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# Highly Enantioselective Hydrogenation of 1-Alkylvinyl Benzoates: A Simple, Nonenzymatic Access to Chiral 2-Alkanols

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Enantiopure 2-alkanols (**A**, Figure 1) constitute a primary class of building blocks for organic synthesis, used in the preparation of a plethora of chiral compounds.[1] Currently, a broad range of alcohols **A** are efficiently obtained in high enantiomeric purity by diverse enzymatic procedures.[2] In contrast, the synthesis of these alcohols by chemocatalytic reactions has not reached such a high performance in terms of enantioselectivity and product scope.[3–5]

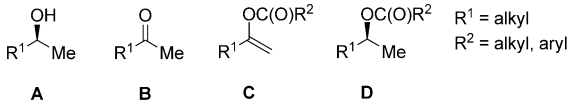


Figure 1. Structures of **A**–**D**-type compounds.

A very convenient synthesis of alcohols **A** can be provided by hydrogenation or transfer hydrogenation reactions of methyl alkyl ketones **B**. However, high enantioselectivities are limited to substrates bearing relatively bulky $R^1$ substituents (e.g. *i*Pr, Cy, *tert*-alkyl), whereas lower enantioselectivities are obtained in the case of ketones with linear alkyl $R^1$ groups.[3] In this regard, promising results have been achieved by the use of a Rh surfactant[3g] type or a Ru–cyclodextrin catalysts,[3d] providing high enantioselectivities (up to 94% *ee*; *ee* = enantiomeric excess) for substrates bearing long $R^1$ chains, such as *n*-decyl methyl ketone, although the enantioselectivity decreases with the length shortening of this substituent (e.g. 74–76% *ee* for *n*-butyl methyl ketone).

An alternative route to the synthesis of alcohols **A**, using catalytic hydrogenation reactions, is based on the enantioselective reduction of enol esters **C**[6] followed by a hydroxyl deprotection of the resulting chiral esters **D**. The hydrogenation of several classes of prochiral enol esters has been described in the literature,[7] but little information about the reduction of 1-alkylvinyl derivatives **C** is available. This is mainly limited to reactions catalyzed by Rh complexes bearing monodentate phosphorus ligands, under relatively high hydrogen pressures (40–60 bar).[8,9] Thus, the groups of Reetz and Goossen have reported enantioselectivities of up to 94% *ee* in the hydrogenation of a 1-*n*-butylvinyl ester by using a carbohydrate-based phosphite.[8a] The latter group has also shown that this catalytic system provides high enantioselectivities (up to 98% *ee*) in the hydrogenation of structurally related 1,2-dimethylvinyl esters, whereas enantioselectivity decreases to values near 80% *ee* for substrates bearing longer alkyl chains at position 1.[8b] On the other hand, the group of Ding has described the application of catalysts based on phosphoramidites in the hydrogenation of 1-*n*-alkylvinyl substrates, giving enantioselectivities between 87 and 90% *ee*.[8c] Inspired by these precedents, and following our interest in asymmetric hydrogenation,[10] we describe herein a study on the hydrogenation of 1-alkylvinyl esters with Rh catalysts based on chelating phosphane–phosphite chiral ligands (P–OP, Figure 2), which provides an efficient route for the preparation of chiral esters **D**.

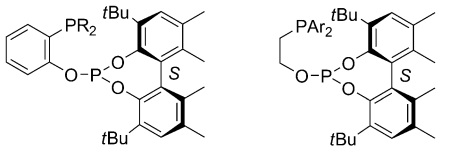


Figure 2. Structure of phosphane–phosphite (P–OP) ligands.

Initially, a family of enol esters **1** (Scheme 1) was prepared in high yield by a Ru-catalyzed condensation between carboxylic acids and terminal alkynes in water, which produces the desired Markovnikov isomer in high yield.[6b] Catalytic hydrogenations were then performed with a set of Rh catalyst precursors of formula $[Rh(NBD)(P{-}OP)]BF_4$ (NBD = norbornadiene; P–OP = (*S*)-**3a** (**4a**), (*R*)-**3a** (**4a′**), (*S*)-**3b** (**4b**), (*S*)-**3c** (**4c**), (*S*)-**3d** (**4d**)).

