RESEARCH ARTICLE doi.org/10.1002/adsc.202301358 Advanced Synthesis & Catalysis

Chiral 1-Phosphabarrelene-Pyridines as Suitable Ligands for the Rh/Ir-Catalyzed Asymmetric Hydrogenation of Olefins

Joan Saltó,+a Daniel Tarr,+a Andrey Petrov,b Dorian Reich,b Manuela Weber,b
Maria Biosca,a,* Oscar Pàmies,a Christian Müller,b,* and Montserrat Diéguez a,*

[a] Universitat Rovira i Virgili, Departament de Química Física i Inorgànica, C/Marcel·lí Domingo, 1, 43007 Tarragona, Spain
Tel: +34-977558780
Fax: +34-977559563
E-mail: maria.biosca@urv.cat; montserrat.dieguez@urv.cat
[b] Institut für Chemie und Biochemie, Freie Universität Berlin, Fabeckstrasse 34/36, 14195 Berlin, Germany
Tel: +49-3083854004
E-mail: c.mueller@fu-berlin.de

[+] These authors contributed equally to this study.

Manuscript received: November 23, 2023; Revised manuscript received: December 14, 2023;
Version of record online: ■■, ■■

Dedicated to Miquel A. Pericàs for his distinguished career and also for establishing the Institut Català d'Investigació Química (ICIQ) as one of the top centers in the world, on the occasion of his retirement from the ICIQ.

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202301358

Abstract: Herein, we report the synthesis of chiral phosphabarrelene-pyridine ligands. Their synthesis benefit from modified reaction conditions to overcome the low yields normally associated with the [4+2] cycloaddition reaction of phosphinines with hexafluoro-2-butyne, which is a key to install the P-stereocenter in the phosphabarrelene. Their potential as chelating ligands in asymmetric catalysis was assessed in the Rh- and Ir-catalyzed hydrogenation of cyclic β-enamides and β-dehydroamino acid derivatives. The catalytic system containing a *tert*-butyl substituent at the *ortho* position of the phosphabarrelene moiety successfully hydrogenates a range of cyclic β-enamides (ee's between 92% to 94%) and β-dehydroamino acid derivatives (ee's between 93% to 95%). Moreover, the reactions can be carried out in the environmentally friendly 1,2-propylene carbonate as solvent with no loss of enantioselectivity. Mechanistic studies with the Rh/P,N catalytic systems agree with the Landis-Halpern mechanism and explain the influence of the substituent at the phosphabarrelene on enantioselectivity. Finally, the hydrogenation reactions can be carried out at large scale maintaining high enantioselectivities.

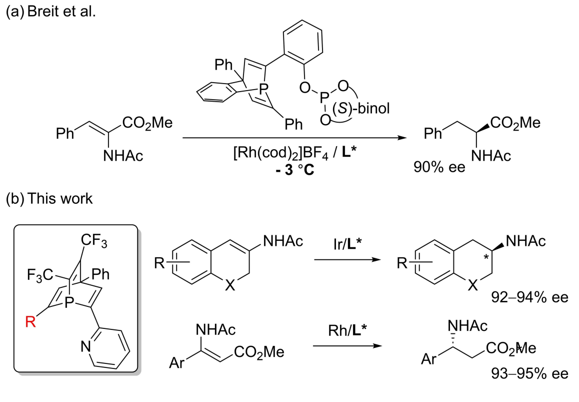
Keywords: Phosphabarrelene; bidentate P,N ligands; asymmetric hydrogenation; olefins; mechanistic insights

Introduction

Asymmetric metal-mediated catalysis has become one of the most important and sustainable tools to produce enantioenriched compounds.[1] Its presence in industry has been gaining preference over the years as the list of manufactured enantiopure drugs, agrochemicals and fine chemicals has been continuously growing.[1] In order to obtain improved levels of reactivity and selectivity in catalytic enantioselective reactions, various reaction parameters must be considered and optimized. Among these parameters, the design and selection of the chiral ligand is regarded as one of the most relevant.[2] Hence, the synthesis of new types of chiral ligands remains crucial to advance the development of catalytic systems.

During the last two decades, 1-phosphabarrelenes have emerged as a new class of ligands for homogeneous catalysis. They have been successfully applied in non-chiral catalytic reactions such as hydroformylation of internal alkenes, Suzuki-Miyaura couplings of aryl chlorides and hydrosilylation, among others.[3] For example, monodentate phosphabarrelenes were applied in the Rh-catalyzed hydroformylation of poorly reactive internal alkenes with excellent activity and surprisingly low alkene isomerization.[3a] Compared to classical phosphines, the special unique features of phosphabarrelenes include a rigid [2,2,2] bicyclic scaffold, a higher s-character of the phosphorus lone pair, along with a π-acceptor character and the possibility to generate a P-stereogenic center in a straightforward manner. All these distinctive attributes make them very appealing also for asymmetric catalysis. However, to the best of our knowledge there is only one report from 2006 about the use of chiral phosphabarrelenes by Breit and co-workers.[4] They reported the use of chiral monophosphabarrelene and bidentate phosphabarrelene-phosphite ligands in the asymmetric hydrogenation of benchmark substrates, such as dimethyl itaconate and α-dehydroamino acid derivatives. Whereas the use of Rh-catalyst precursors with monodentate phosphabarrelenes led to low enantiocontrol, the bidentate phosphabarrelene-phosphite analogues led to enantioselectivities up to 90% ee in the reduction of methyl 2-acetamidoacrylate, although at low temperature (−3 °C) (Scheme 1a).

Chiral bidentate ligands have played a dominant role in the field of asymmetric metal-mediated catalysis. Among them, phosphorus-nitrogen-based compounds (P,N) have emerged as powerful ligands, since the different electronic and steric properties of the heteroatoms can efficiently guide stereocontrol.[5] In addition, catalyst optimization is facilitated since both functionalities can be independently modified. In 2019 one of us reported the synthesis and coordination chemistry of a racemic pyridyl-substituted 1-phosphabarrelene (Scheme 1, R = Ph).[6] In a continuation of this work, we report here the synthesis of chiral 1-phosphabarrelene-pyridine ligands, that differ in the substituent at the *ortho* position of the phosphabarrelene moiety. They combine the advantages of heterodonor ligands and phosphabarrelenes, and benefit from having a stereogenic center close to the metal center. We also report their coordination chemistry towards Rh(I) and Ir(I) and their application in the asymmetric hydrogenation of several β-dehydroamino acid derivatives as well as a range of elusive cyclic β-enamides (Scheme 1b).



