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Broad Scope Synthesis of Ester Precursors of Nonfunctionalized Chiral Alcohols Based on the Asymmetric Hydrogenation of α,β-Dialkyl-, α,β-Diaryl-, and α-Alkyl-β-aryl-vinyl Esters

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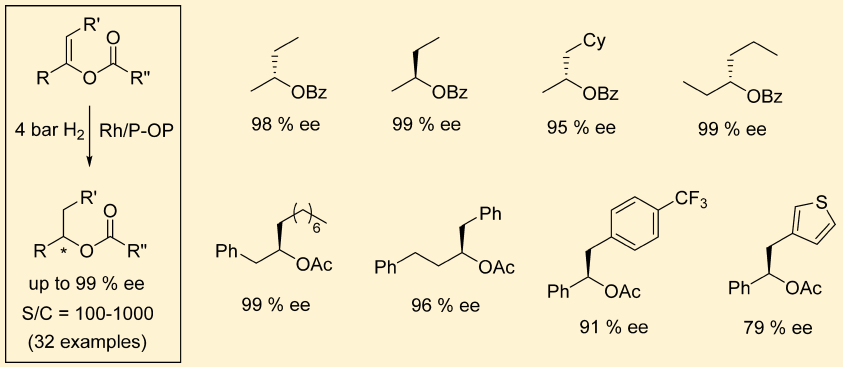
Supporting Information



ABSTRACT: The catalytic asymmetric hydrogenation of trisubstituted enol esters using Rh catalysts bearing chiral phosphine-phosphite ligands (P-OP) has been studied. Substrates covered comprise α,β-dialkyl, α-alkyl-β-aryl, and α,β-diarylvinyl esters, the corresponding hydrogenation products being suitable precursors to prepare synthetically relevant chiral nonfunctionalized alcohols. A comparison of reactivity indicates that it decreases in the order: α,β-dialkyl > α-alkyl-β-aryl > α,β-diaryl. Based on the highly modular structure of P-OP ligands employed, catalyst screening identified highly enantioselective catalysts for α,β-dialkyl (95−99% ee) and nearly all of α-alkyl-β-aryl substrates (92−98% ee), with the exception of α-cyclohexyl-β-phenylvinyl acetate which exhibited a low enantioselectivity (47% ee). Finally, α,β-diarylvinyl substrates showed somewhat lower enantioselectivities (79−92% ee). In addition, some of the catalysts provided a high enantioselectivity in the hydrogenation of *E*/*Z* mixtures (ca. *Z*/*E* = 75:25) of α,β-dialkylvinyl substrates, while a dramatic decrease on enantioselectivity was observed in the case of α-methyl-β-anisylvinyl acetate (*Z*/*E* = 58:42). Complementary deuteration reactions are in accord with a highly enantioselective hydrogenation for both olefin isomers in the case of α,β-dialkylvinyl esters. In contrast, deuteration shows a complex behavior for α-methyl-β-anisylvinyl acetate derived from the participation of the *E* isomer in the reaction.

INTRODUCTION

Catalytic asymmetric hydrogenation constitutes one of the most efficient tools for the preparation of chiral building blocks with high enantioselectivity.[1,2] As well, due to the inherent advantages that usually characterize these kind of processes (e.g., high catalyst efficiency, perfect atom economy, simple workup), they have extensively been used in industrial applications.[3] Among diverse classes of compounds prepared using asymmetric hydrogenation reactions, a particularly remarkable one corresponds to nonfunctionalized chiral alcohols of general structure **A** (R^1, R^2 = alkyl, aryl; Figure 1).

A very convenient and direct route to alcohols **A** is provided by the asymmetric hydrogenation of ketones **B** (path a). The feasibility of this option is, however, strongly dependent on the nature of R^1 and R^2 substituents. Thus, the hydrogenation of aryl-alkyl ketones constitutes one of the highest achievements in asymmetric catalysis due to the exceptional levels of catalyst activity and enantioselectivity reached.[4] As well, very efficient catalysts have been described for the hydrogenation of *tert*-alkyl−alkyl ketones.[5] Nonetheless, the hydrogenation of dialkyl ketones characterized by less bulky alkyl substituents has a considerable difficulty and high enantioselectivities have only been achieved in a limited number of cases.[4i,6,7] Likewise,

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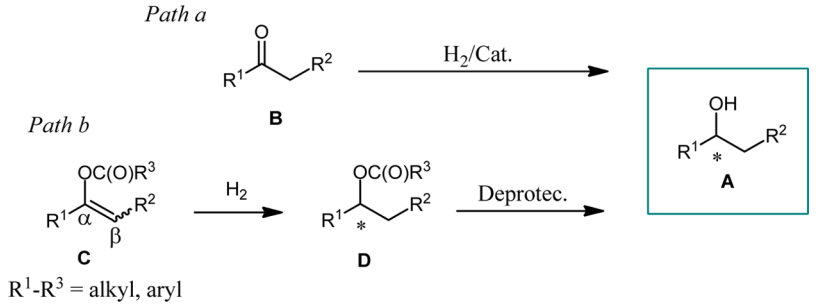
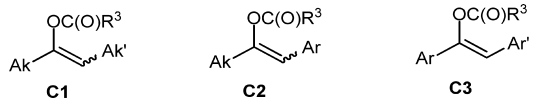


Figure 1. Hydrogenation routes to alcohols **A**.

benzyl-alkyl ketones constitutes another class of problematic substrates and no satisfactory hydrogenation catalysts have so far been reported.[8,9] However, chiral alkanols and homobenzylic alcohols are very versatile building blocks for synthesis,[10] therefore the development of efficient methods to obtain them in a high enantiomeric purity has a considerable interest. Toward this aim, the asymmetric hydrogenation of enol esters **C** constitutes an appealing alternative, as esters **D** can trivially be converted into alcohols **A** through deacylation (path b).[11] Although the hydrogenation of **B** and **C** are mechanistically different reactions, the preparation of **A** with high enantioselectivity by either path a or b ultimately depends on an effective discrimination of prochiral substrate faces by the corresponding hydrogenation catalyst. In this regard, the hydrogenation of enol esters is characterized by substrate chelation, which enables a powerful recognition of the olefinic substrate.[12] In contrast, the differentiation of enantiotopic faces of ketones bearing not very dissimilar R^1 and CH_2R^2 substituents is an extremely difficult task, as evidenced by the background mentioned above. In this context, a meaningful case is provided by the hydrogenation of α-alkylvinyl esters (**C**, R^1 = alkyl, R^2 = H), which has enabled a broad scope and highly efficient route for the synthesis of chiral 2-alkanols.[13]

A highly valuable expansion of path b route corresponds to the hydrogenation of trisubstituted substrates **C** (R^1, R^2 = alkyl, aryl), as it may provide access to a vast range of chiral esters considering the countless possible combinations of R^1 and R^2. Nevertheless, the inclusion of a substituent in β position of the vinyl fragment introduces fundamental reactivity aspects to study. First, in comparison with widely studied disubstituted substrates,[14] increase in olefin substitution should be accompanied by a reduced catalyst activity,[15] further to the relatively low reactivity of enol esters.[16] Second, the enantioselectivity of the hydrogenation may critically be dependent on the olefin configuration,[17] which can limit severely the usefulness of this approach as enol esters are often obtained as *E*/*Z* mixtures and their separation is usually cumbersome. On the other hand, nearly all enol esters examined in asymmetric hydrogenation possess an α-electron-withdrawing substituent (carboxylate, phosphonate, trifluoromethyl, cyano, or aryl), which is an important element in the course of the reaction.[18] As a result of this background, there is very little information in the literature about the enantioselective hydrogenation of trisubstituted substrates bearing an alkyl substituent in α position.[19,20] Precedents are limited to a study on the hydrogenation of α-alkyl-β-methylvinyl esters, as mixtures of the corresponding *E* and *Z* isomers, described by Goossen and co-workers. Thus, these authors have reported enantioselectivities up to 98% ee in the case of the α-methyl-substituted substrates, as well as a decrease down to 82 and 78% ee for esters bearing α-^{n}Pr and α-^{n}Bu substituents, respectively.[19] Finally, we would like to remark also here that no precedents of the asymmetric hydrogenation of α,β-diarylvinyl esters have been described so far in the literature.

In a preliminary contribution we studied the synthesis and hydrogenation of α-alkyl-β-aryl-substituted substrates **C2** (Figure 2),[21] using Rh catalysts based on chiral phosphine−phosphite ligands (P-OP).[22] Herein we present a broader study on the hydrogenation of trisubstituted enol esters covering in addition those of types **C1** and **C3**. Moreover, the reduction of mixtures of *E*/*Z*-isomers, providing information about the influence of substrate configuration on the reaction, has also been studied in detail.



Ak, Ak' = alkyl groups; Ar, Ar' = aryl or heteroaryl groups; R^3 = Ak, Ph

Figure 2. General structures of enol esters **C1**−**C3**.

RESULTS AND DISCUSSION

Synthesis of Substrates. In order to examine the scope of the asymmetric hydrogenation of trisubstituted enol esters of types **C1**−**C3**, a wide range of substrates covering the three types of structures has been prepared (Figure 3). Thus, regarding those of type **C1**, compounds **1a** and **1b** have been prepared by a gold catalyzed addition of benzoic acid to 2-butyne (Scheme 1a), following the procedure described by Kim and Chary.[23,24] Also based on the work of these authors, **1c** and **1d** were synthesized by a gold catalyzed tandem addition-isomerization reaction (Scheme 1b). Worth to note, **1a** and **1b** were obtained as the pure *Z* isomers, while **1c** and **1d** as mixtures with a *Z*/*E* ratio of 74:26 and 72:28, respectively.

Regarding substrates of type **C2**, we have previously prepared α-methyl-β-aryl vinyl acetates **1e**−**1i**, with generally good yields and selectivity (*Z*:*E* ≥ 95:5) upon the acylation of methyl benzyl ketones.[21,25] Moreover, a range of 1-alkyl-2-arylvinyl substrates (**1k**−**1q**, **1t**−**1z**) were stereoselectively prepared as the *Z* isomers by a Suzuki coupling over (*Z*)-β-iodoalkenyl acetates.[21,26] In order to complete the set of compounds **C2**, new substrate **1j** bearing a 1-ethyl substituent has been prepared in good yield (62%) by the former method. Likewise, compounds **1r** and **1s**, possessing 2-phenylethyl and 3-phenylpropyl substituents, have been prepared by the Suzuki coupling route in good yields from the corresponding iodoalkenes **2** (75 and 79%, respectively; Scheme 2).

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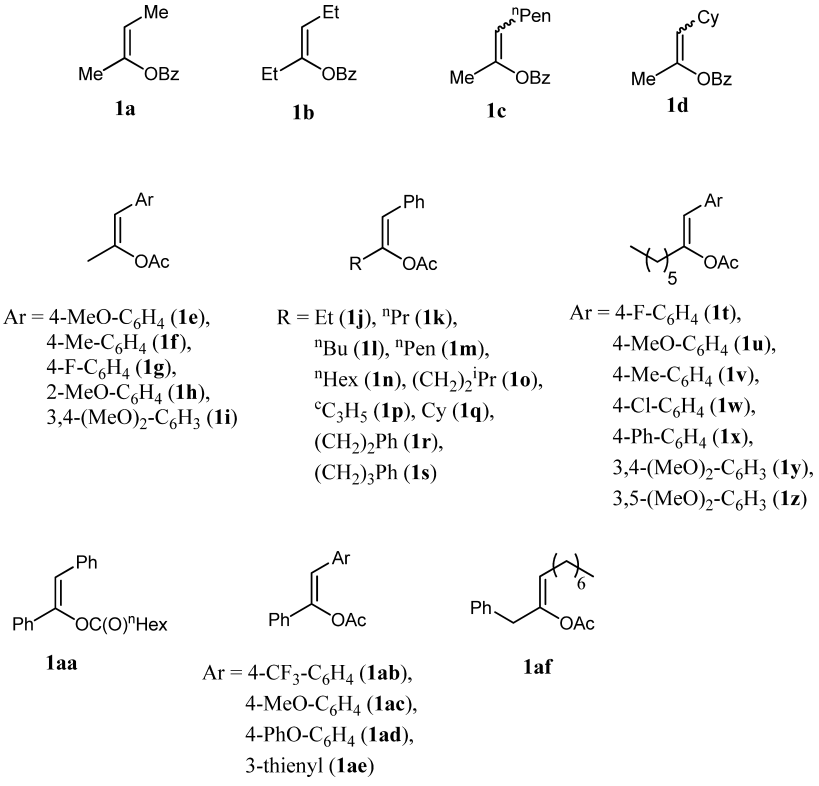
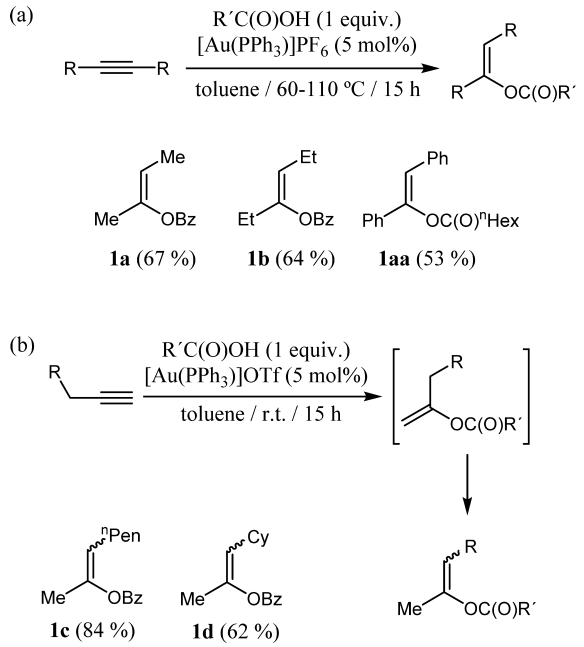


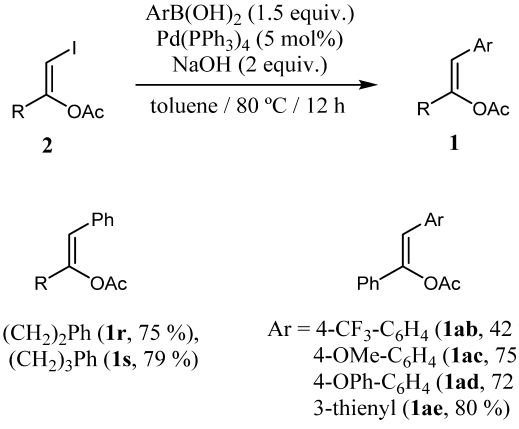
Figure 3. Range of enol esters **1** covered in the present study.

