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Asymmetric Hydrogenation of 1-Alkyl and 1-Aryl Vinyl Benzoates: A Broad Scope Procedure for the Highly Enantioselective Synthesis of 1-Substituted Ethyl Benzoates

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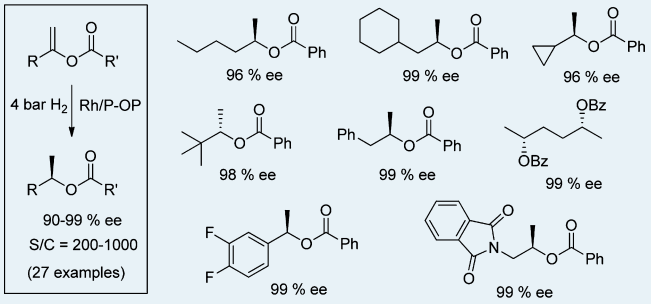
Supporting Information

ABSTRACT: The enantioselective hydrogenation of enol esters of formula CH_2=C(OBz)R with rhodium catalysts based on phosphine−phosphite ligands (P−OP) has been studied. The reaction has a broad scope, and it is suitable for the preparation of products possessing a wide variety of R substituents. For the cases where R is a primary alkyl, high catalyst activity (S/C = 500) and enantioselectivities (95−99% ee) were obtained with a catalyst characterized by an ethane backbone and a PPh_2 fragment. In contrast, for R = *t*-Bu, a catalyst possessing a benzene backbone provided the best results (97% ee). Derivatives with a cycloalkyl R substituent were particularly difficult substrates for this reaction. A broader catalyst screening was required for these substrates, which identified a catalyst possessing a P(*m*-xylyl)$_2$ fragment as the most appropriate one, affording enantioselectivities between 90 and 95% ee. Outstanding enantioselectivities (99% ee) and high catalyst activity (S/C = 500−1000) were also obtained in the case of substrates bearing a Ph or a fluoroaryl R substituent. In addition, the system is also appropriate for the preparation of other synthetically useful esters as those for R = benzyl, 2-phenylethyl or *N*-phthalimido alkyl chains. Likewise, the hydrogenation of divinyl dibenzoates proceeded with very high diastero- and enantioselectivity, generating rather low amounts of the *meso* isomer (3−6%). On the other hand, substrates with Br and MeO substituents at the phenyl benzoate ring, suitable for further functionalization, have also been examined. The results obtained indicate no detrimental effect of these substituents in the hydrogenation. Alternatively, the methodology has been applied to the highly enantioselective synthesis of deuterium isotopomers of 1-octyl benzoate bearing CDH_2, CD_2H, or CD_3 fragments. Finally, as a practical advantage of the present system, it has been observed that the high performance of the catalysts is retained in highly concentrated solutions or even in the neat substrate, minimizing both the amount of solvent added and the volume of the reaction.



KEYWORDS: *asymmetric hydrogenation, enol esters, chiral esters, Rh catalysts*

INTRODUCTION

The enantioselective hydrogenation of enol esters **A** (Scheme 1) constitutes a convenient procedure for the preparation of compounds **B** in high enantiomeric purity.[1] Moreover, this reaction also provides a ready access to the corresponding alcohols **C** due to the straightforward deprotection of **B** (path a). In addition, alcohols **C** constitute a highly important class of chiral compounds with a broad range of synthetic applications.[2]

Since the initial reports on the hydrogenation of **A**, consisting of the reduction of aryl enol esters and α-acyloxyacrylates,[3] a variety of chiral esters **B** with high enantiomeric excesses have been obtained by a proper tuning of the catalytic system. However, the scope of this reaction has largely been limited to substrates bearing an electron-withdrawing substituent at position R[1] (Ar, CF_3, CN, carboxylate, or phosphonate),[4] whereas the investigation of alkyl-substituted substrates has been scarce.

The first report on the Rh-catalyzed asymmetric hydrogenation of 1-alkylvinyl benzoates was reported by the groups of Reetz and Goossen, describing a remarkable 94% ee in the reduction of a 1-*n*-butylvinyl substrate (60 bar H_2, −20 °C, S/C = 200, 20 h) using a catalyst based on a monodentate chiral phosphite.[5,6] Later, the group of Ding described the application of Rh phosphoramidite catalysts under similar reaction

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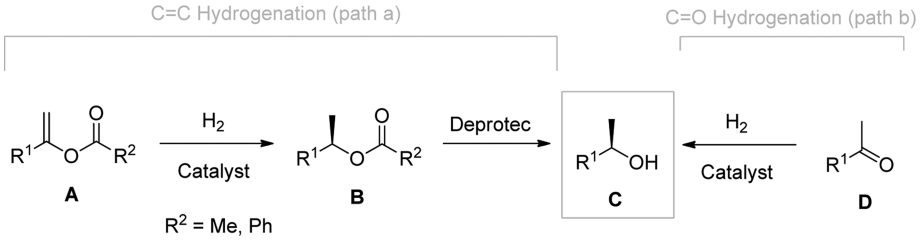
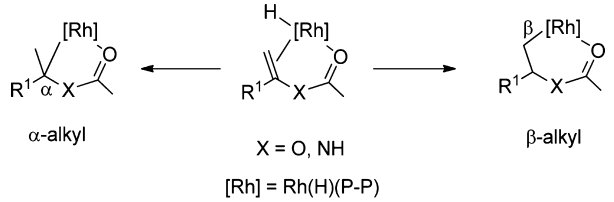
Scheme 1. Hydrogenation Routes to Esters B and Alcohols C



conditions (40 bar H_2, −20 °C, S/C = 100, 10 h) in the hydrogenation of several 1-alkylvinyl substrates, giving enantioselectivities between 87 and 90% ee.[7] On the other hand, Leitner, Franciò, and co-workers demonstrated the suitability of chiral heterobifunctional phosphine−phosphoramidite ligands for this kind of hydrogenation. Thus, a variety of enol acetates and benzoates were hydrogenated with good levels of catalytic activity and enantioselectivity (20 bar of H_2, S/C = 50−1000, 80−99% ee), being particularly efficient for substrates where R^1 is primary alkyl (S/C = 200, 20 bar H_2, 1 h, 98−99% ee).[8] Notably, all these precedents are based on catalysts bearing π-acceptor ligands, while the limited information available regarding the performance of diphosphine catalysts (e.g., Me-DuPHOS, BINAP) in this reaction indicates only moderate enantioselectivities.[4c,5]

Mechanistic studies about the hydrogenation of structurally related enamides (X = NH, Scheme 2) with Rh diphosphine

Scheme 2. Regioselectivity of the Olefin Insertion Step (P−P = Diphosphine Ligand)



catalysts, indicate that the properties of the group R^1 have a strong impact on the reaction. Thus, for substrates with an electron-withdrawing R^1 substituent (e.g., aryl enamides, dehydroamino acids) the formation of a α-alkyl complex intermediate is favored.[9a,b,d,e] In contrast, for enamides bearing a bulky electron-releasing *t*-Bu substituent, a β-alkyl species is preferred.[9c,10] Computational studies have also investigated the influence of the electronic and steric properties of these substituents on the reaction, explaining the regioselectivity observed in the olefin insertion step.[11] Most importantly, pathways leading to α- and β-alkyl intermediates generally have different stereochemical features in such a way that the formation of opposite enantiomers from substrates reacting by one or the other pathway has been observed.[12] These precedents therefore raise the interest in the asymmetric hydrogenation of substrates lying between the two limiting cases, like for instance, enol esters **A** with an alkyl substituent smaller than a *t*-Bu group.

