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P-Stereogenic N-Phosphine-Phosphite Ligands for the Rh-Catalyzed Hydrogenation of Olefins

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KEYWORDS: *Asymmetric hydrogenation, olefins, rhodium, P-P' ligands, P-stereogenic N-phosphine-based ligands, phosphite ligands.*

ABSTRACT: We have identified a successful family of simple P-stereogenic *N*-phosphine-phosphite ligands for the Rh-catalyzed asymmetric hydrogenation of olefins. These catalysts show excellent enantiocontrol for α-dehydroamino acid derivatives and α-enamides (ee's up to >99%) and promising results for the more challenging β-analogues (ee's up to 80%). The usefulness of these catalytic systems was further demonstrated with the synthesis of several valuable precursors of pharmacologically active compounds, with ee's at least as high (up to >99%) as the best ones reported.

INTRODUCTION

Catalytic asymmetric hydrogenation (AH) is one of the most reliable transformations for the preparation of enantiopure compounds. Its operational simplicity, high efficiency and perfect atom economy are key aspects that explain its predominant role in industry.[1] Over the years the scope of this transformation has been extended in terms of reactant structure and catalyst efficiency. Thus, while chiral analogues of the Ir-Crabtree catalyst dominate the reduction of unfunctionalized olefins,[2] the hydrogenation of functionalized olefins is dominated by Rh- and Ru-catalysts containing chiral diphosphine, diphosphinite and diphosphite ligands.[3] Despite the early success of the P-stereogenic diphosphine ligand DIPAMP,[4] used in the industrial production of L-DOPA (a drug used to treat Parkinson's disease),[5] most of the diphosphine ligands have been designed by introducing the stereogenic center at the ligand backbone rather than in the P-atoms, thus losing the advantage that a stereogenic center near the metal center can provide.[3] The main reason is the difficulty in the preparation of phosphines bearing the chirality on the P atom. With the development of new straightforward methodologies to obtain the chirality on the phosphine moiety, some P-stereogenic phosphine ligands have emerged and been successfully applied in this process (e.g. QuinoxP*, BenzP*, Binapine, Zhangphos, Duanphos, BIBOP,TCFP, MaxPHOS …; Figure 1)[6].

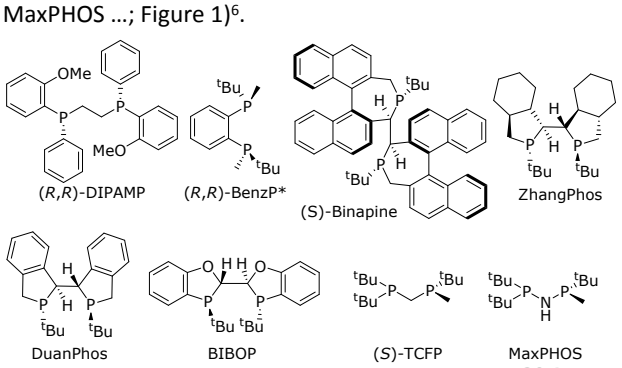


Figure 1. Example of some representative P-stereogenic diphosphine ligands.

The Rh-catalyzed asymmetric hydrogenation has also benefit from the use of heterodonor ligands. The presence of the two functionalities not only enables electronic differentiation, but also facilitates the catalyst optimization, since both functionalities can be independently boosted. Among the heterodonor ligands, mixed P,P'-ligands have been successfully applied in the Rh-catalyzed AH of a broad range of functionalized substrates.[7] Among them, ligands combining a phosphine group with a more π-acceptor phosphorus moiety (i.e. phosphite or phosphoroamidite) have demonstrated a high potential in this process. In this context, some research groups made significant contributions in terms of substrate scope with the development of phosphine-phosphite/phosphoroamidite ligands.[8,9] Nevertheless, for this latter class of ligands, the introduction of a P-stereogenic phosphine moiety on the ligand design has been overlooked.[8b,10] One of the simplest ways to introduce a P-stereogenic center is to use Jugé's approach using a chiral 1,2-aminoalcohol as template.[11] Following this procedure some P-stereogenic *N*-phosphine-phosphinite ligands were developed for this process.[12] To best of our knowledge, there is only one report by Kamer et al. more than 10 year ago, on the use of heterodonor P-stereogenic *N*-phosphine-phosphite ligands.[13] They showed the application of a series of resin-bound P-stereogenic *N*-phosphine-phosphite ligands in the AH of a limited range of α-dehydroamino acids with only moderate-to-good enantioselectivities (ee's up to 89%). To further study the possibilities of this ligand design, we have expanded the range of ligands to include other substituents in the stereogenic *N*-phosphine group (ligands **L1–L3**; Figure 2) and other biaryl phosphite functionalities (**a–c**). In addition, for comparison, we also synthesized ligands **L4b–c** without chirality on the *N*-phosphine moiety.[14]

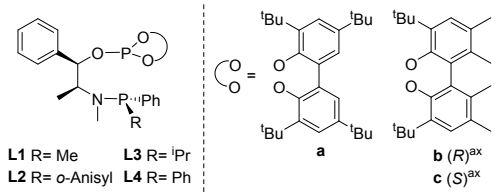


Figure 2. P-stereogenic *N*-phosphine-phosphite ligands **L1–L4a–c**.

RESULTS AND DISCUSSION

Ligands **L1–L4a–c** were easily accessible from readily available (1*R*,2*S*)-(-)-ephedrine **1** (Scheme 1). The synthesis of ligands **L1–L3a–c** started with the condensation of **1** with bis(diethylamino)phenyl phosphine followed by in situ protection of the P-atom to obtain the key intermediate borane-protected oxazaphospholidine **2** (step i).[15] Then, ring opening of **2** with the corresponding organolithium reagent resulted in exclusive cleavage of the P-O bond to give the desired hydroxyl compounds **3–5** (step ii).[15] The ring opening of compound **2** proceeded with retention of the configuration at the phosphorus atom leading to the corresponding enantiopur compounds after recrystallization. Reaction of **3–5** with the desired phosphorochloridite ($ClP(OR)_2$; $(OR)_2$= **a–c**; step iii) under basic conditions followed by deprotection of the P-stereogenic *N*-phosphine moiety lead to ligands **L1–L3a–c**. Note that for ligands **L2b** and **L2c**, the deprotection of phosphine takes place during the introduction of the phosphite moiety. Ligands **L4** were obtained in a two-step procedure by coupling **1** with the desired phosphorochloridite (step iii) to form amino-phosphites **6** and the subsequent reaction of these intermediates with chlorodiphenylphosphine (step v). All ligands were obtained as white solids after purification on neutral silica or alumina and were stable to oxidation under air atmosphere if kept at low temperature. The ligands were therefore manipulated and stored in the air, and it was not necessary to use a dry box. All characterization data (NMR and HRMS-ESI) were as expected for these C_1-symmetric ligands. Thus, for example the ^{31}P NMR spectra showed the two typical signals for the phosphite, around 150 ppm, and for the *N*-phosphine, c.a. 68 ppm, functionalities.

