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Chiral Rhodium Complexes Derived From Electron-Rich Phosphine-Phosphites as Asymmetric Hydrogenation Catalysts

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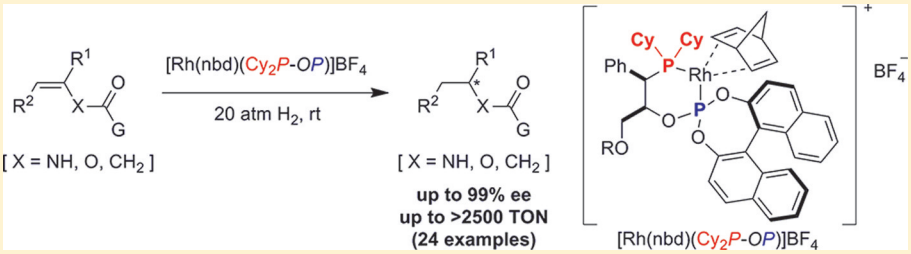
Supporting Information



ABSTRACT: Two new chiral cationic rhodium(I) complexes derived from electron-rich dicyclohexylphosphine-phosphite ligands were prepared from enantiopure Sharpless epoxy ethers. The best-performing catalyst system, which bears a less bulky methyl ether moiety, exhibited remarkably high enantioselectivity (up to 99% ee) and reactivity (up to >2500 TON) in asymmetric hydrogenation reactions of various functionalized alkenes (α-(acylamino)acrylates, itaconic acid derivatives, α-substituted enol esters and α-arylenamides). Our synthetic methodology has been successfully applied to the enantioselective synthesis of the antiepileptic drug (*R*)-lacosamide (Vimpat).

INTRODUCTION

The design and development of novel, efficient, and modular chiral phosphorus ligands and their application in several transition-metal-mediated asymmetric transformations of interest constitute an expanding research area within academia and industry.[1] From a practical perspective, enantioselective hydrogenation offers several advantages for the asymmetric organic synthesis of enantiomerically pure compounds (optimal atom economy, broad substrate scope, high reactivity and selectivity, and operational simplicity). As a consequence, the asymmetric hydrogenation of prochiral substrates (alkenes, imines, ketones, heteroaromatic compounds), mostly catalyzed by chiral Ir, Rh, or Ru complexes, is certainly among the most efficient and reliable methodologies in asymmetric catalysis.[2] Accordingly, many industrial methods for the production of optically active pharmaceuticals, agrochemicals, fragrances, fine chemicals, and natural chemicals rely on catalytic asymmetric hydrogenation reactions.[3]

Despite the remarkably advanced state of the field, numerous research groups are still actively pursuing new catalytic systems that show higher activity and/or improved enantioselectivity for challenging substrates or for recently discovered pharmacologically active compounds. In this context, we described the preparation of a library of enantiomerically pure *P-OP* ligands[4] (phosphine-phosphinites and phosphine-phosphites) whose catalytic properties were assessed in different enantioselective transformations. Our research group has employed a highly modular ligand design in conjunction with a fine-tuning methodology guided by computational analysis of the diastereomeric transition states to improve the performance of the catalytic systems. In this way, an array of enantiopure 1,2-*P-OP* derivatives (mostly phosphine-phosphite ligands) have been developed in an efficient manner for Pd-mediated asymmetric allylic substitution reactions,[5] Ir-mediated asymmetric hydrogenation of heteroaromatic compounds,[6] and Rh-mediated asymmetric hydrogenation of functionalized alkenes.[7]

Regarding the latter asymmetric transformation, our group recently reported the highly enantioselective hydrogenation of a structurally diverse range of substrates catalyzed by cationic Rh complexes of diphenylphosphine-phosphite ligand **1** (Figure 1).

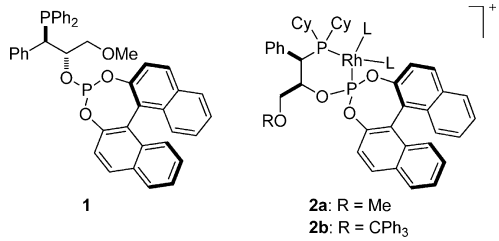


Figure 1. Previously developed "lead" *P-OP* ligand (left) and general structure of the new Rh−(*P-OP*) complexes (right).

β-Substituted α-(acylamino)acrylates, itaconic acid derivatives and analogues, and α-arylenamides have been hydrogenated

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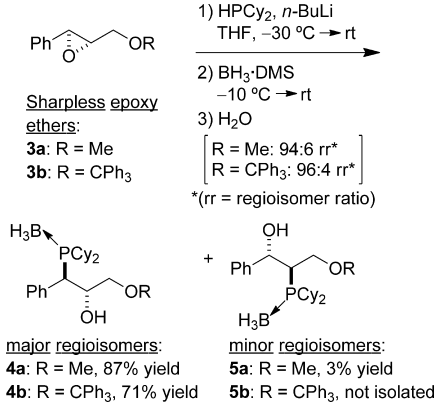
with high enantioselectivities (up to 99% ee) using $[Rh(\mathbf{1})]^+$ complexes as catalysts.[7c,d] We envisioned that the highly modular design of our phosphine-phosphite ligands should enable further optimization of the catalytic systems by modifying the steric and electronic properties of the phosphino group (replacement of the previously featured PPh_2 moiety by a more bulky and more electron-rich PCy_2 group). Furthermore, the catalytic performance of Rh complexes derived from such electron-rich phosphine-phosphite ligands (general structure depicted in Figure 1) can be tuned by varying the steric bulk of the substituent attached to the pendant ether fragment (methyl (**2a**) and triphenylmethyl (**2b**) ether groups). We report here the synthesis of two newly designed chiral cationic Rh(I) complexes derived from electron-rich dicyclohexylphosphine-phosphites and the evaluation of these compounds as catalyst precursors in asymmetric hydrogenation reactions of functionalized alkenes.