Scheme 1. Synthesis of Enol Esters 1a−1d and 1aa



To widen the range of substrates, several examples of type **C3** have also been prepared. Initially, diphenyl substrate **1aa** was prepared in moderate yield by the reaction of Scheme 1a. Moreover, several examples characterized by a α-Ph and diverse aryl or heteroaryl fragments in β position have been synthesized by the Suzuki coupling route (**1ab−1ae**; Scheme 2). Finally, with the intention to explore the introduction of an alkyl substituent in position β of the C=C bond, a Negishi type coupling was studied using (*Z*)-α-benzyl-β-iodovinyl acetate.[27]

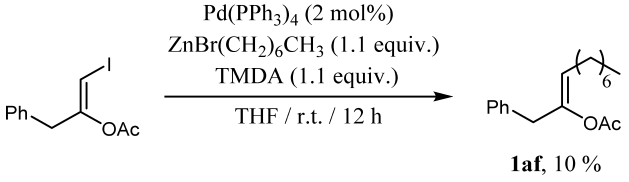
Scheme 2. Synthesis of New Enol-Esters by a Suzuki Coupling on 2-Iodoalkenyl Acetates



This reaction provided the (*Z*)-enol ester **1af**, albeit in a rather low yield (Scheme 3).

Range of Catalysts Examined. In previous contributions we have reported the application of bidentate phosphine−phosphite ligands **3** (P-OP, Figure 4) in asymmetric hydrogenation reactions.[22,28] These ligands are characterized by a

Scheme 3. Preparation of Substrate 1af



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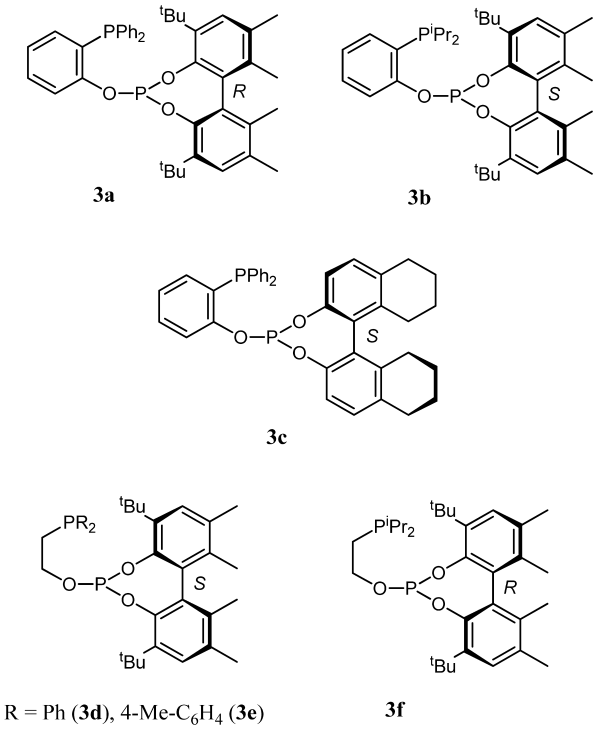
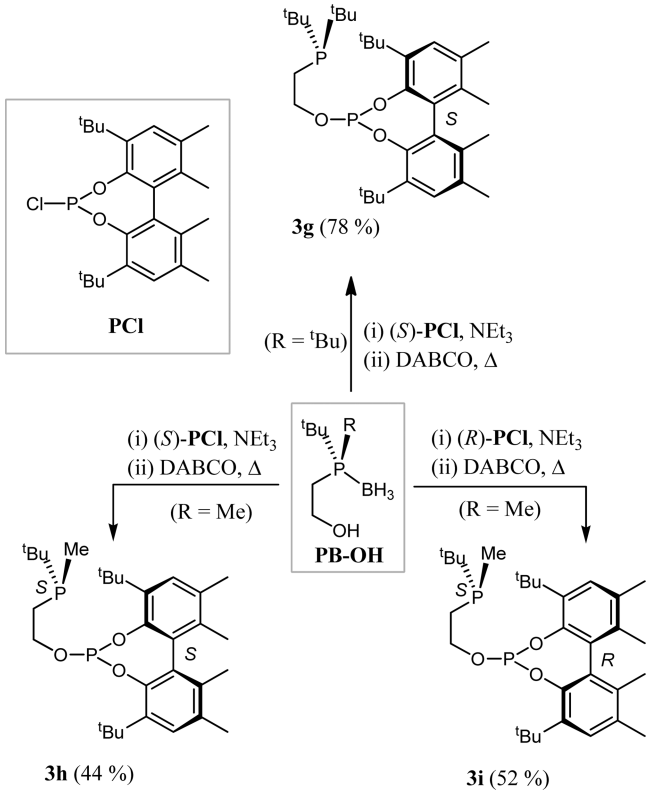


Figure 4. Structure of phosphine−phosphite ligands **3a**−**3f**.

Scheme 4. Synthesis of Ligands 3g−3i



highly modular structure which facilitates the fine-tuning of diverse key elements of the structure of the catalyst, (e.g., the steric effects produced by each P-fragment, the basicity of the phosphine, or the flexibility of the backbone). According to this background we have chosen a wide set of catalyst precursors of general formula [Rh(diene)(P-OP)]BF_4 [diene = NBD, P-OP = **3a** (**4a**), **3c**−**3e** (**4c**-**4e**); diene = COD, P-OP = **3b** (**4b**), **3f**−**3i** (**4f**-**4i**)] to study the hydrogenation of substrates **1**. All ligands **3** possess an atropisomeric biaryl fragment in the phosphite, while ligands **3h** and **3i** (Scheme 4), introduced in our preliminary communication,[21] also possess a *P*-stereogenic P(tBu)Me fragment, which is present in several highly efficient hydrogenation catalysts.[29] For comparison with **3h** and **3i**, the novel ligand **3g** characterized by a P^tBu_2 fragment has also been included in the set. Ligands **3h** and **3i** were prepared by reaction of (*S*)-*tert*-butyl-(2-hydroxyethyl)-methylphosphine borane (**PB−OH**, R = Me; Scheme 4)[30] with each enantiomer of 3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl-2,2′-bisphenoxy-phosphorus chloride (**PCl**), followed by deboronation with DABCO, while **3g** was prepared in an analogous manner starting from di-*tert*-butyl-(2-hydroxyethyl)-phosphine borane (**PB−OH**, R = tBu).

Hydrogenation of *α,β*-Dialkylvinyl Esters. Initially, we chose ester **1a** as an example of a **C1** type structure. It is noteworthy that the asymmetric hydrogenation of this substrate has a high interest due to the importance of enantiopure 2-butanol and,[31] as well, to the fact that its production represents a highly challenging synthetic goal, even by the enzymatic reduction of 2-butanone.[32] Thus, some reactions were prepared in dichloromethane (DCM) using standard reaction conditions (S/C = 100, 4 bar H_2, 40 °C) and diverse catalyst precursors (entries 1−7, Table 1). With the exception of **4b**, all the catalysts examined provided full conversion to **5a** and enantioselectivities over 94% ee, giving **4d** the best enantioselectivity (99% ee, entry 4). Along the catalyst series it is moreover observed that the phosphite fragment has a dominant role in the induction of chirality and controls the product enantiomer. Thus, catalysts characterized by a phosphite fragment with configuration *S* produce (*S*)-**5a** (and conversely an *R* product for an *R* phosphite). On the other hand, in good accord with the positive effect of 1,2-dichloroethane (DCE) in these hydrogenations (see below), no decrease in enantioselectivity was observed in this solvent (entries 8 and 9). Moreover, it was also possible to develop a more practical synthesis of **5a** with a low catalyst loading (S/C = 1000) and high enantioselectivity (95% ee, entry 10) under 20 bar H_2. Substrate **1b** constitutes another interesting case, since it could provide a convenient access to enantiopure 3-hexanol, highly difficult to obtain from 3-hexanone.[32a] As shown for **1a**, catalyst precursors **4a** and **4d** provided satisfactory results in the hydrogenation of **1b**, affording (*R*)-**5b** and (*S*)-**5b**, respectively, with complete conversion and an outstanding enantioselectivity (97−99% ee; entries 11, 12).

Considering that some of the substrates of type **C1** can be obtained in a simple manner, although unselectively, as mixtures of *E* and *Z* isomers, an interesting goal in this topic corresponds to the development of highly enantioselective hydrogenations with these mixtures. Accordingly we examined the reaction of a mixture of *Z* and *E* isomers of **1c** in a 74:26 ratio using several catalysts. For instance, **4a** provided full conversion in DCE, with an outstanding enantioselectivity (99% ee, entry 13), while a decrease down to 90% ee was observed in the case of **4d** (entry 14). Moreover, an important mismatching effect was detected with the couple of complexes **4h** and **4i**, being the former considerably more enantioselective than the latter (92 and 55% ee, respectively; entries 15 and 16). In addition, the hydrogenation of **1d** (*Z*:*E* = 72:28), characterized by a bulky aliphatic substituent in *β* position,

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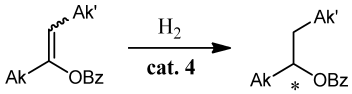
Table 1. Hydrogenation of α,β-Dialkylvinyl Esters Performed with Catalyst Precursors 4[a]



1a-1d **5a-5d**

entry	subs. (Ak, Ak′)	cat. prec.	solvent	S/C	conv (%)	% ee (conf)
1	**1a** (Me, Me)	**4a**	DCM	100	100	98 (*R*)
2	**1a** (Me, Me)	**4b**	DCM	100	37	n.d.
3	**1a** (Me, Me)	**4c**	DCM	100	97	94 (*S*)
4	**1a** (Me, Me)	**4d**	DCM	100	100	99 (*S*)
5	**1a** (Me, Me)	**4e**	DCM	100	100	97 (*S*)
6	**1a** (Me, Me)	**4h**	DCM	100	100	98 (*S*)
7	**1a** (Me, Me)	**4i**	DCM	100	100	95 (*R*)
8	**1a** (Me, Me)	**4h**	DCE	100	100	95 (*S*)
9	**1a** (Me, Me)	**4d**	DCE	100	100	98 (*S*)
10[b]	**1a** (Me, Me)	**4d**	DCE	1000	100	95 (*S*)
11	**1b** (Et, Et)	**4a**	DCE	100	100	99 (*R*)
12	**1b** (Et, Et)	**4d**	DCE	100	100	97 (*S*)
13	**1c** (Me, ^{n}Pen)	**4a**	DCE	100	100	99 (*R*)
14	**1c** (Me, ^{n}Pen)	**4d**	DCE	100	100	90 (*S*)
15	**1c** (Me, ^{n}Pen)	**4h**	DCE	100	100	92 (*S*)
16	**1c** (Me, ^{n}Pen)	**4i**	DCE	100	100	55 (*R*)
17	**1d** (Me, Cy)	**4a**	DCE	100	100	95 (*R*)
18	**1d** (Me, Cy)	**4d**	DCE	100	100	92 (*S*)
19	**1d** (Me, Cy)	**4e**	DCE	100	100	89 (*S*)
20	**1d** (Me, Cy)	**4f**	DCE	100	100	90 (*S*)
21	**1d** (Me, Cy)	**4g**	DCE	100	100	70 (*S*)
22	**1d** (Me, Cy)	**4h**	DCE	100	100	78 (*S*)
23	**1d** (Me, Cy)	**4i**	DCE	100	44	68 (*S*)

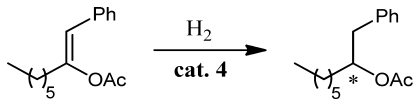
[a]Reactions at 40 °C, [Rh] = 1×10^{-3} M, substrate to catalyst ratio (S/C), solvent, and 4 bar H_2 unless otherwise indicated. 24 h reaction time. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. Configuration was determined by comparison of the optical rotation sign with literature data. [b]Reaction performed under 20 bar H_2.

was also studied. First, catalyst precursors **4a** and **4d** afforded full conversion and high enantioselectivity, with values of 95 and 92% ee, respectively (entries 17 and 18). Moreover, complex **4h** provided a complete reaction as well, but with a substantially lower enantioselectivity (78% ee, entry 22), while diastereomeric **4i** exhibited a mismatching effect manifested both in catalyst activity and enantioselectivity (entry 23). Finally, complexes **4e**, **4f**, and **4g** were also tested (entries 19–21), although they did not provide better results than **4a**.