Regarding the application of the reaction sequence of *path a* to the synthesis of alcohols **C**, the procedure acquires a higher value in cases in which no suitable catalyst for the direct hydrogenation of corresponding ketones **D** is known (*path b*, Scheme 1), thus justifying the additional deprotection step. At this respect, the hydrogenation of 1-alkylvinyl esters (**A**, R^1 = alkyl) is a transformation of great potential. A perusal of the literature indicates that the hydrogenation of methyl alkyl ketones is a particularly difficult reaction, as the stereochemical control of the reaction depends on the relative sizes of Me and R^1 groups. Therefore, high enantioselectivities have been achieved in the case of substrates bearing a relatively bulky R^1 substituent (e.g., ^{i}Pr, Cy, *tert*-alkyl), while lower enantioselectivities are produced by ketones with linear R^1 substituents.[13,14] Alternatively, catalytic systems based on the exploitation of hydrophobic effects have provided some high enantioselectivities with ketones bearing long alkyl substituents, while the enantioselectivity decreases for shorter chains.[13d,g] Due to the synthetic importance of 2-alkanols, other chemocatalytic procedures have also been investigated, evidencing the difficulties to meet broad scope, high enantioselectivity, and high atom economy in the synthesis of these compounds.[15] In contrast, enzymatic procedures either based on the direct reduction of ketones or in the dynamic kinetic resolution of racemic 2-alkanols, allow the efficient synthesis of a wide variety of these alcohols with a high enantiomeric purity.[16]

In previous years, we have developed in our laboratory the synthesis of a fully modular family of phosphine−phosphite ligands **1** and **2** (P−OP, Figure 1), which have been

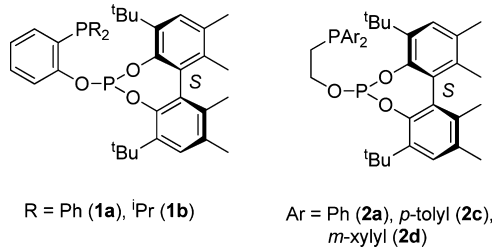


Figure 1. Structure of phosphine−phosphite ligands (P−OP) used in this study.

successfully applied in the rhodium-catalyzed asymmetric hydrogenation of a diverse types of olefins.[17] Because these ligands are characterized by a π-acceptor phosphite fragment, and taking into account that there is a wide diversity of synthetically valuable esters **B** with R^1 alkyl substituents, we considered it of interest to investigate the performance of the corresponding Rh catalysts in the hydrogenation of enol esters **A**. Following a preliminary report on this topic,[18] we present herein a detailed study about the application of these catalysts in the hydrogenation of a broad range of substrates **A**. The investigation has focused on alkyl derivatives (both simple and substituted), although some additional substrates bearing an aryl substituent have also been covered for completion. Finally, an application of the present hydrogenation to the preparation of selectively deuterated products is also reported.

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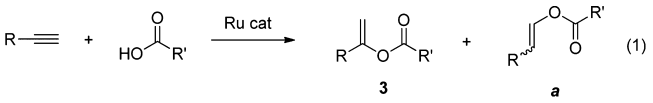
RESULTS AND DISCUSSION

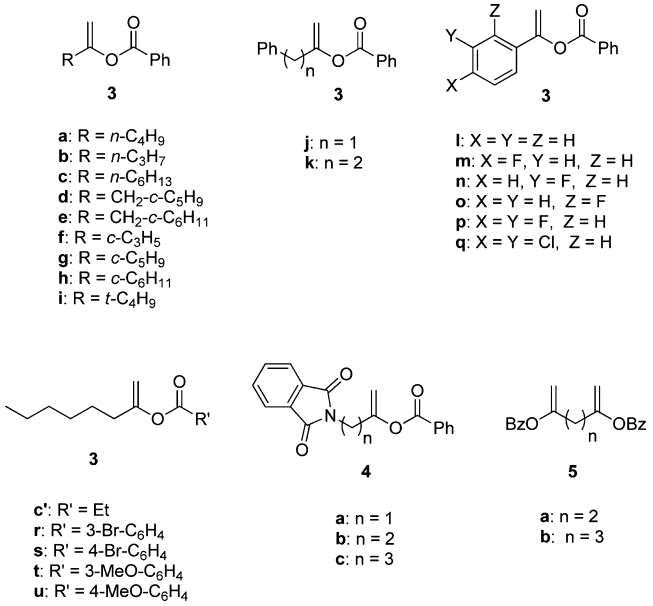
Preparation of Substrates. Enol esters **3** were prepared by the addition of a carboxylic acid to a terminal alkyne catalyzed by $[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(PPh_3)]$ ($C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl) (eq 1, below). In the case of



aliphatic alkynes, the reaction conveniently proceeded in water, as described before.[19] Aromatic alkynes (R = Ar) otherwise showed an extremely low reactivity under these reaction conditions. Alternatively, a moderate conversion was observed under microwave irradiation using toluene as the solvent and $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_3)]$ as the catalyst. It is worth noting that these reactions provide the desired prochiral Markovnikov isomers **3** in high yield, the minor amounts of the *E* and *Z* anti-Markovnikov byproducts (***a***) formed being easily removed by column chromatography.

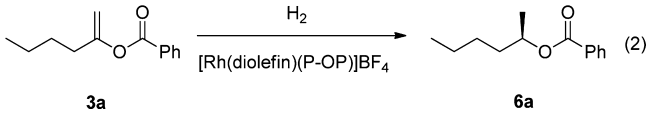
In order to study in detail the scope of the hydrogenation of compounds **3**, a broad range of enol esters were synthesized (Chart 1). A first group of compounds (**3a**–**i**) contains

Chart 1. Range of Enol-Esters 3–5 Covered in the Present Study



different alkyl groups at position R. For comparison, a propionate example (**3c′**) was also considered. On the other hand, we were interested in the performance of benzyl (**3j**) and phenylethyl (**3k**) derivatives. Interestingly, no migration of the double bond was observed in the preparation of these compounds.[20] In addition, a group of aryl substrates (**3l**–**q**), with a particular interest in fluorinated derivatives, was also prepared. Moreover, Br- and MeO-substituted benzoates (**3r**–**u**), suitable for functionalization of the aromatic ring, were also included in the study. Because the previous examples lack functional groups other than the ester function, they are also pertinent the study of phthalimido derivatives **4**, which may be of interest in the syntheses of amino-alcohol derivatives. Finally, we were interested in the hydrogenation of dibenzoates **5** as it would provide a convenient route to the corresponding 1,4 and 1,5 diols.

