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Modular carbohydrate diphosphite and phosphite–phosphoroamidite ligands for asymmetric Rh-catalyzed hydrosilylation of ketones

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Abstract—A series of diphosphite **1**–**6** and phosphite–phosphoroamidite **7** ligands, derived from inexpensive D-(+)-xylose and D-(+)-glucose, were evaluated in the asymmetric Rh-catalyzed hydrosilylation of different ketones. Systematic variation of the configuration of the stereocenters at the ligand backbone and that of the substituents at the phosphite moiety provide useful information about the ligand parameters that control the enantiodiscrimination.

1. Introduction

In the last few decades, the asymmetric rhodium-catalyzed hydrosilylation of ketones has been recognized as a versatile method for providing optically active secondary alcohols.[1] Over many years, a large number of chiral ligands, mainly *P*- and *N*-containing compounds possessing either C_1- or C_2-symmetry, have been used successfully in the asymmetric rhodium-catalyzed hydrosilylation.[1] Of the *P*-ligands, phosphines have played a dominant role in the success of hydrosilylation,[2] although the potential of phosphinite[3] and phosphonite[4] ligands has also been investigated.

Phosphite ligands are a very attractive group of compounds for catalysis and have been successfully applied in other transition-metal-catalyzed reactions such as hydroformylation, hydrocyanation, hydrogenation and allylic alkylation.[5] These ligands have many advantages; for example, they are easy to prepare from readily available starting materials and are less sensitive to oxygen than phosphines.[6] However, little attention has been paid to these kinds of ligands for asymmetric hydrosilylation reactions.[7] To our knowledge, only Pastor et al.[7c] have reported high levels of enantioselectivity using phosphite ligands in the Rh-asymmetric hydrosilylation of ketones. The design of new phosphite ligands is therefore needed to understand the role the phosphite moiety plays in the origin of the stereochemistry of the hydrosilylation reaction.

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For this purpose, carbohydrates are particularly advantageous. They are readily available and highly functionalized compounds with several stereogenic centers. This allows a systematic regio- and stereoselective introduction of different functionalities in the synthesis of series of chiral ligands that can be screened in the search for high activities and enantioselectivities. At the same time, they can provide useful information about the origin of the stereoselectivity of the reaction.[5f,5j]

We report herein the use of a series of phosphite furanoside ligands **1**–**7** (Fig. 1) in the enantioselective Rh-catalyzed hydrosilylation of ketones. These ligands, which are easily prepared from readily available D-(+)-xylose or D-(+)-glucose, allow the systematic variation of different ligand parameters which may provide some insight into the origin of the stereochemistry of the reaction.

2. Results and discussion

2.1. Ligand design

Ligands **1**–**7** consist of a chiral 1,2-*O*-protected furanoside backbone, which determines their underlying structure, a hydroxyl group at C(3) and either a hydroxyl group (diphosphite ligands **1**–**6**) or an amine (phosphite-phosphoroamidite ligands **7**) at C(5). Several phosphoric acid biphenol ester residues are attached to this basic framework (Fig. 1).