These results, together with those reported in the hydrogenation of α-alkylvinyl substrates,[13d] clearly illustrate the high value of Rh catalysts bearing P-OP ligands for the synthesis of ester precursors of aliphatic alcohols, due to the wide range of products obtained with high levels of enantioselectivity and, as well, to the straightforward application of the reaction to the synthesis of the desired product enantiomer.

Enantioselective Synthesis of Homobenzylic Esters by Asymmetric Hydrogenation. In our preliminary study we investigated the hydrogenation of a wide set of substrates of type **C2**, taking **1n** as a representative substrate for the optimization of the catalytic system. For the sake of completeness, we include herein some results of this study to recall the more relevant aspects of the hydrogenation of **1n**, and of the scope of the hydrogenation of substrates of type **C2**. Worth to note, catalyst screening for **1n** in our preliminary communication not only included complexes **4a**–**4e**, **4h**, and **4i** based on P-OP ligands, but also some catalysts based on commercial chiral ligands,[33] finally pointing to catalyst from **4h** as the more efficient one which could reduce **1n** under mild conditions (4 bar H_2, 40 °C, DCE, S/C = 100–250, 24 h) with 98% ee (entries 10, 11, Table 2). A relevant feature of **1n** is a markedly lower reactivity than that of **1a** toward hydrogenation (entries 1–5, 8, and 9). In contrast, the attainment of a good enantioselectivity is not as demanding and relatively good enantioselectivities, with values between 92 and 98% ee, were obtained with catalysts **4e**, **4h**, and **4i** (entries 5, 8, and 9, respectively). As well, a positive effect on conversion was observed when DCE was used as solvent (entry 10). Since the incorporation of the *P*-stereogenic phophine fragment is the most demanding aspect of the preparation of the P-OP ligand **3h**, we explored the behavior of catalysts based on ligands **3f** and **3g**, characterized by a nonstereogenic trialkylphosphine fragment and by a less elaborated synthesis, as a possible

Table 2. Hydrogenation of 1n Performed with Catalyst Precursors 4[a]



1n **5n**

entry	cat. prec.	solvent	conv (%)	% ee (conf)
1	**4a**	DCM	13	n.d.
2	**4b**	DCM	<5	n.d.
3	**4c**	DCM	<5	n.d.
4	**4d**	DCM	<5	n.d.
5	**4e**	DCM	62	96 (*S*)
6	**4f**	DCM	59	92 (*R*)
7	**4g**	DCM	34	94 (*S*)
8	**4h**	DCM	79	98 (*S*)
9	**4i**	DCM	38	94 (*R*)
10	**4h**	DCE	100	98 (*S*)
11[b]	**4h**	DCE	98	98 (*S*)

[a]Reactions at 40 °C, [Rh] = 1×10^{-3} M, S/C = 100, 4 bar H_2 initial pressure, and 24 h reaction time, unless otherwise stated. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. See Experimental Section for determination of configuration. [b][Rh] = 1×10^{-3} M, S/C = 250.

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practical improvement. However, corresponding catalyst precursors **4f** and **4g** provided lower conversion values than **4h**, pointing again to the achievement of a suitable catalyst activity as a challenging aspect of the present catalytic system. Notwithstanding that, **4f** and **4g** showed relatively good enantioselectivities, 92 and 94% ee, respectively (entries 6, 7).

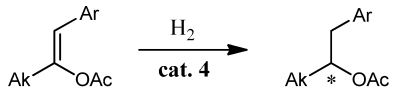
Regarding substrate scope, **4h** provided high enantioselectivities with a wide range of substrates (Table 3). Thus, compounds **1i** (entry 5), **1k**–**1p** (entries 7–12), and **1t**–**1z** (entries 19–25) were hydrogenated with enantioselectivities between 93 and 98% ee using our standard or similar reaction conditions (see footnotes of Table 3 for details). Worth to note, **4h** provided a somewhat lower enantioselectivity in the case of **1e** (91% ee, not shown), outperformed by **4e** (97% ee, entry 1). Upon this result, **4e** was used with satisfactory results in the case of substrates **1f**–**1h** (entries 2–4).

Regarding newly added substrates, **1j** was satisfactorily hydrogenated with **4h** (94% ee, entry 6), while **1r** and **1s** showed a lower reactivity under standard conditions leading to uncompleted reactions (entries 15, 17). A similar decrease was observed in the hydrogenation of 4-phenyl-1-buten-2-yl benzoate[13d] and it is probably related to the formation of low reactive Rh-η^6-arene species.[11a,16b] In contrast, full conversion and good enantioselectivities were observed under 20 bar H_2 for **1r** (93% ee, entry 16) and **1s** (88% ee, entry 18).

Finally, a limitation of the present reaction was found with the α-cyclohexyl-substituted substrate **1q**. This compound exhibited a markedly low reactivity and only a good conversion was obtained with **4i** under 20 bar H_2 (90%), while both **4h** and **4i** provided a rather low enantioselectivity (40–47% ee, entries 13, 14).

Enabled by the rather versatile synthetic procedures for substrates **1**, an appealing application of the present system is the hydrogenation of **1af**, which switches the position of the olefin substituent containing the aryl fragment and should then provide the corresponding homobenzylic ester **5af** with opposite configuration (with regard to that observed in the hydrogenation of **1j**–**1o** with **4h**; entries 6–11 in Table 3). Gratifyingly, hydrogenation of **1af** with **4h** under our standard reaction conditions provided (*R*)-**5af** with excellent conversion and enantioselectivity (Scheme 5).

Table 3. Hydrogenation of α-Alkyl-β-arylvinyl Esters[a]

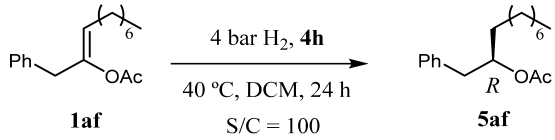


1e-1z **5e-5z**

entry	subs. (Ak, Ar)	cat. prec.	H_2 (bar)	% conv.	% ee (conf.)
1	**1e** (Me, 4-MeO-C_6H_4)	**4e**	4	100	97 (*S*)
2	**1f** (Me, 4-Me-C_6H_4)	**4e**	10	100	91 (*S*)
3	**1g** (Me, 4-F-C_6H_4)	**4e**	4	100	98 (*S*)
4	**1h** (Me, 2-MeO-C_6H_4)	**4e**	4	100	99 (*S*)
5	**1i** [Me, 3,4-$(MeO)_2$-C_6H_3]	**4h**	4	100	93 (*S*)
6	**1j** (Et, Ph)	**4h**	4	100	94 (*S*)
7	**1k** (^{n}Pr, Ph)	**4h**	4	100	94 (*S*)
8	**1l** (^{n}Bu, Ph)	**4h**	4	100	98 (*S*)
9	**1m** (^{n}Pen, Ph)	**4h**	4	100	98 (*S*)
10	**1n** (^{n}Hex, Ph)	**4h**	4	100	98 (*S*)
11	**1o** [$(CH_2)_2{}^i$Pr, Ph]	**4h**	4	100	98 (*S*)
12[b]	**1p** (^{c}C_3H_5, Ph)	**4h**	4	100	92 (n.d.)
13[c]	**1q** (Cy, Ph)	**4h**	20	50	47 (n.d.)
14[c]	**1q** (Cy, Ph)	**4i**	20	90	40 (n.d.)
15	**1r** [$(CH_2)_2$Ph, Ph]	**4h**	4	89	96 (*S*)
16	**1r** [$(CH_2)_2$Ph, Ph]	**4h**	20	100	93 (*S*)
17	**1s** [$(CH_2)_3$Ph, Ph]	**4h**	4	84	87 (*S*)
18	**1s** [$(CH_2)_3$Ph, Ph]	**4h**	20	100	88 (*S*)
19	**1t** (^{n}Hex, 4-F-C_6H_4)	**4h**	4	100	96 (*S*)
20[d]	**1u** (^{n}Hex, 4-MeO-C_6H_4)	**4h**	4	100	93 (*S*)
21	**1v** (^{n}Hex, 4-Me-C_6H_4)	**4h**	20	100	93 (*S*)
22	**1w** (^{n}Hex, 4-Cl-C_6H_4)	**4h**	4	100	95 (*S*)
23	**1x** (^{n}Hex, 4-Ph-C_6H_4)	**4h**	4	100	96 (*S*)
24	**1y** [^{n}Hex, 3,4-$(MeO)_2$-C_6H_3]	**4h**	20	100	95 (*S*)
25	**1z** [^{n}Hex, 3,5-$(MeO)_2$-C_6H_3]	**4h**	4	100	96 (*S*)

[a]Hydrogenations performed at 40 °C in DCE, [Rh] = 1×10^{-3} M, S/C = 100, at initial pressure (bar H_2) indicated, and 24 h reaction time unless otherwise stated. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. See Experimental Section for determination of configuration. [b]Reaction performed at 30 °C. [c]48 h reaction time. [d][Rh] = 2×10^{-3} M, S/C = 100.

Scheme 5. Hydrogenation of 1af



1af **5af**

100 % conv, 99 % ee

Hydrogenation of α,β-Diarylvinyl Esters. To complete this exploratory analysis we next examined the hydrogenation of **1aa** as an example of structure of type **C3**. Reactions performed in DCM under our standard conditions (4 bar H_2, 40 °C and S/C = 100) with several catalyst precursors (entries 1–6, Table 4), afforded rather low conversion values, being only moderate in the case of **4h** (entry 5). However, full conversion and good enantioselectivity was observed when DCE was used as solvent (92% ee, entry 7). Despite the similitude between DCM and DCE, it is noteworthy that a significant increase on conversion with the latter is both observed with representative substrates **1n** and **1aa**, further providing satisfactory results for the series of substrates **C2** and **C3**. In this context it is pertinent to mention that an enhancement on enantioselectivity was observed by the group of Ding in the hydrogenation of related enol esters when using DCE instead of DCM,[13b] while a significantly better performance in DCE over DCM in the hydrogenation of an acyl hydrazone with a Rh-diphosphine catalyst has been reported by Haddad and co-workers.[34] We have not found an explanation to the solvent effect observed herein, but it should be noted that despite DCE and DCM are rather similar solvents, characterized by a poorly coordinating character, the former has some ability to act as a chelating ligand.[35] As intermediates containing coordinated solvent are proposed in the hydrogenation catalytic cycle, it is not unreasonable to expect a different influence of these solvents in the catalytic process.

In addition, some α,β-diarylvinyl substrates of type **C3** were examined to complete the results obtained with **1aa**. By comparison with these results, it appears that substitution of aryl ring of position β is detrimental for conversion (substrates **1ab**–**1ad**; entries 8, 11, 14; Table 4). This is both observed

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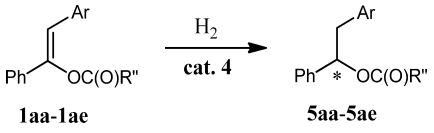
J. Org. Chem. 2017, 82, 5852–5867

Table 4. Hydrogenation of Diaryl-Substituted Substrates C3 Performed with Catalyst Precursors 4[a]



1aa-1ae 5aa-5ae

entry	subs. (Ar)	cat. prec.	solvent	conv (%)	% ee (conf)
1	**1aa** (Ph)	**4a**	DCM	6	n.d.
2	**1aa** (Ph)	**4b**	DCM	<5	n.d.
3	**1aa** (Ph)	**4c**	DCM	7	n.d.
4	**1aa** (Ph)	**4d**	DCM	8	n.d.
5	**1aa** (Ph)	**4h**	DCM	51	93 (*R*)
6	**1aa** (Ph)	**4i**	DCM	43	91 (*S*)
7	**1aa** (Ph)	**4h**	DCE	100	92 (*R*)
8	**1ab** (4-CF_3-C_6H_4)	**4h**	DCE	67	87 (*R*)
9[b]	**1ab** (4-CF_3-C_6H_4)	**4h**	DCE	100	90 (*R*)
10[c]	**1ab** (4-CF_3-C_6H_4)	**4h**	DCE	100	91 (*R*)
11	**1ac** (4-MeO-C_6H_4)	**4h**	DCE	37	86 (*R*)
12[b]	**1ac** (4-MeO-C_6H_4)	**4h**	DCE	100	82 (*R*)
13[c]	**1ac** (4-MeO-C_6H_4)	**4h**	DCE	100	77 (*R*)
14	**1ad** (4-PhO-C_6H_4)	**4h**	DCE	35	69 (*R*)
15[b]	**1ad** (4-PhO-C_6H_4)	**4h**	DCE	100	71 (*R*)
16[c]	**1ad** (4-PhO-C_6H_4)	**4h**	DCE	100	88 (*R*)
17	**1ae** (3-thienyl)	**4h**	DCE	44	71 (*R*)
18[c]	**1ae** (3-thienyl)	**4h**	DCE	100	79 (*R*)

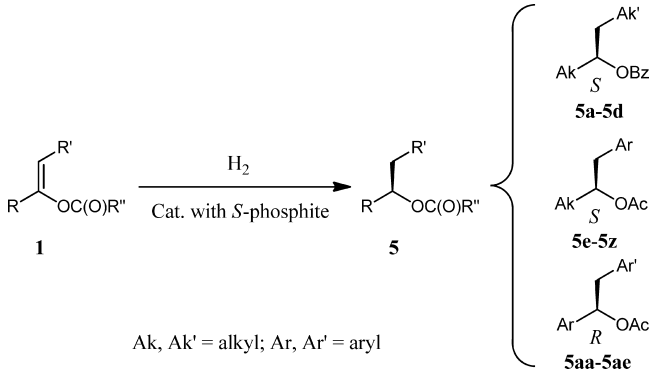
[a]Reactions at 40 °C, [Rh] = 1 × 10^{-3} M, S/C = 100, 4 bar H_2 initial pressure, and 24 h reaction time, unless otherwise stated. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. See Experimental Section for determination of configuration. [b][Rh] = 4 × 10^{-3} M, S/C = 100. [c]Reactions performed under 20 bar H_2.

with electron-donor and electron-withdrawing substituents and may be then attributed to steric effects. Overall, substrates of type **C3** seem less reactive than those of type **C2**. However, full conversion reactions were obtained at higher substrate concentration or under 20 bar of H_2. Thus, enantioselectivities up to 91% ee (**1ab**, entry 10), 82% ee (**1ac**, entry 12), and 88% ee (**1ad**, entry 16) were observed.[36] In addition, the thienyl-substituted enol ester **1ae** also provided full conversion and a relatively good enantioselectivity (79% ee, entry 18).

