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Asymmetric Enamide Hydrogenation Using Phosphinite Thioglycosides: Synthesis of D- and L-Aminoesters Using D-Sugars as Catalyst Precursors

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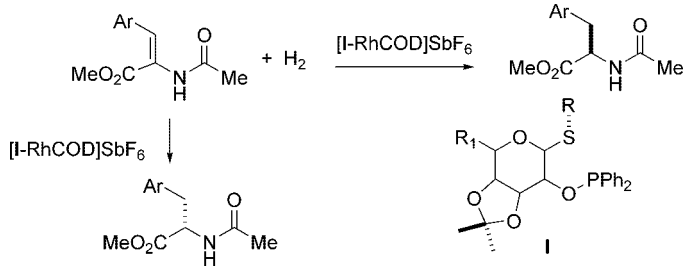
ABSTRACT



Diastereomerically pure cationic Rh(I) complexes derived from phosphinite thioglycosides I were used as catalysts in highly enantioselective hydrogenations of enamides. The conformational similarity of α-D-arabinopyranose with *β*-L-galactopyranose allows the synthesis of both enantiomers of α-amino acid derivatives such as D- and L-DOPA in excellent ee (97% and 98%), using derivatives of the former sugar as catalyst precursors.

Asymmetric catalysis is the method of choice for the synthesis of enantiopure compounds since it combines efficiency and versatility with atom economy, and it is well-matched for the "Green Chemistry" initiative.[1] Commonly, only one enantiomer is needed for a given activity, although there are cases such as α-amino acids where both enantiomers are required in optically pure form. Alternating, for instance, an even number of D- and L-amino acids in cyclic peptides gives rise to supramolecular assemblies known as peptide nanotubes, which are able to form artificial transmembrane channels for ion and glucose transport, as well as exert antibacterial activity.[2] D-Amino acids are constituents of natural and synthetic cytotoxic peptides endowed with important anticancer activities.[3] Finally, with the increasing importance of organocatalysis,[4] there is a growing need for structurally diverse amino acids in both enantiomeric forms since they are among the best organocatalysts.[5] As such,

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(1) Recently, 2 Issues of the Proceedings of the National Academy of Sciences of the USA were dedicated to the Special Feature of asymmetric catalysis, see: *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101* (15), 5311−5696 and *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101* (16) 5697−6327.

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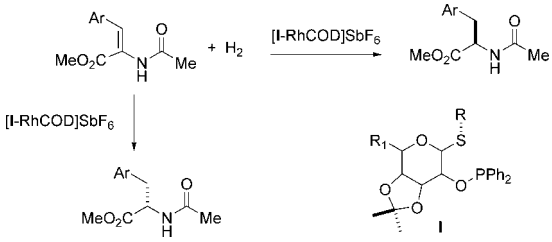
catalyst precursors are often derived from natural products, and access to both enantiomers is not always possible. As a part of our interest in chiral sulfur compounds,[6] we have recently started a research program directed toward the use of sulfur-based ligands derived from carbohydrates in enantioselective catalysis.[7] Following the seminal work of Evans on the use of mixed S/P ligands in asymmetric catalysis,[8] in the present paper we report our results on the Rh-catalyzed asymmetric hydrogenation of enamides using our phosphinite thioglycosides **I** as ligands. In light of the prohibitive price of L-sugars, an important achievement of the present research has been the synthesis of both enantiomers of α-amino acids using natural D-sugars as catalyst precursors[9] (Scheme 1).

Scheme 1



To determine the structural features of the type **I** ligands for optimal catalysis, compounds **1**−**5** derived from 2-diphenylphosphinite-3,4-*O*-isopropyliden thiogalactoside were synthesized (Figure 1).