In a first step of experiments we evaluated N-phosphine-phosphite ligands **L1–L4a–c** in the Rh-catalyzed AH of benchmark α-dehydroamino acid derivatives, methyl 2-acetamidoacrylate **S1** and methyl 2-acetamidocinnmate **S2** (Table 1). Full conversion was obtained in all cases after only two hours of reaction. Comparing the results obtained with ligands **L1a-c**, the fact that the highest enantioselectivity is obtained with ligand **L1c** (entry 1 vs 2 and 3) indicates that the ephedrine ligand backbone is not able to control the tropoisomerism of the biaryl phosphite moiety **a** upon coordination to the rhodium (entry 1 vs 2 and 3). It is also seen that there is a cooperative effect between the configuration of the biaryl phosphite group and that of the N-phosphine moiety that results in a matched combination for ligands containing the enantiopure (*S*)-biaryl phosphite moiety **c** (e.g. entry 3 vs 1 and 2). These results agree with the lower activities and enantioselectivities reported with related P-sterogenic *N*-phosphine-phosphite ligands with an achiral unsubstituted biaryl phosphite moiety by Kamer et al.[16] We also found that the amino-phosphine substituent affect the catalytic performance (Table 1, entries 3, 5 and 7). Thus, the best enantioselectivity (>99%) was achieved with ligand **L2c** with a bulky *ortho*-anisyl substituent at the P-stereogenic N-phosphine group. Finally, albeit enantioselectivities up to 96% ee(entry 9) could be achieved with ligand **L4c**, with a diaryl *N*-phosphine group, the presence of a P-stereogenic unit is crucial to maximize enantioselectivities, up to ≥99% ee for both substrates (entry 5). In summary, the best enantioselectivity was obtained with ligand **L2c** which contains the best combination of ligand parameters.

Interestingly, we also found that the replacement of THF for a more environmentally friendly solvent such as 1,2-propylene carbonate (PC)[17] did not deteriorate activity or enantioselectivity (99% ee, entry 10).

Scheme 1. *N*-phosphine-phosphite ligands L1–L4a–c.

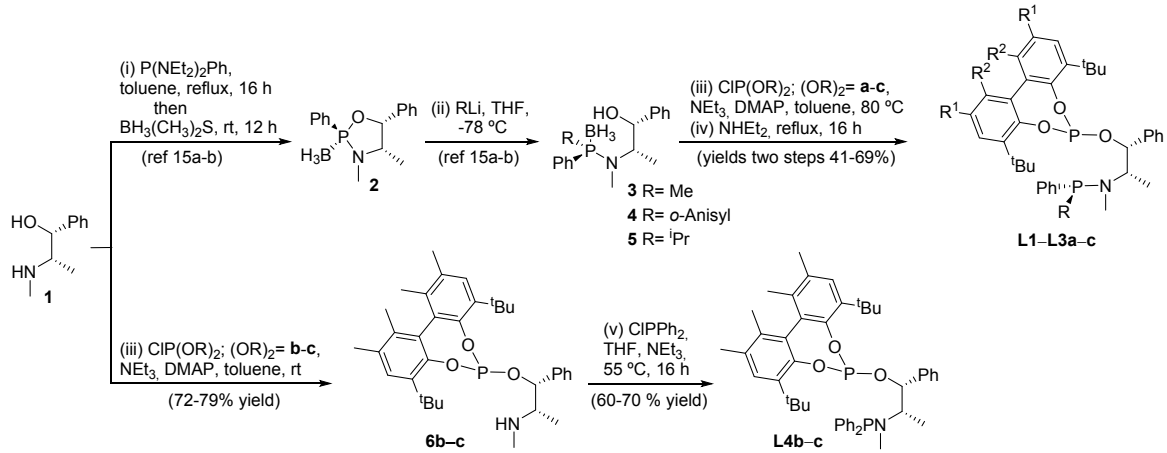
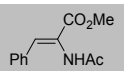


Table 1. Asymmetric hydrogenation of α-dehydroamino acid derivatives S1 and S2 using Rh/L1–L4a–c catalysts precursors[a]


S1


S2

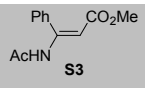
Entry	Ligand	%Conv[b]	% ee[c]	%Conv[b]	% ee[c]
1	**L1a**	100	61 (*R*)	100	61 (*R*)
2	**L1b**	100	66 (*R*)	100	64 (*R*)
3	**L1c**	100	85 (*R*)	100	80 (*R*)
4	**L2b**	100	40 (*R*)	100	37 (*R*)
5	**L2c**	100 (96)	99 (*R*)	100 (97)	>99 (*R*)
6	**L3b**	100	25 (*S*)	100	7 (*R*)
7	**L3c**	100	81 (*R*)	100	68 (*R*)
8	**L4b**	100	50 (*S*)	100	52 (*S*)
9	**L4c**	100	94 (*R*)	100	96 (*R*)
10[d]	**L2c**	99	99 (*R*)	95	99 (*R*)

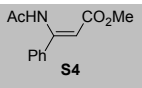
[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), substrate (0.25 mmol), THF (2 mL), H_2 (25 bar), 2 h at rt. [b] Conversions measured by GC. Isolated yields shown in parenthesis. [c] Enantiomeric excesses determined by GC. [d] Reaction carried out using PC as solvent. Conversion measured after 1 h.

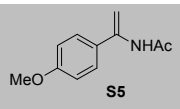
We then proceeded to study ligands **L1–L4a–c** in the hydrogenation of β-dehydroamino acid derivatives and enamides (Table 2). The hydrogenation of such type of substrates lead to important motifs present in many biologically active products (e.g. β-peptides and secondary amines, respectively). In most reported cases, the hydrogenation of β-dehydroamino acid derivatives is highly dependent upon the olefin geometry, being the *Z*-isomers more difficult to be efficiently hydrogenated than the *E*-olefins.[18,19] We therefore chose *E*- and *Z*-methyl 3-acetamido-3-phenylacrylates (**S3** and **S4**) as model substrates. We obtained higher ee's in the hydrogenation of the *Z*-olefin than for the *E*-olefin. As expected, each isomer needs a different ligand to maximize the enantioselectivity. They differ in the substituent of the P-stereogenic *N*-phosphine group and both have *S* configuration in the biaryl phosphite moiety. Thus, while for substrate **S3** (with *E*-geometry) the use of ligand **L2c**, with a bulky *ortho*-anisyl substituent at the P-stereogenic *N*-phosphine group, provided the best enantioselectivity (60% ee, entry 5), the ligand **L1c** afforded the best ee's for substrate **S4** (with *Z*-geometry; 80% ee, entry 3). Results also showed that for this substrate the P-stereogenic *N*-phosphine moiety is crucial to achieve good enantioselectivities (the use of ligands **L4** led to poor ee's, up to 25%, entries 8 and 9).

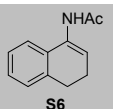
Regarding the AH of enamides, we selected *N*-(1-(4-methoxyphenyl)vinyl)acetamide **S5**, *N*-(3,4-dihydro-1-naphthalenyl)acetamide **S6**, *N*-(2H-chromen-4-yl)acetamide **S7** and *N*-(3,4-dihydro-2-naphthalenyl)acetamide **S8** as substrates (Table 2). High enantioselectivities have been obtained in α-enamide **S5** and the more challenging cyclic α-enamides **S6** and **S7**, for which only a few successful examples can be found in the literature.[20] Again, the results indicated that the ligand parameters have to be carefully selected for each substrate to maximize enantioselectivity. For instance, the highest enantioselectivities for the AH of acyclic α-enamide **S5** were obtained using ligands **L1b–c**, with a methyl at the P-stereogenic *N*-phosphine group (entries 2 and 3), while ligand **L2c** provided the highest ee's for cyclic α-enamides **S6** and **S7** (entry 5). In addition, for acyclic α-enamide **S5**, both enantiomers of the hydrogenated product were accessible by simply varying the configuration of the biaryl phosphite moiety (entries 2 and 3). Albeit the hydrogenation of β-enamide **S8** proceeded with lower enantiocontrol (up to 80% ee, entry 9) than for α-enamides, this was not unexpected since the cyclic β-enamides are one of the most challenging substrates for this transformation.[20d,21] We also performed the reactions in 1,2-propylene carbonate (Table 2). The enantioselectivities remained as high as those achieved with THF.

