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Highly Modular *P-O-P* Ligands for Asymmetric Hydrogenation

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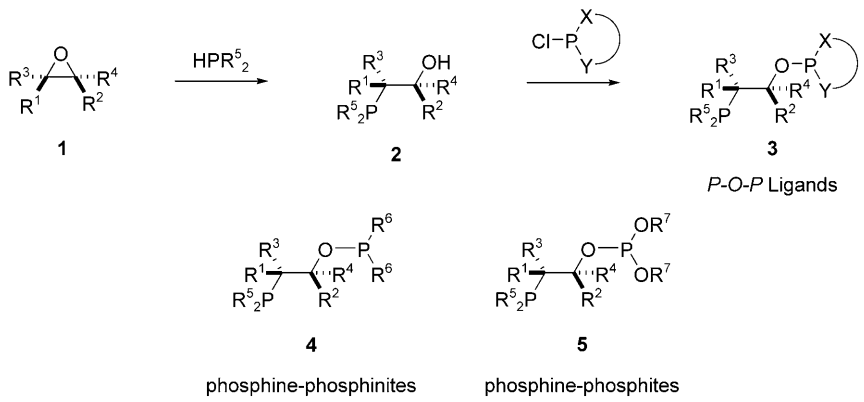
Abstract: The preparation of a library of new *P-O-P* ligands (phosphine-phosphites and phosphine-phosphinites), easily available in two synthetic steps from enantiopure Sharpless epoxy ethers, is reported. The "lead" catalyst of the series has proven to have outstanding catalytic properties in the rhodium-catalysed asymmetric hydrogenation of a wide variety of functionalised alkenes (16 examples). The excellent performance and modular design of the catalysts makes them attractive for future applications.

Keywords: asymmetric catalysis; hydrogenation; ligand design; phosphane ligands; phosphite ligands; rhodium

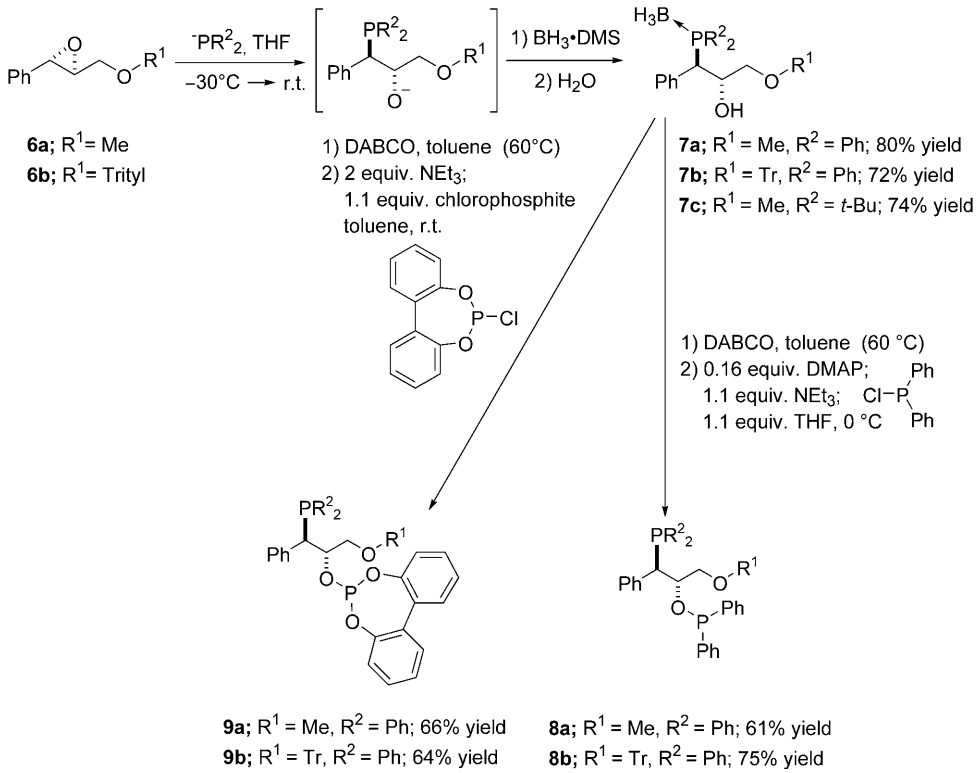
Asymmetric hydrogenation can be considered a well established synthetic methodology that has already been incorporated into the standard "asymmetric tool-box" of the synthetic community.[1] From a practical perspective, it is one of the most efficient methodologies for the generation of new stereogenic carbon centres. There have been several significant breakthroughs in the field[1] and now a myriad of chiral Ru, Rh and Ir coordination compounds (mostly phosphorus-containing derivatives) capable of mediating the addition of H_2 to prochiral C=C, C=N and C=O bonds with very high enantioselectivities are known.[1] The development of commercial processes[2] has rendered this transformation highly desirable to both academia and industry. However, despite the remarkably advanced state of the field, many groups are still actively researching new catalytic systems that show higher activity and/or improved enantioselectivity for challenging substrates. In other cases, research efforts are directed to the development of chiral ligands with an attractive industrial profile, which ultimately means that they should induce high enantioselectivity, be easily prepared and not fall into the claims of any patent currently in force. While computational techniques are becoming increasingly important in the design of new chiral catalysts,[3] many approaches still rely to a great extent on trial-and-error. Not surprisingly, combinatorial and high-throughput synthetic strategies[4] have led to the development of some highly efficient monodentate and bidentate phosphorus-containing ligands for asymmetric hydrogenation, utilising either standard covalent chemistry[4c,5] or supramolecular interactions.[6] In a complementary way, ligand tuning in asymmetric catalysis has allowed the rapid development of efficient catalytic systems. We[3a,7] and others[8] have shown that the modular nature of ligands facilitates the tuning of their performance by modifying the stereoelectronic properties of the different modular fragments (modules). This encouraged us to design a new family of *P-O-P* ligands **3** derived from enantiopure epoxides and the work described here details our initial efforts in this area together with their application in the asymmetric hydrogenation of functionalised alkenes.