RESULTS AND DISCUSSION

Synthesis of [Rh(nbd)(Cy_2*P-OP*)]BF_4 (8a) and [Rh(nbd)-(Cy_2*P-OP*)]BF_4 (8b). The stepwise synthetic route toward the target Rh−(*P-OP*) complexes started with the ring opening of enantiopure Sharpless methyl- and triphenylmethyl-substituted epoxy ethers **3a,b** by using lithium dicyclohexylphosphide (generated in situ from $HPCy_2$ and *n*-BuLi) as the phosphorus nucleophile (Scheme 1). The ring opening of these epoxy

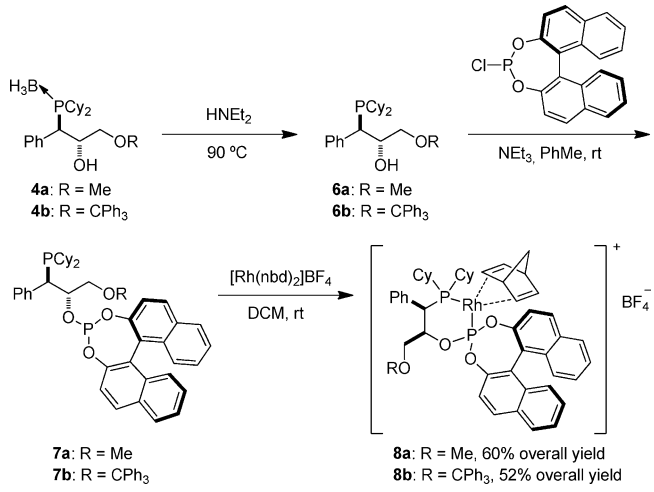
Scheme 1. Ring Opening of Sharpless Epoxy Ethers with Lithium Dicyclohexylphosphide



ethers proceeded smoothly at −30 °C to room temperature, and the intermediate dicyclohexylphosphino alcohols, which proved to be rather prone to oxidation, were subsequently protected in situ as the corresponding borane adducts in order to make handling and storage more convenient. The ring-opening reactions of epoxides **3a,b** with lithium dicyclohexylphosphide were stereospecific——as previously observed for other phosphorus nucleophiles[7c]——and took place in a highly regioselective manner (marked preference for nucleophilic attack at the more reactive benzylic position). ^1H and $^{31}P\{^1H\}$ NMR analyses of the crude mixtures indicated regioisomer ratios (rr) of 94/6 and 96/4 for the methyl and triphenylmethyl ether derivatives, respectively. Purification of the mixtures by column chromatography afforded the desired major regioisomers **4a,b** on the gram scale in 87% and 71% yields, respectively. Furthermore, a very small amount of the methyl ether protected minor regioisomer **5a** was also isolated (3% yield) and this compound was also fully characterized. However, the triphenylmethyl ether protected minor regioisomer **5b** could not be isolated in a chemically pure form.

The preparation of the target Rh complexes **8a,b** was successfully accomplished in three subsequent chromatography-free synthetic steps starting from the borane-protected phosphino alcohols **4a,b** (Scheme 2). First, the free

Scheme 2. Synthesis of Rhodium Complexes Derived from Electron-Rich Dicyclohexylphosphine-Phosphite Ligands



dicyclohexylphosphino alcohols **6a,b** were quantitatively obtained under optimized conditions by deprotection of the borane adducts **4a,b** using neat diethylamine with heating over reflux at 90 °C for 4 h.[8] Phosphino alcohols **6a,b** were subsequently derivatized to the phosphine-phosphite ligands **7a,b** by treatment with (S_a)-BINOL-derived chlorophosphite in the presence of triethylamine as an auxiliary base. The O-phosphorylation reactions were monitored by $^{31}P\{^1H\}$ NMR spectroscopy (using sealed capillaries filled with DMSO-d_6 for deuterium shimming and locking) in order to optimize the reaction time required for the reactions to reach completion. $^{31}P\{^1H\}$ NMR analysis of the reaction mixture leading to the phosphine-phosphite **7a** showed the complete disappearance of the phosphorus signal belonging to the starting phosphino alcohol **6a** (singlet at 12.4 ppm) after 3 h at room temperature. During this time two doublets ($^4J_{P-P}$ = 18.4 Hz) appeared, and these correspond to the phosphino and phosphite moieties in ligand **7a** (13.3 and 158.4 ppm, respectively). In contrast, $^{31}P\{^1H\}$ NMR analysis of the reaction mixture with the bulkier triphenylmethyl ether derivative after 3 h at room temperature indicated incomplete conversion. Complete conversion was achieved on stirring the reaction mixture overnight at room temperature, and the resulting spectrum revealed two doublets at 12.2 and 158.1 ppm with identical long-range $^{31}P-^{31}P$ coupling constants ($^4J_{P-P}$ = 18.5 Hz). These signals are consistent with the expected phosphino and phosphite groups in ligand **7b**.

The capability of the bidentate dicyclohexylphosphine-phosphites **7a,b** to form stable, well-defined chiral Rh chelates was clearly demonstrated after converting them into the cationic Rh(I) complexes **8a,b** by using $[Rh(nbd)_2]BF_4$ as the metal precursor.[7c] Complexes **8a,b** were prepared in a straightforward manner by reacting stoichiometric amounts of the crude ligands **7a,b**[9] with the aforementioned Rh precursor in DCM at room temperature for 2 h (Scheme 2). In this way,

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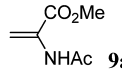
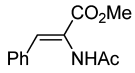
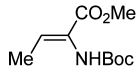
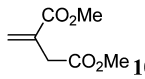
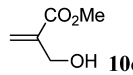
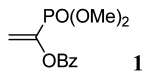
the target Rh−(*P-OP*) complexes **8a,b** were obtained from **4a,b** in three steps (namely deprotection, O-phosphorylation, and complexation), and they were isolated in 60% and 52% overall yields, respectively. The $^{31}P\{^{1}H\}$ NMR spectra of **8a,b** showed two sharp doublet of doublets centered around 40 ppm (phosphino moiety) and 140 ppm (phosphite moiety) for each Rh complex. The multiplicity of these phosphorus signals is due to a direct $^{31}P-^{103}Rh$ ($^{1}J \approx 270$ Hz) coupling along with a geminal $^{31}P-^{31}P$ coupling ($^{2}J \approx 60$ Hz).[10] The NMR data and HRMS measurements for **8a,b** unequivocally confirm the formation of the expected 1/1 Rh/ligand chelates.

