 28.8, 20.8, 20.7, 20.6, 20.6 ppm. HRMS: calcd. for $C_{31}H_{44}NaO_{18}S_2$ [*M* + Na]$^+$ 791.1867; found 791.1894 (–3.4 ppm).

1,2-Ethanediyl Bis(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside) (3): White solid, recrystallized from CH_2Cl_2/hexanes (80%): m.p. 212–213 °C. $[a]_D^{20}$ = –39.3 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.23 (t, *J* = 9.4 Hz, 2 H), 5.09 (t, *J* = 9.7 Hz, 2 H), 5.02 (t, *J* = 9.5 Hz, 2 H), 4.54 (d, *J* = 10.0 Hz, 2 H), 4.24 (dd, *J* = 12.4 Hz, *J* = 4.8 Hz, 1 H), 4.16 (dd, *J* = 12.4 Hz, *J* = 2.3 Hz, 1 H), 3.93 (m, 1 H), 3.74 (m, 2 H), 2.93 (m, 2 H), 2.09 (s, 3 H), 2.06 (s, 6 H), 2.04 (s, 6 H), 2.02 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 170.2, 169.4 and 169.4, 83.4, 76.0, 73.8, 69.8, 68.2, 62.0, 30.4, 29.7, 20.8, 20.7, 20.6 ppm. HRMS: $C_{30}H_{42}O_{20}NaS_2$ [*M* + Na]$^+$: 809.1603; found 809.1609 (–6.1 ppm).

1,2-Phenylene Bis(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside) (4): White solid, purified by column chromatography (ethyl acetate/hexanes, 1:2) (30%); m.p. 64–66 °C. $[a]_D^{20}$ = –79.7 (*c* = 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.53 (dd, *J* = 5.8, *J* = 3.4 Hz, 2 H), 7.27–7.25 (br. s, 2 H), 5.23 (t, *J* = 9.4 Hz, 2 H), 5.09 (t, *J* = 9.9 Hz, 4 H), 4.71 (d, *J* = 10.1 Hz, 2 H), 4.24 (dd, *J* = 12.3, *J* = 5.6 Hz, 2 H), 4.12 (dd, *J* = 12.2, *J* = 1.7 Hz, 2 H), 3.73–3.70 (m, 2 H), 2.10 (s, 6 H), 2.07 (s, 6 H), 2.02 (s, 6 H), 2.00 (s, 6 H) ppm. ^{13}C NMR: ($CDCl_3$, 125 MHz): δ = 170.5, 170.1, 169.6 and 169.4, 135.7, 132.2, 128.4, 85.3, 75.7, 73.8, 69.8, 68.3, 62.2, 20.7, 20.6, 20.5 ppm. HRMS: [*M*]$^+$ calcd. for $C_{34}H_{42}O_{18}S_2$: 802.1813 [*M*]$^+$; found 802.1834 (–2.7 ppm).

α,α′-*o*-Xylylene Bis(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside) (5): White solid, purified by column chromatography (ethyl acetate/hexanes, 1:2) (81%): m.p. 63–65 °C. $[a]_D^{20}$ = –88.9 (*c* = 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.26–7.22 (m, 4 H), 5.13 (t, *J* = 9.2 Hz, 2 H), 5.06 (t, *J* = 9.5 Hz, 2 H), 5.03 (t, *J* = 9.6 Hz, 2 H), 4.30 (d, *J* = 10.0 Hz, 2 H), 4.24 (dd, *J* = 12.3 and 5.1 Hz, 2 H), 4.13 (dd, *J* = 12.3, *J* = 2.1 Hz, 2 H), 4.01 (s, 4 H), 3.61–3.58 (m, 2 H), 2.01 (s, 6 H), 2.0 (s, 6 H), 1.99 (s, 6 H), 1.98 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.6, 170.2, 169.4, 169.3, 135.3, 131.1, 127.9, 82.0, 75.8, 73.8, 69.8, 68.4, 62.2, 30.9, 20.8, 20.6, 20.5 ppm. HRMS: [*M* + 1]$^+$ calcd. for $C_{36}H_{46}NaO_{18}S_2$ [*M* + 1]$^+$: 853.2023; found 853.2036 (–1.5 ppm).