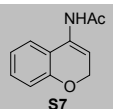
Table 2. Asymmetric hydrogenation of β-dehydroamino acid derivatives S3 and S4 and enamides S5–S8 using Rh/L1–L4a–c catalysts precursors[a]

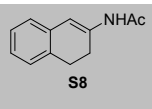

S3


S4


S5


S6

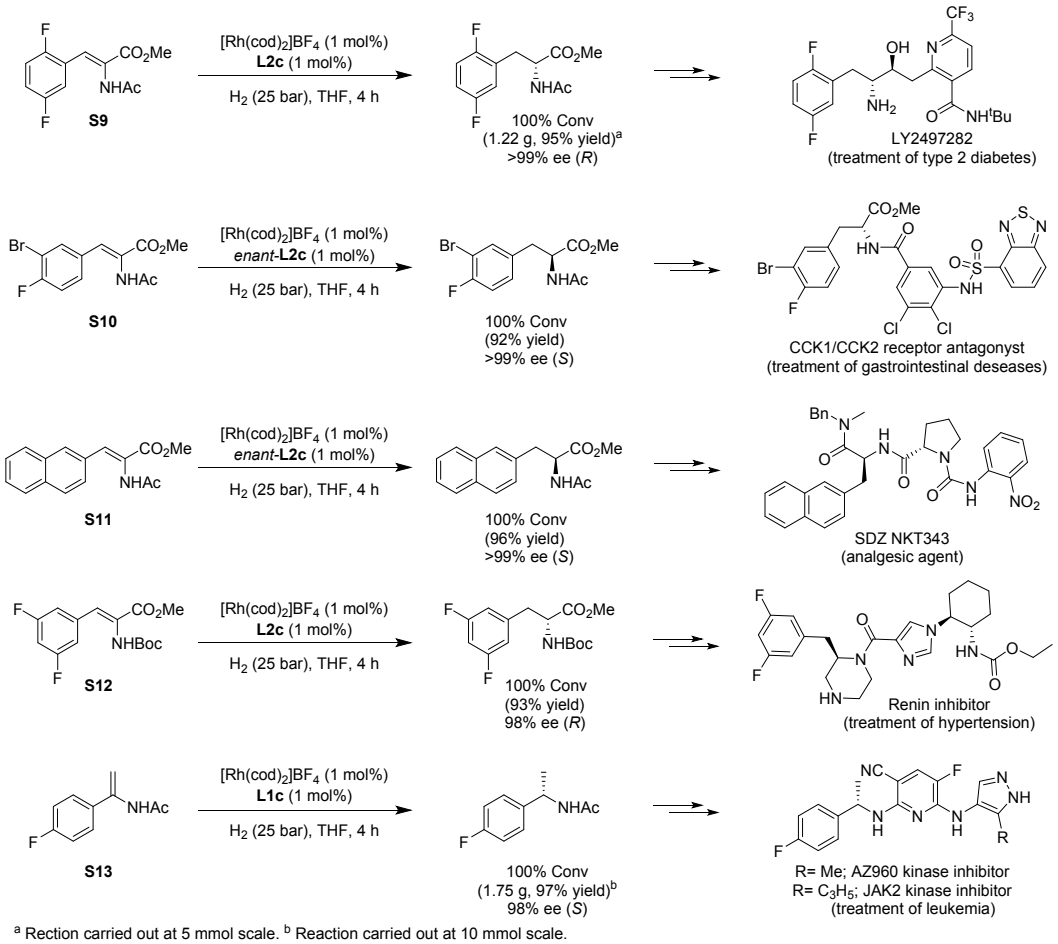

S7


S8

Entry	Ligand	% ee[b]	% ee[b]	% ee[b]	% ee[b]	% ee[b]	% ee[b]
1	**L1a**	14 (*R*)	31 (*R*)	80 (*S*)	35 (*R*)	38 (*R*)	58 (*R*)
2	**L1b**	3 (*S*)	21 (*S*)	96 (*R*)[c,f]	53 (*S*)	51(*S*)	7 (*R*)
3	**L1c**	22 (*R*)	80 (*R*)[c,e]	96 (*S*)[g]	74 (*R*)	73 (*R*)	55 (*R*)
4	**L2b**	3 (*R*)	8 (*S*)	64 (*S*)	5 (*S*)	2 (*S*)	17(*S*)
5	**L2c**	60 (*R*)[c,d]	20(*S*)	84 (*S*)	95 (*R*)[c,h]	94(*R*)[i]	44 (*R*)
6	**L3b**	15 (*S*)	76 (*S*)	76 (*S*)	61 (*R*)	63 (*R*)	5 (*S*)
7	**L3c**	2 (*S*)	15 (*R*)	2 (*R*)	24 (*S*)	22 (*S*)	4 (*R*)
8	**L4b**	25 (*R*)	15 (*S*)	7 (*R*)	2 (*R*)	1 (*R*)	9(*S*)
9	**L4c**	16 (*R*)	1 (*S*)	82 (*S*)	84 (*R*)	85 (*R*)	80 (*R*)[c,j]

[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (1 mol%), ligand (1 mol%), substrate (0.25 mmol), THF (2 mL), H_2 (25 bar), 2 h at rt. Full conversions were achieved in all cases. [b] Enantiomeric excesses determined by GC or HPLC. [c] Full conversions and the same ee's were achieved using PC as solvent under typical reaction conditions. [d] 94% yield. [e] 93% yield. [f] 92% yield. [g] 90% yield. [h] 93% yield. [i] 87% yield. [j] 91% yield.

Scheme 2. Examples of chiral drugs that can be synthesized by using asymmetric hydrogenation with Rh/L1–L4a–c catalysts.



[a] Rection carried out at 5 mmol scale. [b] Reaction carried out at 10 mmol scale.

Encouraged by the previous results, we finally targeted substrates **S9**–**S13** whose hydrogenation led to valuable chiral synthons for the synthesis of a range of drugs such as compound LY2497282,[22] CCK1/CCK2 receptor antagonist,[23] analgesic SDZNKT343,[24] renin inhibitor[25] and AZ960 and JAK2 kinase inhibitors[26] (Scheme 2). In all cases reactions proceeded smoothly with an excellent enantiocontrol. Finally, it should be noted that ligands **L1-L4** are very robust to the different substrate decorations. Thus, the ee's (up to >99%) achieved in the hydrogenation of **S9**–**S13** are at least as high as the best achieved in the literature.[27] In addition, the hydrogenation can also be carried out at large scale (see the hydrogenation of **S9** and **S13** as examples) maintaining the high enantioselectivities.

CONCLUSIONS

In summary, we have identified a successful family of P-stereogenic *N*-phosphine-phosphite ligands with a simple backbone for the Rh-catalyzed AH of functionalized olefins (ee's up to >99%). All ligands can be modulated by a simple and efficient synthetic route from readily available sources. This modularity was key in finding the most efficient catalyst for the reduction of each type of olefin. A chiral biaryl phosphite moiety and a P-stereogenic *N*-phosphine group with the right choice of its substituent are needed to maximize the enantioselectivity. The exception is substrate **S8** that also has good enantioselectivity with an achiral N-phosphine group. Moreover, the reactions can be carried out in the environmentally friendly 1,2-propylene carbonate with no loss of enantioselectivity. Finally, to evaluate the potential impact of these Rh/P-sterogenic N-phosphine-phosphite catalysts in synthesis, we applied them to synthesize several chiral synthons for the preparation of pharmacological compounds, with ee's at least as high (up to >99%) as the best ones reported. These results pave the way for the further development of new generation of modular P-stereogenic N-phosphine-phosphite ligands, with a simple ligand backbone that are readily available and easy-to-synthesize, for the AH of relevant olefins.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Solvents were purified and dried by standard procedures. Borane-protected oxazaphospholidine **2**[15], borane-protected *N*-phosphine-hydroxyl compounds **3–5**[15] and

phosphorochloridites[28] were prepared as previously reported. ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^{1}H, ^{13}C, and ^{31}P assignments were made on the basis of ^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC and ^{1}H-^{31}P gHMBC experiments. Electrospray ionization (ESI) mass spectrometry analysis were run on a chromatographic system Agilent G3250AA liquid chromatography coupled to 6210 time of flight (TOF) mass spectrometer from Agilent Technologies with an ESI interface. Exact m/z values are reported in daltons. Substrates **S2**,[29] **S3**-**S4**,[30] **S5**,[31] **S6**–**S7**,[32] **S8**,[33] **S9**,[22] **S10**,[8f] **S11**,[26e] **S12**[8e] and **S13**[34] were prepared following the reported procedures, while substrate **S1** was commercially available and used as received.