Comparison of the Catalytic Performance of Rh Complexes 8a,b in Asymmetric Hydrogenation of Functionalized Alkenes. Once the envisioned Rh(I) complexes **8a,b** had been prepared, their catalytic activity and selectivity were evaluated in the enantioselective hydrogenation of various prochiral olefins. In the first set of experiments, several model substrates from different representative families of functionalized alkenes were chosen in order to compare the efficiency provided by the sterically different Rh complexes **8a,b**. For this purpose, one *β*-unsubstituted (**9a**), one *β*-aryl-substituted (**9c**), and one *β*-alkyl-substituted (**9k**) *α*-(acylamino)acrylate were selected as test substrates along with dimethyl itaconate **10a**, its analogue **10c**, and the enol ester phosphonate **11** (see Table 1 for the substrate structures). The hydrogenation reactions were carried out under standard screening conditions[7c,d] (1.0 mol % of [Rh(nbd)(*P-OP*)]BF_4 as the catalyst precursor, 20 atm of H_2, THF or DCM as solvent, room temperature, overnight). The results of the comparative study, along with those previously obtained with the Rh complex of diphenylphosphine-phosphite **1** (ligand structure depicted in Figure 1), are summarized in Table 1. In all cases complete conversion was achieved for the functionalized alkenes under investigation and the catalytic performance of the catalyst precursors **8a,b**, with sterically different substituents at the R-oxy position, did not show differences in terms of the catalytic activity. Nonetheless, a significant negative effect on the reaction enantioselectivity can be observed on comparing the less hindered methyl ether protected Rh complex **8a** with the bulkier triphenylmethyl ether counterpart **8b**, which gave rise to dramatic decreases in the ee values for *α*-(acylamino)-acrylates **9a,c,k**, dimethyl itaconate **10a**, and the related alkene **10c**. These results clearly indicate that the steric hindrance arising from the different size of the R-oxy substituent in the chiral backbone of the ligand has a significant influence on the enantioselectivity of the reaction.[11] One exception to this general catalytic behavior was found for the enol ester phosphonate **11**, which was hydrogenated with excellent enantioselectivity regardless of the Rh complex used as the catalyst precursor (Table 1, entries 17 and 18).

Table 1. Asymmetric Hydrogenation of Functionalized Alkenes Catalyzed by Rh Complexes 8a,b[a]

entry	substrate/ solvent	cat.	ee (%)[b] (config.)[c]
1	 **9a**/ THF	**1**[d]	99 (*R*)[e]
2		**8a**	99 (*R*)
3		**8b**	89 (*R*)
4	 **9c**/ THF	**1**[d]	99 (*R*)[e]
5		**8a**	98 (*R*)
6		**8b**	70 (*R*)
7	 **9k**/ THF	**1**[d]	98 (*R*)[f]
8		**8a**	98 (*R*)
9		**8b**	82 (*R*)
10	 **10a**/ DCM	**1**[d]	99 (*S*)[e]
11		**8a**	97 (*S*)
12		**8b**	88 (*S*)
13	 **10c**/ THF	**1**[d]	90 (*S*)[e]
14		**8a**	83 (*S*)
15		**8b**	65 (*S*)
16	 **11**/ DCM	**1**[d]	92 (*S*)[e]
17		**8a**	98 (*S*)
18		**8b**	98 (*S*)

[a]All reactions were run at room temperature with 1.0 mol % catalyst loading for 18 h at 20 atm of H_2. Full conversion was achieved in all cases, as determined by ^{1}H NMR. [b]Determined by GC or HPLC analysis using chiral stationary phases. [c]Absolute configuration was assigned by comparison of the specific rotation with reported data. [d]**1** refers to [Rh(nbd)(**1**)]BF_4. [e]Results from ref 7c. [f]Results from ref 7d.

Enantioselective Hydrogenation of Functionalized Alkenes Catalyzed by Rh Complex 8a. Having obtained very promising results from the preliminary catalyst screening studies, we proceeded to investigate the efficiency of the best-performing Rh complex **8a** in more detail in the enantioselective hydrogenation of *α*-(acylamino)acrylates (see Table 2 for the substrate structures). Regarding the optimal catalyst loading of the Rh complex **8a**, a catalyst loading as low as 0.04 mol % (2500/1 substrate/catalyst ratio, >2500 TON) still gave quantitative conversion in the hydrogenation of model substrate **9a**, without the enantioselectivity being affected (99% ee; compare entry 1 in Table 2 and entry 2 in Table 1) and without requiring an increase in either the H_2 pressure or the reaction time. The *N*-Cbz-protected analogue **9b** was also efficiently hydrogenated under standard conditions (Table 2, entry 2). In addition to the *β*-aryl-substituted *α*-(acylamino)-acrylic acid derivative mentioned above (substrate **9c**; Table 1, entry 5), other substrates of this kind (**9d−i**) were also successfully reduced with full conversions and remarkably high enantioselectivities (91−98% ee; Table 2, entries 3−8). Interestingly, two analogous substrates of the model alkene **9c**, one in which the methyl ester functionality is replaced by a free carboxylic acid group (**9d**) and the other a Weinreb amide (**9e**), were also efficiently hydrogenated with high enantioselectivity (Table 2, entries 3 and 4). The enantioselective hydrogenation of the free acid **9d** proceeded quantitatively under standard conditions, whereas the more difficult substrate **9e** required an increased catalyst loading (up to 2.0 mol %) in order to reach full conversion. Despite the synthetic versatility of the functional group known as the Weinreb amide (*N*-methoxy-*N*-methylcarbamoyl group) as an antecedent of a number of functional groups,[12] the results described herein constitute, to the best of our knowledge, the first reported example of the enantioselective hydrogenation of the Weinreb amide derivative **9e**. The presence of carbamate-type amino protecting groups as well as electron-donating and electron-withdrawing substituents at different positions of the aromatic ring were all well-tolerated by the catalyst precursor **8a** (Table 2, entries 5−8).