1,2-Ethanediyl Bis(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside) (8): White solid (92%): m.p. 53–55 °C. $[a]_D^{20}$ = –22.4 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.42 (d, *J* = 2.9 Hz, 2 H), 5.21 (t, *J* = 9.9 Hz, 2 H), 5.05 (dd, *J* = 10.0 Hz, *J* = 3.3 Hz, 2 H), 4.52 (d, *J* = 9.9 Hz, 2 H), 4.13 (dd, *J* = 6. 63 Hz, *J* = 4.0 Hz, 2 H), 4.10 (dd, *J* = 6.6 Hz, *J* = 2.2 Hz, 2 H), 3.97–3.96 (m, 2 H), 3.06–3.0 (m, 2 H), 2.92–2.86 (m, 2 H), 2.15 (s, 6 H), 2.06 (s), 2.03 (s), 1.97 (s) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.3, 170.2, 170.0 and 170.0, 84.1, 74.5, 71.7, 67.2, 67.1, 61.4, 30.8, 20.8, 20.7, 20.5. HRMS [*M* + 1]$^+$ calcd. for $C_{30}H_{42}O_{18}S_2$: 754.1813 [*M* + 1]$^+$; found 754.1809 (δ = 0.5 ppm).

1,2-Ethanediyl Bis(2,3,4,6-tetra-*O*-acetyl-2-tetrachlorophthalimido-1-thio-2-deoxy-β-D-glucopyranoside) (9): White solid (96%): m.p. 132–135 °C. $[a]_D^{20}$ = +54.12 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.73 (t, *J* = 9.6 Hz, 2 H), 5.38 (d, *J* = 10.6 Hz, 2 H), 5.19 (t, *J* = 9.7 Hz, 2 H), 4.35–4.31 (m, 4 H), 4.19 (dd, *J* = 12.4 Hz, *J* = 1.7 Hz, 2 H), 3.94–3.91 (m, 2 H), 3.02–2.98 (m, 2 H), 2.86–2.81 (m, 2 H) 2.10 (s, 6 H), 2.03 (s, 6 H), 1.9 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.7, 170.4, 169.3, 163.2, 162.6, 140.8, 140.6, 130.1, 127.1, 126.9, 80.1, 76.0, 71.4. 68.5, 62.1, 54.2, 29.6, 20.8, 20.6, 20.5 ppm. HRMS calcd. for $C_{42}H_{36}{}^{35}Cl_8N_2NaO_{18}S_2$ [*M* + Na]$^+$: 1222.8810; found 1222.8845 (–2.8 ppm).

1,2-Ethanediyl Bis(2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-manopyranoside) (10): White solid, purified by column chromatography (ethyl acetate/hexanes, 1:2) (43%): m.p. 110–112 °C. $[a]_D^{20}$ = +91.3 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.28–5.17 (m, 8 H), 4.35–4.31 (m, 2 H), 4.26 (dd, *J* = 12.2 Hz, *J* = 5.7 Hz, 2 H), 4.07 (d, *J* = 12.3 Hz, 2 H), 2.89 (br. s, 4 H), 2.13 (s, 6 H), 2.06 (s, 6 H), 2.02 (s, 6 H), 2.00 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.5, 169.9, 169.8 and 169.7, 83.2, 70.9, 9.3, 69.3, 66.2, 62.5, 32.0, 20.8, 20.7, 20.6, 20.5.

General Procedure for the Zemplén Deacetylation of Peracetylated *C*$_2$-Symmetric Bis(thioglycosides): A catalytic amount of a freshly

prepared solution of MeONa in MeOH (1 M, 0.1 equiv.) was added to a suspension of the peracetylated bis(thioglycoside) in dry methanol (0.1 M). The solution was stirred at room temperature until total consumption of the starting material (indicated by the total dissolution of the suspension) and was then neutralized with acidic resin (Amberlyst IR 120) and filtered, and the solvents were evaporated. The polyol, obtained generally as a white powder, was used in the next reaction without further purification.

1,2-Ethanediyl Bis(1-thio-β-D-glucopyranoside) (11): This compound was obtained from **3** as a white powder (93%): $[a]_D^{20}$ = –22.34 (*c* = 0.5, MeOH). ^{1}H NMR (MeOD, 500 MHz): δ = 4.43 (d, *J* = 9.7 Hz, 2 H), 3.86 (dd, *J* = 12 Hz, *J* = 1.5 Hz, 2 H), 3.64 (dd, *J* = 12.0 Hz, *J* = 5.4 Hz, 2 H), 3.37–3.28 (m, 6 H), 3.19 (t, *J* = 9.5 Hz, 2 H), 3.05–3.03 (m, 2 H), 2.95–2.93 (m, 2 H) ppm. ^{13}C NMR (MeOD, 125 MHz): δ = 85.6, 80.7, 78.2, 73.0, 70.2, 61.6, 30.7. HRMS calcd. for a $C_{14}H_{26}NaO_{10}S_2$ [*M* + Na]$^+$: 441.0865; found 441.0884 (–4.4 ppm).