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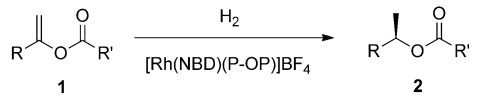



**a**: R = *n*-$C_4H_9$, R' = Ph
**b**: R = *n*-$C_3H_7$, R' = Ph
**c**: R = *n*-$C_6H_{13}$, R' = Ph
**d**: R = *n*-$C_6H_{13}$, R' = Et
**e**: R = $CH_2$-*c*-$C_5H_9$, R' = Ph
**f**: R = $CH_2$-*c*-$C_6H_{11}$, R' = Ph
**g**: R = *c*-$C_6H_{11}$, R' = Ph
**h**: R = *t*-$C_4H_9$, R' = Ph
**i**: R = $CH_2Ph$, R' = Ph
**j**: R = Ph, R' = Ph
**k**: R = *n*-$C_6H_{13}$, R' = 3-Br-$C_6H_4$
**l**: R = *n*-$C_6H_{13}$, R' = 4-Br-$C_6H_4$
**m**: R = *n*-$C_6H_{13}$, R' = 3-MeO-$C_6H_4$
**n**: R = *n*-$C_6H_{13}$, R' = 4-MeO-$C_6H_4$

Scheme 1. Hydrogenation of enol esters **1**.

As a starting point, some hydrogenations of **1a**, chosen as a representative substrate, were performed at room temperature and 20 bar of hydrogen. Under these conditions catalyst precursors **4a** and **4c** completed the reaction with relatively high enantioselectivities (88–89% *ee*, entries 1–2, Table 1). We next noticed that these catalysts also displayed

Table 1. Hydrogenation of **1a** performed with catalyst precursors **4**.[a]

| Entry | Cat. | $H_2$ [bar] | S/C | Conv. [%] | *ee* [%] (conf.) |
|---|---|---|---|---|---|
| 1 | **4a** | 20 | 100 | 100 | 89 (*R*) |
| 2 | **4c** | 20 | 100 | 100 | 88 (*R*) |
| 3 | **4a** | 4 | 200 | 100 | 94 (*R*) |
| 4[b] | **4b** | 4 | 200 | 74 | 83 (*R*) |
| 5 | **4c** | 4 | 200 | 100 | 96 (*R*) |
| 6 | **4d** | 4 | 200 | 100 | 93 (*R*) |
| 7[c] | **4c** | 4 | 500 | 100 | 96 (*R*) |

[a] Hydrogenations in $CH_2Cl_2$, $[Rh]=2\times10^{-4}$ M, $[\mathbf{1a}]=0.02$–0.1 M, at an initial pressure and substrate to catalyst ratio (S/C) indicated. Reactions performed at room temperature for 24 h unless otherwise stated. Conversion was determined by $^1$H NMR spectroscopy and enantiomeric excess by chiral HPLC analysis. Configuration was determined by comparison of the optical rotation sign with literature data. [b] Reaction time 37.5 h. [c] Reaction performed at 40 °C.

good activity at lower pressure (4 bar), enough to complete the reactions at S/C values of 200. Most remarkably, the decrease in hydrogen pressure produced an important enhancement on enantioselectivity.[11] Thus, **4a** gave 94% *ee* (entry 3), whereas **4c** improved this value up to 96% *ee* (entry 5). By comparison, a lower enantioselectivity was observed with the isopropyl-substituted catalyst **4b** (entry 4), whereas *p*-tolyl derivative **4d** also provided a good enantioselectivity, but it did not improve the result of **4c** (entry 6). Finally, it should be remarked that a slight increase in reaction temperature allowed completion of the reaction with a S/C of 500 in 24 h without a decrease in enantioselectivity (entry 7).

Following the finding of a highly effective system for the hydrogenation of **1a**, we have next explored the scope of **4c**, by examining the reaction with substrates **1b–n**. Remarkably, this catalyst precursor showed high enantioselectivities in the hydrogenation of substrates bearing a linear alkyl substituent R. Thus, **1b** and **1c** were hydrogenated with 96 and 95% *ee*, respectively (entries 1 and 2, Table 2). Likewise, the propanoate **1d** also provided high enantioselectivity at a S/C ratio of 1000 (97% *ee*, entry 3). In addition, substrates **1e** and **1f**, bearing cycloalkyl chains, provided exceedingly high values of 98% *ee* (entries 4 and 5).

Table 2. Hydrogenation of **1b–n** with catalyst precursors **4**.[a]

| Entry | Cat. | Substrate | S/C | *ee* [%] (conf) |
|---|---|---|---|---|
| 1 | **4c** | **1b** | 500 | 96 (*R*) |
| 2 | **4c** | **1c** | 500 | 95 (*R*) |
| 3 | **4c** | **1d** | 1000 | 97 (*R*) |
| 4 | **4c** | **1e** | 500 | 98 (*R*) |
| 5 | **4c** | **1f** | 500 | 98 (*R*) |
| 6 | **4c** | **1g** | 500 | 86 (*S*) |
| 7[b] | **4d** | **1g** | 500 | 85 (*S*) |
| 8 | **4c** | **1h** | 500 | 78 (*S*) |
| 9 | **4a** | **1h** | 500 | 97 (*S*) |
| 10 | **4a** | **1h** | 1000 | 97 (*S*) |
| 11 | **4a′** | **1h** | 500 | 96 (*R*) |
| 12 | **4c** | **1i** | 500 | 99 (*R*) |
| 13 | **4a** | **1j** | 200 | 98 (*R*) |
| 14 | **4c** | **1j** | 200 | 98 (*R*) |
| 15 | **4d** | **1j** | 200 | 98 (*R*) |
| 16 | **4d** | **1j** | 500 | 99 (*R*) |
| 17 | **4c** | **1k** | 500 | 95 (*R*) |
| 18 | **4c** | **1l** | 500 | 95 (*R*) |
| 19 | **4c** | **1m** | 500 | 96 (*R*) |
| 20 | **4c** | **1n** | 500 | 96 (*R*) |