We envisaged that the chiral epoxides **1** could be converted into the *P-O-P* ligands **3**, as shown in Scheme 1. Epoxide ring-opening with nucleophilic trivalent phosphorus derivatives would allow the introduction of the phosphine functionality in the chiral skeleton and further derivatisation of hydroxy phosphines **2** with trivalent phosphorus electrophiles should render the target *P-O-P* ligands. As a first set of *P-O-P* ligands, we embarked on the preparation of phosphine-phosphinites **4** and phosphine-phosphites **5**. There is a good literature precedent for the two key transformations in our strategy (oxirane ring-opening with phosphorus nucleophiles[9] and phosphorylation of a hydroxy group with trivalent phosphorus electrophiles[10,11]), however, to the best of our knowledge, they have never been combined to synthesise highly modular *P-O-P* ligands such as the ones



Scheme 1.

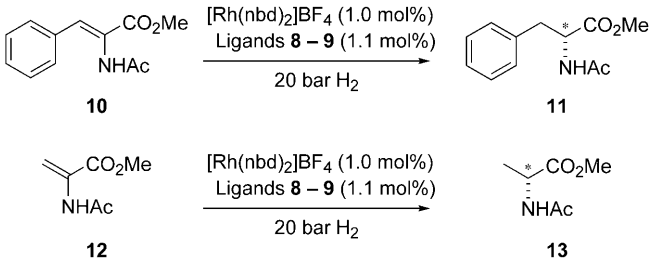
described in this paper. The three constituents of the ligands (chiral epoxide, nucleophilic and electrophilic phosphorus reagents) allow for the simple modification of the *P-O-P* ligands. Furthermore, the use of Sharpless epoxy ethers (**6** in Scheme 2), as discussed in this study, will allow the incorporation into the final *P-O-P* ligands of an additional CH_2OR group. The steric environment at this position has proved to be critical in the catalytic activity of other chiral ligands derived from Sharpless epoxy alcohols in many asymmetric transformations.[3a,7,12] For this reason, epoxy ethers **6a** and **6b** containing a methyl and a trityl groups[13] were chosen as chiral starting materials for our target *P-O-P* ligands. A phenyl substituent *trans* to the CH_2OR was selected due to the ease of its preparation[7a,14] and the favourable reactivity of a benzylic position in the ring-opening of epoxides by nucleophiles. The ring-opening of epoxides **6a** and **6b** with potassium diphenylphosphanide or lithium di-*tert*-butylphosphanide proceeded smoothly at −30 °C to room temperature. Hydroxy phosphines arising from the ring-opening reactions were rather prone to oxidation, subsequent protection as the corresponding borane adducts[15] allowed for more convenient handling and storage (72–80% isolated yield, Scheme 2). The ring-opening reactions were regioselective and