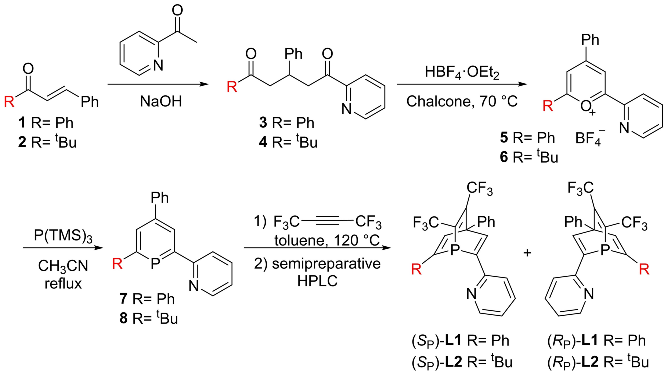
Scheme 1. (a) Precedents in the asymmetric hydrogenation of olefins with chiral bidentate heterodonor 1-phosphabarrelene containing ligands. (b) This work: chiral 1-phosphabarrelene-pyridine ligands for reduction of β-dehydroamino acid derivatives and cyclic β-enamides.

Results and Discussion

Synthesis of Chiral 1-Phosphabarrelene-Pyridine Ligands L1 and L2

Following the methodology reported by the group of Müller for the preparation of the racemic 1-phosphabarrelene-pyridine ligand **L1**,[6] we prepared its chiral version and also the new chiral 1-phosphabarrelene-pyridine ligand **L2**, that differs in a *tert*-butyl group at the *ortho* position of the phosphabarrelene moiety (Scheme 2).

The synthesis consists of only four steps. First, diketone derivatives **3** and **4** were prepared in good yields by condensation of the corresponding chalcone derivatives **1** and **2** with 2-acetylpyridine. Following this, the reaction of **3** and **4** with $HBF_4 \cdot OEt_2$ gave the corresponding pyrylium salts **5** and **6** after recrystallization. Subsequent reaction with $P(TMS)_3$ afforded the desired phosphinine-pyridines **7** and **8** after flash chromatography. Next, the [4 + 2] cycloaddition reaction of **7** and **8** with hexafluoro-2-butyne provided access to the racemic phosphabarrelenes **L1** and **L2**.

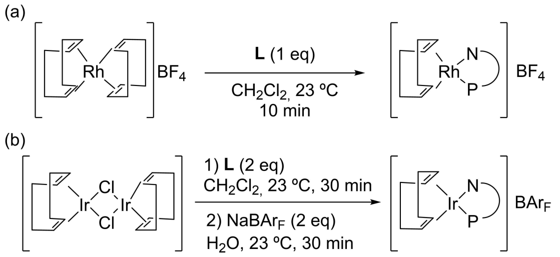


Scheme 2. General procedure for the synthesis of chiral 1-phosphabarrelene-pyridine ligands **L1** and **L2**.

The preparation of the racemic phenyl derivative of 1-phosphabarrelene-pyridine was previously reported using methylcyclohexane as solvent at 85 °C. However, after recrystallization, only a yield of 16% was reached.[6] Upon changing the solvent to toluene, we now found that the conversion increased to 80% with an isolated yield of 61% when the temperature was additionally increased to 120 °C.[7] Those optimized conditions were used for the preparation of the related ^{t}Bu-substituted 1-phosphabarrelene derivative **L2**. We could perform the Diels-Alder reaction of phosphinine-pyridine **8** with hexafluoro-2-butyne to afford the corresponding racemic 1-phosphabarrelene-pyridine ligand **L2** in 55% yield. Finally, resolution of racemic 1-phosphabarrelene-pyridines **L1** and **L2**, was achieved using semipreparative chiral HPLC.[8] The assignment of the absolute configuration of the enantiomers of **L1** and **L2** has been realized by means of circular dichroisms of enantiopure samples and was further confirmed by single crystal X-ray diffraction of enantiopure samples of **L2** (see Supporting information).

Synthesis of Rh- and Ir-Based Catalyst Precursors

For the preparation of the required [Rh(cod)**L**]BF_4 complexes, we followed the methodology reported by the group of Müller[6] for the preparation of the analogous racemic coordination compound with *rac*-**L1**. Thus, reaction of [Rh(cod)$_2$]BF_4 (cod = 1,5 cyclooctadiene) with one equivalent of enantiopure ligands **L1** and **L2**, as well as racemic ligand **L2** yielded in dichloromethane the corresponding catalyst precursors as yellow powders in almost quantitative yield after adding pentane (Scheme 3a). The Ir(I)-complexes were prepared in a one-pot procedure by reaction of the ligand with [Ir(μ-Cl)cod]$_2$ and subsequent chloride abstraction with sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (NaBAr$_F$). The coordination compounds [Ir(cod)**L**]BAr$_F$ (**L** = **L1**–**L2**) were isolated in high yields as red-orange solids after flash chromatography (Scheme 3b). Note that the preparation and purification of the Ir(I) complexes should be strictly performed in the dark, as the coordination compounds are sensitive towards light.



Scheme 3. General procedure for the synthesis of [Rh(cod)**L**]BF_4 and [Ir(cod)**L**]BAr$_F$ complexes.

The NMR spectra showed the typical resonances for these C_1-symmetric complexes. For example, a quadruplet at approximately $\delta = -15$ ppm were observed for all Ir-complexes in the $^{31}P\{^1H\}$ NMR spectra, whereas for the Rh-complexes, the same signal appears as a doublet of quartets. The HRMS-ESI spectra are in agreement with the assigned structures, displaying the heaviest ions at the m/z value, which corresponds to the loss of the BF_4 and BAr$_F$ anions from the parent molecular species.

We were able to obtain crystals suitable for X-ray diffraction of the rhodium complex containing *rac*-**L2** by slow diffusion of toluene into a solution of the complex in fluorobenzene (Figure 1). The crystallographic characterization of this compound clearly indicates the mononuclear nature and confirms that the expected coordination compound has been formed with a bidentate coordination of the P,N ligand through both donor atoms. The geometry of the metal center is slightly distorted square planar (P1–Rh1–C29: 154.1°, P1–Rh1–C28: 169.1°, N1–Rh1–C25: 154.2°, N1–Rh1–C32: 168.7°, C25–Rh1–C28: 78.9°, C29–Rh1–C32: 80.7°).