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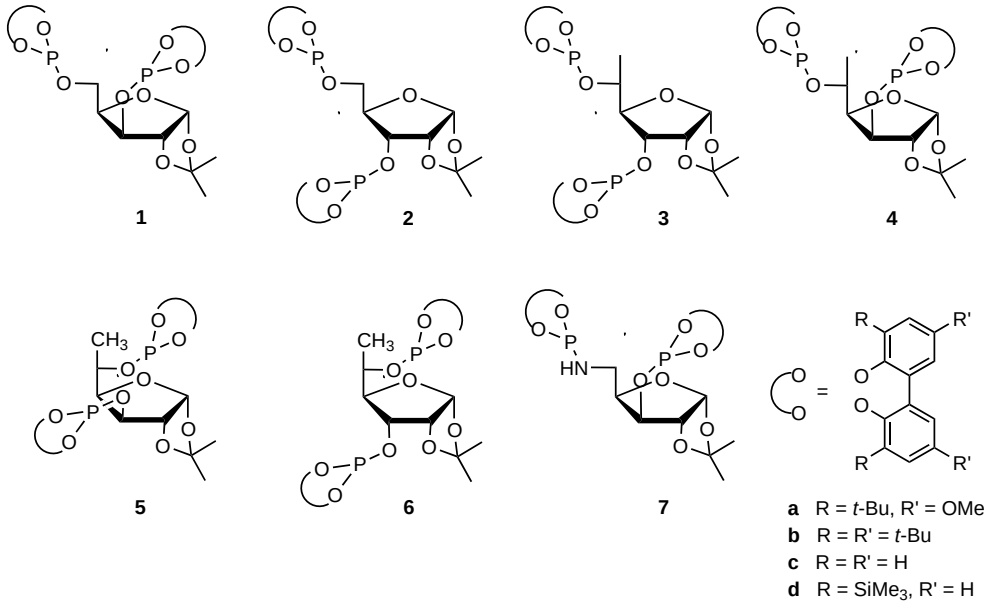


Figure 1.

We then investigated how the different groups attached to the *ortho* and *para* positions of the biphenyl moieties affected the enantioselectivity using ligands **1**–**6**. We also examined the influence of the C(3) stereogenic center by comparing diastereomeric ligands **1** with ligands **2**, which have opposite configuration at C(3) and the same biphenyl substituents. The influence of the C(5) stereogenic center was investigated to determine whether there is a cooperative effect between the C(3) and C(5) stereocenters using ligands **3**–**6**, which result from the systematic variation in the configuration of both stereocenters. Finally, we studied the effect of a phosphoroamidite moiety rather than a phosphite moiety at carbon atom C(5) by using ligands **7**.

2.2. Asymmetric hydrosilylation of ketones

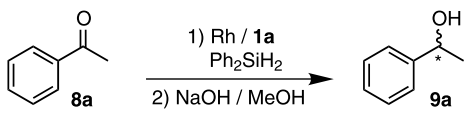
The catalytic performance of ligands **1**–**7** was thoroughly explored in the enantioselective rhodium-catalyzed hydrosilylation reaction. In a first set of experiments, we used these ligands in the rhodium-catalyzed hydrosilylation of acetophenone **8a**. The reaction proceeded smoothly at room temperature. In general, the catalysts were prepared in situ by adding the corresponding ligand to the catalyst precursor.

The effects of several reaction parameters (i.e. solvent, catalyst precursor, catalyst preparation and ligand-to-rhodium ratio) were investigated for the catalytic precursor containing ligand **1a**. The results are summarized in Table 1.

The results show that the efficiency of the process depended on the nature of the catalyst precursor and on the solvent (entries 1–6). Although activity was best when $[Rh(\mu\text{-}Cl)(cod)]_2$ (cod = 1,5-cyclooctadiene) was used as the catalyst precursor (entries 1–3), the enantioselectivity was highest when $[Rh(cod)_2]BF_4$ was used as the catalyst precursor and THF was used as the solvent (entries 5 and 7). Adding a one-fold excess of ligand had a positive effect on enantioselectivity, but significantly lowered the activity (entry 7). Using preformed catalyst precursor $[Rh(cod)(\mathbf{1a})]BF_4$ did not affect the efficiency of the process (entry 8 versus 5).

For comparison, the rest of the ligands were tested under the conditions that gave an optimum compromise between the enantioselectivity and reaction rate, that is a ligand-to-rhodium ratio of 1.1, using $[Rh(cod)_2]BF_4$ as the catalyst precursor and tetrahydrofuran as the solvent (Table 2). The hydrosilylation results with catalyst precursors containing ligands **1**–**7** are summarized as follows.

