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Chiral phosphite–phosphoroamidites: a new class of ligand for asymmetric catalytic hydrogenation

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A series of novel phosphite–phosphoroamidite ligands, derived from readily available D-xylose, has been used for the first time in the asymmetric Rh-catalyzed hydrogenation of a series of α,β-unsaturated carboxylic acid derivatives with excellent enantioselectivity (ee up to > 99%).

Many chiral phosphorus compounds have been synthesized as ligands for enantioselective metal-catalyzed hydrogenation.[1] Most of them are homodonor ligands, mainly diphosphines[1,2] and diphosphinites.[3] However, the combination of different functionalities in a ligand has already proved beneficial in enantiodiscrimination.[4] In this context, we have recently reported the successful application of mixed phosphine–phosphite ligands in asymmetric hydrogenation.[5]

In the last few years, a group of less electron-rich phosphorus compounds—phosphite[6] and phosphoroamidite[7] ligands—have also demonstrated their potential utility in asymmetric hydrogenation. Therefore we here report the development of a new class of chiral phosphite–phosphoroamidite ligands (**1–4**), which have the advantages of both types of ligands for asymmetric hydrogenation (Fig. 1). These ligands are derived from natural D-xylose so they also have the advantages of carbohydrates, such as availability at low price and facile modular construction, which makes tedious optical resolution procedures unnecessary and facilitates regio- and stereoselective introduction of different functionalities.[8] To the best of our knowledge this is the first example of phosphite–phosphoroamidite ligands applied to hydrogenation.[9]

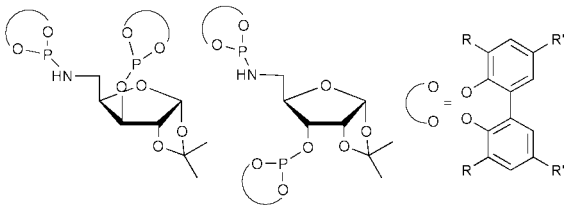
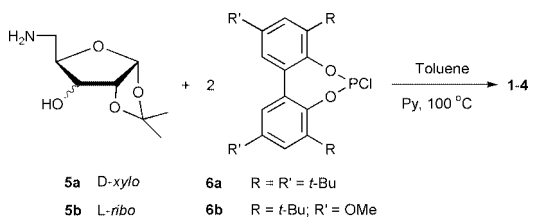


Fig. 1 Phosphite–phosphoroamidite ligands **1–4**.

Ligands **1–4**[10] incorporate a chiral furanoside backbone, which determines their underlying structure, and one amino group at the C5 position. The amino furanosides **5**[11] (Scheme 1) serve as basic frameworks to which several phosphoric acid biphenol esters **6**[12] are attached.



Scheme 1 Synthesis of ligands **1–4**.

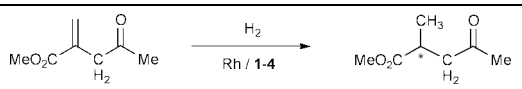
The modular nature of these sugar ligands allows a facile systematic variation in the configuration of the stereocenter at carbon atom C-3 at the ligand bridge and in the biphenyl substituents, so the optimum configuration for maximum stereoselectivity can be determined. Thus, we investigated how the different groups attached to the *para* positions of the bisphenol moieties affected enantioselectivity using ligands **1** and **2**, which have the same configuration on the carbon atom C-3. We also investigated the influence of the stereogenic carbonatom C-3 by comparing diastereomeric ligands **3** and **4** with ligands **1** and **2**, which have the opposite configuration at C-3 and the same substituents in the biphenyl moieties.

In the first set of experiments, we used the rhodium-catalyzed hydrogenation of **7** to scope the potential of ligands **1–4**. The reaction proceeded smoothly at room temperature. The catalysts were prepared *in situ* by adding the corresponding phosphite–phosphoroamidite ligands to $[Rh(cod)_2]BF_4$ as a catalyst precursor.[13] The results are given in Table 1.

Interestingly, both enantioselectivity and activity notably improved when the hydrogen pressure was raised from 1 bar to 2.5 bar (entry 1 *vs.* 2). However, further increasing the hydrogen pressure had a positive effect on the activity, while the enantioselectivity remained the same (entries 3 and 5). This contrasts with the decrease in enantioselectivity usually observed with bidentate ligands when the hydrogen pressure is raised.[1a,7a,14] This allowed us to perform the reaction at lower catalyst concentration without loss in enantioselectivity and good activity (entry 6).

The addition of one fold excess of ligand did not affect the outcome of the reaction (entry 4). An increase in enantioselectivity (> 99%, entry 7) combined with good activity was found by lowering the reaction temperature. There were no changes in the enantioselectivities over time, which indicates that no decomposition of the catalyst took place.

Table 1 Asymmetric hydrogenation of **7** with $[Rh(cod)_2]BF_4$/**1–4**[a]



7 **8**

Entry	Ligand	P_{H2}/bar	% Conv. (*t*/h)[b]	% ee[c]
1	**1**	1	100 (20)	65 (*R*)
2	**1**	2.5	45 (8)	97 (*R*)
3	**1**	5	100 (8)	96 (*R*)
4[d]	**1**	5	100 (8)	96 (*R*)
5	**1**	30	100 (1.5)	97 (*R*)
6[e]	**1**	30	100 (10)	97 (*R*)
7[f]	**1**	30	100 (12)	> 99 (*R*)
8	**2**	5	86 (8)	86 (*R*)
9	**3**	5	46 (8)	34 (*R*)
10	**4**	5	40 (8)	30 (*R*)

[a] $[Rh(cod)_2]BF_4$ = 0.01 mmol. Ligand/Rh = 1.1. Substrate/Rh = 100. CH_2Cl_2 = 6 mL. *T* = 25 °C. [b] % Conversion measured by GC. [c] % Enantiomeric excess measured by GC using a Chiraldex G-TA column. [d] Ligand/Rh = 2. [e] Substrate/Rh = 1000. [f] At 5 °C.