[Rh(cod)(*rac*-**L2**)]BF_4 can be compared with the analogous complex containing *rac*-**L1** as ligand and selected bond angles are shown in Table 1. For the complex Rh/**L2**, we could observe a more open C(1)–P(1)–C(5) angle whereas the C1–P(1)–Rh(1) angle decreased. This indicates that the presence of the *tert*-butyl pushes the remaining part of the molecule slightly towards the pyridine group. Additionally we found that the P(1)–Rh(1) distance in Rh/**L2** is with

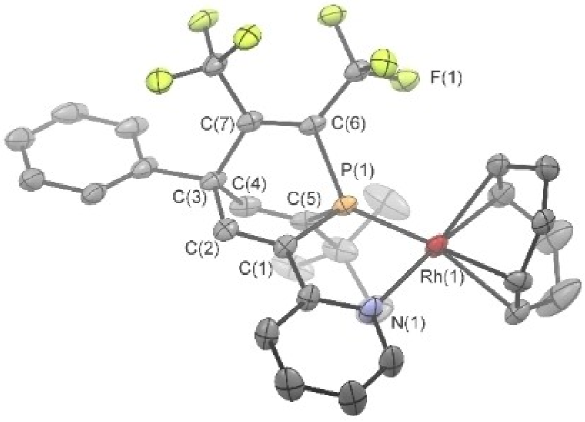


Figure 1. Molecular structure of [Rh(cod)(*rac*-**L2**)]BF_4 in the crystal. Hydrogen atoms and the BF_4 anion are omitted for clarity. Selected bond lengths (Å): P(1)–C(1): 1.832(4); P(1)–C(5): 1.858(4); P(1)–C(6): 1.850(4); C(1)–C(2): 1.327(5); C(2)–C(3): 1.535(5); C(3)–C(4): 1.544(6); C(4)–C(5): 1.329(6); C(3)–C(7): 1.554(6); P(1)–Rh(1): 2.2842(10); N(1)–Rh(1): 2.161(4).

Table 1. Selected structural data of complexes [Rh(cod)(*rac*-**L1/L2**)]BF_4.

Angle (°)	[Rh(cod)**L2**]BF_4	[Rh(cod)**L1**]BF_4[6]
C(1)–P(1)–C(5)	98.1	97.2
C(6)–P(1)–C(1)	97.2	98.9
C(6)–P(1)–C(5)	95.5	91.9
P(1)–Rh(1)–N(1)	81.7	81.6
C(6)–P(1)–Rh(1)	128.3	128.3
C(1)–P(1)–Rh(1)	101.8	104.5

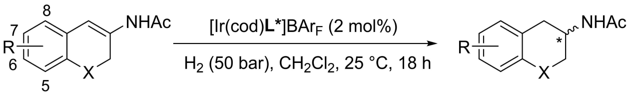
2.2842(10) Å significantly larger than in the Ph-derivative (2.240 Å). This difference should have an impact on catalysis (*vide infra*).

Application in Asymmetric Hydrogenation of Olefins

Asymmetric hydrogenation is one of the most widely used transformations to introduce chirality into a molecule. Its perfect atom economy and operational simplicity have paved the way to industrial applications for the large-scale synthesis of pharmaceutically active ingredients and agrochemicals, among others.[1,9] To evaluate the potential of the new chiral ligands, we have chosen the hydrogenation of cyclic β-enamides and β-dehydroamino acid derivatives, since they give access to important building blocks for preparing drugs.

We started our study with the asymmetric hydrogenation of cyclic β-enamides whose products are key units in many drugs and biologically active natural products such as robalzotan, alnespirone and rotigotine.[10] Their hydrogenation has been dominated by Rh- and Ru-catalysts.[11] However, in contrast to the hydrogenation of α-enamides, most of the catalysts for β-enamides provide a low enantioselectivity. More recently, Ir-catalysts have also shown to be appropriate for the reduction of the elusive cyclic β-enamides.[12,13] In this respect, we first applied both, Rh- and Ir-catalyst precursors in the hydrogenation of the benchmark *N*-(3,4-dihydronaphthalen-2-yl)acetamide, using the optimal reaction conditions found in previous studies.[12c] While the use of Rh-catalyst precursors led to very poor enantioselectivities (up to 10% ee, see Supporting Information), the Ir-counterparts afforded high enantioselectivities at room temperature under 50 bars of H_2 (Table 2). In addition, we also found that the enantioselectivity is highly influenced by the phosphabarrelene substituent. Thus, the introduction of a bulky *tert*-butyl group in the ligand (**L2**) boosted the enantioselectivity to 95% (Table 2, entry 2 vs 1). Interestingly, the reaction could also be run under an H_2 pressure as low as 1 bar, while maintaining the high enantioselectivity (entry 2 vs 3). We then extended our work to the hydrogenation of other cyclic β-enamides (entries 4–9). Positively, the Ir/(S_P)-**L2** catalytic system was also very tolerant to variations in the substitution pattern of the fused benzene ring. A range of substituted cyclic β-enamides derived from β-tetralones were hydrogenated in excellent conversions and with high enantioselectivities (ee's ranging from 92% to 94%; entries 4–8). Among them, it should be noted the high enantioselectivity reached with *N*-(5-methoxy-3,4-dihydronaphthalen-2-yl)acetamide (entry 4), whose hydrogenated product is a key intermediate for the synthesis of rotigotine.[10a] A high enantioselectivity (93% ee, entry 9) was also reached in the reduction of the *N*-(2H-chromen-3-yl)acetamide, which provides a crucial intermediate for the synthesis of alnespirone.[10d]

Table 2. Ir-catalyzed asymmetric hydrogenation of cyclic β-enamides.[a]



Entry	L*	R	X	% Conv (% yield)[b]	% ee[c]
1	**(R_P)-L1**	H	CH_2	100	25 (*R*)
2	**(S_P)-L2**	H	CH_2	100 (96)	93 (*S*)
3[d]	**(S_P)-L2**	H	CH_2	100	91 (*S*)
4	**(S_P)-L2**	5-OMe	CH_2	100 (94)	92 (*S*)
5	**(S_P)-L2**	6-OMe	CH_2	100 (94)	94 (*S*)
6	**(S_P)-L2**	6-Br	CH_2	100 (92)	94 (*S*)
7	**(S_P)-L2**	7-OMe	CH_2	100 (92)	92 (*S*)
8	**(S_P)-L2**	8-OMe	CH_2	100 (91)	92 (*S*)
9	**(S_P)-L2**	H	O	100 (92)	93 (*R*)
10[e]	**(S_P)-L2**	H	CH_2	100	92 (*S*)

[a] Reactions carried out at 0.5 mmol scale using 2 mL of CH_2Cl_2.
[b] Conversions measured by ^{1}H-NMR. Isolated yields in parentheses.
[c] Enantiomeric excesses measured by HPLC.
[d] Reaction carried out at 1 bar of H_2.
[e] 1,2-Propylene carbonate as solvent.