1,2-Ethanediyl Bis(2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside) (12): A solution of the octaol **11** (300 mg, 0.7 mmol) in dry DMF (3 mL) was treated with NaH (3.16 mmol) at 0 °C, and once the evolution of hydrogen had ceased, benzyl bromide (4.16 mmol) was added. After 12 hrs the mixture was treated with methanol (2 mL) and the solvents were evaporated to dryness. The mixture was diluted in CH_2Cl_2 (50 mL) and washed successively with saturated aqueous NH_4Cl solution and brine. Column chromatographic purification (ethyl acetate/hexane, 1:5) afforded **12** as a white solid (75%). m.p. 97–100 °C. $[a]_D^{20}$ = +1.44 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.35–7.22 (m, 32 H), 7.16–7.15 (m, 8 H), 4.88 (d, *J* = 11.0 Hz, 4 H), 4.81 (dd, *J* = 11.0 Hz, *J* = 4.1 Hz, 4 H), 4.73 (d, *J* = 10.3 Hz, 2 H), 4.59–4.53 (m, 8 H), 3.70–3.55 (m, 8 H), 3.48–3.41 (m, 4 H, H-5), 5.72 (s, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.5, 138.1, 138.0, 137.9, 128.4, 128.3, 128.2, 128.0, 127.9 127.8, 127.7, 127.6, 86.6, 81.8, 79.0, 78.0, 75.8, 75.5, 75.0, 73.4, 69.1, 32.7 ppm. HRMS calcd. for $C_{70}H_{74}NaO_{10}S_2$: 1161.4621 [*M* + Na]$^+$; found 1161.4709 (–7.6 ppm).

1,2-Ethanediyl Bis(2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside) (13): Benzoyl bromide (3 mL, 26 mmol) and a catalytic amount of DMAP were added to a solution of the octaol **11** (600 mg, 1.44 mmol) in dry pyridine (30 mL), and the mixture was heated at 90 °C for 8 hrs. After evaporation of pyridine the residue was diluted in dichloromethane (50 mL) and washed with 10% aqueous HCl (25 mL) and the aqueous phase was extracted with CH_2Cl_2 (4×25 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, and was dried with anhydrous sodium sulfate. After evaporation of the solvent the residue was purified by column chromatography (ethyl acetate/hexanes, 1:4), affording **13** as a white solid (82%). M.p. 96–98 °C. $[a]_D^{20}$ = +22.5 (*c* = 8.4 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.02–7.81 (m, 16 H), 7.50–7.24 (m, 24 H), 5.92 (t, *J* = 8.7 Hz, 2 H), 5.70 (t, *J* = 9.6 Hz, 2 H), 5.58 (t, *J* = 9.4 Hz, 2 H), 4.88 (d, *J* = 9.6 Hz, 2 H), 4.67 (d, *J* = 11.0 Hz, 2 H), 4.47 (d, *J* = 7.1 Hz, 2 H), 4.17–4.10 (m, 2 H), 3.12–3.02 (m, 2 H), 3.01–2.91 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.1, 165.8, 165.2, 165.1, 133.5, 133.4, 133.2, 133.1, 130.0, 129.9, 129.8, 129.7, 129.5, 129.0, 128.8, 84.0, 76.4, 74.1, 70.7, 69.6, 63.2, 31.1 (S–*C*H$_2$) ppm. HRMS calcd. for $C_{70}H_{58}NaO_{18}S_2$: 1273.2962 [*M* + Na]$^+$; found 1273.2950 (δ =1.0 ppm).

1,2-Ethanediyl Bis(2,3,4,6-tetra-*O*-pivaloyl-1-thio-β-D-glucopyranoside) (14): DMAP (cat., 0.5 mmol) was added to a solution of **11** (2 g, 4.92 mmol) in pyridine (50 mL), followed by pivaloyl chloride (0.1 mol). The reaction mixture was heated to 80 °C overnight. After evaporation of pyridine, the residue was diluted with CH_2Cl_2 (250 mL) and washed with HCl (10%, 2×100 ml). The aqueous layer was extracted with CH_2Cl_2 (4×100 ml) and the organic layer was successively washed with saturated aqueous $NaHCO_3$ solution and brine and dried (Na_2SO_4), and the solvents were evaporated. The crude mixture was purified by flash column chromatography (AcOEt/hex, 1:6), giving **14** (4 g, 75%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.32 (t, *J* = 9.3 Hz, 2 H), 5.11 (t, *J* = 9.6 Hz, 2 H), 5.03 (t, *J* = 9.8 Hz, 2 H), 4.53 (d, *J* = 10.0 Hz, 2 H), 4.24 (dd, *J* = 12.4 Hz, *J* = 1.6 Hz, 1 H), 4.16 (dd, *J* = 12.4 Hz, *J* = 5.4 Hz, 1 H), 3.93 (m, 1 H), 3.75 (m, 2 H), 2.9 (m, 2 H), 1.22 (s, 18 H), 1.16 (s, 18 H), 1.14 (s, 18 H), 1.10 (s, 18 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.9, 177.1, 176.5, 176.4, 83.2, 76.5, 73.2, 69.6, 67.7, 61.9, 38.9, 38.8, 38.7, 38.6, 30.0, 27.2, 27.2, 27.1, 27.0 ppm.