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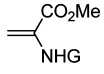
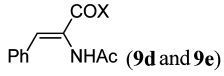
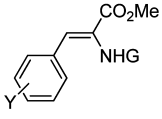
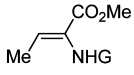
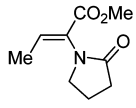
Table 2. Asymmetric Hydrogenation of α-(Acylamino)acrylates Catalyzed by Rh Complex 8a[a]

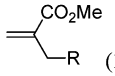
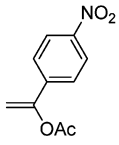
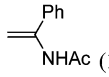
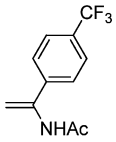
entry	substrate/ solvent/ cat. (mol %)	ee (%) (config.)
	 (**9a** and **9b**)	
1	**9a** (G = Ac)/ THF/ 0.04	99 (*R*)
2	**9b** (G = Cbz)/ THF/ 1.0	98 (*R*)
	 (**9d** and **9e**)	
3	**9d** (X = OH)/ DCM/ 1.0	98 (*R*)
4	**9e** (X = N(Me)OMe)/ DCM/ 2.0	91 (*R*)[b]
	 **9f–9i**/ THF/ 1.0	
5	**9f** (G = Boc, Y = H)	97 (*R*)
6	**9g** (G = Boc, Y = 3,5-F_2)	93 (*R*)
7	**9h** (G = Ac, Y = 3,4-$(AcO)_2$)	98 (*R*)
8	**9i** (G = Ac, Y = 2,5-F_2)	92 (*R*)[b]
	 **9j–9l**/ THF/ 1.0	
9	**9j** (G = Ac)	98 (*R*)
10	**9k** (G = NHBoc)	98 (*R*)
11	**9l** (G = NHCbz)	98 (*R*)[b]
12	 **9m**/ DCM/ 1.0	94 (*R*)

[a]See Table 1 for details on the asymmetric hydrogenations. [b]The absolute configuration was tentatively assigned by analogy, on the basis of the stereochemical outcome for analogous substrates.

The excellent results achieved in the enantioselective hydrogenation reactions of substrates **9j–m** (Table 2, entries 9–12) clearly indicate the good catalytic performance of the Rh complex **8a** for β-alkyl-substituted α-(acylamino)acrylates. At the same time, the results obtained for these differently N-protected β-methyl-substituted alkenes (**9j–m**) strongly evidence the tolerance of the catalytic system to a broad variety of amino protecting groups. It is also worth mentioning that the industrially relevant alkene **9m**, which is the precursor of the antiseizure agent levetiracetam,[13] has proven to be a challenging substrate in Rh-mediated asymmetric hydrogenation, as only moderate enantioselectivities have been achieved even under optimized conditions.[14] Fortunately, the catalyst precursor **8a** showed quite efficient behavior for substrate **9m** and gave the desired product with 94% ee (Table 2, entry 12).

We further extended the substrate scope of the enantioselective hydrogenation catalyzed by the Rh complex **8a** to other representative families of functionalized alkenes: namely, itaconic acid derivatives, α-substituted enol esters, and α-arylenamides. The results obtained in these reactions are summarized in Table 3. The asymmetric hydrogenation of itaconic acid derivatives **10a–c** gave high enantioselectivities (Table 3, entries 1–3) of up to 97% ee for dimethyl itaconate **10a**.

Table 3. Asymmetric Hydrogenation in DCM of other Functionalized Alkenes Catalyzed by Rh Complex 8a[a]

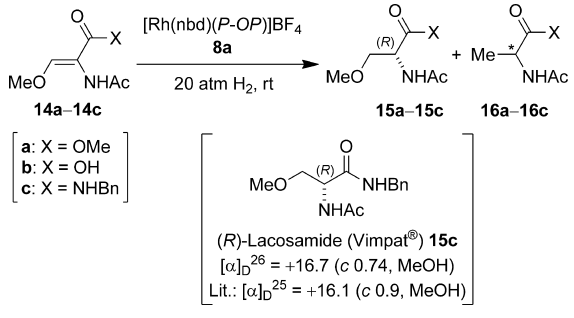
entry	substrate	ee (%) (config.)
	 (**10a–10c**)	
1	**10a**: R = CO_2Me	97 (*S*)
2	**10b**: R = $CONH_2$	91 (*S*)
3	**10c**: R = OH	93 (*S*)
4	 (**12a**)	86 (*R*)
5	 (**12b**)	90 (*R*)
6	 (**13a**)	71 (*R*)
7	 (**13b**)	76 (*R*)

[a]See Table 1 for details on the asymmetric hydrogenations.

The hydrogenations of the α-arylenol acetates **12a,b** proved to be less enantioselective (Table 3, entries 4 and 5), with the *p*-nitrophenyl-substituted derivative **12b** affording the highest ee value. Finally, α-arylenamides **13a,b** were both hydrogenated with moderate enantioselectivity (Table 3, entries 6 and 7).

Enantioselective Synthesis of the Antiepileptic Drug (*R*)-Lacosamide. To demonstrate the synthetic utility of our methodology, we studied the catalytic performance of Rh complex **8a** in the asymmetric hydrogenation of β-alkoxy-substituted α-(acylamino)acrylate derivatives **14a–c** (Scheme 3). It is worth mentioning that precedents for the enantioselective hydrogenation of α-amino acid precursors bearing β-alkoxy substituents have not previously been reported in the literature. Nevertheless, we

Scheme 3. Enantioselective Synthesis of the Antiepileptic Drug (*R*)-Lacosamide



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successfully applied our strategy to this unexplored field and developed an enantioselective approach for the synthesis of (*R*)-lacosamide[15] (**15c**, Scheme 3), the active pharmaceutical ingredient of the antiepileptic agent Vimpat.[16] The results obtained in the hydrogenation reactions of lacosamide precursors **14a**–**c** are summarized in Table 4.

Table 4. Asymmetric Hydrogenation of 14 Catalyzed by Rh Complex 8a[a]

entry	substrate	solvent	amt of cat. (mol %)	conversn (%)	**15**/**16** (molar ratio)	ee of **15** (%) (config)
1[b]	**14a**	THF	1.0	>99	85/15	97 (*R*)
2	**14a**	THF	1.0	44	98/2	94 (*R*)
3	**14a**	THF	2.0	>99	97/3	94 (*R*)
4	**14a**	DCM	2.0	>99	99/1	96 (*R*)
5	**14b**	DCM	2.0	>99	>99/1	99 (*R*)
6	**14c**	THF	2.0	>99	96/4	96 (*R*)
7	**14c**	DCM	2.0	>99	>99/1	99 (*R*)