Optimization of the Catalytic System. In a first stage, some hydrogenations of the representative substrate **3a** with catalyst precursors of formula $[Rh(diolefin)(P{-}OP)]BF_4$ (diolefin =1,4-norbornadiene (NBD), 1,5-cyclooctadiene (COD); P–OP = (*S*)-**1a**, (*R*)-**1a**, (*S*)-**1b**, (*S*)-**2a**) to determine suitable reaction conditions for the catalysis were examined (eq 2). Upon the mentioned literature precedents for this reaction,



some hydrogenations at 20 bar of hydrogen and room temperature were performed. Thus, $[Rh(NBD)((S)\text{-}\mathbf{1a})]BF_4$ and $[Rh(COD)((S)\text{-}\mathbf{2a})]BF_4$ completed reactions at S/C = 100, with good enantioselectivities (89 and 88% ee, respectively, entries 1, 2, Table 1). It is noteworthy that these

Table 1. Hydrogenation of 3a Performed with $[Rh(diolefin)(P{-}OP)]BF_4$[a]

entry	P–OP	H_2 (bar)	S/C	% conv	% ee (conf)
1	(*S*)-**1a**	20	100	100	89 (*R*)
2[b]	(*S*)-**2a**	20	100	100	88 (*R*)
3	(*S*)-**1a**	4	200	100	94 (*R*)
4[b]	(*S*)-**2a**	4	200	100	96 (*R*)
5[c]	(*S*)-**1a**	1	200	100	94 (*R*)
6[c,d]	(*S*)-**1a**	4	200	20	19 (*R*)
7[c]	(*S*)-**1b**	4	200	74	83 (*R*)
8[e]	(*S*)-**2a**	4	200	100	95 (*R*)
9[e]	(*S*)-**2a**	4	500	100	96 (*R*)

[a]Hydrogenations in CH_2Cl_2, [Rh] = 2×10^{-4} M, [**3a**] = 0.02–0.1 M, at initial pressure and substrate to catalyst ratio (S/C) indicated. Reactions performed at room temperature for 24 h with $[Rh(NBD)(P{-}OP)]BF_4$ unless otherwise stated. Conversion determined by ^1H NMR and enantiomeric excess by chiral HPLC. **6a** was the only product detected. Configuration was determined by comparison of the optical rotation sign with literature data. [b]COD catalyst precursor used. [c]Reaction time 37.5 h. [d]2-Me-thf used as solvent. [e]Reaction performed at 40 °C.

catalysts displayed enough activity to complete reactions at lower pressure. In addition, the decrease in pressure has a positive effect on enantioselectivity, which increased to 94% ee for the catalyst bearing ligand (*S*)-**1a** (entry 3) and to 96% ee in the case of (*S*)-**2a** (entry 4). An additional decrease on pressure down to 1 bar of hydrogen has no further effect (entry 5).[21,22] In contrast, the use of 2-Me-thf as a solvent has a negative effect leading to a decrease both in conversion and enantioselectivity (entry 6). On the other hand, catalyst-bearing isopropyl-substituted ligand (*S*)-**1b** showed lower activity and enantioselectivity than its phenyl counterpart (entry 7). Finally, a slight increase in temperature up to 40 °C has no detrimental effect on enantioselectivity (entry 8). Thus, a reaction using a low catalyst loading (S/C = 500) could be completed under very mild conditions with a high enantioselectivity (96% ee, entry 9).

Scope of the Reaction. In a next stage, we examined the scope of complex $[Rh(NBD)((S)\text{-}\mathbf{2a})]BF_4$ in the hydrogenation of diverse enol esters **3**. We initially studied several examples bearing primary alkyl R substituents (eq 3, Table 2).

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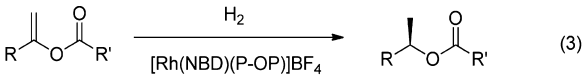

Table 2. Hydrogenation of 3b–e with [Rh(NBD)((*S*)-2a)]BF_4[a]

entry	substrate	S/C	% ee (conf)
1	**3b**	500	96 (*R*)
2	**3c**	500	95 (*R*)
3	**3d**	500	98 (*R*)
4	**3e**	500	99 (*R*)
5	**3c′**	1000	97 (*R*)
6[b]	**3c′**	2000	95 (*R*)

[a]Reactions in CH_2Cl_2 at 40 °C and an initial pressure of 4 bar of hydrogen, [Rh] = 2×10^{-4} M, [**3**] = 0.1–0.2 M. Reaction time: 24 h. Reactions showed full conversion unless otherwise stated. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral GC or HPLC. Compounds **6b–e** were the only products detected. See Supporting Information for determination of configuration. [b]87% conversion.

Most remarkably, this catalyst exhibited suitable activity to complete reactions performed at S/C = 500 in 24 h under very mild conditions (4 bar H_2, 40 °C). As observed for **3a**, high enantioselectivities, ranging from 95 to 99% ee, were obtained in the hydrogenation of enol benzoates **3b–e** (entries 1–4). In addition, propionate **3c′** also gave high conversion and enantioselectivity (entry 5). As expected, the benzoate group is therefore not required for the attainment of high enantioselectivity. Additional information about the activity of this catalyst was provided by another hydrogenation of **3c′** prepared under identical conditions and stopped after 0.5 h, which showed 44% conversion (TOF = 440 h^{-1}). Moreover, a further lowering of the catalyst loading to S/C = 2000 led to an uncompleted reaction in 24 h, although it still afforded a good conversion value (87%, entry 6). Considering the easy deprotection of the hydrogenation products,[8,18,23] these results demonstrate that the present catalytic system provides a reliable access to otherwise difficult to synthesize unhindered 2-alkanols with high enantiomeric purity.

An analysis of the results described by Leitner and Franciò indicates that 1-cycloalkyl vinyl esters are particularly difficult substrates for this hydrogenation. For instance, 80 and 86% ee resulted in the hydrogenation of the cyclohexyl and cyclopropyl acetates, well below the rest of the substrates examined.[8] Likewise, in our preliminary study we obtained an enantioselectivity of 86% ee in the hydrogenation of the cyclohexyl benzoate **3h**.[18] Upon these precedents, we have considered a wider catalyst screening including those with ligands (*S*)-**2c** and (*S*)-**2d**, which are characterized by *p*-tolyl and *m*-xylyl phosphine substituents. In order to provide additional information, we have also examined the hydrogenation of cyclopropyl (**3f**) and cyclopentyl (**3g**) substrates (eq 4). First, the hydrogenation of **3f** showed only a 50% conversion in the reaction prepared with [Rh(NBD)((*R*)-**1a**)]BF_4 (entry 1, Table 3), while [Rh(NBD)((*S*)-**2a**)]BF_4 led to an even lower value (30%, entry 2). In contrast, catalysts bearing ligands (*S*)-**2c** and (*S*)-**2d** provided complete reactions (entries 3, 4). It is remarkable that all the reactions yielded high enantioselectivities, with values around 95% ee. On the other hand, catalysts of ligands (*S*)-**1a** and (*S*)-**2a** produced low conversions in the hydrogenation of substrate **3g** (entries 5, 6), as observed for the cyclopropyl substrate. Likewise, [Rh(NBD)((*S*)-**2c**)]BF_4 catalyst did not complete the reaction under our standard conditions (entry 7). Moreover, an increase on pressure up to 20 bar of hydrogen improved conversion to 90%, although a decrease on enantioselectivity to 76% ee was observed (entry 8).[21] Alternatively, a reduction of the S/C ratio to 200 allowed us to complete the reaction with the latter catalyst with 83% ee (entry 9). Most noteworthy, the *m*-xylyl complex [Rh(NBD)-((*S*)-**2d**)]BF_4 is particularly suitable for substrate **3g** as it was able to complete a reaction at S/C = 500, with a remarkable enhancement of enantioselectivity up to 90% ee (entry 10). For the cyclohexyl substrate **3h** a similar behavior was observed. Thus, catalyst bearing ligand (*R*)-**1a** afforded low conversion (entry 11), while it increased with catalysts based on ligands (*S*)-**2a** and (*S*)-**2c**, giving complete reactions with enantioselectivities of 85 and 84% ee, respectively (entries 12, 13). Finally, the *m*-xylyl catalyst provided best results giving full conversion and 90% ee (entry 14).

