Pyrrolidine-based P,O ligands from carbohydrates: Easily accessible and modular ligands for the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins

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Abstract: The potential of P,O-iminosugar based ligands in the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins is presented. These new ligands were prepared from easily available carbohydrates (D-mannose, D-ribose and D-arabinose). The stereochemical and polyfunctional diversity of carbohydrates allowed the modulation of the ligands, both from their electronic properties and the rigidity of their backbone. High enantioselectivities (ee's up to 99%) can be reached in the hydrogenation of selected tri- and disubstituted substrates.

Introduction

Asymmetric metal-based catalysis offers some of the most efficient, sustainable and straightforward routes for synthesizing enantiomerically pure compounds.[1] These compounds play fundamental roles in pharmacy, agro-chemistry, fine chemistry and natural product chemistry. Among the metal-catalysed processes, the asymmetric hydrogenation (AH) of olefins has dominated both industry and academia for many years, mainly because of its high efficiency in transferring the chiral information from the catalyst to the product, its perfect atom economy and its operational simplicity.[1] In this field, the AH of functionalized olefins (e.g. enamides, dehydroamino acid derivatives, …)[2] is dominated by Rh- and Ru-diphosphine catalysts, while the reduction of minimally functionalized olefins (those without a highly coordinative group)[3] is mostly carried out with Ir-P-oxazoline catalysts. Compared with the AH of functionalized olefins, the reduction of minimally functionalized olefins is underdeveloped and thus has a limited synthetic utility. Although advances in catalyst design with new types of P,N-heterodonor ligands have been made, most catalysts are still specific for a certain olefin geometry and nature of the substrate. To overcome these problems, recent research has focused on the possibility of changing the N-donor atom in these heterodonor ligands by more stable and easier to prepare S- and O-donor functionalities.[4] In this respect, our group reported the first application of a P,thioether ligand family in this process[4b] and further improvements with new generations of P,tioether ligands.[4c-f] In 2011, Pfaltz and coworkers also demonstrated for the first time that phosphine,O ligands (Figure 1), that coordinate to the metal through the carbonyl oxygen atom and the phosphine moiety, can also be used in the AH of minimally functionalized olefins with results comparable to the most commonly used Ir-P-oxazoline catalysts.[4a] However, high enantioselectivities were obtained only for a few trisubstituted olefins and no results were reported for the more challenging disubstituted substrates. The results also showed that high enantioselectivities were obtained when substituents at both the phosphine group and the O-donor moiety were bulky. This is an important drawback because phosphines with bulky substituents are prepared from a much more expensive precursor, and they are much less stable than the commonly used diphenylphosphine analogues. After this initial success, no new developments were published with other P,O-ligands.[5] Therefore, a systematic study of the scope of P,O-ligands for this process is still needed.

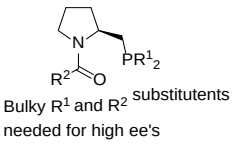

Figure 1. Proline-based P,O-ligands used by Pfaltz and coworkers for the asymmetric hydrogenation of minimally functionalized trisubstituted olefins.

To investigate the potential of P,O-based ligands in the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins, in this study we developed a modular pyrrolidine-based phosphine/phosphite-O ligand library (**L1**-**L10**; Figure 2). The new ligands are relevant not only because they are easily prepared in large quantities from unexpensive carbohydrates (D-mannose, D-ribose and D-arabinose), but also because they can be easily modulated with well-established carbohydrate chemistry. Such modularity allowed us to speed up the evaluation of several ligand parameters and facilitated the iterative optimization of the most promising candidates. They were tested in the AH of 32 alkenes,

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including challenging 1,1-disubstituted and substrates with poorly coordinative groups whose hydrogenated derivatives can be transformed into high-value organic compounds. These series of ligands allowed us to study the effect on catalytic performance of (i) the configuration of the pyrrolidine moiety (with ligands **L1** and **L2**), (ii) the pyrrolidine backbone rigidity (with ligands **L2** and **L3**), (iii) the size of the chelate ring (with ligands **L1** and **L4**), (iv) the type of O-donor group (carbamate, **L1**; amide, **L6**-**L7**; and urea, **L8**-**L9**), (v) the replacement of the phosphine moiety by a chiral biaryl phosphite group (ligands **L10**)[6]. We also studied the replacement of the carbamate O-donor group by a thiourea moiety (ligand **L11**).

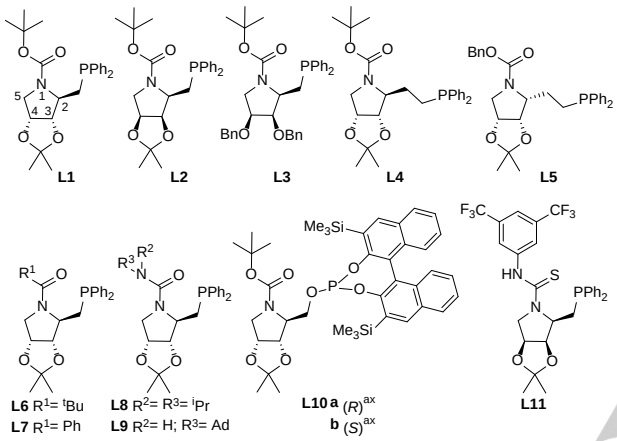


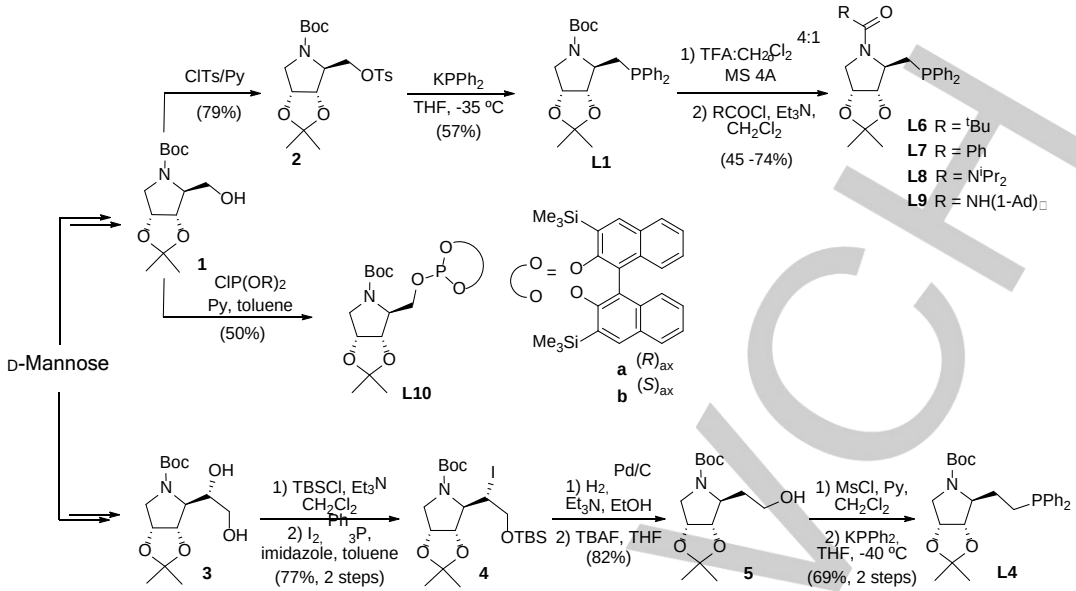
Figure 2. Pyrrolidine-based ligands **L1**-**L11**.