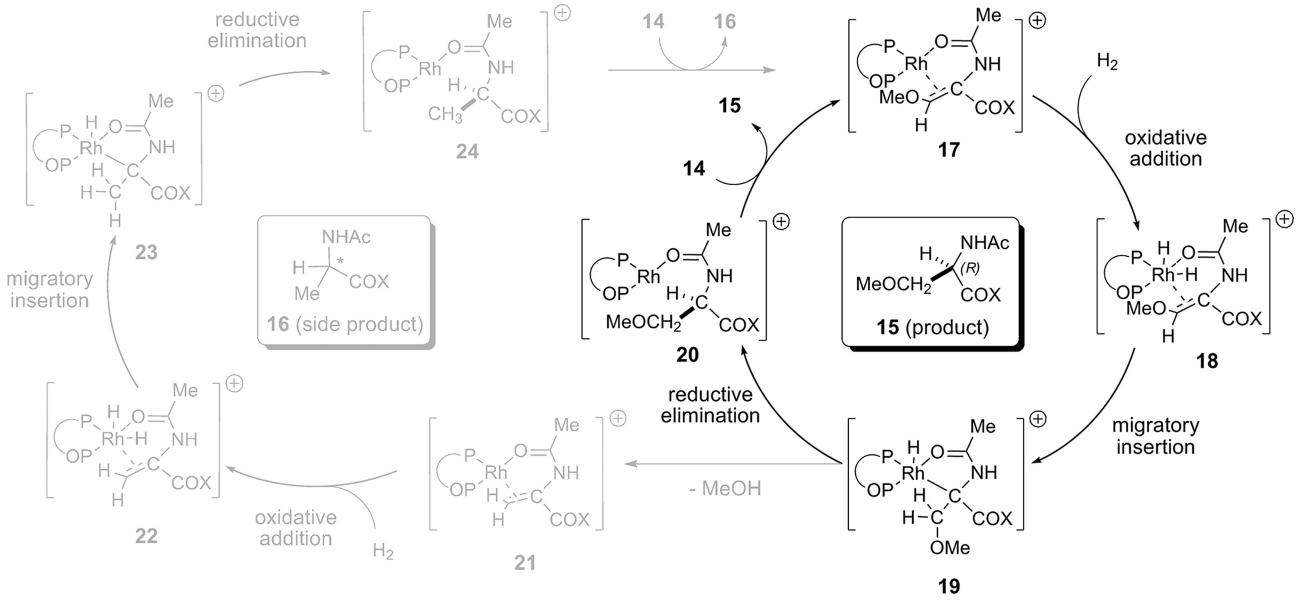
[a]See Table 1 for details on the asymmetric hydrogenations. [b]Results from ref 17 obtained on using in situ generated [Rh(nbd)(**1**)]BF_4.

The enantioselective hydrogenation of the methyl ester derivative **14a** has very recently been performed using the Rh complex of *P-OP* ligand **1** (see Figure 1 for the ligand structure), and this furnished very good results (Table 4, entry 1) under standard reaction conditions (1.0 mol % catalyst loading, 20 atm of H_2, THF, room temperature, 18 h).[17] However, although the conversion of the starting alkene **14a** reached completion, a selectivity of only 85% (85/15 **15a**/**16a** ratio) toward the desired product **15a** was obtained when diphenylphosphine-phosphite ligand **1** was employed. According to the literature,[18] the formation of the MeOH-elimination products **16** may be rationalized as a side reaction of the hydride intermediates **19** involved in the hydrogenation catalytic cycle of alkenes **14** mediated by Rh complexes of *P-OP* ligands[7c] (see Scheme 4). An elimination process[19] from hydride intermediates **19** releases MeOH along with the Rh complex of 2-acetamidoacrylic acid derivatives **21**, which further evolves to the corresponding elimination products **16** through hydrogenation.

In comparison to the Rh complex derived from *P-OP* ligand **1**, the use of complex **8a** led to a marked enhancement in the selectivity (i.e., 98/2 **15a**/**16a** ratio) and a slightly reduced enantioselectivity (i.e., 94% ee) under the same hydrogenation conditions, albeit with only moderate conversion (Table 4, entry 2). The reaction was taken to completion by increasing the catalyst loading to 2.0 mol % (Table 4, entry 3). The formation of the side product **16a** was almost suppressed by switching the reaction solvent from THF to DCM. Furthermore, this reaction medium allowed the desired product **15a** to be obtained with very high enantioselectivity (96% ee; Table 4, entry 4). Most remarkably, the asymmetric hydrogenation of carboxylic acid derivative **14b** in DCM, a solvent in which substrate **14b** was only partially soluble, provided lacosamide precursor **15b** as the exclusive reaction product with excellent enantioselectivity (i.e., 99% ee; Table 4, entry 5). The two *R*-configured hydrogenation products **15a**,**b** constitute direct precursors of the chiral drug (*R*)-lacosamide (**15c**). Indeed, this chiral pharmaceutical target can be readily prepared in one or two steps from **15b** and **15a**, respectively, according to literature procedures.[15c]

Finally, the enantioselective total synthesis of (*R*)-lacosamide **15c** was also attempted by exploring the Rh-mediated asymmetric hydrogenation of the tailored substrate **14c** (see Scheme 3). The hydrogenation reaction of alkene **14c** catalyzed by Rh complex **8a** proceeded with 96% selectivity toward the desired product **15c**, which was obtained in 96% ee when THF was used as the solvent (Table 4, entry 6). These results were significantly improved on using DCM as the reaction solvent. In this way, the antiepileptic drug (*R*)-lacosamide (**15c**) was efficiently prepared with total selectivity and excellent enantioselectivity (i.e., 99% ee; Table 4, entry 7). The measured specific rotation for **15c** is in excellent agreement with the reported value,[15c] as indicated in Scheme 3, unambiguously confirming the absolute configuration of the hydrogenated product.

Scheme 4. Formation of the MeOH-Elimination Products 16 under Hydrogenation Conditions



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CONCLUSION

In summary, we have developed a convenient synthetic route for the preparation of new chiral cationic rhodium complexes derived from tunable electron-rich dicyclohexylphosphine-phosphite ligands with substituents of varying size in the R-oxy position of the ligand. These rhodium complexes have been efficiently applied as catalyst precursors in enantioselective hydrogenation reactions of various functionalized alkenes such as α-(acylamino)acrylates, itaconic acid derivatives, α-substituted enol esters, and α-arylenamides. The best-performing catalyst system (**8a**) gave excellent enantioselectivities (up to 99% ee) and catalytic activities (>2500 TON) for a wide array of substrates (24 examples). The present methodology has been successfully employed for the preparation of the chiral antiepileptic drug (*R*)-lacosamide. Further applications of these rhodium complexes in other asymmetric transformations are currently under investigation, and the results will be reported in due course.