Table 1. Rh-catalyzed asymmetric hydrosilylation of acetophenone using diphosphite ligand **1a**[a]



Entry	Precursor	Solvent	% Conv.[b]	% E.e.[c]
1	$[Rh(\mu\text{-}Cl)(cod)]_2$	CH_2Cl_2	82	32 (*R*)
2	$[Rh(\mu\text{-}Cl)(cod)]_2$	THF	89	32 (*R*)
3	$[Rh(\mu\text{-}Cl)(cod)]_2$	Toluene	57	23 (*R*)
4	$[Rh(cod)_2]BF_4$	CH_2Cl_2	55	31 (*R*)
5	$[Rh(cod)_2]BF_4$	THF	56	39 (*R*)
6	$[Rh(cod)_2]BF_4$	Toluene	65	33 (*R*)
7[d]	$[Rh(cod)_2]BF_4$	THF	5	45 (*R*)
8[e]	$[Rh(cod)(\mathbf{1a})]BF_4$	THF	54	39 (*R*)

[a] Reaction conditions: acetophenone (1 mmol), Ph_2SiH_2 (1 mmol), ligand (0.011 mmol), ligand/Rh = 1.1, solvent (2 mL), T = 25°C.
[b] % Conversion after 16 h.
[c] % Enantiomeric excess measured by GC.
[d] Ligand/Rh = 2.
[e] Using 0.01 mmol of preformed $[Rh(cod)(\mathbf{1a})]BF_4$.

Table 2. Rh-catalyzed asymmetric hydrosilylation of acetophenone using ligands **1**–**7**[a]

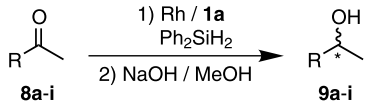
Entry	Ligand	% Conv.[b]	% E.e.[c]
1	**1a**	56	39 (*R*)
2	**1b**	52	45 (*R*)
3	**1c**	62	51 (*R*)
4	**2a**	53	10 (*S*)
5	**2b**	56	9 (*S*)
6	**2c**	56	26 (*S*)
7	**3a**	48	7 (*S*)
8	**3b**	62	12 (*S*)
9	**3c**	47	10 (*S*)
10	**3d**	33	33 (*S*)
11	**4a**	42	25 (*R*)
12	**4b**	63	28 (*R*)
13	**4c**	44	22 (*R*)
14	**4d**	38	40 (*R*)
15	**5a**	41	33 (*R*)
16	**5b**	58	39 (*R*)
17	**6a**	45	9 (*S*)
18	**6b**	63	14 (*S*)
19	**7a**	49	4 (*R*)
20	**7b**	40	12 (*R*)

[a] Reaction conditions: acetophenone (1 mmol), Ph_2SiH_2 (1 mmol), ligand (0.011 mmol), ligand/Rh = 1.1, THF (2 mL), $T = 25°C$.
[b] % Conversion after 16 h.
[c] % Enantiomeric excess measured by GC.

(1) The sense of the enantiodiscrimination is predominantly controlled by the configuration at C(3). Accordingly, ligands **1**, **4**, **5** and **7**, with (*S*)-configuration at C(3), gave (*R*)-phenylethanol (entries 1–3, 11–16, 19 and 20), while ligands **2**, **3** and **6**, with (*R*)-configuration at C(3), gave (*S*)-phenylethanol (entries 4–10, 17 and 18).
(2) There is a cooperative effect between the C(3) and C(5) stereocenters, i.e. the value of enantioselectivity when C(3) has either (*R*)- or (*S*)-configuration depends on the configuration at C(5). For instance, when the configuration of C(3) was *S*, changing C(5) from *R* (ligand **4b**, entry 12) to *S* (ligand **5b**, entry 16) led to increased enantioselectivity from 28% (*R*) to 39% (*R*). However, when the configuration at C(3) was *R*; the same change of C(5) from *R* (ligand **3b**, entry 8) to *S* (ligand **6b**, entry 18) had little effect on the enantioselectivity.
(3) The efficiency of the catalyst systems is greatly affected by the substituents at the *ortho* and *para* positions of the biphenyl moieties. However, there are two different trends depending on the substituents at C(5). Thus, for catalyst precursors **3**–**6** (entries 7–18), which contain a methyl substituent at C(5), the enantioselectivity was better when bulky groups were attached at the *ortho* positions of the biphenyl moieties, and activity was better when *tert*-butyl groups were attached to the *para* positions of the biphenyl moieties. However, for catalyst precursors **1** and **2** (entries 1–6), which do not have substituents at C(5), the activity and enantioselectivity were better when the biphenyl moieties bore no substituents.
(4) A more basic phosphoroamidite moiety rather than a phosphite moiety at C(5) has a negative effect on catalytic activity and enantioselectivity (entries 1 and 2 versus 19 and 20).