Results and Discussion

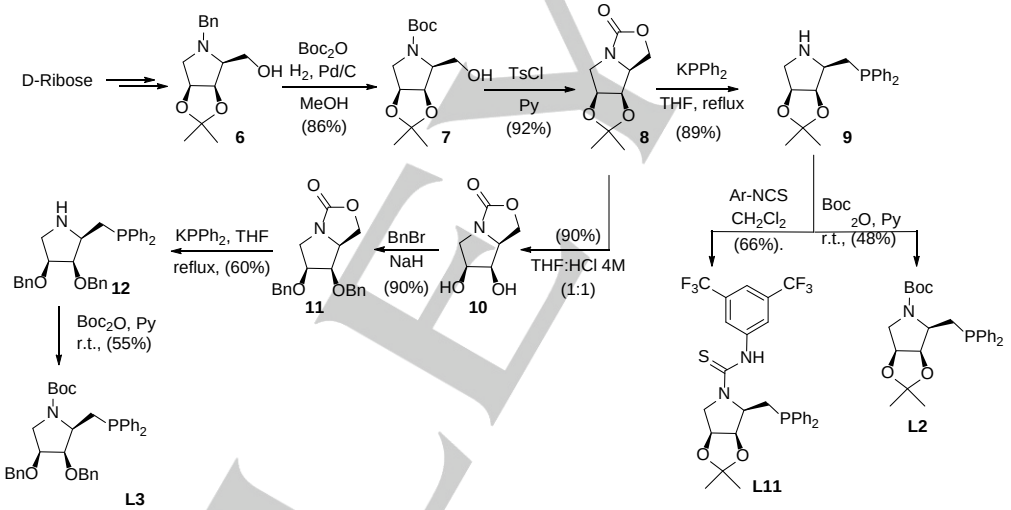
Synthesis of ligands

Schemes 1-3 show the synthetic sequences, first for those ligands derived from D-mannose, then for ligands derived from D-ribose and finally for ligands derived from D-arabinose. Starting from D-mannose (Scheme 1), the phosphine/phosphite-O ligands **L1**, **L4, L6**-**L9** and **L10a**-**b** were obtained. They have the same configuration of the carbons bearing the isopropylidene group and differ on the type of the O-donor group and the type of P-functionality. Their synthesis started from pyrrolidine **1**, easily obtained from D-mannose and recently reported by our group.[7] Tosylation of **1** followed by reaction with $KPPh_2$ in THF at -35 °C afforded amino-phosphine **L1** in 57% yield. Its structure was confirmed by ^{1}H-NMR by the disappearance of the signals corresponding to the tosyl group and the appearance of a multiplet (δ = 7.55-7.33 ppm) for 10 H corresponding to the diphenylphosphino group. In the ^{31}P-NMR spectrum the signal at -23.2 ppm is compatible with the phosphine moiety. Boc deprotection and reaction with different acyl halides in the presence of Et_3N gave compounds **L6**-**L9**, with amide and urea groups, in moderate-to-good yields. Their structures were also confirmed by NMR. Therefore, ^{31}P-NMR spectra showed the expected one singlet in the region compatible with the phosphine moiety, except for **L7** for which the presence of two rotamers was observed. Finally, reaction of alcohol **1** with one equivalent of the corresponding phosphorochloridite ($ClP(OR)_2$) formed *in situ* gave access to carbamate-phosphite ligands **L10a**-**b**, with the desired configuration of the biaryl phosphite group. The ^{31}P-NMR spectra showed two singlets for each compound at around 130 ppm compatible with phosphite moieties. The presence of two rotamers for each ligand, as for **L7**, was confirmed by performing the 2D-^{31}P DOSY NMR experiment that shows that the two isomers have the same diffusion coefficient (see Supporting Information). Both isomers also showed the same HR-mass spectra.

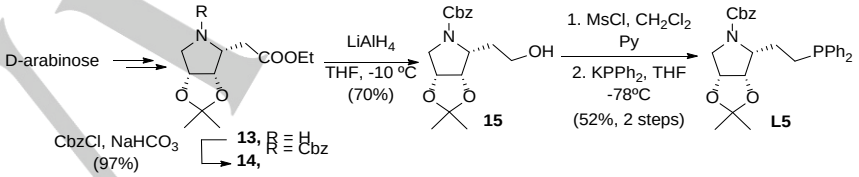
Protected pyrrolidine-phosphine **L4**, with a 2,3-*trans* configuration and which differs from ligand **L1** in a longer phosphine alkyl chain, was also prepared starting from D-mannose (Scheme 1) through intermediate **3** that was recently reported by us.[7] Primary alcohol protection and iodination afforded derivative **4**, which after hydrogenation and subsequent deprotection gave alcohol **5**. Mesylation and displacement with $KPPh_2$ in THF at -40 °C furnished protected pyrrolidine phosphine-carbamate **L4** in 69% yield. The ^{31}P-NMR spectrum shows the expected singlet at -15.4 ppm compatible with a phosphine moiety.



Scheme 1. Synthesis of ligands **L1**, **L4**, **L6**-**L9** and **L10a**-**b** derived from D-mannose.



Scheme 2. Synthesis of ligands **L2**-**L3** and **L11** derived from D-ribose.



Scheme 3. Synthesis of ligand **L5** derived from D-arabinose

The preparation of ligands **L2**, **L3** and **L11** with different configuration at the carbons bearing the isopropylidene group than **L1** and **L4** analogues, is shown in Scheme 2. Starting from D-ribose, pyrrolidine phosphine **9** was prepared following our recently reported procedure.[8] *N*-Boc protection of compound **6**, followed by tosylation afforded cyclic carbamate **8** as was also

observed by us with similar 2,3-*cis* compounds.[9] Nucleophilic ring opening with $KPPh_2$ in THF gave the corresponding pyrrolidine-phosphine **9**. The phosphine moiety was ascertained by the signal at -20.9 ppm in the ^{31}P-NMR. Reaction with 3,5-ditrifluoromethylisothyocyanate and Boc_2O/Py gave thiourea-phosphine ligand **L11** and carbamate-phosphine ligand **L2**, respectively, in moderate yields. Deprotection of cyclic carbamate **8** with THF:HCl 4M (1:1) followed by conventional benzylation gave the benzylated carbamate **11**. The nucleophilic ring opening of **11** using $KPPh_2$ in refluxing THF followed by *N*-Boc protection afforded **L3** in 55% yield.

Finally, protected pyrrolidine-phosphine **L5**, with a 2,3-*cis* configuration and differing from **L4** in the configuration of C-2 of the pyrrolidine ligand backbone and also in the N carbamate (Cbz vs Boc), was obtained from **13** which was prepared from D-arabinose (Scheme 3).[10] Carbamate protection and reduction with $LiAlH_4$ at -10 °C gave alcohol **15** in good yield. Phosphine moiety was introduced by the above described conventional method giving **L5** in 52% yield.

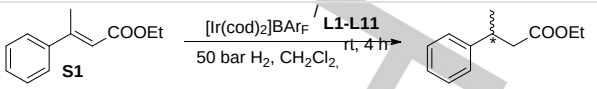
The formation of ligands was confirmed by ^{31}P {^{1}H}, ^{1}H and ^{13}C {^{1}H} NMR spectra and mass spectrometry. The spectra assignments were supported by the information obtained from ^{1}H-^{1}H and ^{1}H-^{13}C correlation measurements. See experimental section for purification and characterization details.

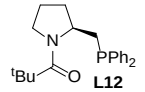
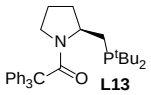
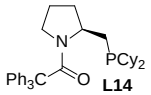
Asymmetric hydrogenation of minimally functionalized olefins

The library of P,O/S ligands **L1**-**L11** was evaluated in the Ir-catalyzed asymmetric hydrogenation of trisubstituted minimally functionalized olefins (**S1**-**S16**) and challenging 1,1-disubstituted olefins (**S17**-**S32**). The catalyst was generated *in situ* by adding the corresponding P,O/S-ligand to the catalyst precursor $[Ir(cod)_2]BAr_F$ following the procedure reported by Pfaltz.[4a]

Initially, following the study with proline-based P,O ligands reported by Pfaltz, we tested ligands **L1**-**L11** in the AH of an α,β-unsaturated ester **S1** (Table 1). This allowed a direct comparison with Pfaltz's P,O catalytic systems.[4a] The results with ligands **L1**-**L3** indicated that activity and enantioselectivity are very sensitive to the chirality and rigidity of the pyrrolidine moiety (entries 1-3). The highest activity and enantioselectivity was achieved with ligand **L1** (entry 1), with an *R*-configuration at C-2 and *3S*,*4R* configuration at the pyrrolidine carbons bearing the isopropylidene group. The results with ligands **L1**, **L4** and **L5** indicated that the chelate ring size also influences the catalytic performance. Ligands **L4**-**L5**, that form a less stable 8-membered chelate ring, gave lower enantioselectivities than ligands **L1** and **L2** (entries 4-5 vs 1-2). This agrees with the hemilabile character of the carbamate group upon coordination to iridium. Even ligand **L4** affected negatively its activity. The results with ligands **L1** and **L6**-**L9** also indicated that the type of O-donor group affects enantioselectivity considerably (entries 1, 6-9), with the highest enantioselectivities (ee's up to 98%) being achieved with a carbamate (ligand **L1**) and an amido (ligands **L6** and **L7**) group. Finally, we also found that the replacement of either the phosphine (ligand **L1**) by a biaryl phosphite moiety (ligands **L10**) or the carbamate moiety (ligand **L1**) by a thiourea group (ligand **L11**) had a detrimental effect on catalytic performance (entry 1 *vs* 10-12).

Table 1. Ir-catalyzed hydrogenation of substrate **S1** using $[Ir(cod)_2]BAr_F$/**L1**-**L11** catalyst precursors.[a]



Entry	Ligand	% Conv[b]	% ee[c]
1	**L1**	80	97 (*R*)
2	**L2**	35	68 (*R*)
3	**L3**	35	58 (*R*)
4	**L4**	<5	nd
5	**L5**	100	30 (*S*)
6	**L6**	29	97 (*R*)
7	**L7**	40	98 (*R*)
8	**L8**	60	70 (*R*)
9	**L9**	58	67 (*R*)
10	**L10a**	50	65 (*R*)
11	**L10b**	<5	3 (*S*)
12	**L11**	<2	nd
13[d]	 **L12**	65	33 (*R*)
14[d]	 **L13**	>99	98 (*R*)
15[d]	 **L14**	>99	94 (*R*)

[a] Reactions carried out using 0.5 mmol of substrate and 2 mol% of $[Ir(cod)_2]BAr_F$, 2 mol% of corresponding ligand at 50 bar of H_2 for 4 h. [b] Conversion determined by ^{1}H NMR. [c] Enantiomeric excesses determined by chiral HPLC. [d] Data from ref [4a].