In order to complete the series of substrates, we also examined the hydrogenation of *tert*-butyl substrate **3i**. In contrast to the results obtained with cycloalkyl substrates **3f–h**, catalyst bearing ligand (*S*)-**1a** showed a high activity. Thus, full

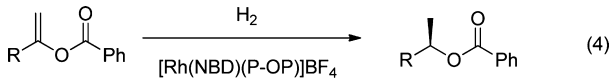

Table 3. Hydrogenation of 3f–i with Catalyst Precursors [Rh(NBD)(P–OP)]BF_4[a]

entry	substrate	P–OP	S/C	% conv	% ee (conf)
1	**3f**	(*R*)-**1a**	500	50	94 (*S*)
2	**3f**	(*S*)-**2a**	500	30	96 (*R*)
3	**3f**	(*S*)-**2c**	500	100	96 (*R*)
4	**3f**	(*S*)-**2d**	500	100	95 (*R*)
5	**3g**	(*S*)-**1a**	500	5	n. d.
6	**3g**	(*S*)-**2a**	500	5	n. d.
7	**3g**	(*S*)-**2c**	500	45	82 (*R*)
8[b]	**3g**	(*S*)-**2c**	500	90	76 (*R*)
9	**3g**	(*S*)-**2c**	200	100	83 (*R*)
10	**3g**	(*S*)-**2d**	500	100	90 (*R*)
11	**3h**	(*R*)-**1a**	200	35	37 (*S*)
12	**3h**	(*S*)-**2a**	200	100	85 (*R*)
13	**3h**	(*S*)-**2c**	200	100	84 (*R*)
14	**3h**	(*S*)-**2d**	500	100	90 (*R*)
15	**3i**	(*S*)-**1a**	200	100	98 (*S*)
16	**3i**	(*S*)-**1a**	1000	100	97 (*S*)
17	**3i**	(*R*)-**1a**	500	100	96 (*R*)
18	**3i**	(*S*)-**2a**	200	100	78 (*S*)
19	**3i**	(*S*)-**2c**	200	100	82 (*S*)

[a]Reactions in CH_2Cl_2 at 40 °C and an initial pressure of 4 bar of hydrogen, [Rh] = 2×10^{-4} M, [**3**] = 0.04–0.2 M. Reaction time: 24 h. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. Compounds **6f–i** were the only products detected. See Supporting Information for determination of configuration. [b]Reaction performed at 20 bar of hydrogen.

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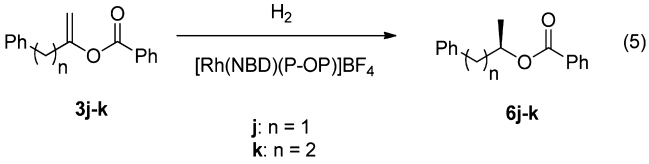
conversion was observed not only at S/C = 200 (entry 15), but as well at a value of 1000 (entry 16). Moreover, a very high enantioselectivity (97−98% ee), was observed in these reactions. Most remarkably, a reversal of product configuration is observed, obtaining the *S* enantiomer. Conversely, (*R*)-**6i** was obtained using catalyst bearing ligand (*R*)-**1a** (entry 17). The same relation between ligand and product configurations were likewise observed in the case of catalysts bearing ligands (*S*)-**2a** and (*S*)-**2c**, which provided (*S*)-**6i** with significantly lower enantioselectivities, 78 and 82% ee, respectively (entries 18, 19).

Another interesting application of the present methodology is the hydrogenation of the benzyl substrate **3j** because it could provide a convenient route to the preparation of enantiopure 3-phenyl-2-propanol (eq 5), valuable for the synthesis of 2-



(5)

phenylpropylamines of pharmaceutical interest.[24] Moreover, to the best of our knowledge, a highly enantioselective catalyst for the hydrogenation of methyl benzyl ketone has not been described to date. Thus, several hydrogenations of **3j** using diverse catalysts were prepared at room temperature with a S/C ratio of 200 (Table 4). There was no satisfactory conversion,

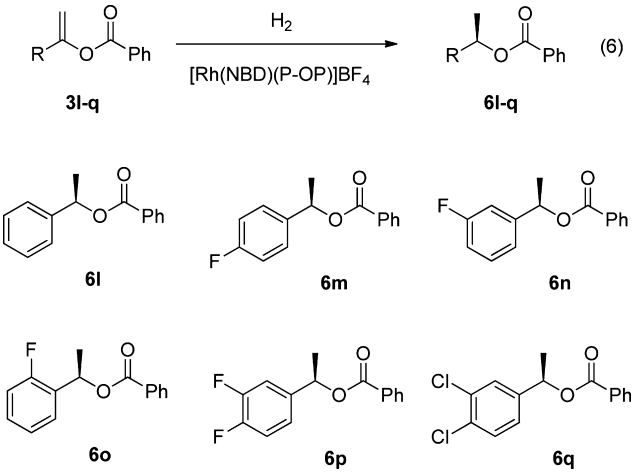
Table 4. Hydrogenation of 3j−k with Catalyst Precursors [Rh(NBD)(P−OP)]BF_4[a]

entry	substrate	P−OP	S/C	% conv	% ee (conf)
1[b,c]	**3j**	(*S*)-**1a**	200	68	96 (*R*)
2[b,c]	**3j**	(*S*)-**2a**	200	89	98 (*R*)
3[b,c]	**3j**	(*S*)-**2c**	200	75	97 (*R*)
4	**3j**	(*S*)-**2a**	500	100	99 (*R*)
5	**3k**	(*S*)-**1a**	500	60	95 (*R*)
6	**3k**	(*S*)-**2a**	500	40	99 (*R*)
7[c]	**3k**	(*S*)-**2c**	500	100	98 (*R*)

[a]Reactions in CH_2Cl_2 at 40 °C and an initial pressure of 4 bar of hydrogen unless otherwise stated, [Rh] = 2×10^{-4} M, [**3**] = 0.04−0.2 M. Reaction time: 24 h. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. Compounds **6j−k** were the only products detected. See Supporting Information for determination of configuration. [b]Reaction performed at room temperature. [c]Reaction time: 37.5 h.

although high enantioselectivities were observed (entries 1−3). In contrast, hydrogenation performed with [Rh(NBD)((*S*)-**2a**)]BF_4 at 40 °C showed full conversion for a S/C ratio of 500 with an outstanding enantioselectivity of 99% ee (entry 4). In addition, substrate **3k** was also examined due to its synthetic interest.[25] This substrate, however, was less reactive than **3j** under the standard conditions, and catalysts bearing ligands (*S*)-**1a** and (*S*)-**2a** did not show full conversion. In contrast, the catalyst of (*S*)-**2c** showed a satisfactory reactivity which allowed us to obtain a high conversion and 98% ee (entry 7).