General procedure for the preparation of *N*-phosphine-phosphite ligands L1–L3a–c. To a solution of *in situ* generated phosphorochloridite (1.1 mmol) in dry toluene (6 mL), triethylamine (0.27 mL, 2.0 mmol) was added. Then, this solution was placed in a 0 ºC bath. After 2 min at that temperature, a solution of the corresponding borane-protected N-phosphine-hydroxyl compound (1.0 mmol) and triethylamine (0.27 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at 0 °C. The mixture was left to warm to 80 ºC using an oil bath and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography or by filtration over neutral silicato afford **L1**·BH_3**a–c**, **L2b–c** and **L3**·BH_3**b–c** as white solids.

L1a·BH_3: Yield: 367 mg (60%) (flash chromatography under argon, using neutral silica and dry toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^{1}H\}$ NMR (161.9 MHz, C_6D_6): δ= 149.5 (bs, P-O), 68.6 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.10 (pt, 6H, CH_3-CH, CH_3-P, *J*= 8.6 Hz), 1.18 (s, 9H, CH_3, ^{t}Bu), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 18H, CH_3, ^{t}Bu), 1.95 (d, 3H, CH_3-N, $^{3}J_{H\text{-}P}$= 8.2 Hz), 4.38-4.44 (m, 1H, CH-N), 5.51-5.54 (m, 1H, CH-O), 6.82-6.85 (m, 2H, CH=), 6.98-7.12 (m, 7H, CH=), 7.21 (s, 1H, CH=), 7.27 (s, 1H, CH=), 7.48-7.54 (m, 3H, CH=). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, C_6D_6): δ= 10.8 (d, CH_3-P, $J_{C\text{-}P}$= 39.1 Hz), 13.4 (CH_3-CH), 28.4 (d, CH_3-N, $J_{C\text{-}P}$= 2.9 Hz), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 34.2 (d, C, ^{t}Bu, $J_{C\text{-}P}$= 8.1 Hz), 35.2 (C, ^{t}Bu), 57.8 (CH-N), 81.3 (CH-O), 124.0-146.4 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{45}H_{65}BNO_3P_2$ 740.4527; Found 740.4528.

L1b·BH_3: Yield: 458 mg (68%) (filtration under argon over neutral silica using dry toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^{1}H\}$ NMR (161.9 MHz, C_6D_6): δ= 143.1 (s, P-O), 68.3 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.01 (d, 3H, CH_3-P, $^{2}J_{H\text{-}P}$= 6.8 Hz), 1.08 (d, 3H, CH_3-CH, $^{3}J_{H\text{-}H}$= 8.8 Hz), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.84 (d, 3H, CH_3-N, $^{3}J_{H\text{-}P}$= 8.2 Hz), 2.00 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 4.34-4.44 (m, CH-N), 5.36 (dd, CH-O, $^{3}J_{H\text{-}P}$= 8.7 Hz, $^{3}J_{H\text{-}H}$= 6.6 Hz), 6.86-6.92 (m, 2H, CH=), 6.98-7.05 (m, 3H, CH=), 7.12-7.16 (m, 5H, CH=), 7.60-7.63 (m, 2H, CH=). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, C_6D_6): δ= 11.0 (d, CH_3-P, $^{1}J_{C\text{-}P}$= 38.8 Hz), 13.4 (CH_3-CH), 16.1 (CH_3), 16.5 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 28.1 (d, CH_3-N, $^{2}J_{C\text{-}P}$= 3.0 Hz), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 57.9 (d, CH-N, $^{2}J_{C\text{-}P}$= 10.1 Hz), 81.2 (CH-O), 127.4-145.4 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{41}H_{57}BNO_3P_2$ 684.3901; Found 684.3905.

L1c·BH_3: Yield: 492 mg (72%) (filtration under argon over neutral silica using dry toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^{1}H\}$ NMR (161.9 MHz, C_6D_6): δ= 140.9 (s, P-O), 68.4 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.10 (d, 3H, CH_3-P, $^{2}J_{H\text{-}P}$= 8.7 Hz), 1.14 (d, 3H, CH_3-CH, $^{3}J_{H\text{-}H}$= 6.5 Hz), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.13 (d, 3H, CH_3-N, $^{3}J_{H\text{-}P}$= 8.2 Hz), 4.31-4.37 (m, CH-N), 5.37 (dd, CH-O, $^{3}J_{H\text{-}P}$= 8.7 Hz, $^{3}J_{H\text{-}H}$= 6.6 Hz), 6.91-6.94 (m, 3H, CH=), 6.95-7.04 (m, 5H, CH=), 7.11 (s, 2H, CH=), 7.18-7.22 (m, 2H, CH=). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, C_6D_6): δ= 10.7 (d, CH_3-P, $^{1}J_{C\text{-}P}$= 38.8 Hz), 13.9 (CH_3-CH), 16.2 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 28.8 (d, CH_3-N, $^{2}J_{C\text{-}P}$= 3.0 Hz), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 57.9 (d, CH-N, $^{2}J_{C\text{-}P}$= 10.1 Hz), 80.2 (CH-O), 125.7-145.5 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{41}H_{57}BNO_3P_2$ 684.3901; Found 684.3903.

L2b: Yield: 259 mg (69%) (filtration under argon over neutral silica using dry toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^{1}H\}$ NMR (161.9 MHz, C_6D_6): δ= 143.4 (s, P-O), 55.9 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.34 (d, 3H, CH_3-N, $^{3}J_{H\text{-}H}$= 6.6 Hz), 1.52 (s, 18H, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.07 (d, CH_3-N, $^{3}J_{H\text{-}P}$= 2.7 Hz), 3.09 (s, 3H, CH_3-O), 3.97-4.04 (m, 1H, CH-N), 5.35 (pt, 1H, CH-OP, *J*= 8.8 Hz), 6.44 (dd, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.3 Hz, $^{4}J_{H\text{-}H}$= 4.1 Hz), 6.74 (t, 1H, CH=, $^{3}J_{H\text{-}H}$= 7.4 Hz), 6.85-6.86 (m, 2H, CH=), 6.93-7.05 (m, 4H, CH=), 7.06-7.20 (m, 6H, CH=), 7.47-7.50 (m, 2H, CH=). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, C_6D_6): δ= 15.7 (d, CH_3-CH, $^{3}J_{C\text{-}P}$= 4.2 Hz), 16.2 (CH_3), 16.6 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.3 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.3 Hz), 31.5 (CH_3-N), 31.6 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 54.4 (CH_3-O), 65.5 (d, CH-N, $^{2}J_{C\text{-}P}$= 41.8 Hz), 81.3 (dd, CH-O, $^{2}J_{C\text{-}P}$= 10.7 Hz, $^{3}J_{C\text{-}P}$= 6.6 Hz), 110.0-160.8 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{47}H_{58}NO_4P_2$ 762.3836; Found 762.3841.