In summary, high enantioselectivities (up to 98% ee) were achieved with the pyrrolidine-based phosphine-carbamate and phosphine-amido ligands **L1**, **L6** and **L7**. The best combination of activity and enantioselectivity was obtained with ligand **L1**. Compared with the results obtained with the proline-based P,O analogues (33% ee, entry 13, ligand **L12**),[4a] the introduction of a more rigid bicyclic backbone increased enantioselectivity to 97% ee (entry 6, our ligand **L6**). In addition, our results are comparable with the excellent enantioselectivities achieved with the bulkier, less stable and more costly di-*tert*-butyl- or dicyclohexyl-phosphine analogues **L13** and **L14** developed by Pfaltz's group (Table 1, entries 14 and 15).

To further assess the performance of the new P,O-ligands in the AH of α,β-unsaturated carboxylic esters, we reduced **S2**-**S11** (see Figure 3) with the Ir/**L1** catalytic system, that had provided the best combination of activity and enantioselectivity. Advantageously, the ee's were independent of the electronic nature of the substrate phenyl ring (**S1**-**S4**) and the steric

properties of the alkyl substituent (**S1**, **S5**-**S7**). High ee's were also attained in the reduction of the challenging *Z*-analogues (**S8** and **S9**) and α-substituted carboxylic esters (**S10** and **S11**). It is worth noting that being able to hydrogenate such a range of α,β-unsaturated esters is highly significant since the reduced products are found in relevant products,[11] such as natural products, agrochemicals and fragrances.

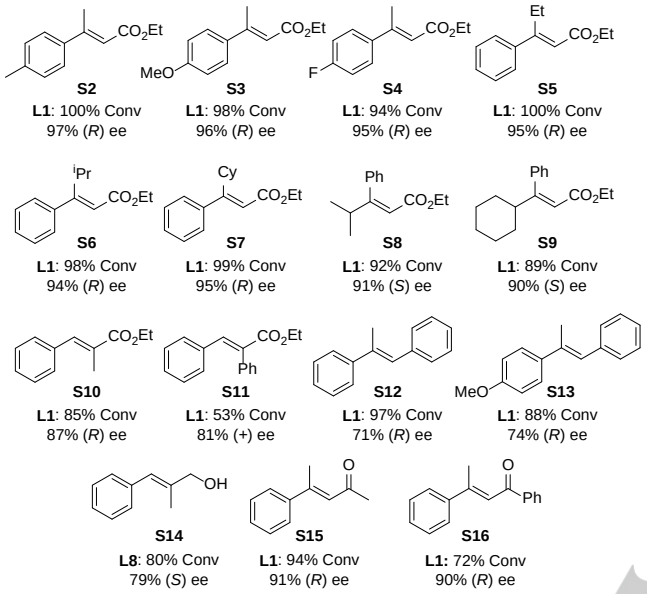
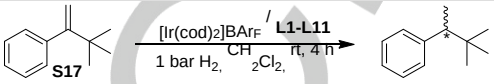


Figure 3. Minimally functionalized trisubstituted olefins and selected asymmetric hydrogenation results. Reaction conditions: 2 mol% of catalyst precursor, 2 mol% of ligand, CH_2Cl_2 as solvent, 50 bar of H_2, 4 h.

We next tested the P,O/S-ligands in the AH of other representative minimally functionalized trisubstituted substrates, namely trisubstituted alkenes **S12**-**S16**, including the widely studied α-methylstilbenes **S12**-**S13** and the allylic alcohol **S14** (see Figure 3 and the Supporting Information for a complete set of results). The pyrrolidine-based Ir-P,O catalytic systems were less appropriate for the reduction of α-methylstilbenes **S12**-**S13** and allylic alcohol **S14** (ee's up to 79%) but high enantioselectivities (up to 91% ee) were achieved for β-substituted unsaturated ketones **S15** and **S16**. The effective hydrogenation of this type of ketones opens up a sustainable route to obtain chiral β-substituted ketones.[12] These results are comparable with those reported with the successful proline-based P,O-ligand,[4a] with the added advantage that our pyrrolidine-based P,O-ligand contains a more stable and cheaper diphenylphosphine donor group.

We finally tested ligands **L1**-**L11** in the AH of 1,1-disubstituted olefins. Unlike trisubstituted substrates, only a few recent catalysts have provided high enantioselectivitites in the hydrogenation of 1,1-disubstituted olefins.[3e] In these reductions, the catalyst must not only control the face selectivity coordination (there are only two substituents while in trisubstituted olefins there are three) but also avoid the isomerization of the olefins into *E*-trisubstituted substrates, which are then hydrogenated giving the opposite enantiomer. As a model substrate, we have chosen the 3,3-dimethyl-2-phenyl-1-butene **S17**. The results (see Table 2) indicated that, except the nature of the O-donor group, all ligand parameters behave as described for the hydrogenation of trisubstituted olefins. The highest enantioselectivity (74% ee at only 1 bar of H_2, entry 1) was therefore achieved with the pyrrolidine-based carbamate-phosphine ligand **L1**. Ligands **L6** and **L7**, that provided also high enantioselectivity in the reduction of trisubstituted olefins, gave much lower enantioselectivities in this case (entries 6 and 7).

Table 2. Ir-catalyzed hydrogenation of substrate **S17** using Ir(cod)BAr$_F$/**L1**-**L11** catalyst precursors.[a]



Entry	Ligand	% Conv[b]	% ee[c]
1	**L1**	80	74 (*R*)
2	**L2**	25	44 (*R*)
3	**L3**	33	42 (*R*)
4	**L4**	40	7 (*R*)
5	**L5**	100	9 (*S*)
6	**L6**	15	50 (*R*)
7	**L7**	16	12 (*R*)
8	**L8**	75	45 (*R*)
9	**L9**	35	33 (*R*)
10	**L10a**	12	29 (*S*)
11	**L10b**	10	8 (*R*)
12	**L11**	<2	nd

[a] Reactions carried out using 0.5 mmol of substrate and 2 mol% of [Ir(cod)$_2$]BAr$_F$, 2 mol% of the corresponding ligand at 1 bar of H_2 for 4 h. [b] Conversion determined by chiral GC. [c] Enantiomeric excesses determined by chiral GC.

Continuing with the AH of 1,1-disubstituted alkenes, we tested the substrates shown in Figure 4 (see Supporting Information for a complete set of results). Advantageously, we found that the Ir/**L1** system was robust against variations in the electronic and steric nature of the substrate aryl substituent, with ee's ranging from 73% to 76%. Thus, terminal olefins **S18**-**S22** were reduced in good enantioselectivity comparable to **S17**. Among other published results, we also found an important effect of the type of the alkyl chain on enantioselectivity, with high enantioselectivities only obtained for substrates with a *tert*-butyl group (i.e. 74% ee for **S17** vs <20% ee for substrates **S23**–**S25**). These results are in accordance with the existence of a competing isomerization process, which was confirmed by studying the degree of indirect incorporation of deuterium due to the isomerization process in the deuteration of **S23** (Scheme 4). It was found that deuterium was not only added to the double bond but also at the allylic position. Accordingly, the mass spectra of the corresponding deuterated products indicated the presence of reduced species with more than two deuterium atoms.

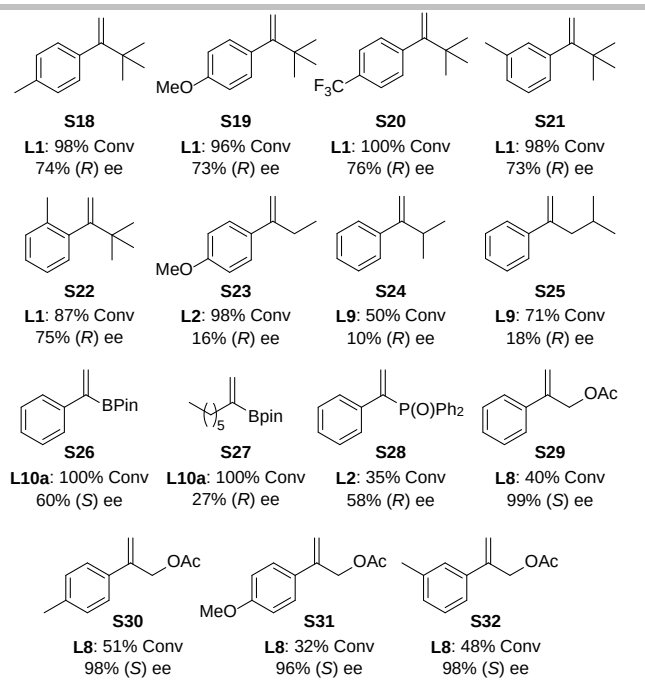
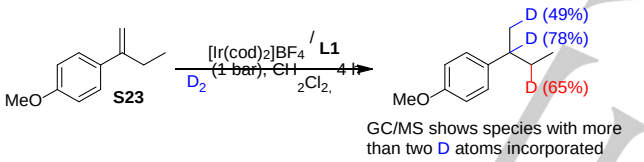


Figure 4. Selected results for the asymmetric hydrogenation of 1,1-disubstituted substrates **S18**-**S32** using [Ir(cod)$_2$]/**L1-L11** as catalyst precursor. Reaction conditions: 2 mol% of [Ir(cod)$_2$]BAr$_F$, 2 mol% of ligand, CH_2Cl_2 as solvent, 1 bar of H_2, 4 h.