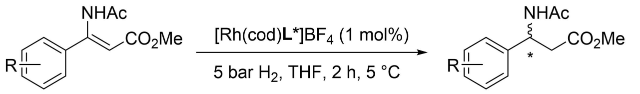
Encouraged by the results we also performed the reaction with 1,2-propylene carbonate[14] as a more environmental solvent than dichloromethane. Positively, high enantioselectivity was also obtained (Table 2, entry 10).

We then moved to the asymmetric hydrogenation of β-dehydroamino acid derivatives whose products are key units for the synthesis of natural products and pharmacologically important compounds (e.g. β-peptides and β-lactam antibiotics).[15] To evaluate the efficiency of Rh- and Ir-catalytic precursors, we focused on the hydrogenation of the challenging β-dehydroamino acid derivatives with *Z*-geometry, whose hydrogenation usually provides much lower enantioselectivities than their *E*-analogues.[9a,15d,16] In contrast to our results described above on the asymmetric hydrogenation of cyclic β-enamides, the use of Ir-catalyst precursors led to much lower activities and enantioselectivities (up to 15% ee, see Supporting Information) than those obtained with the Rh-analogues (Table 3). This is not surprising as the asymmetric hydrogenation of β-dehydroamino acid derivatives has been dominated by Rh-catalysts with diphosphine and monophosphoramidite ligands.[9a,15d,16] The effect of the solvent, hydrogen pressure and temperature in the Rh-catalyzed hydrogenation of methyl (*Z*)-3-acetamido-3-phenylacrylate indicated that it can be hydrogenated in only two hours with low hydrogen pressure (5 bars) and that enantioselectivities were maximized with THF as solvent (see Supporting Information). Results again indicate that a bulky *tert*-butyl substituent at the phosphabarrelene ligand improved substantially the enantioselectivity (up to 95% ee, entry 2 vs 1).

We could extend the substrate scope by successfully reducing, with the Rh/**L2** system, a series of olefins containing different electronic and steric modifications at the phenyl ring of the substrate. Enantioselectivities between 93% to 95% ee were obtained regardless of the aromatic decoration (entries 3–6). With the aim of making the process more sustainable, the reaction was run in MeTHF (entry 7) and 1,2-propylene carbonate (entry 8). In this way, enantioselectivities as high as those observed with THF were found with both solvents.[14]

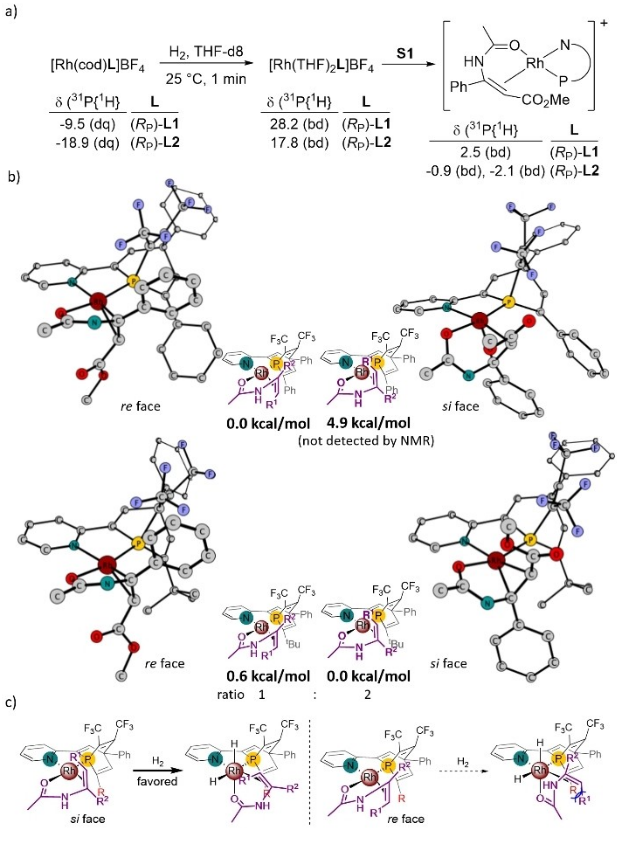
Because the Rh-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives is dominated by the use of chelating P,P-donor ligands,[9a,15d,16] we found interesting to study the mechanism with this new type of Rh/P,N catalytic system. We first studied the oxidative addition of H_2 to the [Rh(cod)**L**]BF_4 (**L** = (R_P)-**L1** and (R_P)-**L2**) catalyst precursors, either by bubbling H_2 into the solution, or under 5 bars of H_2 using a high-pressure NMR tube. In all cases the formation of a [Rh(cod)**L**H_2]$^+$ complex was not detected even at low temperature. However, at room temperature, fast hydrogenation of 1,5-cyclooctadiene was observed with the concomitant formation of the species [Rh(THF)$_2$**L**]$^+$ (Scheme 4a). After addition of methyl (*Z*)-3-acetamido-3-phenylacrylate (**S1**), the complexes [Rh(**S1**)**L**]$^+$ were formed (Scheme 4a). The downfield shift of the ^{31}P{^{1}H} signals of [Rh(**S1**)**L**]$^+$ is consistent with the formation of diastereoisomers with the phosphobarrelene *trans* to the substrate C=O fragment. The NMR spectra also show an effect of the phosphabarrelene substituent on the ratio of the diastereoisomers. Thus, whereas the formation of a single diastereomeric [Rh(**S1**)**L**]$^+$ species was observed for (R_P)-**L1**, the use of (R_P)-**L2** led to a diastereomeric mixture in a ratio of approximately 2:1. DFT calculations are in agreement with the diastereoisomeric populations and provided a 3D structure of the key intermediates (Scheme 4b and Supporting Infor-