L2c: Yield: 224 mg (59%) (filtration under argon over neutral silica using dry toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^{1}H\}$ NMR (161.9 MHz, C_6D_6): δ= 140.1 (s, P-O), 54.4 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.40 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 12H, CH_3, ^{t}Bu, CH_3-CH), 1.63 (s, 6H, CH_3), 2.00 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.26 (d, 3H, CH_3-N, $^{3}J_{H\text{-}P}$= 2.6 Hz), 3.11 (s, 3H, CH_3-O), 3.92-3.99 (m, 1H, CH-N), 5.49 (pt, 1H, CH-O, *J*= 7.7 Hz), 6.44-6.47 (m, 1H, CH=), 6.79 (t, 1H, CH=, $^{3}J_{H\text{-}H}$= 7.4 Hz), 6.77-6.81 (m, 1H, CH=), 6.90-7.01 (m, 8H, CH=), 7.08-7.13 (m, 5H, CH=). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, C_6D_6): δ= 16.0 (d, CH_3-CH, $^{3}J_{C\text{-}P}$= 5.3 Hz), 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.1 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.1 Hz), 31.4 (C, ^{t}Bu), 32.7 (d, CH_3-N, $^{2}J_{C\text{-}P}$= 9.5 Hz), 34.4 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 54.4 (CH_3-O), 65.3 (dd, CH-N, $^{2}J_{C\text{-}P}$= 39.7 Hz, $^{3}J_{C\text{-}P}$= 5.0 Hz), 80.9 (dd, CH-O, $^{2}J_{C\text{-}P}$= 9.9 Hz, $^{3}J_{C\text{-}P}$= 5.3 Hz), 110.1-160.9 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{47}H_{58}NO_4P_2$ 762.3836; Found 762.3840.

L3b·BH_3**:** Yield: 206 mg (58%) (filtration under argon over neutral silica using dry toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^{1}H\}$ NMR (161.9 MHz, C_6D_6): δ= 144.2 (s, P-O), 77.2 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.84-0.93 (m, 9H, CH_3, ^{i}Pr, CH_3-CH), 1.43 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu),

1.62 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.92 (d, 3H, CH_3-N, $^3J_{H-P}$= 7.8 Hz), 1.98 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.09-2.14 (m, 1H, CH, ^{i}Pr), 4.36-4.42 (m, 1H, CH-N), 5.50 (dd, 1H, CH-O, $^3J_{H-P}$= 8.8 Hz, $^3J_{H-H}$= 4.5 Hz), 6.97-7.01 (m, 4H, CH=), 7.07-7.16 (m, 4H, CH=), 7.50-7.54 (m, 2H, CH=), 7.62-7.64 (m, 2H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 11.5 (CH_3-CH), 15.4 (CH_3), 16.1 (CH_3), 16.4 (CH_3), 16.5 (d, CH_3, *J*= 5.5 Hz), 20.0 (d, CH_3, *J*= 3.1 Hz), 21.4 (CH_3), 21.9 (CH_3), 28.0 (d, CH_3-N, $^2J_{C-P}$= 4.2 Hz), 29.4 (CH-^{i}Pr), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 31.4 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 58.3 (d, CH-N, $^2J_{C-P}$= 8.3 Hz), 82.3 (d, CH-O, $^2J_{C-P}$= 4.4 Hz), 125.3-145.5 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{43}H_{61}BNO_3P_2$ 712.4214; Found 712.4218.

L3c·BH_3: Yield: 203 mg (57%) (filtration under argon over neutral silica using dry toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^1H\}$ NMR (161.9 MHz, C_6D_6): δ= 141.0 (s, P-O), 78.6 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.94-0.96 (d, 3H, CH_3-CH, $^4J_{H-P}$= 6.9 Hz), 0.99-1.05 (dd, 3H, CH_3-^{i}Pr, *J*= 17.3 Hz, *J*= 7.0 Hz), 1.20-1.26 (dd, 3H, CH_3-^{i}Pr, *J*= 15.4 Hz, *J*= 7.0 Hz), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.70 (s, 9H, CH_3, ^{t}Bu), 2.04 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.26-2.33 (m, 1H, CH-^{i}Pr), 2.47 (d, 3H, CH_3-N, $^3J_{H-P}$= 7.8 Hz), 4.54-4.61 (m, 1H, CH-N), 5.74 (dd, 1H, CH-O, $^3J_{H-P}$= 8.2 Hz, $^3J_{H-H}$= 3.8 Hz), 6.96-7.32 (m, 10H, CH=), 7.65-7.67 (m, 2H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 11.3 (CH_3-CH), 15.9 (CH_3), 16.2 (CH_3), 16.4 (CH_3), 16.7 (CH_3), 20.0 (CH_3), 20.2 (CH_3), 29.1 (d, CH_3-N, $^2J_{C-P}$= 4.2 Hz), 29.5 (CH-^{i}Pr), 31.0 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 31.5 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 58.2 (CH-N), 81.6 (CH-O), 121.0-150.6 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{43}H_{61}BNO_3P_2$ 712.4214; Found 712.4219.

For deprotection, the borane-adduct (0.68 mmol) was dissolved in dry and deoxygenated diethylamine (20 mL) and heated to 55 ºC using an oil bath for 16 h. After this time, the mixture was evaporated to dryness and the residue was purified by flash chromatography to afford the corresponding ligands as white solids.

L1a: Yield: 221 mg (75%) (flash chromatography under argon using neutral alumina and dry and deoxygenated toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^1H\}$ NMR (161.9 MHz, C_6D_6): δ= 147.8 (bs, P-O), 49.5 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.10 (d, 3H, CH_3-P, $^2J_{H-P}$= 8.4 Hz), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.26 (s, 9H, CH_3, ^{t}Bu), 1.31 (d, 3H, CH_3-CH, $^3J_{H-H}$= 6.6 Hz), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 2.08 (d, 3H, CH_3-N, $^3J_{H-P}$= 8.0 Hz), 3.73-3.80 (m, 1H, CH-N), 5.38 (pt, 1H, CH-O, *J*= 8.4 Hz), 6.82-6.86 (m, 1H, CH=), 6.96-7.09 (m, 7H, CH=), 7.27 (s, 2H, CH=), 7.33-7.35 (m, 2H, CH=), 7.51-7.53 (m, 2H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 12.2 (d, CH_3-P, $^1J_{C-P}$= 21.7 Hz), 16.3 (d, CH_3-CH, $^3J_{C-P}$= 6.5 Hz), 30.5 (d, CH_3-N, $^2J_{C-P}$= 8.2 Hz), 30.6 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 34.3 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 64.7 (d, CH-N, $^3J_{C-P}$= 38.1 Hz), 80.6 (CH-O), 123.9-146.4 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{45}H_{62}NO_3P_2$ 726.4199; Found 726.4236.

L1b: Yield: 74 mg (60%) (flash chromatography under argon using neutral alumina and dry and deoxygenated toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^1H\}$ NMR (161.9 MHz, C_6D_6): δ= 143.0 (s, P-O), 51.2 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.03 (d, 3H, CH_3-P, $^1J_{H-P}$= 6.3 Hz), 1.21 (d, CH_3-CH, $^3J_{H-H}$= 6.7 Hz), 1.53 (s, CH_3, 18H, ^{t}Bu), 1.66 (s, CH_3), 1.74 (CH_3), 1.95 (d, CH_3-N, $^2J_{H-P}$= 3.5 Hz), 2.01 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 3.74-3.84 (m, 1H, CH-N), 5.23 (pt, CH-O, *J*= 8.9 Hz), 6.70-6.74 (m, 2H, CH=), 6.94-6.99 (m, 4H, CH=), 7.04-7.16 (m, 5H, CH=), 7.47-7.49 (m, 2H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 12.2 (d, CH_3-P, $^1J_{C-P}$= 22.2 Hz), 16.2 (CH_3), 16.4 (d, CH_3-CH, $^3J_{C-P}$= 4.7 Hz), 16.5 (CH_3), 20.1 (CH_3), 29.7 (d, CH_3-N, $^2J_{C-P}$= 8.9 Hz), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.6 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 64.8 (CH-N, $^2J_{C-P}$= 37.0 Hz), 80.7 (CH-O), 126.9-145.5 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{41}H_{54}NO_3P_2$ 670.3573; Found 670.3576.