Scheme 4. Deuteration of substrate **S23**. The percentage of incorporation of deuterium atoms is shown in brackets. The result of the indirect addition of deuterium due to the isomerization process is shown in red.

Finally, due to the importance of AH of olefins with poorly coordinative groups we also studied the hydrogenation of this type of disubstituted substrates (Figure 4, see Supporting Information for a complete set of results). We focused on the reduction of the aryl boronic ester (**S26**), the alkyl boronic ester (**S27**), the enol phosphinate (**S28**) and allylic acetates (**S29**–**S32**). Although low-to-moderate enantioselectivities were obtained with **S26** to **S28**, the pyrrolidine-based P,O ligands were well suited for the reduction of allylic acetates. Excellent enantioselectivities (ranging from 97% to 99% ee) comparable to the best one reported were achieved with ligand **L8** for several substituted allylic acetates (**S29**–**S32**), maintaining the mild reaction conditions (1 bar of H_2). The reduction of allylic acetates provides a straightforward route to the synthesis of relevant products which are used in the cosmetic industry as components of fragrance mixtures (e.g., Pamplefleur) and also in the pharmaceutical industry (e.g., intermediates for the synthesis of modulators of dopamine D3 receptors).[13]

Conclusions

New pyrrolidine-based phosphine/phosphite-O/S ligands have been applied in the asymmetric hydrogenation of 32 minimally functionalized olefins. The new ligands are relevant not only because they are easily prepared in a large scale from unexpensive carbohydrates (D-mannose, D-ribose and D-arabinose), but also because they can be easily modulated with a well-established carbohydrate chemistry. Such modularity proved to be crucial for the search of the most efficient catalyst for each type of substrate. High enantioselectivities (ee's up to 99%) could be achieved in the hydrogenation of selected tri- and disubstituted substrates. In comparison with the related successful proline-based P,O ligands[4a], the use of a more-rigid bicyclic backbone affected positively the enantioselectivity and extended the range of substrates that can been reduced, including 1,1-disubstituted allylic acetates. In addition, our ligands have a diphenyl phosphine moiety, which improves stability compared to related proline-based P,O ligands that contain the bulkier phosphine groups. These results pave the way for further development of new generations of modular and readily available sugar based-P,O-ligands for the asymmetric hydrogenation of minimally functionalized substrates, including the more challenging *Z*-tri- and disubstituted alkenes.

Experimental Section

General remarks

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Commercial chemicals were used as received. Solvents were dried by standard procedures and stored under argon. Phosphorochloridites were easily prepared in one step from the corresponding biphenols.[14] Compounds **1**-**3**,[7] **6**-**9**[8] and **13**[10c] were prepared as previously reported. Optical rotations were measured in a 1.0 cm or 1.0 dm tube with a Jasco P-2000 spectropolarimeter. Infrared spectra were recorded with Jasco FTIR-410 spectrometer. ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra were recorded using a Bruker, AV300, AV500 and Varian Mercury-400 MHz spectrometer for solutions in $CDCl_3$, C_6D_6 and DMSO-d_6 at room temperature or heating (343 K, 363 K). Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C{^{1}H}) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H and ^{13}C assignments were made on the basis of ^{1}H-^{1}H gCOSY and ^{1}H-^{13}C gHSQC experiments. Mass spectra (CI and ESI) were recorded on Micromass AutoSpeQ and QTRAP (Applied Biosystem) and Orbitrap Elite spectrometers. NMR and mass spectra were registered in CITIUS (University of Seville) and in SRCiT (Universitat Rovira i Virgili).

(2R,3S,4R)-N-terc-Butoxycarbonyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (L1).

Tosylate **2**[7] (300 mg, 0.700 mmol) was disolved in dry THF (9 mL) under Ar and was cooled to -35 °C. Then $KPPh_2$ (1.7 mL, 0.9 mmol, 0.5 M in THF) was slowly added and the reaction mixture was stirred for 50 min. IRA-120H$^+$ was added, stirred for several minutes and then filtered through Celite, washed with AcOEt and evaporated to dryness. Column chromatography on silica gel (Cyclohexane → AcOEt:cyclohexane, 1:5), gave **L1** (176 mg, 0.400 mmol, 57%) as a colourless oil. ^{31}P NMR (121.5 MHz, DMSO-d_6 343 K, δ ppm) δ -23.2 (s). ^{1}H NMR (300 MHz, DMSO-d_6, 343 K, δ ppm, *J* Hz) δ 1.22 (s, 3H, CH_3), 1.29 (s, 12H, CH_3, ^{t}Bu, NBoc, CH_3), 2.27 (m, 2H, CH_2-P), 3.34 (dd, 1H, CH_2-N $^2J_{H\text{-}H}$= 12.9, $^3J_{H\text{-}H}$ = 4.5), 3.66 (m, 1H, CH_2-N), 3.97 (m, 1H, CH-N), 4.73 (m, 2H, CH-O), 7.44 (m,

10H, CH=). ^{13}C NMR (75.4 MHz, DMSO-d_6, 343 K, δ ppm) δ 24.5 (CH_3), 26.4 (CH_3), 27.1 (CH_3, ^{t}Bu, NBoc), 29.1 (CH_2-P), 50.2 (CH_2-N), 60.9 (CH-N), 78.4 (CH-O), 83.7 (CH-O), 110.3 (C), 139.0-128.1 (aromatic carbons), 153.2 (C=O). α_D +48.4 (*c* 0.56, CH_2Cl_2). IR ν_{max} 2980, 2927, 1691 (C=O), 1162, 1055, 695 cm^{-1}.

(2R,3R,4S)-N-terc-Butoxycarbonyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (L2).

To a solution of **9** (239.3 mg, 0.70 mmol) in dry pyridine (3.5 mL) Boc_2O (382 mg, 1.75 mmol) was added and the reaction mixture was stirred at r.t. for 6.5 h. Then, the mixture was evaporated to dryness. The residue was dissolved in EtOAc and washed with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography on silica gel (AcOEt:cyclohexane - 1:8) afforded **L2** (148.8 mg, 0.34 mmol, 48%) as a pale yellow oil. ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ: -20.1 (s). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) δ: 1.31 (s, 3H, CH_3), 1.37 (s, 9H, CH_3, ^{t}Bu, NBoc), 1.44 (s, 3H, CH_3), 2.43 (dd, 1H, CH_2-P, $^2J_{H\text{-}H}$ = 13.2 Hz, $^3J_{H\text{-}H}$ = 10.4 Hz), 2.87 (d, 1H, CH_2-P), 3.34 (dd, 1H, CH_2-N, $^2J_{H\text{-}H}$ = 13.2 Hz , $^3J_{H\text{-}H}$ = 4.5 Hz), 3.78 (m, 1H, CH_2-N), 3.98 (m, 1H, CH-N), 4.66 (m, 1H, CH-O), 4.76 (br t, 1H, CH-O, $^3J_{H\text{-}H}$ = $^3J_{H\text{-}H}$ = 6.2 Hz), 7.32 (m, 5H, CH=), 7.45 (m, 2H, CH=), 7.55 (m, 2H, CH=). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ ppm) δ: 25.4 (CH_3), 27.0 (CH_3), 28.6 (CH_3, ^{t}Bu), 29.0 (d, CH_2-P, $J_{C,P}$ = 15.1 Hz), 51.1 (CH_2-N), 58.1 (d, CH-N, $J_{C,P}$ = 24.2 Hz), 77.4 (CH-O), 80.3 (d, CH-O, $J_{C,P}$ = 21.3 Hz), 112.8 (C), 128.6-139.6 (aromatic carbons), 154.5 (C=O). α_D +61.1 (*c* 0.82, CH_2Cl_2). ESI-HRMS *m/z* found 442.2134, calc. for $C_{25}H_{33}NO_4P$ $[M+H]^+$: 442.2142. IR ν_{max} 2978, 2932, 1692 (C=O), 1162, 854, 695 cm^{-1}.

(2R,3R,4S)-N-tert-Butoxycarbonyl-3,4-di-O-benzyl-2-diphenylphosphinomehyl-pyrrolidine-3,4-diol (L3).