1,2-Ethanediyl Bis(1-thio-β-D-galactopyranoside) (15): This compound was obtained from **8** by using the general method described for the Zemplén deacetylation, as a white powder (quant. yield). $[a]_D^{20}$ = +3.58 (*c* = 0.4, MeOH). ^{1}H NMR (500 MHz, MeOD): δ = 4.42 (d, *J* = 9.7 Hz, 2 H), 3.86 (d, *J* = 3.1 Hz, 2 H), 3.67–3.59 (m, 6 H), 3.53 (dd, *J* = 9.5 Hz, *J* = 3.3 Hz, 2 H), 3.45 (t, *J* = 9.6 Hz, 2 H), 3.01–2.86 (m, 4 H) ppm. ^{13}C NMR (125 MHz, MeOD): δ = 86.4, 79.0, 73.9, 69.7, 68.8, 61.1, 30.9 ppm. HRMS calcd. for $C_{14}H_{26}NaO_{10}S_2$: 441.0865 [*M* + Na]$^+$; found 441.0874 (–2.0 ppm).

1,2-Ethanediyl Bis(2,3,4,6-tetra-*O*-pivaloyl-1-thio-β-D-galactopyranoside) (16): This compound was obtained from **15** by applying the same procedure as described for the synthesis of compound **14**. The product was obtained as white solid (75% yield): m.p. 86–88 °C. $[a]_D^{20}$ = +28.39 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.44 (d, *J* = 2.9 Hz, 2 H), 5.27 (t, *J* = 9.9 Hz, 2 H), 5.13 (dd, *J* = 10.0 Hz, *J* = 2.8 Hz, 2 H), 4.55 (d, *J* = 9.9 Hz, 2 H), 4.15–4.11 (dd, *J* = 9.5 Hz, *J* = 5.1 Hz, 2 H), 3.96–3.90 (m, 4 H), 3.03–3.01 (m, 2 H), 2.88–2.85 (m, 2 H), 1.18 (s, 18 H), 1.09 (s, 18 H), 1.08 (s, 18 H), 1.02 (s, 18 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8, 177.2, 176.8, 176.7, 83.8, 74.8, 71.9, 66.9, 66.8, 61.1, 39.1, 38.8, 38.7, 38.7, 30.2, 27.1, 27.0 ppm. HRMS calcd. for $C_{54}H_{90}O_{18}S_2$: 1113.5466 [*M* + 1]$^+$; found 1113.5444 (δ =2.0 ppm).

1,2-Ethylene Bis-(1-thio-α-D-manopyranoside) (17): This compound was obtained as a white powder (94% yield) from **10** by applying the general method described for the Zemplén deacetylation. $[a]_D^{20}$ = +160.8 (*c* = 0.4, MeOH). ^{1}H NMR (500 MHz, MeOD): δ = 5.30 (s, 2 H), 3.90 (br. s, 7 H), 3.84 (dd, *J* = 11.9 Hz, *J* = 1.9 Hz, 2 H), 3.72 (dd, *J* = 11.9 Hz, *J* = 6.1 Hz, 2 H), 3.63 (d, 4 H), 2.96–2.89 (m, 4 H) ppm. ^{13}C NMR (125 MHz, MeOD): δ = 85.3, 73.7, 72.2, 71.8, 67.5, 61.4, 31.1 ppm. HRMS calcd. for $C_{14}H_{26}NaO_{10}S_2$: 441.0865; found 441.0867 (–0.4 ppm).