Mechanistic Considerations. The catalyst screening performed with representative substrates **1a**, **1n**, and **1aa** indicates that product configuration is determined by the configuration of the biaryl fragment of the phosphite. Thus, for catalysts with a configuration *S* of this fragment, *S* enantiomers are observed for products proceeding from dialkylvinyl substrates (**1a**−**1d**, Scheme 6). Likewise, *S* enantiomers are selectively formed from *α*-alkyl-*β*-aryl vinyl esters (**1e**−**1z**) using **4h** or **4e**. On the other hand, *R* products are obtained in the case of the hydrogenation of diaryl vinyl substrates (**1aa**-**1ae**) catalyzed by **4h**. Therefore, the sense of hydrogen addition is coincident for the three types of products (the changes in product configuration are due to the change of priority order of substituents of the stereogenic carbon). It should be finally added that this stereochemical relation between phosphite configuration and the sense of hydrogen addition is analogous to that observed in the hydrogenation of structurally related olefins (enamides and *α*-acyloxyphosphonates) and discussed in detail elsewhere.[22a,b]

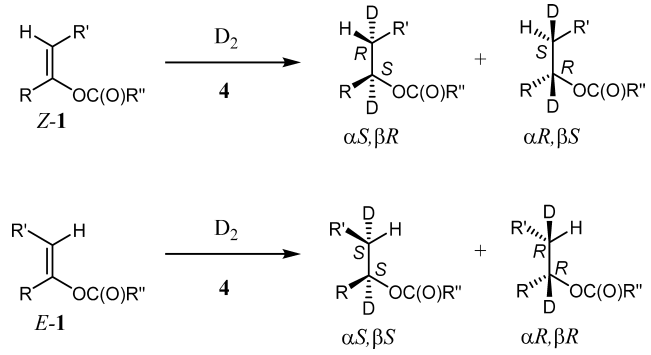
The high enantioselectivity obtained in the hydrogenation of mixtures of olefin isomers of **1c** and **1d** with **4a** is remarkable. This can be attributed to an efficient transfer of chirality of

Scheme 6. Comparison of Product Configuration Observed in the Hydrogenation of 1



catalyst to both isomers of the substrate or, alternatively, to the existence of an *E*-*Z* olefin isomerization process prior to the hydrogenation.[37] Following well established *cis* addition of hydrogen to the olefin bond,[38] the deuteration of *E* and *Z* isomers will produce different diastereomers (Scheme 7), which

Scheme 7. Stereoisomers of Dideuterated 5-d_2 Resulting from *cis* Deuteration of *Z* and *E* Isomers of Enol Esters 1



could eventually be distinguished by NMR. As a requisite for this analysis, diastereotopic protons at position *β* should generate separate signals. This was observed for **5c** (as well as for **5e**, see below) while **5d** exhibited overlapped signals. Thus, the deuteration of **1c** with **4a** showed a 72:28 ratio of diastereomers by ^{1}H NMR, labeled at positions *α* and *β*, namely M-**5c**-d_2 and m-**5c**-d_2 (major and minor, respectively).[39] This ratio is rather close to that of isomers of the starting material (74:26) and is in accord with the absence of a significant isomerization between the isomers of the starting material. Moreover, analysis by ESI-MS did not show appreciable amounts of trideuterated products, typically formed in olefin isomerization reactions by a reversible olefin insertion step.[37a] In this context, it is also pertinent to recall that the variation on enantioselectivity upon deuteration has been taken as an indication of competing mechanistic pathways in asymmetric olefin hydrogenation reactions catalyzed by Rh complexes.[40] This seems not to occur in the present case, as a value of 96% ee was observed in the deuteration of **1c**, slightly lower to that obtained in the standard hydrogenation (99% ee; entry 13 in Table 1). Overall, the results obtained are in good accord with an independent hydrogenation of each isomer of **1c** by **4a** both producing (*R*)-**5c** with high enantioselectivity.

In our preliminary communication we observed only moderate enantioselectivities in the hydrogenation of a mixture

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of isomers of **1e** in a *Z*:*E* = 58:42 ratio,[41] in sharp contrast with results obtained in the hydrogenation of **1c** and **1d**. This committed us to investigate in more detail the hydrogenation of **1e**. To this aim mixtures with *Z*:*E* = 95:5 and 58:42 ratios were tested with several catalyst precursors (Table 5). Remarkably,

Table 5. Hydrogenation of 1e (*Z*:*E* = 58:42) Performed with Catalyst Precursors 4[a]

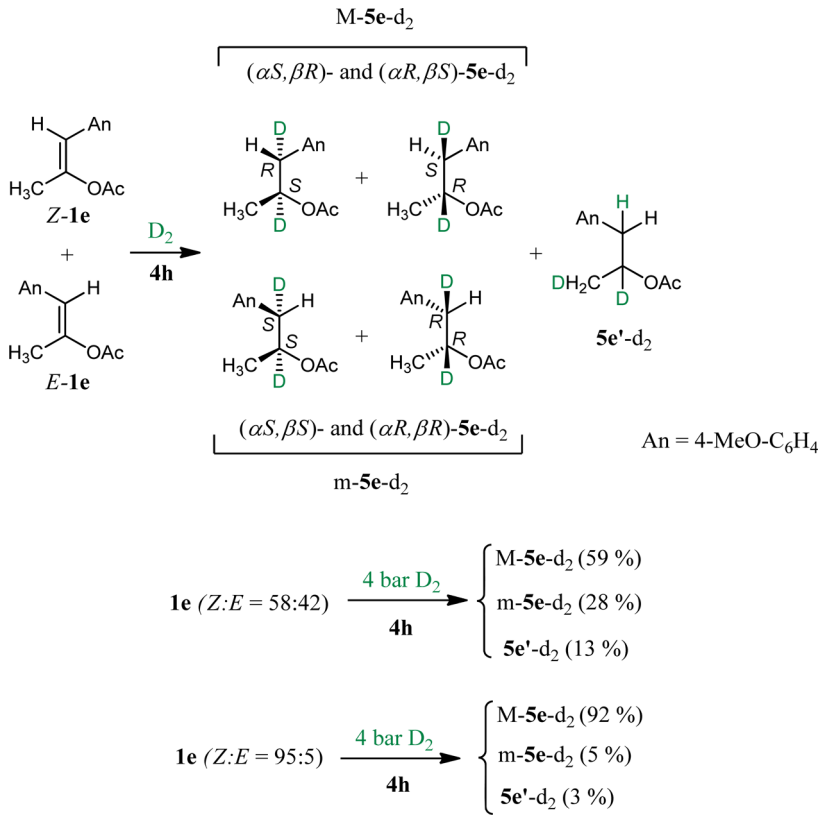
entry	cat. prec.	conv (%)	*Z*:*E* (%)[b]	% ee (conf)[c]	% ee (conf)[d]
1	**4a**	94	0:100	58 (*R*)	78 (*R*)
2	**4d**	75	0:100	80 (*S*)	95 (*S*)
3	**4e**	76	12:88	81 (*S*)	97 (*S*)
4	**4h**	100		44 (*S*)	91 (*S*)
5	**4i**	89	23:77	55 (*R*)	74 (*R*)

[a]Reactions at 40 °C in DCE, [Rh] = 1×10^{-3} M, S/C = 100, 4 bar H_2 initial pressure, and 24 h reaction time. Conversion determined by ^{1}H NMR and enantiomeric excess by chiral HPLC. Configuration was determined by comparison of the optical rotation sign with literature data. [b]*Z*/*E* ratio of remaining substrate. [c]% ee of **5e** obtained in the hydrogenation of *Z*/*E*-**1e**. [d]% ee of **5e** obtained in the hydrogenation of the *Z*:*E* = 95:5 ratio mixture.

the hydrogenation of the *Z*:*E* = 58:42 mixture provided significantly lower enantioselectivities with all catalysts tested (|Δ% ee| = 15−47% ee) than those performed with the *Z*:*E* = 95:5 mixture, indicating that the hydrogenation of *E*-**1e** is appreciably less enantioselective with catalysts **4** than that of *Z*-**1e**. The difference is particularly dramatic in the case of **4h**, for which values of 44 and 91% ee, respectively, were observed (entry 4). As well, slower reactions with the 58:42 mixture were observed. Thus, with the exception of the reaction prepared with **4h**, no complete conversions were observed in the rest of the hydrogenations (entries 1−3, 5). Moreover, an analysis of the remaining unreacted substrate in these reactions showed an enrichment in isomer *E*, indicating a slower reaction of the latter compared with the *Z* isomer. Accordingly, the decrease in enantioselectivity observed in reactions performed with **4d** and **4e** is attenuated by uncompleted reactions.

In addition, we have studied the deuteration of the isomer mixtures of **1e** differing in the *E*/*Z* ratio with **4h**, as this precursor provides the only catalyst able to complete the reaction in both cases. In contrast to the experiment with **1c**, the deuteration of the *Z*:*E* = 58:42 mixture not only showed the expected M-**5e**-d_2 and m-**5e**-d_2, but as well a third isotopomer **5e′**-d_2 labeled at positions α and β' (Scheme 8, see SI for NMR spectra), with a 59:28:13 respective ratio. Worth to note, an analysis by MS-ESI did not show an appreciable presence of tri- or monodeuterated species, confirming the dideuterated nature of the three isomers. In contrast, compound **5e′**-d_2 was hardly visible in the deuteration of the 95:5 mixture and a ratio M-**5e**-d_2:m-**5e**-d_2:**5e′**-d_2 of 92:5:3, respectively, could be estimated (**5e′**-d_2 is detected as an AB quartet in the ^{1}H NMR, partially overlapped with singlets of M-**5e**-d_2 and m-**5e**-d_2). As well, no tri- or monodeuterated products were detected by MS-ESI. A comparison of the ratio of isotopomers obtained in the deuteration of the two isomer mixtures indicates that **5e′**-d_2 is mainly formed from *E*-**1e**, although some formation from *Z*-**1e** cannot be ruled out. Enantioselectivity for deuteration of the *Z*:*E* = 95:5 mixture was 89% ee, which is only slightly lower than the value obtained in the standard hydrogenation (91% ee; entry 4 in Table 5). In contrast, an appreciable difference was observed in the case the *Z*:*E* = 58:42 mixture, providing 54% ee in the deuteration and 44% ee in the hydrogenation (entry 4,

Scheme 8. Deuteration Reactions of 1e by Complex 4h



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Scheme 9. Proposed Formation of Products M-5e-d_2, m-5e-d_2, and 5e′-d_2

