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Rh-catalyzed asymmetric hydrogenation using a furanoside monophosphite second-generation ligand library: scope and limitations

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ABSTRACT

The ligand design of one of the most successful monophosphite ligand classes in Rh-catalyzed hydrogenation was expanded upon by introducing several substituents at the C-3 position of the furanoside backbone. A small but structurally important library of monophosphite ligands was developed by changing the substituents at the C-3 position of the furanoside backbone and the substituents/configurations at the biaryl phosphite group. These new furanoside monophosphite ligands were evaluated in the Rh-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives and enamides. The results show that the effect of introducing a substituent at the C-3 position of the furanoside backbone on the enantioselectivity depends not only on the configuration at the C-3 position of the furanoside backbone and the binaphthyl group but also on the substrate. Thus, the new ligands afforded high to excellent enantioselectivities in the reduction of carboxylic acid derivatives (ee's up to >99.9%) and moderate ee's (up to 67%) in the hydrogenation of enamides.

1. Introduction

The asymmetric hydrogenation of functionalized prochiral olefins catalyzed by chiral transition metal complexes has been widely used in organic synthesis and some processes have found industrial applications.[1] Many chiral ligands, mainly P- and containing ligands with either C_2- or C_1-symmetry, have been successfully applied.[1] For a long time, it was generally accepted that enantioselective hydrogenation was more effective in the presence of bidentate ligands.[1] Less attention was therefore paid to catalysts containing monodentate ligands in this process. The first successful report on the use of monodentate ligands in this process was reported in 2000 with the application of monophosphonites derived from binaphthol.[2] Soon after, Reetz et al. obtained excellent enantioselectivities with catalyst precursors containing monophosphite ligands, derived from D-(+)-mannitol, in the hydrogenation of dimethyl itaconate.[3] Since then, other successful monodentate ligands have been developed.[4] Research in this field has mainly focused on the selection/design of new chiral ligands prepared from readily available, inexpensive/renewable raw materials. For this purpose, carbohydrates are particularly advantageous thanks to their low price and easy modular construction.[5] In this respect, Reetz et al.[4d] and Zheng et al.[4e–g] have independently reported the successful use of furanoside ligands **1** and **2**, derived from D-(+)-glucose, in the Rh-catalyzed asymmetric hydrogenation of a range of carboxylic acid derivatives, enamides, and vinyl carboxylates (Fig. 1).

Following our interests in carbohydrates as an inexpensive and highly modular chiral source for preparing ligands,[5] and encouraged by the results of monophosphite ligands **1** and **2** in asymmetric hydrogenations,[4d–g] we decided to go one step further and develop a second generation of furanoside ligands **L1**–**L6a**–**c** (Fig. 2)[6] to be used in the Rh-catalyzed enantioselective hydrogenation of a range of carboxylic acid derivatives and enamides. These ligands differ from previous monophosphite ligands **1** and **2** because new substituents with different electronic and steric properties have been introduced at the C-3 position of the sugar backbone. With this library we therefore fully investigated the effects of systematically varying the configuration of the C-3 carbon atom in the sugar backbone **L1**–**L2**, the electronic and steric hindrance of the new substituent at C-3 **L2**–**L6**, and the substituents/configuration of the biaryl phosphite moieties **a**–**c**.

2. Results and discussion

2.1. Asymmetric hydrogenation of dimethyl itaconate S1

Initially, we evaluated furanoside monophosphite ligands **L1**–**L6a**–**c** (Fig. 2) in the Rh-catalyzed asymmetric hydrogenation of

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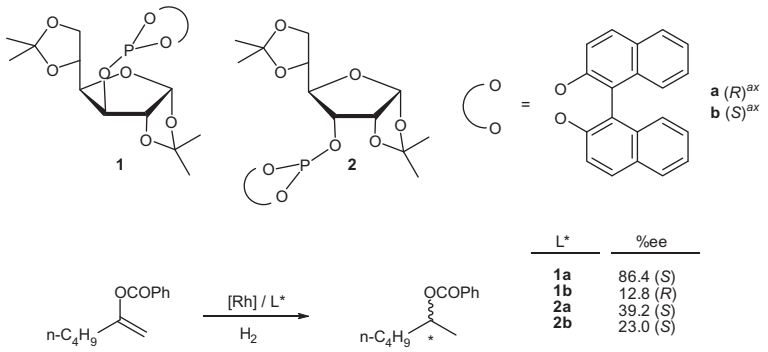


Figure 1. Furanoside monophosphite ligands **1**–**2a**–**b**. The enantioselectivities obtained in the asymmetric hydrogenation of a vinyl carboxylate are shown as examples.