1,2-Ethylene Bis-(2,3,4,6-tetra-*O*-pivaloyl-1-thio-α-D-manopyranoside) (18): This compound was prepared from **17** by using the same procedure as described for the synthesis of compound **14**. The product was obtained as a white solid (72% yield). m.p. 83–87 °C. $[a]_D^{20}$ = +78.2 (*c* = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.50 (t, *J* = 10.1 Hz, 2 H), 5.32 (t, *J* = 1.4 Hz, 2 H), 5.26–5.23 (m, 4 H), 4.39 (dd, *J* = 10.2, *J* = 3.2 Hz, 2 H), 4.25 (dd, *J* = 12.6 Hz, *J* = 4.2 Hz, 2 H), 4.08 (d, *J* = 11.6 Hz, 2 H), 2.93–2.86 (m, 4 H), 1.27 (s, 18 H), 1.23 (s, 18 H), 1.16 (s, 18 H), 1.11 (s, 18 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.0, 177.1, 177.0, 76.6, 83.0, 70.9, 69.7, 66.6, 65.1, 62.0, 39.0, 38.9, 38.8, 38.7, 31.5, 27.2, 27.1, 27.0 ppm. HRMS calcd. for $C_{54}H_{90}O_{18}NaS_2$: 1113.5466 [*M* + Na]$^+$; found 1113.5536 (–6.3 ppm).

1,2-Ethylene Bis-(2,3,4-tri-*O*-acetyl-1-thio-β-D-arabinopyranoside) (20): This compound was prepared from **19** and ethane-1,2-dithiol by the general procedure described for the synthesis of peracety-

lated C_2-symmetric bis(thioglycosides). The product was obtained as a white solid (70%): m.p. 49–52 °C. $[\alpha]_D^{20}$ = +9.63 (*c* = 0.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.19 (d, *J* = 1.6 Hz, 2 H), 5.11 (t, *J* = 8.7 Hz, 2 H), 4.99 (dd, *J* = 8.9 Hz, *J* = 4 Hz, 2 H), 4.49 (d, *J* = 8.4 Hz, 2 H), 4.03–3.98 (m, 2 H), 3.61 (dd, *J* = 12.8 Hz, *J* = 1.4 Hz, 2 H), 2.97–2.89 (m, 2 H), 2.88–2.70 (m, 2 H), 2.09 (s, 6 H), 2.06 (s, 6 H), 2.02 (s, 6 H), 2.01 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 170.0, 169.6, 83.9, 70.7, 68.1, 67.8, 66.0, 30.8, 20.9, 20.8, 20.7 ppm. HRMS calcd. for $C_{24}H_{34}NaO_{14}S_2$: 633.1288 [*M* + Na]$^+$; found: 633.1274 (δ =2.1 ppm).

1,2-Ethylene Bis-(1-thio-α-D-arabinopyranoside) (21): This compound was obtained as a white powder (93% yield), from **20**, following the general method described for the Zemplén deacetylation. $[\alpha]_D^{20}$ = –22.34 (*c* = 0.5, MeOH). ^1H NMR (500 MHz, MeOD): δ = 4.43 (d, *J* = 9.7 Hz, 2 H), 3.86 (dd, *J* = 12.0 Hz, *J* = 1.5 Hz, 2 H), 3.64 (dd, *J* = 12.0 Hz, *J* = 5.4 Hz, 2 H), 3.37–3.28 (m, 6 H), 3.19 (t, *J* = 9.5 Hz, 2 H), 3.05–3.03 (m, 2 H), 2.95–2.93 (m, 2 H) ppm. ^{13}C NMR (125 MHz, MeOD): δ = 85.6, 80.7, 78.2, 73.0, 70.2, 61.6, 30.7 ppm. HRMS calcd. for $C_{14}H_{26}NaO_{10}S_2$: 441.0865 [*M* + Na]$^+$; found 441.0884 (–4.4 ppm).

1,2-Ethylene Bis-(2,3,4,6-tetra-*O*-pivaloyl-1-thio-α-D-arabinopyranoside) (22): This compound was obtained from **21** by using the same procedure as described for the synthesis of compound **14**. The product was obtained as a white solid (68% yield): m.p. 182–184 °C. $[\alpha]_D^{20}$ = +21 (*c* = 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.26–5.22 (m, 4 H), 5.12 (dd, *J* = 8.7 Hz, *J* = 3.2 Hz, 2 H), 4.55 (d, *J* = 8.1 Hz, 2 H), 4.05 (dd, *J* = 12.7 Hz, *J* = 3.7 Hz, 2 H), 3.67 (d, *J* = 12.6 Hz, 2 H), 3.01–2.97 (m, 2 H), 2.87–2.82 (m, 2 H), 1.23 (s, 18 H), 1.17 (s, 18 H), 1.14 (s, 18 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.3, 177.2, 176.7, 83.9, 70.6, 67.9, 67.7, 38.9, 38.8, 38.7, 30.7, 27.2, 27.1, 27.0 ppm. HRMS calcd. for $C_{42}H_{70}O_{14}NaS_2$: 885.4105 [*M* + Na]$^+$; found 885.4108 (δ =6.3 ppm).