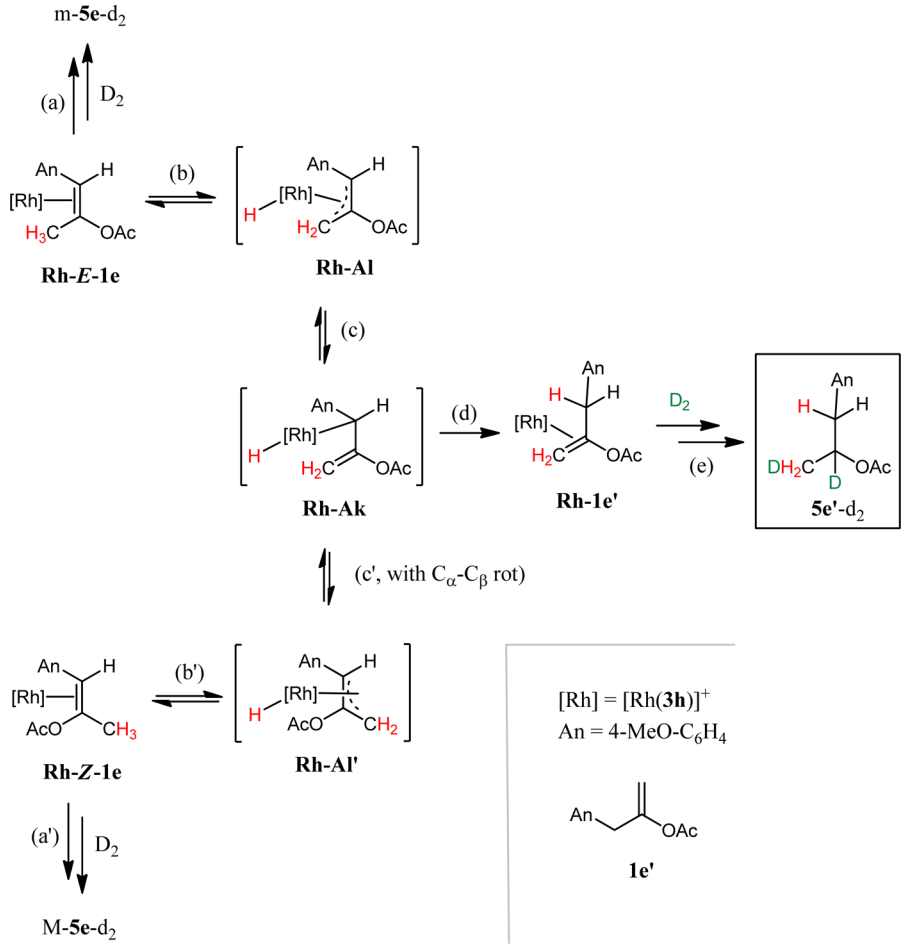
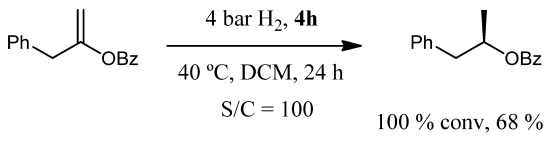


Table 5), suggesting a complex behavior of *E*-**1e** in the catalytic process.

Regarding the products formed in the deuteration of **1e**, the main ones M-**5e**-d_2 and m-**5e**-d_2 should be formed by *cis* deuteration on olefin complexes **Rh**-*Z*-**1e** and **Rh**-*E*-**1e**, respectively (steps a′ and a, Scheme 9), while a reasonable pathway leading to **5e**′-d_2 would be the deuteration of 3-(*p*-methoxyphenyl)-1-propen-2-yl acetate (**1e**′), generated by an olefin migration process in **1e**. From the lack of observation of trideuterated species, a typical reversible insertion pathway can be disregarded. Alternatively, a mechanism for olefin isomerization through η^3-allyl hydride intermediates has been well documented in the literature.[42−44] Particularly interesting in this regard, Budzelaar et al. have observed an equilibrium between olefin and hydrido allyl Rh complexes bearing diiminate ligands, while deuteration of 2,3-dimethyl-2-butene by these complexes produced 1,2-dideutero-2,3-dimethylbutane, resulting from an olefin isomerization to 2,3-dimethyl-1-butene prior to the reduction.[43] According to this background, an isomerization through a η^3-allyl hydride intermediate **Rh**−**Al** from **Rh**-*E*-**1e** olefin complex (b) may be proposed. In a subsequent step, **Rh**−**Al** could produce β-alkyl complex **Rh**−**Ak** (c) which after C−H formation and olefin coordination would finally render **Rh**-**1e**′ (d). Moreover, the sequence of steps b−d results in a 1,3-H migration, in good accord with the experimental observations. Despite results suggest that **5e**′-d_2 is mainly formed from *E*-**1e**, an analogous transformation from **Rh**-*Z*-**1e** (steps b′, c′, and d) may also be possible. As a consequence of this mechanistic scheme, the exchange between allyl complexes **Rh**−**Al** and **Rh**−**Al**′ would enable an *E*-*Z* isomerization of **1e**. It is interesting to note, in addition, that free **1e**′ is expected to be thermodynamically less stable than parent *E*-**1e**,[45] but the complex of the former should be sterically less congested, driving the hydrogenation of **1e**′.[42] Moreover, previous studies with catalysts **4** demonstrate a faster hydrogenation of 1-benzylvinyl benzoate, closely related to **1e**′, than observed for **1e** in the present study.[13d]

Most interestingly, the pathway involving Rh-**1e**′ should lead to a product enantioreversal giving the *R* enantiomer. In this regard, hydrogenation of closely related 1-benzylvinyl benzoate provided the *R* product with complexes **4d** and **4e**.[13d] Likewise, **4h** produced the *R* enantiomer with 68% ee in the hydrogenation of the latter substrate (Scheme 10). It is worth noting, finally, that the **1e**→**1e**′ isomerization is made possible by the methyl substituent at position α, while α-acyloxyacrylates mentioned above possess a carboxylate group at this position and showed a clean *cis* deuteration of both olefin isomers.[11a]

Scheme 10. Hydrogenation of 1-Benzylvinyl Benzoate



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CONCLUSIONS

A broad scope and practical method for the preparation of chiral esters **5** by the asymmetric hydrogenation of trisubstituted enol esters **1** has been described. The set of substrates analyzed comprises α,β-dialkyl, α-alkyl-β-aryl, and α,β-diarylvinyl esters, while catalysts used are based on Rh complexes bearing chiral phosphine−phosphite ligands (P-OP). A comparison of the reactivity between the different types of enol esters studied indicates that it decreases in the order: α,β-dialkyl > α-alkyl-β-aryl > α,β-diarylvinyl (the asymmetric hydrogenation of the latter has been addressed for the first time in the literature). Enabled by a highly precise tuning of the P-OP ligand, suitable catalysts have been identified for each type of substrate. Thus, for α,β-dialkylvinyl esters **4a** provided high enantioselectivities both for the *Z* isomer and for *Z*/*E* mixtures. On the other hand, for *Z*-α-alkyl-β-aryl and *Z*-α,β-diaryl substrates best results were provided by catalyst precursor **4h**. The latter is characterized by a highly basic *P*-stereogenic trialkylphosphine fragment and shows important mismatching effects in catalyst activity with respect to diastereomeric **4i**. Notwithstanding that, for some of the α-Me-β-aryl substrates (**1e**-**1h**) more satisfactory enantioselectivities were obtained with catalyst precursor **4e**. In contrast to the behavior shown by *Z*/*E* mixtures of α,β-dialkylvinyl esters, the hydrogenation of such a mixture of an α-alkyl-β-aryl substrate (**1e**, *Z*/*E* = 58:42) showed a significantly poorer enantioselectivity than in the reaction performed with nearly pure *Z* isomer (*Z*/*E* = 95:5). The decrease is particularly dramatic in the case of catalyst precursor **4h** (44 vs 91% ee). Deuteration experiments indicate the existence of a secondary route in the hydrogenation of **1e**, mainly associated with *E*-**1e**, characterized by a product enantioreversal, justifying the decrease on enantioselectivity observed with the mixture of isomers of **1e**.

EXPERIMENTAL SECTION

General Information. 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 isopropanol. Rh complexes **4a**−**4b**,[22a] **4c**,[28] **4d**,[22b] **4e**,[11d] and **4f**[22c] were prepared as described previously. Moreover, the synthesis and characterization of enol esters **1e**−**i**, **1k**−**q**, and **1t**−**z**, their corresponding hydrogenation products **5**, the ligands **3h**−**i**, and the catalyst precursors **4h**−**i** have been included in our preliminary communication.[21] With the exception of the (*Z*)-β-iodoenol acetates **2**,[26] 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 spectrometer. NMR spectra were obtained on a Bruker DPX-300, DRX-400, DRX-500, or Ascend 600 spectrometers. $^{31}P\{^1H\}$ NMR shifts were referenced to external 85% H_3PO_4 and $^{19}F\{^1H\}$ NMR to $CFCl_3$, 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. HPLC analyses were performed at 30 °C by using a Waters 2690 chromatograph. HRMS data were obtained on a Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer in the General Services of Universidad de Sevilla (CITIUS). Optical rotations were measured on a PerkinElmer Model 341 polarimeter.

General Procedure for the Synthesis of Enol Esters 1a, 1b, and 1aa. Under an argon atmosphere, the corresponding internal alkyne (1.2 mmol) and carboxylic acid (1 mmol), $[AuCl(PPh_3)]$ (0.024 g, 0.05 mmol), $AgPF_6$ (0.013 g, 0.05 mmol), and toluene (3.0 mL) were introduced into a Teflon-capped sealed tube, and the reaction mixture stirred at 60 (**1a**−**b**) or 110 °C (**1aa**) for 15 h. After that time, the solvent was removed *in vacuo* and the crude reaction mixture purified by column chromatography over silica gel using diethyl ether/hexane (1:10) as eluent, yielding the corresponding enol esters as pure *Z* isomers.

*(Z)-But-2-en-2-yl Benzoate (**1a**).*[19,24] Colorless oil. Yield: 0.118 g (67%).

*(Z)-Hex-3-en-3-yl Benzoate (**1b**).*[24,46] Pale yellow oil. Yield: 0.131 g (64%).

*(Z)-1,2-Diphenylvinyl Heptanoate (**1aa**).*[24] White solid. Yield: 0.163 g (53%).

General Procedure for the Synthesis of Enol Esters 1c,d. Under an argon atmosphere, the corresponding terminal alkyne (1.2 mmol) and benzoic acid (0.122 g, 1 mmol), $[AuCl(PPh_3)]$ (0.024 g, 0.05 mmol), AgOTf (0.016 g, 0.05 mmol), and toluene (5.0 mL) were stirred at room temperature for 15 h. After that time, the solvent was removed *in vacuo* and the crude reaction mixture purified by column chromatography over silica gel using diethyl ether/hexane (1:10) as eluent. The corresponding enol esters **1c,d** were obtained as a mixture of stereoisomers in 62−84% yield. Configuration of corresponding isomers was assigned by 2D-NOESY experiments.

*Oct-2-en-2-yl Benzoate (**1c**).*[47] Pale yellow oil. Yield: 0.195 g (84%, *Z*/*E* = 74:26). *Z*-**1c**: ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.10 (m, 2H), 7.58 (m, 1H), 7.45 (m, 2H), 5.11 (t, *J*(H,H) = 6.8 Hz, 1H), 2.00 (s, 3H), 1.97 (m, 2H), 1.31 (m, 6H), 0.86 (t, *J*(H,H) = 6.9 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 164.5, 145.0, 133.3, 130.0 (3C), 128.5 (2C), 117.5, 31.5, 28.9, 25.5, 22.5, 19.7, 14.0 ppm. *E*-**1c**: ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.10 (m, 2H), 7.58 (m, 1H), 7.45 (m, 2H), 5.26 (t, *J*(H,H) = 7.7 Hz, 1H), 2.09 (q, *J*(H,H) = 7.8 Hz, 2H), 1.97 (s, 3H), 1.31 (m, 6H), 0.89 (t, *J*(H,H) = 7.4 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 165.4, 145.5, 133.2, 130.3, 129.9 (2C), 128.4 (2C), 118.0, 31.7, 29.3, 26.7, 22.6, 15.4, 14.1 ppm.

*1-Cyclohexylprop-1-en-2-yl Benzoate (**1d**).* Pale yellow oil. Yield: 0.151 g (62%, *Z*/*E* = 72:28). *Z*-**1d**: ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.10 (m, 2H), 7.58 (m, 1H), 7.45 (m, 2H), 4.97 (d, *J*(H,H) = 9.2 Hz, 1H), 2.20 (m, 1H), 1.98 (d, *J*(H,H) = 0.5 Hz, 3H), 1.68 (m, 5H), 1.20 (m, 5H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 164.7, 143.6, 133.2, 130.0 (3C), 128.5 (2C), 123.1, 35.0, 32.9 (2C), 26.0, 25.8 (2C), 19.7 ppm. *E*-**1d**: ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.10 (m, 2H), 7.58 (m, 1H), 7.45 (m, 2H), 5.12 (d, *J*(H,H) = 9.7 Hz, 1H), 2.20 (m, 1H), 2.0 (d, *J*(H,H) = 0.8 Hz, 3H), 1.68 (m, 5H), 1.20 (m, 5H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 165.3, 143.6, 133.1, 130.6, 129.9 (2C), 128.4 (2C), 123.5, 36.2, 33.3 (2C), 26.0 (2C), 25.9, 15.5 ppm. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{16}H_{21}O_2$ 245.1542; Found 245.1538.