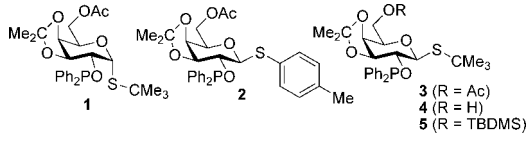
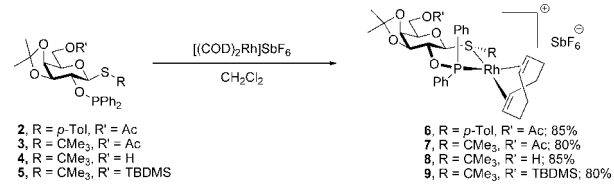


Figure 1. Structure of phosphinite thioglycosides **1**−**5** used as chiral ligands in asymmetric enamide hydrogenation.

The new ligands **4** and **5** were evaluated to determine the steric and electronic effects of the 6-hydroxyl group on the catalytic behavior of those types of ligands. They were obtained from 6-*O*-acetyl-2-diphenylphosphinite-3,4-*O*-isopropylidene thiogalactoside **3** in three and four steps, respectively (see Supporting Information). Before conducting the first catalytic study, we first synthesized an advanced catalytic precursor with well-defined structure. Treatment of the starting mixed S/P ligands with $Rh(cod)_2SbF_6$ in methylene chloride afforded the corresponding Rh(I) complexes in variable yield (Scheme 2).[10] In the case of ligands **2**−**5**,

Scheme 2



the corresponding Rh(I) complexes were obtained in excellent yields, while the use of ligand **1** afforded a complex mixture, most likely as a result of the 1,2-*cis* orientation of the bulky $SC(Me)_3$ and the $OPPh_2$. One of the most salient features of mixed ligands **I** is that, upon coordination to the rhodium, the sulfur atom becomes stereogenic. Consequently, highly enantioselective processes are expected with these complexes, based on the close proximity of the chiral sulfur atom to the coordination sphere of the transition metal, provided that the low inversion barrier of the sulfur metal bond can be surmounted.[11] Interestingly, the ^1H, ^{13}C, and ^{31}P NMR spectra indicated that complexes **6**−**9** were obtained as a single diastereoisomer, highlighting the excellent stereochemical control exerted by the sulfur substituent.

The preformed catalyst precursors **6**−**9** as well as the in situ formed catalyst precursor derived from ligand **1** were assayed in the hydrogenation of the model olefin methyl (*Z*)-α-acetamido cinnamate **10**, in various solvents and at different hydrogen pressures using 1 mol % of the catalyst. The results are summarized in Table 1.

As can be seen from Table 1, the α-thioglycoside ligand **1** is completely inactive in the hydrogenation of the model olefin, as the starting material was obtained unchanged (Table 1, entry 1). The aromatic S/P complex **6** afforded the phenyl alanine derivative **11** with low conversion and essentially as a racemate, even though high hydrogen pressure was used (Table 1, entry 2). Surprisingly, replacement of the aromatic ring on the sulfur atom with a bulky alkyl group afforded an excellent catalyst for the hydrogenation of methyl (*Z*)-α-acetamido cinnamate **10**. The use of 1 mol % of catalyst **7** at room temperature, and 4 atm of hydrogen pressure, smoothly afforded the desired amino ester in quantitative yield and 94% ee (Table 1, entry 3). Both catalysts **8** and **9** afforded the (*S*)-*N*-acetyl phenyl alanine methyl ester **11** in 92% ee, although 8 atm of hydrogen pressure was needed for the reaction to reach completion (Table 1, entries 4 and

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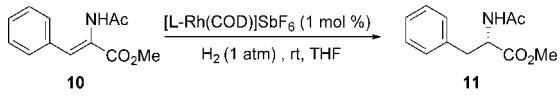
Table 1. Enantioselective Hydrogenation of Methyl (*Z*)-α-Acetamido Cinnamate **10** with Cationic Rh(I) Complexes **6**−**9**[a]