To a solution of **11** (150.6 mg, 0.44 mmol) in dry THF (4 mL) cooled to 0 ºC, $KPPh_2$ (1.8 mL, 0.89 mmol, 0.5 M in THF) was slowly added and the mixture was heated at reflux for 1.5 h. Then, IRA-120H$^+$ resin was added, filtered through Celite and washed with CH_2Cl_2. Evaporation of the solvent and purification by column chromatography on silica gel (CH_2Cl_2, 1% Et_3N) afforded pyrrolidine **12** (171.1 mg, 0.36 mmol, 80%). Boc_2O (194 mg, 0.89 mmol) in dry pyridine (2 mL) was subsequently added and the reaction mixture was stirred at r.t. for 6 h. Then, the mixture was evaporated to dryness. The residue was dissolved in EtOAc and washed with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography on silica gel (AcOEt:cyclohexane - 1:8) afforded **L3** (114 mg, 0.20 mmol, 55%) as a pale yellow oil. ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ: -19.2 (s). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) δ: 1.32 (s, 9H, CH_3, ^{t}Bu, NBoc), 2.52 (m, 1H, CH_2-P), 2.75 (m, 1H, CH_2-P), 3.29 (dd, 1H, CH_2-N, $^2J_{H\text{-}H}$ = 11.3 Hz , $^3J_{H\text{-}H}$ = 4.0 Hz), 3.62 (m, 1H, CH_2-N), 4.07 (m, 1H, CH-N), 4.16 (m, 2H, 2xCH-O), 4.67 (m, 4H, CH_2Ph), 7.37 (m, 20H, CH=). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ ppm) δ: 27.7 (CH_3, ^{t}Bu, CH_2-P), 48.7 (CH_2-N), 56.1 (d, CH-N, $J_{C,P}$ = 22.4 Hz), 71.2 (CH_2Ph), 71.8 (CH_2Ph), 76.6 (CH-O), 78.4 (CH-O), 78.7 (C, ^{t}Bu), 126.9-138.1 (aromatic carbons), 153.5 (C=O. α_D +32.9 (*c* 0.78, CH_2Cl_2). ESI-HRMS *m/z* found 582.2760, calc. for $C_{36}H_{41}NO_4P$ $[M+H]^+$: 582.2768. IR ν_{max} 2976, 2923, 1688 (C=O), 1391, 1100, 695 cm^{-1}.

(2S,3S,4R)-N-tert-Butoxycarbonyl-2-diphenylphosphinoethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (L4).

To a solution of **3**[7] (650 mg, 2.14 mmol) in dry CH_2Cl_2 (3 mL), NEt_3 (595 µL, 4.28 mmol) and TBSCl (612 mg, 2.14 mmol) were added. After stirring at r.t overnight, the reaction was quenched with sat. aq. soln. of NH_4Cl and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated. To a solution of the crude product in dry toluene (18 mL), imidazole (466 mg, 6.85 mmol), PPh_3 (1.30 g, 4.92 mmol) and I_2 (868 mg, 3.42 mmol) were added and the mixture was refluxed for 2 h. After cooling to r.t. and diluting with AcOEt, the mixture was washed with sat. aq. $Na_2S_2O_3$, water and brine. The reaction mixture was dried (Na_2SO_4), filtered and evaporated. Purification by column chromatography on silica gel (cyclohexane → AcOEt:cyclohexane - 1:20) afforded *N-tert*-butoxycarbonyl-1,4,5-trideoxy-6-*O*-*tert*-butyldimethylsilyl-1,4-imino-5-iodo-2,3-*O*-isopropyli-dene-D-talitol (**4**) (865 mg, 77%, 2 steps) as a colorless oil, that was used immediately in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 0.09 (s, 6H, CH_3), 0.91 (s, 9H, CH_3, ^{t}Bu), 1.31 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.47 (s, 9H, CH_3), 3.81 (m, 4H), 4.11 (m, 1H), 4.62 (m, 3H).

To a solution of **4** (705 mg, 1.34 mmol) in EtOH (14 mL), Et_3N (450 µL) and Pd/C (10%, cat.) were added and the reaction hydrogenated at 1 atm for 4 h. The crude product was filtered through Celite and the solvent evaporated under vacuum. The resulting residue was purified by column chromatography on silica gel (EtOAc:cyclohexane - 1:10 → AcOEt) to give the dehalogenated derivative (490 mg, 82%). 1 M TBAF in THF (0.49 mL, 0.49 mmol) was added to a solution of this compound (180 mg, 1.49 mmol) in THF (6 mL) and the mixture was stirred at r.t. for 6 h and then the solvent evaporated under vacuum. Purification by column chromatography on silica gel (CH_2Cl_2:MeOH - 50:1) afforded compound **5** (128 mg, quant.) as a colorless oil, that was used immediately in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.27 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.33 (m, 1H), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.72 (m, 1H), 3.22 (dd, 1H, *J* = 13.2 Hz, *J* = 4.9 Hz), 3.46 (m, 3H), 3.89 (m, 1H), 4.24 (m, 1H), 4.43 (m, 1H), 4.67 (t, 1H, *J* = 5.3 Hz),

Then a solution of MsCl (55 µL, 0.71 mmol) in pyridine (1 mL) was added dropwise to a 0 ºC solution of alcohol **5** (67.5 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) and the mixture stirred at r.t. for 2 h. Water was then added dropwise under stirring and the mixture evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude mesylate was dissolved in anhydrous THF (2 mL) and cooled to -40 ºC. $KPPh_2$ (565 µL, 0.28 mmol, 0.5 M in THF) was slowly added and the mixture was stirred at -40 ºC for 15 min. IRA-120H$^+$ resin was added and the mixture diluted with AcOEt, filtered through Celite and washed with AcOEt and CH_2Cl_2. Evaporation of the solvent and purification by column chromatography on silica gel (AcOEt:cyclohexane - 1:10→1:5) afforded **L4** (74 mg, 69%, 2 steps). ^{31}P NMR (121.5 MHz, DMSO-d_6, δ ppm, mixture of rotamers) δ -15.4 (s), -16.1 (s). ^{1}H-NMR (300 MHz, DMSO-d_6, 363 K, δ ppm) δ 1.24 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.53 (m, 2H, CH_2-CH_2P), 2.08 (m, 2H, CH_2-P), 3.23 (dd, 1H, CH_2-N, $^3J_{H\text{-}H}$ = 4.8 Hz), 3.65 (ap.d, 1H, CH_2-N, $^2J_{H\text{-}H}$ = 12.9 Hz), 3.98 (m, 1H, CH-N), 4.48 (m, 1H, CH-O), 4.68 (t, 1H, CH-O, $^3J_{H\text{-}H}$= $^3J_{H\text{-}H}$= 5.1 Hz), 7.41 (m, 8H, CH=), 7.52 (m, 1H, CH=), 7.77 (m, 1H, CH=). ^{13}C NMR (75.4 MHz, DMSO-d_6, 363 K, δ ppm) δ 23.0 (d, , CH_2-CH_2P, $J_{C\text{-}P}$ = 12.1 Hz), 24.5 (CH_3), 26.3 (CH_3), 26.8 (d, CH_2-P, $J_{C\text{-}P}$= 17.3 Hz), 27.6 (CH_3, ^{t}Bu), 50.3 (CH_2-N), 63.7 (d, CH-N, $J_{C\text{-}P}$= 12.8 Hz), 78.2 (CH-O, C, ^{t}Bu), 83.1 (CH-O), 110.2 (C), 138.1-127.9 (Aromatic carbons), 153.3 (C=O), α_D +14.8 (*c* 1.3, CH_2Cl_2). ESI-HRMS *m/z* found 456.2292, calc. for $C_{26}H_{35}NO_4P$ $[M+H]^+$: 456.2298.

(2R,3S,4R)-N-Benzyloxycarbonyl-2-diphenylphosphinoethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (L5).

To a solution of **15** (257 mg, 0.799 mmol) in dry CH_2Cl_2 (5 mL) cooled to 0 °C, a solution of MsCl (187 µL, 2.39 mmol) in dry pyridine (2.5 mL) was added. The reaction mixture was left to stand at r.t. under Ar for 2 h. Then it is cooled to 0°C and H_2O (3 mL) is added dropwise, left at r.t. for 15 min and concentrated to dryness. The obtained residue was dissolved in CH_2Cl_2 (15 mL) and washed with H_2O (3 x 10 mL). The organic phase is dried (Na_2SO_4), filtered and concentrated to dryness. The resulting crude product is then dissolved in dry THF (5.8 mL) under Ar, cooled to -78 °C, and $KPPh_2$ (4.46 mL, 0.5 M in THF, 2.23 mmol) was added dropwise. The reaction mixture was left to stand at that temperature for 15 min under Ar. Then, a saturated aqueous solution of NH_4Cl (3 mL) was added and the solution allowed to reach r.t. The aqueous phase is extracted with CH_2Cl_2 and the combined organic phases are dried (Na_2SO_4), filtered and

concentrated to dryness. Purification by column chromatography on silica gel (AcOEt: cyclohexane - 1:5) gave **L5** (201 mg, 0.42 mmol, 52%, 2 steps) as a colorless oil. ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ -15.0 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.33 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.85 (m, 1H, CH_2-CH_2P), 2.04 (m, 2H, CH_2-CH_2P, CH_2-P), 2.24 (m, 1H, CH_2-P), 3.29 (dd, 1H, CH_2-N, $^2J_{H\text{-}H}$= 12.6 Hz, $^3J_{H\text{-}H}$= 4.2 Hz), 3.90 (dd, 1H, CH_2-N, $^2J_{H\text{-}H}$= 12.6 Hz, $^3J_{H\text{-}H}$= 6.9 Hz), 4.07 (m, 1H, CH-N), 4.72 (m, 2H, CH-O), 5.06 (d, 1H, $^2J_{H,H}$= 12.3 Hz, CH_2Ph), 5.11 (d, 1H, CH_2Ph, $^2J_{H,H}$= 12.3 Hz), 7.31 (m, 11H, CH=), 7.43 (m, 4H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 24.6 (d, CH_2-CH_2P, $J_{C,P}$= 11.5 Hz), 25.3 (CH_3), 26.2 (d, CH_2-CH_2P CH_2-P, $J_{C,P}$= 18.0 Hz), 26.6 (CH_3), 50.5 (CH_2-N), 60.9 (d, CH-N, $J_{C,P}$= 14.9 Hz), 67.0 (CH_2Ph), 77.9 (CH-O), 80.0 (CH-O), 113.1 (C), 139.2-128.0 (C-arom.), 154.8 (C=O). α_D -57.6 (*c* 0.78, CH_2Cl_2). IR ν_{max} 2985, 2929, 1698 (C=O), 1408, 1209, 695 cm^{-1}. ESI-HRMS *m/z* found 490.2134, calc. for $C_{29}H_{33}NO_4P$ $[M+H]^+$: 490.2142.