Scheme 2.

stereospecific, as reported by Brunner[9d] and Togni[9e] for the ring-opening of related Sharpless epoxides with trivalent phosphorus nucleophiles. Phosphine-phosphinites **8** and phosphine-phosphites **9** were further prepared following the synthetic protocol indicated in Scheme 2. The free hydroxy phosphines derived from **7a,b**[16] were generated by cleavage of the borane group using DABCO at 60 °C and derivatised *in situ* in the presence of an auxiliary base with either chlorodiphenylphosphine or (1,1′-biphenyl-2,2′-dioxy)-chlorophosphine following well established procedures for related compounds.[10,11] The target *P-O-P* ligands **8** and **9** were easily isolated after column chromatography, in yields ranging from 61 to 75% (Scheme 2).

To achieve highly efficient enantioselective catalysis for a given transformation or substrate of interest, the tuning of the catalyst to make a perfect match amongst the ligand, metallic ion and substrate is a key issue: by using a modular catalyst design, the structural features responsible for asymmetric induction can simply be modified and adjusted.[7,8] The synthetic strategy used in the present work has allowed the synthesis of a set of ligands that comprises two extreme situations in terms of steric congestion around the CH_2OR chain (methyl and trityl) and two different phosphorus functionalities at C-2 [OPR_2 and $OP(OR)_2$]. As the starting point in our optimisation process towards new and efficient ligands for the hydrogenation of C=C bonds, we studied the effect of the aforementioned modules in the activity of [Rh(*P-O-P*)]BF_4 complexes in the hydrogenation of **10** and **12** (Scheme 3, Table 1). The chiral rhodium complexes were generated *in situ* from [$Rh(nbd)_2$]BF_4 and a 10 mol% excess of the corresponding *P-O-P* ligand. The reaction conditions and results are summarised in Table 1. Complete conversions were observed after 12 h at room temperature in dichloromethane for both substrates and for the different phosphine-phosphinites (entries 1 and 2) and phosphine-phosphites (entries 3 and 4) which were assayed. However, complexes with the ligands **8a,b** mediated the hydrogenation of **10** and **12** with poor enantioselectivities (26–64% *ee*), indicating that the stereoelectronics around the Rh centre were not optimal. On the other hand, the phosphine-phosphites **9a,b** showed a higher enantioselectivity than their phosphine-phosphinite congeners (79–86%). Enantioselectivity could be further improved by carrying out the hydrogenation at lower temperatures (−40 °C). The reaction proceeded smoothly at this temperature and enantioselectivities ranged from 89–98% *ee* (entries 5 and 6). Steric congestion at the CH_2OR chain was found to be slightly detrimental towards selectivity; trityl-substituted phosphine-phosphite **9b** mediates the hydrogenation with lower enantioselectivity than its methyl substituted analogue **9a** (compare entry 3 with 4, and 5 with 6).



Scheme 3.

Although the enantioselectivies achieved with the *P-O-P* ligand **9a** were reasonably high, the required low temperatures reduced its attractiveness in regards to applicability. With the aim of developing a more efficient phosphine-phosphite for this reaction, we decided to introduce a fragment with an additional stereogenic element in the optimised *P-O-P* ligand. As the best catalyst of the initial set, **9a**, contained the bi-

Table 1. Asymmetric hydrogenation of functionalised acrylates **10** and **12** mediated by [Rh(*P-O-P*)]BF_4 complexes.