*Synthesis of Enol Ester **1j**.* Over a suspension of NaH (0.35 g, 60% in mineral oil, 8.8 mmol), washed with pentane (3 × 10 mL) in dry 1,2-dimethoxyethane (10 mL), was added dropwise a solution of 1-phenylbutan-2-one (0.78 g, 5.2 mmol) in 1,2-dimethoxyethane (10 mL). The resulting mixture was stirred for 1 h, giving a bright yellow suspension, which was allowed to stand for 1 h. The supernatant was added slowly over distilled acetic anhydride (1.0 mL, 10 mmol) cooled at 0 °C. After all the supernatant enolate solution was transferred, the residual sodium hydride was washed with additional 1,2-dimethoxyethane (5 mL), the mixture allowed to stand for 30 min and the resulting supernatant added to the acetic anhydride solution. The mixture obtained was stirred at room temperature for 0.5 h and poured into a mixture of *n*-hexane (25 mL), water (25 mL), and $NaHCO_3$ (2.5 g, 30 mmol). Phases obtained were separated and the aqueous one was extracted with *n*-hexane (30 mL). The combined *n*-hexane fractions were dried over anhydrous $MgSO_4$ overnight, filtered, and solvent evaporated. The resulting oil was purified by column chromatography over silica gel using *n*-hexane/AcOEt (90:10) as eluent, yielding **1j** as the pure *Z* isomer in 62% yield.

*(Z)-1-Phenylbut-1-en-2-yl Acetate (**1j**).* Pale orange oil. Yield: 0.600 g (62%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.38 (d, *J*(H,H) = 7.7 Hz, 2H), 7.31 (t, *J*(H,H) = 7.9 Hz, 2H), 7.21 (t, *J*(H,H) = 7.5 Hz, 1H), 5.99 (s, 1H), 2.42 (q, *J*(H,H) = 7.6 Hz, 2H), 2.19 (s, 3H), 1.17 (t, *J*(H,H) = 7.7 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ

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J. Org. Chem. 2017, 82, 5852−5867

= 168.7, 151.4, 134.6, 128.4, 128.3 (2C), 127.0 (2C), 114.9, 27.5, 21.2, 11.4 ppm. IR (film): ν = 1757 (s, C═O), 1679 (m, C═C) cm^{-1}. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{14}O_2Na$ 213.0886; Found 213.0882.

General Procedure for the Synthesis of Enol Esters 1r−s and 1ab−1ae. Under an argon atmosphere, the corresponding (*Z*)-*β*-iodoenol acetate **2** (1.0 mmol), $[Pd(PPh_3)_4]$ (0.058 g, 0.05 mmol), and toluene (3.0 mL) were introduced into a Teflon-capped sealed tube, and the mixture was stirred at room temperature for 10 min. Then, 0.5 mL of a 4.0 M NaOH aqueous solution (2.0 mmol of NaOH) and the corresponding boronic acid (1.5 mmol) were added to the sealed tube and the reaction mixture stirred at 80 °C for 12 h. After that time, the solvent was removed *in vacuo* and the crude reaction mixture purified by column chromatography over silica gel using diethyl ether/hexane (1:100) as eluent. The corresponding enol esters **1r−s** and **1aa−1ad** were obtained as pure *Z* isomers in 42−80% yield.

*(Z)-1,4-Diphenylbut-1-en-2-yl Acetate (**1r**).* Orange oil. Yield: 0.200 g (75%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.46 (m, 2H), 7.41 (m, 4H), 7.32 (m, 4H), 6.07 (s, 1H), 2.99 (t, J(H,H) = 7.7 Hz, 2H), 2.83 (t, J(H,H) = 7.7 Hz, 2H), 2.22 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 168.5, 149.0, 140.9, 134.3, 128.4 (4C), 128.3 (2C), 128.2 (2C), 127.1, 126.1, 116.4, 36.1, 33.3, 20.9 ppm. IR (film): ν = 1757 (s, C═O), 1602 (m, C═C) cm^{-1}. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{18}O_2Na$ 289.1204; Found 289.1199.

*(Z)-1,5-Diphenylpent-1-en-2-yl Acetate (**1s**).* Orange oil. Yield: 0.221 g (79%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.47 (m, 2H), 7.40 (m, 4H), 7.30 (m, 4H), 6.08 (s, 1H), 2.80 (t, J(H,H) = 10.2 Hz, 2H), 2.54 (t, J(H,H) = 10.2 Hz, 2H), 2.26 (s, 3H), 1.99 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 168.5, 149.4, 141.8, 134.4, 128.5 (2C), 128.4 (4C), 128.2 (2C), 127.1, 125.9, 116.2, 35.2, 33.9, 28.5, 21.1 ppm. IR (film): ν = 1755 (s, C═O), 1602 (m, C═C) cm^{-1}. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{20}O_2Na$ 303.1361; Found 303.1356.

*(Z)-1-Phenyl-2-(4-(trifluoromethyl)phenyl)vinyl Acetate (**1ab**).* Yellow solid. mp: 46−49 °C. Yield: 0.129 g (42%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.62 (brs, 4H), 7.56 (m, 2H), 7.41 (m, 3H), 6.73 (s, 1H), 2.32 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 168.4, 148.5, 138.1, 135.2, 129.4 (q, J(C,F) = 32.4 Hz), 129.3, 128.9 (4C), 125.6 (q, 2C, J(C,F) = 3.6 Hz), 125.1 (2C), 124.2 (q, J(C,F) = 270.3 Hz), 115.6, 21.2 ppm. $^{19}F\{^1H\}$ NMR ($CDCl_3$, 376 MHz): δ = −62.6 ppm. IR (KBr): ν = 1753 (s, C═O), 1615 (m, C═C) cm^{-1}. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{13}F_3O_2Na$ 329.0765; Found 329.0761.

*(Z)-2-(4-Methoxyphenyl)-1-phenylvinyl Acetate (**1ac**).*[48] Yellow solid. Yield: 0.201 g (75%).

*(Z)-2-(4-Phenoxyphenyl)-1-phenylvinyl Acetate (**1ad**).* Yellow solid. mp: 122−124 °C. Yield: 0.238 g (72%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.51 (m, 4H), 7.35 (m, 5H), 7.14 (m, 1H), 7.05 (m, 2H), 6.99 (m, 2H), 6.68 (s, 1H), 2.33 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 168.7, 157.0, 156.8, 146.0, 135.7, 130.3 (2C), 130.0 (2C), 129.4, 128.8 (2C), 128.7, 124.7 (2C), 123.8, 119.4 (2C), 118.7 (2C), 116.2, 21.3 ppm. IR (KBr): ν = 1761 (s, C═O), 1607 (m, C═C) cm^{-1}. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{18}O_3Na$ 353.1154; Found 353.1149.

*(Z)-1-Phenyl-2-(thiophen-3-yl)vinyl Acetate (**1ae**).* Yellow solid. mp: 103−105 °C. Yield: 0.195 g (80%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.55 (m, 2H), 7.37 (m, 6H), 6.80 (s, 1H), 2.38 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 168.6, 145.7, 135.3, 135.2, 128.7 (2C), 128.6, 127.8, 125.7, 124.6 (2C), 124.4, 111.3, 21.2 ppm. IR (KBr): ν = 1755 (s, C═O), 1595 (m, C═C) cm^{-1}. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{12}O_2SNa$ 267.0456; Found 267.0449.

*Synthesis of (Z)-1-Phenyldec-2-en-2-yl Acetate (**1af**).* Under an argon atmosphere, $[Pd(PPh_3)_4]$ (0.04 g, 0.034 mmol) and THF (5.0 mL) were introduced into a Teflon-capped sealed tube, followed by TMEDA (0.280 mL; 1.9 mmol) and (*Z*)-1-iodo-3-phenylprop-1-en-2-yl acetate (0.5 g, 1.7 mmol). *n*-Heptylzinc bromide (0.5 M in THF; 3.8 mL, 1.9 mmol) was then added dropwise to the sealed tube and the reaction mixture stirred at room temperature for 12 h. After that time, the reaction was quenched with saturated NH_4Cl solution and the product extracted with dichloromethane, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude reaction mixture was then purified by column chromatography over silica gel using diethyl ether/hexane (1:50) as eluent, yielding (*Z*)-**1af** in 10% yield.

*(Z)-1-Phenyldec-2-en-2-yl Acetate (**1af**).* Yellow oil. Yield: 0.047 g (10%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.31 (m, 2H), 7.23 (m, 3H), 5.03 (t, J(H,H) = 7.3 Hz, 1H), 3.51 (s, 2H), 2.09 (s, 3H), 1.93 (q, J(H,H) = 7.1 Hz, 2H), 1.31 (m, 10H), 0.88 (t, J(H,H) = 6.5 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 169.0, 147.4, 137.6, 129.2 (2C), 128.5 (2C), 126.7, 118.6, 40.0, 31.9, 29.3, 29.2, 29.1, 25.6, 22.8, 20.8, 14.2 ppm. IR (film): ν = 1760 (s, C═O), 1605 (m, C═C) cm^{-1}. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{26}O_2Na$ 297.1830; Found 297.1825.

General Procedure for Asymmetric Hydrogenation. In a glovebox, a solution of **4** (0.5 μmol) and substrate **1** (0.05 mmol) in 1,2-dichloroethane (0.5 mL) was placed in a HEL CAT-18 or in a HEL 16 mL reactor. The reactor was purged with hydrogen and finally pressurized at 4 bar. Deuteration reactions were prepared in the 16 mL reactor, deoxygenating it with argon and vacuum cycles and finally pressurizing it under 4 bar D_2. 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 and subsequently dissolved in a *i*-PrOH/*n*-hexane (1:10) mixture and passed through a short pad of silica gel to remove catalyst decomposition products. The solution obtained was carefully evaporated and the residue obtained was analyzed by chiral chromatography to determine enantiomeric excess as described below. Racemic mixtures were obtained by hydrogenation of **1** with commercially available $[Rh(COD)(DiPFc)]BF_4$ [DiPFc = 1,1′-bis-(diisopropylphosphino)ferrocene] with the exception of **5p**. In the hydrogenation of **1p** a complex mixture was observed and (*rac*)-**5p** was alternatively prepared by acylation of 1-cyclopropyl-2-phenyl-ethan-1-ol.[21]

*sec-Butyl Benzoate (**5a**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 7.6 min (*R*), t_2 = 8.2 min (*S*).

*Hexan-3-yl Benzoate (**5b**).* Chiralcel AD-H, 99:1 *n*-hexane:*i*-PrOH, flow 0.5 mL/min, t_1 = 9.2 min (*R*), t_2 = 9.4 min (*S*).

*Octan-2-yl Benzoate (**5c**).* Chiralcel AD-H, *n*-hexane, flow 1.0 mL/min, t_1 = 20.0 min (*R*), t_2 = 21.8 min (*S*).

*1-Cyclohexylpropan-2-yl Benzoate (**5d**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 5.2 min (*R*), t_2 = 6.3 min (*S*).

*1-(4-Methoxyphenyl)propan-2-yl Acetate (**5e**).* Chiralcel AD-H, 99:1 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 10.4 min (*R*), t_2 = 11.0 min (*S*).

*1-(4-Methylphenyl)propan-2-yl Acetate (**5f**).* Chiralcel AD-H, 99:1 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 12.4 min (*R*), t_2 = 15.6 min (*S*).

*1-(4-Fluorophenyl)propan-2-yl Acetate (**5g**).* Chiralcel AD-H, *n*-hexane, flow 1.0 mL/min, t_1 = 22.0 min (*R*), t_2 = 24.7 min (*S*).

*1-(2-Methoxyphenyl)propan-2-yl Acetate (**5h**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 29.2 min (*S*), t_2 = 32.8 min (*R*).

*1-(3,4-Dimethoxyphenyl)propan-2-yl Acetate (**5i**).* Chiralcel AD-H, 98:2 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 22.9 min (*R*), t_2 = 24.9 min (*S*).

*1-Phenylbutan-2-yl Acetate (**5j**).* Chiralcel AD-H, *n*-hexane, flow 1.0 mL/min, t_1 = 23.3 min (*S*), t_2 = 25.8 min (*R*).

*1-Phenylpentan-2-yl Acetate (**5k**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 14.8 min (*S*), t_2 = 16.9 min (*R*).

*1-Phenylhexan-2-yl Acetate (**5l**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 16.8 min (*R*), t_2 = 18.1 min (*S*).

*1-Phenylheptan-2-yl Acetate (**5m**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 18.2 min (*R*), t_2 = 22.8 min (*S*).

*1-Phenyloctan-2-yl Acetate (**5n**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 9.7 min (*R*), t_2 = 10.8 min (*S*).

*5-Methyl-1-phenylhexan-2-yl Acetate (**5o**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 12.8 min (*R*), t_2 = 15.3 min (*S*).

*1-Cyclopropyl-2-phenylethyl Acetate (**5p**).* Chiralcel OB-H, 99:1 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 17.5 min (*S*), t_2 = 18.8 min (*R*).

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J. Org. Chem. 2017, 82, 5852−5867

*1-Cyclohexyl-2-phenylethyl Acetate (**5q**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 7.3 min (*R*), t_2 = 8.1 min (*S*).

*1,4-Diphenylbutan-2-yl Acetate (**5r**).* Chiralcel AD-H, 99.5:0.5 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 10.6 min (*R*), t_2 = 11.7 min (*S*).

*1,5-Diphenylpentan-2-yl Acetate (**5s**).* Chiralcel AD-H, 99.5:0.5 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 8.6 min (*S*), t_2 = 12.0 min (*R*).