Despite the fact there is ample precedent in the literature about the Rh-catalyzed asymmetric hydrogenation of 1-aryl vinyl esters,[4a,d,i,k] we were interested in examining the performance of our catalysts in the hydrogenation of some substrates of this class to complete the present study. Initially, a set of hydrogenations of **3l** performed at a S/C ratio of 200 were prepared (eq 6). Interestingly, catalysts bearing ligands



(6)

(*S*)-**1a**, (*S*)-**2a**, and (*S*)-**2c** provided full conversion and very high enantioselectivities (98−99% ee, entries 1−3, Table 5),

Table 5. Hydrogenation of 3l−q with Catalyst Precursors [Rh(NBD)(P−OP)]BF_4[a]

entry	substrate	P−OP	S/C	% conv	% ee (conf)
1	**3l**	(*S*)-**1a**	200	100	98 (*R*)
2	**3l**	(*S*)-**2a**	200	100	98 (*R*)
3	**3l**	(*S*)-**2c**	200	100	99 (*R*)
4	**3l**	(*S*)-**2c**	500	100	99 (*R*)
5	**3m**	(*S*)-**2c**	1000	100	99 (*R*)
6	**3n**	(*S*)-**2c**	500	100	99 (*R*)
7	**3o**	(*S*)-**2c**	750	100	99 (*R*)
8	**3p**	(*S*)-**2c**	750	100	99 (*R*)
9	**3q**	(*S*)-**2c**	500	10	n. d.
10	**3q**	(*S*)-**2c**	200	100	99 (*R*)

[a]Reactions in CH_2Cl_2 at 40 °C and an initial pressure of 4 bar of hydrogen, [Rh] = 2×10^{-4} M, [**3**] = 0.04−0.2 M. Reaction time: 24 h. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. Compounds **6l−q** were the only products detected. See Supporting Information for determination of configuration.

indicating that this substrate is not very sensitive to changes made in the catalyst structure. Moreover, the latter catalyst displayed enough reactivity to complete the reaction at S/C = 500 with an excellent enantioselectivity (99% ee, entry 4). These satisfactory results led us to examine the hydrogenation of fluoro-aryl substrates, due to the broad range of applications of the corresponding alcohols.[26] Thus, hydrogenation of the *p*-F-substituted substrate **3m** performed with complex [Rh(NBD)((*S*)-**2c**)]BF_4 exhibited both high catalyst activity and enantioselectivity (99% ee, entry 5). Analogously, the same catalyst afforded very high enantioselectivity in the hydrogenation of *m*-F **3n** (99% ee, entry 6) and *o*-F **3o** (99% ee, entry 7) substituted substrates. Likewise, the disubstituted *m,p*-F_2 substrate **3p** was also hydrogenated with full conversion and a very high enantioselectivity (99% ee, entry 8). In this context, it should be noted that the group of Vidal has reported the hydrogenation at 20 bar of H_2 of the corresponding monofluoroaryl acetates using an alternative Rh phosphine−phosphite catalyst, with enantioselectivities ranging from 94 to 98% ee.[4k] In addition, the hydrogenation of the dichloro substrate **3q** has also been considered due to the synthetic

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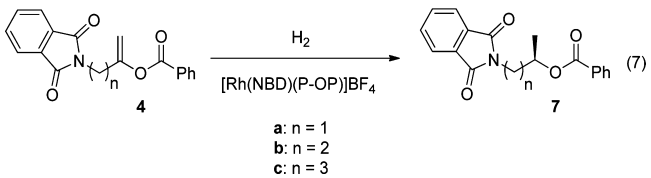
interest of the corresponding alcohol in the preparation of biologically active derivatives.[27] This compound was less reactive, and a low conversion (10%, entry 9) was observed under our standard conditions. Alternatively, the use of a smaller S/C ratio ensured a complete reaction, while an excellent enantioselectivitity value of 99% ee was observed (entry 10).

Notably, a comparison of configurations obtained in the hydrogenations of substrates **3i** and **3l** indicates an opposite product configuration. This is a general trend, as it is observed in reactions performed with catalysts based on ligands (*S*)-**1a**, (*S*)-**2a**, and (*S*)-**2c**. As mentioned, an analogous phenomenon has been observed in the hydrogenation of closely related 1-phenylvinyl and 1-*tert*-butylvinil acetamides with Rh diphosphine catalysts.[12a−d] Considering the structural similarity between **3l** and **3i** with the mentioned enamides, the shift of configuration can reasonably be assigned to an analogous opposed regioselectivity in the olefin insertion step.[9c,11a] Accordingly, **3l** would follow a α-alkyl pathway, while **3i** a β-alkyl one. Attending to product configuration, substrates **3a−e** characterized by nonhindered alkyl R substituents would also follow the α-alkyl pathway. Analogously, cyclopropyl substrate **3f** showed a similar behavior to the latter and the *R* product with high enantioselectivity was obtained.[28] Upon these considerations, it is not unreasonable to consider that both reaction pathways can be feasible in the case of substrates bearing larger cycloalkyl substituents, possessing steric and electronic properties between primary and *t*-Bu alkyl substituents. Most noteworthy, the competition between the α- and β-alkyl pathways would be accompanied by an erosion on enantioselectivity. Thus, the generally lower enantioselectivities observed in the hydrogenation of **3g** and **3h** may be attributed to this effect. Alternatively, an inherently difficult stereocontrol may be claimed to explain the generally low enantioselectivities provided by these substrates. In this context, it is pertinent to recall that in the hydrogenation of enamides using Rh catalysts bearing highly donating diphosphine ligands, Gridnev and Imamoto have proposed the competition of the α- and β-alkyl pathways in some reactions exhibiting low to moderate enantioselectivities.[29] Moreover, an appreciable decrease in enantioselectivity in such reactions, attributed to an influence of the isotopic composition of the catalyst in the competition between the two pathways, was observed when hydrogen was substituted by deuterium. Likewise, in the present system, no significant change in enantioselectivity was observed in the deuteration of **3c** and **3l** with catalyst-bearing ligand (*S*)-**2a**, which were obtained with 94 and 99% ee, respectively. In contrast, deuteration of **3h** with the same catalyst precursor produced **6h**-1,2-d_2 with a 76% ee, which is a significantly lower value than the corresponding to the hydrogenation reaction (85% ee, entry 12, Table 3).

Considering that *N*-phthalimido alkynes are readily available compounds, an appealing application of the present methodology is the hydrogenation of enol esters **4** for the obtention of masked aminoalcohols **7** (eq 7).[30] Moreover, the hydrogenation of **4** also has a fundamental interest, due to the presence of the phthalimido carbonyl groups which may be able to compete with the ester group for the coordination to the Rh atom (Figure 2).[31] Important to note, the generation of structurally similar chelates, by imide or ester coordination, involve the binding to the metal by different olefin faces, which presumably would lead to opposite product configurations. Therefore, if both coordination modes participate in the reaction, a drop in enantioselectivity should be observed.

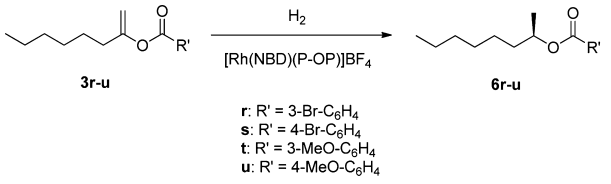


(7)

Initially, a set of reactions with representative **4a** were examined at 4 bar of H_2 and 40 °C. We were pleased to observe that catalysts based on ligands (*S*)-**2a** and (*S*)-**2c** were very effective in the hydrogenation of this substrate and completed reactions performed at S/C = 500. Moreover, product (*R*)-**7a** was obtained with a very high enantioselectivity (99% ee, entries 2, 3, Table 6).