General Procedure for the Synthesis of C_2-Symmetric Bis(thioglycoside) Pd^{II} Complexes: A solution of C_2-symmetric bis(thioglycoside) (1 equiv., 0.52 mmol) in dry deoxygenated CH_2Cl_2 (5 ml) was added by cannula to a suspension of dichlorobis(acetonitrile)palladium(II) (135 mg, 0.52 mmol) in dry deoxygenated CH_2Cl_2 (10 ml). After 2 h the solvent was removed under vacuum and the obtained residue was washed three times with dry deoxygenated diethyl ether, affording the desired C_2-symmetric bis(thioglycoside) Pd^{II} complex as a yellow orange solid.

***cis*-Dichloro[1,2-ethylene Bis-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside)]palladium(II) (23):** This compound was obtained from **4** as a yellow solid (90%): m.p. 134–136 °C. $[\alpha]_D^{20}$ = –164.63 (*c* = 0.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.34 (m, 2 H), 5.13–5.12 (m, 4 H), 5.07 (t, *J* = 9.8 Hz, 2 H), 4.46 (dd, *J* = 12.6, *J* = 6.0 Hz, 2 H), 4.08 (dd, *J* = 12.6 Hz, *J* = 1.9 Hz, 2 H), 4.04–4.00 (m, 2 H), 3.37–3.27 (m, 4 H), 2.16 (s, 6 H), 2.12 (s, 6 H), 2.04 (s, 6 H), 2.01 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 170.3, 169.5 and 169.45, 83.2, 77.8, 72.8, 67.9, 67.5 and 61.4, 26.0, 24.5, 21.1 20.5, 20.4 ppm. Anal. (%) $C_{30}H_{42}Cl_2O_{18}PdS_2$: C 38.66, H 4.54; found C 38.65, H 4.30.

***cis*-Dichloro[1,2-ethylene Bis-(2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside)]palladium(II) (24):** ^1H NMR (500 MHz, $CDCl_3$): δ = 8.01–8.00 (m, 4 H), 7.91–7.90 (m, 8 H), 7.79–7.78 (m, 4 H), 7.53–7.26 (m, 24 H), 5.99 (t, *J* = 9.0 Hz, 2 H), 5.64 (t, *J* = 9.6 Hz, 2 H) 5.55–5.51 (m, 4 H), 4.69 (d, *J* = 12.2 Hz, 2 H), 4.52–4.48 (m, 2 H), 4.43–4.42 (m, 2 H), 3.55–3.54 (m, 2 H), 3.43–3.41 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0, 165.9, 165.3, 165.1, 134.2, 133.8, 133.5, 133.3, 130.2, 129.9, 129.7, 128.9, 128.7, 128.6, 128.4, 128.2, 127.6, 83.5, 78.3, 72.8, 68.9, 68.5, 62.2, 35.1 ppm.

***cis*-Dichloro[1,2-ethylene Bis-(2,3,4,6-tetra-*O*-pivaloyl-1-thio-β-D-glucopyranoside)]palladium(II) (25):** This compound was obtained from **14** as a yellow solid (95%). $[\alpha]_D^{20}$ = –172.33 (*c* = 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.41 (t, *J* = 9.4 Hz, 2 H), 5.20 (d, *J* = 10.3 Hz, 2 H), 5.13–5.08 (m, 4 H), 4.25–4.23 (m, 2 H), 4.18 (dd, *J* = 12.8 Hz, *J* = 4.9 Hz, 2 H), 4.02–3.99 (m, 2 H), 3.36–3.24 (m, 4 H), 1.26 (s, 18 H), 1.16 (s, 18 H), 1.15 (s, 18 H), 1.11 (s, 18 H) ppm. ^{13}C NMR(125 MHz, $CDCl_3$): δ = 177.8, 177.6, 176.5, 176.4, 83.8, 78.2, 71.8, 67.7, 66.8, 61.2, 39.0, 38.9, 38.8, 38.8, 36.3, 27.4, 27.1, 27.0 ppm. Anal. (%) $C_{54}H_{90}Cl_2O_{18}PdS_2$: C 51.12, H 7.15; found C 50.73, H 6.99.