*1-(4-Fluorophenyl)octan-2-yl Acetate (**5t**).* Chiralcel AD-H, 98:2 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 13.9 min (*S*), t_2 = 15.0 min (*R*).

*1-(4-Methoxyphenyl)octan-2-yl Acetate (**5u**).* Chiralcel OB-H, 99:1 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 9.9 min (*R*), t_2 = 11.5 min (*S*).

*1-(4-Methylphenyl)octan-2-yl Acetate (**5v**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 14.4 min (*R*), t_2 = 18.2 min (*S*).

*1-(4-Chlorophenyl)octan-2-yl Acetate (**5w**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 15.5 min (*R*), t_2 = 20.7 min (*S*).

*1-([1,1′-Biphenyl]-4-yl)octan-2-yl Acetate (**5x**).* Chiralcel AD-H, 98:2 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 12.5 min (*S*), t_2 = 14.0 min (*R*).

*1-(3,4-Dimethoxyphenyl)octan-2-yl Acetate (**5y**).* Chiralcel OB-H, 95:5 *n*-hexane:*i*-PrOH, flow 0.7 mL/min, t_1 = 20.0 min (*R*), t_2 = 22.9 min (*S*).

*1-(3,5-Dimethoxyphenyl)octan-2-yl Acetate (**5z**).* Chiralcel AD-H, 98:2 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 12.9 min (*S*), t_2 = 13.5 min (*R*).

*1,2-Diphenylethyl Heptanoate (**5aa**).* Chiralcel OB-H, *n*-hexane, flow 1.0 mL/min, t_1 = 7.7 min (*R*), t_2 = 8.3 min (*S*).

*1-Phenyl-2-(4-(trifluoromethyl)phenyl)ethyl Acetate (**5ab**).* Chiralcel AD-H, 99:1 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 7.2 min (*S*), t_2 = 8.9 min (*R*).

*2-(4-Methoxyphenyl)-1-phenylethyl Acetate (**5ac**).* Chiralcel AD-H, 99:1 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 14.0 min (*R*), t_2 = 21.5 min (*S*).

*2-(4-Phenoxyphenyl)-1-phenylethyl Acetate (**5ad**).* Chiralcel AD-H, 97:3 *n*-hexane:*i*-PrOH, flow 0.6 mL/min, t_1 = 13.3 min (*S*), t_2 = 14.2 min (*R*).

*1-Phenyl-2-(thiophen-3-yl)ethyl Acetate (**5ae**).* Chiralcel OB-H, 97:3 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 10.0 min (*R*), t_2 = 12.3 min (*S*).

*1-Phenyldecan-2-yl Acetate (**5af**).* Chiralcel AD-H, 99:1 *n*-hexane:*i*-PrOH, flow 1.0 mL/min, t_1 = 6.6 min (*R*), t_2 = 7.5 min (*S*).

Determination of Configuration of Products 5. For products **5a**,[49] **5c**,[11d] **5d**,[11d] **5e**,[50] **5g**,[51] and **5h**[52] configuration was assigned by comparison of the sign of optical rotation with that described in the literature. For compounds **5b**, **5f**, **5i**, and **5j** configuration was assigned by analogy with the previous data. For ester **5n** configuration was determined by deacylation and comparison of the sign of optical rotation of the resulting alcohol with that described in the literature.[53] For compounds **5k**−**5m**, **5o**, and **5r**−**5z** configuration was assigned assuming an analogous stereochemical course of the hydrogenation with that of **5n**. In addition, configuration of **5ac** was assigned upon comparison of the sign of optical rotation with that described in the literature,[54] while configuration of products **5aa**, **5ab**, **5ad**, and **5ae** were assigned by analogy with the latter data. Finally, for **5af**, configuration was assigned assuming an analogous stereochemical course of the hydrogenation with that of **5b** and **5c**.

Characterization of Compounds 5. Full characterization of products **5e**−**i**, **5k**−**q**, and **5t**−**z** has been reported in our preliminary communication.[21]

*(S)-sec-Butyl Benzoate (**5a**).*[49] Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4d** and DCM, instead of DCE, as solvent (8.4 mg, 94% yield, 99% ee). Alternatively, obtained using 0.5 mmol **1a** and 0.5 μmol **4d** in DCE (0.5 mL) under 20 bar H_2 at 40 °C for 24 h (83.0 mg, 93% yield, 95% ee).

*(R)-Hexan-3-yl Benzoate (**5b**).*[19] Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4a** (9.8 mg, 95% yield, 99% ee). $[\alpha]_D^{20}$ = −2.1° (*c* 1.1, $CHCl_3$, 99% ee).

*(R)-Octan-2-yl Benzoate (**5c**).*[11d] Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4a** (11.7 mg, 94% yield, 99% ee).

*(R)-2,3-Dideutero-octan-2-yl Benzoate (**5c**-d_2).* Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4a** under 4 bar D_2 (11.1 mg, 93% yield, 96% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.04 (d, *J*(H,H) = 8.1 Hz, 2H), 7.55 (t, *J*(H,H) = 7.3 Hz, 1H), 7.44 (t, *J*(H,H) = 7.7 Hz, 2H), 1.71 (m, 0.7 H, CDH major diastereomer), 1.58 (m, 0.3 H, CDH minor diastereomer), 1.32 (m, 11H), 0.87 (t, *J*(H,H) = 6.5 Hz, 3H) ppm. ^{2}H NMR ($CHCl_3$, 61 MHz): δ = 5.14 (brs), 1.71 (brs, CDH minor diastereomer), 1.59 (brs, CDH major diastereomer) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 166.3, 132.8, 131.1 (2C), 129.6 (2C), 128.4, 70.1 (t, *J*(C,D) = 19 Hz), 35.7 (t, *J*(C,D) = 19 Hz), 31.9, 29.3, 25.6, 22.7, 20.1, 14.2 ppm. IR (film): ν = 1717 (s, C═O) cm^{-1}. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{15}H_{20}D_2O_2Na$ 259.1638; Found 259.1641.

*(R)-1-Cyclohexylpropan-2-yl Benzoate (**5d**).*[11d] Obtained according to the general procedure using **4a** (S/C = 100) as a pale yellow oil (11.1 mg, 90% yield, 95% ee).

*(S)-1,2-Dideutero-1-(4-methoxyphenyl)propan-2-yl Acetate (**5e**-d_2).* Obtained according to the general procedure (S/C = 100) as a light orange oil using **4h** under 4 bar D_2 (9.5 mg, 95% yield, 89% ee). Major diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.10 (d, *J*(H,H) = 8.0 Hz, 2H), 6.83 (d, *J*(H,H) = 8.05 Hz, 2H), 3.79 (s, 3H), 2.86 (brs, 1H, CHD), 2.00 (s, 3H), 1.19 (s, 3H) ppm; minor diastereomer: 2.69 (brs, CHD). ^{2}H NMR ($CHCl_3$, 61 MHz): δ = 5.06 (brs, CDO), 2.69 (brs, CHD) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz): δ = 170.6, 158.3, 130.4 (2C), 129.7, 113.8 (2C), 71.4 (t, *J*(C,D) = 22 Hz), 55.4, 41.0 (t, *J*(C,D) = 20 Hz), 21.5, 19.3 ppm. IR (film): ν = 1731 (s, C═O) cm^{-1}. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{12}H_{14}D_2O_3Na$ 233.1117; Found 233.1117.

*(S)-1-Phenylbutan-2-yl Acetate (**5j**).* Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4h** (9.2 mg, 96% yield, 94% ee). $[\alpha]_D^{20}$ = +5.8° (*c* 0.9, $CHCl_3$, 94% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.31 (m, 2H), 7.23 (m, 3H), 5.04 (m, 1H), 2.86 (m, 2H), 2.02 (s, 3H), 1.60 (m, 2H), 0.94 (t, *J*(H,H) = 7.5 Hz, 3H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 170.7, 137.7, 129.4 (2C), 128.3 (2C), 126.4, 75.9, 40.1, 26.4, 21.2, 9.7 ppm. IR (film): ν = 1737 (s, C═O) cm^{-1}. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{12}H_{16}O_2Na$: 215.1043; Found 215.1039.

*(S)-1,4-Diphenylbutan-2-yl Acetate (**5r**).* Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4h** under 20 bar H_2 (12.6 mg, 94% yield, 93% ee). $[\alpha]_D^{20}$ = +2.3° (*c* 0.9, $CHCl_3$, 93% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30 (m, 5H), 7.20 (m, 5H), 5.17 (quint, *J*(H,H) = 6.2 Hz, 1H), 2.95 (m, 1H), 2.95 (m, 1H), 2.68 (m, 2H), 2.03 (s, 3H), 1.91 (m, 2H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 170.8, 141.6, 137.5, 129.6 (2C), 128.5 (2C), 128.5 (2C), 128.4 (2C), 126.6, 126.0, 74.5, 40.7, 35.3, 31.9, 21.3 ppm. IR (film): ν = 1736 (s, C═O) cm^{-1}. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{18}H_{20}O_2Na$ 291.1356; Found 291.1353.

*(S)-1,5-Diphenylpentan-2-yl Acetate (**5s**).* Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4h** under 20 bar H_2 (13.3 mg, 94% yield, 88% ee). $[\alpha]_D^{20}$ = +1.3° (*c* 1.1, $CHCl_3$, 88% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25 (m, 10H), 5.15 (quint, *J*(H,H) = 6.2 Hz, 1H), 2.87 (m, 2H), 2.62 (m, 2H), 2.02 (s, 3H), 1.69 (m, 4H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 170.6, 142.1, 137.6, 129.4 (2C), 128.4 (2C), 128.3 (4C), 126.4, 125.8, 74.5, 40.6, 35.6, 33.1, 27.3, 21.2 ppm. IR (film): ν = 1737 (s, C═O) cm^{-1}. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{19}H_{22}O_2Na$ 305.1512; Found 305.1506.

*(R)-1,2-Diphenylethyl Heptanoate (**5aa**).* Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4h** (14.1 mg, 91% yield, 92% ee). $[\alpha]_D^{20}$ = +6.4° (*c* 0.8, $CHCl_3$, 92% ee). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29 (m, 8H), 7.14 (m, 2H), 5.99 (m, 1H), 3.22 (m, 1H), 3.09 (m, 1H), 2.29 (t, *J*(H,H) = 7.5 Hz, 2H), 1.55 (m, 2H), 1.26 (m, 6H), 1.26 (t, *J*(H,H) = 6.8 Hz, 3H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 173.0, 140.4, 137.2, 129.6 (2C), 128.5 (2C), 128.3 (2C), 129.0 (2C), 126.7, 126.6, 76.4, 43.2, 34.7, 31.6, 28.8, 25.0, 22.6, 14.2 ppm. IR (film): ν = 1737 (s, C═O) cm^{-1}. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{21}H_{26}O_2Na$ 333.1825; Found 333.1815.

*(R)-1-Phenyl-2-(4-(trifluoromethyl)phenyl)ethyl Acetate (**5ab**).* Obtained according to the general procedure (S/C = 100) as a pale

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J. Org. Chem. 2017, 82, 5852−5867

yellow oil using **4h** under 20 bar H_2 (14.9 mg, 97% yield, 91% ee). Alternatively, obtained using 0.1 mmol **1ab** and 1 μmol **4h** in DCE (0.25 mL) under 4 bar H_2 at 40 °C for 24 h (27.7 mg, 90% yield, 90% ee). $[\alpha]_D^{20}$ = +2.0° (*c* 0.8, $CHCl_3$, 91% ee). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.52 (d, *J*(H,H) = 7.9 Hz, 2H), 7.33 (m, 5H), 7.23 (d, *J*(H,H) = 8.2 Hz, 2H), 5.98 (m, 1H), 3.98 (m, 1H), 3.14 (m, 1H), 2.06 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 170.0, 141.1, 139.5, 129.8 (2C), 128.9 (q, *J*(C,F) = 32 Hz), 128.5 (2C), 128.2, 126.5 (2C), 125.1 (q, *J*(C,F) = 4 Hz, 2C), 124.2 (q, *J*(C,F) = 272 Hz), 76.0, 42.7, 21.1 ppm. $^{19}F\{^1H\}$ NMR ($CDCl_3$, 380 MHz): δ = −62.4 ppm. IR (film): ν = 1743 (s, C═O) cm^{-1}. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{17}H_{15}O_2F_3Na$ 331.0916; Found 331.0915.

*(R)-2-(4-Methoxyphenyl)-1-phenylethyl Acetate (**5ac**).*[54] Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4h** under 20 bar H_2 (12.1 mg, 90% yield, 77% ee). Alternatively, obtained using 0.1 mmol **1ac** and 1 μmol **4h** in DCE (0.25 mL) under 4 bar H_2 at 40 °C for 24 h (24.8 mg, 92% yield, 82% ee).