In addition, (*S*)-**7a** was obtained with 99% ee by using [Rh(NBD)((*R*)-**1a**)]BF_4 (entry 1). It is noteworthy that substrates **4b** and **4c** behaved in a similar way. Thus, the three catalysts displayed high activity with enantioselectivities ranging from 95 to 98% ee (entries 5−7 and 9−11, respectively). Finally, with the intention to increase reaction productivity, a set of reactions were prepared with substrates **4a−c** and complex [Rh(NBD)((*S*)-**2c**)]BF_4 at S/C ratios of 1000. Remarkably, complete reactions and excellent enantioselectities (98−99% ee) were observed in the three cases (entries 4, 8, and 12, respectively). A comparison of the configuration of products **7** indicated an *R* configuration for reactions performed with catalyst precursor [Rh(NBD)((*S*)-**2a**)]BF_4, coincident with that observed in the hydrogenation of **3a** and **3b** with the same catalyst. Considering the different distance of the phthalimido group to the olefin bond, the similar behavior exhibited by compounds **4** in the reaction, indicates a strong specificity of the catalyst for the vinyl benzoate fragment. In connection with these observations, it should be mentioned that a mechanism for enantioselection in Rh-catalyzed asymmetric hydrogenation based on a enantiodiscriminating coordination of the olefin bond in octahedral dihydrides, outlining a highly precise substrate recognition by the catalyst, has recently been proposed.[10b,32]

Another interesting application of the present catalytic system is the preparation of alkyl benzoates appropriately substituted at the aromatic ring for further functionalization. These compounds have interest, for instance, in the synthesis of chiral dopants for the preparation of liquid crystals,[33] such as the widely used enantiomers R811 and S811 (Figure 3).[34] To this aim, Br- and OMe-substituted benzoates **3r−u** were prepared and their hydrogenations examined. In the hydrogenation of 3-Br-substituted substrate **3r** several catalysts were tested at S/C = 200 (eq 8). Among them, that bearing ligand



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(*S*)-**2a** provided the highest enantioselectivity (entries 1−3, Table 7). Interestingly, this catalyst also completed the reaction at S/C = 500 with a 95% ee (entry 4). Application of the latter reaction conditions for substrates **3s−u** also showed good

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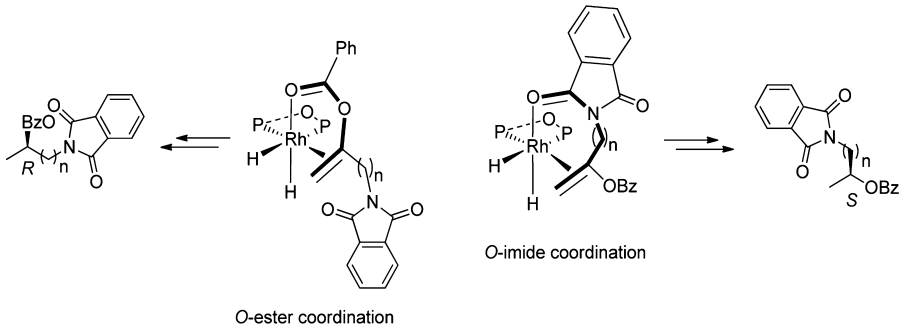


Figure 2. Possible coordination modes of substrates **4** in $[RhH_2(P{-}OP)(\mathbf{4})]^+$ complexes (phosphorus substituents have been omitted for clarity).

Table 6. Hydrogenation of 4a−c with Catalyst Precursors [Rh(NBD)(P−OP)]BF_4[a]

entry	substrate	P−OP	S/C	% ee (conf)
1	**4a**	(*R*)-**1a**	500	99 (*S*)
2	**4a**	(*S*)-**2a**	500	99 (*R*)
3	**4a**	(*S*)-**2c**	500	99 (*R*)
4	**4a**	(*S*)-**2c**	1000	98 (*R*)
5	**4b**	(*S*)-**1a**	500	97 (*R*)
6	**4b**	(*S*)-**2a**	500	95 (*R*)
7	**4b**	(*S*)-**2c**	500	98 (*R*)
8	**4b**	(*S*)-**2c**	1000	98 (*R*)
9	**4c**	(*R*)-**1a**	500	96 (*S*)
10	**4c**	(*S*)-**2a**	500	96 (*R*)
11	**4c**	(*S*)-**2c**	500	98 (*R*)
12	**4c**	(*S*)-**2c**	1000	98 (*R*)

[a]Reactions in CH_2Cl_2 at 40 °C and an initial pressure of 4 bar of hydrogen, [Rh] = 2×10^{-4} M, [**4**] = 0.04−0.2 M. Reaction time: 24 h. Reactions showed full conversion. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral GC or HPLC. Compounds **7a−c** were the only products detected. See Supporting Information for determination of configuration.

performances producing the desired esters **6s−u** with enantioselectivities between 94 and 96% ee (entries 5−7).

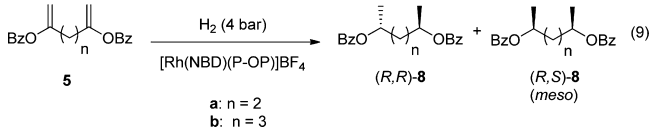
To enhance the range of synthetic applications of the present methodology, we have also considered the hydrogenation of dibenzoates for the generation of synthetically useful chiral diols. For instance, 1,4-hexanediol has extensively been used in the synthesis of diverse chiral compounds including the synthesis of chiral auxiliaries and ligands.[35] The synthesis of this diol is very effectively done by the enzymatic reduction of 2,4-hexanedione,[36] while in this context, it is also worthwhile to mention that the group of Bäckvall has described a dynamic kinetic resolution procedure (DYKAT) using a Ru racemization catalyst together with a lipase, able to produce 2,5-hexanediacetate with 94:6 *R,R*/*meso* ratio.[37] Likewise, 2,5-heptanediol is also a rather versatile building block for the preparation of diverse chiral compounds, like for instance, 2,6-dimethylpiperidine. In this case, the DYKAT process efficiently provides the corresponding diacetate in 96:4 *R,R*/*meso* ratio.[38]

Table 7. Hydrogenation of 3r−u with Catalyst Precursors [Rh(NBD)(P−OP)]BF_4[a]

entry	substrate	P−OP	S/C	% ee (conf)
1	**3r**	(*S*)-**1a**	200	93 (*R*)
2	**3r**	(*S*)-**2a**	200	95 (*R*)
3	**3r**	(*S*)-**2c**	200	93 (*R*)
4	**3r**	(*S*)-**2a**	500	95 (*R*)
5	**3s**	(*S*)-**2a**	500	94 (*R*)
6	**3t**	(*S*)-**2a**	500	96 (*R*)
7	**3u**	(*S*)-**2a**	500	96 (*R*)

[a]Reactions in CH_2Cl_2 at 40 °C and an initial pressure of 4 bar of hydrogen, [Rh] = 2×10^{-4} M, [**3**] = 0.04−0.1 M. Reaction time: 24 h. Reactions showed full conversion. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. Compounds **6r−u** were the only products detected. See Supporting Information for determination of configuration.

Upon these precedents, we considered it of interest to examine the hydrogenation of dibenzoates **5a** and **5b** (eq 9). We initially



(9)

examined the performance of catalysts of ligands (*S*)-**1a**, (*S*)-**2a**, and (*S*)-**2c** in the hydrogenation of **5a** in reactions performed at S/C = 200 (i.e., 400 olefin bonds per Rh atom). Gratifyingly, the three catalysts showed a good activity and afforded complete reactions (entries 1−3, Table 8). Moreover, high stereoselectivities for the *R,R* isomer were observed. Thus, only a minor amount of the *meso* isomer, between 2 and 6%, was observed, while the *S,S* enantiomer was not detected. In an attempt to increase the productivity of the process, an alternative reaction performed at S/C = 500 was prepared using the most selective catalyst. Remarkably, this reaction showed only 3% of the *meso* compound and full conversion (entry 4). A similar study was next undertaken with dibenzoate **5b**. As in the previous case, catalyst-bearing ligand (*S*)-**2a** led to the best results at S/C = 200 (entries 5−7), while at S/C = 500

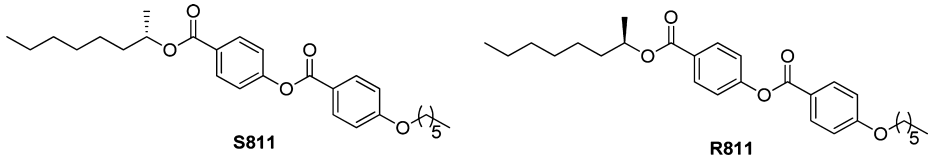


Figure 3. Structures of alkyl benzoates used as chiral dopants.