L1c: Yield: 60 mg (67%) (flash chromatography under argon using neutral alumina and dry and deoxygenated toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^1H\}$ NMR (161.9 MHz, C_6D_6): δ= 140.6 (s, P-O), 49.0 (s, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 1.11 (d, 3H, CH_3-P, $^1J_{H-P}$= 6.5 Hz), 1.40 (d, CH_3-CH, $^3J_{H-H}$= 6.7 Hz), 1.43 (s, CH_3, 9H, ^{t}Bu), 1.57 (s, CH_3, 9H, ^{t}Bu), 1.63 (s, CH_3), 1.99 (CH_3), 2.06 (s, 3H, CH_3), 2.09 (d, CH_3-N, $^2J_{H-P}$= 3.6 Hz), 3.72-3.78 (m, 1H, CH-N), 5.33 (pt, CH-O, J= 7.7 Hz), 6.80-6.84 (m, 2H, CH=), 6.95-7.16 (m, 10H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 12.3 (d, CH_3-P, $^1J_{C-P}$= 21.4 Hz), 16.2 (CH_3), 16.3 (CH_3), 16.6 (d, CH_3-CH, $^3J_{C-P}$= 7.2 Hz), 20.0 (CH_3), 20.1 (CH_3), 30.8 (d, CH_3-N, $^2J_{C-P}$= 8.0 Hz), 31.0 (d, CH_3, ^{t}Bu, J_{C-P}= 5.2 Hz), 31.5 (CH_3, ^{t}Bu), 34.4 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 64.8 (CH-N), 80.2 (CH-O), 125.3-145.6 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{41}H_{54}NO_3P_2$ 670.3573; Found 670.3578.

L3b: Yield: 92 mg (70%) (flash chromatography under argon using neutral alumina and dry and deoxygenated toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^1H\}$ NMR (161.9 MHz, C_6D_6): δ= 143.6 (s, P-O), 70.4 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.60-0.74 (m, 6H, CH_3, ^{i}Pr), 1.05 (d, 3H, CH3-CH, $^3J_{H-H}$= 6.7 Hz), 1.49 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.97 (d, 3H, CH_3-N, $^3J_{H-P}$= 3.7 Hz), 1.99 (s, 3H, CH_3), 1.99-2.01 (m, 1H, CH, ^{i}Pr), 2.06 (s, 3H, CH_3), 3.82-3.92 (m, 1H, CH-N), 5.13-5.17 (m, 1H, CH-O), 6.94-7.18 (m, 9H, CH=), 7.33-7.40 (m, 3H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 14.7 (CH_3-CH), 16.1 (CH_3), 16.4 (CH_3), 17.5 (CH_3), 17.7 (CH_3), 17.9 (CH_3), 18.0 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 22.7 (d, CH-^{i}Pr, $^1J_{C-P}$= 6.2 Hz), 29.6 (d, CH_3-N, $^2J_{C-P}$= 7.6 Hz), 31.2 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 31.6 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 65.5 (d, CH-N, $^2J_{C-P}$= 36.7 Hz), 81.3 (CH-O), 125.3-145.5 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{43}H_{58}NO_3P_2$ 698.3886; Found 698.3891.

L3c: Yield: 48 mg (68%) (flash chromatography under argon using neutral alumina and dry and deoxygenated toluene/hexane (1:1) as eluent system (1% NEt_3)). $^{31}P\{^1H\}$ NMR (161.9 MHz, C_6D_6): δ= 140.6 (s, P-O), 70.6 (bs, P-N). ^{1}H NMR (400 MHz, C_6D_6): δ= 0.79-0.87 (m, 6H, CH_3, ^{i}Pr), 1.24 (d, 3H, CH3-CH, $^3J_{H-H}$= 6.8 Hz), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 6H, CH_3), 2.02 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.13-2.15 (m, 1H, CH, ^{i}Pr), 2.25 (d, 3H, CH_3-N, $^3J_{H-P}$= 3.7 Hz), 3.90-3.97 (m, 1H, CH-N), 5.34 (m, 1H, CH-O), 6.97-7.01 (m, 10H, CH=), 7.47 (m, 2H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 14.5 (CH_3-CH), 15.6 (CH_3), 16.1 (CH_3), 16.3 (CH_3), 17.5 (CH_3), 17.8 (CH_3), 18.2 (CH_3), 19.9 (CH_3), 20.0 (CH_3), 22.6 (d, CH-^{i}Pr, $^1J_{C-P}$= 6.3 Hz), 29.4 (CH_3-N), 31.4 (d, CH_3, ^{t}Bu, J_{C-P}= 5.1 Hz), 31.5 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 65.7 (CH-N),

81.1 (CH-O), 120.9-150.5 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{43}H_{58}NO_3P_2$ 698.3886; Found 698.3980.

Preparation of amino-phosphites 6b–c. To a solution of *in situ* generated phosphorochloridite (0.55 mmol) in dry toluene (3 mL), triethylamine (0.14 mL, 1.0 mmol) was added. Then, this solution was placed in a 0 ºC bath. After 2 min at that temperature, a solution of ephedrine **1** (82.0 mg, 0.5 mmol), DMAP (6.7 mg, 0.055 mmol) and triethylamine (0.14 mL, 1.0 mmol) in toluene (3 mL) was added dropwise at 0 °C. The mixture was left to warm to rt and stirred for 4 h at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography to produce the corresponding to afford the corresponding amino-phosphite compound **6b–c** as white solids.

6b: Yield: 197 mg (72%) (filtration under argon over neutral silica using toluene/NEt_3= 100/1 as eluent). $^{31}P\{^1H\}$ NMR (161.9 MHz, C_6D_6): δ= 142.7 (s). ^1H NMR (400 MHz, C_6D_6): δ= 0.71 (d, 3H, CH_3-CH, $^3J_{H-H}$= 6.5 Hz), 1.42 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.16 (s, 3H, CH_3-N), 2.56-2.59 (m, 1H, CH-N), 5.23 (dd, 1H, CH-O, $^3J_{H-P}$= 7.7 Hz, $^3J_{H-H}$= 3.1 Hz), 7.01-7.03 (m, 1H, CH=), 7.07-7.12 (m, 2H, CH=), 7.17-7.20 (m, 3H, CH=), 7.22 (s, 1H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 14.2 (CH_3-CH), 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.8 (d, CH_3, ^{t}Bu, J_{C-P}= 4.8 Hz), 31.3 (CH_3, ^{t}Bu), 33.5 (CH_3-N), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 61.1 (CH-N), 77.8 (d, CH-O, $^2J_{C-P}$= 8.7 Hz), 125.3-146.4 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{34}H_{47}NO_3P$ 548.3288; Found 548.3291.

6c: Yield: 216 mg (79%) (filtration under argon over neutral silica using toluene/NEt_3= 100/1 as eluent). $^{31}P\{^1H\}$ NMR (161.9 MHz, C_6D_6): δ= 141.7 (s). ^1H NMR (400 MHz, C_6D_6): δ= 0.86 (d, CH_3-CH, $^3J_{H-H}$= 6.5 Hz), 1.34 (s, 9H, ^{t}Bu), 1.56 (s, 9H, ^{t}Bu), 1.65 (s, 6H, CH_3), 1.99 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.19 (s, 3H, CH_3-N), 2.89-2.95 (m, 1H, CH-N), 5.22 (dd, 1H, CH-O, $^3J_{C-P}$= 8.9 Hz, $^3J_{H-H}$= 3.9 Hz), 6.97-7.22 (m, 7H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 15.1 (CH_3-CH), 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 30.9 (d, CH_3, ^{t}Bu, J_{C-P}= 5.2 Hz), 31.5 (CH_3, ^{t}Bu), 33.8 (CH_3-N), 34.3 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 59.8 (d, CH-N, $^3J_{C-P}$= 6.0 Hz), 80.3 (d, CH-O, $^2J_{C-P}$= 11.2 Hz), 125.3-145.7 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{34}H_{47}NO_3P$ 548.3288; Found 548.3289.