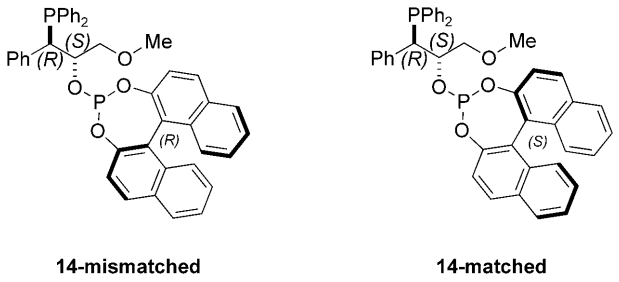
Entry	Reaction conditions[a]	Conversion [%][b] of **10**	*ee* [%][c] (configuration)[d] of **11**	Conversion [%][b] of **12**	*ee* [%][c] (configuration)[d] of **13**
1	**8a**, DCM, r.t., 12 h	>99	26 (*S*)	>99	40 (*S*)
2	**8b**, DCM, r.t., 12 h	>99	52 (*S*)	>99	64 (*S*)
3	**9a**, DCM, r.t., 12 h	>99	86 (*R*)	>99	82 (*R*)
4	**9b**, DCM, r.t., 12 h	>99	79 (*R*)	>99	81 (*R*)
5	**9a**, THF, −40 °C, 12 h	>99	98 (*R*)	>99	96 (*R*)
6	**9b**, THF, −40 °C, 12 h	>99	92 (*R*)	>99	89 (*R*)
7	**14-mismatched**, THF, r.t., 12 h	>99	86 (*S*)	>99	88 (*S*)
8	**14-matched**, THF, r.t., 12 h	>99	99 (*R*)	>99	99 (*R*)

[a] All reactions were run under at 20 bar H_2 at the stated temperature. Reactions were run over-night (12 h) for the sake of convenience, as in the case of the lead catalyst, **14-matched** (entry 8), full conversion (>99%) was observed after 10 min.
[b] Conversions were determined by ^1H NMR.
[c] Enantiomeric excesses were determined by GC or HPLC using chiral stationary phases.
[d] Absolute configurations were assigned by comparison with published optical rotation data.

phenyl-2,2′-diol unit, phosphites derived from (*R*)- and (*S*)-BINOL were the obvious choice for incorporating this new element of chirality. The two new phosphine-phosphites derived from **7a** and the (*R*)- and (*S*)-BINOL moieties could be straightforwardly prepared with our synthetic strategy in good yields (71 and 66%, respectively).

Whereas the phosphine-phosphite derived from (*R*)-BINOL did not lead to improved enantioselectivities (entry 7, Table 1), we were pleased to observe that the *P-O-P* ligand incorporating the (*S*)-BINOL fragment, **14-matched**, mediated the hydrogenation of alkenes **10** and **12** in 99% *ee* (Figure 1, entry 8, Table 1). Interestingly, the biaryl moiety strongly influences the stereochemical outcome of the reaction: opposite absolute configurations of **11** and **13** were obtained with **14-mismatched** and **14-matched** (*cf.* entries 7 and 8 in Table 1).[4c,17]

With the optimised ligand **14-matched** in hand, we studied its catalytic properties in the hydrogenation of a variety of functionalised alkenes **15a–n** (Figure 2). The results are summarised in Table 2.



14-mismatched **14-matched**

Figure 1.

Ligand **14-matched** exhibited a remarkably good profile (very high conversions and *ee*s up to 99%) over the whole range of alkenes studied. The results for aryl-substituted cinnamates (substrates **10**, **15a** and **15c–k**) indicated very high levels of stereoselection (96–99%, entry 8 in Table 1; entries 1, 3–11 in Table 2) regardless of the electronic nature or position of substituents on the aromatic ring. Ligand **14-matched** mediated very efficiently the hydrogenation both for carboxylic acids or their methyl esters. A wide variety of *N*-protecting groups was also tolerated (Ac, Cbz, Boc and Fmoc), enantioselectivity remaining very high in all cases (entry 9 in Table 1 and entries 8–11 in Table 2). Interestingly, the asymmetric hydrogenation of two Fmoc-protected dehydro arylalanines (**15j** and **15k**) was possible with ligand **14-matched**; thus our strategy constitutes, to the best of our knowledge, the first example of the preparation of enantioenriched Fmoc-protected non-natural amino acids by asymmetric hydrogenation.