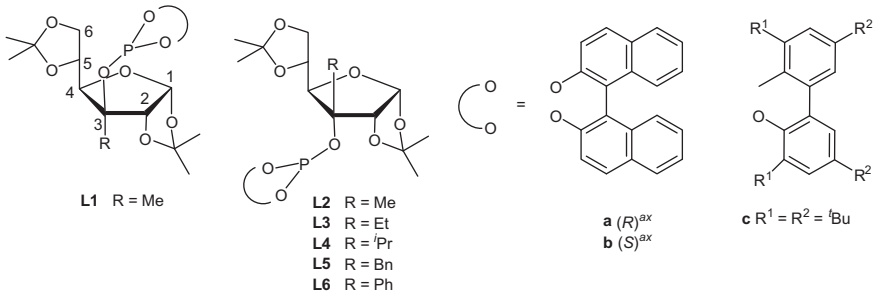


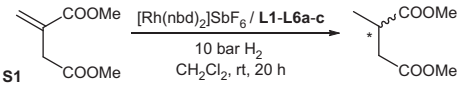
Figure 2. Furanoside monophosphite ligand library **L1**–**L6a**–**c**.

dimethyl itaconate **S1**, which is used as a model substrate. The catalysts were prepared in situ by adding the corresponding ligands to the catalyst precursor $[Rh(nbd)_2]SbF_6$. For the purpose of comparison, we chose the same reaction conditions that had previously been used with ligands **1**–**2** (i.e., 10 bar of H_2, dichloromethane as solvent, 1 mol % catalyst precursor, a ligand-to-rhodium ratio of 2.2 and room temperature).[4e]

The results, which are summarized in Table 1, indicated that the catalytic activity is almost suppressed when using bulky biaryl substituents, that is ligands **L1**–**L2c** and **1**–**2c** (entries 3, 6, 13 and 16). We also found that enantioselectivities were greatly affected by the substituents/configuration at the C-3 position of the furanoside backbone and the configuration of the binaphthyl group. The results indicated that the effect on the enantioselectivity of introducing the new substituent at C-3 depends on the configuration at C-3 of the furanoside backbone and at the binaphthyl moiety. Thus, for glucofuranoside ligands **1**, the introduction of a methyl substituent at C-3 (new ligands **L1**) had a positive effect on the enantioselectivity if an (*S*)-binaphthyl group **b** was present (ligand **L1b**, ee's up to >99.9%, entry 2 vs 12). However, the presence of a methyl substituent at C-3 in combination with an (*R*)-biaryl group **a** had a negative effect on the enantioselectivity (ligand **L1a**; entry 1 vs 11). For allofuranoside ligands **2**, the enantioselectivities decreased considerably when a substituent was introduced at C-3, regardless of the configuration at the binaphthyl group (ligands **L2**–**L5**; entries 4, 7–9 vs 14 and entry 5 vs 15). However with ligand **L6a**, which had a phenyl substituent, the enantioselectivities obtained were similar to those reported with ligand **2a** (entry 10 vs 14).

In summary, the best results were achieved (ee's up to >99.9%) with ligand **L1b** (Table 1, entry 2), which contains the optimal combination of ligand parameters (substituent at C-3 and configuration at the C-3 position of the furanoside ring and at the biaryl group). When this latter result is compared with the enantioselectivity obtained with the corresponding Rh/**1b** catalytic system, it can be concluded that introducing a methyl group into ligand **1b** at C-3 is advantageous. This result is among the best that have been reported.[1]

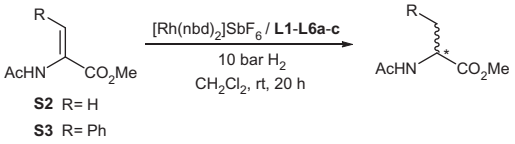
Table 1
Selected results for the Rh-catalyzed hydrogenation of **S1** using the furanoside monophosphite ligand library **L1**–**L6a**–**c**[a]



Entry	Ligand	Conv[b] (%)	ee[c] (%)
1	**L1a**	100	86 (*R*)
2	**L1b**	100	>99.9 (*S*)
3	**L1c**	<5	nd[e]
4	**L2a**	100	33 (*R*)
5	**L2b**	100	15 (*S*)
6	**L2c**	<5	nd[e]
7	**L3a**	100	4 (*R*)
8	**L4a**	100	52 (*R*)
9	**L5a**	100	12 (*R*)
10	**L6a**	100	93 (*S*)
11	**1a**	100	92.8 (*R*)[d]
12	**1b**	100	99.1 (*S*)[d]
13	**1c**	<5	nd[e]
14	**2a**	100	93.6 (*R*)[d]
15	**2b**	100	77.5 (*S*)[d]
16	**2c**	<5	nd[e]

[a] $[Rh(nbd)_2]SbF_6$ (1 mol %), ligand (1.1 mol %), **S1** (1 mmol), CH_2Cl_2 (6 mL), 10 bar of H_2, room temperature.
[b] % Conversion measured by GC.
[c] Enantiomeric excess measured by GC.
[d] Data from Ref. 4e.
[e] Not determined.