Preparation of *N*-phosphine–phosphite ligands L4b–c. The corresponding amino-phosphite compound **6b–c** (136.9 mg, 0.25 mmol) was dissolved in THF (2 ml), and triethylamine was added (0.045 mL, 0.32 mmol) at rt, followed by the addition of chlorodiphenylphosphine (0.05 mL, 0.27 mmol) via syringe. The reaction was stirred for 16 h at 55 ºC using an oil bath. The solvent was removed *in vacuo*, and the product was purified by flash chromatography to produce the corresponding ligand as white solid.

L4b: Yield: 128 mg (70%) (flash chromatography under argon using neutral alumina and dry and deoxygenated toluene/NEt_3= 100/1). $^{31}P\{^1H\}$ NMR (161.9 MHz, C_6D_6): δ= 143.3 (s, P-O), 64.2 (s, P-N). ^1H NMR (400 MHz, C_6D_6): δ= 1.23 (d, 3H, CH_3-CH, $^3J_{H-H}$= 6.7 Hz), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.66 (CH_3), 1.75 (CH_3), 2.01 (CH_3), 2.02 (d, 3H, CH_3-N, $^3J_{H-P}$= 2.9 Hz), 2.05 (s, 3H, CH_3), 3.92-4.03 (m, 1H, CH-N), 5.35 (pt, 1H, CH-O, *J*= 7.3 Hz), 6.85-6.89 (m, 1H, CH=), 6.91-7.12 (m, 9H, CH=), 7.17-7.22 (m, 4H, CH=), 7.45-7.49 (m, 2H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 16.1 (d, CH_3-CH, $^3J_{C-P}$= 4.4 Hz), 16.2 (CH_3), 16.5 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 31.3 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.5 (CH_3-N), 31.6 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 65.6 (d, CH-N, $^2J_{C-P}$= 39.6 Hz), 81.1 (dd, CH-O, $^2J_{C-P}$= 11.0 Hz, $^3J_{C-P}$= 7.5 Hz), 125.3-145.4 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{46}H_{56}NO_3P_2$ 732.3730; Found 732.3733.

L4c: Yield: 109 mg (60%) (flash chromatography under argon using neutral alumina and dry and deoxygenated toluene/NEt_3= 100/1). $^{31}P\{^1H\}$ NMR (161.9 MHz, C_6D_6): δ= 140.1 (s, P-O), 63.3 (s, P-N). ^1H NMR (400 MHz, C_6D_6): δ= 1.43 (d, 3H, CH_3-CH, $^3J_{H-H}$= 7.5 Hz), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.18 (d, 3H, CH_3-N, $^3J_{H-P}$= 2.9 Hz), 3.92-3.96 (m, 1H, CH-N), 5.45 (pt, 1H, CH-O, *J*= 7.8 Hz), 6.93-7.02 (m, 10H, CH=), 7.05-7.14 (m, 5H, CH=), 7.21-7.26 (m, 2H, CH=). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ= 16.2 (CH_3), 16.3 (CH_3), 16.4 (d, CH_3-CH, $^3J_{C-P}$= 6.3 Hz), 20.0 (CH_3), 20.1 (CH_3), 31.0 (d, CH_3, ^{t}Bu, J_{C-P}= 5.2 Hz), 31.4 (C, ^{t}Bu), 32.1 (d, CH_3-N, $^2J_{C-P}$= 10.0 Hz), 34.4 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 65.4 (dd, CH-N, $^2J_{C-P}$= 37.8 Hz, $^3J_{C-P}$= 5.8 Hz), 80.7 (dd, CH-O, $^2J_{C-P}$= 10.6 Hz, $^3J_{C-P}$= 5.6 Hz), 125.3-145.7 (aromatic carbons). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{46}H_{56}NO_3P_2$ 732.3730; Found 732.3732.

General procedure for the asymmetric hydrogenation. $[Rh(cod)_2]BF_4$ (1 mg, 2.5 μmol), the corresponding ligand (2.5 μmol) and the desired substrate (0.25 mmol) were dissolved in THF (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 Celite. Conversions were determined by ^1H NMR and enantiomeric excesses were determined by chiral HPLC or GC.

*(R)-Methyl acetylalaninate (**7**)*.[35] Yield: 35 mg (96%). Enantiomeric excess determined by GC using a L-Chirasil-Val column (100 kPa H_2, Isotherm at 100 °C). t_R 5.9 min (*R*); t_R 7.0 min (*S*). $[\alpha]_D^{20}$ –9.2 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$), δ: 1.33 (d, 3H, CH_3, J_{H-H}= 7.2 Hz), 1.95 (s, 3H, CH_3, NAc), 3.68 (s, 3H, CH_3, COOMe), 4.52 (m, 1H, CH), 6.34 (bs, 1H, NH).

*(R)-Methyl acetylphenylalaninate (**8**)*.[35] Yield: 54 mg (97%). Enantiomeric excess determined by GC using a L-Chirasil-Val column (150 kPa H_2, Isotherm at 150 °C). t_R 9.9 min (*R*); t_R 11.3 min (*S*). $[\alpha]_D^{20}$ –105.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$), δ: 1.92 (s, 3H, CH_3, NAc), 3.06 (m, 2H, CH_2), 3.66 (s, 3H, CH_3, COOMe), 4.82 (m, 1H, CH), 5.84 (bs, 1H, NH), 7.01-7.03 (m, 2H, CH=), 7.18-7.24 (m, 3H, CH=).

*(R)-Methyl 3-acetamido-3-phenylpropanoate (**9**)*.[36] Yield: 52 mg (94%). Enantiomeric excess determined by GC using a L-Chirasil-Val column (150 kPa H_2, Isotherm at 150 °C). t_R 13.8 min (*S*); t_R 14.4 min (*R*). $[\alpha]_D^{20}$ 64.1 (*c* 1.0, MeOH). ^1H NMR (400 MHz, $CDCl_3$), δ: 2.01 (s, 3H, CH_3, NAc), 2.81 (dd, 1H, CH_2, J_{H-H}= 15.8 Hz, J_{H-H}= 6.0 Hz), 2.93 (dd, 1H, CH_2, J_{H-H}= 15.8 Hz, J_{H-H}= 6.0 Hz), 3.60 (s, 3H, CH_3, COOMe), 6.56 (bs, 1H, NH), 7.25-7.34 (m, 4H, CH=).

*(R)-N-(1-(4-Methoxyphenyl)ethyl)acetamide (**10**).*[8e] Yield: 44 mg (92%). Enantiomeric excess determined by HPLC using Chiracel AD column (hexane/2-propanol=95/5, 1 mL/min, 220 nm). t_R 18.4 min (*S*); t_R 23.4 min (*R*). $[\alpha]_D^{25}$ 144.8 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.46 (d, 3H, CH_3, J_{H-H}= 6.9 Hz), 1.96 (s, 3H, NHAc), 3.79 (s, 3H, OMe), 5.03-5.13 (m, 1H, CH), 5.65 (bs, 1H, NH), 6.87 (d, 2H, CH=, J_{H-H}= 8.7 Hz), 7.24 (d, 2H, CH=, JH-H= 8.7 Hz).