EXPERIMENTAL SECTION

General Considerations. All syntheses were carried out on using chemicals as purchased from commercial sources unless otherwise stated. All manipulations and reactions were run under an inert atmosphere using anhydrous solvents, either in a glovebox or with standard Schlenk-type techniques. Glassware was dried under vacuum and heated with a hot air gun before use. All solvents were dried by using a Solvent Purification System (SPS). Silica gel 60 (230–400 mesh) was used for column chromatography. NMR spectra were recorded in $CDCl_3$ unless otherwise cited, using a 400 or 500 MHz spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts are quoted in ppm relative to residual solvent peaks, whereas ^{31}P{^{1}H} NMR chemical shifts are quoted in ppm relative to 85% phosphoric acid in water and ^{19}F{^{1}H} NMR chemical shifts are quoted in ppm relative to BF_3·OEt_2 in $CDCl_3$. High-resolution mass spectra (HRMS) were recorded by using an ESI ionization method in positive mode. Melting points were measured in open capillaries and are uncorrected. Enantiomeric excesses were determined by GC or HPLC on using chiral stationary phases.

Synthesis of [Rh(nbd)(7a)]BF_4 (8a). The reaction mixture was prepared into an Ace pressure tube loaded with a stirring bar by working under an N_2 atmosphere inside a glovebox. First, the borane adduct **4a** (300 mg, 0.80 mmol) was charged into the pressure tube and then $HNEt_2$ (16.4 mL, 160 mmol) was syringed inside. Once the pressure tube had been sealed under an inert atmosphere, it was taken out of the glovebox and the reaction mixture was further heated to 90 °C and stirred for 4 h. After the mixture was cooled to room temperature, the pressure tube was introduced into a glovebox, where the reaction mixture was filtered through a short deoxygenated silica gel pad (ca. 3.0 cm) on employing anhydrous toluene (2 × 10.0 mL) as the solvent for the elution. The filtrate was collected in a Schlenk flask under an inert atmosphere, and once outside the glovebox, the solvent was evaporated off under vacuum. The resulting phosphino alcohol **6a**, obtained as a white solid, was subsequently introduced into a glovebox in order to carry out the next step therein. The freshly prepared phosphino alcohol **6a** (0.80 mmol theoretical) was dissolved in anhydrous toluene (20.0 mL). On the other hand, commercially available (S_a)-BINOL-derived chlorophosphite (317 mg, 0.88 mmol) was loaded into a vial and then anhydrous toluene (10.0 mL) and distilled Et_3N (0.22 mL, 1.59 mmol) were successively syringed into the vial. The previous solution was syringed drop by drop over the solution containing the starting phosphino alcohol. After completion of the addition, the reaction mixture was stirred for 3 h at room temperature under an N_2 atmosphere inside the glovebox. The reaction mixture was treated by addition of anhydrous Et_2O (2 × 10.0 mL). The resulting whitish suspension was filtered through a short deoxygenated silica gel pad (ca. 3.0 cm), and the filtrate was collected in a Schlenk flask under inert atmosphere. After evaporation of the solvent under vacuum the resulting crude phosphine-phosphite ligand **7a**, obtained as a spongy white solid, was straightforwardly used in the next step. By operating inside a glovebox, the previous crude compound **7a** (0.80 theoretical mmol, 74% chemical purity by ^{31}P{^{1}H} NMR) was dissolved in anhydrous DCM (8.0 mL) and then $[Rh(nbd)_2]BF_4$ (216 mg, 0.58 mmol) was added to the reaction mixture, which was stirred at room temperature for 2 h. After this period the solvent was evaporated off under vacuum until its volume was reduced approximately to one-fourth. Then, anhydrous Et_2O (30.0 mL) was slowly syringed over the remaining solution. In this manner a great deal of orange solid was immediately formed inside the orangish solution. The solvent was filtered off under an Ar atmosphere by employing a filter cannula, and the resulting solid was washed with additional volumes of anhydrous Et_2O (2 × 10.0 mL). The solvent was again filtered off by employing the same filter cannula. Drying of the resulting solid under vacuum for several hours afforded 463 mg (60% overall yield) of pure Rh(I) complex **8a** as an orange powder. Norbornadienerhodium(I) tetrafluoroborate complex of (11bS_a)-4-((1*R*,2*S*)-1-dicyclohexylphosphino-3-methoxy-1-phenylpropan-2-yloxy)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine **7a** (**8a**): $[\alpha]_D^{25}$ = +114.9° (*c* 1.02, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 0.75–2.15 (m, 22H, 18CH_2(PCy_2), 2C*H*(PCy_2), and CH_2(nbd)), 2.24–2.37 (m, 2H, CH_2(PCy_2)), 3.35 (s, 3H, O*Me*), 3.39 (ddd, *J* = 9.9, 5.5, and 2.2 Hz, 1H, C*H*HOMe), 3.44–3.50 (m, 1H, CH*H*OMe), 3.59 (dd, *J* = 13.2 and 2.2 Hz, 1H, C*H*PCy_2), 4.05–4.11 (m, 2H, C$H_{\text{head of bridge}}$(nbd) and C$H_{\text{alkene}}$(nbd)), 4.17–4.21 (m, 1H, C$H_{\text{head of bridge}}$(nbd)), 5.00–5.08 (m, 1H, C*H*OP), 5.62–5.68 (m, 1H, CH_{alkene}(nbd)), 6.15–6.21 (m, 1H, CH_{alkene}(nbd)), 6.47–6.53 (m, 1H, CH_{alkene}(nbd)), 7.10–7.46 (m, 8H, H_{arom}), 7.53 (d, *J* = 9.0 Hz, 1H, H_{arom}), 7.55–7.69 (m, 3H, H_{arom}), 7.75 (d, *J* = 8.8 Hz, 1H, H_{arom}), 8.04 (d, *J* = 8.4 Hz, 1H, H_{arom}), 8.09 (d, *J* = 9.0 Hz, 1H, H_{arom}), 8.15 (d, *J* = 8.4 Hz, 1H, H_{arom}), 8.33 (d, *J* = 8.8 Hz, 1H, H_{arom}); ^{13}C{^{1}H^{31}P} NMR (125 MHz, CD_2Cl_2) δ 25.9 (CH_2(PCy_2)), 26.1 (CH_2(PCy_2)), 26.6 (CH_2(PCy_2)), 26.9 (CH_2(PCy_2)), 27.1 (CH_2(PCy_2)), 27.2 (CH_2(PCy_2)), 28.2 (CH_2(PCy_2)), 28.3 (CH_2(PCy_2)), 30.2 (CH_2(PCy_2)), 35.1 (CH_2(PCy_2)), 35.4 (*C*H(PCy_2)), 36.9 (*C*H(PCy_2)), 38.0 (*C*HPCy_2), 55.5 (*C*H$_{\text{head of bridge}}$(nbd)], 55.6 (*C*H$_{\text{head of bridge}}$(nbd)), 59.0 (O*Me*), 72.6 (CH_2(nbd)), 72.9 (*C*H_2OMe), 80.8 (*C*H–OP), 81.4 (*C*H$_{\text{alkene}}$(nbd)), 89.8 (*C*H$_{\text{alkene}}$(nbd)), 101.1 (*C*H$_{\text{alkene}}$(nbd)), 104.2 (*C*H$_{\text{alkene}}$(nbd)), 120.5 (*C*H$_{\text{arom}}$), 121.2 (*C*H$_{\text{arom}}$), 122.0 (*C*$_{\text{q arom}}$–(O)*C*$_{\text{q arom}}$), 123.0 (*C*$_{\text{q arom}}$–(O)*C*$_{\text{q arom}}$), 126.0 (*C*H$_{\text{arom}}$), 126.3 (*C*H$_{\text{arom}}$), 126.5 (*C*H$_{\text{arom}}$), 126.9 (*C*H$_{\text{arom}}$), 127.1 (*C*H$_{\text{arom}}$), 127.3 (*C*H$_{\text{arom}}$), 128.2 (*C*H$_{\text{arom}}$), 128.6 (*C*H$_{\text{arom}}$), 128.8 (*C*H$_{\text{arom}}$), 128.9 (2*C*H$_{\text{arom}}$), 130.7 (*C*H$_{\text{arom}}$), 131.5 (*C*H$_{\text{arom}}$), 131.8 (*C*$_{\text{q arom}}$), 131.9 (*C*$_{\text{q arom}}$), 132.2 (*C*$_{\text{q arom}}$), 132.4 (*C*$_{\text{q arom}}$), 132.5 (*C*$_{\text{q arom}}$), 146.5 (*C*$_{\text{q arom}}$–O), 146.8 (*C*$_{\text{q arom}}$–O); ^{31}P{^{1}H} NMR (202 MHz, CD_2Cl_2) δ 38.5 (dd, $^1J_{P-Rh}$ = 141.4 Hz, $^2J_{P-P}$ = 59.8 Hz, 1P, *P*–C), 141.1 (dd, $^1J_{P-Rh}$ = 272.9 Hz, $^2J_{P-P}$ = 59.8 Hz, 1P, *P*–O); ^{11}B{^{1}H} NMR (128 MHz, CD_2Cl_2) δ −1.16 (s, *B*F_4^-); ^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ −153.2 (s, *B*F_4); HRMS (ESI$^+$): *m*/*z* [M − BF_4]$^+$ calcd for $C_{49}H_{54}O_4P_2Rh$ 871.2552, found 871.2565.