General procedure for the formation of compounds L6–L9.

TFA (20 mol%) was added dropwise at 0 °C to a solution of **L1** (0.2 mmol) in dry CH_2Cl_2 (3 mL) containing 4 Å molecular sieves. The mixture was stirred at r.t. for 1 h, then filtered and evaporated to dryness. The residue was dissolved in CH_2Cl_2, treated with Ambersep 900 (OH^-) resin, filtered and evaporated. A solution of Et_3N (2.0 eq.), the corresponding carbonyl compound (1.3 eq.) and the deprotected amine was stirred at rt for 2-4 h. After addition of sat. aqueous NH_4Cl, the mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography on silica gel afforded the corresponding acylated compound.

(2R,3S,4R)-N-Pivaloyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (L6). Compound **L6** (74% yield) was prepared according to general procedure from **L1** and pivaloyl chloride, followed by column chromatography on silica gel (AcOEt:cyclohexane - 1:5). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ -24.2 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.14 (s, 9H, CH_3, ^{t}Bu), 1.28 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.18 (m, 1H, CH_2-P), 2.44 (m, 1H, CH_2-P), 3.51 (m, 1H, CH_2-N), 4.09 (m, 1H, CH_2-N), 4.68 (br.s, 1H, CH-N), 4.81 (m, 2H, CH-O), 7.35 (m, 6H, CH=), 7.43 (m, 2H, CH=), 7.53 (m, 2H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 25.0 (CH_3), 26.7 (CH_3), 27.7 (CH_3, ^{t}Bu), 29.7 (CH_2-P), 38.7 (C), 53.0 (CH_2-N), 63.0 (CH-N), 80.2 (CH-O), 82.3 (CH-O), 111.7 (C), 138.5-128.7 (aromatic carbons), 176.4 (C=O), α_D +198.4 (*c* 0.56, CH_2Cl_2). ESI-HRMS *m/z* found 426.2186, calc. for $C_{25}H_{33}NO_3P$ $[M+H]^+$: 426.2193. IR ν_{max} 2980, 2920, 1611 (C=O), 1207, 1042, 697 cm^{-1}.

(2R,3S,4R)-N-Benzoyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (L7). Compound **L7** (72% yield) was prepared according to the general procedure from **L1** and benzoyl chloride, followed by column chromatography on silica gel (AcOEt:hexane - 1:7). α_D +85.5 (*c* 0.6, CH_2Cl_2). ESI-HRMS *m/z* found 446.1873, calc. for $C_{27}H_{29}NO_3P$ $[M+H]^+$: 446.1880. IR ν_{max} 2990, 2917, 1627 (C=O), 1208, 1058, 695 cm^{-1}. Major rotamer (63%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm): -24.8 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.28 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.42 (dd, 1H, CH_2-P, $^2J_{H\text{-}H}$ = 14.1 Hz,$^2J_{H\text{-}H}$ = 8.4 Hz), 2.52 (ddd, 1H, CH_2-P, $^2J_{H\text{-}H}$ = 14.1 Hz, $^3J_{H\text{-}H}$ = 5.4 Hz, $^4J_{H\text{-}H}$ = 1.8 Hz), 3.63 (m, 2H, CH_2-N), 4.88 (m, 3H, CH-N, 2x CH-O), 7.31 (m, 15H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): 25.0 (CH_3), 26.9 (CH_3), 30.5 (d, CH_2-P, $J_{C\text{-}P}$ = 16.1 Hz), 54.5 (CH_2-N), 61.3 (d, CH-N, $J_{C\text{-}P}$ = 14.9 Hz), 79.7 (CH-O), 84.2 (d, CH-O, $J_{C\text{-}P}$= 9.7 Hz), 111.9 (C,), 138.2-127.3 (aromatic carbons), 170.8 (C=O). Minor rotamer (37%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm), -24.8 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.33 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.95 (m, 1H, CH_2-P), 2.14 (m, 1H, CH_2-P), 4.00 (m, 1H, CH_2-N), 4.14 (m, 1H, CH-N), 4.29 (d, 1H, CH_2-N, $^2J_{H\text{-}H}$ = 13.8 Hz), 4.74 (m, 1H, CH-O), 4.88 (m, 1H, CH-O), 7.31 (m, 15H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): 24.8 (CH_3), 26.8 (CH_3), 31.3 (d, CH_2-P, $J_{C\text{-}P}$ = 17.4 Hz), 50.4 (CH_2-N), 63.2 (d, CH-N, $J_{C\text{-}P}$= 18.2 Hz), 78.4 (CH-O), 83.8 (d, CH-O, $J_{C\text{-}P}$= 10.1 Hz), 111.8 (C), 138.2-127.3 (aromatic carbons), 169.9 (C=O).

(2R,3S,4R)-N,N-Diisopropylcarbamoyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (L8). Compound **L8** (45% yield) was prepared according to the general procedure from **L1** and *N*,*N*-diisopropylcarbamoyl chloride, followed by column chromatography on silica gel (AcOEt:hexane - 1:3). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ -23.4 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.00 (d, 6H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.6 Hz), 1.22 (d, 6H, CH_3, ^{i}Pr, $^3J_{H\text{-}H}$= 6.6 Hz), 1.28 (s, 3H, CH_3,), 1.42 (s, 3H, CH_3), 2.15 (d, 2H, CH_2-P, $^3J_{H\text{-}H}$= 8.1 Hz), 3.38 (d, 1H, CH_2-N, $^2J_{H\text{-}H}$= 12.6 Hz), 3.51 (m, 3H, CH_2-N, CH, ^{i}Pr), 4.18 (m, 1H, CH-N), 4.67 (m, 1H, CH-O), 4.78 (m, 1H, CH-O), 7.36 (m, 6H, CH=), 7.45 (m, 4H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 20.6 (CH_3, ^{i}Pr), 22.4 (CH_3, ^{i}Pr), 25.0 (CH_3), 26.7 (CH_3), 29.6 (d, CH_2-P, $J_{C\text{-}P}$= 16.3 Hz), 47.3 (CH, ^{i}Pr), 53.3 (CH_2-N), 62.2 (d, CH-N, $J_{C\text{-}P}$ = 17.9 Hz), 78.7 (CH-O), 84.2 (d, CH-O, $J_{C\text{-}P}$= 9.7 Hz), 111.5 (C), 138.1-128.6 (aromatic carbons), 161.3 (C=O). α_D -5.2 (*c* 1.3, CH_2Cl_2). ESI-HRMS *m/z* found 469.2610, calc. for $C_{27}H_{38}N_2O_3P$ $[M+H]^+$: 469.2615. IR ν_{max} 2988, 2932, 1685 (C=O), 1141, 1058, 695 cm^{-1}.

(2R,3S,4R)-N-Adamantan-1-carbamoyl-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-3,4-diol (L9). Compound **L9** (55% yield) was prepared according to the general procedure from **L1** and 1-adamantyl isocyanate, followed by column chromatography on silica gel (AcOEt: hexane - 1:3). ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ -23.8 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.29 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.63 (s, 6H, CH_2, ad), 1.85 (s, 6H, CH_2, ad), 2.02 (s, 3H, CH, ad), 2.22 (m, 1H, CH_2-P), 2.34 (m, 1H, CH_2-P), 3.29 (m, 1H, CH_2-N), 3.70 (d, 1H, CH_2-N, $^2J_{H\text{-}H}$ = 12.6 Hz), 4.00 (m, 1H, CH-N), 4.78 (br.s, 2H, CH-O), 7.41 (m, 10H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 25.1 (CH_3), 27.0 (CH_3), 29.7 (CH), 30.6 (d, CH_2-P, $J_{C\text{-}P}$ = 16.3 Hz), 36.6 (CH_2), 42.4 (CH_2), 51.4 (CH_2-N), 61.6 (d, CH-N, $J_{C\text{-}P}$ = 16.7 Hz), 79.1 (CH-O), 85.0 (d, CH-O, $J_{C\text{-}P}$ = 9.6 Hz), 111.9 (C), 137.8-128.7 (aromatic carbons), 155.5 (C=O). α_D +37.3 (*c* 0.75, CH_2Cl_2). ESI-HRMS *m/z* found 519.2766, calc. for $C_{31}H_{40}N_2O_3P$ $[M+H]^+$: 519.2771. IR ν_{max} 2905, 2845, 1643 (C=O), 1508, 1056, 696 cm^{-1}.