In summary, we describe a library of new *P-O-P* ligands (phosphine-phosphites and phosphine-phosphinites) easily available in two synthetic operations from enantiopure Sharpless epoxy ethers. The "lead" catalyst of the series (ligand **14-matched**) has shown to have outstanding catalytic properties in the asymmetric hydrogenation of a wide variety of functionalised alkenes (16 examples). The remarkably good performance and modular nature of the catalyst makes it attractive for future applications. The strategy described in this paper to discover new chiral catalysts – tuning of the performance of the catalyst by modifying the stereoelectronic properties of the molecular fragments or modules – is based on a correct hypothe-

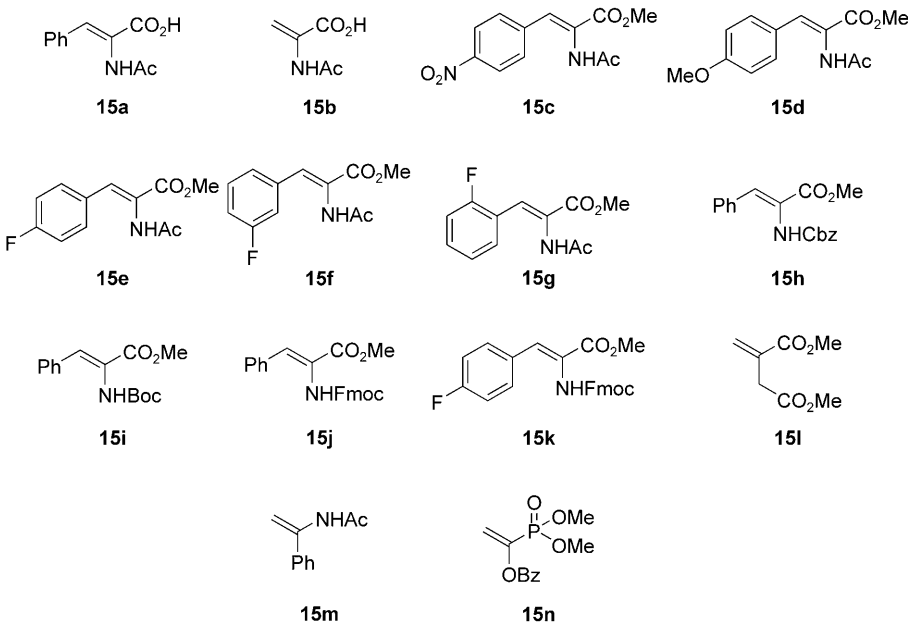


Figure 2.

Table 2. Asymmetric hydrogenation of alkenes **15a–n** mediated by **14-matched**.[a]

Entry	Substrate	Pressure [bar]	Solvent	Conversion[b] [%]	*ee*[c] [%] (configuration)[d]
1	**15a**	20	THF	>99	99 (*R*)
2	**15b**	20	THF	>99	98 (*R*)
3	**15c**	20	THF	>99	99 (*R*)
4	**15d**	20	THF	>99	99 (*R*)
5	**15e**	20	THF	>99	99 (*R*)
6	**15f**	20	THF	>99	99 (*R*)
7	**15g**	20	THF	>99	99 (*R*)
8	**15h**	20	THF	>99	99 (*R*)
9	**15i**	20	THF	>99	96 (*R*)
10	**15j**	40	THF	99	98 (*R*)[e]
11	**15k**	40	THF	94	97 (*R*)[e]
12	**15l**	20	DCM	>99	99 (*R*)
13	**15m**	20	THF	>99	98 (*R*)
14	**15n**	20	DCM	>99	92 (*S*)

[a] All reactions were run at room temperature for 12 h at the H_2 pressure indicated.
[b] Conversions were determined by ^{1}H NMR.
[c] Enantiomeric excesses were determined by GC or HPLC using chiral stationary phases.
[d] Absolute configurations were assigned by comparison with published optical rotation data.
[e] Their absolute configurations were tentatively assigned by analogy based on the stereochemical outcome for **10, 15a,c–i**.

sis. The results described show that the different parts of a given chiral catalyst can be optimised separately, so it is possible to achieve high levels of enantioselectivity even starting from a mediocre ligand. Work is in progress to discover new catalysts for asymmetric hydrogenation in still challenging fields (C=N and unfunctionalised C=C bonds).

Experimental Section

General remarks about the experimental section can be found in the Supporting Information.

General Procedure for the Ring-Opening of Sharpless Epoxy Ethers with Phosphorus Nucleophiles

A solution of the phosphorus nucleophile in THF (0.98 mmol) was syringed into a solution of the corresponding epoxy ether (1 mmol) in dry THF (8.0 mL), which was previously cooled at −30 °C under argon. The mixture was stirred for 1 h at this temperature and then was slowly allowed to reach room temperature and stirred for 1 h. After this period of time, the mixture was cooled at −10 °C and BH_3·DMS (2.94 mmol) was added dropwise. The mixture was stirred for 1 h at this temperature and then allowed to reach room temperature and stirred at this temperature for further 1 h. The reaction mixture was quenched with water (8.0 mL), and the two phases were separated. The aqueous phase was extracted with AcOEt (3×15 mL). The combined organic phases were washed with brine (2×15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography using hexane/AcOEt as eluent to give the corresponding hydroxy phosphine-borane complexes.