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The rest of the ligands were compared under 'standard' conditions *i.e.* dichloromethane as a solvent, 5 bar of hydrogen pressure, a ligand-to-rhodium ratio of 1 and at room temperature. Using ligand **2**, with methoxy groups instead of the *tert*-butyl groups in *para* positions of the biphenol moieties, resulted in slightly lower activity and enantioselectivity (entry 3 *vs.* 8). Ligands **3** and **4** whose configuration of carbon atom C-3 is opposite to those of ligands **1** and **2**, respectively, produced a lower reaction rate and enantioselectivity (entry 3 and 8 *vs.* 9 and 10).

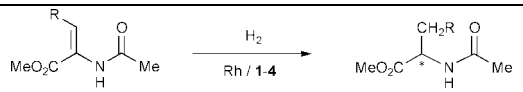
The results clearly show that the enantiomeric excesses and activities depend strongly on the absolute configuration of the C3 stereocenter of the carbohydrate backbone and the substituents in the biphenyl moities. Therefore, enantioselectivities and activities were best using ligand **1** with a *S* configuration at C-3 and *tert*-butyl groups in the *ortho*- and *para*-positions of the biphenyl moieties.

We subsequently applied these new highly efficient phosphite–phosphoroamidite ligands **1**–**4** in the Rh-catalyzed hydrogenation of other benchmark dehydroaminoacid derivatives (Table 2). The results followed the same trend as for substrate **7**. The absolute configuration of the hydrogenated products **10** and **12** is opposite that of the hydrogenated product **8**, but they have the same spatial arrangement.[15] The catalyst precursor with ligand **1** produced the highest enantiomeric excess (98%, entries 5 and 10).

It is remarkable that these phosphite–phosphoroamidite ligands showed a much higher degree of enantioselectivity and higher reaction rates than their corresponding diphosphite analogues under similar reaction conditions (entries 1–4 *vs.* 11 and 12).[13,16]

In summary, we have described the first application of phosphite–phosphoroamite ligands in the asymmetric hydrogenation reaction. These ligands can be easily prepared in a few steps from commercial D-(+)-xylose as an inexpensive natural chiral source. Regarding both good activity and the excellent enantioselectivity (up to >99% ee) obtained in simple unoptimised asymmetric hydrogenation of a series of α,β-unsaturated carboxylic acid derivatives, we feel that a promising new class of ligands—the phosphite–phosphoroamidite—has been disclosed for enantioselective Rh-catalyzed asymmetric hydrogenation. Moreover, because of the modular construction of these phosphite–phosphoroamidite ligands,

Table 2 Asymmetric hydrogenation of methyl *N*-acetylaminoacrylate **9** and methyl (*Z*)-*N*-acetylaminocinnamate **11** with $[Rh(cod)_2]BF_4$/**1**–**4**[a]

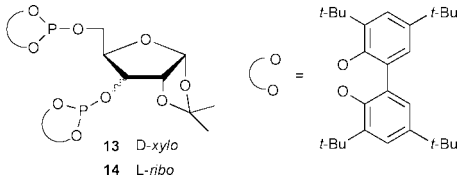


9 R = H
11 R = Ph

10 R = H
12 R = Ph

Entry	Substrate	Ligand	P_{H_2}/bar	% Conv. (*t*/h)[b]	% ee[c]
1	**9**	**1**	5	100 (8)	92 (*S*)
2	**9**	**2**	5	71 (8)	82 (*S*)
3	**9**	**3**	5	46 (8)	15 (*S*)
4	**9**	**4**	5	33 (8)	12 (*S*)
5[d]	**9**	**1**	30	100 (12)	98 (*S*)
6	**10**	**1**	5	77 (8)	94 (*S*)
7	**10**	**2**	5	53 (8)	85 (*S*)
8	**10**	**3**	5	29 (8)	18 (*S*)
9	**10**	**4**	5	35 (8)	17 (*S*)
10[d]	**10**	**1**	30	72 (12)	98 (*S*)
11	**9**	**13**	5	94 (20)	33 (*S*)
12	**9**	**14**	5	56 (20)	4 (*R*)

[a] $[Rh(cod)_2]BF_4$ = 0.01 mmol. Ligand/Rh = 1.1. Substrate/Rh = 100. CH_2Cl_2 = 6 mL. T = 25 °C. [b] % Conversion measured by GC. [c] % ee measured by GC using a Permabond L-Chirasil-Val column. [d] At 5 °C.



further structural diversity is easy to achieve, so enantioselectivity and catalyst performance can be maximized for each new substrate as required. Studies of this kind, as well as mechanistic studies, are currently under way.

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10 The new ligands **1**–**4** were synthesized very efficiently in one step by treatment of the corresponding aminoalcohols **5**, easily prepared on large scale from readily available D-(+)-xylose, with two equivalents of the desired *in situ* formed phosphorochloridites **6** in the presence of pyridine. Selected NMR data. **1**: δ_P ($CDCl_3$) 144.8 (br s), 145.1 (s). **2**: δ_P ($CDCl_3$) 144.0 (s), 145.9 (s). **3**: δ_P ($CDCl_3$) 143.2 (s), 150.2 (s). **4**: δ_P ($CDCl_3$) 143.5 (s), 149.3 (s).

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