Table 2
Selected results for the Rh-catalyzed hydrogenation of α-dehydroamino acid esters **S2**–**S3** using the furanoside monophosphite ligand library **L1**–**L6a**–**c**[a]



Entry	Ligand	S2		S3	
		Conv[b] (%)	ee[c] (%)	Conv[b] (%)	ee[c] (%)
1	**L1a**	100	23 (*S*)	100	25 (*S*)
2	**L1b**	100	85 (*S*)	100	84 (*S*)
3	**L1c**	<5	nd[e]	<5	nd[e]
4	**L2a**	100	32 (*R*)	100	38 (*R*)
5	**L2b**	100	45 (*S*)	100	43 (*S*)
6	**L2c**	<5	nd[e]	<5	nd[e]
7	**L3a**	100	29 (*R*)	100	64 (*R*)
8	**L4a**	100	10 (*R*)	100	7 (*R*)
9	**L5a**	100	34 (*R*)	100	35 (*S*)
10	**L6a**	100	58 (*R*)	100	73 (*R*)
11	**1a**	100	87.9 (*S*)[d]	100	84 (*S*)
12	**1b**	100	79.9 (*R*)[d]	100	68 (*R*)
13	**1c**	<5	nd[e]	<5	nd[e]
14	**2a**	100	26.5 (*R*)[d]	100	30 (*R*)
15	**2b**	100	5.5 (*S*)[d]	100	7 (*S*)
16	**2c**	<5	nd[e]	<5	nd[e]

[a] $[Rh(nbd)_2]SbF_6$ (1 mol %), ligand (1.1 mol %), **S2** (1 mmol), CH_2Cl_2 (6 mL), 10 bar of H_2, room temperature, 20 h.
[b] % Conversion measured by GC.
[c] Enantiomeric excess measured by GC.
[d] Data from Ref. 4f.
[e] Not determined.

2.2. Asymmetric hydrogenation of α-dehydroamino acid esters S2–S3

We also screened monophosphite ligands **L1**–**L6a**–**c** in the asymmetric reduction of some benchmark α-dehydroamino acid derivatives, methyl 2-acetamidoacrylate **S2** and methyl 2-acetamidocinnamate **S3**. The results, which are summarized in Table 2, again showed that bulky biaryl substituents **c** have a detrimental effect on the catalytic activity (i.e., ligands **L1**–**L2c** and **1**–**2c**; entries 3, 6, 13 and 16).

As for **S1**, the effect on the enantioselectivity of introducing a new substituent at C-3 depends on the configuration at C-3 of the furanoside backbone and at the binaphthyl moiety. For glucofuranoside ligands, this again led to a matched combination for glucofuranoside ligand **L1b**, containing an (*S*)-binaphthyl moiety (entry 2 vs 12), and a mismatched combination for **L1a** with an (*R*)-binaphthyl group (entry 1 vs 11). However, the effect of the substituents for allofuranoside ligands is slightly different than for **S1**. Thus, regardless of the configuration of the binaphthyl group, the introduction of a new substituent at C-3 generally had a positive effect on the enantioselectivity (i.e., entries 4–5 vs 14–15, respectively). Again, for the allofuranoside ligands, the highest enantioselectivity was achieved when using ligand **L6a** (i.e., for **S3**, the ee's increased from 30% to 73% by introducing a phenyl substituent at C-3; entry 10 vs 14).

In summary, the results again show that the introduction of a methyl substituent at the C-3 position in a glucofuranoside ligand containing an (*S*)-binaphthyl moiety has a positive effect on the enantioselectivity (ligand **L1b**; i.e., for **S3**, ee's increased from 68% to 84%; Table 2, entry 2 vs 12).