[a] Reactions in $CH_2Cl_2$ at 40 °C and an initial pressure of 4 bar of hydrogen, $[Rh]=2\times10^{-4}$ M, $[\mathbf{1}]=0.04$–0.2 M. Reaction time: 24 h. Reactions showed full conversion unless otherwise stated. Conversion determined by $^1$H NMR spectroscopy and enantiomeric excess by chiral GC or HPLC analysis. See the Supporting Information for determination of configuration. [b] 95% conversion.

Along the series, cyclohexyl-substituted substrate **1g** constituted the most difficult case. Indeed, using **4a** under the standard conditions only a low conversion (34%) could be reached. In turn, **4c** exhibited full conversion and provided a good enantioselectivity (86% *ee*, entry 6, Table 2), but unexpectedly, with an opposite *S* configuration. Moreover, **4d** did not improve this value (entry 7). In contrast with the above results, the catalyst precursor **4c** provided a remarkably lower enantioselectivity for the *tert*-butyl-substituted enol ester **1h** (78% *ee*, entry 8), whereas complex **4a** provided the best catalyst for this substrate and afforded the *S* product with a 97% *ee* (entry 9). Despite the presence of a bulky R substituent in **1h**, it showed a good reactivity that allowed us to complete a reaction with a S/C of 1000 (entry 10).

An added value of the present system is that it allows a ready preparation of both product enantiomers. For instance hydrogenation of **1h** with precatalyst **4a′** provided (*R*)-**2h** with a 96% *ee* (entry 11, Table 2).

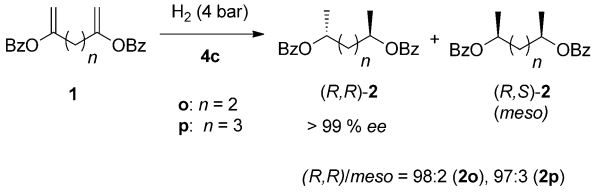
On the other hand, the benzyl derivative **1i** was very efficiently hydrogenated with **4c** to give (*R*)-**2i** with a 99% *ee* (entry 12, Table 2). This is a remarkable result since the product is useful for the preparation of 2-phenylpropylamines of pharmaceutical interest.[12] In addition, for comparative purposes, Ph derivative **1j** was also examined. This substrate is less sensitive to the structure of the catalyst and complexes **4a**, **4c**, and **4d** provided (*R*)-**2j** with very high enantioselectivities, between 98 and 99% *ee* (entries 13–16).

It is interesting to note that the enantioreversal observed in the hydrogenation of **1h**, relative to **1j**, parallels that observed before in the hydrogenation of *tert*-butyl and aryl enamides.[13] This phenomenon has been studied in detail in the literature and assigned to an opposite regioselectivity of the olefin insertion step depending on the nature of the olefin substituent, favoring a β-alkyl in the case of the *t*Bu enamide.[13b–c] Similar to the hydrogenation of **1h**, the *S* enantiomer is also favored in the case of the cyclohexyl substrate **1g**, although the enantioselectivity is lower. Apparently, the size of the Cy substituent is not high enough to completely disfavor an α-alkyl pathway; therefore, competition with the β-alkyl pathway may operate, with a concomitant erosion on enantioselectivity.

A particularly appealing application of the present hydrogenation is the preparation of chiral benzoates substituted at the benzene ring. These derivatives have interest, for instance, in the preparation of liquid crystals.[14] Accordingly, a set of Br and MeO-substituted benzoates (**1k**–**n**) were also examined. Worth noting is that the substitution did not significantly affect the reaction and compounds **2k**–**n** were obtained with full conversion and enantioselectivities between 95 and 96% *ee* (entries 17–20, Table 2), which are similar to that shown by unfunctionalized benzoate **1c**.