General procedure for the preparation of the pyrrolidine-phosphite ligands L10a-b.

The corresponding phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (3.8 mmol, 0.3 mL) was added. The corresponding alcohol **1** (1 mmol) was azeotropically dried with toluene (3x1 mL) and dissolved in toluene (5 mL) to which pyridine (3.8 mmol, 0.3 mL) was added. The solution was transferred slowly at 0 °C to the solution of the phosphorochloridite. The reaction mixture was stirred overnight at 80 °C, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in alumina (toluene:triethylamine – 100:1) to produce the corresponding ligand as a white solid.

L10a: Yield: 167.2 mg (50%). TOF-MS (ESI+): *m/z:* calcd for $C_{39}H_{50}NO_7PSi_2$: 754.2756 $[M\text{-}Na]^+$; found 754.2761. α_D -420.5 (*c* 1.4, CH_2Cl_2). IR ν_{max} 2953, 1698 (C=O), 1399, 1174, 973, 831 cm^{-1}. Major rotamer (63%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm), 134.2 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.45 (s, 9H, CH_3, $SiMe_3$), 0.52 (s, 9H, CH_3, $SiMe_3$), 1.08 (s, 3H, CH_3), 1.09 (s, 9H, CH_3, ^{t}Bu, NBoc), 1.28 (s, 3H, CH_3), 3.24 (dd, 1H, CH_2-N, $^2J_{H\text{-}H}$ =12.5 Hz, $^3J_{H\text{-}H}$ =5.2 Hz), 3.43 (m, 1H, CH), 3.55 (m, 1H, CH_2-OP), 4.07 (m, 2H, CH_2-N, CH-O), 4.39 (m, 1H, CH_2-O), 4.73 (d, 1H, CH-O, $^3J_{H\text{-}H}$ =5.2 Hz), 6.83 (m, 2H, CH=), 7.07 (m, 2H, CH=,), 7.18 (m, 1H, CH=), 7.27 (m, 1H, CH=), 7.65 (m, 2H, CH=), 8.04 (m, 2H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): -0.6 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 21.1 (C, ^{t}Bu, NBoc), 24.6 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 27.9 (CH_3, ^{t}Bu, NBoc), 52.8 (CH_2-N), 63.3 (CH), 64.5 (CH_2-OP), 79.3 (CH-O), 82.5 (CH-O), 111.3 (C), 122.5 – 153.6 (aromatic carbons) 153.0 (C=O). Minor rotamer (37%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm), 138.0 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.49 (s, 9H, CH_3, $SiMe_3$), 0.53 (s, 9H, CH_3, $SiMe_3$), 1.03 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.34 (s, 9H, CH_3, ^{t}Bu, NBoc), 2.79 (dd, 1H, CH_2-N, $^2J_{H\text{-}H}$ =12.3 Hz, $^3J_{H\text{-}H}$ =5.3 Hz), 3.55 (m, 1H, CH_2-N), 4.07 (m, 3H, CH_2-OP, CH), 4.23 (m, 1H, CH-O), 4.66 (d, 1H, CH-O, $^3J_{H\text{-}H}$

=5.3 Hz), 6.83 (m, 2H, CH=), 7.07 (m, 2H, CH=), 7.18 (m, 1H, CH=), 7.27 (m, 1H, CH=), 7.65 (m, 2H, CH=), 8.04 (m, 2H, CH=), 8.12 (s, 1H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): NMR (C_6D_6), δ: -0.4 (CH_3, $SiMe_3$), -1.0 (CH_3, $SiMe_3$), 21.1 (C, ^{t}Bu, NBoc), 24.5 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 28.0 (CH_3, ^{t}Bu, NBoc), 52.8 (CH_2-N), 63.4 (CH), 64.0 (CH_2-OP), 78.9 (CH-O), 82.0 (CH-O), 111.3 (C), 122.5 – 153.6 (aromatic carbons), 153.3 (C=O).

L10b: Yield: 167.2 mg (50%). TOF-MS (ESI+): *m/z:* calcd for $C_{39}H_{50}NO_7PSi_2$: 754.2756 [M-Na]$^+$; found 754.2759. α_D 473.3 (*c* 2.4, CH_2Cl_2). IR ν_{max} 2956, 1696 (C=O), 1399, 1174, 955, 829 cm^{-1}. Major rotamer (61%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm): 129.7 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.48 (m, 18H, CH_3, $SiMe_3$), 1.18 (s, 3H, CH_3), 1.32 (m, 3H, CH_3), 1.40 (s, 9H, CH_3, ^{t}Bu, NBoc), 3.53 (dd, 1H, CH_2-N, $^2J_{H-H}$ =11.9 Hz, $^2J_{H-H}$ =5.7 Hz), 3.76 (m, 2H, CH_2-OP, CH_2-N), 4.00 (m, 2H, CH_2-OP, CH), 4.54 (m, 1H, CH-O), 4.61 (m, 1H, CH-O), 6.85 (m, 2H, CH=), 7.08 (m, 2H, CH=), 7.33 (m, 2H, CH=), 7.66 (m, 2H, CH=), 8.07 (m, 2H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): -0.6 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 21.1 (C, ^{t}Bu, NBoc), 24.6 (CH_3), 28.0 (CH_3, ^{t}Bu, NBoc), 28.2 (CH_3), 54.2 (CH_2-N), 63.3 (CH), 64.6 (CH_2-OP), 78.9 (CH-O), 82.4 (CH-O), 111.0 (C), 124.9 – 153.7 (aromatic carbons), 153.7 (C=O). Minor rotamer (39%): ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm), 130.6 (s). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.48 (m, 18H, CH_3, $SiMe_3$), 1.12 (s, 3H, CH_3), 1.20 (m, 9H, CH_3, ^{t}Bu, NBoc), 1.32 (m, 3H, CH_3), 3.15 (m, 1H, CH_2-N), 3.25 (dd, 1H, CH_2-OP, $^2J_{H-H}$ =12.6 Hz, $^3J_{H-H}$ =5.7 Hz), 4.00 (m, 3H, CH_2-N, CH_2-OP, CH), 4.25 (m, 1H, CH-O), 4.54 (m, 1H, CH-O), 6.85 (m, 2H, CH=), 7.08 (m, 2H, CH=), 7.21 (m, 2H, CH=), 7.66 (m, 2H, CH=), 8.07 (m, 2H, CH=). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm): -0.5 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 21.1 (C, ^{t}Bu, NBoc), 24.6 (CH_3), 26.8 (CH_3, ^{t}Bu, NBoc), 28.2 (CH_3), 52.5 (CH_2-N), 63.7 (CH), 64.0 (CH_2-OP), 78.8 (CH-O), 82.6 (CH-O), 111.2 (C), 124.9 – 153.7 (aromatic carbons), 153.2 (C=O).

(2R,3R,4S)-N-(3,5-Bis (trifluoromethyl) phenyl)-2-diphenylphosphinomethyl-3,4-O-isopropylidene-pyrrolidine-1-carbothioamide-3,4-diol (L11).

To a solution of **9**[8] (195 mg, 0.570 mmol) in dry CH_2Cl_2 (6 mL) 3,5-bis(trifluoromethyl) phenylisothiocyanate (0.26 mL, 1.5 mmol) was added. The reaction mixture was allowed to stand at r.t. for 3.5 h and then concentrated to dryness. Purification by column chromatography on silica gel (AcOEt: cyclohexane - 1:5) gave **L11** (230 mg, 0.370 mmol, 66%) as a white foam. ^{31}P NMR (121.5 MHz, $CDCl_3$, δ ppm) δ -20.6 (s). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) δ 1.40 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.60 (ddd, 1H, CH_2-P, $^2J_{H-H}$ = 14.0 Hz, $^2J_{H-H}$ = 4.5 Hz, $^3J_{H-H}$ = 2.5 Hz), 2.79 (dd, 1H, CH_2-P, $^2J_{H-H}$ = 14.0 Hz, $^3J_{H-H}$ = 9.0 Hz), 3.65 (dd, 1H, CH_2-N, $^3J_{H-H}$ = 4.5 Hz), 4.40 (m, 1H, CH-N), 4.55 (dd, 1H, CH_2-N, $^2J_{H-H}$ = 13.0 Hz, $^3J_{H-H}$ = 7.5 Hz), 4.84 (m, 1H, CH-O), 4.94 (br t, 1H, CH-O, $^3J_{H-H}$ = $^3J_{H-H}$ = 6.5 Hz), 6.93 (br d, 1H, NH, *J* = 2.5 Hz), 7.28 (m, 3H, CH=), 7.36 (m, 3H, CH=), 7.48 (m, 4H, CH=), 7.64 (m, 3H, CH=), ^{13}C NMR (125.7 MHz, $CDCl_3$, δ ppm) δ 25.3 (CH_3), 26.6 (CH_3), 28.8 (d, CH_2-P, $J_{C,P}$ = 13.9 Hz), 54.9 (CH_2-N), 60.2 (d, CH-N, $J_{C,P}$ = 23.1 Hz), 77.1 (CH-O), 79.9 (d, CH-O, $J_{C,P}$ = 3.0 Hz), 114.0 (C), 118.9 (c, $J_{C,F}$ = 3.8 Hz, CH=), 123.2 (c, $J_{C,F}$ = 272.6, CF_3), 140.5-124.9 (Aromatic carbons), 179.3 (C=S), α_D +42.4 (*c* 0.58, CH_2Cl_2). ESI-HRMS *m/z* found 613.1497, calc. for $C_{29}H_{28}F_6N_2O_2PS$ [M+H]$^+$: 613.1508. IR ν_{max} 3238 (NH), 2993, 2927, 1371, 1275 (C=S), 1126 (C-F), 695 cm^{-1}.

