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# Enantioselective Rh-Catalyzed Hydrogenation of Vinyl Carboxylates with Monodentate Phosphite Ligands†

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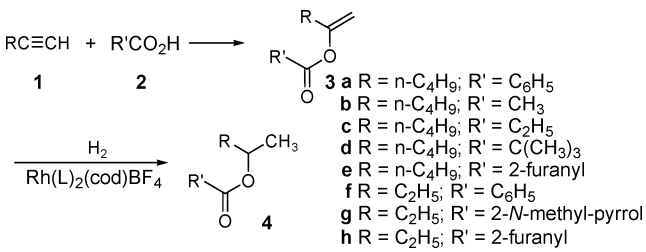
## ABSTRACT


**Alkyl-substituted vinylcarboxylates, which normally show poor enantioselectivity in Rh-catalyzed hydrogenation with traditional chiral diphosphines, undergo highly enantioselective reactions with BINOL- and carbohydrate-based monophosphite ligands.**

The asymmetric Rh-catalyzed hydrogenation of enol esters with formation of chiral esters constitutes an alternative to the enantioselective reduction of the corresponding prochiral ketones. Moreover, enol esters are not only accessible from ketones, but also from alkynes by metal-catalyzed reaction with carboxylic acids.[1] A particularly mild and efficient version of the latter reaction **1** + **2** → **3**, using commercially available $[(p\text{-cymene})RuCl_2]_2PR_3$, was recently reported by one of us (Scheme 1, top).[2]

**Scheme 1**




The goal of the present study was to test compounds of the type **3** in our previously described method of Rh-catalyzed asymmetric olefin hydrogenation using cheap and readily accessible BINOL-derived monodentate phosphites (Scheme 1, bottom).[3] Other groups have already reported efficient ligand systems for the hydrogenation of enol acetates, although high enantioselectivities (ee > 90%) were restricted to substrates bearing aryl, vinyl, or trifluoromethyl groups at the olefinic function.[4] In the case of alkyl residues, enantioselectivity is consistently mediocre (e.g., 64% ee in the case of the hydrogenation of **3** with R = *n*-$C_7H_{15}$ and R′ = $CH_3$).[5] In the present study we focus on this problem. To tune the reaction, we envisioned the variation of the nature of the R′ group in **3** as well as optimization of the modular chiral monophosphite **6** employed as the ligand in the Rh

† Dedicated to Professor Dr. Helmut Schwarz on the occasion of his 60th birthday.

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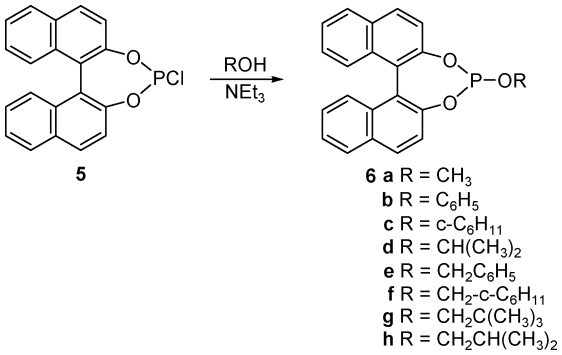
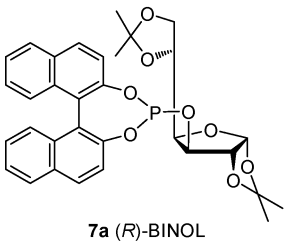
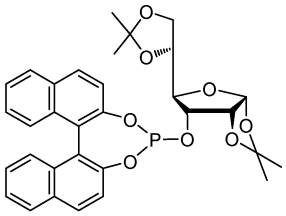
catalyst (Scheme 2). Specifically, we use chiral carbohydrate-based alcohols in the synthesis of the phosphites.

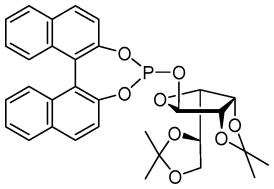
**Scheme 2**

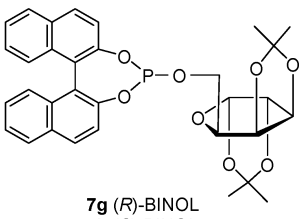



In exploratory experiments the benzoate **3a** was hydrogenated by using a selected number of previously described phosphites **6a**−**h** in addition to several new carbohydrate-based derivatives **7a**−**h**. The synthesis of the latter ligands proceeded without any problems in analogy to the reaction shown in Scheme 2.[3] The carbohydrate alcohols are all commercially available. In all cases the cationic rhodium catalyst was prepared in situ by treating $Rh(cod)_2BF_4$ (cod = 1,5-cyclooctadiene) with 2 equiv of a monodentate ligand **6** or **7**, in full analogy to our previous studies.[3]




The results of these experiments are summarized in Table 1. Most of the simple phosphites lead to low degrees of enantioselectivity, with the exception of the neopentyl-derived ligand **6g** (entry 7). The ee value of 64.8% is respectable for this type of transformation (ee upon using BINAP: 13.6%), although it is of no practical value. In the case of the carbohydrate-derived ligands, a remarkable trend evolves. In all instances a pronounced difference in the matched versus mismatched combinations becomes apparent (entries 9−16), a phenomenon that has not been previously observed with other substrates and other chiral phosphites containing two sources of chirality.[3] The best case involves the use of phosphite **7a** prepared from *R*-BINOL and a glucose derivative, resulting in an ee value of 86.4% (entry 9).