An alternative application of the present reaction is the hydrogenation of bis-enol benzoates suitable for the preparation of synthetically useful diols.[7a,15] To this aim, the novel dibenzoate **1o** was prepared and examined (Scheme 2). By using **4c** and a S/C ratio of 200 (i.e. 400




Scheme 2. Hydrogenation of dibenzoates.

olefin bonds per Rh atom), the reaction was completed under our standard conditions and only 2% of the *meso* compound was observed. The remaining product corresponds to the *R*,*R* enantiomer, as the *S*,*S* enantiomer was not observed. For the dibenzoate **1p**, similar results were observed. Thus, 3% of the *meso* and an enantioselectivity higher than 99% *ee* was observed. Remarkably, this procedure gives comparable results to the dynamic kinetic resolution process of analogous 1,4- and 1,5-diacetates described by Bäckvall and co-workers.[15a]

Considering the synthetic application and scale-up of the hydrogenations of enol esters **1**, an important point to consider is the catalyst performance at a high substrate concentration or even in the neat substrate. Thus, a minimization of solvent added has a high environmental interest and,[16] in addition, the reduction of the volume reaction for a certain amount of product is an aspect of industrial value.[17] Prompted by these considerations, we performed the hydrogenation of **1a** with precatalyst **4c** at a S/C ratio of 500 in the neat substrate. Worth noting is that the catalyst is not inhibited at high substrate concentration and full conversion was obtained after 24 h, leading to **2c** with a 96% *ee* (entry 1, Table 3). Likewise, reactions performed in neat **1h**,

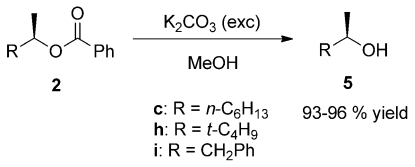
Table 3. Hydrogenations performed with precatalysts **4** at high substrate concentration.[a]

| Entry | **1** | Cat. | **1**/$CH_2Cl_2$[b] | *ee* [%] (conf) |
|---|---|---|---|---|
| 1 | **1a** | **4c** | ***n*** | 96 (*R*) |
| 2 | **1h** | **4a** | ***n*** | 95 (*S*) |
| 3 | **1i** | **4c** | 1:1 | 99 (*R*) |
| 4 | **1j** | **4c** | ***n*** | 99 (*R*) |
| 5 | **1n** | **4c** | ***n*** | 96 (*R*) |
| 6[c] | **1p** | **4c** | 1:1 | >99 (*R*,*R*) |

[a] Reactions at 40°C and an initial pressure of 4 bar of hydrogen, S/C = 500. Reaction time: 24 h. [b] Substrate: solvent weight ratio, ***n*** denotes a reaction performed in the neat substrate. [c] 2% of *meso* compound observed.

**1j**, and **1n** provided high conversions and enantioselectivities (entries 2, 4 and 5, respectively). This procedure is not suitable for benzyl substrate **1i**, which is solid. In turn, a reaction in a **1i**/$CH_2Cl_2$ 1:1 (w/w) mixture was performed. As in the previous examples, an excellent enantioselectivity was obtained and (*R*)-**2j** was obtained with a 99% *ee* (entry 3). Likewise, **1p** was hydrogenated more satisfactorily by using a substrate/$CH_2Cl_2$ 1:1 mixture. Noticeably, this reaction gave only 2% of the *meso* product (entry 6).

Despite the fact that the corresponding debenzoylation is a simple, well-known reaction in the literature,[18] due to the interest of products **2** in the preparation of alcohols, we wanted to fully validate the concept including some examples of deprotection of benzoates **2** (Scheme 3). Thus, treat-




Scheme 3. Deprotection of benzoates **2**.

ment of **2c** with an excess of $K_2CO_3$ in methanol provided (*R*)-2-octanol (**5c**) in high yield without a decrease on enantioselectivity (95% *ee*). A similar reaction was performed with **2h**, which also proceeded without loss on enantioselectivity (98% *ee*). Finally, particularly interesting debenzoylation of **2i** provided synthetically useful[12] (*R*)-1-phenyl-2-propanol **5i** with 93% yield and 99% *ee*.

In summary, a highly enantioselective hydrogenation of enol esters **1** by using Rh catalysts bearing chiral phosphane–phosphite ligands has been described.[19] The reaction has a broad scope and provides a wide range of esters **2** with high enantiomeric purity, which are suitable precursors

of widespread 2-alkanols. In addition, catalysts keep a high activity under high substrate concentration and even in the neat substrate. These features, along with a very convenient preparation of substrates from commercially available reagents in water, conforms a highly practical and sustainable synthesis of valuable esters **2**. Further research on the scope and mechanism of this hydrogenation is currently in progress.

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**Keywords:** alcohols · asymmetric hydrogenation · enantioselectivity · esters · rhodium

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[19] In parallel to the present work, Leitner, Franciò, and co-workers have just reported that chiral phosphane–phosphoramidites also provide highly enantioselective Rh catalysts for these hydrogenations, see: T. M. Konrad, P. Schmitz, W. Leitner, G. Franciò, *Chem. Eur. J.* **2013**, *19*, 13299–13303.

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