Table 3. Rh-catalyzed asymmetric hydrogenation of β-dehydroamino acids.[a]



Entry	L*	R	% Conv (% yield)[b]	% ee[c]
1	**(R_P)-L1**	H	100	7 (*S*)
2	**(S_P)-L2**	H	100 (95)	95 (*R*)
3	**(S_P)-L2**	*p*-CF_3	100 (96)	95 (*R*)
4	**(S_P)-L2**	*p*-OMe	100 (94)	94 (*R*)
5	**(S_P)-L2**	*m*-OMe	100 (94)	95 (*R*)
6	**(S_P)-L2**	*o*-OMe	100 (97)	93 (*R*)
9[d]	**(S_P)-L2**	H	100	95 (*R*)
10[e]	**(S_P)-L2**	H	100	95 (*R*)

[a] Reactions carried out at 0.5 mmol scale using 2 mL of THF.
[b] Conversions measured by GC. Isolated yields in parentheses.
[c] Enantiomeric excesses measured by GC or HPLC.
[d] Me-THF as solvent.
[e] 1,2-Propylene carbonate as solvent.



Scheme 4. a) Detected intermediates for the Rh-catalyzed hydrogenation of methyl (*Z*)-3-acetamido-3-phenylacrylate (**S1**). ^{31}P{^{1}H} chemical shifts for each of the intermediates are shown. b) DFT structures and energies of the [Rh(**S1**)(R_P)-**L**]$^+$ intermediates (R^1 = Ph; R^2 = CO_2Me). c) Rotation mechanism upon oxidative addition.

mation), where the most stable intermediate of [Rh-(**S1**)(R_P)-**L1**]$^+$ contains the olefin coordinated through the *re* face, while in [Rh(**S1**)(R_P)-**L2**]$^+$ the coordination through the *si* face is favored.

Under hydrogenation conditions, the presence of the hydride [Rh(**S1**)**L**H_2]$^+$ was not observed in the ^{1}H NMR spectrum. All these data suggest that the oxidative addition of H_2 to the [Rh(substrate)**L**]$^+$ species is the rate determining step, which is consistent with the Landis-Halpern mechanism.[17] To further support this conclusion, we carried out several kinetic experiments. In agreement with the Landis-Halpern mechanism, the hydrogenation was 0th order in substrate concentration and 1st order in catalyst concentration and hydrogen pressure (Table 4 and Figure 2).

According to the Landis-Halpern mechanism, the enantioselectivity is mainly dictated by the different rate of the hydrogen oxidative addition for both diastereoisomers. In addition, to accommodate the coordination of the dihydrogen in a *cis* fashion, the carbonyl fragment of the substrate migrates, which is accompanied by a concomitant rotation of the alkene fragment (Scheme 4c).[18] The structure of our [Rh-(**S1**)(R_P)-**L**]$^+$ intermediates for both ligands clearly suggests that the oxidative addition from the top of the complex is favored. This, and the fact that the alkene coordinates *cis* to the sterically demanding phosphabarrelene moiety (Scheme 4a–b) favors the alkene rotation from the diastereoisomer with the substrate coordinated through the *si* face (Scheme 4c), because the rotation through the *re* faced diastereoisomer is disfavored due to a steric clash between the phosphabarrelene substituent and the ester group of the substrate. This, together with the fact that the most reactive diastereoisomer is the most abundant for the Rh/**L2** catalytic system, explains the higher enantioselectivity of the Rh/**L2** catalytic system over the Rh/**L1**.

Table 4. Kinetic data for the hydrogenation of methyl (*Z*)-3-acetamido-3-phenylacrylate catalyzed by [Rh(cod)**L1**]BF_4 in THF.

[Rh(cod)**L1**]BF_4[a]	PH_2[b]	TOF[c]
0.002	5	51
0.002	1	10.5
0.002	10	107
0.001	5	27.5
0.004	5	103

[a] Concentration in $mol \cdot l^{-1}$.
[b] Pressure in bar.
[c] Initial TOF measured in $mol \cdot molRh^{-1} \cdot h^{-1}$.

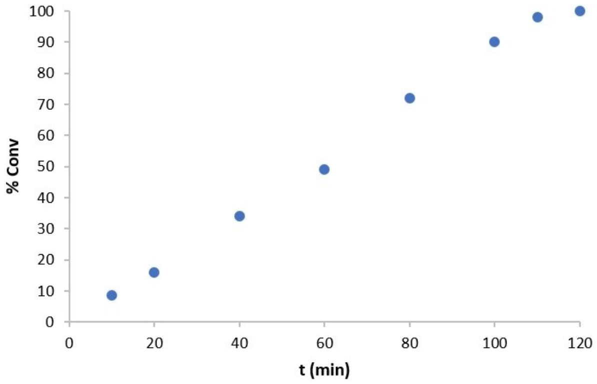
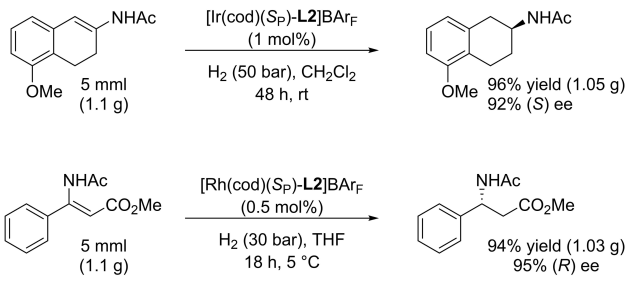


Figure 2. Hydrogenation of methyl (*Z*)-3-acetamido-3-phenylacrylate.

Finally, to validate the potential utility of these Ir/(S_P)-**L2** and Rh/(S_P)-**L2** catalyst precursors, we performed the hydrogenation of *N*-(5-methoxy-3,4-dihydronaphthalen-2-yl)acetamide and methyl (*Z*)-3-acetamido-3-phenylacrylate at 5 mmol scale and at low catalyst loading (Scheme 5).