2.3. Asymmetric hydrogenation of enamides S4–S8

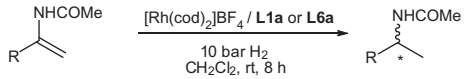
To further expand upon the scope of monophosphite ligands **L1**–**L6a**–**c** and further investigate the influence of introducing a new substituent at the C-3 position of the furanoside backbone, we examined the Rh-catalyzed enantioselective hydrogenation of several 1,1-disubstituted-α-arylenamides (Eq. 1). The hydrogenation of this substrate class provides access to chiral secondary amines, which are highly valuable intermediates for preparing chiral pharmaceutical and agricultural products.[7]

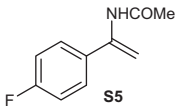
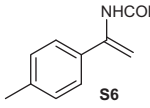
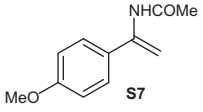
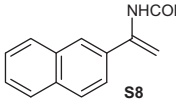
Table 3
Selected results for the Rh-catalyzed hydrogenation of **S4** using the furanoside monophosphite ligand library **L1**–**L6a**–**c**[a]

Entry	Ligand	Conv[b] (%)	ee[c] (%)
1	**L1a**	100	54 (*S*)
2	**L1b**	100	24 (*R*)
3	**L1c**	<5	nd[e]
4	**L2a**	100	32 (*R*)
5	**L2b**	100	44 (*S*)
6	**L2c**	<5	nd[e]
7	**L3a**	100	29 (*R*)
8	**L4a**	100	18 (*R*)
9	**L5a**	100	26 (*R*)
10	**L6a**	100	58 (*R*)
11	**1a**	100	93.9 (*S*)[d]
12	**1b**	100	85.5 (*R*)[d]
13	**1c**	<5	nd[e]
14	**2a**	100	49.1 (*R*)[d]
15	**2b**	100	87.1 (*S*)[d]
16	**2c**	<5	nd[e]

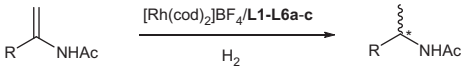
[a] $[Rh(nbd)_2]SbF_6$ (1 mol %), ligand (1.1 mol %), **S2** (1 mmol), CH_2Cl_2 (6 mL), 10 bar of H_2, room temperature, 8 h.
[b] % Conversion measured by GC.
[c] Enantiomeric excess measured by GC.
[d] Data from Ref. 4e.
[e] Not determined.

Table 4
Selected results for the Rh-catalyzed hydrogenation of enamides **S5**–**S8** using the Rh/**L1a** and Rh/**L6a** catalytic system[a]



Entry	Ligand	Ligand	Conv[b] (%)	ee[c] (%)
1	 **S5**	**L1a**	100	53 (*S*)
2		**L6a**	100	57 (*R*)
3	 **S6**	**L1a**	100	59 (*S*)
4		**L6a**	100	61 (*R*)
5	 **S7**	**L1a**	100	56 (*S*)
6		**L6a**	100	59 (*R*)
7	 **S8**	**L1a**	100	64 (*S*)
8		**L6a**	100	67 (*R*)

[a] $[Rh(cod)_2]BF_4$ (1 mol %), ligand (1.1 mol %), substrate (0.5 mmol), CH_2Cl_2 (6 mL), 30 bar of H_2, room temperature.
[b] % Conversion measured by GC.
[c] Enantiomeric excess measured by GC.



S4 R= C_6H_5
S5 R= 4-F-C_6H_4
S6 R= 4-Me-C_6H_4
S7 R= 4-MeO-C_6H_4
S8 R= 2-Naphthyl

(1)

First, we used *N*-(1-phenylvinyl)-acetamide **S4** as a substrate in order to study the potential of the ligand library. The results are summarized in Table 3. In general, the catalytic activity and enantioselectivity are affected by the same parameters that affect the α,β-unsaturated carboxylic acid derivatives **S1**–**S3**.

Therefore for this class of compounds, the presence of a very bulky biphenyl substituent in the phosphite moiety of the catalyst ligand completely suppresses activity (see Table 3, entries 3, 6, 13, 16). However, in all cases except for ligand **L6a** (entry 10 vs 14), the introduction of a substituent at C-3 has a negative effect on the enantioselectivity (i.e., entries 1–2 vs 11–12, and entries 4–5 vs 14–15). As observed for previously reported ligands **1**–**2**, both enantiomers of the hydrogenation product can be obtained using diastereomeric ligands **L1a** and **L6a** (entries 1 and 10).

Based on this first screening, the best performing ligands **L1a** and **L6a** among the novel synthesized ones were tested in the Rh-catalyzed hydrogenation of other enamides with different aryl substituents. The results, which are shown in Table 4, indicate that the catalytic performance (activity and enantioselectivity) is hardly affected by the presence of either electron-donating or electron-withdrawing groups at the *para* position of the aryl group. However, the enantioselectivity was highest when *N*-(1-(2-naphthyl)vinyl)-acetamide **S8** was used as the substrate (ee's up to 67%; Table 4, entries 7 and 8).

