Highly enantioselective hydrogenation of enol ester phosphonates catalyzed by rhodium phosphine-phosphite complexes†

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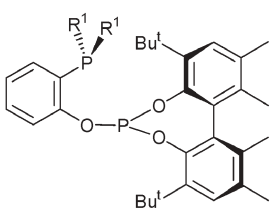
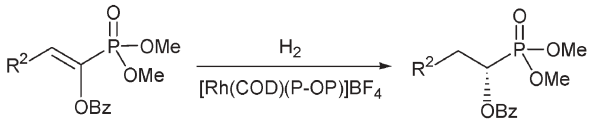
Chiral phosphine-phosphites provide versatile catalysts for the highly enantioselective hydrogenation of α-acyloxy α,β-unsaturated phosphonates.

Chiral α-hydroxy phosphonates are important compounds with biological significance as enzyme inhibitors,[1] as well as synthetic interest because they can lead to a broad variety of α-functionalized optically active phosphonates.[2] Interestingly, the enantioselective hydrogenation of enol ester phosphonates provides a convenient access to the synthesis of chiral α-hydroxy phosphonates,[3] but this reaction has received limited attention. Studies covering the scope of this transformation comprise the application of rhodium catalysts bearing strong donor C_2 symmetric diphosphines.[3,4] It is noteworthy that these complexes provide good to excellent enantioselectivities in the hydrogenation of β-alkyl substituted phosphonates, while their performance is significantly reduced with β-aryl substrates. The latter constitute an important group of compounds that can allow, for instance, the synthesis of phosphonic acid analogues of phenylalanine and tyrosine.[2d]

In the search for efficient catalysts, the use of two tunable coordinating functions in C_1 symmetric ligands has become an invaluable tool. Thus, a variety of ligands combining phosphorus, sulfur, nitrogen or carbon based fragments have been applied to a wide range of asymmetric catalytic transformations with excellent results.[5] In particular, we have been interested in the application of phosphine-phosphites in asymmetric hydrogenation. We have synthesized a family of modularly designed ligands **1** and employed it in the highly enantioselective reduction of dimethyl itaconate and methyl *Z*-α-acetamido cinnamate (MAC).[6] The easily tunable structures of compounds **1** make them appropriate to pursue the hydrogenation of more challenging unsaturated phosphonates **2** (eqn. 1), and in this contribution we report catalysts based on phosphine-phosphites which hydrogenate with high enantioselectivities both β-alkyl and β-aryl substrates.



R^1 = Ph (**1a**), Pr^i (**1b**), Me (**1c**)



2 **3** (1)

Studies were initiated with the hydrogenation of substrate **2a** (R^2 = Et, Table 1) with rhodium precatalysts of formulation [Rh(COD)(P-OP)]BF_4 (P-OP = **1a** (**4a**), **1b** (**4b**), **1c** (**4c**)). Uncompleted reactions were observed in all cases, with moderate enantioselectivities for **4a** and **4b**, and lower for methyl derivative **4c**. An important feature of substrates **2** is the existence of a tetrahedral phosphorus functionality bonded to the olefin, which can make these hydrogenations more sensitive to steric effects than those of olefins bearing an sp^2 hybridized carbon at this position (*e.g.* MAC, dimethyl itaconate). Based on recent mechanistic investigations,[4] as well as on the coordination mode of MAC observed in phosphine-phosphite complexes,[6a] it is reasonable to assume that the olefin bond of **2a** coordinates *cis* to the phosphite in the reaction (Fig. 1). Hence, we postulate that bulkiness on the latter group can be detrimental in the hydrogenation of **2a**.‡ To test this hypothesis we prepared sterically less demanding ligands **7** based on chiral bisphenol **5** (Scheme 1),[7] as well as their corresponding catalyst precursors [Rh(COD)(P-OP)]BF_4 (P-OP = **7a** (**8a**), **7b** (**8b**)). We were pleased to observe that both complexes **8a** and **8b** produced a complete conversion in the reduction of **2a** (Table 2). Moreover, while the first slightly raised the enantioselectivity to 89% ee, in comparison with an 85% ee provided by **4a**, the isopropyl derivative afforded an excellent value of 95% ee. The latter data, as well as those obtained with alkyl substituted phosphonates **2b–2d** (91–98% ee, entries 3–5), are comparable with enantioselectivities originated by DuPHOS and MiniPHOS ligands.[3,4] Most noteworthy is the result produced by phenyl substrate **2e**, which was hydrogenated with complete conversion and 92% ee. This value competes very favourably with the best

Table 1 Hydrogenation of **2a** with [Rh(COD)(P-OP)]BF_4[a]

Entry	Precatalyst	% Conversion	% ee (conf.)
1	**4a**	25	85 (*S*)
2	**4b**	18	78 (*S*)
3	**4c**	74	59 (*S*)

[a] All reactions were carried out at room temperature with an initial hydrogen pressure of 4 bar, in methylene chloride at a S/C = 100. Reaction time 24 h. Conversion was determined by ^{1}H NMR and enantiomeric excess (ee) by chiral HPLC. Configuration was determined by comparison of optical rotation with literature values.[3,4]

† Electronic supplementary information (ESI) available: representative experimental procedures and crystallographic information for **8a**. See http://www.rsc.org/suppdata/cc/b4/b414288h/

