Highly enantioselective hydrogenation of 1-alkylvinyl benzoates: a simple, non-enzymatic, 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]

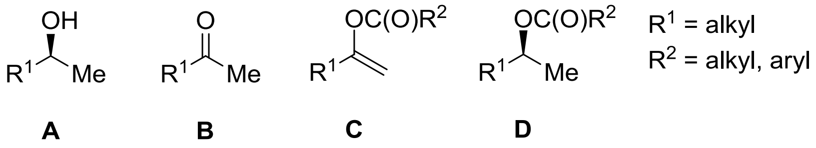


Figure 1. Structures of **A**-**D** type compounds.

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), while lower enantioselectivities are obtained in the case of ketones with linear alkyl R^1 groups.[3] At 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) 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 up to 94 % ee in the hydrogenation of a 1-*n*-butylvinyl ester 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, while enantioselectivity decreases to values near 80 % ee for substrates bearing longer alkyl chains in 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**.

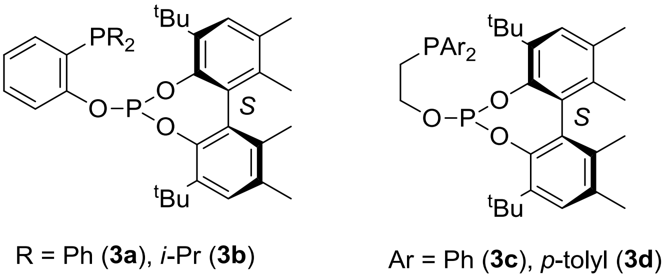
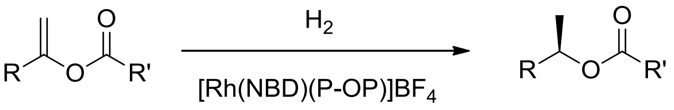


Figure 2. Structure of phosphane-phospite (P-OP) ligands.

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 catalysts 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**)].

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 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 a 94 % ee (entry 3), while **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), while *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 completing the reaction with a S/C of 500 in 24 h without decrease on enantioselectivity (entry 7).



1 **2**

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**.

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] = 2×10^{-4} M, [**1a**] = 0.02-0.1 M, at initial pressure and substrate to catalyst ratio (S/C) indicated. Reactions performed at room temperature for 24 h unless otherwise stated. Conversion determined by ^1H NMR and enantiomeric excess by chiral HPLC. Configuration was determined by comparison of the optical rotation sign with literature data. [b] Reaction time 37.5 h. [c] Reaction performed at 40 ºC.

Following the finding of a highly effective system for the hydrogenation of **1a** we have next explored the scope of **4c**, examining the reaction with substrates **1b**-**1n**. 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 ºC and an initial pressure of 4 bar of hydrogen, [Rh] = 2 × 10^{-4} M, [**1**] = 0.04-0.2 M. Reaction time: 24 h. Reactions showed full conversion unless otherwise stated. Conversion determined by ^1H NMR and enantiomeric excess by chiral GC or HPLC. See supplementary material 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), 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), while 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 which allowed us to complete a reaction with a S/C of 1000 (entry 10).

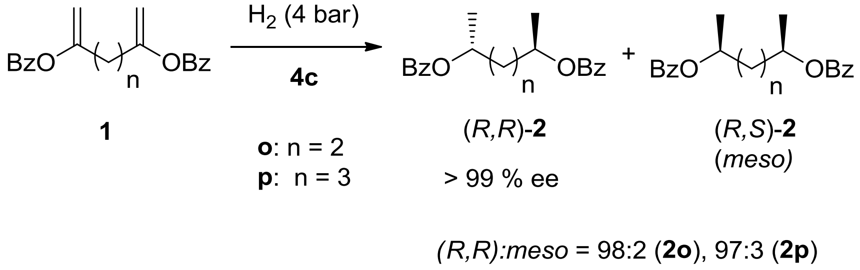
An added value of the present system is that it allows a ready preparation of both product enantiomers. For instance hydrogenation of **1h** with precatalyst **4a'** provided (*R*)-**2h** with a 96 % ee (entry 11).

On the other hand, the benzyl derivative **1i** was very efficiently hydrogenated with **4c** giving (*R*)-**2i** with a 99 % ee (entry 12). 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**, compared 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, favouring a β-alkyl in the case of the *t*-Bu enamide.[13b-c] Similarly to the hydrogenation of **1h**, the *S* enantiomer is also favoured 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 disfavour 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**-**1n**) were also examined. Noteworthy, the substitution did not significantly affect the reaction and compounds **2k**-**2n** were obtained with full conversion and enantioselectivities between 95 and 96 % ee (entries 17-20), 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). Using **4c** and a S/C ratio of 200 (i.e. 400 olefin bonds per Rh atom), the reaction was completed under our standard conditions and only a 2 % of *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 coworkers.[15a]



Scheme 2. Hydrogenation of dibenzoates.

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. Noteworthy, 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**, **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 using a substrate:CH_2Cl_2 1:1 mixture. Noticeably, this reaction gave only a 2 % of the *meso* product (entry 6).

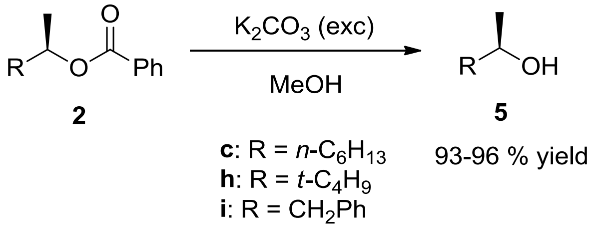
Table 3. Hydrogenations performed with precatalysts **4** at high substrate concentration[a]

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 ºC 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.

Despite 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, treatment of **2c** with an excess of K_2CO_3 in methanol provided (*R*)-2-octanol (**5c**) in high yield without 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.



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

In summary, a highly enantioselective hydrogenation of enol esters **1** 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.

Acknowledgements

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