(6S,7R,7aS)-6,7-Dihydroxy-tetrahydropyrrolo [1,2-c]-oxazol-3-one (10).

To a solution of compound **8**[8] (170 mg, 0.850 mmol) in THF (8 mL) cooled to 0 °C, a solution of 4M HCl (8 mL) was added dropwise. After 3 h at r.t., the reaction mixture was concentrated to dryness and the resulting crude was purified by column chromatography on silica gel (CH_2Cl_2: MeOH - 20: 1 → 10: 1) to give **10** (122 mg, 0.770 mmol, 90%) as a white solid. The NMR data and IR are consistent with those of its enantiomer.[7] α_D +28.4 (*c* 0.49, CH_2Cl_2). ESI-HRMS *m/z* found 182.0420, calc. for $C_6H_9NO_4Na$ [M+Na]$^+$: 182.0424.

(6S,7R,7aS)-6,7-O-Bis(benzyloxy)-tetrahydropyrrolo[1,2-c]oxazol-3-one (11) .

To a mixture of **10** (36 mg, 0.23 mmol) and NaH (35 mg, 1.4 mmol) in dry DMF (1.8 mL) at 0 °C BnBr (163 µL, 1.37 mmol) was added dropwise. The reaction mixture was stirred at r.t. under Ar for 5.5 h, cooled to 0 °C and then Et_3N (2 mL) and MeOH (2 mL) were added. The reaction mixture is concentrated to dryness. The residue was diluted with CH_2Cl_2 and washed with H_2O and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated to dryness. Purification by column chromatography on silica gel (AcOEt: cyclohexane - 1:2 → 1:1) furnished **11** (70 mg, 0.21 mmol, 90%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 3.27 (dd, 1H, CH_2-N, $^2J_{H,H}$ = 11.4 Hz, $^3J_{H,H}$ = 5.7 Hz), 3.74 (dd, 1H, CH_2-N, $^2J_{H-H}$= 11.4 Hz, $^3J_{H,H}$ = 5.7 Hz), 3.95 (m, 2H, CH-O, CH-N), 4.14 (td, 1H, CH-O, $^3J_{H-H}$= $^3J_{H-H}$= 5.7 Hz, $^3J_{H-H}$= 3.3 Hz), 4.31 (t, 1H, CH_2-O,$^2J_{H-H}$= $^3J_{H-H}$= 8.4 Hz), 4.57-4.48 (m, 3H, CH_2Ph, CH_2Ph, CH_2-O), 4.65 (d, 1H, CH_2Ph), 4.87 (d, 1H, CH_2Ph, $^2J_{H,H}$= 12.0 Hz), 7.31 (m, 10H, CH=), ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 49.0 (CH_2-N), 59.2 (CH-N), 63.9 (CH_2-O), 72.2 (CH_2Ph), 73.2 (CH_2Ph), 77.4 (CH-O), 80.2 (CH-O), 137.9-127.9 (Aromatic carbons), 162.8 (C=O), α_D +36.9 (*c* 0.78, CH_2Cl_2). IR ν_{max} 2922, 2894, 1749 (C=O), 1244, 766, 697 cm^{-1}. ESI-HRMS *m/z* found 362.1353, calc. for $C_{20}H_{21}NO_4Na$ [M+Na]$^+$: 362.1363.

(2R,3S,4R)-N-Benzyloxycarbonyl-2-ethoxycarbonylethyl-yl-3,4-O-isopropyliden-pyrrolidine-3,4-diol (14).

To a solution of **13**[10] (751 mg, 3.28 mmol) in EtOH:H_2O (1:1) (12 mL) $NaHCO_3$ (276 mg, 3.28 mmol) and CbzCl (0.55 mL, 3.6 mmol) were added. The reaction mixture was stand at r.t. for 3 h. Then saturated aqueous solution of $NaHCO_3$ (25 mL) was added and the aqueous phase was extracted with AcOEt (3 x 15 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to dryness. Purification by column chromatography on silica gel (AcOEt: cyclohexane - 1:3) gave **14** (1.15 g, 3.16 mmol, 97%) as a colorless oil. NMR and IR data coincide with those of its enantiomer.[10b] α_D -55.2 (*c* 0.73, CH_2Cl_2). CI-HRMS *m/z* found 364.1756, calc. for $C_{19}H_{26}NO_6$ [M+H]$^+$: 364.1760.

(2R,3S,4R)-N-Benzyloxycarbonyl-2-hydroxyethyl-3,4-O-isopropiliden-pyrrolidine-3,4-diol (15).

To a suspension of $LiAlH_4$ (35 mg, 0.91 mmol) in dry Et_2O (3 mL) cooled at -10 °C, a solution of **14** (275 mg, 0.756 mmol) in dry Et_2O (5 mL) was added dropwise under Ar. After 10 min, sat. aq. soln. of Na_2SO_4 (30 mL) was added dropwise and the mixture was diluted with water and extracted with AcOEt (3x50 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to dryness. The resulting crude was purified by column chromatography on silica gel (toluene: acetone - 5:1) to afford **15** (171 mg, 0.532 mmol, 70%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 1.34 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.78 (m, 1H, CH_2-CH_2O), 1.98 (m, 1H, CH_2-CH_2O), 3.31 (dd, 1H, CH_2-N, $^2J_{H-H}$= 12.3 Hz, $^3J_{H-H}$= 4.2 Hz), 3.63 (m, 2H,-CH_2O), 3.97 (dd, 1H, CH_2-N, $^2J_{H-H}$= 12.3 Hz, $^3J_{H-H}$= 6.9 Hz), 4.24 (m, 1H, CH-N), 4.75 (m, 2H, CH-O), 5.12 (s, 2H, CH_2Ph), 7.34 (m, 5H, CH=), ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 25.2 (CH_3), 26.4 (CH_3), 32.4 (CH_2-CH_2O), 49.7 (CH_2-N), 57.0 (CH-N), 59.3 (CH_2O), 67.5 (CH_2Ph), 78.3 (CH-O), 79.7 (CH-O), 113.5 (C), 136.4-128.5 (Aromatic carbons), 155.4 (C=O). α_D -25.6 (*c* 0.78, CH_2Cl_2). IR ν_{max} 3472 (OH), 2948, 1677 (C=O), 1422, 1079, 696 cm^{-1}. ESI-HRMS *m/z* found 344.1466, calc. for $C_{17}H_{23}NO_5Na$ [M+Na]$^+$: 344.1468.

Typical Procedure for the hydrogenation of minimally functionalized olefins

The corresponding ligand (**L1**-**L11**) (0.01 mmol) was dissolved in CH_2Cl_2 (2 mL) and $[Ir(cod)_2]BAr_F$ (0.01 mmol, 4.0 mg) was added. Then, substrate (0.5 mmol) was added to the solution. The mixture was introduced in a high-pressure autoclave. The autoclave was purged four times with

hydrogen and then pressurized to the desired hydrogen 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 Celite plug. The enantiomeric excess was determined by chiral GC or chiral HPLC, and the conversions were determined by ^1H NMR or chiral GC (see Supporting Information for characterization and ee determination details).

Acknowledgements

Financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P and CTQ2016-77270-R) and European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2014SGR670 and 2017SGR1472), and the ICREA Foundation (ICREA Academia award to M.D) is gratefully acknowledged. We also acknowledge the Spanish Ministry of Education for a FPU fellowship (PER), Dr. Elena Moreno-Clavijo for helpful discussions and CITIUS-NMR-MS service of the University of Seville for technical assistance.

Keywords: asymmetric hydrogenation • iridium • P,O ligands • olefins • unfunctionalized

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Entry for the Table of Contents

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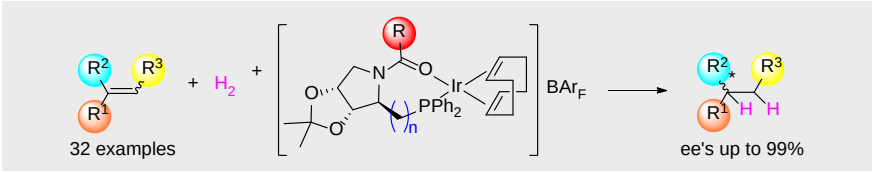

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Page No. – Page No.

Pyrrolidine-based P,O ligands from carbohydrates: Easily accessible and modular ligands for the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins

The potential of P,O-iminosugar based ligands in the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins is presented. Improving previous results, we have demonstrated that the use of a more-rigid bicyclic backbone not only affected positively the enantioselectivity but also extended the range of substrates that can be efficiently reduced.