*(R)-N-(1,2,3,4-Tetrahydronaphthalen-1-yl)acetamide (**11**).*[8e] Yield: 44 mg (93%). Enantiomeric excess determined by HPLC using Chiracel OD-H column (hexane/2-propanol=90/10, 0.5 mL/min, 220 nm). t_R 18.8 min (*S*); t_R 23.9 min (*R*). $[\alpha]_D^{25}$ +102.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.73-1.89 (m, 3H, CH_2), 1.95-2.09 (m, 4H, CH_2 and NHAc), 2.68-2.89 (m, 2H, CH_2), 5.08-5.23 (m, 1H, CH), 5.69 (bs, 1H, NH), 7.05-7.22 (m, 4H, CH=).

*N-(Chroman-4-yl)acetamide (**12**).*[20a] Yield: 41 mg (87%). Enantiomeric excess determined by HPLC using Chiralcel OD-H column (87% hexane/2-propanol, flow 1 mL/min). t_R 8.0 min (*S*); t_R 11.8 min (*R*). $[\alpha]_D^{20}$ 76.9 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.03 (s, 3H, CH_3, NAc), 2.05-2.09 (m, 1H, CH), 2.17-2.25 (m, 1H, CH), 4.11-4.17 (m, 1H, CH), 4.24-4.29 (m, 1H, CH), 5.10-5.15 (m, 1H, CH), 5.77 (bs, 1H, NH), 6.83 (d, 1H, CH=, *J*= 8.0 Hz), 6.89-6.93 (m, 1H, CH=), 7.16-7.22 (m, 2H, CH=).

*(R)-N-(1,2,3,4-Tetrahydronaphthalen-2-yl)acetamide (**13**).*[37] Yield: 43 mg (91%). Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (80% hexane/2-propanol, flow 1 mL/min). t_R 5.7 min (*R*); t_R 6.6 min (*S*). $[\alpha]_D^{20}$ 34.1 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.69-1.74 (m, 1H, CH_2), 1.91 (s, 3H, CH_3, NAc), 1.95-1.99 (m, 1H, CH_2), 2.58 (dd, 1H, CH_2, J_{H-H}= 16.0 Hz, J_{H-H}= 8.0 Hz), 2.78-2.83 (m, 2H, CH_2), 3.04 (dd, 1H, CH_2, J_{H-H}= 16.0 Hz, J_{H-H}= 8.0 Hz), 4.19-4.23 (m, 1H, CH-N), 5.61 (bs, 1H, NH), 6.97-7.07 (m, 4H, CH=).

*(R)-Methyl-2-acetamido-3-(2,5-difluorophenyl)propanoate (**14**).*[8f] Reaction carried out using 5 mmol of **S9**. Yield: 1.22 g (95%). Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (90% hexane/2-propanol, flow 1 mL/min). t_R 13.2 min (*R*); t_R 17.1 min (*S*). $[\alpha]_D^{25}$ –77.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.88 (s, 3H, CH_3, NAc), 2.98 (dd, 1H, CH_2, *J*= 13.9 Hz, *J*= 6.0 Hz), 3.09 (dd, 1H, CH_2, *J*= 13.9 Hz, *J*= 6.0 Hz), 3.64 (s, 3H, CH_3, COOMe), 4.72-4.77 (m, 1H, CH), 5.94 (bs, 1H, NH), 6.70-675 (m, 1H, CH=), 6.79-6.90 (m, 2H, CH=).

*(S)-Methyl-2-acetamido-3-(3-bromo-4-fluorophenyl)propanoate (**15**).*[8f] Yield: 73 mg (92%). Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (90% hexane/2-propanol, flow 1 mL/min). t_R 17.3 min (*R*); t_R 20.8 min (*S*). $[\alpha]_D^{25}$ 56.2 (*c* 0.45, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.00 (s, 3H, CH_3, NAc), 3.02 (dd, 1H, CH_2, *J*= 14.0 Hz, *J*= 5.8 Hz), 3.11 (dd, 1H, CH_2, *J*= 14.0 Hz, *J*= 5.8 Hz), 3.73 (s, 3H, CH_3, COOMe), 4.79-4.84 (m, 1H, CH), 6.11 (bs, 1H, NH), 7.00-7.03 (m, 2H, CH=), 7.25-7.29 (m, 1H, CH=).

*(S)-Methyl-2-acetamido-3-(naphthalen-2-yl)propanoate (**16**).*[38] Yield: 65 mg (96%). Enantiomeric excess determined by HPLC using Chiralcel AD column (90% hexane/2-propanol, flow 1 mL/min). t_R 8.4 min (*R*); t_R 12.0 min (*S*). $[\alpha]_D^{20}$ 96.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.95 (s, 3H, NHAc), 3.22 (dd, 1H, CH_2, *J*= 20.2 Hz, *J*= 6.3 Hz), 3.30 (dd, 1H, CH_2, *J*= 19.9 Hz, *J*= 6.0 Hz), 3.71 (s, 3H, COOMe), 4.97 (dt, 1H, CH, *J*= 6.9 Hz, *J*= 6.0 Hz), 6.02 (bs, 1H, NH), 7.19-7.77 (m, 7H, CH=).

*(R)-Methyl-2-((tert-butoxycarbonyl)amino)-3-(3,5-difluorophenyl)propanoate (**17**).*[8e] Yield: 73 mg (93%). Enantiomeric excess determined by HPLC using Chiralcel OJ-H column (98% hexane/2-propanol, flow 0.5 mL/min). t_R 19.5 min (*R*); t_R 22.0 min (*S*). $[\alpha]_D^{20}$ –52.2 (*c* 1.0, MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.41 (s, 9H, CH_3, NBoc), 2.96-3.01 (m, 1H, CH_2), 3.09-3.14 (m, 1H, CH_2), 3.72 (s, 3H, CH_3, COOMe), 4.53-4.58 (m, 1H, CH), 5.02 (bs, 1H, NH), 6.64-6.70 (m, 3H, CH=).

*(S)-N-(1-(4-Fluorophenyl)ethyl)acetamide (**18**).*[39] Reaction carried out using 10 mmol of **S13**. Yield: 1.75 g (97%). Enantiomeric excess determined by HPLC using Chiralcel AD column (95% hexane/2-propanol, flow 1 mL/min). t_R 11.1 min (*S*); t_R 13.9 min (*R*). $[\alpha]_D^{25}$ –123.2 (*c* 1.0, EtOH). ^{1}H NMR ($CDCl_3$), δ: 1.40 (m, 3H, CH3), 1.91 (s, 3H, NAc), 5.01-5.05 (m, 1H, CH), 6.94-6.99 (m, 2H, CH=), 7.22-7.25 (m, 2H, CH=).

ASSOCIATED CONTENT

Copies of NMR spectra of intermediates (**6b–c**, **L1**·BH_3**a–c** and **L3**·BH_3**b–c** and ligands (**L1–L4a–c**). Copies of ^{1}H–NMR and GC/HPLC traces for all hydrogenated products and copies of ^{1}H-NMR of substrates **S2–S13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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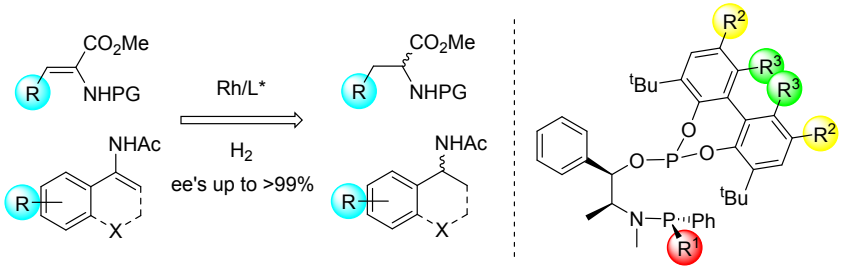
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