Conclusion

In conclusion, we have discovered a chiral phosphabarrelene-pyridine ligand, which contains a *tert*-buthyl substituent on the phosphabarrelene moiety, that has been successfully applied in the Rh-/Ir-catalyzed hydrogenation of several β-dehydroamino acid derivatives and a range of elusive cyclic β-enamides (ee's between 92 to 94%). The ligand combines the advantages of heterodonor ligands and phosphobarrelenes, and benefits from having a stereogenic center close to the metal center. It is synthetized in four steps from available starting sources. The synthesis was optimized to overcome the low yields associated to the [4+2] cycloaddition reaction of phosphinine intermediates with hexafluoro-2-butyne, which is a key step to install the phosphabarrelene P-stereocenter. This allowed us to obtain several grams of the *rac*-phosphabarrelene-pyridine ligand in a single batch, which were successfully deracemized by semipreparative chiral HPLC. In addition, the corresponding Rh- and Ir-complexes are obtained as air stable solids, which are easy to manipulate. Finally, the applicability



Scheme 5. Practical synthesis of (*S*)-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide and methyl (*R*)-3-acetamido-3-phenylpropanoate.

of these new Ir/Rh–P,N catalysts has been further tested in the environmentally friendly propylene carbonate and by carrying out the hydrogenation at large scale, maintaining the high enantioselectivities. These results pave the way for the development of new chiral 1-phosphabarrelene-pyridine ligands that are readily available and simple-to-synthesize, for their application to synthetically relevant asymmetric processes.

Experimental Section

General Procedure for the Preparation of 1-Phosphabarrelene-Pyridine Ligands L1 and L2

A solution of the corresponding phosphine-pyridine (12.8 mmol) in toluene (25 ml) was degassed 3 times under freeze-pump cycles. After that, the flask was immersed into a liquid N_2 bath and hexafluorobutyne (3.7 g, 23 mmol) were condensed into the reaction flash. Then, the reaction mixture was allowed to reach room temperature and stirred at 120 °C for 3 days. After that, the solvent was evaporated and reaction mixture was purified by flash chromatography (gradient 300:1 to 5:1 hexanes:EtOAc) to afford the corresponding ligands as a pale yellow solid.

***rac*-L1**: Yield: (3.8 g, 61%).[6] Enantiomers separated by semipreparative HPLC using Chiracel OD-H column (90% hexane/2-propanol). t_R 5.6 min (*R*); t_R 6.5 min (*S*).

***rac*-L2**: Yield: (3.3 g, 55%). Crystals suitable for X-ray diffraction for (R_P)-**L2** were obtained by diffusion of toluene into a fluorobenzene solution (CCDC 2308686). Enantiomers separated by semipreparative HPLC using Chiracel OD-H column (99% hexane/2-propanol). t_R 8.8 min (*S*); t_R 9.6 min (*R*).

General Procedure for the Preparation of [Rh(cod)L]BF$_4$ Catalyst Precursors

To a solution of $Rh(cod)_2BF_4$ (40.6 mg, 0.1 mmol) in CH_2Cl_2 (5 mL, the corresponding ligand (0.1 mmol) was added. The resulting solution was stirred for 15 min. Then, the crude was concentrated to ca 1 mL and the product was precipitated by adding cold pentane (10 mL). The solid was then filtered, washed with pentane (3×3 mL) and dried under vacuum to afford the corresponding complexes as yellow solids.

[Rh(cod)(*S*$_P$)-L1]BF$_4$: Yield: (75 mg, 96%).[6]

[Rh(cod)L2]BF$_4$: Yield: (74 mg, 98%). Crystals suitable for X-ray diffraction for [Rh(cod)(*rac*-**L2**)]BF_4 were obtained by diffusion of toluene into a fluorobenzene solution (CCDC 2308687).

General Procedure for the Preparation of [Ir(cod)L]BAr$_F$ Catalyst Precursors

To a light protected solution of $[Ir(\mu\text{-}Cl)(cod)]_2$ (25 mg, 0.037 mmol) in CH_2Cl_2 (2.5 mL), the corresponding ligand (0.074 mmol) was added. After stirring at room temperature for 30 min, $NaBAr_F$ (73 mg, 0.082 mmol) and degassed water (2.5 mL) were added. The biphasic mixture was stirred for a further 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2x2 mL). The combined organic phases were dried with $MgSO_4$, evaporated in vacuo and purified by flash column chromatography (neutral SiO_2, 100% CH_2Cl_2) to afford the corresponding Ir complexes as red-orange solids.

[Ir(cod)L1]BAr$_F$: Yield: (108 mg, 89%).

[Ir(cod)L2]BAr$_F$: Yield: (109 mg, 90%).

General Procedure for the Asymmetric Hydrogenation

The alkene (0.5 mmol) and the corresponding catalyst precursor were dissolved in the corresponding solvent (2 mL) and placed in a high-pressure autoclave. The autoclave was purged 4 times with hydrogen. Then, it was pressurized at the desired pressure. After the desired reaction time, the autoclave was depressurized and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 mL) and filtered through a short plug of silica. Conversions were determined by GC or ^1H NMR and the enantiomeric excesses were determined by GC or HPLC (see Supporting Information for details).

In Situ NMR Characterization Experiments

The *in situ* NMR experiments were carried out in an NMR tube by bubbling hydrogen to a THF-d8 solution of the corresponding complex and substrate at different reaction temperatures as well as in a sapphire NMR tube under hydrogen pressure (10 bars).

Acknowledgements

This work was supported by grants from FEDER/Ministerio de Ciencia e Innovación (MICINN)/AEI (PID2019-104904GB-I00 and PID2022-139996NB-I00) and from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 945413. Grant 2021SGR00163 funded by the Catalan Government are also gratefully acknowledged. C. M. is grateful to the German Research Foundation (DFG) for financial support. M. B. also thanks Ministerio de Ciencia e Innovación for a Juan de la Cierva fellowship.

References

[1] For books on asymmetric catalysis, see for example: a) R. Noyori in *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; b) E. N. Jacobsen, A. Pfaltz, H. Yamamoto in *Comprehensive Asymmetric Catalysis*, Springer-Verlag, Berlin, **1999**; c) B. Cornils, W. A. Herrmann, J.-H. Xu, H.-W. Zanthoff in *Catalysis from A to Z: A Concise Encyclopedia*, 5th ed., Wiley-VCH, Weinheim, **2019**; d) T. Akiyama, I. Ojima in *Catalytic Asymmetric Synthesis*, 4th ed., John Wiley & Sons, Inc., Hoboken, **2022**. For more specific reviews on the application of asymmetric catalysis on industry, see for instance: e) H.-U. Blaser, H.-J. Federsel, in *Asym-*

metric Catalysis in Industrial Scale: Challenges, Approaches and Solutions, 2nd ed., Wiley, Weinheim, **2010**; f) J. G. de Vries, *Account. Top. Catal.* **2014**, *57*, 1306–1317; g) H. U. Blaser, *Chimia* **2015**, *69*, 393–406; h) M. Biosca, M. Diéguez, A. Zanotti–Gerosa, *Adv. Catal.* **2021**, *68*, 341–384.