10 **11**

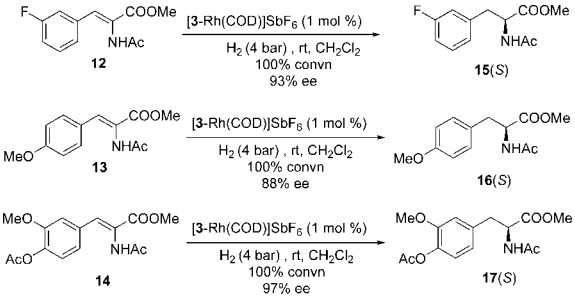
entry[a]	[L-Rh(cod)]SbF_6	solv.	*P* (bar)	convn (%)[c]	% ee (conf)[d]
1	**1**[b]	CH_2Cl_2	4	0	–
2	**6**	CH_2Cl_2	35	20	8 (*S*)
3	**7**	CH_2Cl_2	4	100	94 (*S*)
4	**8**	CH_2Cl_2	8	100	92 (*S*)
5	**9**	CH_2Cl_2	8	100	92 (*S*)
6	**7**	CH_2Cl_2	1	100	94 (*S*)
7	**7**	THF	4	100	92 (*S*)
8	**7**	THF	18	100	90 (*S*)

[a] All reactions were conducted in CH_2Cl_2 using 1 mol % of the catalyst. [b] The reaction was conducted with the in situ generated catalyst. [c] Determined by ^1H NMR after 24 h. [d] Determined by chiral HPLC using the Chiracel-OJ column.

5). These results demonstrate that the key structural motifs of the catalyst are the relative configurations at C1 and C2, together with the nature of the substituent at the anomeric sulfur atom. The best catalyst **7** was able to give the desired product in 100% yield and 94% ee, using only 1 atm of hydrogen pressure (Table 1, Entry 6).

To determine the synthetic value of the process, aryl enamides **12**−**14** were hydrogenated under the optimal conditions, determined for **10**, and the results are given in Scheme 3.

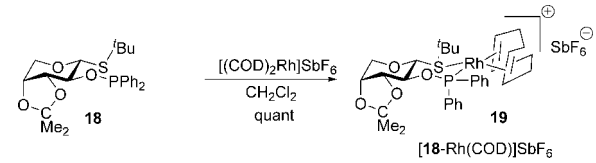
Scheme 3



In all cases, the final amino esters were obtained in quantitative yields and good to excellent ee's, using simple reaction conditions. It is worth mentioning that the 3-fluorophenyl alanine derivative **15**, which is obtained in 93% ee, is currently being industrially produced by a chemoenzymatic approach, where the first step is an asymmetric hydrogenation of the enamide using DUPHOS as ligand. The latter produces **15** with only 86% ee.[12] Interestingly enough, while the *p*-methoxy-phenylalanine derivative **16** was obtained in 88% ee, the L-DOPA precursor **17** was obtained in an excellent 97% ee and quantitative yield.[13] As stated in the introduction, the main challenge when employing carbohydrates in asymmetric catalysis is the access to both enantiomers of the catalyst. As an illustration, while D-glucose is one of the less expensive chiral compounds in the market (1.2 Eu/mol), commercially available L-glucose is exceedingly expensive (8690 Eu/mol). To solve this problem, we have recently made use of the similarity between α-D-arabinose, a cheap commercially available D-pentopyranose and *β*-L-galactose.

Treatment of arabinose-based mixed S/P ligand **18** with $[(cod)_2Rh]SbF_6$ in methylene chloride at room temperature afforded the cationic Rh(I) complex **19** in quantitative yield, as a single diastereoisomer (Scheme 4). Fortunately, in this

Scheme 4



case, we obtained adequate crystals for X-ray analysis (Figure 2). In the crystal form, the pentopyranose ring is in the $^1C_4$

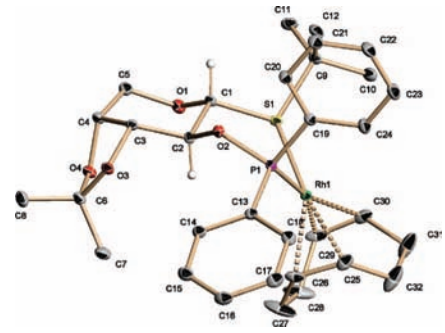


Figure 2. ORTEP plot for the cationic Rh(I) complex **19**.