Synthesis of [Rh(nbd)(7b)]BF_4 (8b). The reaction mixture was prepared into an Ace pressure tube loaded with a stirring bar by working under an N_2 atmosphere inside a glovebox. First, the borane adduct **4b** (482 mg, 0.80 mmol) was charged into the pressure tube, and then $HNEt_2$ (16.4 mL, 160 mmol) was syringed inside. Once the pressure tube had been sealed under an inert atmosphere, it was taken out of the glovebox and the reaction mixture was further heated at 90 °C and stirred for 4 h. After the mixture was cooled to room temperature, the pressure tube was introduced into a glovebox, where the reaction mixture was filtered through a short deoxygenated silica gel pad (ca. 3.0 cm) on employing anhydrous toluene (2 × 10.0 mL) as the solvent for the elution. The filtrate was collected in a Schlenk flask under an inert atmosphere, and once outside the glovebox, the solvent was evaporated off under vacuum. The resulting phosphino alcohol **6b**, obtained as a white solid, was subsequently introduced into a glovebox in order to carry out the next step therein. The freshly prepared phosphino alcohol **6b** (0.80 mmol theoretical) was dissolved in anhydrous toluene (20.0 mL). On the other hand, commercially available (S_a)-BINOL-derived chlorophosphite (317 mg, 0.88 mmol)