We then studied how the steric and electronic properties of the ketone affected the outcome of the reaction. For this purpose, a series of substituted benchmark ketones **8a**–**i** were tested using the catalyst precursor containing ligand **1a**. The results are summarized in Table 3. The results when using acetophenones **8a**–**e**, which contain different *para*-phenyl substituents, clearly show that catalyst performance (activity and enantioselectivity) is affected by the electronic properties of the substrate. Therefore, both activity and enantioselectivity were better for electron-rich ketones. If we compare the results from using *para*-, *meta*- and *ortho*-substituted methoxy acetophenones **8c**, **8f** and **8g** (entries 3, 6 and 7), we can clearly see that the steric bulk caused by the *ortho*-methoxy substituent led to increased enantioselectivity. As expected, when 2-naphthylmethyl ketone **8h** was used the enantioselectivity was similar to that seen when acetophenone **8a** was used (entry 1 versus 8) and with the less sterically hindered cyclopropylmethyl ketone **8i**, low enantioselectivity was observed (entry 9).

Table 3. Rh-catalyzed asymmetric hydrosilylation of ketones **8** using diphosphite ligand **1a**[a]



8a-i **9a-i**

Entry	Substrate	R	% Conv.[b]	% E.e.[c]
1	**8a**	C_6H_5	56	39 (*R*)
2	**8b**	4-F-C_6H_4	51	34 (*R*)
3	**8c**	4-OMe-C_6H_4	66	42 (*R*)
4	**8d**	4-CH_3-C_6H_4	59	40 (*R*)
5	**8e**	4-CF_3-C_6H_4	46	15 (*R*)
6	**8f**	3-OMe-C_6H_4	42	41 (*R*)
7	**8g**	2-OMe-C_6H_4	54	50 (*S*)
8	**8h**	2-Naphthyl	59	38 (*R*)
9	**8i**	Cyclopropyl	48	22 (*R*)

[a] Reaction conditions: Substrate (1 mmol), Ph_2SiH_2 (1 mmol), ligand (0.011 mmol), ligand/Rh = 1.1, THF (2 mL), $T = 25°C$.
[b] % Conversion after 16 h.
[c] % Enantiomeric excess measured by GC.

3. Experimental

3.1. General comments

All syntheses were performed using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. Complexes $[Rh(\mu\text{-}Cl)(cod)]_2$,[8] $[Rh(cod)_2]BF_4$[9] and $[Rh(cod)(\mathbf{1a})]BF_4$[10] and ligands **1**,[11] **2**,[12] **3**–**6**[5f,13] and **7**[14] were prepared according to the literature procedures. All other reagents were used as commercially available. Gas chromatographic analyses were run on a Hewlett–Packard HP 5890A

instrument equipped with a CP-chirasil-Dex CB column.

3.2. General procedure for asymmetric hydrosilylation reactions

In a typical run, to a solution of catalyst precursor $[Rh(cod)_2]BF_4$ (0.01 mmol) in dichloromethane (2 mL) the ligand (0.011 mmol) was added. After 5 min, the dichloromethane was evaporated and THF (2 mL) was added. Ketone (1 mmol), Ph_2SiH_2 (1 mmol) and undecane as GC internal standard (0.1 mL) were then added. The reaction mixture was then stirred at room temperature for 16 h. The solution was then quenched with MeOH (7 mL) and 2.5 M aqueous NaOH (5 mL). The mixture was extracted with diethyl ether (3×5 mL) and the combined ether phases were dried over Na_2SO_4, filtered and the filtrate was concentrated. The conversion and enantiomeric excesses were obtained by GC.

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