[2] For reviews, see for example: a) A. Börner in *Phosphorus ligands in Asymmetric Catalysis. Synthesis and applications*, Wiley-VCH, Weinheim, **2008**; b) W. Sommer, D. Weibel, *Sigma Aldrich's Chemfiles* **2008**, *8*, 1–91; c) Q.-L. Zhou in *Privileged Chiral Ligands and Catalysts* Wiley-VCH, Weinheim, **2011**; d) M. Diéguez in *Chiral Ligands. Evolution of Ligand Libraries for Asymmetric Catalysis*, CRC Press, **2021**.

[3] a) B. Breit, E. Fuchs, *Chem. Commun.* **2004**, 694–695; b) O. Piechaczyk, M. Doux, L. Ricard, P. Le Floch, *Organometallics* **2005**, *24*, 1204–1213; c) P. Le Floch, *Coord. Chem. Rev.* **2006**, *250*, 627–681; d) M. Fuchs, M. Keller, B. Breit, *Chem. Eur. J.* **2006**, *12*, 6930–6939; e) M. Blug, X.-F. Le Goff, N. Mézailles, P. Le Floch, *Organometallics* **2009**, *28*, 2360–2362; f) M. Blug, C. Guibert, X.-F. Le Goff, N. Mézailles, P. Le Floch, *Chem. Commun.* **2009**, 201–203; g) P. S. Bäuerlein, I. Arenas Gonzalez, J. J. M. Weemers, M. Lutz, A. L. Spek, D. Vogt, C. Müller, *Chem. Commun.* **2009**, 4944–4946; h) C. Müller, D. Vogt in *Catalysis and Material Science Applications* (Eds.: M. Peruzzini, L. Gonsalvi), Vol. 36, chapter 6, Springer, **2011**; i) C. Müller in *Phosphorus Ligand Effects in Homogeneous Catalysis: Design and Synthesis* (Eds.: P. C. J. Kamer, P. W. N. M van Leeuwen), Wiley-VCH, **2012**; j) M. Rigo, E. R. M. Habraken, K. Bhattacharyya, M. Weber, A. W. Ehlers, N. Mezailles, C. J. Nicolas, C. Mueller, *Chem. Eur. J.* **2019**, *25*, 8769–8779; k) J. A. Werra, K. Wurst, P. Löwe, F. Dielmann, *ChemPlusChem* **2023**, *88*, e202200458.

[4] B. Breit, E. Fuchs, *Synthesis* **2006**, *13*, 2121–2128.

[5] a) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336–345; b) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *101*, 4151–4202; c) G. C. Hargaden, P. J. Guiry, *Chem. Rev.* **2009**, *109*, 2505–2550; d) M. P. Carroll, P. J. Guiry, *Chem. Soc. Rev.* **2014**, *43*, 819–833; e) M. Biosca, O. Pàmies, M. Diéguez, *Catal. Sci. Technol.* **2020**, *10*, 613–624; f) J. C. Carretero, J. Adrio, M. Rodríguez Rivero in *Chiral Ferrocene in Asymmetric Catalysis* (Ed.: L.-X. Dai, X.-L. Hou), Wiley-VCH, Weinheim, **2010**, 257–282; g) J. Margalef, O. Pàmies, M. A. Pericàs, M. Diéguez, *Chem. Commun.* **2020**, *56*, 10795–10808; h) J. Margalef, M. Biosca, P. De La Cruz-Sánchez, J. Faiges, O. Pàmies, M. Diéguez, *Coord. Chem. Rev.* **2021**, *446*, 214120–214205; i) R. Connon, B. Roche, B. V. Rokade, P. J. Guiry, *Chem. Rev.* **2021**, *121*, 6373–6521; j) P. Rojo, A. Riera, X. Verdaguer, *Coord. Chem. Rev.* **2023**, *489*, 215192–215226.

[6] M. Bruce, M. Papke, A. W. Ehlers, M. Weber, D. Lentz, N. Mézailles, J. C. Slootweg, C. Müller, *Chem. Eur. J.* **2019**, *25*, 14332–14340.

[7] Reactions carried out at temperatures higher than 120 °C promoted a retro-Diels-Alder reaction with the regeneration of the starting phosphinine-pyridine compound.

[8] Racemate resolution via recrystallization of the diastereomeric mixture formed upon reaction with enantiopure acids (e.g. (+)-camphor sulfonic acid) was not possible.

[9] For reviews, see for example: a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3070; b) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713–1760; c) Y. Zhu, K. Burgess, *Acc. Chem. Res.* **2012**, *45*, 1623–1636; d) P. Etayo, A. Vidal-Ferran, *Chem. Soc. Rev.* **2013**, *42*, 728–754; e) J. J. Verendel, O. Pàmies, M. Diéguez, P. G. Andersson, *Chem. Rev.* **2014**, *114*, 2130–2169; f) Z. Zhang, N. Butt, W. Zhang, *Chem. Rev.* **2016**, *16*, 14769–14827; g) C. Margarita, P. G. Andersson, *J. Am. Chem. Soc.* **2017**, *139*, 1346–1356; h) A. N. Kim, B. M. Stoltz, *ACS Catal.* **2020**, *10*, 13834–13851; i) M. Diéguez, A. Pizzano in *Metal-catalyzed Asymmetric Hydrogenation. Evolution and Prospect in Advances in Catalysis*, Elsevier, Oxford, Vol. 68, **2021**; j) A. Cabré, X. Verdaguer, A. Riera, *Chem. Rev.* **2022**, *122*, 269–339.