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was loaded into a vial and then anhydrous toluene (10.0 mL) and distilled Et_3N (0.22 mL, 1.59 mmol) were successively syringed into the vial. The previous solution was syringed drop by drop over the solution containing the starting phosphino alcohol. After completion of the addition, the reaction mixture was stirred for 18 h at room temperature under an N_2 atmosphere inside the glovebox. The reaction mixture was treated by addition of anhydrous Et_2O (2 × 10.0 mL). The resulting whitish suspension was filtered through a short deoxygenated silica gel pad (ca. 3.0 cm), and the filtrate was collected in a Schlenk flask under an inert atmosphere. After evaporation of the solvent under vacuum the crude phosphine-phosphite ligand **7b**, obtained as a spongy white solid, was straightforwardly used in the next step. By operating inside a glovebox, the crude compound **7b** (0.80 mmol theoretical, 65% chemical purity by $^{31}P\{^1H\}$ NMR) was dissolved in anhydrous DCM (8.0 mL) and then $[Rh(nbd)_2]BF_4$ (190 mg, 0.51 mmol) was added to the reaction mixture, which was stirred at room temperature for 2 h. After this period the solvent was evaporated off under vacuum until its volume was reduced approximately to one-fourth. Then, anhydrous Et_2O (30.0 mL) was slowly syringed over the remaining solution. In this manner a great deal of orange solid was immediately formed inside the orangish solution. The solvent was filtered off under an Ar atmosphere by employing a filter cannula, and the resulting solid was washed with additional volumes of anhydrous Et_2O (2 × 10.0 mL). The solvent was again filtered off by employing the same filter cannula. Drying of the resulting solid under vacuum for several hours afforded 496 mg (52% overall yield) of pure Rh(I) complex **8b** as an orange powder. Norbornadienerhodium(I) tetrafluoroborate complex of (11bS_a)-4-((1*R*,2*S*)-1-dicyclohexylphosphino-1-phenyl-3-triphenylmethoxypropan-2-yloxy)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine **7b** (**8b**): $[\alpha]_D^{26}$ = +34.4° (*c* 0.85, CH_2Cl_2); ^1H NMR (400 MHz, CD_2Cl_2) δ 0.75−2.19 (m, 23H, 9.5CH_2(PCy_2), 2CH(PCy_2), and CH_2(nbd)), 2.39−2.50 (m, 1H, 0.5CH_2(PCy_2)), 3.21 (dd, *J* = 9.1 and 9.1 Hz, 1H, CHHOMe), 3.29−3.37 (m, 1H, CHHOMe), 3.93 (bd, *J* = 13.8 Hz, 1H, CHPCy_2), 4.05−4.15 [m, 2H, C$H_{\text{head of bridge}}$(nbd) and C$H_{\text{alkene}}$(nbd)], 4.19−4.26 [m, 1H, C$H_{\text{head of bridge}}$(nbd)], 4.82−4.95 (m, 1H, CHOP), 5.59−5.68 (m, 1H, CH_{alkene}(nbd)), 6.12−6.19 (m, 1H, CH_{alkene}(nbd)), 6.45−6.54 (m, 1H, CH_{alkene}(nbd)), 6.90 (d, *J* = 8.8 Hz, 1H, H_{arom}), 7.06−7.63 (m, 26H, H_{arom}), 7.70 (d, *J* = 8.8 Hz, 1H, H_{arom}), 7.79 (d, *J* = 8.8 Hz, 1H, H_{arom}), 7.97 (d, *J* = 8.3 Hz, 1H, H_{arom}), 8.12 (d, *J* = 8.3 Hz, 1H, H_{arom}), 8.30 (d, *J* = 8.8 Hz, 1H, H_{arom}); $^{13}C\{^1H^{31}P\}$ NMR (125 MHz, CD_2Cl_2) δ 25.8 (CH_2(PCy_2)), 26.4 (CH_2(PCy_2)), 26.6 (CH_2(PCy_2)), 26.9 (2CH_2(PCy_2)), 27.2 (CH_2(PCy_2)), 28.3 (CH_2(PCy_2)), 28.6 (CH_2(PCy_2)), 30.6 (CH_2(PCy_2)), 34.7 (CH_2(PCy_2)), 35.5 (CH(PCy_2)), 36.6 (CH(PCy_2)), 37.5 (CHPCy_2), 55.6 (C$H_{\text{headofbridge}}$(nbd)), 55.7 (C$H_{\text{headofbridge}}$(nbd)), 62.3 (CH_2OCPh_3), 73.0 (CH_2(nbd)), 80.8 (CH_{alkene}(nbd)), 81.1 (CHOP), 87.6 ($OCPh_3$), 90.1 (CH_{alkene}(nbd)), 101.5 (CH_{alkene}(nbd)), 104.5 (CH_{alkene}(nbd)), 120.3 (CH_{arom}), 120.5 (CH_{arom}), 122.0 ($C_{q\ \text{arom}}$−(O)$C_{q\ \text{arom}}$), 122.8 ($C_{q\ \text{arom}}$−(O)$C_{q\ \text{arom}}$), 126.0 (CH_{arom}), 126.3 (CH_{arom}), 126.5 (CH_{arom}), 126.9 (CH_{arom}), 127.0 (CH_{arom}), 127.2 (CH_{arom}), 127.4 (CH_{arom}), 127.8 (CH_{arom}), 128.0 (CH_{arom}), 128.2 (CH_{arom}), 128.4 (CH_{arom}), 128.5 (CH_{arom}), 128.6 (CH_{arom}), 128.9 (CH_{arom}), 131.0 (CH_{arom}), 131.6 (CH_{arom}), 131.9 ($C_{q\ \text{arom}}$), 132.0 ($C_{q\ \text{arom}}$), 132.1 ($C_{q\ \text{arom}}$), 132.2 ($C_{q\ \text{arom}}$), 132.5 ($C_{q\ \text{arom}}$), 143.1 ($C_{q\ \text{arom}}$), 146.4 ($C_{q\ \text{arom}}$−O), 146.4 ($C_{q\ \text{arom}}$−O); $^{31}P\{^1H\}$ NMR (162 MHz, CD_2Cl_2) δ 36.9 (dd, $^1J_{P-Rh}$ = 140.7 Hz, $^2J_{P-P}$ = 60.4 Hz, 1P, *P*−C), 141.0 (dd, $^1J_{P-Rh}$ = 273.6 Hz, $^2J_{P-P}$ = 60.4 Hz, 1P, *P*−O); $^{11}B\{^1H\}$ NMR (128 MHz, CD_2Cl_2) δ −1.16 (s, BF_4^-); $^{19}F\{^1H\}$ NMR (376 MHz, CD_2Cl_2) δ −152.8 (s, BF_4); HRMS (ESI$^+$): *m*/*z* $[M - BF_4]^+$ calcd for $C_{66}H_{66}O_4P_2Rh$ 1099.3491, found 1099.3555.

General Procedure for the Rh-Mediated Asymmetric Hydrogenations. A solution of the required amount of [Rh(nbd)(*P*-*OP*)]BF_4 (**8a**,**b**; 0.04−2.0 mol %) and the corresponding functionalized alkene among substrates **9**−**14** (0.10 mmol) in anhydrous and degassed THF or DCM (0.50 mL) was prepared inside a glass vessel under an N_2 atmosphere in a glovebox. In all cases the molar concentration of a given substrate in the reaction medium was adjusted to 0.20 M. Once the reaction mixture had been loaded, the glass vessel was then placed into one of the holes of a steel autoclave reactor (HEL Cat-24 parallel pressure multireactor). The autoclave was purged three times with H_2 gas at 10 atm, and finally, the autoclave was pressurized under 20 atm of H_2 gas. The reaction mixture was stirred at room temperature for 18 h (overnight reaction). The autoclave was subsequently depressurized slowly, and further the reaction mixture was filtered through a short pad of SiO_2 and eluted with EtOAc (1.0 mL). The resulting solution was concentrated under vacuum, and thus the conversion was determined by ^1H NMR analysis and the enantiomeric excess was determined by GC or HPLC analysis on using chiral stationary phases.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text and figures giving experimental procedures, analytical and spectral characterization data for ligand precursors, substrates, and products, analysis data for the enantioselectivities of hydrogenation products, and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Reaction under pressure carried out safely inside an Ace pressure tube.

(9) Dicyclohexylphosphine-phosphites **7a,b** proved to be highly sensitive to oxidation by air and, as a consequence, once formed and after a simple workup, **7a,b** were immediately used as crude compounds without purification by column chromatography. Fortunately, the corresponding rhodium complexes were cleanly formed from those crude compounds and these were stable in air, which provided great operational convenience for handling.
(10) See the Experimental Section for details.
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