3. Conclusion

We have expanded upon the ligand design of one of the most successful monophosphite ligand classes in Rh-catalyzed hydrogenations by introducing several substituents at the C-3 position of the furanoside backbone. Thanks to the modular nature of carbohydrate feedstocks, these modifications were easily made by using D-(+)-glucose as a readily available chiral source. These new furanoside monophosphite ligands were evaluated in the Rh-catalyzed asymmetric hydrogenation of a range of α,β-unsaturated carboxylic acid derivatives and enamides. The effect that these new substituents have on the enantioselectivity generally depends not only on the configuration at the C-3 position of the furanoside backbone and at the binaphthyl moiety but also on the substrate. Thus for α,β-unsaturated carboxylic acids, enantioselectivities improved when a methyl substituent was introduced at the C-3 position in a glucofuranoside ligand containing an (*S*)-binaphthyl group (ligand **L1a**). Enantioselectivities were therefore increased to >99.9% ee and 85% ee in the asymmetric reduction of dimethyl itaconate and dehydroamino acid derivatives, respectively. However, in the reduction of enamides, the introduction of substituents at the C-3 position of the furanoside backbone had a negative effect and enantioselectivities were only moderate (ee's up to 67%).

4. Experimental

4.1. General

All syntheses were performed by using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Monophosphite ligands **1**–**2a**–**c**[4d,8] and **L1**–**L6a**–**c**[6] were prepared as previously reported. Methyl (*Z*)-*N*-acetylaminocinnamate **S3**[9] and enamides **S4**–**S8**[10] were prepared following the literature. All other reagents were used as commercially available. ^{1}H NMR spectra experiments were recorded using a 400 MHz spectrometer.

4.2. General procedure for asymmetric hydrogenation

In a typical run, $[Rh(nbd)_2]SbF_6$ (5.2 mg, 0.01 mmol), and the corresponding ligand (0.022 mmol, 2.2 equiv) were dissolved in dichloromethane (6 mL) and the resulting solution was stirred at room temperature for 30 min. The catalyst solution was then transferred to a steel autoclave equipped with a glass liner already containing the substrate (1 mmol). The autoclave was purged five times with hydrogen gas. Next, it was pressurized to the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (2 mL) and filtered through a short plug of Celite. The enantiomeric excess was determined by chiral GC and conversions were determined by GC and confirmed by ^{1}H NMR. The enantiomeric excesses of the hydrogenated products were determined by GC.[11]

S1. Enantioselectivity determined using a Chiraldex β-DM column (100 kPa H_2, Isotherm at 60 °C). t_R 25.6 min (*R*); t_R 26.5 min (*S*).
S2. Enantioselectivity determined using a L-Chirasil-Val column (100 kPa H_2, Isotherm at 100 °C). t_R 4.8 min (*R*); t_R 5.7 min (*S*).
S3. Enantioselectivity determined using a L-Chirasil-Val column (150 kPa H_2, Isotherm at 150 °C). t_R 8.7 min (*R*); t_R 9.8 min (*S*).
S4. Enantioselectivity determined using a Chiraldex CB column (80 kPa H_2, temperature program: 125 °C for 4 min–3 °C/min – 140 °C for 5 min – 20 °C/min – 180 °C). t_R 15.4 min (*S*); t_R 15.7 min (*R*).
S5. Enantioselectivity determined using a Chiraldex CB column (80 kPa H_2, temperature program: 100 °C for 5 min – 3 °C/min – 155 °C for 5 min – 20 °C/min – 180 °C). t_R 29.0 min (*S*); t_R 29.5 min (*R*).
S6. Enantioselectivity determined using a Chiraldex CB column (80 kPa H_2, temperature program: 125 °C for 4 min – 3 °C/min – 140 °C for 5 min – 20 °C/min – 180 °C). t_R 26.4 min (*S*); t_R 27.1 min (*R*).
S7. Enantioselectivity determined using a Chiraldex CB column (80 kPa H_2, temperature program: 100 °C for 5 min – 3 °C/min – 155 °C for 5 min – 20 °C/min – 180 °C). t_R 38.4 min (*S*); t_R 38.8 min (*R*).
S8. Enantioselectivity determined using a Chiraldex CB column (80 kPa H_2, temperature program: 150 °C for 5 min – 1 °C/min – 155 °C for 5 min – 20 °C/min – 180 °C). t_R 54.7 min (*S*); t_R 55.2 min (*R*).

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