Compound **7a** was obtained following this procedure, starting from epoxy ether **6a** (0.309 g, 1.88 mmol), $KPPh_2$ (3.69 mL, 1.84 mmol) and BH_3·DMS (0.53 mL, 5.65 mmol) after column chromatography through SiO_2 (hexanes/AcOEt, 100:0/80:20) as a white solid; yield: 0.552 g (80%); mp: 117.1–117.6 °C; $[\alpha]_D^{28}$: −154.2 (*c* 1.0 g/100 mL, $CHCl_3$); IR (neat): ν = 3449 , 2389 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.96 (m, 2H), 7.57–7.12 (m, 13H), 4.48 (m, 1H), 4.15 (dd, $^2J_{H\text{-}P}$ = 17.2 Hz, $^3J_{H\text{-}H}$ = 3.6 Hz, 1H), 3.21 (ddd, $^2J_{H\text{-}H}$ = 9.6 Hz, $^3J_{H\text{-}H}$ = 5.2 Hz, $^4J_{H\text{-}P}$ = 1.6 Hz, 1H), 3.13 (s, 3H), 3.12 (dd, $^2J_{H\text{-}H}$ = 9.6 Hz, $^3J_{H\text{-}H}$ = 6.8 Hz, 1H), 3.01 (d, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H), 1.81–0.77 (bs, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 133.00 (d, $J_{C\text{-}P}$ = 8.6 Hz, CH), 132.96 (d, $J_{C\text{-}P}$ = 8.4 Hz, CH), 131.69 (d, $J_{C\text{-}P}$ = 2.2 Hz, CH), 131.36 (d, $J_{C\text{-}P}$ = 4.9 Hz, CH), 130.95 (d, $J_{C\text{-}P}$ = 2.1 Hz, CH), 129.08 (d, $J_{C\text{-}P}$ = 9.7 Hz, CH), 128.61 (C), 128.24 (CH), 128.17 (C), 128.14 (CH), 128.08 (C), 127.61 (C), 127.48 (d, $J_{C\text{-}P}$ = 2.1 Hz, CH), 73.17 (d, $^3J_{C\text{-}P}$ = 8.1 Hz, CH_2), 69.12 (d, $^2J_{C\text{-}P}$ = 5.9 Hz, CH), 58.84 (CH_3), 45.05 (d, $^1J_{C\text{-}P}$ = 31.9 Hz, CH); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 20.61 (bs, PPh_2·BH_3); ^{11}B NMR (128 MHz, $CDCl_3$): δ = −39.05 (bs, BH_3); HR-ESI-MS: *m/z* = 387.1658; calcd. for $C_{22}H_{26}O_2PBNa$ (M - Na^+): 387.1661.

General Procedure for the Preparation of Phosphine-Phosphite Ligands

The phosphine-borane complexes (**7**, 1.0 mmol) and diazabyciclo[2.2.2]octane (2.2 mmol) were charged in a flame-dried Schlenk flask. The system was purged three times with argon, then dry and deoxygenated toluene (5.0 mL) was added. The reaction mixture was heated at 60 °C and stirred for 2 h, allowed to cool down to room temperature, passed through a short pad of SiO_2 under argon and further eluted with dry and deoxygenated toluene (6.0 mL) giving a solution of the corresponding hydroxy phosphine which was directly used in the following step.

This solution was added dropwise *via* cannula to another solution of the appropriate chlorophosphite (1.1 mmol) and

NEt_3 (2.0 mmol) in toluene (17.0 mL). The mixture was stirred for 16 h at room temperature. The reaction mixture was filtered through Celite under argon and the filtrate was evaporated under vacuum. The resulting residue was dissolved in dry and deoxygenated diethyl ether (20.0 mL) and passed through a short pad of alumina (3 g, previously dried under vacuum). Evaporation of the solvent yielded the corresponding phosphine-phosphite ligand.