***cis*-Dichloro[1,2-ethylene Bis-(2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside)]palladium(II) (26):** $[\alpha]_D^{20}$ = –221.85 (*c* = 0.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.04–8.05 (m, 4 H), 7.97–7.93 (m, 8 H), 7.78–7.76 (m, 4 H), 7.60–7.57 (m, 2 H), 7.50–7.46 (m, 8 H), 7.43–7.40 (m, 2 H), 7.38–7.35 (m, 8 H), 7.26–7.23 (m, 4 H), 6.02 (d, *J* = 3.2 Hz, 2 H), 5.84 (t, *J* = 9.9 Hz, 2 H) 5.65 (dd, *J* = 3.3 Hz, *J* = 9.9 Hz, 2 H), 4.92 (d, *J* = 9.9 Hz, 2 H), 4.61(dd, *J* = 6.2 Hz, *J* = 11.2 Hz, 2 H), 4.39–4.31 (m, 4 H), 3.26–3.23 (m, 2 H), 3.09–3.07(m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.02, 165.5, 165.4, 165.3, 133.7, 133.4, 133.3, 133.2, 130.2, 129.9, 129.8, 129.7, 129.3, 129.1, 129.0, 128.8, 128.7, 128.5, 128.4, 128.3, 84.7, 75.1, 72.6, 68.4, 68.2, 62.1, 31.6 ppm.

***cis*-Dichloro[1,2-ethylene Bis-(2,3,4,6-tetra-*O*-pivaloyl-1-thio-β-D-galactopyranoside)]palladium(II) (27):** This compound was obtained as a yellow solid from **16** in 80% yield. m.p. 158–160 °C. $[\alpha]_D^{20}$ = –109.35 (*c* = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.53 (d, *J* = 2.8 Hz, 2 H), 5.35–5.26 (m, 6 H), 4.30–4.23 (m, 4 H), 4.02 (dd, *J* = 4.8 Hz, *J* = 10.7 Hz, 2 H), 3.38–3.36 (m, 2 H), 3.29–3.27 (m, 2 H), 1.28 (s, 18 H), 1.22 (s, 18 H), 1.19 (s, 18 H), 1.11 (s, 18 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2, 178.0, 176.6, 176.2, 83.4, 77.1, 70.7, 67.0, 65.2, 60.8, 39.1, 39.0, 38.9, 38.8, 34.4, 27.3, 27.2, 27.0, 26.9 ppm. Anal. (%) $C_{54}H_{90}Cl_2O_{18}PdS_2$: C 51.12, H 7.15; found C 50.57, H 6.81.

***cis*-Dichloro[1,2-ethylene Bis-(2,3,4-tri-*O*-pivaloyl-1-thio-α-D-arabinopyranoside)]palladium(II) (28):** This compound was obtained as a yellow solid from **20** in 75% yield. m.p. 131–133 °C. $[\alpha]_D^{20}$ = +137.7 (*c* = 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.35 (m, 2 H), 5.31 (t, *J* = 10.0 Hz, 2 H), 5.21 (dd, *J* = 9.8, *J* = 3.2 Hz, 2 H), 5.14 (d, *J* = 10.1 Hz, 2 H), 4.14 (dd, *J* = 13.3, *J* = 1.9 Hz, 2 H), 3.94 (d, *J* = 13.2 Hz, 2 H), 3.30–3.19 (m, 4 H), 1.26 (s, 18 H), 1.17 (s, 18 H), 1.11 (s, 18 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2, 176.6, 176.5, 84.2, 70.5, 69.8, 67.9, 65.6, 38.9, 38.8, 34.2, 27.2, 27.0; Analysis calcd. (%) for $C_{42}H_{70}Cl_2O_{14}PdS_2$: C 48.48, H 6.78; found C 49.09, H 6.77.