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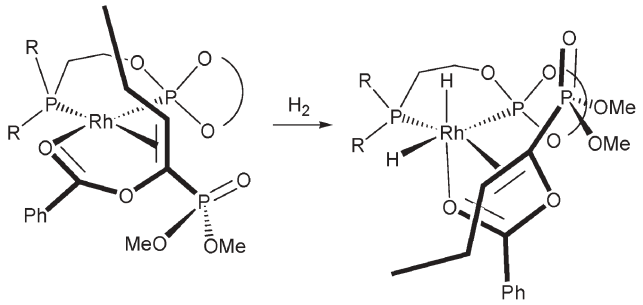
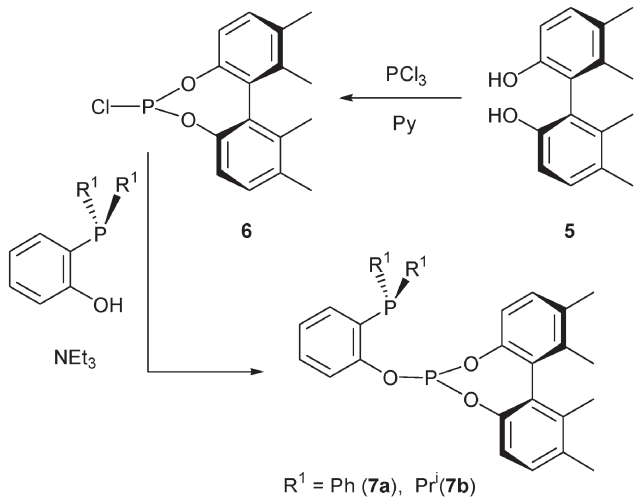


Fig. 1



Scheme 1 Synthesis of ligands **7**.

Table 2 Hydrogenation of **2** with [Rh(COD)(P-OP)]BF_4[a]

Entry	Substrate	R^2	Precatalyst	% ee (conf.)
1	**2a**	Et	**8a**	89 (*R*)
2	**2a**	Et	**8b**	95 (*R*)
3	**2b**	H	**8b**	91 (*R*)
4	**2c**	Pr^i	**8b**	98 (*R*)
5	**2d**	Bu^n	**8b**	96 (*R*)
6	**2e**	Ph	**8b**	92 (*R*)
7	**2f**	*p*-MeO-C_6H_4	**8a**	82 (*R*)
8[b]	**2f**	*p*-MeO-C_6H_4	**8b**	91 (*R*)

[a] See footnote of Table 1 for conditions and determinations. All reactions were completed unless otherwise stated. [b] 43% conversion.

reported for this olefin of 70% ee.[4a] Analogously, anisyl derivative **2f** produced a 91% ee with **8b** (best reported 68% ee[3]), although the reaction was slow under our standard conditions and afforded a 43% conversion. Otherwise phenyl catalyst completed the reaction with a good enantioselectivity of 82% ee.

With the intention of gaining information about the improvement produced by **7** we have performed an X-ray diffraction study of compound **8a** (see ESI for an ORTEP view). It is noteworthy that this complex displays conformation **A** for the Rh-**7a** fragment (Fig. 2), with the phenylene backbone *syn* to the inner aryl group of the biphenyl moiety. Interestingly, this conformation has not been observed in complexes derived from **1**, which in turn display an *anti* arrangement of type **B**, which minimizes steric interactions between the backbone and biphenyl groups.[6a] Conformation type

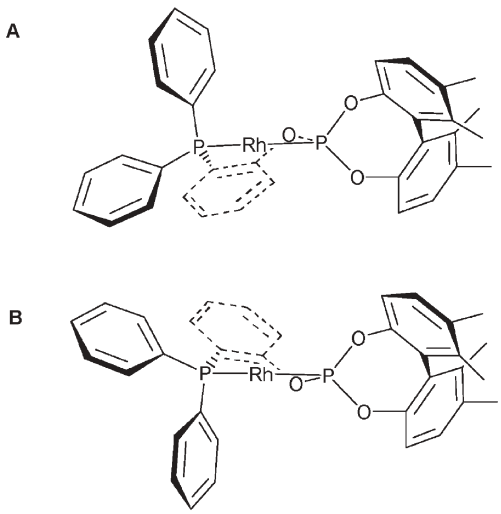


Fig. 2 Conformations of the Rh-**7a** fragment.

B should be accessible as well to complexes **8**, thus allowing backbone mobility.§ Thus, the higher reactivity of **8** (compared to **4**) can be ascribed not only to the lower steric bulkiness of the phosphite group, but also to a higher ligand flexibility.[8]

In summary we have developed hydrogenation catalysts, based on chiral phosphine-phosphites, for the highly enantioselective synthesis of β-alkyl and -aryl α-acyloxy phosphonates. Optimization of the catalyst has been achieved by a proper tuning of the chiral ligand, facilitated by its high modularity. Studies further investigating the scope of these catalysts are currently in progress.¶

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Notes and references

‡ In ref 4a Imamoto and coworkers propose that hydrogenation of compounds **2** should proceed predominantly by a dihydride mechanism, but an alternative unsaturated pathway can also occur. However, interaction between phosphite and olefinic fragments can take place either in a Rh(I) adduct or a Rh(III) dihydride.

§ Backbone mobility in **8b** has been detected by NOESY experiments. Details will be given in a full account.

¶ Crystal data for **8a·H_2O**: $C_{84}H_{88}B_2F_8O_8P_4Rh_2$, M = 1728.86, orthorhombic, $P2_12_12_1$, a = 16.3320(12), b = 21.0373(15), c = 23.4288(19) Å, V = 8049.7(11) Å^3, T = 100 K, Z = 4, μ = 0.563 mm^{-1}, 88996 reflections collected, 25153 independent (R(int) = 0.0535), $R1$ = 0.0586, $wR2$ = 0.1393 ($I > 2\sigma(I)$). CCDC 246371. See http://www.rsc.org/suppdata/cc/b4/b414288h/ for crystallographic data in .cif or other electronic format.

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