*(R)-2-(4-Phenoxyphenyl)-1-phenylethyl Acetate (**5ad**).* Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4h** under 20 bar H_2 (15.1 mg, 91% yield, 88% ee). Alternatively, obtained using 0.1 mmol **1ad** and 1 μmol **4h** in DCE (0.25 mL) under 4 bar H_2 at 40 °C for 24 h (31.9 mg, 96% yield, 71% ee). $[\alpha]_D^{20}$ = +5.2° (*c* 1.0, $CHCl_3$, 88% ee). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (m, 7H), 7.10 (m, 3H), 7.01 (d, *J*(H,H) = 8.4 Hz, 2H), 6.92 (d, *J*(H,H) = 8.4 Hz, 2H), 5.95 (m, 1H), 3.21 (m, 1H), 3.06 (m, 1H), 2.07 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 170.2, 157.5, 155.9, 140.1, 132.1, 130.9 (2C), 129.8 (2C), 128.5 (2C), 128.1, 126.7 (2C), 123.2, 118.9 (2C), 118.8 (2C), 76.8, 42.4, 21.3 ppm. IR (film): ν = 1739 (s, C═O) cm^{-1}. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{22}H_{20}O_3Na$ 355.1305; Found 355.1298.

*(R)-1-Phenyl-2-(thiophen-3-yl)ethyl Acetate (**5ae**).* Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4h** under 20 bar H_2 (11.3 mg, 92% yield, 79% ee). $[\alpha]_D^{20}$ = +3.0° (*c* 1.0, $CHCl_3$, 79% ee). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.30 (m, 5H), 7.20 (m, 1H), 6.89 (m, 1H), 6.84 (m, 1H), 5.93 (m, 1H), 3.24 (m, 1H), 3.10 (m, 1H), 2.05 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 170.3, 140.1, 137.3, 128.8, 128.5 (2C), 128.2, 126.7 (2C), 125.4, 122.5, 76.1, 37.4, 21.4 ppm. IR (film): ν = 1738 (s, C═O) cm^{-1}. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{14}H_{14}O_2NaS$ 269.0607; Found 269.0608.

*(R)-1-Phenyldecan-2-yl Acetate (**5af**).* Obtained according to the general procedure (S/C = 100) as a pale yellow oil using **4h** (13.1 mg, 95% yield, 99% ee). $[\alpha]_D^{20}$ = −1.7° (*c* 1.0, $CHCl_3$, 99% ee). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.31 (m, 2H), 7.23 (m, 3H), 5.10 (m, 1H), 2.86 (m, 2H), 2.01 (s, 3H), 1.55 (m, 2H), 1.30 (m, 12H), 0.90 (t, *J*(H,H) = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 170.7, 137.7, 129.4 (2C), 128.3 (2C), 126.4, 74.8, 40.6, 33.5, 31.8, 29.5, 29.4, 29.2, 25.4, 22.7, 21.2, 14.1 ppm. IR (film): ν = 1737 (s, C═O) cm^{-1}. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{18}H_{28}O_2Na$ 299.1982; Found 299.1977.

*Synthesis and Characterization of [Rh(COD)(**3g**)]BF_4 (**4g**). Ditert-butyl-(2-hydroxyethyl)-phosphine Borane.* Over a stirring solution of di-*tert*-butylphosphine borane (100 mg, 0.62 mmol) and 2-bromoethanol (78 mg, 0.62 mmol) in THF (5 mL), *n*-butyllithium (0.78 mL, 1.24 mmol) was added dropwise and the mixture stirred for 2 h. Excess of NH_4Cl and deoxigenated water (1 mL) were then added and the mixture stirred for 1 h. The solvent was then evaporated with vacuum and the resulting residue dried with toluene (2 × 5 mL) under vacuum, then disolved in Et_2O and filtered in a short pad of Celite. Evaporation of Et_2O in vacuum gave the desired product as a whitish oil (48 mg, 38% yield). ^1H NMR (C_6D_6, 500 MHz): δ = 3.83 (m, 2H), 2.43 (br, 1H), 1.50 (m, 2H), 0.97 (s, 9H), 0.94 (s, 9H) ppm (BH_3 signal partially observed as broad humps at 1.42 and 1.22 ppm). $^{31}P\{^1H\}$ NMR (C_6D_6, 162 MHz): δ = 39.9 (q, *J*(P,B) = 56 Hz) ppm. $^{13}C\{^1H\}$ NMR (C_6D_6, 125 MHz): δ = 59.4, 31.8 (d, *J*(C,P) = 27 Hz, 2C), 27.6 (6C), 21.6 (d, *J*(C,P) = 27 Hz) ppm. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{10}H_{26}OBNaP$ 227.1707; Found 227.1708.

*2-(Ditert-butylphosphinoethyl)-(S)-1,1′-(3,3′-ditert-butyl-5,5′,6,6′-tetramethyl)biphen-2,2′-diyl phosphite Borane (**3g**-BH_3).* Over a stirring solution of di-*tert*-butyl-(2-hydroxyethyl)-phosphine borane (20 mg, 0.1 mmol) and Et_3N (30 μL, 0.22 mmol) in toluene (2 mL) was added dropwise a solution of (*S*)-3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl-2,2′-bisphenoxyphosphorous chloride (41 mg, 0.1 mmol). The mixture was stirred for 24 h and the resulting suspension was evaporated, dissolved in Et_2O, and filtered through a short pad of neutral alumina. Alumina was washed with Et_2O (2 × 5 mL), ethereal phases collected and evaporated yielding **3g**-BH_3 as a white powder (49 mg, 88% yield). ^1H NMR (C_6D_6, 500 MHz): δ = 7.29 (s, 1H), 7.21 (s, 1H), 4.15 (m, 1H), 3.91 (m, 1H), 2.23 (s, 3H), 2.07 (s, 3H), 1.98 (m, 1H), 1.86 (s, 3H), 1.81 (m, 1H), 1.70 (s, 3H), 1.59 (s, 9H), 1.58 (s, 9H), 0.93 (d, *J*(H,P) = 2.5 Hz, 9H), 0.91 (d, *J*(H,P) = 2.5 Hz, 9H) ppm (BH_3 signal partially observed as a broad hump at 0.65 ppm). $^{31}P\{^1H\}$ NMR (C_6D_6, 162 MHz): δ = 126.3, 41.3 (bd, *J*(P,B) = 62 Hz) ppm. $^{13}C\{^1H\}$ NMR (C_6D_6, 125 MHz): δ = 146.2 (d, *J*(C,P) = 4 Hz), 146.2 (d, *J*(C,P) = 3 Hz), 138.2 (d, *J*(C,P) = 2 Hz), 137.4, 135.6, 134.9, 132.7, 132.6, 132.2 (d, *J*(C,P) = 5 Hz), 131.2 (d, *J*(C,P) = 2 Hz), 129.1, 128.3, 62.9 (dd, *J*(C,P) = 9 Hz, *J*(C,P) = 5 Hz), 35.0, 34.9, 31.9 (d, *J*(C,P) = 8 Hz), 31.7 (d, *J*(C,P) = 8 Hz), 31.6 (d, *J*(C,P) = 5 Hz), 31.3, 27.5 (d, *J*(C,P) = 16 Hz), 27.5 (d, *J*(C,P) = 16 Hz), 20.8 (d, *J*(C,P) = 25 Hz), 20.5, 20.4, 16.8, 16.5 ppm. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{34}H_{58}O_3BP_2$ 587.3949; Found 587.3960.

*2-(Ditert-butylphosphinoethyl)-(S)-1,1′-(3,3′-ditert-butyl-5,5′,6,6′-tetramethyl)biphen-2,2′-diyl Phosphite (**3g**).* A mixture of 2-(di-*tert*-butylphosphinoethyl)-(*S*)-1,1′-(3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl)biphen-2,2′-diyl phosphite borane (20 mg, 0.03 mmol) and 1,4-diazabicyclo[2.2.2]octane (18.4 mg, 0.16 mmol) in toluene (2 mL) was heated for 72 h at 70 °C. The resulting suspension was evaporated, dissolved in Et_2O, and filtered through a short pad of neutral alumina. Alumina was washed with Et_2O (2 × 5 mL), and the ethereal phases collected and evaporated yielding **3g** as a white foamy solid (16 mg, 89% yield). $[\alpha]_D^{20}$ = +141° (*c* 0.1, THF). ^1H NMR (CD_2Cl_2, 500 MHz): δ = 7.18 (s, 1H), 7.16 (s, 1H), 3.66 (m, 1H), 3.51 (m, 1H), 2.25 (s, 3H), 2.24 (s, 3H), 1.81 (s, 3H), 1.75 (m, 4H), 1.58 (m, 1H), 1.47 (s, 9H), 1.43 (s, 9H), 1.03 (d, *J*(H,P) = 11.5 Hz, 9H), 0.93 (d, *J*(H,P) = 11.5 Hz, 9H) ppm. $^{31}P\{^1H\}$ NMR (CD_2Cl_2, 162 MHz): δ = 128.2, 18.1 ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 125 MHz): δ = 145.9 (d, *J*(C,P) = 4 Hz), 145.7 (d, *J*(C,P) = 2 Hz), 138.5 (d, *J*(C,P) = 3 Hz), 137.3, 135.3 (d, *J*(C,P) = 1 Hz), 134.8 (d, *J*(C,P) = 1 Hz), 132.9 (d, *J*(C,P) = 1 Hz), 132.1 (d, *J*(C,P) = 1 Hz), 132.0 (d, *J*(C,P) = 5 Hz), 130.9 (d, *J*(C,P) = 3 Hz), 128.5 (d, *J*(C,P) = 1 Hz), 128.1, 67.1 (d, *J*(C,P) = 50 Hz), 34.9, 34.9, 31.5 (d, *J*(C,P) = 5 Hz), 31.3, 31.2, 31.1 (d, *J*(C,P) = 10 Hz), 29.6 (d, *J*(C,P) = 6 Hz), 29.5 (d, *J*(C,P) = 6 Hz), 24.8 (dd, *J*(C,P) = 22 Hz, *J*(C,P) = 2 Hz), 20.5, 20.5, 16.7, 16.5 ppm. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{34}H_{55}O_3P_2$ 573.3621; Found 573.3625.

*[Rh(COD)(**3g**)]BF_4 (**4g**).* Over a stirred solution of bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (17 mg, 0.042 mmol) in dichlorometane (2 mL) was added 2-(di-*tert*-butylphosphinoethyl)-(*S*)-1,1′-(3,3′-di-*tert*-butyl-5,5′,6,6′-tetramethyl)biphen-2,2′-diyl phosphite (24.5 mg, 0.042 mmol) and the mixture obtained stirred for 4 h. The resulting suspension was concentrated to a fourth of the volume and precipitated with Et_2O, washed with additional Et_2O (3 × 2 mL), and the resulting solution evaporated under vacuum to yield **4g** as an orange solid (32 mg, 89% yield). ^1H NMR (CD_2Cl_2, 400 MHz): δ = 7.30 (s, 1H), 7.21 (s, 1H), 6.24 (m, 1H), 5.99 (m, 1H), 5.54 (m, 1H), 4.57 (m, 1H), 4.39 (m, 1H), 3.45 (m, 1H), 2.44 (m, 2H), 2.34 (m, 2H), 2.30 (s, 3H), 2.24 (m, 7H), 2.10 (m, 1H), 2.01 (m, 1H), 1.80 (s, 3H), 1.69 (s, 3H), 1.62 (s, 9H), 1.59 (d, *J*(H,P) = 13.6 Hz, 9H), 1.38 (s, 9H), 1.26 (d, *J*(H,P) = 13.1 Hz, 9H) ppm. $^{31}P\{^1H\}$ NMR (CD_2Cl_2, 162 MHz): δ = 121.3 (dd, *J*(P,Rh) = 250 Hz, *J*(P,P) = 48 Hz), 23.9 (dd, *J*(P,Rh) = 134 Hz, *J*(P,P) = 48 Hz) ppm. $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 100 MHz): δ = 145.5 (d, *J*(C,P) = 8 Hz), 144.9 (d, *J*(C,P) = 14 Hz), 137.5 (d, *J*(C,P) = 2 Hz), 137.4 (d, *J*(C,P) = 4 Hz), 136.7 (d, *J*(C,P) = 1 Hz), 136.0 (d, *J*(C,P) = 2 Hz), 134.5 (d, *J*(C,P) = 2 Hz), 134.4 (d, *J*(C,P) = 2 Hz), 129.5 (d, *J*(C,P) = 2 Hz), 129.5 (d, *J*(C,P) = 2 Hz), 128.9, 128.8, 114.2 (dd, *J*(C,P) = 11 Hz, *J*(C,Rh) = 5 Hz), 101.8 (dd, *J*(C,P) = 14 Hz, *J*(C,Rh) = 5 Hz), 99.3 (dd, *J*(C,P) = 10 Hz, *J*(C,Rh) = 4 Hz), 84.0 (dd, *J*(C,P) = 13 Hz, *J*(C,Rh) = 7 Hz), 65.2, 39.7 (d, *J*(C,P) = 14 Hz), 38.9 (d, *J*(C,P) = 11 Hz), 35.2, 35.0, 32.8, 32.2, 31.8, 31.6 (d, *J*(C,P) = 5 Hz), 30.1, 30.1, 29.9 (d, *J*(C,P) = 4 Hz),

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27.8, 20.5, 20.3, 20.2 (dd, J(P,P) = 20 Hz, J(P,P) = 7 Hz), 16.6, 16.3 ppm. Elem Anal. Calcd (%) for $C_{42}H_{66}BF_4O_3P_2Rh$ C 57.94, H 7.64; Found C 57.51, H 7.44.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00710.

Selected NMR spectra and chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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