form while the six-membered metallacycle ring is in a twist-boat conformation. Interestingly, the bulky *tert*-butyl group is in a pseudoaxial disposition outlying from the pyranose substituents, fixing the configuration of the sulfur atom as *R*. The pseudoaxial disposition of the sulfur substituent is actually well documented;[14] though not fully understood, this forces the aromatic rings of the phosphine to adopt an edge-

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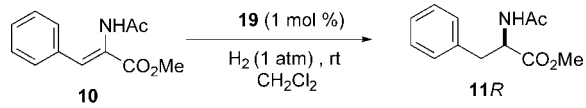
on face-on conformation (Figure 2), which is suggested to be of crucial importance in the enantiocontrol behavior of C_2-symmetric bisaryl phosphines.[15]

On the other hand, there is a large difference between the bond lengths (around 0.1 Å) *trans* to the phosphorus [Rh−C(29) = 2.298 Å y Rh−C(30) = 2.275 Å], compared to those *trans* to the sulfur [Rh−C(25) = 2.157 y Rh−C(26) = 2.167 Å], highlighting the major *trans* influence of the phosphorus atom compared to the sulfur atom.[16] To compare the performance of complex **19** with that derived from galactose **7**, the hydrogenation of the model substrate methyl (*Z*)-α-acetamido cinnamate **10** was conducted under the same conditions as before.

Employing 1 mol % of the complex **19**, and 1 atm of hydrogen, the desired phenyl alanine derivative **11** was obtained in quantitative yield (Scheme 5). Interestingly, the

Scheme 5



11*R* enantiomer, the opposite to that produced by the galactose-derived catalyst **7**, was obtained in 94% ee in both methylene chloride and THF. To generalize the pseudoenantiomeric behavior of catalyst **19** with that of **7**, the enamides **12**−**14** were hydrogenated as before, and the results are summarized in Table 2.

As can be seen from Table 2, using 1 mol % of the catalyst **19**, the final amino esters **15**−**17** were obtained with the *R* absolute configuration, which is the opposite of the one obtained with the galactose-derived catalyst **7**. While higher hydrogen pressures were needed (Table 2, entries 2, 4, and 5), the final amino esters were all obtained with high enantiomeric excesses. Interestingly, and contrary to the behavior of the starting ligands **3** and **18** in Pd-catalyzed allyllic substitution, in the present case, the arabinose-based

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Table 2. Enantioselective Hydrogenation of Methyl Enamides **12**−**14** with the Cationic Rh(I) Complex **19**

entry[a]	substrate	*P* (bar)	convn (%)[b]	% ee (conf)[c]
1	**12**	4	18	93 (*R*)
2	**12**	15	100	93 (*R*)
3	**13**	4	48	92 (*R*)
4	**13**	15	100	91 (*R*)
5	**14**	15	100	98 (*R*)

[a] All reactions were conducted in CH_2Cl_2 using 1 mol % of the catalyst. [b] All the reactions were stopped after 24 h. [c] Determined by chiral HPLC using the Chiracel-OJ column.

catalyst always gave higher enantioselectivities. This result is of some importance as it indicates that, while flexibility of the ligand has a negative effect on Pd-catalyzed allylic substitution, in the case of asymmetric hydrogenation of enamides it is helpful.[17]

In conclusion, the results reported in this work illustrate the high potential of phosphinite thioglycosides **I** in asymmetric hydrogenation of enamides for the synthesis of proteogenic and nonproteogenic α-amino acids in high enantiomeric excesses. Using commercially accessible D-sugars as catalyst precursors, we secured both enantiomers of important proteogenic and nonproteogenic α-amino acid derivatives such as D- and L-DOPA **17** in quantitative yields with 97% and 98% ee's, respectively. The tuning of other parameters implemented in the synthetic design, such as the electronic character of the phosphine moiety and the conformation of the pyranose ring, may certainly lead to more efficient catalysts. Work along these lines is under active investigation in our group.

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Supporting Information Available: Representative experimental procedures for the synthesis of compounds **4** and **5** and the Rh(I) complexes **6**−**9** and **19** and HPLC data for the determination of enantiomeric excesses of **11** and **15**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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