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Table 8. Hydrogenation of 5a,b with Catalyst Precursors [Rh(NBD)(P−OP)]BF_4[a]

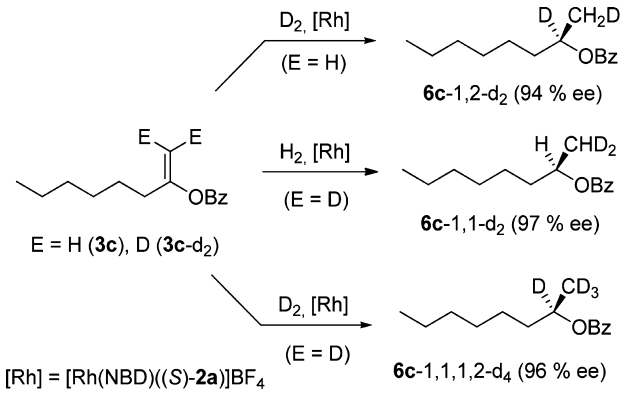
entry	substrate	P−OP	S/C	(*R*,*R*):*meso*	% ee (conf)
1	**5a**	(*S*)-**1a**	200	96:4	>99 (*R*,*R*)
2	**5a**	(*S*)-**2a**	200	98:2	>99 (*R*,*R*)
3	**5a**	(*S*)-**2c**	200	94:6	>99 (*R*,*R*)
4	**5a**	(*S*)-**2a**	500	97:3	>99 (*R*,*R*)
5	**5b**	(*S*)-**1a**	200	95:5	>99 (*R*,*R*)
6	**5b**	(*S*)-**2a**	200	97:3	>99 (*R*,*R*)
7	**5b**	(*S*)-**2c**	200	95:5	>99 (*R*,*R*)
8	**5b**	(*S*)-**2a**	500	98:2	>99 (*R*,*R*)

[a]Reactions in CH_2Cl_2 at 40 °C and an initial pressure of 4 bar of hydrogen, [Rh] = 2×10^{-4} M, [**5**] = 0.04−0.1 M. Reaction time: 24 h. Reactions showed full conversion. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. Compounds **8a,b** were the only products detected. See Supporting Information for determination of configuration.

a complete reaction and only a 2% of the *meso* isomer were achieved (entry 8).

Preparation of Labeled Compounds. An inherent difference in the preparation of alcohols **A** by *path a* or *path b*, regards the relative position of the hydrogen atoms transferred to the substrate. This feature allows to advantageously label the methyl substituent adjacent to the stereogenic center in the case of the hydrogenation of enol esters. Committed by the current interest in the preparation of deuterated pharmaceuticals,[39] we have studied the preparation of some methyl labeled products **6**. For instance, the deuteration of **3l** provides a convenient synthesis of 1,2-dideutero-1-phenylethyl benzoate (**6l**-1,2-d_2) with high enantiomeric purity (99% ee, see Supporting Information). We were then interested to test the present methodology (Ru-catalyzed synthesis of enol esters followed by hydrogenation) in a more challenging sequentially controlled labeling of the methyl group. As a previous requirement, we have synthesized 2,2-dideutero-1-hexylvinyl benzoate (**3c**-d_2) by an adaptation of our standard methodology (eq 1). Thus, addition of benzoic acid to 1-deutero-octyne in deuterated water provided the desired labeled **3c**-d_2. Hydrogenation of this compound generated a CHD_2 group in **6c**-1,1-d_2 (Scheme 3). In contrast, deuteration of **3c** produced a CH_2D fragment in the corresponding **6c**-1,2-d_2, also labeled at position 2. Finally, a CD_3 fragment, can be generated by deuteration of **3c**-d_2, which provides the tetradeuterated compound **6c**-1,1,1,2-d_4. Remarkably, the labeled compounds were obtained with high enantioselectivities, ranging from 94 to 97% ee.

Scheme 3. Preparation of Selectively Deuterated 2-Octyl Benzoates



Reactions Performed at High Substrate Concentration. The wide scope exhibited by the present catalytic system along with the synthetic interest of the chiral benzoates obtained justifies the examination of practical aspects of the transformation. In this regard, a decrease of the amount of solvent used or ideally the absence of added solvent is of paramount importance in a scale-up process, regarding cost, environmental aspects, and the volume of reactor used.[40] Following these considerations, we examined the hydrogenation of substrate **3a** with the catalyst precursor [Rh(NBD)((*S*)-**2a**)]BF_4 in the neat substrate at 4 bar of hydrogen and 40 °C at a S/C = 500 ratio (entry 1, Table 9). Notably, we

Table 9. Hydrogenation of Selected Substrates at High Concentration[a]

entry	substrate	cat	S/C	cond.[b]	% ee (conf)
1	**3a**	(*S*)-**2a**	500	*n*	96 (*R*)
2	**3b**	(*S*)-**2a**	1000	*n*	96 (*R*)
3	**3i**	(*S*)-**1a**	500	*n*	95 (*S*)
4	**3j**	(*S*)-**2a**	1000	1:1	99 (*R*)
5	**3l**	(*S*)-**2a**	500	*n*	99 (*R*)
6	**3m**	(*S*)-**2a**	1000	6:5	99 (*R*)
7	**3u**	(*S*)-**2a**	500	*n*	96 (*R*)
8[c]	**5b**	(*S*)-**2a**	250	1:1	>99 (*R*,*R*)
9	**4a**	(*S*)-**2a**	1000	2:5	99 (*R*)
10	**4c**	(*S*)-**2a**	1000	4:5	96 (*R*)

[a]Reactions at 40 °C and an initial pressure of 4 bar of hydrogen, reaction time: 24 h. Reactions showed full conversion into the corresponding hydrogenated products. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. See Supporting Information for determination of configuration. [b]Substrate: solvent weight ratio; *n* denotes a reaction performed in the neat substrate. [c]3% of *meso* compound observed.

observed full conversion after 24 h with 96% ee, coincident with that obtained in a 0.1 M solution of **3a**. Therefore, the catalyst is not inhibited at a high product concentration. Prompted by this result, we examined if this behavior is more general. Then, the hydrogenation of **3b** was examined at S/C = 1000 under the same reaction conditions (entry 2). Full conversion and a high enantioselectivity were also observed. Likewise, *tert*-butyl substrate **3i** was hydrogenated using complex [Rh(NBD)((*S*)-**1a**)]BF_4 with high catalytic activity and enantioselectivity (entry 3). Moreover, the methodology is applicable to the phenyl substrate **3l** (entry 5). Therefore, despite the high concentration of the product, no product inhibition by the plausible formation of η^6-arene complexes is observed.[4b,41] Likewise, reactions in the neat substrate also provided satisfactory results in the case of substrate **3u** (entry 7). Alternatively, for solid substrates the use of highly concentrated solutions conveniently afforded the desired results.[42] Thus, the hydrogenation of a **3j**:CH_2Cl_2 (1:1 w/w) mixture exhibited a full conversion at S/C = 1000 with 99% ee (entry 4). Analogously, fluorinated substrate **3m** also provided high conversion and enantioselectivity (entry 6). Likewise, the hydrogenation of dibenzoate **5b** at a S/C ratio of 250 afforded the desired dibenzoate with only 3% of the *meso* isomer (entry 8). Finally, due to the presence of the potentially coordinating phthalimido group in substrates **4**, it looked of interest to examine their hydrogenation at high concentration. As these

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olefins are solids at room temperature, the minimum amount of solvent to solubilize them was used. Thus, hydrogenation performed in a **4a**:CH_2Cl_2 (2:5 w/w) mixture showed full conversion and a high enantiomeric excess (99% ee, entry 9). Likewise, hydrogenation of a **4c**:CH_2Cl_2 (4:5 w/w) mixture also showed full conversion after 24 h with a 96% ee (entry 10).