[10] a) D. Q. Pharm, A. Nogid, *Clin. Ther.* **2008**, *30*, 813–824; b) J. I. Osende, D. Shimbo, V. Fuster, M. Dubar, J. J. Badimon, *J. Thromb. Haemostasis* **2004**, *2*, 492–497; c) S. B. Ross, S.-O. Thorberg, E. Jerning, N. Mohell, C. Stenfors, C. Wallsten, I. G. Milchert, G. A. Ojteg, *CNS Drug Rev.* **1999**, *5*, 213–232; d) B. Astier, L. Lambás Señas, F. Soulière, P. Schmitt, N. Urbain, N. Rentero, L. Bert, L. Denoroy, B. Renaud, M. Lesourd, C. Muñoz, G. Chouvet, *Eur. J. Pharmacol.* **2003**, *459*, 17–26.

[11] a) J. L. Renaud, P. Dupau, A.-E. Hay, M. Guingouain, P. H. Dixneouf, C. Bruneau, *Adv. Synth. Catal.* **2003**, *345*, 230–238; b) X.-B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 1245–1249; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223–1227; c) M. Revés, C. Ferrer, T. León, S. Doran, P. Etayo, A. Vidal-Ferran, A. Riera, X. Verdaguer, *Angew. Chem.* **2010**, *122*, 9642–9645; *Angew. Chem. Int. Ed.* **2010**, *49*, 9452–9455; d) Z. Wu, T. Ayad, V. Ratovelomanana-Vidal, *Org. Lett.* **2011**, *13*, 3782–3785; e) I. Arribas, M. Rubio, P. Kleman, A. Pizzano, *J. Org. Chem.* **2013**, *78*, 3997–4005; f) G. Liu, X. Liu, Z. Cai, G. Jiao, G. Xu, W. Tang, *Angew. Chem.* **2013**, *125*, 4329–4332; *Angew. Chem. Int. Ed.* **2013**, *52*, 4235–4238.

[12] a) E. Salom, S. Orgué, A. Riera, X. Verdaguer, *Angew. Chem.* **2016**, *128*, 8120–8124; *Angew. Chem. Int. Ed.* **2016**, *55*, 7988–7992; b) M. Magre, O. Pàmies, M. Diéguez, *ACS Catal.* **2016**, *6*, 5186–6005; c) J. Margalef, O. Pàmies, M. Diéguez, *Chem. Eur. J.* **2017**, *23*, 813–822; d) M. Biosca, M. Magre, O. Pàmies, M. Diéguez, *ACS Catal.* **2018**, *8*, 10316–10320.

[13] Very recently an example on the Co-catalyzed hydrogenation of β-enamides has also been reported. T. Chen, Y. Zou, Y. Hu, Z. Zhang, H. Wei, L. Wei, W. Zhang, *Angew. Chem.* **2023**, *135*, e202303488; *Angew. Chem. Int. Ed.* **2023**, *62*, e202303488.

[14] Propylene carbonate has become a “green” alternative to standard organic solvents because of its high boiling point, low toxicity and environmentally friendly synthesis. B. Schäffner, F. Schäffner, S. P. Verevkin, A. Börner, *Chem. Rev.* **2010**, *110*, 4554–4581.

[15] a) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219–3232; b) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide in *Enantioselective Synthesis of β-Amino Acids*, 2nd ed. (Eds.: E. Juaristi, V. Soloshonok), John Wiley & Sons, Hoboken, **2005**; c) B. Weiner, W. Szymanski, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2010**, *39*, 1656–1691; d) E. Forró, F. Fülöp, *Curr. Med. Chem.* **2012**, *19*, 6178–6187.

[16] a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3070; b) H.-J. Drexler, J. You, S. Zhang, C. Fisher, W. Baumann, A. Spannenberg, D. Heller, *Org. Process Res. Dev.* **2003**, *7*, 355–361; c) C. Bruneau, J. L. Renaud, T. A. Jerphagnon, *Coord. Chem. Rev.* **2008**, *252*, 532–544.

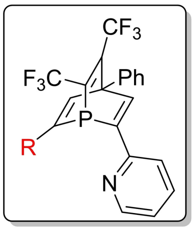
[17] a) C. R. Landis, J. Halpern, *J. Am. Chem. Soc.* **1987**, *109*, 1746–1754; b) J. M. Brown, P. A. Chaloner, G. A. Morris, *J. Chem. Soc. Chem. Commun.* **1983**, 644–646; c) J. M. Brown, P. L. Evans, *Tetrahedron Lett.* **1988**, *44*, 4905–4916; d) P. L. Bodgan, J. J. Irwin, B. Bosnich, *Organometallics* **1989**, *8*, 1450–1453; e) D. G. Allen, S. B. Wild, D. L. Wood, *Organometallics* **1986**, *5*, 1009–1015; f) J. M. Brown, P. J. Maddox, *J. Chem. Soc. Chem. Commun.* **1987**, 1278; g) J. M. Brown, P. A. Chaloner, G. A. Morris, *J. Chem. Soc. Perkin Trans. 2* **1987**, 1583–1588; h) B. M. McCulloch, J. T. Halpern, M. R. Thompson, C. R. Landis, *Organometallics* **1990**, *9*, 1392–1395; i) J. M. Brown, *Chem. Soc. Rev.* **1993**, *22*, 25–41; j) C. R. Landis, T. W. Brauch, *Inorg. Chim. Acta* **1998**, *270*, 285–297; k) B. F. M. Kimmich, E. Somsook, C. R. Landis, *J. Am. Chem. Soc.* **1998**, *120*, 10115–10125; l) C. R. Landis, P. Hilfenhaus, S. Feldgus, *J. Am. Chem. Soc.* **1999**, *121*, 8741–8754; m) T. V. RajanBabu, B. Radetich, K. K. You, T. A. Ayers, A. L. Casalnuovo, J. C. Calabrese, *J. Org. Chem.* **1999**, *64*, 3429–3447.

[18] C. R. Landis, S. Feldgus, *Angew. Chem.* **2000**, *112*, 2985–2988; *Angew. Chem. Int. Ed.* **2000**, *39*, 2863–2866.

Chiral 1-Phosphabarrelene-Pyridines as Suitable Ligands for the Rh/Ir-Catalyzed Asymmetric Hydrogenation of Olefins

Adv. Synth. Catal. **2024**, *366*, 1 – 10

J. Saltó, D. Tarr, A. Petrov, D. Reich, M. Weber, M. Biosca*, O. Pàmies, C. Müller*, M. Diéguez*



- Rigid [2,2,2] bicyclic scaffold
- Increasing s-character of the P lone pair
- π-acceptor character
- P-stereogenic center