We then studied the effect of the nature of the acid **2** used in the synthesis of **3**, although not all of the phosphite ligands were tested. Table 2 shows that this type of influence is rather

**Table 1.** Rh-catalyzed Hydrogenation of **3a**[a]

| entry | ligand | conversion,[b] % | *ee*, % (config of product)[b] |
|---|---|---|---|
| 1 | **6a** (*R*) | 100 | 21.8 (*S*) |
| 2 | **6b** (*R*) | 40 | 25.2 (*S*) |
| 3 | **6c** (*R*) | 100 | 31.6 (*S*) |
| 4 | **6d** (*R*) | 100 | 20.8 (*S*) |
| 5 | **6e** (*R*) | 100 | 39.4 (*S*) |
| 6 | **6f** (*S*) | 100 | 43.8 (*R*) |
| 7 | **6g** (*R*) | 100 | 64.8 (*S*) |
| 8 | **6h** (*R*) | 100 | 37.4 (*S*) |
| 9 | **7a** | 100 | 86.4 (*S*) |
| 10 | **7b** | 100 | 12.8 (*R*) |
| 11 | **7c** | 100 | 39.2 (*S*) |
| 12 | **7d** | 82 | 23.0 (*S*) |
| 13 | **7e** | 100 | 68.0 (*S*) |
| 14 | **7f** | 100 | 17.2 (*R*) |
| 15 | **7g** | 100 | 51.2 (*S*) |
| 16 | **7h** | 100 | 4.2 (*R*) |

[a] Catalyst prepared in situ from $Rh(cod)_2BF_4$ and 2 equiv of ligand **6** or **7** in $CH_2Cl_2$; substrate:catalyst = 200:1; 60 bar $H_2$; 30 °C; 20 h. [b] Determined by GC.

**Table 2.** Rh-Catalyzed Hydrogenation of **3b**−**e**[a]

| entry | substrate | ligand | conversion,[b] % | *ee*, % (config of product)[b] |
|---|---|---|---|---|
| 1 | **3b** | **7a** | 100 | 73.6 (*S*) |
| 2 | **3b** | **7b** | 93 | 31.6 (*R*) |
| 3 | **3c** | **7a** | 100 | 74.4 (*S*) |
| 4 | **3c** | **7b** | 88 | 6.2 (*R*) |
| 5 | **3d** | **7a** | 100 | 41.6 (*S*) |
| 6 | **3d** | **7b** | 44 | 10.4 (*S*) |
| 7 | **3e** | **7a** | 100 | 90.4 (*S*) |
| 8 | **3e**[c] | **7a** | 100 | 94.0 (*S*) |
| 9 | **3e**[c,d] | **7a** | 100 | 93.0 (*S*) |
| 10 | **3e** | **7b** | 76 | 22.0 (*R*) |

[a] The same conditions were used as already described in Table 1. [b] Determined by GC. [c] This reaction was carried out at −20 °C. [d] The substrate:catalyst ratio was increased to 500:1.

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pronounced, the highest enantioselectivity (ee = 90.4%) resulting from the use of substrate **3e** derived from furan-2-carboxylic acid in combination with ligand **7a** (entry 7). Upon reducing the temperature to −20 °C, enantioselectivity increases to ee = 94.0%. Hydrogenation of 2-hexanone is not a better alternative since the most effective ligand (Penn PHOS) leads to an ee value of only 75%.[6] Moreover, the analogous BINOL-derived phosphoramidite[7] is also not well suited in these cases (<10% conversion of **3a** under the standard reaction conditions as defined in Table 1).

The beneficial effect of using furan-2-carboxylic acid also arises when employing ligands other than **7**. An example concerns the hydrogenation of **3e** with ligand **6d**, which results in an ee value of 41.2% (*S*). In contrast, the hydrogenation of the corresponding benzoate **3a** employing the same ligand leads to an enantioselectivity of only 20.8% (Table 1, entry 4).

Upon turning to the even more difficult substrates **3f**−**h** having an ethyl substituent at the olefinic function, a similar trend was observed (Table 3). Again, ligand **7a** turned out to be most effective, specifically in the hydrogenation of the furanyl substrate **3h**, leading to ee = 83.6% at room temperature and 88.6% at −20 °C (entries 6−8). Currently it is difficult to pinpoint the reason for enhanced enantioselectivity when using substrates derived from furan-2-carboxylic acid.

In summary, we have demonstrated that by tuning the nature of the carboxylate as well as varying the chiral monophosphite ligand the rhodium-catalyzed hydrogenation of particularly difficult vinyl carboxylates **3** can be performed with high enantioselectivity. Since the vinyl carboxylates are accessible not only from ketones, but also by the Ru-catalyzed addition of carboxylic acids to alkynes, interesting synthetic possibilities arise.

**Table 3.** Rh-catalyzed Hydrogenation of **3f**−**h**[a]

| entry | substrate | ligand | conversion,[b] % | *ee*, % (config of product)[b] |
|---|---|---|---|---|
| 1 | **3f** | **7a** | 100 | 80.4 (*S*) |
| 2 | **3f** | **7b** | 79 | 10.8 (*R*) |
| 3 | **3g** | **7a** | 100 | 71.6 (*S*)[c] |
| 4 | **3g** | **7b** | 100 | 4.8 (*R*)[c] |
| 5 | **3h** | **7a** | 100 | 83.6 (*S*) |
| 6 | **3h**[d] | **7a** | 100 | 88.4 (*S*) |
| 7 | **3h**[d,e] | **7a** | 99 | 88.6 (*S*) |
| 8 | **3h** | **7b** | 66 | 34.2 (*R*) |

[a] The same conditions were used as already described in Table 1. [b] Determined by GC. [c] Configurational assignment based on analogy. [d] This reaction was carried out at −20 °C. [e] The substrate: catalyst ratio was increased to 500:1.

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**Supporting Information Available:** Spectral data of all new ligands as well as a typical procedure for hydrogenation. This material is available free of charge via the Internet at http://pubs.acs.org.

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