CONCLUSIONS

The enantioselective hydrogenation of a broad range of enol esters of formula CH_2=C(OBz)R has been examined with rhodium catalysts bearing chiral phosphine−phosphite ligands. These catalysts show a good activity, being able to complete the reaction under very mild reaction conditions at S/C ratios ranging between 500 and 1000. A catalyst screening has determined the more appropriate catalyst for each type of substrate. Thus, high enantioselectivities ranging from 90 to 99% ee were obtained for the 27 substrates examined. The scope of the present catalytic system is rather broad and is appropriate for substrates bearing alkyl, aryl, or benzyl R substituents. Moreover, *N*-phthalimido substrates **4** lead to the masked aminoalcohol derivatives **7** with high levels of catalyst activity and enantioselectivity. In addition, the reaction is also suitable for the highly enantio and diastereoselective hydrogenation of dibenzoates. Most importantly, the catalytic system is suitable for the preparation of both product enantiomers, as *R* and *S* phosphine−phosphite ligands **1** and **2** are readily available as exemplified by enantiomers of **1a**. As the chiral benzoates obtained can be deprotected easily (some representative examples were given in our preliminary communication),[18] the present methodology provides a convenient access to the synthesis of a wide variety of chiral alcohols **C**. In connection with the interest in selectively deuterated chiral compounds, the methodology has been applied to the controlled stepwise labeling of the methyl group adjacent to the stereogenic center of a representative example. Finally, no inhibition of the hydrogenation even at high concentration was observed. This feature allowed us to run the hydrogenation at high substrate concentration or even in the neat substrate, increasing the practical value of this catalytic hydrogenation.

EXPERIMENTAL SECTION

General Procedures. All reactions and manipulations were performed under nitrogen or argon, either in a Braun Labmaster 100 glovebox or using standard Schlenk-type techniques. All solvents were distilled under nitrogen with the following desiccants: sodium−benzophenone−ketyl for diethyl ether and tetrahydrofuran (THF); sodium for hexanes and toluene; CaH_2 for dichloromethane; and NaO^iPr for isopropanol. Phosphine−phosphite ligands **1a−b** and **2a−d** as well as their Rh complexes were prepared as described previously.[17a,c,d,43] All other reagents were purchased from commercial suppliers and used as received. IR spectra were recorded on a PerkinElmer 1720-XFT or in a Bruker Vector 22 spectrometers. NMR spectra were obtained on a Bruker DPX-300, DRX-400, or DRX-500 spectrometers. $^{31}P\{^1H\}$ NMR shifts were referenced to external 85% H_3PO_4, while $^{13}C\{^1H\}$ and ^1H shifts were referenced to the residual signals of deuterated solvents. All data are reported in ppm downfield from Me_4Si. All NMR measurements were carried out at 25 °C, unless otherwise stated. GC and HPLC analyses were performed by using a Hewlett-Packard Model HP 6890 and Waters 2690 chromatographs, respectively. HPLC analyses were performed at 30 °C. HRMS data were obtained on a JEOL JMS-SX 102A mass spectrometer in the General Services of Universidad de Sevilla (CITIUS) and Instituto de Ciencia de Materiales de Zaragoza. Optical rotations were measured on a PerkinElmer Model 341 polarimeter.

Representative Synthesis of Enol-Esters 3−5. Enol esters **3a−k**, **3r−u**, **4a−c**, and **5a−b** (method 1)[19b] and **3l−q** (method 2)[19c] were prepared by a Ru-catalyzed condensation between a terminal alkyne and a carboxylic acid according to the respective literature procedure.

As a representative example of method 1, the novel enol-ester **3g** has been synthesized by mixing into a Teflon-capped sealed tube, under an argon atmosphere, cyclopentylacetylene (0.129 mL; 1.0 mmol), benzoic acid (0.123 g; 1.0 mmol), the ruthenium catalyst $[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(PPh_3)]$ (0.011 g; 0.02 mmol), and water (1.0 mL). The resulting mixture was stirred at 60 °C for 24 h. After elimination of the solvent under reduced pressure, chromatographic workup of the crude reaction mixture over silica gel, using an ethyl acetate−hexane mixture (1/300 v/v) as eluent, provided enol-ester **3g** as a yellow oil (86% yield).

As a representative example of method 2, the novel enol-ester **3o** has been synthesized by mixing into a crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer, under an argon atmosphere, 1-ethynyl-2-fluorobenzene (0.152 mL; 1.3 mmol), benzoic acid (0.123 g; 1.0 mmol), the ruthenium catalyst $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PPh_3)]$ (0.011 g; 0.02 mmol, and toluene (4.0 mL)). The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 160 °C (temperature monitored by a built-in infrared sensor), for 3 h. After elimination of the solvent under reduced pressure, chromatographic workup of the crude reaction mixture over silica gel, using an ethyl acetate−hexane mixture (1/300 v/v) as eluent, provided enol-ester **3o** as a yellow oil (35% yield).

General Procedures for Asymmetric Hydrogenation. In a glovebox, a solution of $[Rh(NBD)((S)\text{-}\mathbf{2a})]BF_4$ (0.33 mg, 0.37 μmol) and the corresponding substrate **3−5** (0.175 mmol, S/C = 500) in CH_2Cl_2 (2.0 mL) was placed in a HEL CAT-18 reactor. The reactor was purged with hydrogen and finally pressurized at 4 bar. The reaction was heated at 40 °C and magnetically stirred for 24 h. Then, the reactor was depressurized and the resulting solution slowly evaporated under vacuum. The remaining residue was analyzed by ^1H NMR to determine conversion. Then it was dissolved in a ^{i}PrOH/*n*-hexane 1:10 mixture and passed through a short pad of silica to remove catalyst decomposition products. The solution obtained was carefully evaporated yielding the corresponding product **6−8**. Enantiomeric excess of the latter was determined by chiral chromatography.

For reactions without added solvent, the reaction was prepared in an analogous manner using the substrate as solvent. In these reactions, an aliquot of the reaction was taken for ^1H NMR analysis, while catalyst impurities were removed by diluting the reaction media with a ^{i}PrOH/*n*-hexane 1:10 mixture and filtering the resulting solution through a short pad of silica. The solution obtained was evaporated yielding the desired hydrogenated product. The latter was analyzed by chiral chromatography to determine enantiomeric excess.

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■ ASSOCIATED CONTENT

Supporting Information

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Full characterization of new compounds (PDF).

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Notes

The authors declare no competing financial interest.

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