Compound **14-matched** was obtained following this procedure, starting from **7a** (0.233 g, 0.64 mmol), DABCO (0.158 g, 1.41 mmol), NEt_3 (0.18 mL, 1.27 mmol) and the chlorophosphite derived from (*S*)-BINOL (0.255 g, 0.42 mmol) as a white solid; yield: 281 mg (66%); mp: 103.4–108.7 °C; $[\alpha]_D^{26}$: +161.9 (*c* 0.50 g/100 mL, THF); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99–7.92 (m, 3H), 7.82–7.75 (m, 3H), 7.54–7.41 (m, 8H), 7.30–7.04 (m, 13H), 4.52 (m, 1H), 3.78 (dd, $^2J_{H\text{-}P}$ = $^3J_{H\text{-}H}$ = 4.2 Hz, 1H), 3.30 (dd, $^2J_{H\text{-}H}$ = 10.0 Hz, $^3J_{H\text{-}H}$ = 5.0 Hz, 1H), 3.28 (s, 3H), 3.23 (dd, $^2J_{H\text{-}H}$ = 10.0 Hz, $^3J_{H\text{-}H}$ = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 148.22 (d, $J_{C\text{-}P}$ = 4.5 Hz, C), 147.97 (d, $J_{C\text{-}P}$ = 1.6 Hz, C), 136.84 (d, $J_{C\text{-}P}$ = 11.1 Hz, C), 136.66 (d, $J_{C\text{-}P}$ = 15.4 Hz, C), 135.96 (d, $J_{C\text{-}P}$ = 17.5 Hz, C), 134.95 (d, $J_{C\text{-}P}$ = 21.6 Hz, CH), 133.30 (d, $J_{C\text{-}P}$ = 19.1 Hz, CH), 132.94 (d, $J_{C\text{-}P}$ = 29.6 Hz, C), 131.44 (d, $J_{C\text{-}P}$ = 46.1 Hz, C), 130.07 (d, $J_{C\text{-}P}$ = 31.8 Hz, CH), 129.52 (CH), 128.88 (d, $J_{C\text{-}P}$ = 7.8 Hz, CH), 128.48 (CH), 128.35 (d, $J_{C\text{-}P}$ = 6.6 Hz, CH), 128.12 (CH), 127.95 (d, $J_{C\text{-}P}$ = 6.9 Hz, CH), 127.25 (d, $J_{C\text{-}P}$ = 6.1 Hz, CH), 126.87 (d, $J_{C\text{-}P}$ = 1.4 Hz, CH), 126.18 (d, $J_{C\text{-}P}$ = 19.1 Hz, CH), 124.95 (d, $J_{C\text{-}P}$ = 20.1 Hz, CH), 124.69 (d, $J_{C\text{-}P}$ = 5.2 Hz, C), 123.34 (d, $J_{C\text{-}P}$ = 1.8 Hz, C), 122.36 (CH), 122.26 (CH), 74.85–74.62 (m, CH_2 and CH), 58.91 (CH_3), 48.03 (dd, $^1J_{C\text{-}P}$ = 14.8 Hz, $^3J_{C\text{-}P}$ = 5.9 Hz, CH); ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$): δ = 156.20 (d, $^4J_{P\text{-}P}$ = 11.4 Hz, P-O), −5.49 (bs, d, $^4J_{P\text{-}P}$ = 11.4 Hz, P-C); HR-ESI-MS: *m/z* = 665.2020; calcd. for $C_{42}H_{35}O_4P_2$ (M - H^+): 665.2011].

See Supporting Information for the rest of the recipes and physical and spectroscopic data of the rest of the compounds.

General Procedure for the Asymmetric Hydrogenation of Alkenes 10, 12 and 15a–n

A solution of the chiral ligand (0.011 mmol), bis(norbornadiene)rhodium tetrafluoroborate (0.4 mg, 0.01 mmol) and the substrate (1 mmol) in the corresponding dry and deoxygenated solvent (0.6 mL) was charged into an autoclave under an N_2 atmosphere. The autoclave was purged three times with hydrogen gas (10 bar). Finally, the autoclave was pressurised with hydrogen. The reaction mixture was stirred at the desired temperature for the stated reaction time. The autoclave was subsequently depressurised and the conversion was determined by ^{1}H NMR. The *ee* values were determined by chiral chromatography, and the configurations of the hydrogenated products were established by comparison with reported optical rotations (see Supporting Information).

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