[1,2-Ethylene Bis-(2,3,4,6-tetra-*O*-pivaloyl-1-thio-β-D-galactopyranoside)palladium(II)(η^3–1,3-diphenylpropenyl)] Hexafluroantimonate (31): Silver antimony hexafluoride (69 mg, 0.2 mmol) was added under argon to a suspension of [Pd(η^3-PhCHCHPh)-(μ-Cl)]$_2$[46] (67 mg, 0.1 mmol) and **16** (218 mg, 0.2 mmol) in a 1:1 mixture of MeOH/CH_2Cl_2 (10 mL). The reaction was stirred overnight in the dark, and silver chloride was then removed by filtration through celite, and the solvent by vacuum. The solid obtained was washed with diethyl ether, affording complex **31** in quantitative yield as a yellow solid. $[\alpha]_D^{20}$ = –195.8 (*c* = 0.6, $CHCl_3$). ^1H NMR (500 MHz, CD_2Cl_2): δ = 7.81–7.78 (m, 10 H), 6.96 (t, *J* = 12.1 Hz, 1 H), 5.68 (d, *J* = 12.2 Hz, 1 H), 5.61 (d, *J* = 11.9 Hz, 1 H), 5.53 (d, *J* = 2.7 Hz, 1 H), 5.36 (d, *J* = 2.6 Hz, 1 H), 5.23 (t, *J* = 9.9 Hz, 1 H), 5.17–5.11 (m, 2 H), 4.57 (dd, *J* = 10.1 Hz, *J* = 3.0 Hz, 1 H), 4.30–4.25 (m, 1 H), 4.24–4.12 (m, 1 H), 4.10–4.08 (m, 1 H), 4.10 (d, *J* = 9.6 Hz, 1 H), 3.94 (dd, *J* = 10.5 Hz, *J* = 7.8 Hz, 1 H), 3.78 (dd, *J* = 11.2 Hz, *J* = 7.3 Hz, 1 H), 3.60 (t, *J* = 6.6 Hz, 1 H), 3.45–

3.40 (m, 1 H), 3.36–3.27 (m, 1 H), 3.22–3.17 (m, 1 H), 3.02–2.96 (m, 1 H), 2.32 (d, J = 10.0 Hz, 1 H), 1.26, 1.25, 1.23, 1.21, 1.16, 1.09, 1.08, 0.95 ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 177.9, 177.5, 177.4, 177.3, 176.8, 176.4, 176.0, 136.8, 136.7, 136.5, 130.1, 129.8, 127.8, 127.7, 107.2, 91.6, 86.3, 82.1, 80.0, 75.8, 71.3, 70.9, 66.4, 65.1, 64.2, 60.4, 59.4, 38.8, 38.7, 33.5, 31.1, 27.3, 27.2, 27.1, 27.0, 26.9, 26.8 ppm. Analysis calcd. (%) for $C_{69}H_{102}O_{18}PdS_2$: C 50.97, H 6.32; found C 50.91, H 6.22.

Representative Procedure for Allylic Alkylation of 3-Acetoxy-1,3-diphenylprop-1-ene (6) with Bis(thioglycosides) as Chiral Ligands: In a dry vial flushed with argon, allylpalladium chloride dimer (2.56 mg, 0.007 mmol) and the chiral ligand (**16** in this case, 0.046 mmol) were dissolved in dry degassed dichloromethane (0.5 mL) and the solution was stirred at room temperature. After 1 h, 1,3-diphenylpropenyl acetate (**6**, 116 mg, 0.46 mmol) was added, followed by dimethyl malonate (0.16 mL, 1.38 mmol), *O*,*N*-bis(trimethylsilyl)acetamide (0.34 mL, 1.38 mmol), and solid potassium acetate (2 mg, 0.02 mmol). After 12 h the reaction mixture was diluted with Et_2O (20 mL) and washed with NH_4Cl, the aqueous layer was further extracted with CH_2Cl_2 (3 × 10 mL), and the organics were dried with Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography (EtOAc/hexanes, 1:20), affording the product **7** (124 mg, 83%). $[\alpha]_D^{20}$ = –21 (c = 0.9, $CHCl_3$); ref.[47] $[\alpha]_D^{20}$ = –22.4 (c = 1.8, $CHCl_3$) for (*S*)-**7**. ^{1}H NMR (500 MHz): δ = 7.36–7.19 (m, 10 H), 6.49 (d, J = 15.7 Hz, 1 H), 6.4 (dd, J = 15.7 Hz, J = 8.6 Hz, 1 H), 4.28 (dd, J = 10.9 Hz, J = 8.6 Hz, 1 H), 3.97 (d, J = 10.9 Hz, 1 H), 3.71 (s, 3 H), 3.52 (s, 3 H). HRMS calcd. for $C_{15}H_{14}O$: 210.1045 [M + Na]$^+$; found 210.1054 (–4.6 ppm). The enantiomeric excess was determined by HPLC (Chiralcel AD column, 1.0 mL min^{-1}, hexane/2-propanol, 94:6).

Supporting Information (for details see the footnote on the first page of this article): Dynamic NMR studies of compounds **23**, **25**, and **29**, copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **24** and **27**, 2D NOESY experiment of compound **25**, 1D TOCSY experiments of compound **31** at different mixing times, 2D TOCSY and HMQC experiments of compound **31**.

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